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George P. Rédei

Encyclopedia of Genetics, Genomics, Proteomics, and Informatics

3rd Edition

 Springer

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**Volume 1
A–L**

With 1914 figures and 94 tables

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Encyclopedia of Genetics, Genomics, Proteomics, and Informatics

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**Volume 2
M–Z**

With 1914 figures and 94 tables

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Some of the chemical formulas are based on the Merck Index, on the Aldrich Catalog and Fluka Catalog.

During the preparation of the third edition, Mark Jarvis has been most helpful in resolving a variety of computer problems.

I appreciated the comments from the readers on the first and second editions. The first e-mail from Dr. SLC said: "Thank you for assembling such concise explanations of all genetic concepts in a single volume". Similar letters came from many others, which for reasons of space, I cannot quote here.

I am thankful to the public reviews for the constructive comments and suggestions.

Author is much indebted to Anil Chandy for expert advice, friendship, cooperation and understanding during all phases of the production of this book.



Cudweed by Konrad von Gessner (1597), the famous Swiss savant and zoological and botanical illustrator. Von Gessner's work has been borrowed by many, among them the German Joachim Camerarius (1500–1576) of Tübingen, a great authority on classics, religion and science and whose descendant Rudolph Jacob Camerarius (1665–1721) would become the first experimental geneticist, and discover the love life of plants.

Preface to the First Edition

The primary goal of this Manual is the facilitation of communication and understanding across the wide range of biology that is now called genetics. The emphasis is on recent theoretical advances, new concepts, terms and their applications. The book includes about 18 thousand concepts and over 650 illustrations (graphs, tables, equations and formulas). Most of the computational procedures are illustrated by worked-out examples. A list of about 900, mainly recent books, is provided at the end of the volume, and additional references are located at many entries and illustrations. The most relevant databases are also listed. The cross-references following the entries connect to a network within the book, so this is not just a dictionary or glossary. By a sequential search, comprehensive, integrated information can be obtained as you prepare for exams, or lectures, or develop or update a course, or need to review a manuscript, or just wish to clarify some problems. In contrast to standard encyclopedias, I have used relatively short but greater variety of entries in order to facilitate rapid access to specific topics. This Manual was designed for students, teachers, scientists, physicians, reviewers, environmentalists, lawyers, administrators, and to all educated persons who are interested in modern biology. Concise technical information is available here on a broad range of topics without a need for browsing an entire library. This volume can always be at your fingertips without leaving the workbench or desk. Despite the brevity of the entries, the contents are clear even for the beginner. Herbert Macgregor made the remarkable statement that in 1992 about 7,000 articles related just to chromosomes were scattered among 627 journals. Since then, the situation has become worse. Many publications—beyond a person's specialization—are almost unreadable because of the multitude of unfamiliar acronyms and undefined terms. Students and colleagues have encouraged me to undertake this effort to facilitate reading of scientific and popular articles and summarize briefly the current status of important topics. According to Robert Graves (a good poem) “makes complete sense and says all that it has to say memorably and economically”. I hope you will appreciate the sense and economy of this Manual. I will be much indebted for any comment, suggestion and correction.

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“I almost forgot to say that genetics will disappear as a separate science because, in the 21st century, everything in biology will become gene-based, and every biologist will be a geneticist.” Sydney Brenner, 1993

Preface to the Second Edition

The majority of the users of the first edition considered this book as an encyclopedia because the cross-references tied the short entries into comprehensive reviews of the topics. In contrast to “big encyclopedias” in this work only a few entries exceed a couple of thousand words and that make it much faster to find the specific concept or term of interest. Unlike multi-author works this is practically free of redundancy and it is compact in size but not in depth of information. One of the reviewers pointed out that many of the topics covered could not be found in any other single book, including encyclopedias, dictionaries or glossaries. Another reviewer appreciated it as a broad resource of information that may take a lengthy search to uncover without it.

Since the publication of the 1st edition, I have steadily updated and improved on the topics. I have added many new concepts, illustrations, books and database addresses. (The database addresses are in an unfortunate flux and some may be out existence by the time you wish to log in; therefore I provided several to minimize the problem beyond my control.) This second edition contains about 50% more information and more than twice as many illustrations than the 1st edition. A new feature is the predominantly current, over 7,000 text references to journal articles. Their bibliographies may help to locate additional key and classical papers. The General References at the end include about 2,000 books. For additional medical genetics references I suggest the use of OMIM at The National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>, see also Grivell, L 2002. *EMBO Rep.* 3:200). I have greatly expanded the cross-references among the entries because the users found this feature especially useful. Color plates were added to the end of the book. At the end of the files there are some historical vignettes.

Since the publication of the first edition the need for such a book became even more evident. In the literature unexplained concepts, terms and acronyms are on the increase and even a name DAS (*dreaded abbreviation syndrome*) has been coined for the malaise (*Science*, 283:1118). The users of the first edition agreed with the Nobel-laureate geneticist, HJ Muller who posed and answered the still current problem: “Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so.” (*Amer. Nat.* 1922, 56:32).



The vision of genetics today is not less than the complete understanding how cells and organisms are built, how they function metabolically and developmentally, and how they have evolved. This requires the integration of previously separate disciplines, based on diverse concepts and tongues. Whatever is your specialization or interest, I hope you will find this single volume helpful and affordable.

Although I had the aim of comprehensiveness beyond all the available compendiums, there were hard decisions of what to include and what to pass. The same science may appear different depending on who, how and when looks at it (up or down) as Gerald H Fisher's art above (man or woman or both) illustrates the point.*

Thank you for the appreciation of the first edition. I will be much indebted for your comments and suggestions.

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*By permission of Perception and Psychophysics 4:189 (1968).

Preface to the Third Edition

“When I acquired the right words..., it was easier for me to understand what I was thinking: it is difficult to reason through a problem if you cannot articulate what the problem is.”

(John F Bruzzi 2006 *New England J. Med.* 354:665).

This volume is essentially an improved and enlarged new version of the previous, much-acclaimed book. The third edition has over 1,000 pages more of new material than the second. The latest progress in current hot topics such as stem cells, gene therapy, small RNAs, transcription factories, chromosomal territories, networks, genetic networks, ENCODE project, epigenetics, histone and protein biology, prions, hereditary diseases, and even patents are covered. The number of illustrations increased to nearly 2,000 and several hundreds are in four-color. The old entries have been revised, updated and expanded. Cross-references among entries have been increased. Retractions and corrigenda are pointed out. Nearly 1,800 database and web server addresses, about 14,000 journal paper references and more than 3,000 current book titles are included. Interesting historical vignettes lend some insight into the lighter sides of biology. I hope the reader finds the absence of laboratory jargon refreshing.

The encyclopedia will equip its reader to prepare journal papers, write or review research proposals or help organize a new course or update a current course. Students will find the topics useful for preparing for exams or for writing term papers. It may also appeal to basic and applied biologists and to practitioners of many other fields. The readers of previous editions appreciated the clarity of the basics in this book. A sample of what professional reviewers wrote about the book is carried for the reader's reference. In addition, about the current publications in general, the Editor of Science had the following comment. “Each specialty has focused in to a point at which even the occupants of neighboring fields have trouble understanding each others’ papers”... “The language used in Reports and Research Articles is sufficiently technical and arcane that they are hard to understand, even for those in related disciplines.” (Kennedy, D 2007 *Science* 318:715).

One of the most fascinating features of science is its continuous evolution. My goal was to emphasize the principles, provide numerical data and guide to resources that are more difficult to access from other publications. The book can assist the reader to make better use of the Internet but the Internet and textbooks are no substitutes for this book. Unlike the majority of books, this Encyclopedia will not be outdated because the continuously renewed and updated databases and web sites listed assure its usefulness even in the distant future. Describing individual genes in different organisms—with some exceptions—is no longer practical in a single book or even with the aid of an excellent resource such as PubMed due to the multitude of abstracts (more than 15,000,000 entries from more than 19,000 journals). The web sites—listed in this book—can however, provide great help in identifying many genes, their synonyms, functions and interacting partners as well as critical references to them. Although basic statistical concepts are explained in simple terms, most of the theoretical mathematical models or detailed laboratory procedures are not included because of the difficulties of describing the techniques within the limited space available in a single book. The abundance of references can lead the reader in the right direction.

Selection of papers for inclusion is also a continuous challenge. During 1992 to 2001 4,061 journals published more than 3.47 million peer-reviewed articles in health-related areas alone (Paraje, G et al. 2005 *Science* 308:959). Although this book is quite complex, integrated, and referenced, it does not include everything but it might be a useful guide to almost everything one needs in biology. For a proof of principle, I suggest that you look up any concept what you know or what you are uncertain or have doubts about.

I welcome all readers and I promise to respond to questions or comments.

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First to Read for the Third Edition

The organization of the expanded and revised third edition is slightly different from that of the previous ones. The material is still in alphabetical order but in a somewhat different style. Numbers involved with the entries do not affect the order. Entries beginning with Greek letters are sorted as if they would be in Roman or the Greek letter follows the term. Words followed by a comma and another word precede entry words without comma, e.g., “antibody, secondary” is followed by “antibody detection”. Hyphenated entries are sorted as single words. The spelling of some terms vary because in the scientific literature some technical terms are written either with a *c* or *k* or with an *e* or *ae*. Some abbreviations are used in the literature as e.g., PGD or P.G.D. and both may not be used in this book. Here the most common usage is favored. Some entries are qualified by another word added after and in others the qualifier comes first. Most entries are followed by cross-references that guide to relevant topics. In particular cross-references qualifiers are not separated by comma even when they are with comma in the main list. In case you make electronic searches it is frequently more practical to use only part of the words because in the alphabetical list their ending may be different, e.g., maximum or maximal. An attempt has been made to guide the reader to the desired entry when necessary. In rare instances the reader may need to search for synonyms or related terms to find the desired entry. Thank you for your patience.

This book contains a large number of Internet addresses under the heading of “databases” and even more after many entries. Every effort has been made to keep the web addresses current. Unfortunately, they are altered frequently and it is likely that some will cease to exist or will change by the time the book gets to your hands. In some instances Word alone may not open the URL site directly, but Internet Explorer or Safari or even the search engines Google, Yahoo, AltaVista or others can be used to access the sites.

It must be remembered that data are not knowledge. The data must be integrated into science and the aim of the author has been the facilitation of such integration. The contents of the entries are based on the best information available in the literature at the time of the completion of the writing. As sources of information like most human products, are not always perfect, the author and publishers cannot claim perfection or assume legal responsibility for errors beyond their control.

“Knowledge...built on opinion only, will not stand”. Linnaeus, 1735



A

A: Adenine is a purine base of nucleic acids. ►adenine

2,5-A (adenine) oligonucleotides: Adenine oligonucleotides are generated by 2,5-A synthetase from double-stranded RNA. These oligonucleotides activate RNase L, which attacks infecting viruses of vertebrates. If the two genes encoding these two enzymes are transformed into plants, they provide resistance against RNA viruses. ►host-pathogen relationship, ►ribonuclease L

Å (ångström): A unit of length, 1/10 of 1 nm; 10^{-7} mm.

A6: *Agrobacterium tumefaciens* strain with a Ti plasmid coding for octopine production in the plant cell. ►Agrobacterium, ►opines, ►octopine

A20: A cytoplasmic Zn-finger protein that limits TNF-induced NF-κB responses. It reduces apoptosis. Its deficiency may increase inflammation and may result in death. ►TNF, ►NF-κB, ►apoptosis; Kumar-Sinha C et al 2002 J Biol Chem 277:575.

a: atto-, 10^{-18} , e.g., attomole/amole.

α: Average inbreeding coefficient, $\alpha = \sum p_i F_i$ where p_i is the relative frequency of inbred individuals with F_i coefficient of inbreeding. This value in most human populations is less than 0.001 while in isolated human groups it may exceed 0.02 or 0.04. ►inbreeding coefficient, ►error types

A Box: An internal control region of genes (5S ribosomal RNA and tRNA) transcribed by DNA-dependent RNA polymerase III; the consensus is 5'-TGGCNNAGTGG-3'. The tRNA genes also have an essential *intermediate segment* of about a dozen bases that has no consensus, yet its length is necessary for function. Nearby there is also another regulatory consensus, the B box 5'-GGTTCGAANNC-3'. The matrix attachment region (MAR) is also an A box (with a consensus of AATTAAC/AAA). ►MAR; Borovjagin AV, Gerbi SA 2001 Mol Cell Biol 21:6210.

A Chromosome: A member of the regular chromosome set in contrast to a B or supernumerary chromosome. ►B chromosome, ►accessory chromosome

α Complex: One of the alternate chromosome translocation complexes in *Oenothera*. ►β complex, ►translocation, ►Oenothera

A DNA: ►DNA

α Mating Type Factor of Yeast: Responsible for the secretion of the α factor (a pheromone), composed of 13 amino acids and it acts on *a* type cells. ►mating type determination in yeast

A Medium: For *E. coli*, g/L: K_2HPO_4 10.5, KH_2PO_4 4.5, $(NH_4)_2 SO_4$ 1.0, Na-citrate.2 H_2O , 0.5 plus glucose 0.4%, thiamin 1 mg/L, $MgSO_4$ 1 mM, and an appropriate antibiotic. For different bacterial culture media. Winkler U et al 1976 Bacterial, phage and molecular genetics. An experimental course, Springer-Verlag, New York; ►culture media

α Particles: ►alpha particles

A Priori: A philosophical concept indicating that certain knowledge does not presuppose experience. In contrast, *a posteriori* concept is based on the acquisition of certain prior information.

A Rule: Adenylic acid is the preferred nucleotide for incorporation opposite to an abasic site of the DNA during repair. abasic sites, ►DNA repair; Otterlei M et al 2000 EMBO J 19:5542.

α Satellite: The centromeric DNA that is normally heterochromatic. However, it may have important role in controlling chromosome segregation and other centromere functions. The 171-bp tandemly repeated sequence has been found in all human centromeric area. It is connected by 17 bp (missing in the human, mouse and green monkey Y centromeres) with protein CENP-B, a common autoimmune antigen. All human centromeres and neocentromeres apparently include also CENP-A, a histone H3-like protein. Introduction of exogenous alphoid DNA into the cells may cause chromosomal instabilities. The CENP-B protein bears sequence similarity to the pogo transposases. ►centromere, ►neocentromere, ►satellite DNA, ►heterochromatin, ►segregation, ►meiosis, ►human artificial chromosome, ►microchromosome, ►hybrid dysgenesis; Buno I et al 2001 Genome 44:120.

A Site (decoding site): A compartment on the ribosome; at the beginning of the translation process the first codon, Met or fMet lands at the P site and the next amino acid is delivered to the A site. Then the elongation of the peptide chain proceeds. The decoding site of the 16S ribosomal RNA has the universally conserved |A1492 and |A1493 nucleotides as the location. (see Fig. A1). ►protein synthesis, ►ribosome, ►aminoacyl-tRNA synthetase; Rodnina MV, Wintermeyer W 2001 Annu Rev Biochem 70:415.

A



← UGAA 1498
 GC  GUGG
 CG  CACC
 → UCAC 1412

Figure A1. Decoding site

AAA Proteins: AAA Proteins are ATPases, enzymes cleaving off phosphates from ATP. They are equipped with Walker boxes. AAA domain proteins are molecular chaperones and have important roles in vesicular transport, organelle biogenesis, microtubule rearrangements, etc. Some of this group of enzymes is related to the prokaryotic RuvA proteins. The Mgs1 protein (maintenance of genome stability) of yeast has homologs in all prokaryotes and eukaryotes. Their defects contribute to increased mitotic recombination. ▶ [ATP](#), ▶ [ATPase](#), ▶ [RuvABC](#), ▶ [chaperone](#), ▶ [Walker box](#), ▶ [MD1](#); Dalal S, Hanson PI 2001 Cell 104:5; Gadal O et al 2001 EMBO J 20:3695; Hishida T et al 2001 Proc Natl Acad Sci USA 98:8283; Sauer RT et al 2004 Cell 119:9; evolution and structure: Erzberger JP, Berger JM 2006 Annu Rev Biophys Biomol Struct 35:93.

AAAS: ▶ [ALADIN](#)

AAF: ▶ [alpha accessory factor](#)

α -Amanitin: A protein synthesis inhibitor fungal octapeptide. It blocks RNA pol II (0.1 μ g/mL); RNA polymerase III is also blocked by it but at much higher concentrations (20 μ g/mL), but pol I is insensitive to it even at 200 μ g/mL. LD₅₀ in albino mice is 0.1 mg/kg. ▶ [RNA polymerase](#), ▶ [pol](#), ▶ [LD₅₀](#); Begun DJ, Whitley P 2000 Heredity 85:184.

AAR1: ▶ [TUP1](#)

Aarskog Syndrome (Aarskog-Scott syndrome, facio-genital dysplasia): A genetic disorder that is autosomal dominant, autosomal recessive, X-linked (Xq12) recessive short stature, hypertelorism (increased distance between organs or parts), scrotum (the testis bag) anomaly, pointed hairline (Widow's peak), broad upper lip, floppy ears, etc. The basic defect involves the RHO/RAC member of the RAS family of GTP-binding proteins. ▶ [stature in humans](#), ▶ [head/face/brain defects](#), ▶ [RAS](#), ▶ [faciogenital dysplasia](#), ▶ [hypertelorism](#); Orrico A et al 2007 Am J Med Genet 143:58.

AATAAA: A consensus of 10–30 bp upstream from a CA dinucleotide at the site where cleavage, then polyadenylation of the mRNA commonly takes place. This consensus may also be a signal for transcription termination although normally, RNA polymerase II

continues to work after passing it. ▶ [polyadenylation signal](#), mRNA tail, ▶ [transcription termination](#); Curuk MA et al 2001 Hemoglobin 25:255.

AATDB: *Arabidopsis thaliana* database provided general information on all aspects of the plant, including genes, scanned images of mutants, nucleotide sequences, genetic and physical map data, cosmid and YAC clones, bibliographical information. <http://www.weeds.harvard.edu/index.html>, or e-mail curator@frodo.mgh.harvard.edu. ▶ [AIMS](#), ▶ [Arabidopsis thaliana](#), ▶ [databases](#)

AAUAAA: Consensus for polyadenylation of the mRNA. Apparently, the poly-A RNA polymerase enzyme and associated protein attach to this sequence before cleavage of the transcript and post-transcriptional polyadenylation take place. Yeast does not have this consensus. ▶ [AATAAA consensus's role in polyadenylation](#)

Ab: ▶ [antibody](#)

Ab Initio: Meaning from the beginning in Latin. For e.g., genes *ab initio* indicates the genes as first recognized by sequencing but the exact exon/intron structure had not been identified.

$\alpha\beta$ T Cells: Represent the early stages of T cell development in the thymus and later recognize the major histocompatibility complex-bound peptide antigens resulting in the differentiation of B and T lymphocytes. The expression of the co-receptor CD4 and CD8 may involve the formation of the double negative CD4⁻ CD8⁻ to CD4⁺ CD8⁺ and the CD4⁻ CD8⁺ and the CD4⁺ CD8⁻, a process requiring the rearrangement of the α and β subunits of the T cell receptor, and the ligands existing within the thymocytes. At the same time, the T cells differentiate into the rather distinct CD4 T-helper cell and the CD8 T-killer cells. The CD4 expression in the mature T cells corresponds to their specificity toward class II and the CD8 expression toward the class I major histocompatibility complex (MHC) molecules. The differentiation into this two cell lineages is a selective process controlled by the relative strength and duration of the engagement with the T cell receptor (TCR). The HD (helper deficient) recessive mutation in mouse cause loss of CD4 T cell development because these cells were switched over to the CD8 T cell path. This HD locus encodes the zinc finger transcription factor Th-POK (T helper-inducing POZ/Krüppel), which under constitutive expression mediates the development toward the class I MHC molecules. Thus, Th-POK is a master regulator of T lymphocyte development (He X et al 2005 Nature [Lond] 433:826). ▶ [lymphocytes](#), ▶ [MHC](#), ▶ [\$\gamma\delta\$ T cells](#), ▶ [T cell](#), ▶ [POZ](#), ▶ [Krüppel](#)

ABA (abscisic acid, 3-methyl-5-[1'-hydroxy-4'-oxo-2'-cyclohexen-1'-yl]-cis-2,4-pentadienoic acid): A terpenoid, synthesized from mevalonate and xanthins, apparently through two pathways. It has multiple physiological functions in concert with other plant hormones, particularly with gibberellins and cytokinins, by regulating seed dormancy, germination, leaf abscission, stomatal opening, drought response, etc. Glucose-conjugated ABA is biologically not active. Activation of glycosidase, however, rapidly increases the active pool of ABA and the concomitant physiological responses to environmental cues (Lee KH et al 2006 Cell 126:1109). In the ABA signal transduction farnesyl transferase seems to be involved. Cyclic ADP-ribose, regulated by Ca^{2+} , seems to be another signaling molecule for ABA. Ca^{2+} ion channels are activated by H_2O_2 produced by the guard cells upon the induction of ABA and thus the stomatal opening/closing is controlled. Responses to ABA are regulated by ABRC (ABA response complex) in the genes that include an ACGT box and a variable coupling element. A G protein-coupled receptor interacts with the G protein subunit GPA1 to mediate all known ABA responses in *Arabidopsis* (Liu X et al 2007 Science 315:1712). The RNA-binding protein FCA, which plays a role in the control of flowering, is a receptor of abscisic acid (Razem FA et al 2006 Nature [Lond] 439:290). The Mg-chelatase H subunit is an ABA receptor (Shen Y-Y et al 2006 Nature [Lond] 443:823). Several *aba* genes have been cloned.

New evidence indicates that in human granulocytes ABA stimulates phagocytosis, production of reactive oxygen species and nitric oxide (NO) and chemotaxis through a signaling pathway sequentially involving a pertussis toxin (PTX)-sensitive G protein/receptor complex, protein kinase A activation, ADP-ribosyl cyclase phosphorylation, and consequent cyclic-ADP-ribose overproduction, leading to an increase of the intracellular Ca^{2+} concentration. Thus, it can be considered as a pro-inflammatory cytokine in humans (Bruzzzone S et al 2007 Proc Natl Acad Sci USA 104:5759). ▶[abscisic acid](#), ▶[prenylation](#), ▶[farnesyl pyrophosphate](#), ▶[plant hormones](#), ▶[stoma](#), ▶[ion channels](#), ▶[glucosidase](#), ▶[chelation](#), ▶[G protein](#), ▶[pertussis toxin](#), ▶[protein kinase](#), ▶[ARF](#), ▶[cytokine](#); Lopez-Molina L et al 2001 Proc Natl Acad Sci USA 98:4782; Nambara E, Marion-Poll A 2005 Annu Rev Plant Biol 56:165.

Abasic Endonucleases (APE): APEs mediate base excision repair. Its deficiency in mouse leads to embryo lethality. Besides base excision, it is involved in acetylation-mediated gene regulatory function (Izumi T et al 2005 Proc Natl Acad Sci USA 102:5739). ▶[DNA repair](#), ▶[endonuclease](#), ▶[acetylation](#); Demple B, Harrison L 1994 Annu Rev Biochem 63:915.

Abasic Sites: Found in DNA where glycosylases (base exchange repair) have removed bases by cleaving the glycosylic bond. According to an estimate, approximately 100,000 abasic sites are generated per mammalian cell daily and their number increases by senescence. These sites may be intermediates in chemical mutagenesis and repair. DNA polymerases ζ and η can insert nucleotides opposite 8-oxoguanine (C) and O^6 -methylguanine sites (C or T). The repair may not be highly efficient. ▶[glycosylases](#), ▶[DNA repair](#), ▶[A rule](#), ▶[oxidative damages](#), ▶[DNA polymerases](#), ▶[apurinic site](#); Haracska L et al 2001 J Biol Chem 276:6861; Guillet M, Boitaux S 2003 Mol Cell Biol 23:8386; Auerbach P et al 2005 Proc Natl Acad Sci USA 102:17711.

Abaxial: That which is not in the axis of body or of an organ.

ABC Excinuclease: A 260,000 M_r protein complex containing the subunits coded for by the *uvrA*, *uvrB* and *uvrC* genes of *E. coli*. UvrA is an adenosine triphosphatase and brings into position UvrB, which after attaching to the DNA cuts it at the 3' position, and that provides the opportunity for UvrC to incise at the 5' position. UvrD, a helicase releases the damaged oligomer along with UvrC. Following these events, DNA polymerase fills in the correct nucleotides. In yeast, the RAD1, 2, 3, 4, 10, and 14, carry out the same tasks as the ABC excinucleases of bacteria. In humans, the XPA (a damage recognition protein, comparable to UvrA), binds to the XPF-ERCC1 (excision repair cross-complementing protein) heterodimer and to the human single strand binding replication protein, HSSB. XPF (3' cut) and XPG (5' cut) are nucleases. The gap-filling polymerases are pol δ and pol ϵ . XPB and XPD are helicase subunits of the TFIIH transcription factor. The excinuclease complex is released at the end of the process with the aid of the proliferating cell nuclear antigen (PCNA). This complex is capable of excision of cyclobutane pyrimidine dimers, 6-4 photoproducts (adjacent pyrimidines cross linked through C6-C $4'$), nucleotideadducts (molecules with added groups) formed by mutagenic agents. ▶[excision repair](#), ▶[adduct](#), ▶[DNA polymerases](#), ▶[DNA ligase](#), ▶[helicase](#), ▶[baseflipping](#), ▶[transcription factors](#), ▶[PCNA](#), ▶[cyclobutane](#), ▶[pyrimidine-pyrimidinone photoproduct](#); Zou Y et al 2001 Biochemistry 40:2923; Gu C et al 2006 Biochemistry 45:10739.

ABC Transporters (ATP-binding cassette transporters, 9q22-q31): ABC transporters constitute a large family of proteins, which hydrolyze ATP and mediate transfers through membranes. Altogether 56 ABC transporter genes are known and 38 of them are present in all vertebrates. These are now often called TAP. The ABC

A

transporters have two membrane-spanning (MSD) and the dimeric ATP-nucleotide binding domains (NBD). MSDs may show greater variations, depending whether they operate as a pump or a conductance channel. The NBD subunits play the role of the engines of the transport and interact through their arm 1 with the two MSDs. The ABCA4/ABCR mutations may account for Stargardt disease (STGD1), fundus flavimaculatus (FFM, retinitis pigmentosa (RP) and cone-rod dystrophy (CRD), all recessive with somewhat overlapping retinal symptoms. ABC transporters may affect adrenoleukodystrophy, cystic fibrosis, retinal degeneration, hypercholesterolemia and cholestasis (see Fig. A2). By 2001, 48 ABC transporters belonging to 7 gene families have been identified. ▶TAP, ▶protein-conducting channel, ▶TRAM, ▶signal hypothesis, ▶SRP, ▶translocon, ▶translocase, ▶Stargardt disease, ▶Tangier disease, ▶pseudoxanthoma, ▶Byler disease, ▶high-density lipoprotein, ▶multidrug resistance, ▶multiple drug resistance, ▶retinitis pigmentosa, ▶cone dystrophy, ▶dwarfism; Dean M et al 2001 Genome Res 11:1156; Neufeld EB et al 2001 J Biol Chem 276:27584; Chang G, Roth CB 2001 Science 293:1793 [this paper was retracted in (2006) because of software error]; Borst P, Elferink RO 2002 Annu Rev Biochem 71:537; Stacey G et al 2002 Trends Plant Sci 7:257; Dean M, Annilo T 2005 Annu Rev Genomics and Hum Genet 6:123; crystal structure of bacterial ABC transporter: Roger JP et al 2006 Nature [Lond] 443:180; structure with binding protein: Hollenstein K et al 2007 Nature [Lond] 446:213.

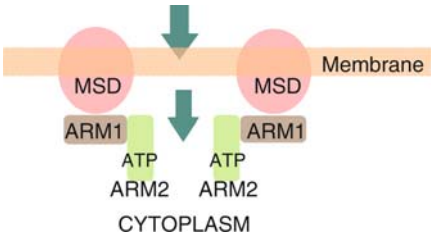


Figure A2. ABC transporter

ABCB: ▶multidrug resistance

ABCD Model: An environmental matrix for the study of the performance of species (see Table A1).

Table A1. ABCD model

| | Environment 1 | Environment 2 |
|------------|---------------|---------------|
| Genotype 1 | A | B |
| Genotype 2 | C | D |

Abdomen in *Drosophila*: The body segment between the thorax and telson. ▶*Drosophila*

Abelson Murine Leukemia Virus Oncogene (*abl*): Mammalian homolog of the avian Rous sarcoma virus. It codes for a plasma membrane tyrosine kinase. When this enzyme acquires constitutive catalytic activity in the presence of the Philadelphia chromosome, it causes chronic myelogenous leukemia (CML) in humans. It is treated effectively by STI-571 tyrosine kinase inhibitor. ▶oncogenes, ▶Rous sarcoma, ▶tyrosine kinase, ▶leukemia, ▶Gleevec, ▶Philadelphia chromosome; Wang JY et al 1984 Cell 36:349; Shore SK et al 2002 Oncogene 21:8568.

Abembryonic: After fertilization, a blastomere is formed and its progeny generates the embryonic part of the blastocyst and another line of cells of the blastomere populates the space away from the embryo at the parietal trophoctoderm, and the more superficial abembryonic cell mass away from the embryo. ▶blastomere, ▶blastocyst

Aberrant Genetic Ratios: Occur when the chromosomes carrying the wild type or mutant allele of a gene, respectively, have reduced transmission through meiosis or the viability of the gametes is diminished. Depending on the chromosomal location of the defect, either the one (wild type), or the other (recessive) allele may appear in excess of expectation of normal phenotypic ratios.

Aberration Chromosomal: ▶chromosome breakage

Abetalipoproteinemia (microsomal triglyceride transfer protein deficiency, 4q22-q24): Abetalipoproteinemia involves very low levels of the very low density (VLDL), low density (LDL, apolipoprotein B, 2p24) and high density (HDL) of these lipoproteins (microsomal triglyceride transfer protein [MTP] defect). The rare recessive anomaly is accompanied by excretion of lipoproteins, malabsorption of fat, acanthocytosis (see Fig. A3) thorny type erythrocytes rather than the normal doughnut-shaped, retinitis pigmentosa (sclerosis (hardening), pigmentation and atrophy [wasting away] of the retina of the eye and irregular coordination of the nerves (ataxia). ▶neuromuscular disease, ▶beta-lipoproteins, ▶hypobetalipoproteinemia, ▶hyperlipoproteinemia

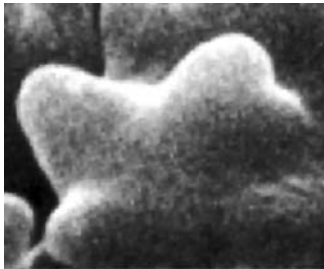


Figure A3. Abetalipoproteinemia

ABF-1: A nuclear transcriptional repressor belonging to the basic helix-loop-helix family. ▶[helix-loop-helix](#); Wong J et al 2001 DNA Cell Biol 20:465.

Abf (autonomously replicating sequence binding factor): Abf is involved in silencing of yeast mating types. Also it may bind to various promoters and thus may initiate replication or transcription. ▶[mating type determination in yeast](#), ▶[ARS](#), ▶[ORC](#), ▶[HML](#) and [HMR](#)

ABH antigens: In humans, ABH antigens are secreted in the saliva and other glycoprotein-containing mucus in the presence of the *Se* (dominant allele, human chromosome 19q13.13), and the gene codes for the α 2L-fucosyltransferase enzyme. The secreted glycoproteins, A and B are about 85% carbohydrate and about 15% protein. Approximately 75–80% of Caucasoids are secretors (homozygous or heterozygous for *Se*). The precursors of the antigens are Galactose(β 1-3)*N*-acetyl-D-glucosamine-R and Gal (β 1-4)*N*-acetyl-glucosamine-R (where R stands for the extension of the carbohydrate chain). Antigen H has the critical structure of that shown in figure (see Fig. A4). Antigenic determinant A is formed by *N*-acetylgalactosamine, and the B antigen by galactose addition at non-terminal position to the H antigen. Thus, the A, B and H antigens are different from each other by these carbohydrates and in some variants by the number of fucose molecules. The A and B alleles are codominant. The recessive O blood group lacks fucosidase activity that places a fucose, by an α 1-2 linkage on a galactose. The Lewis blood group (Le [Les], 19q13.1-q13.11) is distinguished on the basis that its dominant allele Le places fucose in an α -1,4 linkage to the *N*-acetylglucosamine. Individuals that have no secretor activity but are Le belong to the Lewis blood group Le^a whereas when both *Se* and Le are expressed they represent the Le^b type. ▶[ABO blood group](#), ▶[Bombay blood type](#), ▶[fucosyl transferase](#), ▶[secretor](#); Domino SE et al 2001 J Biol Chem 276:23748.

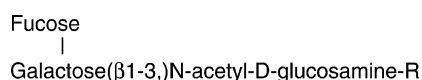


Figure A4. ABH antigens

Abilene (advanced networking for leading-edge research and education): Abilene is an advanced backbone network to connect aggregation points such as virtual laboratories, digital libraries and distance education at national and international scale. By the end of 2003, it is expected to communicate at 10 Gigabytes/ second. ▶[Internet2](#), ▶[BIRN](#); <http://abilene.internet2.edu/>.

Abiogenesis: Spontaneous generation of life, origin of living cells from organic material during the early history of the earth. spontaneous generation, ▶[origin of life](#); Trifonov EN, Berezovsky IN 2002 FEBS Lett 527:1.

ABL: ▶[abetalipoproteinemia](#)

ABL (Abelson murine leukemia virus oncogene): Located to human chromosome 9q34.1 and mouse chromosome 2. When translocated to human chromosome 22 it may transcribe a fusion protein with an abnormal protein tyrosine kinase activity, which is probably the cause of chronic myeloid leukemia. Acute lymphocytic leukemia is also associated with a similar translocation, the Philadelphia chromosome, but it appears that tyrosine kinase activation is different from that of the fusion protein. The ABL gene has about 300-kb intron down-stream from the first exon. This intron appears to be the target of the translocations and causes acute lymphocytic leukemia. Insertion of DNA sequence into the *abl* gene of mouse results in several morphological alterations and death. Abl also controls differentiation, cell division, and stress responses. The SH3 domain negatively regulates Abl activity and deletion of SH3 makes it an oncogenic protein. Mutations in the SH3, or in the catalytic domain or and in the linker region between the SH3 and SH2 domains are also oncogenic. ABL deficiency in mice leads also to osteoporosis. ▶[oncogenes](#), ▶[ARG](#), ▶[Philadelphia chromosome](#), ▶[leukemia](#), ▶[SH2](#), ▶[SH3](#), ▶[osteoporosis](#); Maru Y 2001 Int J Hematol 73:308.

abl: B cell lymphoma (Abelson leukemia). Oncogene encoding a non-receptor protein tyrosine kinase. Ionizing radiation and alkylating agents activate this oncogene. In the Philadelphia chromosome the contact between BCR and ABL most commonly leads to myelogenous leukemia. In the absence of ABL the JNK/SAP kinases (Jun kinase) are not stimulated. ▶[leukemia](#), ▶[lymphoma](#), ▶[JUN](#), ▶[JNK/SAP](#), ▶[Philadelphia chromosome](#), ▶[BCR](#), ▶[tyrosine kinase](#)

Ablation: Mechanical or chemical/toxin-mediated removal of cells or tissues of stem cells or plant meristems to study the role of those cells in differentiation and development. The purpose can also be achieved by obtaining genetic deletions in these areas, heterozygous for appropriate marker genes. The deletion of the dominant allele reveals the function of the recessives and permits tracing cell lineages on the basis of the visible sectors formed. Familial retina ablation may occur in animals as a hereditary abnormality. ▶[gene fusion](#), ▶[intercellular immunization](#), ▶[pseudodominance](#), ▶[deletion](#), ▶[cell lineages](#)

ABM Paper: ▶[diazotized paper](#)

A

ABO Blood Group: Represented by three major types of alleles (human chromosome 9q34) displaying codominance (see Table A2).

These blood types are extremely important because inappropriate mixing (in blood transfusion) results in agglutination that prevents the flow of blood through the veins and oxygen transfer, and it is potentially lethal. These antigens are actually carbohydrates (attached to polypeptides), and the genes A and B specify α -D-N-acetylgalactosaminyltransferase and α -D-galactosyltransferase enzymes, respectively. Gene O is not active as an enzyme. The A and B enzymes (M_r about 100,000) are dimeric and structurally similar to each other. The A and B molecules are identified as A and B antigens. Occasionally maternal antibodies against the A and B antigens may enter, through the placenta, the fetal blood stream and affect adversely the erythrocytes causing anemia and hyperbilirubinemia. In such cases medical treatment may be required. The ABO system has also a limited use in forensic medicine in paternity suites, in typing bloodstains, semen and saliva in criminal cases. Immunologically active forms may be recovered in old human remains and can also be used in archeological research. This blood group provided some correlative information in cancer research, e.g., in O individuals afflicted with carcinomas A antigen may be detected in 10–20% of the cases. The major clinical characteristics are as follows.

It appears, changes in glycosyltransferase activity are not uncommon in several types of tumors. The frequency of the various ABO alleles varies a great deal in the world population. It has been shown that the O blood type provided some protection against the most severe form of syphilis (*Treponema pallidum*) but somewhat higher susceptibility to diarrhea caused by some viral and bacterial infections.

The B blood group may have afforded some protection against smallpox, plague and cholera.

Universally compatible red blood cells can be obtained by two bacterial glycosidase gene families that provide enzymes capable of efficient removal of A and B antigens at neutral pH with low consumption of recombinant enzymes. The crystal structure of a member of the -N-acetylgalactosaminidase family reveals an unusual catalytic mechanism involving NAD^+ (Liu QP et al 2007 Nature Biotechn 25:454).
▶ABH antigen, ▶Lewis blood group, ▶blood groups, ▶*Treponema pallidum*, ▶forensic genetics; Race EE, Sanger R 1975 Blood groups in man, Blackwell, Oxford; Chester MA 2001 Transfus Med Rev 15:177; Patenaude SI et al 2002 Nature Struct Biol 9:685.

Aborigine: The first group of inhabitants, humans, animals or plants.

Abortion, Medical: Medical abortion is induced during the early period of pregnancy usually by antiprogesterin (mifepristone) in combination with prostaglandins (in countries where approved), or by the less costly and not very effective misoprostol. Progesterin is synthetic progesterone. In Western Europe, about 3.5/1000 pregnancies are medically terminated because of severe fetal anomalies. selective abortion, ▶contraceptives, ▶ensoulment, ▶prostaglandins, ▶mifepristone, ▶progesterone, ▶genetic screening, ▶family planning, ▶mortality

Abortion, Spontaneous: Spontaneous abortion is frequently caused by disease, stress, incompatibility genes or chromosomal aberrations. Various types of chromosomal defects were cytologically detected in 30–50% of the aborted fetuses. About 15–20% of the verified human pregnancies are aborted

Table A2. ABO blood group

| Blood Group (Frequency in Caucasoids*) | Genotype | Antigens Formed | Antibodies Formed | Clumping With | Blood Type Acceptable for Transfusion |
|---|------------------------|--------------------|----------------------|------------------|---|
| O (0.45) | $i^O i^O$ | neither | anti-A anti-B | A,B AB | O |
| A (0.44) | $i^A i^A$ or $i^A i^O$ | A | anti-B | B,AB | A,O |
| B (0.08) | $i^B i^B$ $i^B i^O$ | B | anti-A | A,AB | B,O |
| AB (0.03) | $i^A i^B$ | A,B | neither | neither | A,B,O |

*The frequency of these alleles varies in different populations. For the calculation of frequencies, see gene frequencies. Actually, the A type exists in $A_1 A_2$ forms; in about 1–2% of the A_2 and 25% of the $A_2 B$ individuals, anti- A_1 antigens occur.

spontaneously and an estimated 22% of the abortions occur before pregnancy is clinically detected (5 weeks after the last menstruation). For placentation, the main source of steroid, the corpus luteum is replaced by appropriate supply of estrogens and progesterone. Pregnancies of increased maternal level of cortisol are more likely to become aborted spontaneously during the first 3 weeks after conception (Nepomnaschy PA et al 2006 Proc Natl Acad Sci USA 103:3938). Different molecular mechanisms may account for abortion. Th2 lymphocytes and IL-10 and TGF- β may suppress incompatible paternal antigens in the fetus. Th1 cytokines, IL-2, INF- γ , and TNF- α may contribute to abortion. Indolamine 2,3-dioxygenase (IDO) by catabolizing tryptophan may help in suppressing allo-specific maternal T cells in the lining of the uterus (decidua). The special V α 14 natural killer T cells (NKT) when activated by α -galactosyl-ceramide or by glycosyl-phosphatidylinositols (the latter is present in blood parasites) may cause abortion. Perforin, TNF- α and INF- γ of the NKT cells may destroy the embryonic trophoblasts. Semi invariant natural killer cells (iNKT) recognize glycosphingolipids presented by monomorphic class I MHC-like glycoprotein molecules presented by CD1d (antigen-presenting molecules for T cells). In early gestation of mice a perforin like molecule and in later stages, a cytokine-dominated mechanism is responsible for pregnancy loss in a strain-dependent manner (Boyson JE et al 2006 Proc Natl Acad Sci USA 103:4580). ▶selective abortion, ▶trisomy, ▶chromosomal rearrangements, ▶chromosome breakage, ▶IL-2, ▶TNF, ▶INF, ▶T cells, ▶perforin, ▶CD1, ▶allospecific, ▶trophoblast, ▶ceramides, ▶inositines, ▶miscarriage, ▶family planning, ▶corpus luteum, ▶progesterone, ▶estradiol, ▶cortisol; Hamerton JL 1971 Human cytogenetics, Academic Press, New York; Hallermann FB et al 2001 Eur J Hum Genet 9:539.

Abortive Infection: Occurs when bacteria are infected with a phage capsule that carries bacterial rather than phage DNA and thus cannot result in the liberation of phage particles. Abortive response by infection of mammalian cells may be caused by any deficiency of the interacting system. (Hosel M et al 2001 Virus Res 81:1).

Abortive Transduction: When the transduced DNA is not incorporated into the bacterial genome and in the absence of a replicational origin, it can be transmitted but cannot be propagated. Therefore, the transduced fragment is contained in a decreasing proportion of the multiplied bacteria. ▶transduction, ▶transduction abortive; Stocker BAD et al 1953 J Gen Microbiol 9:410; Benson NR, Roth J 1997 Genetics 145:17.

Abraxane: A new type of anti-breast cancer drug consisting of taxol/paclitaxel, attached to blood serum protein as an injectable nanoparticle. Clinical trials indicate better effectiveness than taxol alone. ▶taxol, ▶nanotechnology, ▶breast cancer

Abrin: Agglutinin, a toxic lectin and hemagglutinin extracted from the seed of the tropical leguminous plant jequirity (*Abrus precarius*). Abrins A, B, C, D are glycoproteins of two polypeptide chains. The small A chain is an inhibitor of aminoacyl-tRNA binding and has nothing to do with agglutination. Abrin is more toxic to a variety of cancer cells (ascites, sarcomas) than to normal cells. ▶aminoacyl tRNA synthetase, ▶lectins, ▶hemagglutinin, ▶RIP; Wu AM et al 2001 Life Sci 69:2027.

ABRINE: *N*-methyl-L-tryptophan (α -methylamino- β -[3-indole]propionic acid). An inflammatory drug; unrelated to abrin. (See Richou R et al 1966 C R Acad Sci Hebd D [Paris] 263:308).

Abscisic Acid: It is a plant hormone regulating a variety of physiological processes, including modification of the action of other plant hormones (see Fig. A5). Originally, it was detected as a substance involved in the abscission of leaves. ▶ABA, ▶plant hormones, ▶stoma; Hugouvieux V et al 2001 Cell 106:477; Finkelstein RR 2002 Plant cell 14:S15.

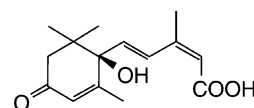


Figure A5. Absciscic acid

Abscission Zone: The thin-walled tissue layer (low in lignin and suberin) formed at the base of the plant organs before abscission (falling off) takes place. ▶abscisic acid

Absinthe: A green liqueur, containing thujone, and it is a GABA antagonist. ▶GABA

Absolute Dating: Determines the age of archeological objects by using either radiometry (using the rate of decay of radioactive isotopes), or electron spin resonance (measures age of crystals from a few thousand to 300,000 years), or thermoluminescence (Heated objects release light and energy. When they are heated again the time elapsed since they were heated last can be estimated). (Renne PR et al 2000 Sci Progr 83:107).

Absolute Linkage: There is no recombination between (among) the genes in a chromosome. ▶recombination, ▶linkage

A

Absolute Risk Increase/Decrease: Change in risk when from an old therapy the patient is subjected to a new one compared to the risk without the treatment.

Absolute Weight: The mass of 1000 seeds or kernels after appropriate cleaning.

Absorption: Uptake of compounds through cell membranes or through the intestines into the bloodstream.

Absorption Spectrum: The characteristic absorption peaks of a compound at various wavelengths of light, e.g., guanine has maximal absorption at about 278 nm at pH 9 but its maximum at pH 6.8 is at ca. 245 nm ultraviolet light; chlorophyll-a has an absorption maximum in benzene at ca. 680 and 420 nm visible light, whereas chlorophyll-b maxima are at ca. 660 and 460 nm, respectively. These characteristics vary according to the pH and the solvents used and are determined by spectrophotometers.

Abundance: Average number of molecules in cells.

Abundant mRNAs: A small number of RNAs that occur with great numbers in the cells. ▶[mRNA](#)

Abzymes: Monoclonal antibodies with enzyme-like properties. If these antibodies can recognize the transition state analogs of enzyme-substrate reactions, they might have enzymatic properties. These abzymes would have numerous chemical and pharmaceutical applications. monoclonal antibody, ▶[antibody](#), ▶[catalytic antibody](#), ▶[transition state](#); Takahashi N et al 2001 Nature Biotechnol 19:563.

Ac—Ds (Activator-Dissociator): The first transposable element system recognized on the basis of its genetic behavior in maize. It contains 4563 bp and bordered by 11 bp imperfect, inverted repeats. The independently discovered *Mp* (*Modulator of p1* [pericarp color]) is the same transposon. *Ac* is an autonomous element and can move by its own transposase function. The *Ac/Mp* element makes a 3.5 kb transcript, initiated at several sites upstream, and a 2,421 base mRNA. A defective (deleted) version of it, *Ds* (*Dissociator*), is non-autonomous and requires the presence of *Ac* for transposition. *Ds* was originally discovered on the basis of frequent chromosome breakage associated with it. The *Ds* elements are quite varied in size but practically identical at the terminal sections to *Ac*. These elements have been identified first on the basis of mutation at known loci (*a*, *Adh*, *sh*, *wx*, etc.) upon insertion and reversions when the inserted element is evicted (see Fig. A6).

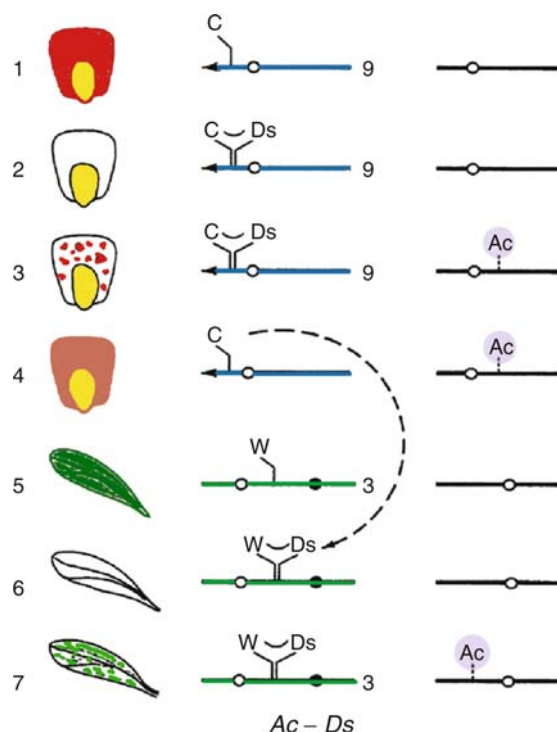


Figure A6. *Ac-Ds*. The possible phenotypic expression of genes in the presence of the *Ac-Ds* elements in maize. (1) The expression of the *C* allele in chromosome 9 in the absence of the transposable elements. (2) If *Ds* is introduced into the locus the function of *C* is disrupted and the kernel becomes colorless (2). If *Ac* (transposase) is introduced into any other location of the genome, it may cause the movement of the transposable element and colored spots appear (3). In case *Ds* is entirely dislodged from the germline, in the following generation full or partial function of the *C* gene is restored, depending whether the original site was completely restored or some modifications took place, and only diluted color appears (4). The *W* allele in chromosome 3 controls the development of green leaf color (5). If *Ds* moves into the gene it may disrupt its function and albinism is observed (6). In case *Ac* is introduced by crossing, *Ds* may move as indicated by the green stripes (7). Remember, *Ds* lacks transposase function although *Ac*, which carries the transposase, may move it

More recently it has been shown that many of the insertions do not lead to observable change in the expression of the genes or their effect is minimal and only sequencing of the target loci may then reveal their presence. The *Ac* element is transposed by a non-replicative manner and after meiosis only one of the sister-chromatids displays *Ac/Mp* at the original site (called *donor site*). In the other chromatid the element may be at another location (*recipient site*)

and the original location becomes “empty.” The recipient sites are most commonly in the same chromosome and quite frequently within the vicinity of the donor site. The *Ds* element frequently initiates a series of events resulting in chromosomal breakage by the mechanism of *breakage-fusion-bridge cycles* and duplications between the original donor and recipient sites. The *Ds* element may move in an inverted manner to the vicinity of a locus and thus, the revertants may still contain a *Ds* element. In the control of transposition the 11-bp inverted terminal repeats and – in addition – sequences 0.05 to 0.18-kb have importance. The *Ac-Ds* target sites display 8-bp duplication, which remains even after the removal of the element. The empty target sites may show internal deletions and rearrangements. A transposase enzyme that can mobilize the *Ac* element, which codes for it, mediates the transposition but it may act on the *Ds* elements too (which are transposase-defective *Ac* elements). It appears that an increase in the number of some but not of other *Ac* elements results in proportionally smaller revertant sectors, and the genetic background, developmental specificities (e.g., somatic or germline tissues) and physiological factors may influence the timing and frequency of transposition. There is evidence in favor of methylation being one of the factor(s) affecting *Ac* expression. This family of transposable elements has additional members such *MITE* (miniature transposable element) that has the same termini but it is very short. The *Ds1* element is similar to *Ds* but it carries retrotransposons within its sequences. *Ac* has been successfully transferred to other species such as tobacco, *Arabidopsis* and yeast and it functions there similarly as in maize. The *Ac-Ds* system can operate also in zebrafish and mammalian cells (Emelyanov A et al 2006 Genetics 174:1095).
 ▶controlling elements, ▶transposable elements, ▶hybrid dysgenesis, ▶insertional mutation, ▶transposase; Fedoroff NV 1989 Mobile DNA, In: Berg DE, Howe MM (eds) American Society of Microbiology, Washington, DC, pp. 377–411; Ros F, Kunze R 2001 Genetics 157:1723; AC distribution; Kolkman JM et al 2005 Genetics 169:981.

Acanthocytosis: ▶*abetalipoproteinemia*, ▶*elliptocytosis*; Wong P 2004 Med Hypotheses 62:966.

Acanthosis Nigricans: Hyperkeratosis and hyperpigmentation of the skin that may accompany the Crouzon syndrome and the Berardinelli-Seip syndrome. Interleukin IL-22 mediates interleukin IL23-induced dermal inflammation and acanthosis (Zheng Y et al 2007 Nature [Lond] 445:648).
 ▶Crouzon syndrome, ▶Donahue syndrome,

▶*achondroplasia*, ▶*lipodystrophy*, ▶IL-22, ▶IL-23, ▶T cell

AcAP: An anticoagulant protein isolated from *Ancylostoma caninum* hookworm (see Fig. A7).



Figure A7. Hookworm

ACAT: ▶sterol

Acatalasemia (CAT, 11p13): A rare dominant/semi-dominant/recessive trait involving the deficiency of the enzyme catalase. This enzyme has a protective role in the tissues by removing the H_2O_2 . Symptoms include small painful ulcers around the neck, gangrenes in the mouth and atrophy of the gum and very low catalase activity in the blood and other tissues. The heterozygotes have intermediate levels of catalase activity. Acatalasemia may be classified into different groups according to the clinical symptoms, both in humans and in animals. The gene extends to 34 kb with 14 introns. It is closely linked to WAGR. ▶Wilms tumor

Acatalasia: ▶*acatalasemia*

ACC (1-aminocyclopropane-1-carboxylic acid): A precursor of the plant hormone ethylene. ▶ethylene

Accelerator Mass Spectrometry (AMS): Quantifies isotopes such as C^{14} , H^3 , Ca^{41} , Cl^{36} , Al^{26} , in biological, archeological, pharmacological, or other materials with attomole sensitivity and high precision. It can be used to study the tissue distribution, metabolism, pharmacokinetics, and radiological hazards of isotopes. It is also a potent tool for paleontological analysis and dating archeological remains. ▶MALDI/TOF/MS

Acceptable Daily Intake: The safe dose of a chemical substance proven by experiment and it is generally divided by 100 for caution.

Acceptor Splicing Site: The junction between the right end of one exon and the left end of the next exon.
 ▶introns, ▶splicing

Acceptor Stem: A part of the tRNA, including the site (5'-CCA-3') where amino acids are attached. aminoacyl-tRNA.

Access Time: The time interval between callings in a piece of information from a storage source to the actual delivery of that information to the caller.
 ▶real time

A

Accessibility: Genetically determined ability of the genome to provide access for the V(D)J recombinase to rearrange the immunoglobulin genes. The accessibility depends on the increased activity of the loci, i.e., status of transcription, demethylation and increased DNase-sensitivity. ▶V(J)D recombinase, ▶RAG, ▶immunoglobulins, ▶CDR, ▶RSS

Accession: A stable strain isolated or collected from natural habitat. ▶provenance

Accession Number: In bioinformatics, accession number identifies permanently a particular molecular sequence submitted to a database. ▶BankIt, ▶Bio-seq, ▶gi, ▶ASN.1. Accession number is used by various biological collections for the identification of specimens such as plants in a herbarium, differently acquired strains of organisms.

Accessory Cells (companion cells): Epidermal cells next to the guard cells around the plant stomata that appear different from the usual epidermal cells. In animals, they promote adaptive immunity although they are not directly involved in antigen recognition.

Accessory Chromosome: ▶B chromosome

Accessory DNA: A product of DNA amplification in the cell. ▶amplification

Accessory Gland: A relatively minor tissue aiding the function of a gland. ▶epididymis

Accessory Pigments: Complement chlorophylls in absorbing light (carotenoids, xanthophyll, phycobilins).

Accessory Proteins: Accessory proteins such as transcription factors bind to upstream DNA elements for controlling transcription and other binding proteins that take part (not necessarily the main part) in a particular function. Accessory host proteins are also involved in the orientation or directionality of transposons. ▶transcription factors, ▶transposable elements, ▶Transposons

Accessory Sexual Characters: The structures and organs of the genital tract including accessory glands and external genitalia, but not the gonads, which are the primary sexual characters. ▶sex determination, ▶gonad, ▶sex phenotypic, ▶secondary sexual character

Accommodation: ▶decoding, ▶ribosomal

Accuracy: The percentage of correct identification of carcinogens and non-carcinogens based on mutagenicity tests. The mutagenicity tests are much faster and less expensive than direct carcinogenicity assays but it is important to know how well these simpler tests reveal the carcinogenic (or non-carcinogenic) properties of the chemicals tested. Accuracy also means when a measurement conforms to a prediction based on physical-chemical properties of the structure

of a protein. ▶sensitivity, ▶specificity of mutagen assays, ▶predictivity, ▶bioassays in genetic toxicology; Rédei GP et al 1984, Mutation, cancer and malformation, In: Chu EHY, Generoso WM (eds) Plenum, New York, p. 689.

Accuracy of DNA Replication: ▶DNA replication error

ACE (angiotensin converting enzyme): ▶angiotensin

ACE (affinity capillary electrophoresis): A procedure to test the binding strength of ligands.

Ace.mbl: Shotgun and directed sequencing evaluation program. ▶shotgun sequencing, gene predictor.

ACEDB: A *Caenorhabditis elegans* (a nematode, useful for genetic analyses) database. ▶*Caenorhabditis elegans*

Acenaphthene: A spindle fiber poison and thus polyploidization agent (see Fig. A8); it is also a fungicide and insecticide. ▶polyploid, ▶colchicine, ▶spindle poison

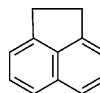


Figure A8. Acenaphthene

Acentric Fragment: The broken off piece of a chromosome that lacks centromere and therefore, its distribution to the poles during nuclear divisions is random and often lost. Acentric fragments are frequent consequences of irradiation of cells with X rays and other ionizing radiations (see Fig. A9). Chromosomal inversions may generate bridges (shown between the two poles) and three acentric chromosome fragments of substantial size that drift in the middle of the cell and are not distributed to the poles. ▶centromere, ▶chromosome morphology



Figure A9. Acentric fragment

Aceruloplasminemia (3q23-q24): Generally recessive deficiency of ceruloplasmin resulting in dementia, ataxia, diabetes, etc. Ceruloplasmin mediates the peroxidation of transferrin FeII to the FeIII form. ▶ceruloplasmin, ▶transferrin, ▶iron metabolism; Hellman NE et al 2002 J Biol Chem 277:1375.

Acervulus: A disk-like conidia-bearing reproductive structure of fungi. ▶conidia

Acesims (affinity capture-release electrospray mass spectrometry): Acesims uses biotinylated tags similarly to ICAT to capture conjugates in complex biological mixtures and to target specific enzymes that have role is metabolic defects such as disease. ▶MALDI, ▶ICAT, ▶proteomics; Turecek F 2002 J Mass Spectrom 37:1.

Acetabularia: Single-celled green algae that may reach the size of 2–3 cm and may be differentiated into rhizoids, stem and cap. It can survive enucleation for several months. The rhizoids, containing the nucleus, may regenerate into complete plants; $x \approx 10$. enucleate (see Fig. A10).

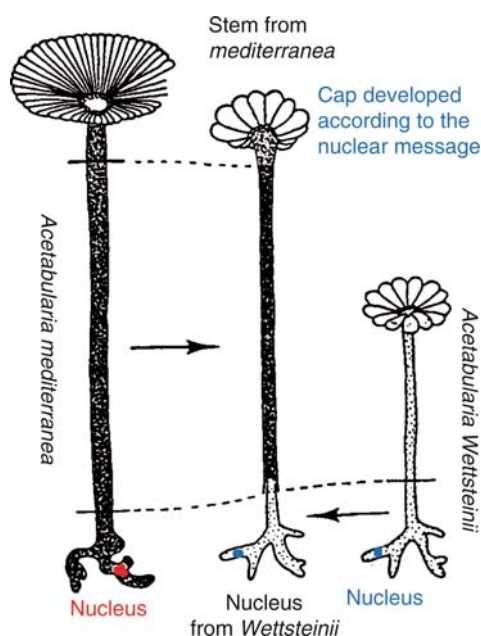


Figure A10. *Acetabularia* species are useful objects for developmental genetic studies and show dramatically the role of the cell nucleus. Grafting of the nucleus-containing section of the cell of *A. wettsteinii* to *A. mediterranea* caused *A. mediterranea* to develop a cap according to the instructions of the nucleus donor species. Experiment of J. Hämmerling in the 1940s. (Modified after Goldschmidt RB 1958 Theoretical Genetics. Univ. California Press. Berkeley, CA, USA)

Aceto-Carmine: ▶stains

Acetonitrile (methyl cyanide): A highly poisonous liquid with ether-like odor, flash point 12.8 °C (beware of the vapors) a polar solvent used (among others) for the separation of oligonucleotides by reverse-phase chromatography on silica gels.

Aceto-Orcein: ▶stains

Acetosyringone: (4-acetyl-2,6-dimethoxyphenol) and hydroxyacetosyringone are produced in plant cells (tobacco) and are one group of the compounds that induce the *vir* gene system of the *Agrobacterium* Ti plasmid. ▶*Agrobacterium*, ▶transformation [plants], ▶virulence genes of *Agrobacterium*

Acetyl Coenzyme A: ▶acetyl-CoA

Acetyl Group: Derived from acetic acid CH_3COOH ; the R stands for different chemical groups (see Fig. A11). ▶acyl group

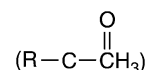


Figure A11. Acetyl group

Acetylation: Acetylation of histones opens the nucleosomal structure for transcription of the DNA. Acetylation of H3 and H4 histones may generate bromodomains for protein-protein interactions. Several non-histone proteins involved in the regulation of transcription are also acetylated. HMG proteins, nuclear import proteins and tubulins are also acetylated primarily at selected lysine sites. In the DNA-binding transcription factors (p53, E2F1, EKLF, GATA), the sites near to the binding domain is acetylated and this increases binding. Acetylation of some of the HMG-BOX proteins results in reduced binding to DNA. Acetylation of TCF may disrupt its binding to other proteins or acetylation may prevent binding together of some regulatory proteins. Acetylation may increase protein half-life (e.g., E2F1, α -tubulin) and may enhance protein targeting (e.g., p53). Signaling molecules may provide cues for acetylation. The roles of acetylation may bear similarity to that of kinases although the number of acetyltransferases is much much smaller than that of kinases. (See terms ▶mentioned under separate entries, ▶GCN5, ▶histone acetyltransferases; Kouzarides T 2000 EMBO J 19:1176).

Acetyl-CoA (acetyl coenzyme A, ACoA): A heat-stable cofactor involved in the transfer of acetyl groups in many biological reactions (citric acid cycle, fatty acid metabolism, etc.). It has three major domains: the β -mercapto ethylamine unit, the pantothenate unit and adenylic acid. ▶epinephrine, ▶sirtuin (see Fig. A12).

A

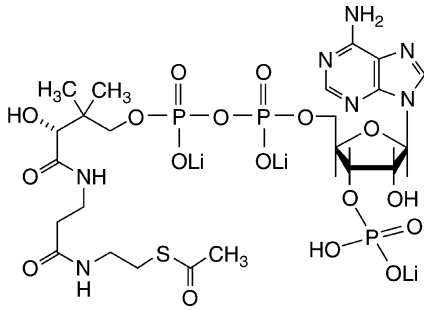


Figure A12. Acetyl coenzyme, Li salt

Acetyl-CoA Carboxylase Deficiency (ACAC): The recessive ACACA is in human chromosome 17q21. The cytosolic ACACA is primarily expressed in the liver and in adipose tissues. ACACB (12q24.1) is in the mitochondria and expressed mainly in the heart and muscles. ACAC causes multiple interferences with gluconeogenesis, fatty acid and the branched-chain amino acid metabolism. ACACB deficiency leads to continuous oxidation of fatty acids and reduced fat storage in mice. Acetyl-CoA carboxylase (also called ACCase) is a biotin-dependent enzyme in the pathway of long-chain fatty acids located in the cytosol and in the chloroplasts of plants. ACC1 deficiency is lethal for mouse embryos but ACC2-null mice are viable (Abu-Elhaiga L et al 2005 Proc Natl Acad Sci USA 102:12011). This enzyme is the target of oxyphenoxypionate and cyclohexanedione herbicides. ▶[branched-chain amino acids](#), ▶[herbicides](#), ▶[obesity](#), ▶[fatty acids](#), ▶[obesity](#); Mao J et al 2003 Proc Natl Acad Sci USA 100:7515.

Acetylcholine (ACh, M_r 149): The acetylcholine receptor provides the connection between synapsing neurons and it is thus a signal transmitter. When acetylcholine binds to a receptor a Na^+/K^+ channel opens. The muscarinic acetylcholine receptors are activated by the fungal alkaloid, muscarine, whereas the nicotinic acetylcholine receptors are operating in the nerve and muscle cells. Acetylcholine receptors are diffusely distributed on the embryonic myotubes but become highly concentrated in a minute area in the post-synaptic membrane and they tether the synaptic cytoskeletal complex. ▶[ion channels](#), ▶[synapse](#), ▶[cytoskeleton](#), ▶[rapsyn](#), ▶[myotube](#), ▶[neuregulin](#), ▶[agrin](#), ▶[neurotransmitters](#), ▶[acetylcholine receptors](#), ▶[muscarinic acetylcholine receptors](#), ▶[myasthenia](#), ▶[memory](#), ▶[game theory](#), ▶[organophosphates](#); Smit AB et al 2001 Nature [Lond] 411:261; Miyazawa A et al 2003 Nature [Lond] 423:949.

Acetylcholine Receptors: Acetylcholine regulated cation (Na^+ , K^+ and Ca^{2+}) channels between the motor neurons and the skeletal muscles. The receptor in the

skeletal muscle contains five transmembrane polypeptides, encoded by four separate yet similar genes. When acetylcholine attaches to the receptor, a conformational change ensues resulting in a brief opening of the channel. They are easily isolated from the electric organs of some fishes. ▶[muscarinic acetylcholine receptors](#), ▶[nicotinic acetylcholine receptors](#), ▶[ion channels](#), ▶[agrin](#); Brejc K et al 2001 Nature [Lond] 411:269.

Acetylcholinesterase (ACHE): Encoded in human chromosome 3q25.2 by codominant alleles. It hydrolyzes acetylcholine into acetate and choline and it restores the polarized state in the postsynaptic nerve membranes. ACHE inhibitors are insecticides and drugs. Nerve gases are also ACHE inhibitors. ▶[acetylcholine](#), ▶[acetylcholine receptors](#), ▶[pseudocholinesterase deficiency](#), ▶[NTE](#), ▶[organophosphates](#)

Acetylglutamate Synthetase Deficiency: A form of autosomal recessive hyperammonemia. ▶[hyperammonemia](#)

Acetyltransferases: When first identified, it was believed that such enzymes acetylated histones but several enzymes became known later that acetylate other proteins and some that do not acetylate ▶[histones](#), ▶[histone acetyltransferases](#); Yang X-J 2004 Nucleic Acids Res 32:959.

ACF (ATP-utilizing chromatin assembly and remodeling factor): ▶[chromatin remodeling](#) (Fyodorov D, Kadonaga JT 2002 Nature [Lond] 418:897).

aCGH: A microarray-based Comparative Genomic Hybridization (aCGH) technique used to identify and characterize DNA copy number variations across the genome. (See <http://genome-www.stanford.edu/aCGH/>; <http://asterias.bioinfo.cnio.es/>; ▶[microarray hybridization](#)).

Achaete-scute Complex: A complex X-chromosomal (1-0.0) locus of *Drosophila* regulating bristle formation and nerve differentiation. The posterior dorso-central bristles are usually missing and the hairs are also sparse in that area. The *achaete* phenotype is generally due to some type of chromosomal rearrangement or loss (see Fig. A13). ▶[complex locus](#)



Figure A13. *Achaete-scute* complex. (From Bridges, C. & Brehme, K. Carnegie Inst. Washington 552: 12)

Achalasia-Addisonianism-Alacrima Syndrome (AAA, 12q13): Also known as triple A syndrome it is a complex glucocorticoid/adrenal/ deficiency causing failure of some muscles to relax, hypotension and weakness, failure in shedding tears normally and various nervous anomalies. The basic defect may involve a WD-repeat protein. Using a mutant of nucleoporin protein ALADIN^{L482S} it was shown that karyopherin- α/β -mediated import pathway was reduced and consequently DNA single-strand break repair (mediated by aprataxin protein) and ligase I activities were diminished leading to the symptoms of the disease (Hirano M et al 2006 Proc Natl Acad Sci USA 103:2298). ▶WD-40; Handschug K et al 2001 Hum Mol Genet 10:283.

Acheiropodia: Recessive 7q36 developmental human anomaly (incidence ~ 0.000004) involving bilateral amputation of the extremities, hands and feet (see Fig. A14). The corresponding mouse locus is *Lmbr1*. It may be accompanied by polydactyly and can occur in both hands and feet.



Figure A14. Acheiropodia

Achene: A single-seed dry fruit.

Achiasmate: Nuclear division without the formation of chiasmata. Chiasma is generally a requisite for orderly segregation of the meiotic chromosome. In male *Drosophila* chiasma and crossing over are usually absent yet chromosomes segregate normally. Stromalin (member of the cohesin family) and *Modifier of Mdg4 in meiosis* (MNM), a member of the SMC family assure the normal process. ▶meiosis, ▶recombination, ▶chiasma, ▶distributive pairing, cohesin, ▶SMC, ▶Mdg; Thomas SE et al 2005 Cell 123:555.

Achilles' Heel Technique: A technique applicable to systems where there is abundant sequence information, and it permits the cleavage of only a small set of restriction sites. It works this way: DNA sequences around the site or set of sites are synthesized and added to the genomic DNA along with RecA, and a methylase. After deproteinization, a restriction enzyme is added. All the (methylated) restriction sites are protected from cleavage except those that were covered by the RecA-DNA complex. ▶DNA sequencing, ▶Rec, ▶methylase, ▶methylation of DNA, ▶restriction enzyme; Szybalski W 1997 Curr Opin Biotechnol 8:75.

Achondrogenesis: Achondrogenesis has been described in two or more autosomal recessive forms involving deficiency in bone formation at the hip area and large head, short limbs, stillbirth or neonatal death. The phenotypes show variations and clear-cut differentiation of the symptoms is difficult. ▶achondroplasia, ▶hypochondroplasia, ▶stature in humans, ▶collagen

Achondroplasia (ACH): A rather common chromosome 4p16.3 dominant (homozygous perinatal lethal) type of human dwarfness that was observed (see Fig. A15), e.g., in Denmark at a frequency of 1.1×10^{-4} . Its mutation frequency (predominantly of paternal origin) was estimated to be within the range 4.3 to 7×10^{-5} .

The proximal bones in the limbs are most reduced. Large head with disproportionally small mid-face, abnormal hip and hands are characteristic. The heterozygotes are generally plagued by heart, respiratory and other problems. Hypochondroplasia appears to be allelic to achondroplasia. The so-called Swiss type achondroplasia is recessive and the afflicted individuals show reduced amount of leukocytes (lymphopenia) and agammaglobulinemia. Pseudo-achondroplastic dysplasias (PSACH, spondyloepiphyseal dysplasia) are autosomal recessive (19p13.1) but some ambiguities were noted regarding the pattern of inheritance because of apparent gonadal mosaicism. PSACH is apparently due to defect in the cartilage matrix. The different forms do not have clear phenotypic distinctions within the group and from the dominant achondroplasia. Some of the skeletal reductions and defects are aggravated by face, eye defects, cleft palate and muscle weakness. Achondroplasia is caused by defects in lysosomal targeting of the fibroblast growth factor receptor 3 (FGFR-3), located



Figure A15. Autosomal dominant type achondroplasiac adolescent. (Courtesy of Dr. Rimoin DL Harbor General Hospital, Los Angeles, CA, and Dr. Judith Miles)

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in human chromosome 4p16.3. A recurrent missense mutation in a CpG doublet of the transmembrane domain of FGFR-3 caused an arginine substitution for glycine. Achondroplasia with developmental delay and acanthosis nigricans and thanatophoric dysplasia are also defective in fibroblast growth-factor receptor 3. Achondroplasiacs usually display normal intelligence. ▶stature in humans, ▶hypochondroplasia, ▶pseudoachondroplasia, ▶achondrogenesis, ▶Ellis-van Creveld syndrome, ▶agammaglobulinemia, ▶cleft palate, ▶fibroblast growth factor, ▶dwarfism, ▶receptor tyrosine kinase acanthosis nigricans, ▶thanatophoric dysplasia; Cho JY et al 2004 Proc Natl Acad Sci USA 101:609.

Achromatic: Parts of the cell nucleus, which are not stained by nuclear stains. A microscope lens that does not refract light into different colors is achromatic.

Achromatopsia: Recessive inability to distinguish colors, low visual acuity and involuntary eye movements (nystagmus) is a rod monochromatism due to defects in the α -subunit or β -subunit of the cone cyclic nucleotide-gated cation channel (8q21-q22). This normally generates the light-evoked electrical responses of the cone receptors. Another locus 2q11-q12 with defect in the α -subunit of the cGMP gated ion channel debilitates the cone photoreceptor, and a third locus (Xp11.4) with cone dystrophy cause achromatopsia.

Acid-Base Catalysis: Acids and bases are common catalysts of organic reactions in proportion of the presence of H^+ or OH^- ions in the medium. Enzymes are particularly well-suited catalysts because they can carry out either acid or base, or simultaneously both acid and base catalysis. Ribozymes are also potential acid/base catalysts. ▶transition state

Acid Blob: A sequence of acid amino acids (negatively charged), responsible for activation of a transcription factor. ▶transcription factors; Almlof T et al 1995 J Biol Chem 270:17535.

Acid Fuchsin: A histological stain used to detect connective tissue and secretion granules (Mallory's acid fuchsin, orange G and aniline blue, and in the Van Gieson's solution of trinitrophenol staining of connective tissue of mammals). ▶stains

Acid Maltase Deficiency: A type II glycogen storage disease involving defect(s) in α -1,4-glucosidase activity. The disease causes accumulation of glycogen in most tissues, including the heart. The first symptoms appear by 2 months after birth and by 5–6 months death results due cardiorespiratory (heart and lung) failures. Although it is classified as an autosomal recessive trait in humans (GAA, 17q25.2-q25.3), the heterozygotes may be distinguished

clinically. ▶glucosidase, ▶Gaucher diseases, ▶glycogen storage diseases

Acid Phosphatase: Cleaves phosphate linkages at low pH. Its levels are increased in most lysosomal storage diseases, particularly in Gaucher's diseases involving glucosyl ceramide lipidosis (defect in lipid metabolism involving cerebroside, a complex of basic amino alcohols [sphingosine], fatty acids and glucose). Other diseases may also cause increase of acid phosphatase. In plants, only acid phosphatases are found in appreciable quantities. Yeast has at least 4 genes with acid phosphatase function; one of them is constitutive, others are repressed by inorganic phosphate. ACP1 is in human chromosome 2p25, ACP2 in 11p12-p11. ▶alkaline phosphatase

Acid Reflux: Retrograde movement of stomach acid and bile to the throat and mouth. ▶Barrett metaplasia

Acidic Dyes: Stain basic cellular residues.

Acidic Sugars: ▶sialic acids

Acidocalcisomes: ▶organelle

Acidosis: A reduction of buffering capacity of the body resulting in lower pH of fluids.

Acid-Sensing: Acid-sensing is mediated by proton-gated ion channels in the sensory neurons. ▶ion channels

Acinar Cells: Exocrine cells, for e.g., mammary gland cells that secrete milk, lacrimal cells that secrete tears, etc. Acinar cells resemble sacs. ▶exocrine

Acinus (apoptotic chromatin condensation inducer in the nucleus): Apparently the substrate of caspase-3 and this cleavage activates pyknosis in the cell nucleus. ▶pyknosis, ▶karyorrhexis, ▶apoptosis, ▶caspase, ▶CAD; Seewaldt VL et al 2001 J Cell Biol 155:471.

Acinetobacter: Oxidase-negative, Gram-negative coccobacilli of widespread habitat but become infective primarily in hospitals affecting immune-compromised or wounded individuals. (Rahal JJ, Urban C 2000 Semin Resp Crit Care Med21(4):341). The bacteria are resistant to the majority of antibiotics and cause up to 40% death. ▶nosocomial; Huys G et al 2005 J Med Microbiol 54(Pt 9):851.

ACIS (automated cellular image analysis): Detects rare cells (e.g., metastatic tumor cells occurring at a frequency of 10^{-6} to 10^{-7}) after immunocytochemical staining. Its efficacy far exceeds that of the manual detection. metastasis, ▶FAST; Bauer KD et al 2000 Clin Cancer Res 6:3552.

AcMNPV (*Autographa californica* nuclear polyhedrosis virus): AcMNPV can be used for the construction

of insect and mammalian transformation vector.
 ► [baculovirus](#), ► [polyhedrosis virus](#)

Acne: Inflammation of the sebaceous glands (that secrete oily stuff on the skin). It does not appear to be under strict genetic control, but rather caused by various environmental conditions, including bacterial infections, mechanical irritation, cosmetics, etc. It usually appears in puberty and disappears after but may leave behind permanent scars. Occasionally it occurs on infants. *Propionibacterium acnes* is one of the major causes of acne has a completely sequenced genome of 2,560,265 base pairs contains about (2333) genes and can cause several other diseases (Brüggemann H et al 2004 Science 305:671). ► [skin diseases](#)

Aconitase: An enzyme controlling the dehydration of citrate to cis-aconitate and the hydration of the latter to isocitrate. This enzyme has also an important role in the transport of iron. Iron-containing proteins regulate many processes in both prokaryotes and eukaryotes. In eukaryotic cells, the level of the storage protein ferritin increases when soluble iron level increases in the cytosol. The control of the process is mediated by a 30-nucleotide *iron-response element* to what aconitase binds and then blocks the downstream translation of RNA. Aconitase is an iron-binding protein, and the increasing level of iron within the cell dissociates it from the ferritin mRNA resulting in about two order of magnitude increase of ferritin by releasing the translation suppressor from the ferritin mRNA. The increased level of iron also decreases the stability of several mRNAs encoding the receptor that binds the iron-transporting transferrin and thereby reduces the amount of the receptor. Aconitase also binds to the 3' untranslated tract of the transferrin receptor mRNA and enhances the production of the receptor, probably by stabilizing the mRNA. The human ACO1 gene is in chromosome 9p22-p14 and the mitochondrially located ACO2 is encoded in 22q11-q13. The mitochondrial aconitase, besides its metabolic function, contributes to the maintenance of mitochondrial DNA (Chen XJ et al 2005 Science 307:714). ferritin, ► [translation repressor protein](#), ► [IRE](#), ► [rabbit reticulocyte in vitro translation system](#); Bulteau A-L et al 2004 Science 305:242.

α -CPM: (α -connecting peptide domain): Connects the α and β chains of the $\alpha\beta$ T cell receptor but it is absent from the $\gamma\delta$ T cell receptor. This domain is required for positive selection of T cells although negative selection may take place in its absence. ► [T cell](#), ► [T cell receptor](#), ► [positive selection of lymphocytes](#)

Acquired: Alteration that occurred during the lifetime of an individual. ► [constitutional](#)

Acquired Characters, Inheritance of: An ancient idea supposing that the minor and major environmental

effects may cause long-lasting heritable changes in the genetic material. This view was proved incorrect by the advances of biology in the ninetieth century. However, poorly trained ideologues of Marxism, the followers of Mitchurin and Lysenko, revived it in the Soviet Union. Modern biologists, who claim the existence of environmentally inducible selective mutations, periodically resurrect it. Most of these recent experiments remain controversial because alternative explanations of the experimental data seem to be as good or even more satisfactory (see directed and local mutagenesis). Genetic transformation by plasmid vectors has been compared with inheritance of acquired characters. However, substantial differences exist between the two phenomena; in transformation, the actual transfer or loss of genetic material (DNA or RNA) has been demonstrated by standard molecular methods. In many cases, claims of inheritance of acquired characters in higher plants and animals have not been demonstrated. Landman (1993 BioScience 43:696) states "so far as I know, only changes in nucleic systems can be transmitted through the germline." Nevertheless, Landman (1991 Annu Rev Genet 25:1) lists a few apparent exceptions (unicorns in the garden, in the words of Frank Stahl) such as the cortical inheritance of *Paramecia* or the epigenetic changes in histone methylation or prions. Recently observed paramutation-like unorthodox cases of inheritance in plants and animals are rather unorthodox phenomena. These examples are in sharp contrast to those published during the soviet era, which do not meet the current scientific standards because the experiments did not use reliable controls and the genetic constitution of the material was either obscure or obviously contaminated.

Advantageous frameshift backmutations may take place, however, under selective conditions by recombination. The inheritance of acquired characters has also been attributed to a mechanism of canalization. The change in the environment permits selection of hidden variations in chaperones adapted to the environmental change. Even after the release of the stress, the selected new forms of the chaperones may persist and simulate inheritance of acquired characters. ► [Lamarckism](#), ► [Mitchurinism](#), ► [Lysenkoism](#), ► [soviet genetics](#), ► [graft hybridization](#), ► [transformation](#), ► [recombination](#), ► [frameshift](#), ► [backmutation](#), ► [chaperones](#), ► [canalization](#), ► [evolution](#), ► [epimutation](#), ► [paramutation](#), ► [cortical inheritance](#), ► [epigenesis](#), ► [epigenetics](#), ► [prions](#), ► [transformation genetic](#); Zirkle C 1946 The Early History Of The Idea Of The Inheritance Of Acquired Characters And Pangenesis. American Philosophical Society, Philadelphia; Lindegren CC 1966 The Cold War In Biology, Planarian Press, Ann Arbor, Michigan.

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Acquired Immunity (adaptive immunity): The consequence of natural infection or vaccination or direct transfer of antibodies or lymphocytes from an appropriate donor. The acquired immunity is based on potential variations in the immunoglobulins in response to invading antigens. Somatic gene rearrangements lead to the generation of immune receptors in lymphocytes and the activated lymphocytes are clonally propagated. This immunity system consists of CD4⁺ and CD8⁺ T cells. T cells recognize antigens after being processed by the antigen presenting cells (dendritic cells, macrophages and B cells), which express MHC class II molecules. After the recognition, T helper cells (T_H-1 and T_H-2) differentiation begins. T_H-1 cells characteristically produce gamma interferon (INF- γ), which attacks intracellular invader microbes. For T_H-2 cells interleukin-4 (IL-4) is diagnostic. T_H-2 cells requires MHC class I molecules while T_H-1 cells depend on MHC class II. Both helper T cells utilize a variety of cytokines for the development of effector function, i.e., to be fully activated. In insects (*Drosophila*) the phagocytic plasmatocytes represent the cellular defense. In addition, the humoral reaction develops to microbial challenge by the secretion antimicrobial peptides into the hemolymph. ►innate immunity, ►immune system, ►immunity, ►vaccine, ►antimicrobial peptide; Crowe JE Jr et al 2001 J Immunol 167:3910; in vivo test model for human adaptive immunity in mice: Traggiai E et al 2004 Science 304:104; evolution of adaptive immunity: Cooper MD, Alder MN 2006 Cell 124:815.

Acquired Immunodeficiency Syndrome (AIDS): Caused apparently by the HIV-1 (HTLV-III) and HIV-2 (human immunodeficiency virus [lentivirus]), retroviruses. The general structure of the HIV-1 virus includes three major structural proteins: gag, pol and env, and several regulatory and accessory proteins: vif, vpr, vpu, vpt, tev/tnt (see Fig. A16).

The gag proteins serve as structural elements: 132 amino acid matrix [MA], 152–231 amino acid capsid [CA], 55 amino acid nucleocapsid [NC] and 51 amino acid p6 [vpr-binding protein]. The pol is processed into the dimer of two 99 amino acid protease [PR], reverse transcriptase [RT] is heterodimer of 560 and 440 residues, and the tetrameric, and the tetrameric integrase [IN] of 288-residue monomers. The reverse transcriptase generates the enzyme, which transcribes RNA into DNA and this viral copy can be inserted into the human chromosome and survive there for a long time as a provirus. The protease processes the polyproteins into the various enzymes of the virus and integrase facilitates the entry of the virion into the host cells. When HIV-1 traverses the inner nuclear envelope of the cell (macrophages) it contacts the emerin protein that facilitates viral integration into the

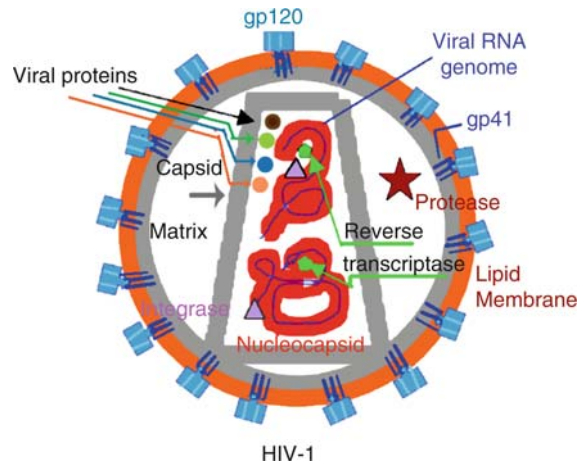


Figure A16. HIV-1. The schematic structure of the HIV-1 virus. The gp120-gp41 heterodimer associate in a trimer to form the spikes. This and the envelope determine antigenicity and immunogenicity (gp indicates envelope glycoproteins). Cryoelectron microscopy tomography revealed ~14 spikes per HIV-1 virions and ~73 spikes per particle of SIV. The surface gp120 of the trimeric SIV spike contains a primary mass with two secondary lobes. The transmembrane glycoprotein stalk of each trimer is composed of three independent legs projecting from the trimer head in tripod-like form (Zhu P et al 2006 Nature [Lond] 441:847)

chromatin (Jacque J-M, Stevenson M 2006 Nature [Lond] 441:641). The von Hippel–Lindau binding protein 1 (VBP1), a subunit of the prefolding chaperone, is an integrase cellular binding protein that bridges interaction between integrase and the cullin2 (Cul2)-based von Hippel–Lindau (VHL) ubiquitin ligase. VBP1 and Cul2/VHL are required for proper HIV-1 expression at a step between integrase-dependent proviral integration into the host genome and transcription of viral genes. VBP1 and the Cul2/VHL ligase cooperate in the efficient polyubiquitylation of integrase and its subsequent proteasome-mediated degradation (Mousnier A et al 2007 Proc Natl Acad Sci USA 104:13615).

The env envelope protein includes a surface glycoprotein, gp120 [SU] and a transmembrane glycoprotein, gp41 [TM] that are processed from gp160 molecule. Protein gp120 facilitates binding the virus to the cell membrane and gp41 promotes fusion to the membrane. Human monoclonal antibody may block the virus by binding a critical region of gp41 epitope and may offer an approach of prevention of infection (Miller MD et al 2005 Proc Natl Acad Sci USA 102: 145759). The processing facilitates the interaction of the virus with the CD4 host cells and the CXCR4 and CCR co-receptors. The envelope protein vpr (14 kDa) accelerates replication

and infection. Vpr facilitates the transport of the viral core into the nucleus, stimulates the expression of viral genes and mediates cell cycle arrest at the G₂ stage (de Noronha CMC et al 2001 Science 294:1105).

Rev (19 kDa) is transcribed from two exons, regulates viral replication and its basic amino acid domain (nuclear export signal, NES) interacts with the Rev response element (RRE, within *env*) targeting the viral transcripts to the cell nucleus. Within the nucleus, the exportin-1/CRM1 protein represents a receptor for NES. Tat (14 kDa, two exons) is the primary regulator of the virus. Vpu (15–20-kDa) membrane protein attacks CD4 with the assistance of the proteasome degradation pathway. Nef (25–27 kDa) mediates the degradation of CD4 on the cell surface and promotes endocytosis through the clathrin-coated pits. Nef and Tat proteins may be produced before the integration of HIV into the chromosome. These two proteins activate quiescent T cells, a requisite for viral integration and replication. Activation of CD4⁺ T lymphocytes and apoptosis that follows is an important sign of infection by HIV-1 and the Nef gene mediates this process through the T cell receptor-CD3 complex. The majority of other lentiviruses down-modulate this complex and less likely to give infection.

If Nef is inactivated AIDS progression slows down because T cells are not destroyed. Thus, it appears that human HIV-1 evolved by the loss of this function of Nef, resulting in immune evasion and AIDS (Schindler M et al 2006 Cell 125:1055).

Active genes are preferential targets of integration. (Schröder ARW et al 2002 Cell 110:521). Nef also inhibits the cellular protein ASK1, an apoptosis signaling serine/threonine kinase. That protects the infected cells from apoptosis although neighboring cells may die through bystander effect. Successful entry and productive infection requires the cooperation of the cellular protein cyclophilin A. In case cyclophilin is inhibited, HIV cannot infect neighboring cells even if HIV is within the originally infected cell. Similarly, by blocking the activity of MAPK, virulence of HIV is reduced. The viral Vif (virion infectivity factor) protein (23 kDa) is also required for the assembly of the viral coat proteins after infection (see Fig. A17). Vif also prevents deamination of cytidine into uracil by host APOBEC3 to avoid the

damage to viral RNA (Priest S et al 2005 Mol Cell 17:479). Non-permissive host cells produce the CEM15 protein, which prevents viral infectivity of Vif-deficient HIV. CEM15 is absent from permissive cells and this permits infection by Vif-deficient virus (Pomerantz JR 2002 Nature [Lond] 418:594). For entry into the cell nucleus, the virion needs the nuclear localization signal (NLS) provided by the uncoated viral nucleoprotein pre-integration complex (PIC). Viral protein Vpr interacts with PIC and thus assists nuclear localization of HIV. The virus is not transmitted through the germline. The *tat* gene functions only through the 5' RNA hairpin TAR (transactivation response element, 59 nucleotides) present within the repeat region (R) of the 5' LTR. The 5'LTR includes also the basal core promoter, the core enhancer and a modulatory region. The eukaryotic eIF2 elongation initiation element recognizes TAR. The 5' LTR serves also as the binding sites for a large number of host transcription factors (Pereira LA et al 2000 Nucleic Acid Res. 28:663). The Tat (14 kDa) primarily regulates the elongation of the transcript, generated by host RNA polymerase II. Pol II starts working at the 5' LTR. The Tak-associated kinase (TAK) complex phosphorylates the COOH end (CTD) of transcriptase pol II. The phosphorylation is the job of Cdk9 (formerly called (PITALRE). Cdk9 is bound to Tat by cyclin T (CycT) and enhances the specificity of Cdk9 to 5'-TAR. The TATA box is situated –24 to –28 positions from the GGT initiator codon. Further upstream in the enhancer region are the binding sites for the USF (upstream enhancer), Ets-1 (thymocyte-enriched protein), LEF (lymphocyte-specific high-mobility group protein), NK-κB (nuclear factor κ binding protein) and Sp1 (a mammalian transcription factor) binding proteins within the region –166 to –45 in the 5'-LTR. Around the transcription initiation site are the overlapping SSR (initiator) and IST (initiator of short transcripts) sequences. The virus does not have known genetic repair system and displays great antigenic variability; therefore, it is difficult to develop an effective vaccine against it (Rossio JL et al 1998 J Virol 72:7992; Gaschen B et al 2002 Science 296:2354; cardiolipin).

The Nef protein protects the infected primary cells from cytotoxic T cells. The viral coding RNA genome

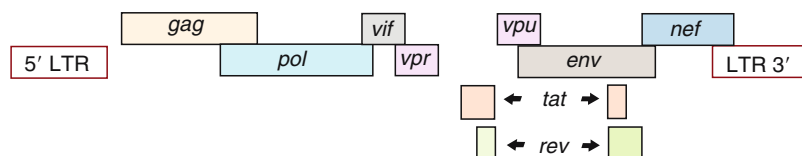


Figure A17. Genetic organization of HIV-1

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is about 9 kb. HIV1 and lentiviruses are suitable for the construction of transformation vectors that may integrate into non-dividing cells. Two of the viral proteins interact with nuclear import and mediate the active transport of the HIV pre-integration complex into the nucleus through the nuclear pores. The infection begins when the virus penetrates the cell membrane and its own lipid membrane fuses with the cell membrane and the viral core is released into the cell. Inside the cell, the viral reverse transcriptase synthesizes DNA copies of its RNA genome, and this DNA provirus integrates into the host genome with the aid of its terminal repeats, characteristic also for all types of insertion elements yet HIV is not transmitted through the germline. The HIV contains genes for proteins and their regulation. HIV does not have a lytic phase so it does not kill the cells directly. Instead, it assembles its particles in the cytoplasm and then infects other cells.

Upon infection by the HIV, monocytes, macrophages, endothelial cells and fibroblasts overproduce IL-1, IL-6 and TNF α . The anti-inflammatory IL-1ra and IL-10 are also hyperproduced. The latter ones inhibit the synthesis of the inflammatory lymphokines and IL-12. Soluble tumor necrosis factor receptors (sTNFR) hinder the binding of TNF to the cell membrane receptors. *Staphylococcus*-stimulated monocytes produce an order of magnitude less IL-12. After HIV infection CD4⁺ T cells lower the output of IL-2. Since IL-2 stimulates several players of the immune system, the immune response decreases. The dysregulation of cytokine balance results in a deficiency of cell-mediated immunity. The delayed-type hypersensitivity reaction (DTH) cannot control then the intracellular microorganisms. The main cause of the immunological failures is the defect in the CD4⁺ T cells, in the antigen presenting cells and the destruction of the CD4⁺ T cells although several billion CD4⁺ T cells are produced every day after the infection. A portion of the AIDS patients—upon induction by a gp41 peptide—express the natural cytotoxicity receptor, NKp44 and consequently the natural killer cells deplete the CD4 T cells and increase HIV load (Vieillard V et al 2005 Proc Natl Acad Sci USA 102:10981). The killer cell immunoglobulin-like receptor (KIR) family members similar to other NK cell receptors are expressed on T cells as well as on NK cells. Activating *KIR3DS1* allele in combination with *Bw4-80I*, associates with protection against HIV disease progression, as well as against opportunistic infections in HIV⁺ individuals. *KIR3DL1* and *HLA-B Bw4* combination effectively increases the protective effect of NK (killer T cell) against HIV (Martin MP et al 2007 Nature Genet 39:733).

The primary targets are the helper T lymphocytes carrying the CD4 receptors. The immune system is

debilitated when impairing these cells and that is the primary cause of the disease. In the endoplasmic reticulum of the infected cell 845–870 amino acid protein precursors of the viral envelope are formed. After the addition of asparagine-linked mannose chains, the glycoprotein gp160 precursor is synthesized. The trimeric gp160 is carried to the Golgi apparatus where through proteolysis the gp120 envelope protein and gp41 transmembrane proteins are formed.

Targeting the gp41 carboxy-terminus by a small protein, called 5-Helix, inhibits the entry of HIV-1 into the cell. A 20-residue peptide, called virus-inhibitory peptide (VIRIP) similar to the C-proximal region of $\alpha 1$ antitrypsin protease inhibitor interferes HIV-1 entry by targeting gp41 envelope protein of the virus. A few amino acid replacements in this natural peptide may increase its potency by two orders of magnitude (Münch J et al 2007 Cell 129:263). The binding of CD4 on the lymphocytes, monocytes, dendritic cells and brain microglia by the gp120 viral surface protein results in a conformational change in gp120. These changes may make available binding sites for chemokine receptors (primarily CCR5 and ligand CXCR4) to secure the necessary second receptors for the viral entry into the cell. Sulfated tyrosines of the CCR5 co-receptor play an important role in binding the gp-120 viral glycoprotein and HIV-1 infection (Choe H et al 2003 Cell 114:161). Mutation in CCR5 (CCR5 Δ 32) reduces the chance of HIV infection and disease progression (Agrawal L et al 2004 J Virol 78:2277). A chemically modified RANTES through inhibition of CCR5 provides protection against vaginal infection of simian/human immunodeficiency virus (Lederman MM et al 2004 Science 306:485). Polymorphism of these receptors and the stromal-derived factor (SDF-1) may either accelerate or retard the progression of the disease. Organ culture method permitted the identification of HIV infection sites in the vaginal and cervical mucosa and the virion binding can be reduced by pre-treatment with antibodies against $\beta 1$ integrin (Maher D et al 2005 Proc Natl Acad Sci USA 102:11504). Another approach would be populating the vaginal, cervical or rectal mucosa with bacteria secreting antiviral peptide. Such initiatives indicate that such a procedure might be effective (Rao S et al 2005 Proc Natl Acad Sci USA 102:11993).

The feline immunodeficiency virus uses directly the chemokine receptors and the V3 loop of the variable region is the most important for binding of the chemokine receptors. The constant regions in between the V regions are folded into the core of the glycoprotein. A so-called bridging sheet that binds to CD4 connects the outer and inner domains of the core. Mutations in the core area may influence infectivity and may serve as target for medical attack on the virus.

The CD4 induced antibodies (CD4i and its 17b epitope) may block the binding of the gp120—CD4 complexes to the chemokine receptors. The crystal structure of the V3-containing core of gp120 is known (Huang C-c et al 2005 Science 310:1025).

For neutralizing HIV probably the CD4BS epitopes, directed to the gp120 inner core are most significant. The 2G12 antibody recognizes the outer domain of gp120. The antigenic surface of gp120 is largely shielded from humoral immune responses by the glycosylation and other barriers. Conformational changes in gp120 provide additional structural means for the evasion of the immune reactions.

Avoidance of infection through body fluids (blood, semen, saliva, etc.) is the only effective defense until a clinically effective immunization or cure can be developed.

Human monoclonal neutralizing antibody b12 recognizes a conformational epitope that overlaps with the CD-4-binding site of the HIV-1 gp120 (see Fig. A18). In animals, b12 has a broad specificity.

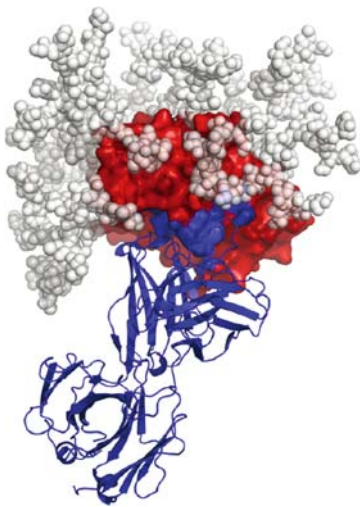


Figure A18. The b12 antibody (blue) to the HIV-1 exterior glycoprotein (red). The sugar (gray) occludes most of the gp120 surface from recognition. The blue surface (the epitope) marks where the receptor CD4 binds overlapping the b12 recognition site. (Courtesy of Peter D. Kwong and Jonathan Stuckey, Vaccine Research Center, NIAID/NIH)

Unfortunately b12-like antibodies are rarely produced in infected and vaccinated human subjects, indicating that the b12 epitope is poorly immunogenic for gp120—gp41 proteins. The gp120 viral glycoprotein has great ability to evade the human immune system.

The crystal structure of a constructed and stabilized gp120 molecule, which stays in the CD4-bound

conformation even in the absence of CD4 was tested regarding antibody binding. The broadly acting antibody b12 in complex with this gp120 molecules was stabilized to various extents in the CD4-bound conformation and revealed the functionally conserved surface that allows for initial CD4 attachment, but also provides an atomic-level description of the b12 epitope, which serves as a key target for humoral neutralization of HIV-1. Thus, a site of vulnerability was revealed that shows promise for antibody targeting HIV-1 (Zhu T et al 2007 Nature 445:732; see structure diagram). Another type of vaccine using gp140R2 immunogen induced antibodies that achieved 50% to 80% neutralization of diverse HIV-1 subtypes (B and C and others) tested on rabbits. The effectiveness of gp120R2 induced antibodies was less good. The rare R2 type was selected because it had unusual CD4-independent phenotype and the exceptionally broad neutralizing response in the infected donor. Neutralization was IgG-mediated and HIV-1-specific. These results demonstrate that induction of truly broad-spectrum neutralizing antibodies is an achievable goal in HIV-1 vaccine development (Zhang PF et al 2007 Proc Natl Acad Sci USA 104:10193).

Generally, the first sign of the disease is the susceptibility to *Pneumocystis carinii*, an opportunistic fungal pathogen causing influenza-like symptoms. This happens because the AIDS patients have only 200 CD4 helper cells per mL of blood versus 800 in normals. The other, most critical, diagnostic feature of AIDS is the development of Kaposi's sarcoma, a disease causing bluish eruptions all over the body that becomes cancerous. In tissue culture, the infected and uninfected cells fuse into syncytia and this and immunological methods are used as laboratory diagnostic procedures for the infections. AIDS, one of the most dreaded diseases of the twentieth century is now being battled with the most advanced techniques of molecular genetics; yet no effective cure has been devised till year 2008.

Although the majority of the specialists in medical virology and molecular biology maintain the view that the causative agent of the disease is HIV, some reject this assumption and others look at the mechanism with some reservations. They find likely or conceivable that AIDS is the result of the synergistic action of viral and other requisites such as the use of drugs (antibiotics, etc.), some types of autoimmune predisposition, and thus has multifactorial origin.

The AIDS disease has infected >21 million people worldwide and their numbers are increasing daily by 8,500–14,000 individuals. There are now three main groups of HIV-1: (i) M type, which is the most widely spread, (ii) the O group in Cameroon, Gabon and equatorial Guinea and a new (iii) N type found in (1998) in Cameroon, Africa. There are also 10 known

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subtypes of the virus. The three main types appear to have originated independently from the chimpanzee virus SIVcpz. The HIV-2 strains seem to be originated in West Africa from the simian virus strain SIVsm of the sooty mangabeys (*Cercopithecus atys*). Adaptation to infectious forms of the virus required mutation as well as recombination. There are at least 10 host genes involved in the degree of susceptibility (Heeney JL et al 2006 Science 313:462).

A whole-genome study identified polymorphisms that explain nearly 15% of the variation among individuals in viral load during the asymptomatic set-point period of infection. One of these is found within an endogenous retroviral element and is associated with major histocompatibility allele human leukocyte antigen (HLA)-B*5701, whereas a second is located near the HLA-C gene. An additional analysis of the time to HIV disease progression implicated two genes, one of which encodes an RNA polymerase I subunit (Fellay J et al 2007 Science 317:944).

The suggestions that the AIDS epidemics originated through SIV contamination of the early polio vaccines do not seem to have scientific basis.

The pharmaceutical industry is developing various drugs to combat the disease. None of the drugs so far provides a full cure or prevention, yet definite progress is made. The first and best-known chemicals (AZT) attack the viral replication system; protease inhibitors are aimed at the assembly process of the viral coat protein in order to prevent multiplication of HIV (Prejdova J et al 2004 Curr Drug Targets Infect Disord 4(2):137). The virus depends on cutting and processing of host cellular protein and uses protease to this end. Unfortunately, the protease inhibitors may cause very unpleasant side effects and HIV may develop resistance against the drugs by inhibiting primarily the mitochondrial DNA polymerase γ and possibly other DNA polymerases (Feng JY et al 2001 J Biol Chem 276:23832). None of the current drugs actually kills and/or removes the virus; instead only limit its functions. Halting the treatment may lead the virus to re-emerge from its hiding place in the lymph nodes. Other potential drug targets may be the cells' entry sites and CXCR4 and CCR5 receptors. According to some estimates HIV may produce >10 billion virions daily. Since its genome contains 10^4 nucleotides, the virus can readily test all possible mutational combinations. The estimated number of mutations/replication/nucleotide is 3×10^{-5} . The generation time is about 2.5 days. Drug resistance is based primarily on new mutation rather than on transmission of resistant virus. In addition, recombination facilitates the production of new variants. The combination of two nucleoside-analogs and protease inhibitor may reduce the level of the viral RNA copies

from 20,000 and 1,000,000 copies/mL plasma below detectability (i.e., below 200 to 400 copies/mL). These figures are concerned with viral levels in the blood. The newer techniques may detect even 20 virions/cell and reveal that the best medication available in (2001) cannot completely deplete the virus from the body. The lymph nodes and other sanctuaries may regenerate the virus after the discontinuation of the therapy. Additional problems may arise from the irreversibility of the tissue (thymus) damage. HIV-1 replication requires the REV oncogene cofactor and eukaryotic peptide elongation factor EIF-5A. Some mutations in the elongation factor retained the ability to bind to the HIV-1 REV response element: REV complex, and were expressed in human cells. When such T lymphocytes were infected with replication-competent virus, replication was inhibited. RNA decoys of the Tat and Rev genes may mimic the viral TAR and RRE RNAs but are non-functional yet sequester HIV-1 regulatory functions needed for the viral replication and gene expression. RNA polymerase III synthesizes these decoys and the transcript is a tRNA-TAR chimera. The decoys may, however, tie up some cellular molecules that could interfere with TAR and RRE. Type III RNases Dicer and Drosha, responsible for miRNA processing, inhibited virus replication both in peripheral blood mononuclear cells from HIV-1-infected donors and in latently infected cells. In turn, HIV-1 actively suppressed the expression of the polycistronic miRNA cluster miR-17/92. This suppression was found to be required for efficient viral replication and was dependent on the histone acetyltransferase Tat cofactor PCAF (Triboulet R et al 2007 Science 315:1579).

Antisense/ribozyme RNAs against various (TAR, U5, *tat*, *rev*, *pol*, *vpu*, *gag*, *env*) transcripts have also been explored. Double-stranded 54-mer oligodeoxynucleotide (ODN), which consists of an antisense strand targeting the highly conserved polypurine tract of HIV, and a second strand, compatible with triple-helix formation, interferes with viral replication. Upon treatment of HIV-infected cells with ODN early after infection no viral nucleic acids, syncytia or p24 viral antigen expression was observed (Moelling K et al 2006 FEBS Lett 580:3545). ODN prematurely activates RNase H and thus inhibits the synthesis of the 2nd strand of retroviruses.

RNAi has been shown to be an effective inhibitor of HIV replication. Unfortunately, the virus can mutate at the siRNA recognition sites and escape the inhibition by producing an alternative secondary structure of the target (Westerhout EM et al 2005 Nucleic Acids Res 33:796). The viral Tat protein can abrogate the cellular RNA-silencing defense by subverting the Dicer enzyme (Bennasser Y et al 2005 Immunity 22:607).

The latent provirus, integrated into the cells, may possibly be eliminated from the body by induced apoptosis of the cells harboring the provirus. CD4 protein, conjugated with ricin or *Pseudomonas* exotoxin, may home on the gp120 viral surface proteins and may destroy the infected cells. For the incapacitation of the HIV virus self-inactivating E-vectors, removing the encapsidation signal (Ψ , psi) from the 5' LTR have been designed. Vectors containing the Cre/LoxP system are also capable of deleting the packaging signal (Ψ) and replacing it with a desired sequence. An emerging novel approach would be to employ substrate-linked protein evolution of a tailored recombinase that recognizes an asymmetric sequence within an HIV-1 LTR. This type of recombinase efficiently excised integrated HIV proviral DNA from the genome of infected cells. This approach is different from others because it would actually remove HIV from the infected human genome. Preliminary data are promising yet it is not clinically applicable (Sarkar I et al 2007 Science 316:1912). Other current research attempts are focusing on the immune system to prevent infection. Although several interpretations are available, it is still uncertain why the period required for the development of full scale AIDS requires such a different length of latency after the initial infection. It had been assumed that the immune system is weakened by the ever-increasing viral diversity. Others believe that an immune dysregulation is responsible for the outbreak. Others suggest that the cellular immune system against AIDS be directed to both conserved and variable epitopes. It is assumed that the cytotoxic T lymphocytes alone cannot eliminate the virus and there is a need to achieve a balance between the viral load and the CD4⁺ T lymphocytes. After a period, the increasing variations in the HIV-1 population deplete and foul up the immune system. In the so-called non-progressor individuals, AIDS may not develop for more than 10 or even 20 years after the infection (HIV-exposed persistently seronegatives [HEPS]). There are high levels of CD8⁺ CD38⁺ cytotoxic lymphocytes, high peripheral blood CD8⁺ major histocompatibility class I-restricted anti-HIV cytotoxic lymphocytes in the cells of such a person, and those stay at an even level. There is also a strong CD8⁺ non-MHC-restricted HIV suppressor activity and high level of antibody against HIV. Most untreated HIV-1-infected individuals have continuous viral replication and ultimately progress to AIDS. However, a rare subpopulation of HIV-infected patients spontaneously controls viral replication for long periods in the absence of treatment. These individuals, called HIV controllers (HIC), are characterized by undetectable plasma HIV-1 RNA. Some of these are infected by replication-incompetent

viruses yet these individuals display a potent immune response to HIV-1. The controllers generally exhibit a strong CD8⁺ T cell specific response and high frequencies of HIV-specific CD8⁺ T cells despite very low levels of viral antigens. These HIC cells express the activation marker HLA-DR but not CD38. The HIV-specific CD8⁺ T cells from HIC are thus qualitatively different from those of progressors. Some HLA-B haplotypes (e.g., B27 and B57) are over represented in HIC suggesting an important role of class I-restricted CD8⁺ T cells and multi-epitopic and *de novo* CD8⁺ T cell responses are associated with suppression of viremia despite cytotoxic T lymphocyte escape mutations (Saez-Cirión, A et al 2007 Proc Natl Acad Sci USA 104:6776).

The window of opportunity to clear HIV and prevent long-term, established infection might close permanently once a pool of latently infected cells is in place. This aspect of HIV infection puts it in sharp contrast with almost all other viral infections, in which the initial rounds of viral replication do not establish a permanent reservoir of infection. For this reason, HIV poses a greater challenge to the classic vaccination paradigm in which prevention of clinically relevant infection ultimately leads to the eradication of the microbe, even though initial rounds of viral replication may occur (Johnston MI, Fauci AS 2007 New England J Med 356:2073).

Any vaccine developed against HIV should stimulate CD4⁺ and/or CD8⁺ cytotoxic T lymphocytes. Several vaccines are under clinical trials. These are based on various viral vectors (Canary pox virus, replication defective adenovirus, adeno-associated virus) carrying some HIV-1 protein genes. The viral spikes carry gp120 and gp41 glycoproteins and facilitate viral entry of the host cells. The host cell produces an N-linked glycan on its membrane surface and this protects HIV from recognition by the host immune system. Some spike proteins evade detection by host antibodies. The spike protein gp120 can fuse to CD4⁺ before the host antibody could recognize and neutralize the viral spikes. In addition, the virus has great natural diversity and all these factors combined make vaccine development difficult. In vaccine development, two functions of the virus must be targeted: preventing HIV from finding cellular co-receptors and reducing the chance of effective fusion between the virus and the host. Antibody b12 can prevent CD4 binding or antibodies 2F5 and 4E10 can interfere with fusion. Various molecular designs are under development that creates new epitopes that elicit effective response by host paratopes. It is of consideration that the antibodies function not only in the circulation system but be expressed effectively at mucosal anatomical sites of the viral entry. CD4⁺ memory T cells may reduce viremia upon challenging

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SIV-protein vaccinated monkeys during the initial phase of SIV infection and improves survival. The survival was associated with the preservation of memory CD4⁺ T lymphocytes and this feature may guide the evaluation of AIDS vaccines in humans (Letvin NL et al 2006 Science 312:1530). There is no vaccine available in (2006) that would prevent the infection for sure or attenuate the progression of the diseases (Douek DC et al 2006 Cell 124:677).

In case of chronic HIV infection CD8⁺ lymphocytes are impaired, display low cytokine production and reduced ability for proliferation. The cause of this is that the PD-1/PDCD1 (programmed death) and its ligand (PD-L/CD274) inhibit T cell function by antibodies to CD3 immunoglobulins. Blocking the engagement of PD-1 to PD-L1 restores lymphocyte function and reduces viral load in the cells (Trautmann L et al 2006 Nature Med 12:1198; Day CL et al 2006 Nature [Lond] 443:350). These new findings may improve the chances of fighting AIDS.

Studies indicate that in the non-progressors the gene coding for the chemokine receptors (of the non-syncytium inducing viral isolates [NSI]) CCR2 or CCR5 is mutated (contain deletion[s]), and thus it appears that CCR5 and 2 assist infection by HIV-1. These receptors are ligands for a group of CC-chemokines (CC, CXC) and MIP α and β and RANTES produced by CD8⁺ T lymphocytes. These and siRNA are able to suppress HIV replication in vitro probably by competition for the CCR5 receptors (Quin X-F et al 2003 Proc Natl Acad Sci USA 100:183). Mutation in HIV may facilitate the use by other members of the chemokine receptor family, including CCR3 and CCR2. Mutations in CX₃CR1 reduce the binding to the chemokine fractalkine and enhance the progression toward the development of AIDS. In late-disease stage cases the chemokine CXCR4/SDF1 may be used for entry into the cell. The CCR5 receptors may be polymorphic. Homozygosity and heterozygosity for the mutant alleles of CCR5 of the cells also appear to convey reduced susceptibility to infection. The viral protein gp120 reduces the response to chemokines. The frequency of the mutant alleles in Caucasian populations is about 0.092 and thus, the predictable frequency of homozygosity ($0.092^2 \approx 0.0085$) is about 1%. This type of mutation seems to be much less common in African and Japanese populations. It is also likely that some non-progressors were infected with less aggressive HIV variants. The residual genetic constitution of the infected individual may also affect the course of the disease.

A (2005) study revealed that homozygosity for a mutation in the chemokine receptor CCR5 (synonym CKR5) and CCR2 protects against HIV infection and heterozygosity may be of some advantage. Segmental duplication in human chromosome

7q11-q21 may involve one or more copies of the (CCL3L1) chemokine ligand 3-like gene (synonym MIP-1 α) and similar effects are conveyed by CCL4L1 (MIP-1 β -like). CCL3L1 is a suppressor of HIV-1 and a co-ligand of CCR5. Individuals with low copy number of CCL3L1 had 69 to 97% higher risk of infection by HIV, and an increasing risk of rapid progression to AIDS and death. Interestingly, however, various African populations—with high rates of AIDS—displayed higher copy numbers (mean 5.95) of the gene than European and other populations (2.99). Similarly, chimpanzees had higher copy numbers (9.30). The absolute gene copy number was however, substantially confounded by the overall genetic constitution. Nevertheless, in the large and diverse populations examined 42% of the infections and about 30% of the accelerated progression was attributed to CCL3L1 and CCR5 (Gonzalez E et al 2005 Science 307:1434). HIV infection takes place through these receptors. The average rate of HIV transmission was 0.0082/coital acts within approximately 2.5 months after seroconversion of the index partner, 0.0015/coital acts within 6–15 months and 0.0028/coital act 6–25 months before the death of the index partner. Higher HIV load, genital ulcer disease, and younger age of the index partner were significantly associated with higher rates of transmission in African populations (Wawer MJ et al 2005 J Infect Dis 191:1403).

A homozygous mutant form of the chemokine SDF-1 gene, which codes for the principal ligand of a co-receptor of CXCR4 of the CD4 T cells of the HIV-1 virus, substantially restricts AIDS pathogenesis. It seems to offer better protection than the CCR5 and CCR2 chemokine receptor variants. Heterozygosity for the HLA class I loci A, B and C conveys longer survival after infection by HIV-1. The latest evidence indicates that HLA-B restricted HIV-1 more than two-fold through CD8⁺ T lymphocytes than HLA-A (Kiepiela P et al 2004 Nature [Lond] 432:769). But the presence of alleles B*35 and Cw*04 potentiate rapid progression of the disease. Screening of the blood donations for possible HIV infection is based on the determination of the proportion of CD4/CD8 molecules. The normal ratio is about 2 and in infected blood it is below 1. It has been claimed that in infants, the HIV-1 infection may be transient but further analysis of these cases did not confirm the claims. None of the HIV vaccines tested so far provided protection. Attenuated live HIV with *nef* gene deletions appeared successful at first, but because of the high viral mutation rate, infective virus is recovered by time. In macaques the *nef*-defective SIV vaccine was protective. Compounds that inhibit the virus attachment to cells (CMPD167, C52L, BM-378806) applied to the vagina of rhesus monkeys

provided protection against simian-HIV-1 (SHIV-162P3) infection (Veazey RS et al 2005 Nature [Lond] 438:99). The HIV-1 virus can infect Old World monkeys but reverse transcription is blocked in these species. SIV and HIV infection involves the general destruction of 30 to 60% of memory CD⁺ T cells and indicates the onset of immunodeficiency symptoms (Mattapallil JJ et al 2005 Nature [Lond] 434:1093). The host cytoplasmic body component TRIM5 α appears to block uncoating of the retroviral capsid (Stremlau M et al 2004 Nature [Lond] 427:848). Recombinant envelope-protein-subunit vaccines also failed to elicit envelope-specific CTL or antibody-specific immune responses that could effectively neutralize HIV-1 in humans. Attempts to provide immunological protection against the V3 hypervariable loop of the viral envelope protein (essential for the viral gp120—CD4—chemokine interaction) is still being explored. Recombinant vaccinia virus carrying HIV protein fragments raised some hopes because similar constructs were effective in monkeys against SIV. Another possibility is to use engineered avian pox viral vectors, which have shown some promise (displaying some CTL activity), yet the immunogenicity generated may be too low. Unfortunately, in immuno-suppressed humans, serious side effects were encountered and the vaccines became impractical. BCG and other bacteria have also been considered as a potential vaccine vectors. DNA vaccines provide CTL activation and immune response but so far, the levels are very low to be effective. In rhesus monkeys infected with SIV lacking N-linked glycosylation at the 4th, 5th and 6th sites of the envelope protein reduced the immune evasion of the virus. Normally cytotoxic T lymphocytes (CTL) recognize the invading HIV by their surface Tat peptides. Unfortunately, through mutation this Tat peptide mutates very rapidly and becomes unrecognizable by CTLs. Immunization before infection by an appropriate Tat vaccine may provide a headway for CTL to gain control over the virus. Antisense RNA, complementary to the viral genome or to messenger RNA may also curtail viral functions by blocking transcription, translation or activation of RNase H. RNase H may significantly reduce the effectiveness of drugs inhibitory to viral replication (Nikolenko GN et al 2005 Proc Natl Acad Sci USA 102:2093)

Gene therapy using a suicide gene under the control of the HIV promoter may be activated by TAT and all the infected lymphocytes may be eliminated before the virus replication gets out of control (Caruso M et al 1995 Virology 206:495). RNA decoys that curtail replication of the virus have also been targeted at TAT. Transdominant Rev has also been used to limit productive infection (Escaich S et al 1995 Hum Gene Ther 6:625). Intrabodies were also explored as a protective measure (Marasco WA et al 1999 J

Immunol Methods 231:223). siRNA may also inhibit HIV-1 infection (Novina CD et al 2002 Nature Med 8:681). New type of drugs attempts to block the entry of the virus (Moore JP, Doms RW 2003 Proc Natl Acad Sci USA 100:10598). The integrase inhibitor drug, naphthyl pyridine carboxamide (L-870812), blocks the integration of the viral nucleic acid into the chromosome. Other well-established drugs target the reverse transcriptase (Hogberg M et al 1999 J Med Chem 42:4150), or the protease (Lebon F, Ledecq M 2000 Curr Med Chem 7:455), or both. HIV-susceptible transgenic outbred Sprague–Dawley rats can be used as an animal model for rapid and predictive preclinical evaluation of the inhibitory potency and of the pharmacokinetic properties of antiviral compounds targeting early steps in the HIV replication cycle (Goffinet C et al 2007 Proc Natl Acad Sci USA 104:1015).

So far the most effective protection from AIDS is behavioral, the avoidance of exposure to the virus. Infection by the virus is the easiest through blood cells, plasma or cerebrospinal fluids. The semen transmits 10 to 50 times more viruses than the vaginal/cervical fluids. Injection of drug, contamination by tainted blood and sexual transmission are major risk factors in the disease worldwide (Piot P et al 2001 Nature [Lond] 410:968). In the USA, the major route of infection is male homosexual contacts whereas in Africa heterosexual copulation is the predominant means of spreading the disease. ►retroviruses, ►CD4, ►CD8⁺, ►CD38, ►antibody, ►HLA, ►proteasome, ►clathrin, ►endocytosis, ►cyclophilin, ►MAPK, ►fusin, ►telomere, ►T cells, ►thymus, ►CTL, ►MIP-1 α , ►NF- κ B, ►Sp1, ►kissing loop, ►TBP, ►RANTES, ►AZT, ►TRIM5, ►Nevirapine, ►circumcision, ►SDF-1, ►TIBO, ►NF- κ B, ►Sp1, ►HMG, ►enhancer, ►herpes, ►gene therapy, ►chemokines, ►CCR, ►CXCR, ►SIV, ►cyclam, ►primates, ►chimpanzee, ►hominidae, ►vaccinia virus, ►BCG, ►immune system, ►immunization genetic, ►anti-trypsin, ►therapeutic vaccine, ►antibody neutralizing, ►antisense technologies, ►RNAi, ►seronegative, ►Kaposi sarcoma, ►HIV-1, ►integron, ►antisense technologies, ►peptide nucleic acid, ►RNAi, ►antivector cellular immunity, ►ribosome, ►ricin, ►exotoxin, ►apoptosis, ►CD4, ►E vector, ►Cre/LoxP, ►liposome, ►raft, ►biolistic transformation, ►DC-SIGN, ►DNA flap, ►reverse transcriptase and protease sequences, ►retroviral restriction factors, ►Pneumocystis carinii, ►decoy RNA, ►numt, ►APOBEC3G, ►enfuvirtide, ►von Hippel-Lindau, ►cullin, ►ubiquitin, ►prefoldin; Science 288:2129 ff; Amara RR et al 2001 Science 292:69; Nature [Lond] 410: 963 ff; Pognard P et al 2001 Annu Rev Immunol 19:253; Englert Y et al

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2001 Hum Reprod 16:1309; Wu Y, Marsh JW 2001 Science 293:1503; Gallo RC, Montagnier L 2002 Science 298:1730; evolution; Rambaut A et al 2004 Nature Rev Genet 5:52; HIV issue of Science 313:467–490 2006, status of HIV vaccine potentials in 2007: Johnston MI, Fauci AS 2007 New England J Med 356:2073; HIV drug resistance: <http://hivdb.stanford.edu>; vaccine trials: www.iavi.org; Vanderbilt program: <http://www.hivvaccineresearch.com/links.html>; HIV Protein Interaction Database: <http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/index.html>; mutation selection: <http://www.bioinformatics.ucla.edu/HIV/>.

Acridine Dyes: Such as proflavin, acriflavine, acridine orange are potential frameshift mutagens by intercalating between the nucleotides of DNA. Some acridines act by photosensitization of the DNA. It has been used to cure bacteria from plasmids (by selective removal), and to induce respiration-deficient mitochondrial mutations in yeast. mtDNA, ►fluorochromes, ►curing of plasmids, ►frameshift

Acriflavine: ►acridine dyes; formula (see Fig. A19).

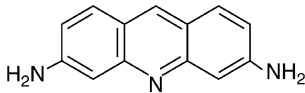


Figure A19. Acriflavine

Acrocentric Chromosome: Has a near terminal centromere and one arm is very short (see Fig. A20); acrocentric chromosomes may fuse or become translocated and may generate biarmed chromosomes. ►Robertsonian translocations

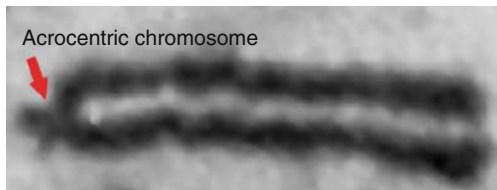


Figure A20. Acrocentric chromosome

Acrocephalosyndactyly: ►Apert syndrome; ►Pfeiffer syndrome

Acrodermatitis Enteropathica (8q24.3): A recessive blistering of the skin usually accompanied by lack of hairs on the head, eyebrows and eyelashes, and partial pancreatic hyperplasia and thymus hypoplasia. The deficiency in zinc-binding is characteristic and causes low levels of zinc and alkaline phosphatase (a zinc metalloenzyme) in the plasma. The treatment with zinc is very successful. ►alkaline phosphatase, ►zinc

►fingers, ►skin disease, ►Wilson disease, ►Menke disease, ►hemochromatosis, ►hyperkincemia; Wang K et al 2002 Am J Hum Genet 71:66.

Acrodysostosis: An autosomal dominant defect of bone development of paternal origin and increased occurrence by the age of the father.

Acromesomelic Dysplasia: A type of dwarfism based on shortening of the forearm and foreleg and other bones because of defect in the bone morphogenetic protein-1 gene (AMDM, 9p13-q12). The Hunter-Thompson dwarfism is based on a defect of the cartilage-derived morphogenetic protein-1 (CDMP1, 20q11.2). ►bone diseases

Acromegaly: Increased growth due to over-production of the pituitary hormone. (See for review: Melmed S 2006 New England J Med 355:2558).

Acropetal: The youngest leaf on the stem is at the tip of the stem of the plant.

Acrosomal Process: A spike-like actin structure on the head of the sperms of several animals and at its base is the acrosome, a sac of hydrolytic enzymes destined to facilitate the penetration through the gelatinous coat of the egg. Before acquiring competence for fertilization the spermatozoa must be activated by bicarbonate mediated soluble cAMP. The process is enhanced by progesterone, probably by acting on a GABA_A receptor. In the starfish egg jelly *ARIS* (polysaccharide with repeating units of sulfated pentasaccharide), *Co-Aris* (steroid saponin) and *asterosap* (a variety of 34 amino acid peptides) are required for the acrosomal process. In sea urchins, FSP (sulfated fucose polymer) activates the acrosomal process. In mammalian egg, the three ZP (zona pellucida) proteins bind to the receptors on the sperm plasma membrane and stimulate the exocytosis of the acrosomal vesicle in the front part of the sperm. Activated sperm contains nitric oxide synthase and nitric oxide is important for fertilization. Phospholipase Cδ4 is also required for the process. ►acrosome, ►sperm, ►GABA, ►progesterone, ►fertilization, ►ICSI; Tulsiani DR, Abou-Haila A 2001 Zygote 9:51; Kang-Decker N et al 2001 Science 294:1531; acrosome structure: Schmid MF et al 2004 Nature [Lond] 431:104.

Acrosome: ►acrosomal process (see Fig. A21)

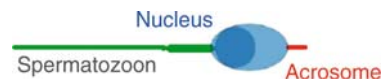


Figure A21. Acrosome

Acrosome Reaction: ►acrosomal process

Acrosyndesis: A spurious end-to-end pairing of the chromosomes during meiosis.

Acrylaldehyde: It is a toxic compound made from allyl alcohol by the enzyme alcohol dehydrogenase. Cells defective in this enzyme permit the selective survival on allyl alcohol as it is not converted to acrylaldehyde. ►mutant isolation, ►alcoholdehydrogenase

Acrylamide: In the presence of ammonium persulfate and TEMED (*N,N,N',N'*-tetramethylethylenediamine) it is polymerized into chains with various length depending on the concentration used. In the presence of *N,N'*-methylenebisacrylamide it becomes cross-linked and pores are formed depending on the length of the chains and the degree of crosslinking. It can be used to separate nucleotides by electrophoresis from 2000 to 6 bp, depending on the pore size of the gels. Acrylamide is a potent neurotoxin and potential carcinogen. It can be absorbed through the skin. Although the polymerized form is considered non-toxic, it should be handled only with gloves because of the trace amounts of monomers. Acrylamide may be formed in small quantities in deep-fried starchy food. ►electrophoresis, ►gel electrophoresis; Mottram DS et al 2002 Nature [Lond] 419:448.

ACT: Activator of CREM (in the testis) by binding through a LIM domain. ►CREM, ►LIM

ACT: An Artemis based DNA sequence comparison viewer program. ►Artemis; <http://www.sanger.ac.uk/Software.ACT/>.

ACTH (adrenocorticotropin hormone): ACTH controls adrenocortical growth and steroidogenesis. The hypothalamus controls the ACTH releasing factor and in response to that, the anterior pituitary releases this hormone. ACTH is encoded in human

chromosome 2. ►animal hormones, ►adrenocorticotropin, ►cAMP, ►steroid hormones, ►hormone-response elements, ►pituitary gland, ►brain, ►POMC

Actin: A protein of the cytoskeleton and the thin muscle fibers. Actin gene number varies in different organisms; yeast has only one, *Dictyostelium* 8, *Drosophila* 6, *Caenorhabditis* 4, humans about two dozen at dispersed locations. The cytoplasmic actins involved in cellular motility are similar in all eukaryotes. α -Actins are located in the smooth, skeletal and cardiac muscles. The smooth muscles have in addition γ -actin. In the cytoplasm of mammals and birds, there are β - and γ -actins. The amino acid sequence and composition of the actins is rather well conserved and differences exist mainly at the amino terminals. Actin genes have different numbers of introns and pseudogenes, permitting evolutionary inferences partly because the flanking sequences are much more variable than the genes. Some proteins bind actin in monomeric or filamentous form such as myosin (a contractile protein in muscles), α -actinin (involved in cross-linking actins). Profilin (mediates the formation of actinin bundles), fimbrin (cross-linking parallel actin filaments), filamin (promotes the gel-formation by actins), tropomyosin (strengthens actin filaments), spectrin (attaches filaments to plasma membranes), gelsolin (fragments filaments), etc. The natural products jasplakinolide and latrunculin B have opposite effects on actin filaments (see Fig. A22), the former is stabilizing while the latter is destabilizing the filaments. ►cytoskeleton, ►podosome, ►myosin, ►filament, ►microfilament, ►microtubule, ►myofibril, ►tropomyosin, ►cofilin 1, ►CDC42, ►mRNA migration, ►Wiskott-Aldrich syndrome, ►cardiomyopathy dilated, ►glomerulosclerosis, ►cytoskeleton, ►pollen, ►nemaline myopathy, ►pollen; Geeves

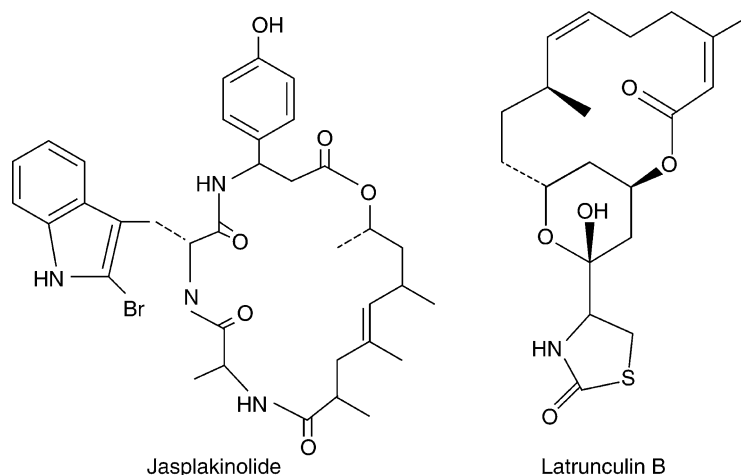


Figure A22. Jasplakinolide and Latrunculin B

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MA, Holmes KC 1999 Annu Rev Biochem 68:687; Higgs HN, Pollard TD 2001 Annu Rev Biochem 70:649; Quinlan ME et al 2005 Nature [Lond] 433:382.

Actin Contractile Ring: Formed prior to the separation of the dividing chromosomes and contracts after anaphase. It may be involved in the formation of the septum between the two cells. ►[cell cycle](#)

Actinin, α (M_r 120 K): Antiparallel peptide in muscle Z lines, focal adhesion and intermediate junction structures. Actinin α 2 (1q42-q43) and actinin α 3 (11q13-q14) are somewhat different, yet partially compensate for each other. Their function is required for fast (not the enduring) muscle function, and the frequency of the latter gene (R577X) is significantly higher in athletes who require high velocity muscle functions (sprint, judo, short distance cyclists, speed skaters). In 18% of healthy white population, the R577X is inactive because of homozygosity of a stop codon in the gene. The female sprint athletes also show higher frequencies, however, they are generally heterozygous for the 577RX allele (Yang N et al 2003 Am J Hum Genet 73:627). ►[glomerulosclerosis](#), ►[actin](#), ►[CAM](#), ►[junction complex](#)

Actinomorphic: A structure (flower) in multiple symmetry patterns (see Fig. [A23](#)).



Figure A23. Actinomorphic

Actinomycetes: Filamentous prokaryotes rather than fungi as they once were assumed to be. ►[Streptomyces](#), ►[streptomycin](#), ►[actinomycin](#)

Actinomycin D: An antibiotic from *Streptomyces*; it is an inhibitor of transcription because it intercalates into the DNA between neighboring GC base pairs and hinders the movement of the transcriptase on the DNA template without interfering with replication; it is used in reverse transcriptase reactions to prevent self-primed second strand synthesis. Actinomycin D is a teratogen and carcinogen. (There are several other actinomycin antibiotics). ►[Actinomycetes](#), ►[Streptomyces](#), ►[transcriptase](#), ►[reverse transcription](#); Graves DE 2001 Methods Enzymol 340:377.

Action Potential: Rapid, transient, self-propagating electrical excitation in muscle or neuron membranes. It may mediate long-distance nerve signaling.

Action Spectrum: A representation of a degree of response to certain type of treatment(s),

e.g., photosynthesis in relation to wavelength of irradiation. ►[photomorphogenesis](#)

Activating Enzyme: ►[aminoacylation of tRNA](#)

Activation Analysis: A nuclear technique used for the very sensitive detection of radionuclides for various purposes including forensic analysis. ►[radionuclide](#)

Activation Domain: Generally, a loop of the proteins where phosphorylation takes place at serine, threonine or tyrosine residues.

Activation Energy: The energy required for converting 1-gram molecular weight of a compound from the ground state to the transition state. It is required, from outside, by molecules and atoms to undergo chemical reaction(s). ►[transition state](#)

Activation of Genes: ►[suppression](#), ►[activator proteins](#)

Activation of Mutagens: Many mutagens (and carcinogens) require chemical alterations to become biologically active. The mutagenic and carcinogenic properties of many agents overlap and thus active in mutagenesis and carcinogenesis. The activation generally requires enzymatic reactions. The most important enzymes are the mixed-function oxidases contained by the cytochrome P-450 cellular fraction. These reactions require NADPH and molecular oxygen and the general process is: RH (reduced reactant) + $NADPH + H^+ + O_2 \rightarrow ROH + NADP^+ + H_2O$. These enzymes occur in multiple forms and can utilize a variety of substrates, hydrocarbons, amines and amides, hydrazines and triazines, nitroso compounds, etc. They occur in different tissues of animals, primarily in the endoplasmic reticulum of cells what is generally called microsomal fraction after isolation following grinding and centrifugal separation of the cellular fractions. These enzymes are subject to induction by phenobarbitals, methylcholanthrene and a variety of substrates. Other related activating enzymes are flavoprotein N-oxygenases, hydrolases, and reductases. Other enzymes of activating ability include various transferases that add glucuronyl, sulfuryl, glutathione, acetyl and other groups and either detoxify the compounds or further enhance their reactivity. The cellular and membrane transport, protein binding, excretion affect these reactions. Genetic differences exist among the species and individuals. Differences by age, circadian rhythm and nutritional status, etc., are known. If the clearance of these compounds from the body is slow, the risk for the individuals increases. ►[promutagen](#), ►[proximal mutagen](#), ►[ultimate mutagen](#), ►[environmental mutagens](#), ►[mutagen assays](#), ►[Ames test](#), ►[bioassays of mutagenesis](#), ►[cytochromes](#), ►[P450](#); Baum M et al 2001 Chem Res Toxicol 14:686.

Activation Tagging: Random insertions of transcriptional enhancers of the 35S cauliflower mosaic virus promoter with the aid *Agrobacterium* vector into the plant genome resulting in misexpression and overexpression of many different genes concerned. ▶cauliflower mosaic virus, ▶T-DNA, ▶Ti plasmid; Weigel D et al 2000 Plant Physiol 122:1003.

Activator: *Ac*, the autonomous element of the *Ac-Ds* controlling element system of maize (see *Ac*). Also, any DNA binding protein that enhances transcription, a positive modulator of an allosteric enzyme. More than one activator of transcription may operate at different activator binding sites of a single promoter. Their action may be synergistic, or each may have special affinity to a separate surface of the RNA polymerase II molecule or one stabilizes the other activator. ▶allosteric control, ▶modulation, ▶transcriptional activator, ▶*Ac-Ds*

Activator A: Synonymous with RF-C, a cellular replicator. ▶RF-C

Activator I: Same as ▶RF-C

Activator Proteins: Stimulate transcription of genes by binding to TATA box binding protein (TBP) and the recruitment of TFIID complex to the promoter. Sometimes they require coactivator metabolites for function. The primary role of these is probably the remodeling of the nucleosomal structure so DNA-binding proteins can access their target. The DNA has multiple binding sites for activators in the promoter region. The potency of the activation domains of the activators may vary. An activator may turn into a repressor by binding a corepressor. ▶transcription factors, ▶TBP, ▶regulation of gene activity, ▶promoter, ▶co-activator, ▶corepressor, ▶transcriptional activator, ▶enhancer, ▶chromatin, ▶nucleosome, ▶VDR, ▶recruitment, ▶suppression, ▶signal transduction, ▶chromatin remodeling, ▶GCN5; Evans R et al 2001 Genes Dev 15:2945.

Active Immunity: ▶immunity

Active Site: A special part of an enzyme where its substrate can bind and where the catalytic function is performed, the catalytic site. ▶substrate, ▶enzymes, ▶catalysis

Active Telomeric Expression Site: Variable surface glycoprotein (VSG) genes are responsible for the diversity of antigenic variants in *Trypanosomas*. These generate different antigenic properties of the parasite. There are about thousand genes in this gene family and their activation is interpreted by their transposition to the vicinity of the telomere, the expression site of the silent copies. ▶*Trypanosomas*, ▶mating type determination in yeast, ▶silent site; Borst P, Ulbert S 2001 Mol Biochem Parasitol 114:17.

Active Transport: Passing solutes through membranes with the assistance of an energy donor required for the process. ▶passive transport

Activin: Soluble protein that may contribute to the formation of dorsal and mesodermal tissues in the developing animal embryo; its activity may be blocked by *folliculin*. *Activins* belong to the family of *transforming growth factor-β* superfamily of proteins. They are serine/threonine protein kinases. Activins respond to Smad signal transducers. Activin receptor-like kinase 1 (ACVRLK1) modulates TGF signaling in angiogenesis. Its absence or deficiency results in lack of response to TGF-β family growth factors and mice afflicted by mid-gestation die due to fusion of major arteries and veins. Cultures rich in activin A facilitate endoderm production up to 80% of the experiments (D'Amour KA et al 2005 Nature Biotechnol 23:1534). ▶protein kinases, ▶TGF, ▶organizer, ▶folliculin, ▶SMAD, ▶angiogenesis, ▶fibrodysplasia ossificans progressiva; Luisi S et al 2001 Eur J Endocrinol 145:225.

Activity-Based Protein Profiling: Monitors the expression dynamics of a family of proteins on the basis of chemical tagging with common inhibitors. This type of test reveals more important information on the role of proteins in health and disease than measuring the quantity of proteins (See Liu Y et al 1999 Proc Natl Acad Sci USA 96:14694; Okerberg ES et al 2005 Proc Natl Acad Sci USA 102:4996).

Activity Coefficient: Obtained by multiplying with it the concentration of a solute to obtain its thermodynamic activity.

Actomyosin: A complex of actin and myosin. ▶actin, ▶myosin

ACTR (acetyl transferase): ▶acetyl transferases

Actuarial Analysis: Analysis of life expectancy; it is generally compared in a cohort. ▶cohort, ▶life expectancy

Acuminate: Tapered (see Fig. A24).



Figure A24. Acuminate

Acupuncture: A traditional Chinese method of releasing pain by strategically employed punctures to the body by needles. The methods are not standardized and is used by different styles. Although the physiological bases are not understood, it may be an effective treatment. (See Ahn AC, Kaptchuk TJ 2005 Altern Ther Health Med 11:50).

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Acute Transforming Retrovirus: Contains a v-oncogene and it is an efficient oncogenic transformation agent.

►v oncogene, ►oncogenes, ►retrovirus

Acyclovir: see ►gancyclovir

Acyl Group: See Fig. A25 where R can be a number of different chemical groups. ►acetyl group

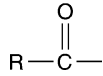


Figure A25. Acyl group

Acyl-CoA Dehydrogenase Deficiency (ACAD): Three different diseases have been described with short (SCAD, 12q22-qter), long (LCAD, 2q34-q35) and medium chain defects (MCAD, 1p31) involving β -oxidation of fatty acids. The clinical symptoms include hypoglycemia, dicarboxylaciduria, hyperammonemia, fatty liver, etc. Some of the symptoms overlap with those of the Reye syndrome and maple syrup urine disease. ►Reye syndrome, ►isovaleric acidemia, ►isoleucine-valine biosynthetic pathway

Acylation: Attaching one or more acyl groups to a molecule. ►acyl group

Acylcyclohexanedione: An inhibitor of gibberellin biosynthesis. ►plant hormones

Ad4BP: ►SF-1

Ad5 E1B: An adenovirus oncoprotein. ►adenovirus, ►oncogenes

ADA: Zn-containing proteins that transfer methyl groups to their own cysteine and thus repair aberrantly methylated DNA (e.g., 6-O-methylguanine), and by binding to specific DNA sequences it activates genes involved in conveying resistance to methylation. Some of the ADA proteins are involved in repression of transcription. ►adenosine deaminase, ►histone acetyltransferase

Adactyly: The absence of digits of the hand or foot. It may occur as part of several syndromes (see Fig. A26). ►Holt-Oram syndrome, ►polydactyly, ►ectrodactyly



Figure A26. Adactyly

ADAM (a disintegrin and metalloprotease): A family of metalloprotease enzymes such as KUZ (kuzbanian), responsible for partitioning of neural and non-neural cells during the development of the central and peripheral nervous system. ADAMs may have proteolytic, cell adhesion, signaling and fusion functions of cell surface molecules. It is apparently involved with the Notch receptor function. ADAM motifs are found in the aggrecanase enzyme eroding cartilage in arthritis. ADAM 10 (α -secretase) cleaves also the amyloid precursor protein (APP). ►neurogenesis, ►bone morphogenetic protein, ►CAM, ►Notch, ►fertilin, ►cyritestin, ►arthritis, ►secretase, ►Alzheimer disease, ►metalloproteinase, ►cardiomyopathy hypertrophic; Stone AL et al 1999 J Protein Chem 18:447; in cancer: Fridman JS et al 2007 Clin Cancer Res 13:1892.

ADAM Complex (amniotic band sequence, congenital constricting band, amputations): Acronym for Amniotic deformity, Adhesions, Mutilations phenotype complexed with other anomalies caused by mechanical constriction of the amniotic sac, but there is evidence for the role of autosomal recessive inheritance. The phenotype may include bands on fingers, and loss of finger bones or even parts of legs (amputations), etc. ►limb defects; Keller H et al 1978 Am J Med Genet 2:81.

Adams-Oliver Syndrome: Autosomal dominant mutilations of the limbs, skin and skull lesions yet apparently normal intelligence. ►ectodermal dysplasia

Adaptation: Process by which organisms develop fitness to a special environment. Mutation provides the genetic variations from which the evolutionary process selects the genes that convey the best adapt.

Adaptation may be acquired by major mutations although most commonly it is based on mutations with small cumulative effects without serious deleterious pleiotropic or epistatic consequences. R.A. Fisher expressed adaptation in “geometric” terms (see algebraic figure)

$$\frac{1}{2} \left(1 - \frac{r}{d} \right)$$

where r is the distance to what a mutation moves the population in a sphere (d) from the sphere of previous adaptation of A . If r is very small, the chances are equal to bring improvement or becoming deleterious. When however r moves beyond the sphere of A , he considered no chance for improvement. “The chance of improvement thus decreases steadily from its limiting value $1/2$ when r is zero, to zero when r equals d .” The probability for adaptive change—he concluded—is rapidly diminished when the change (d/\sqrt{n}) has manifold effects (n). Adaptation

actually limits diversification in bacterial populations (Buckling A et al 2003 Science 302:2107). In physiology, it defines adjustment to specific stimuli. Long-term evolutionary changes can be best studied under defined conditions by using bacterial cultures for thousands of life cycles (Elena SF, Lenski RE 2003 Nature Rev Genet 4:457). ▶fitness, ▶shifting balance theory of evolution, ▶plasticity, ▶noise, ▶reaction norm; Travisano M 2001 Curr Biol 11: R440; Orr HA 2005 Nature Rev Genet 6:119.

Adapter Ligation PCR: ▶capture PCR, ▶polymerase chain reaction

Adaptins (AP-1, AP-2, AP-3): Major coat proteins in a multisubunit complex on vesicles. These proteins bind the clathrin coat to the membrane and assist in trapping transmembrane receptor proteins that mediate the capture of cargo molecules and deliver them inside the vesicles. ▶clathrin, ▶cargo receptors, endocytosis, ▶epsin, ▶AP1, ▶AP180, ▶arrestin; Robinson MS, Bonifacione JS 2001 Curr Opin Cell Biol 13:444.

Adaptive Amplification: A concept somewhat similar to adaptive mutation. It has been argued that the two are different because adaptive amplification—unlike mutation—is a flexible and more readily reversible alteration. The argument has been that if the days required to reform colonies equals the number of days after selection when, e.g., the original *Lac*⁺ colony arose the original revertant was preexisting. If the days required to reform colonies is less than the number of days after selection when the revertant emerged, then the alteration permitting growth on lactose is attributed to an adaptive response to the selective condition. ▶adaptive mutation; Hastings PJ et al 2000 Cell 103:723.

Adaptive Convergence: Similarity in morphology and function among unrelated species within a particular environment, e.g., fins on fishes and mammalian whales.

Adaptive Enzyme: Same as inducible enzyme. ▶*Lac* ▶operon

Adaptive Evolution: A theory that claims evolution is largely based on mutations that increase fitness of the individuals and species involved. In contrast, the neutral mutation theory postulates the significance of the role of random neutral mutations based on synonymous codon substitutions. The relative abundance of synonymous (D_s) and non-synonymous (D_n) mutations can be estimated as (a = adaptive substitution):

$a = D_n - D_s (P_n/P_s)$ where P_n and P_s stand for the numbers of non-synonymous and synonymous substitutions, respectively. Hence, α (the amino acid substitutions brought about by positive selection) is $\alpha = 1 - (D_s P_n)/(D_n P_s)$. By using this method, 45% of the amino acid substitutions in some *Drosophila* species appeared to be adaptive.

Parallel and convergent changes in different lineages indicate adaptive evolution. It can be studied experimentally by morphology or by comparative genomics. ▶fitness, ▶mutation beneficial, ▶mutation neutral, ▶genomics; Smith NGC, Eyre-Walker A 2002 Nature [Lond] 415:1022; Cooper TF et al 2003 Proc Natl Acad Sci USA 100:1072.

Adaptive Immunity: Develops in response to an antigen. ▶acquired immunity, ▶innate immunity

Adaptive Landscape: Represents the frequency distribution of alleles corresponding to fitness of the genotypes, e.g., *Aabb* and *aaBB* means the fixation (*peak*) of the allelic pairs (see Fig. A27).

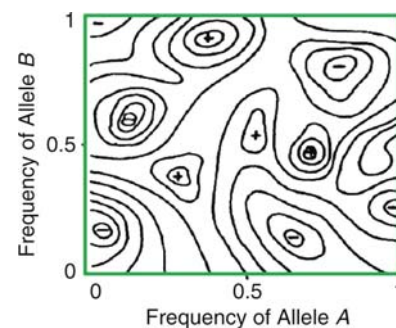


Figure A27. Adaptive landscape. (Modified after Mohay, J. 1996 Genetika)

The *pits* of fitness may mean the fixation of *AABB* or *aabb*, and the *saddle* usually corresponds to the polymorphic condition *AaBb*. A two-dimensional model of the allelic topography may represent the allelic constitutions with the corresponding fitness in a third dimension showing “mountain ranges” and “valleys.”

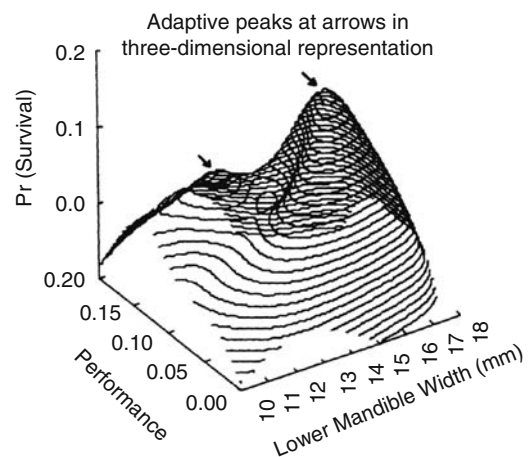


Figure A28. Adaptive topography (From Smith TB., Girman DJ 2000 In: Mousseau TA et al (eds) Adaptive Genetic Variation in the Wild. © Oxford Univ Press, New York p 139)

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The landscape may be subject to evolutionary change due to change in allelic frequencies and the environment. The landscape may become complex if several allelic pairs are considered. The (+) and (−) signs indicate high and low fitness, respectively. The adaptive landscape may be represented also in three-dimensional plot (see Fig. A28). The term is the same as adaptive topography. The adaptive landscape of molecules can also be determined by engineered replacements at, e.g., coenzyme attachment sites of metabolic enzymes (Lunzer M et al 2005 Science 310:499). ▶fitness, figs., ▶mutational landscape models; Rokyta DR et al 2005 Nature Genet 37:441.

Adaptive Mutation: Occurs at higher frequency in response to conditions of selection although the mutation is not induced by the conditions of selection. A relevant assumption is that the gene number increase under the specific conditions facilitated “amplification mutagenesis.” The phenomenon is not non-darwinian as it may appear. It takes place in three steps, e.g., (i) growth limitation favors the propagation of a subpopulation with an amplification of the *lac* gene, (ii) then *lac*⁺ revertant cells are favored, (iii) eventually a stable *lac*⁺ revertant allele arises and overgrows the colony (Hendrickson H et al 2002 Proc Natl Acad Sci USA 99:2164). The selective conditions do not increase the mutation rate but instead favor the growth of rare cells with a duplication of leaky *lac* alleles. A further increase in copy number (amplification) improves growth and increases the likelihood of a sequence change by adding more mutational targets to the clone (Kugelberg E et al 2006 Proc Natl Acad Sci USA 103:17319). Similar amplification of gene number can occur in various eukaryotes.

The increased frequency of mutation under some specific selection regimes may be attributed to the differences in genetic repair. Caution is warranted in calculating the mutation rate. If, e.g., 10 mutations are observed under both the selective and non-selective conditions but the number of survivors is 50 and 100, respectively, the apparent mutation rate is double in the first lot but it is caused only by the method of assessment, 10/50 and 10/100. It is customary to calculate the rate based on survivors but it remains unknown how many of the dead individuals were mutant. If it is assessed because of the input cells, the rate may be the same under the two conditions. ▶directed mutation, ▶adaptive amplification, ▶neofunctionalization; Foster PL 1999 Annu Rev Genet 33:57; Hall BG 2001 Mol Biol Evol 18:1389.

Adaptive Peak: The highest value(s) of fitness in an adaptive landscape. ▶adaptive landscape

Adaptive Radiation: Phyletic lines spread over a variety of different ecological niches resulting in a rapid adaptation to these locales and appearing in strikingly different forms. Competition for limited resources may form a basis for adaptive radiation (Chow SS et al 2004 Science 305:84). Adaptive mutation may account also for adaptive radiation as in sequential steps—as environmental changes take place—and the adaptive mutation is selectively reinforced. ▶phylogeny, ▶niche, ▶diversity [Shannon—Weaver index], ▶frequency-dependent selection; Francino MP 2005 Nature Genet 37:573.

Adaptive Response: Induction of (bacterial) repair enzymes, which activate glycosylases or O⁶-methylguanine methyltransferase and thereby mutated DNA is repaired. The name comes from the property of adaptation to higher doses of mutagens after an initial shorter exposure; it is mediated by the *Ada* gene product (37-kDa) of *E. coli*. ▶alkylating agent, ▶chemical mutagens, ▶DNA repair, ▶glycosylases, ▶methylation of DNA

Adaptive Value: ▶fitness

Adaptor: tRNA is called an adaptor in older literature as it adapts the genetic information in DNA through mRNA to protein synthesis. ▶tRNA, ▶aminoacyl-tRNA synthetase, ▶protein synthesis; Ibba M et al 2000 Trends Biochem Sci 25:311.

Adaptor Ligation PCR: Determines the flanking sequences of a DNA sequence by the use of nested promoters and DNA adaptor in order to amplify an entire stretch of the chromosome.

Adaptor Proteins (AP): Adaptor proteins play key roles in cellular signaling such as phosphorylation, dephosphorylation, signal transduction, organization of the cytoskeleton, cell adhesion, regulation of gene expression, all distinct yet interacting systems. Proteins equipped with the Rous sarcoma oncogen (Src) homology domains SH2 and SH3 mediate the interactions between the phosphotyrosine kinase receptors of mitogenic signals and the RAS-like G proteins. The SH2 domain selects the phospho-Tyr-Glu-Glu-Ile sequences. Phospholipase C (PLC-γ1) and the protein-tyrosine phosphatase (PTPase) recognize several hydrophobic residues following pTyr on the ligand-binding molecule. The SHC homology proteins and the insulin-receptor substrate (IRS-1) recognize somewhat different sequences: Asn-Pro-X-pTyr. The SH3 binding sites involve about 10 proline-rich amino residues. The SH3-binding peptides can bind either in NH₂→COOH or in the reverse orientation. The SOS (son of sevenless) adaptor protein

binds to Grb2 (growth factor receptor-bound protein) is attached in C→N orientation. The pleckstrin domains are widespread in occurrence (serine/threonine and tyrosine kinases, and their substrates, phospholipases, small GTPases, dynamin, cytoskeletal proteins, etc.). Pleckstrin domains occur in cytoplasmic and membrane signaling molecules. The LIM domains facilitate binding of signaling molecules, transcription factors as well as the units of the cytoskeleton. These adaptor proteins may form partnerships with a variety of proteins and thus generate complex networks of signaling. (See separate entries mentioned; Hübener C et al 2001 *Immunogenetics* 53:337; Beer S et al 2001 *Biochim Biophys Acta* 1520:89).

Adaptors: ► [linker](#)

ADAR (adenosine deaminase of acting on RNA, ADAR1, ADAR2, ADAR3): ADAR2 edits the pre-mRNA of the glutamate-sensitive ion channel receptor B subunit and adenine is converted to inosine that behaves in coding as guanine. Thus, glutamine is replaced by arginine in the protein with over 99% efficiency. ADAR1 functions overlap with ADAR2 and ADAR3. ADAR3 is specific to the brain. The enzymes contain a double-strand-binding domain and a catalytic deaminase domain. Thus alternative forms of the protein appear. At the NH₂ terminus, it includes domain Z α , responsible for the high-affinity binding to Z DNA. Point mutations in AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor may compensate for lethality in ADAR2-deficient mice. ADAR2 is concentrated in the nucleolus but can shuttle to the nucleoplasm and increasing editing of the endogenous substrate (Sansam CL et al 2003 *Proc Natl Acad Sci USA* 100:14018). Inositol hexakisphosphate (IP₆) bound to ADAR2 core is required for RNA editing (Macbeth MR et al 2005 *Science* 309:1534). ► [mRNA](#), ► [Z DNA](#), ► [Z RNA](#), ► [RNA editing](#), ► [adenosine deaminase](#), ► [DRADA](#), ► [IP₅/IP₆](#); Wang Q et al 2000 *Science* 290:1765; Bass BL 2002 *Annu Rev Biochem* 71:817; Levanon EY et al 2005 *Nucleic Acids Res* 33:1162.

AddAB: An enzyme complex involved in double-strand DNA repair in Gram-positive bacteria in a manner similar to RecBCD in Gram-negative bacteria. In the Gram-negative α -proteobacteria, however the AddAB system can function. ► [Gram-positive](#), ► [RecBCD](#); Zuniga-Castillo J et al 2004 *J Bacteriol* 186:7905.

ADCC (antibody-dependent cell cytotoxicity): Mediates some of the immune responses. ► [antibody](#), ► [immune system](#); Hinterberger-Fischer M, Hinterberger W 2001 *Expert Opin Biol Ther* 1:1029.

Addiction: A complex phenotype relative to the abuse of drugs, alcohol, smoking or habituation to other non-natural behavior. It is generally controlled by multiple genes, deeply influenced by several social conditions, and commonly associated with antisocial behavior. It is assumed that the long-term abuse of these substances causes molecular changes in the neuronal signaling. The adaptation may modify the autonomic somatic functions causing dependence and when the agent is withdrawn, result in withdrawal anomalies. The agent may alter the motivational control system resulting in craving. Chronic use of morphine upregulates components of the cAMP signal transduction pathway. In mice, with a deletion of the CREB α element the withdrawal symptoms were reduced indicating that CREB-dependent gene transcription is a factor of opiate dependence. The major receptor for opiates (morphine, heroine) is the trimeric G protein-linked μ . Long-term opiate use decreases the μ -opiate receptor signaling without reducing the number of receptors and leading to tolerance and dependence. In non-addicted individuals, the opiate receptor opens an outward rectifying K⁺ channel and reduces the phosphorylated state of a Na⁺ channel. In an addicted individual the K⁺ channel is shut off, however, and the G protein—adenylate cyclase activates a protein kinase (PKA) and the phosphorylated Na⁺ channel moves sodium inward the locus ceruleus, a pigmented structure at the floor of the brain. As a consequence, the cyclic AMP response element (CRE) binding proteins (CREB) stimulate the transcription of RNA required for adaptation to the addictive drug. The psychoactive effects of cocaine can be superseded in rats by active immunization using a cocaine conjugate, GNC-KLH (a hapten and keyhole limpet hemocyanin). Addictive agents usually raise the dopamine level in the nucleus accumbens of the brain. Recently the glutamate receptors gained attention for their role in addiction and for their chemical blocking for a cure. The glutamate receptor seems to control the Δ FosB transcription factor and enhances the sensitivity to cocaine. The genetic component of various addictions (alcohol, opiates, cocaine, etc.) may exceed 50%. The genetic bases of addiction are generally polygenic and may be studied by the methods of quantitative genetics although the specific genetic factors responsible are hard to identify and few genetic tools exist for the identification of the determination. Heritability of response to addictive agents is generally determined based on comparison of monozygotic and dizygotic twins. Heritability of addiction to smoking and alcohol abuse may exceed 0.5; heritability to opiates and cocaine is even higher. Serotonin, nicotinic cholinergic, dopamine, cannabinoid-like receptors, neuropeptides may affect responses to various drugs. Addiction may

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occur also in rats (Deroche-Gamonet V et al 2004 Science 305:1014; Vanderschuren LJMJ, Everitt BJ *ibid* p. 1017). ▶ion channels, ▶G protein, ▶cAMP, ▶adenylate cyclase, ▶CRE, ▶CREB, ▶behavioral genetics, ▶keyhole-limpet hemocyanin, ▶dopamine, ▶glutamate receptors, ▶neurotransmitters, ▶alcoholism, ▶smoking, ▶bulimia, ▶heritability, ▶twinning; Nestler EF, Landsman D 2001 Nature [Lond] 409:834; Goldman D et al 2005 Nature Rev Genet 6:521.

Addiction Module: Represents a prokaryotic system with resemblance to apoptosis in eukaryotes. The module includes the products of two genes: one is long lasting and toxic, the other is short lived and protects against the toxic effect. The “addiction” is a dependence on the antagonist of the toxin. This system is usually controlled by plasmid elements. In the *hok-sok* module of the R1 plasmid the *sok* gene product is an antisense RNA, subject to degradation by a nuclease. Homologs of this plasmid system have been found also in the main bacterial chromosome. Encoded by the bacterial *rel* operon the MazE antitoxin protein is subject to degradation by the *clpPA* serine protease. It protects from the toxic effects of MazF toxin protein. MazE-MazF are regulated by the level of ppGpp which itself is toxic to the cells. MazE-MazF expression is regulated also by 3',5'-bispyrophosphate, synthesized by the RelA protein under amino acid starvation. ▶apoptosis, ▶partitioning; Engelberg-Kulka H, Glaser G 1999 Annu Rev Microbiol 53:43.

Addison Disease (adrenocortical hypofunction, Xq28): An autosomal dominant defect of the kidneys cortical layer resulting in excess potassium and sodium in the urine, decreased levels of cortisol and hyperpigmentation of the skin. Some forms indicate autoimmune phenotype. ▶adrenoleukodystrophy, ▶pigmentation defects, ▶kidney diseases, ▶cortisol

Addison-Schilder Disease: An Xq28-chromosome-linked adrenocortical (kidney outer layer) atrophy and diffuse cerebral sclerosis (hardening). The cerebral lesions resemble the symptoms of multiple sclerosis. ▶multiple sclerosis

Addition Lines: Carry an extra chromosome(s) coming from another genome. ▶alien addition, ▶*Haynaldia villosa* for photomicrograph

Additive Effects: Genes' additive effects means that each allele contributes quantitatively to the phenotype of an individual that carries it, i.e., there is no dominance. ▶polygenic inheritance

Additive Genes: Each allele has a definite quantitative contribution to the phenotype without dominance within a locus and without epistasis between loci or overdominance between alleles. ▶additive variance,

▶quantitative genetics, ▶heritability, ▶epistasis, ▶overdominance

Additive Variance: Each allele contributes a special value (quantity) to the phenotype and there is no interallelic (overdominance) or interlocus (epistasis) effects on the variance. ▶genetic variance, ▶heritability, ▶QTL

Additivity of Genetic Maps: Ideally means that the distance between genes A–C is equal to the sum of the distance between A–B and B–C if the order of genes is A B C. To this generally valid rule exceptions exist because of genetic interference. ▶mapping genetic, ▶recombination frequency, ▶interference, ▶coincidence

Adducin: A membrane protein mediating the binding of spectrin to actin. ▶spectrin, ▶actin

Adduct: As a verb means to draw to the median plane or axial line. As a chemical it stands for the complex of two or more components such as the cyclobutane ring of pyrimidine dimers, benzo(a)pyrene-guanine, and other alkyl groups of mutagens added to nucleic acid bases. Lipid peroxidation generates various DNA adducts with mutagenic effects similar to that caused by exogenous carcinogens. This may be the cause by the “spontaneous” cases of carcinogenicity by high-fat diet. ▶pyridine dimers, ▶ethyl-methane sulfonate, ▶benzo(a)pyrene, ▶excision repair, ▶ABC excinuclease, ▶malondialdehyde, ▶pyrimidopurines

Adelphogamy: Sib-pollination of vegetatively propagated individual plants. ▶sibling

Adenine: A purine base in either DNA or RNA. purines.

Adenine Phosphoribosyltransferase (APRT, 16q24.3): Recessive deficiency of APRT may lead to dihydroxyadenine accumulation in the urine and kidney disease. APRT may repair cyclobutane pyrimidine dimers. ▶cyclobutane dimer

Adeno-Associated Virus (AAV): A simple, icosahedral, non-enveloped, 22 nm, non-pathogenic, single-stranded DNA (4,681 nucleotides) virus that infects a wide range of cell types in various species and integrates preferentially into human chromosomal site AAVS1 at 19q13.2-qter most frequently as an inverted repeat (←---|---→). Some forms such as episomal and multimeric circular AAV are known. Several serotypes exist. Its loading capacity is ~4.7 kb. It has only two internally situated genes, *rep* (replication) and *cap* (capsid) encoding 4 replication (Rep78, Rep68, Rep52, Rep40) and 3 viral coat proteins (VP1, VP2, VP3) using different promoters and alternative splicing. AAV has two ~145-nucleotide inverted terminal repeats (ITR), which

form double-strand structure. During replication, the ss-DNA is the template for the new strand. In vector plasmids carrying AAV its DNA is double-stranded (see Fig. A29).

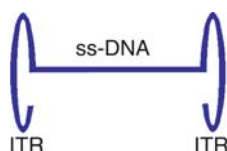


Figure A29. Adeno-associated virus

Cis-acting functions required for replication (*rrs*) and binding to the human chromosome site (Sp1, 19q13.3-qter), helicase, site-specific and strand-specific endonuclease activity, packaging, integration, excision, and initiator (*inr*) of transcription site for RNA are encoded within the ITR. AAV has been used as vector for gene therapy. The AAV vectors usually cannot carry more than 4.5 kb but because of the small size of the particles, they can penetrate easier small targets (e.g., skeletal muscles, neurons). The estimates of the frequency of integration of AAV vectors into chromosomal sites are not unanimous. Some vectors carry AAV concatamers, which have ~9 kb capacity. These vectors greatly benefit by the presence of adenovirus (AV) or herpes virus helper. In the presence of adenovirus helper, it may produce more than 100,000 particles per cell. AAV vectors transfect non-dividing cells or dividing cells and because of concatamer formation, they express transgenes for long periods and do not suffer immune rejection. The recombinant AAV molecule with deletions within the viral *rep* gene is called rAAV. The *rep* guides the integration into the host chromosome and facilitates non-homologous recombination. AAV vectors can target homologous mammalian chromosomal locations and alter ~1% of the cells without additional mutations. AAV may protect the cells against human melanoma or cervical carcinoma due to the product of the *rep* gene transcribed from the open reading frame beginning at map position of promoter p5. The *rep*-minus strains do not integrate to preferential sites. For infection, AAV requires a helper function provided by adenovirus or herpes virus. In the absence of a helper, AAV becomes latent but can be rescued. The AAV based vectors frequently used as a two-plasmid co-transfection system by relying on the complementary ITR-promoter-transgene and ITR-rep-cap packaging system. Unlike the adenoviral vector, AAV vectors remain in the cell. The host immune system usually does not react much to the AAV vectors beyond the initial stage of introduction. AAV vectors appear safe for the subjects and the environment (do not cause diseases) although in

some instances unexpected tumors and chromosomal defects were observed. Tumor formation in mouse occurred at the chromosome 12 integration site that corresponds to human chromosome 14 (Donsante A et al 2007 Science 317:477). AAV can be targeted to specific cells either by the use of bispecific antibodies on the capsid that recognize AAV and the target. The tropism can be engineered also by specific amino acid insertions into the capsid for recognition of specific cell receptors. Although generally no serious immunological reaction against AAV occurs, the immune system may neutralize the passenger DNA. In the latter cases, immunosuppressive treatment may be beneficial. AAV has great potentials in gene therapy for different hereditary conditions. ►gene therapy, ►adenoma, ►herpes, ►viral vectors, ►parvoviruses, ►autonomous parvovirus, ►concatamer; Russel DW, Kay MA 1999 Blood 94:864; Miller DG et al 2002 Nature Genet 30:147; Nakai H et al 2003 Nature Genet 34:297; McCarty DM et al 2004 Annu Rev Genet 38:819.

Adenocarcinoma: Cancer of glandular tissues.
►pancreatic adenocarcinoma

Adenoma: Usually benign gland-shape epithelial tumor. The deficit of E-cadherin-mediated cell adhesion is one of the control steps in the change from adenoma to carcinoma. ►endocrine neoplasia, ►carcinoma, ►cadherins; Sieber OM et al 2002 Proc Natl Acad Sci USA 99:2954.

Adenomatosis, Endocrine, Multiple (MEN): The autosomal dominant MEN I (human chromosome 11q13) pancreatic adenomas are prevalent, in MEN II pheochromocytoma and thyroid carcinoma (10q11) and in MEN III cancers of the nerve tissues are most common although the latter two conditions appear allelic in the pericentric region of human chromosome 10q. ►pheochromocytoma, ►SHC, ►adenoma, ►cancer

Adenomatous Polyposis Coli (APC): ►Gardner syndrome, ►FAP

Adenosine: Adenine with a ribose added (see Fig. A30).
►adenine, ►nucleoside

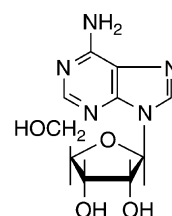


Figure A30. Adenosine

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Adenosine 3', 5' Cyclic Monophosphate (cAMP):

Formed from ATP by adenylate cyclase enzyme. It has important regulatory functions as “second messenger” for microbial and animal cells. ►cAMP, ►adenylate cyclase, ►G-proteins, ►signal transduction

Adenosine Deaminase (ADA): An enzyme that hydrolyzes adenosine monophosphate to inosine. Its deficiency causes severe immunodeficiency and the patient's lymphocytes are disabled to fight infections successfully. ADA is synthesized in the cells for the purpose of detoxification of excessive amounts of adenosine or its analogs; it inactivates 9-β-D-xylofuranosyl adenine, a DNA damaging chemical, and thus it can be used as a dominant selection agent in tissue culture. Its synthesis in the cells can be overproduced over ten thousand times by a strong inhibitor of ADA, 2'-deoxycytosine (dCF), and a transition-state analog for adenine nucleotide enzymes. It is encoded in human chromosome 20q13.11. RNA-specific adenosine deaminase (ADAR2, 21q22.3) is an editing enzyme. ►adenosine deaminase deficiency, ►SCID, ►severe combined immunodeficiency, ►mosaic, ►immunodeficiency, ►transition state, ►ADAR

Adenosine Deaminase Deficiency (ADA deficiency):

Also known as severe combined immunodeficiency disease (SCID). ADA deficiency may be treated with gene therapy or bone marrow transplantation or by enzyme replacement with polyethylene glycol adenosine deaminase (Peg-ADA). In case of the defect, deoxyadenosine (dAdo) or deoxyadenosine triphosphate reaches toxic levels. Into T lymphocytes isolated from the patients, retroviral vectors introduce the normally functional human ADA gene and the lymphocytes are injected into the afflicted children. Upon periodically renewed treatment, symptoms of the disease (chronic infections, diarrhea and muscle weakness) usually recede. Post-exercise cramping of the muscles may be caused by inadequate level of this enzyme. The ADA gene was located to human chromosome 20q13 area. ►adenosine deaminase, ►SCID, ►Lesch-Nyhan syndrome, ►gout, ►gene therapy, ►immunodeficiency, ►viral vectors, ►lymphocytes, ►deamination, ►dyschromatosis symmetrica hereditaria

Adenosine Diphosphate: ►ADP**Adenosine Monophosphate Deaminase (AMPD1,**

1p21-p13): Recessive deficiency of AMPD1 leads to cramps, myopathy and weakness after exercising. Most commonly, the enzyme in the skeletal muscles is affected and therefore it is called myoadenylate deaminase deficiency.

Adenosine Receptors: Mediate the activities of diverse cell types (neurons, platelets, lymphocytes, muscle cells) in response to adenosine released by the degradation of ATP. The four types of receptors are A₁, A_{2a}, A_{2b} and A₃. aggressiveness.

Adenovirus: A large mammalian (1.8×10^8 Da), icosahedral, (diameter about 80 nm) double-stranded DNA virus with ca. 36-kbp genetic material. The most commonly used serotypes for gene therapy are Ad2 and Ad5 although about 50 serotypes are known. The human adenovirus DNA has a 55-kDa protein covalently bond to both 5'-ends. The initiation of replication depends on a viral 80-kDa protein reacting with the first deoxycytidylic residue and its 3'-OH group serves as the starting point. The complementary DNA strand is a template. After replication, the 80-kDa protein is cleaved off but the 55-kDa protein stays on. The replication does not require the synthesis of Okazaki fragments because first, one of the strands is completed with the aid of the protein-dCTP primer, then the other strand is replicated. Replication can start at either end because of protein primer is used. Both strands of the DNA are transcribed into overlapping transcripts. The integrated viral DNA is generally smaller than the genome of adenoviruses. After lytic infection, a cell may release about 100,000 virus particles. Upon infection, it may produce a flu-type ailment, and can cause cancer upon integration into the genome. In humans, adenovirus is not carcinogenic and because it stays episomal it does not induce insertional mutation. The adenoviruses have broad host range and this makes them suitable for veterinary vaccine production. The adenovirus oncoprotein E1A induces progression of the cycle by binding to a protein complex p300/CBP. A histone acetylase (P/CAF) competes in this with E1A and inhibits its mitogenic activity. The main function of E1A is to disrupt the association between p300/CBP and the histone acetylase. The viral E1B gene encoded 55-kDa protein inactivates the p53 tumor suppressor gene and the cancerous proliferation begins. However, a mutant form of adenovirus (dl1520) that cannot express this 55 K protein can still replicate in cells that are defective in the p53 suppressor and consequently can lyse these defective cells. This finding offers a promise for the destruction of p53-deficient cancer cells by injection with dl1520 mutants. Normally wild type p53 (apoptosis) is a requisite for the productive infection (destruction of the cells) by wild type adenovirus. Adenoviruses have been used as vectors for genetic transformation after some regulatory sequences have been deleted and replaced. For the production of adenoviral vectors most commonly, cell line 293 is used.

This line carries the E1 viral gene in trans and thus enables replication of the vector that is deleted for it. Homologous recombination between the cell's chromosome and the vector should be avoided to prevent the formation of replication-competent adenovirus.

The maximal carrying capacity is about 6–8 kbp. Since adenovirus preferentially infects the respiratory tract, it may be used for somatic gene therapy of, for e.g., cystic fibrosis. It has also been used to transfer genes to skeletal muscles (see Fig. A31).



Figure A31. The general design of an adenoviral vector. ITR = inverted terminal repeat, Ψ = packaging signal, E1 is replaced by the transgene and E3 is deleted in the majority of vectors. The removal of E1 is important to prevent the infectivity of the viral DNA. For the lost E1 function the host cells may provide complementation in trans. Recombination, however, may give a chance for regeneration of replication competent virus.

The cell can take up adenovirus vector and its load DNA by a specific virus receptor, e.g., CAR1, and the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ surface integrins. In mice incubated in vitro with a Cre-expressing adenovirus vector, Cre-mediated recombination occurred at an efficiency of 49–76%, and the infected spermatogonial stem cells could reinitiate spermatogenesis after transplantation into seminiferous tubules of infertile recipient testes. No evidence of germ-line integration of adenovirus vector could be found in offspring but this possibility cannot be ruled out because there is no known mechanism that would prevent it (Takehashi M et al 2007 Proc Natl Acad Sci USA 104:2596). Usually the adenoviral vector, taken up by non-dividing or dividing cells, is not integrated into the human genome and thus does not lead to permanent genetic change and they have to be reapplied periodically (in days, weeks or months). The adenovirus proteins evoke rapid immune responses and that may be the cause of the short duration of the transformation effects. In addition, the current vectors may cause inflammation because of antivector cellular immunity. Immunosuppressive drugs (cyclosporin A, cyclophosphamide) may mitigate the immune response but may cause undesirable side effects.

The immunogenic property of the adenoviral vectors may eventually be exploited for immunological destruction of the targeted cancer cells. An advantage of this vector is that it can be used in very high titers (10^{11} to 10^{13} particles/mL). Adenovirus is not known to induce human cancer. Adenoviral vector-mediated interleukin-12 gene therapy seems to protect mice with metastatic colon carcinoma.

Construction of improved vectors is of major interest. *Gutless* or *fully deleted* adenoviral vectors are *helper-dependent* because most of the viral genome is removed to reduce the risk of adverse immune reaction and increase the duration of expression. ▶icosahedral, ▶Okazaki fragment, ▶replication, ▶cancer, ▶viral vectors, ▶CAR1, ▶titer, ▶gene therapy, ▶p53, ▶cystic fibrosis, ▶antivector cellular immunity, ▶adeno-associated virus, ▶tumor vaccination, ▶seroswitch vector, ▶targeting vector; Benihoud K et al 1999 Curr Opin Biotechnol 10:440; Frisch SM, Mymryk JS 2002 Nature Rev Mol Cell Biol 3:441.

Adenylylate: Salt of adenylic acid.

Adenylylate Cyclase (adenylyl cyclase): An integral membrane enzyme with an active site facing the cytosol, generating cAMP (cyclic AMP) from ATP and releases inorganic pyrophosphate (two phosphates). G_{sa} subunit-bound GTP activates this enzyme. The enzyme has a weak GTPase activity that eventually breaks the G_{sa} —GTP links and thus turns off the cyclase function. The activation of the cyclase function is initiated by the hormone epinephrine, which binds to a membrane receptor and activates the G_s proteins. cAMP itself is degraded by cyclic nucleotide phosphodiesterase. The cellular level of Ca^{2+} regulates oscillation of its level. The type I enzyme is stimulated by neurotransmitters which elevate the level of Ca^{2+} . The Type II enzyme requires stimulation by G_{as} in the presence of the $G_{\beta\gamma}$ subunits of the G protein. ▶adenosine 3',5'▶cyclic monophosphate, G_s , ▶G-protein, ▶GTP-ase, ▶GTPase activating protein, ▶cyclic AMP-dependent protein kinase, ▶animal hormones, ▶epinephrine, ▶calcium ion channel, ▶anthrax, ▶junction of cellular network; Jaiswal BS, Conti M 2001 J Biol Chem 276:31698; Onda T et al 2001 J Biol Chem 276:47785.

Adenylylate Kinase Deficiency (AK1): Dominant in human chromosome 9q34.1, it causes hemolytic problems. Several AKI alleles were named. Adenylylate kinases catalyze the reversible transfer of the γ -phosphate from ATP to AMP and regulate adenine nucleotide metabolism and intracellular ATP levels. By 2005, six AK enzymes have been characterized (Ren H et al 2005 Proc Natl Acad Sci USA 102:303). ▶hemolysis, ▶hemolytic diseases

Adenylyc Acid: It is a phosphorylated adenosine.

Adenylyl Cyclase: ▶adenylylate cyclase

Adenylosuccinase Deficiency (adenylosuccinate lyase, ADSL, 22q13.1): Normally the enzyme catalyzes the reaction: succinylaminoimidazole carboxamide ribotide → aminoimidazole carboxamide ribotide and

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the removal of fumarate from adenylosuccinate to yield adenosine monophosphate. Homozygosity for the recessive mutations may cause autism, mental and psychomotor retardations. ►autism

Adenylylation: Addition of adenine to an amino acid near the active site in a protein (by the enzyme adenylyl transferase); it may regulate the activity of the target.

ADEPT (antibody-directed prodrug therapy): A prodrug is supplied to an organism afflicted by cancer. The prodrug itself is not toxic until it is enzymatically activated. Care should be taken that the enzymes of the body would not convert the prodrug automatically into a toxin. An antibody, specific for the cancer, is conjugated with an activating enzyme. The conjugate seeks up the cancer cells and by generating locally high concentration of the toxin it is expected to kill the cancer cells. It would be desirable that the toxin would not diffuse from the tumor into normal cells. Enzymes of potential use with prodrug→toxin:

Pseudomonas carboxypeptidase/glutamic acid derivatives→benzoic acid mustards, *E. coli* β-lactamase/cephalosporin derivatives→nitrogen mustards, yeast cytosine deaminase/5-fluoro-cytosine→5-fluorouracil, almond β-glucosidase/amygdalin→hydrogen cyanide, etc. ►magic bullet, ►vascular targeting; Xu G, McLeod HL 2001 Clin Cancer Res 7:3314.

ADH (antidiuretic hormone): A short peptide (vasopressin). antidiuretic hormone.

ADH (alcohol dehydrogenase): An enzyme catalyzing the reversible reaction: acetaldehyde + NADH + H⁺ ⇌ ethanol + NAD⁺

The ADH subunits (α, β, γ) are encoded in human chromosome 4q21. ►adh⁻, ►acetaldehyde dehydrogenase, ►mutant isolation, ►ethanol, ►allyl alcohol

adh⁻: A mutant with a defective ADH enzyme. ►acrylaldehyde, ►mutation detection

Adhalin: ►muscular dystrophy

ADHD: ►attention-deficit hyperactivity

Adherence Reaction: The binding of molecules to the complement receptors of cell surface or agglutination of antibody and antigen complexes. ►antibody, ►complement, ►complement fixation

Adherens Junction: The cell surface where actin filaments attach. AJ is regulating cell adhesions, mediated by Rap1 GTPase. β-catenin, ►RAP1A, ►Knox, ►formin; AL, Brown NH 2002 Science 295:1285; Tepass U 2002 BioEssays 24:690.

Adherin: Chromosomal proteins that are similar in function to cohesin. ►sister chromatid cohesion

Adhesion: Sticking together, e.g., water molecules clinging to various surfaces. ►integrins, ►selectins, ►cadherins, ►plakoglobin, ►vinculin, ►talin, ►adherens junction

Adhesion Belt: Adherens belt connects neighboring cells. ►adherens junction

Adhesion Plaque (focal contact): The spot where a cell is anchored to the extracellular matrix by transmembrane proteins.

Adipocere (grave wax): Hydrolyzation product of body fats after death; its formation may help the preservation of DNA of the brain in some ancient animal/human remains. ►ancient DNA

Adipocyte: Fat storage cell; it is used as a depository of excess caloric intake or reserve when expenditure exceeds intake of calories. The white adipose stores energy as triglycerides, the brown adipose tissue is involved in thermogenesis (see Fig. A32). Membrane-associated metalloproteinase, MT1-MMP modulates pericellular collagenase and subsequently the growth of white adipose tissue cells (Chun T-H et al 2006 Cell 125:577). Adipocyte differentiation is regulated by the CCAAT/enhancer-binding proteins, adipocyte differentiation determinant (ADD1)/sterol response element-binding protein (SREBP1), and the peroxisome proliferator-activated receptors (PPAR). Sequential phosphorylation of CCAAT enhancer-binding protein by MAPK and GSK3β in vitro leads to DNA-binding function and clonal expansion of adipocytes (Tang Q-Q et al 2005 Proc Natl Acad Sci USA 102:9766). In addition retinoic acid, vitamin D₃, thyroid hormone receptors are involved. The retinoic receptors (RXR) are indispensable for the viability of mice. Adipocytes secrete leptin, adiponectin, resistin, TNF-α IL-6 and visfatin (Fukuhara A et al 2005 Science 307:426). ►retinoic acid, ►PPAR, ►vitamin D, ►animal hormones, obesity, ►resistin, ►brown fat, ►mesenchyma, ►MAPK, ►GSK3β; Gregoire FM et al 1998 Physiological Revs 78:783; Rosen ED, Spiegelman BM 2000 Annu Rev Cell Dev Biol 16:145; Zhang J-W et al 2004 Proc Natl Acad Sci USA 101:43; regulation of energy balance by adipocytes; Rosen ED, Spiegelman BM 2006 Nature [Lond] 444:847.

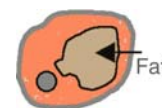


Figure A32. Adipocyte

Adiponectin: A cytokine produced by adipocytes in response to metabolic or extracellular signals. It

lowers blood glucose level and reduces the level of triglycerides in the muscles and the production of fat. It may be exploited for treatment of insulin-resistant diabetes. ▶cytokines, ▶triglyceride, diabetes, ▶osmotin, ▶resistin, ▶obesity; Yamauchi T et al 2001 *Nature Med* 7:887; Berg AH et al *ibid.* p. 947.

Adipose: Related to fat, e.g., adipose tissue = fat tissue.

Adjacent Disjunction: Neighboring members of translocation rings or chains move to the same pole; adjacent-1 when centromeres are non-homologous, adjacent-2 when centromeres are homologous (non-disjunctional) at the poles. ▶translocation chromosomal

Adjacent Distribution: ▶adjacent disjunction

Adjuvant, Immunological: If the immune response to an antigen is unsatisfactory because of the small amount present, the immune reaction may be enhanced by protecting the antigen from degradation and promoting slow release and increase its uptake by macrophages. For this purpose mineral oils, alum (a hydrated aluminium oxide), charcoal, Freund adjuvant, specific nucleotide sequences, CD154, etc. can be used. ▶immune response, ▶immunization genetic, ▶antigen, ▶Freund adjuvant, ▶vaccine, ▶CD154

Ad Libitum (ad lib.): As much as wanted; for e.g., feeding animals at level they wish to eat.

ADM (automated digital microscopy): ▶ACIS, ▶FAST, ▶microscopy

Admissibility Criteria: Legal concepts concerning the appropriateness whether a certain type of evidence, scientific method or logical arguments would be helpful for the jury to determine the facts in the court. Regarding scientific evidence, the judge decides, whether the methodology and techniques have been validated by peer reviews and publication in respected publications, whether the techniques have an acceptable error rate, and the methodology is generally acceptable by the scientific community (*Daubert factors*). The scientific methods generally improve with time and so the admissibility criteria is also subject to change within the above guiding principles. ▶forensic genetics

Admixture in Populations: May take place when two potentially interbreeding populations share a habitat for a period. When the frequency of about 50 or more markers is analyzed, statistical information may be derived on the extent and time of the admixture (admixture mapping: Patterson N et al 2004 *Am J Hum Genet* 74:979). Availability of SNP markers may permit association studies between disease genes and SNPs even when this approach may not yield much information on the molecular associations.

Using nine autosomal markers (and mtDNA), ten populations of African descent were analyzed by sampling different regions of the U.S. for European admixture. In Jamaica 6.8% and in New Orleans 22.5% appeared introgressive. The gene flow from Europeans was sex-biased, the male contribution was substantially higher than that by females (Parra EJ et al 1998 *Am J Hum Genet* 63:1839). ▶introgression, ▶linkage disequilibrium; Chikhi L et al 2001 *Genetics* 158:1347; Zhu X et al 2005 *Nature Genet* 37:177.

Admixture Mapping: Chromosomal blocks can remain intact in linkage disequilibrium after admixture of different populations. These blocks eventually decay because of recombination yet, based on the linkage disequilibrium, gene loci can be mapped. (Chakraborty R, Weiss KM 1988 *Proc Natl Acad Sci USA* 85:9119)

aDNA: ancient DNA. ▶ancient DNA

Adnfile: ▶epilepsy

AdoMet: S-adenosyl-L-methionine (current abbreviation is SAM) is a methyl donor for the enzymes guanosine 7-methyl transferase and the 2'-O-methyl transferase enzymes in the cap of pre-mRNAs and for other methylation reactions. ▶SAM, ▶cap, ▶methylase, ▶methylation of DNA, ▶methylation of RNA, homocystinuria, ▶methionine adenosyl transferase; LeGros L et al 2001 *J Biol Chem* 276:24918.

Adopted Children: Frequently used in human genetics to determine the relative effects of genes and environment. These studies are sometimes hampered, however, because either the families do not have biological children or the biological parents of the adopted children are not available for examination. According to civil law, adopted children may lose any legal ties to and identity with the natural parents. This loss of identity may carry some genetic caveats because of chances of inbreeding due to lack of information about descent. These problems are similar to the ones encountered by artificial insemination using anonymous sperm donors. ▶twinning, ▶artificial insemination

Adoptive Cellular Therapy (adoptive transfer): Infusion of immune effector cells (NK cells, macrophages, $\gamma\delta$ T cells, $\alpha\beta$ T cells, B cells, etc.) for the treatment or prevention of disease (lymphoma, leukemia, myeloma). Although this may appear an attractive alternative to chemotherapy or radiation, the allogeneic cells may induce graft-versus-host disease (immune rejection). To avoid these complications herpes simplex virus thymidine kinase gene (HStk) may be targeted to the malignant cells by a Moloney murine leukemia retroviral vector. This vector selectively seeks

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up dividing cells. Since cancer cells divide more frequently than normal cells, the vector does not usually hit normal cells. The cells are then infused by ganciclovir, which when metabolized to ganciclovir triphosphate it is incorporated into DNA and RNA resulting in selective termination of replication in the HStk⁺ cells by this suicide technique. More differentiated tumor-specific CD8⁺ T cells were less effective than naïve ones for in vivo tumor treatment. The possible causes may be down-regulation of lymphoid homing and co-stimulatory molecules, inability to produce IL-2 and access homeostatic cytokines and entry into a pro-apoptotic and senescent state (Gattinoni L et al. 2005 J Clin Invest 115:1616). ▶cell therapy, ▶gene therapy, ▶ganciclovir, ▶TK, ▶Moloney mouse leukemia oncogene, ▶viral vectors, ▶suicide vector, ▶stem cells, ▶diabetes; Link CJ et al 2000 Stem Cells 18:220.

ADP: Adenosine 5'-diphosphate, a phosphate group acceptor in various cellular processes. It is produced by hydrolysis of ATP; it can also regenerate ATP by oxidative phosphorylation.

ADP-Ribosylation Factor: ▶ARF

Adr: A positive regulator protein of transcription.

Adrenal: Adjacent or pertinent to the kidney.

Adrenal Hyperplasia, Congenital (CAH): Occurs in both X-linked and autosomal forms and apparently controlled by several loci. Cortisol deficiency is involved. The X-linked form is attributed to gonadotropin deficiency. The steroid hormone overproduction indicates a defect in steroid 21-hydroxylase, encoded within the boundary of the HLA complex in human chromosome 6p21.3. The affected female babies are masculinized. Masculinization is preventable by the administration of dexamethasone but side effects may occur. It may be associated with Addison disease (hypotension, anorexia, weakness and pigmentation). One form of the disease is accompanied by difficulties in salt retention in the newborns. The prevalence is about 7×10^{-5} . The 17- α -hydroxylase deficiency is encoded at 10q24.3 and it involves an excessive amount of corticosterones and hypertension and hypokalemic alkalosis (increase of bases [e.g., K⁺] yet lower pH). An autosomal form in chromosome 8q21 is deficient in 11- β -hydroxylase and/or corticosteroid methyl oxidase II (HSD11B1, 1p13.1) occurs at a frequency of 1×10^{-5} . Masculinization may be caused by several other genetic anomalies and by various medications administered to the mother or maternal androgen-producing tumors. Prenatal diagnosis may use allele-specific PCR on DNA from chorionic villi. ▶HLA, ▶hermaphroditism, ▶genital anomaly syndromes, ▶adrenal hypoplasia, ▶Addison disease,

▶STAR, ▶dexamethasone, ▶PCR, ▶chorionic villi, ▶congenital adrenal hyperplasia

Adrenal Hypoplasia, Congenital (AHC): Characterized by abnormal underdevelopment (hypoplasia) of the genitalia and the gonads, insufficient function of the kidneys, hypoglycemia (reduced blood sugar), seizures, etc. Several forms of the disease (hypoadrenocorticism, polyglandular autoimmune syndrome, Addison disease) were reported with autosomal recessive inheritance. The X-chromosome-linked DAX1/AHC (Xp21.3-p21.2) locus encodes a dominant negative regulator of transcription, a nuclear hormone receptor protein with a DNA-binding domain. The DAX-1 transcription is mediated by the retinoic acid receptor. AHC may modify male determination by SRY and it seems to regulate also the steroidogenic factor Sf-1 but it does not affect ovarian development. ▶hypogonadism, ▶Kallmann syndrome, ▶adrenal hyperplasia, ▶epilepsy, ▶retinoic acid, ▶RAR, ▶dominant negative, ▶transcriptional activator, ▶SRY, ▶Sf-1, ▶Addison disease

Adrenaline: ▶epinephrine, ▶animal hormones

Adrenergic Receptors: Occur in the forms of α_1 , α_2 , β_1 , β_2 distinguished on the basis of their responses to agonists and antagonists and tissue-specificity. They all respond to the adrenal hormones, epinephrine and norepinephrine. ▶epinephrine, ▶membrane proteins, ▶receptors, ▶agonist, ▶antagonist, ▶arrestin, ▶hypotension, ▶GRK2

Adrenocortical: Pertains to the cortex (the outer layer) of the kidney.

Adrenocorticotropin (ACTH): A pituitary peptide hormone that controls the secretion of steroid hormones of the kidney in response to cAMP. ACTH unresponsiveness (familial glucocorticoid deficiency) is recessive autosomal defect of resistance to ACTH, causing hypoglycemia and childhood infections. Mutations in ACTH receptor (melanocortin 2 receptor) cause familial glucocorticoid deficiency (FGD 2) in chromosome 21q22.1. The mutation in FGD 2 involves the melanocortin 2 receptor accessory protein (Metherell LA et al 2005 Nature Genet 37:166). ▶cAMP, ▶glucocorticoids, ▶cortisol, ▶ACTH, ▶POMC, ▶melanocortin

Adrenodoxin: An electron carrier iron-sulphur protein in the mitochondria of the kidney cortex and assist cholesterol biosynthesis. ▶cerebral cholesterinosis

Adrenoleukodystrophy (ALD, Addison disease, Xq28): The X-linked neonatal form is a defect in peroxisome assembly. The disease is associated with very long chain fatty acid (VLCFA) acyl coenzyme A synthase

defects. Neural degeneration and blindness are the consequences of the disease. Autosomal forms encoding different peroxins and peroxin receptors are at 2p15, 12p13.3, 7q21-q22. ▶microbodies, ▶Zellweger syndrome, ▶Refsum disease, ▶peroxins

Adrenomedullin: A 22-amino acid vasodilator, a calcitonin-related peptide. In its absence hydrops fetalis may develop. ▶hydrops fetalis

Adriamycin: ▶doxorubicin

Adrogenital Syndrome: A complex genetic disorder based on anomalies of steroid biosynthesis and adrenal hyperplasia. Gene frequencies vary a great deal in different populations from 0.026 of Alaskan Eskimos to 0.004 in Maryland, USA. ▶adrenal hyperplasia, ▶allelic frequency, ▶steroid hormones

Adsorption: The tendency of molecules to adhere to a surface (different from absorption that is uptake through a membrane).

Adsorption Chromatography: ▶column chromatography, ▶thin layer chromatography

Adsorptive Endocytosis: ▶receptor-mediated endocytosis

Advantage of Heterozygotes: Indicates that fitness (the reproductive value) of the heterozygotes exceeds that of both types of homozygotes in a population and this may lead to balanced polymorphism. ▶balanced polymorphism, ▶polymorphism, ▶fitness

Advantageous Mutations: Favored by a particular environment and they are expected to propagate under steady-state conditions by a rate per generation: $v = \sigma\sqrt{2s}$ where σ is the standard deviation caused by diffusion (migration) and s = selective advantage in the absence of dominance. E.g., if $\sigma = 10$ km, and $s = 0.02$ then the advance per generation in kilometers will be $10\sqrt{2 \times 0.02} = 2$ then it would take 250 generations to advance 500 km. (▶mutation, ▶mutation beneficial, ▶migration, ▶selection coefficient; Cavalli-Sforza LL, Bodmer WF 1971 The Genetics Of Human Populations, Freeman, San Francisco, California.

Adventitia: The outer coating of organs by loose connective tissues composed mainly of fibrillin and elastin.

Adventive Embryos: Adventive Embryos develop from the diploid tissues of the plant nucellus (without fertilization); they occur commonly in citrus. ▶apomixis, ▶nucellus

AE Genes: Annotated expressed genes. ▶annotation, ▶ANE genes, ▶NAE genes

Aecidiospore: A dikaryon of plant rust fungi formed through a sexual process that did not involve nuclear

fusion; the aecidiospores are products of the aecidium, a group of sporangia. ▶aecidium, ▶dikaryon, ▶sporangium, ▶fungal life cycle

Aecidium or aecium: A fruiting structure of fungi (Basidiomycetes-Uredinales) such as *Puccinia graminis tritici*. Aecidia are formed only on the intermediate host, barberry, but the spores infect only wheat.

Aedes aegypti: The mosquito, which transmits yellow fever and dengue fever viruses. (See Rai KS, Black WC 1999 Adv Genet 41:1). The draft sequence of its genome has been determined as ~1376 million base pairs and it is about 5 times the size of the genome of the malaria vector *Anopheles gambiae*. Nearly 50% of the *Ae. aegypti* genome consists of transposable elements (Nene V et al 2007 Science 316:1718). ▶Anopheles mosquito, ▶malaria

Aegilops caudata: A diploid representative of the *Triticum* genus ($2n = 14$) carrying the 7-chromosome C genome (current name *Triticum dichasians*). *Aegilops cylindrica*: an allotetraploid of the wheat genus containing the CD genomes (C from *T. dichasians* and D from *T. tauschii*). Current name *Triticum cylindricum*. *Aegilops squarrosa*: *Triticum tauschii* by current name, is a diploid species in the wheat genus with the D genome (see Fig. A33).



Figure A33. Glume of *T. peregrinum*. (Courtesy of Drs. Gordon Kimber and Moshe Feldman)

Aegilops umbellulata, by current name *Triticum umbellulatum*, a diploid species of the wheat genus with the C^u genome. *Aegilops variabilis*, currently *Triticum peregrinum*, a species of the wheat genus; occurs in nature both as tetraploid (DM) and hexaploid (DDM) genomic constitution. ▶*Triticum*

Aegricorpus: A genetic-physiological complex determined by the host-pathogen interaction; the phenotype of the disease in plants. ▶host-pathogen relations, ▶Flor's model

Aequorin (GFP): Luminescent protein (green fluorescent protein of 238 amino acids) from jellyfish (*Aequorea victoria*); its activation is dependent on the level of the available Ca²⁺ and on this basis minute quantities and differences in this ion can be measured

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by optical means within the range of 0.5–10 mM. This may be of major importance because calcium may play regulatory functions in all eukaryotic cells. The chromophore results from the cyclization and oxidation of the Ser⁶⁵ (Thr⁶⁵)Tyr⁶⁶ Gly⁶⁷ amino acid sequence in the central helix of the 11-stranded β barrel. Aequorin has also the advantage that is non-invasive and non-destructive label in various organisms. Its excitation peaks are at 395 and 475 nm, and the emission peak of the pure GFP is at 470 nm. Mutant proteins with higher absorption peaks and different colors (red, yellow) exist. By the use of fluorescence resonance energy transfer (FRET), linking GFP reversibly to peptide spacers result in conformational changes and altered light emission (color). GFP is sensitive to pH, temperature, and prior illumination. Excitation by 488 nm light increases fluorescence 100 folds and remains stable for days (Patterson GH, Lippincott-Schwartz J 2002, Science 297:1873). The gene has been cloned and sequenced and has been widely used in animals and plants, in various modified forms, as a reporter gene. GFP is a strong immunogen. ►calmodulin, ►Renilla GFP, ►BFP, ►EGFP, ►FRET, ►drFP583, ►barrel; Methods in Enzymology, vol 302, 1999; Tsien RY 1998 Annu Rev Biochem 67:509; Labas YA et al 2002 Proc Natl Acad Sci USA 99:4256; van Roessel P, Brand AH 2002 Nature Cell Biol 4:E15; <http://www.conncoll.edu/ccacad/zimmer/GFP-ww/GFP-1.htm>.

AER: Apical ectodermal ridge.

Aerobe: An organism that uses oxygen as the terminal electron acceptor in respiration. ►electron acceptor, ►respiration

Aerobic: A reaction (or organism) requires or takes place in the presence of oxygen.

AF (activation function protein): Activates and recruits co-activators of gene expression.

a/ α -Factors: ►mating type determination in yeast

Affected Individual: Expresses a particular (disease) trait.

Affected-Relative-Pair Method: Similar to ASP, but other relative pairs are used.

Affected-Sib-Pair Method: (ASP): A non-parametric method for linkage analysis of susceptibility genes. For this purpose the risk ratio (λ_s) is determined, that is the risk of a sib of an affected proband compared to the average prevalence in the population. For e.g., diabetes has a prevalence of 0.004 in the general population but its incidence among sibs of affected individuals is 0.06, hence $\lambda_s = 0.06/0.004 = 15$. This λ_s is for all loci responsible for the phenotype. The

larger λ_s the higher is the genetic contribution. It is also affected by the interaction (can be multiplicative or additive) of the various factors contributing to the phenotype. The strength of the proof for linkage depends on the so-called *maximal lod score* (MLS) symbolized by T and means the log odds in favor of linkage. Usually, the estimation is carried out in steps by selecting at each step linkage with markers increasing from $T > 1.0$. Statistically valid linkage is expected when the T score reaches or exceeds 3. The T value may also increase by the use of larger populations. Recombination decreases MLS and the use of multiple loci increases the estimate. Another advantage of this approach is that both recessive and dominant alleles can be studied. It is applicable also for quantitative traits. This procedure may not necessarily be applicable only to sibs but cousins or other close relatives (uncles, aunts) may also be included. ►recombination, ►frequency, ►maximum likelihood method applied to recombination, ►lod score, ►non-parametric tests, ►allele sharing, ►GSMA; Dupuis J, Van Eerdewegh P 2000 Am J Hum Genet 67:462.

Affective Disorders: Psychological illnesses, psychoses. manic depression, ►autism, ►hyperactivity [ADHD], ►Tourette's syndrome, ►neurodegenerative diseases, ►bipolar mood, ►unipolar depression, ►schizophrenia, ►paranoia, ►obsessive-compulsive behavior, ►addiction; Evans KL et al 2001 Trends Genet 17:35.

Afferent: Conducting or transferring toward the middle.

Affibody: Engineered binding protein using the 58 amino acid Z domain of *Staphylococcus aureus* Protein A (SPA). SPA strongly binds the Fc domain of immunoglobulins. ►antibody, ►receptin; Wahlberg E et al 2003 Proc Natl Acad Sci USA 100:3185.

Affine Gap Cost: Expresses the “penalty” for gaps in a sequence alignment also according to the length of a gap. ►genome projects, ►contig

Affinity (Michie D, Wallace ME 1953 Nature [Lond] 171: 26): Unlinked genes segregate to the same gamete more frequently (quasi-linkage, Robinson, R. 1971) or less frequently (reverse linkage) than expected on the basis of randomness (Bailey NTJ 1961 Introduction to the mathematical theory of genetic linkage, Oxford, Clarendon Press, England). (►translocation chromosomal) In immunogenetics: the intensity of interaction between a particular antigen receptor and its epitope. ►epitope

Affinity Capture: ►acesims

Affinity Chromatography: Polyadenylated mRNA can be separated from other RNAs by adsorption on oligo T (thymine) cellulose or sepharose columns by virtue of the complementarity of the A and T bases. Similar

procedures are used for the purification of antibodies on immobilized antigen media (antibody purification) and DNA-binding proteins can be isolated and enriched by a factor of 10^4 with the aid of affinity chromatography. ►gel retardation assay, ►cDNA library screening, ►immunoprecipitation

Affinity Labeling: Most commonly a photo-affinity hapten is used (i.e., one that is activated only upon illumination). The affinity label is bound to the antigen-binding site amino acids of the antibody and thus reveals the site on the antibody where the attachment is taking place. ►hapten, ►antigen, ►antibody

Affinity Maturation: Selection of cells with high affinity for the antigen as clonal selection progresses. It takes place by accumulation of mutations in the *germinal center* of a lymphoid follicle in the paracortex of a lymphoid node and combinatorial assembly of the variable, joining and diversity sequences of the immunoglobulin genes. These alterations take place in response to the antigens arriving there through small capillary veins on the surface of the antigen-presenting cells and helper T cells. Immunoglobulin G (IgG) usually responds well after the second immunization. Affinity maturation is also a process for the selection of memory cells. TRAF and CD40 regulate the affinity maturation. ►clonal selection, ►antibody, ►antigen-presenting cell, ►immune response, ►repertoire shift, ►immunoglobulins, ►hapten, ►memory immunological, ►lymphoid organ, ►TRAF, ►CD40, ►vaccine; Ahonen CL et al 2002 Nature Immunol 3:451; Meffre E et al 2001 J Exp Med 194:375.

Affinity Purification: Required unless the antibody reacts with more than one antigen. If this is not the case, an affinity chromatography column is prepared by using pure antigen. Alternatively, monoclonal antibody must be used or the immunoglobulin library must be carefully analyzed for true or false positive immune reactions. ►antibody, ►antigen, ►monoclonal antibody, ►TAP

Affinity Tag: A short peptide or protein domain is fused to all members of a set of proteins. The tag facilitates the selective binding of these proteins to specific resins and thereby isolation, purification and elution under conditions that retain their activity (Nilsson J et al 1997 Protein Exp Purif 11:1).

Affinity-Directed Mass Spectrometry: Detects interaction between proteins, receptors-ligands, proteins-nucleotides, etc. ►mass spectrum, ►TAP

AFI: amaurotic familial idiocy, now called Tay-Sachs disease (TSD). ►Tay-Sachs disease

Afibrinogenemia: 4q28 recessive deficiency of fibrinogen (blood coagulation factor I). The afflicted individuals bleed very heavily after injury. Periodic blood accumulation under the skin (ecchymosis), nose bleeding (epistaxes), bloody tumors (hematomas), bloody cough (hemoptysis) or stomach-intestinal or genitourinary bleeding occur. Characteristically, for longer periods no symptoms appear. Therapy is intravenous injection of concentrated human fibrinogen. ►antihemophilic factors, ►hemophilia, ►dysfibrinogenemia, ►fibrin-stabilizing factor

Aflatoxins: Group of heterocyclic mycotoxins produced under appropriate conditions by the *Aspergillus flavus* and *Aspergillus parasiticus* fungi (see Fig. A34). The aflatoxins are extremely carcinogenic because they affect DNA synthesis. The LD₅₀ of aflatoxins orally administered to monkeys may be as low as (1750) µg per kg. Aflatoxin may be a contaminant on grains, peanuts, dry chili pepper, and on many other material humans and animals eat or are exposed to. Aflatoxins frequently cause mutations in *p53* tumor suppressant at codon 249 (AGG→AGT) resulting in hepatocarcinomas. The 8,9-oxide of aflatoxin B forms a mutagenic adduct in the DNA at N⁷-guanine. ►environmental mutagens, ►p53, ►toxins, ►mycotoxins, ►adduct; Smela ME et al 2001 Carcinogenesis 22:535; Cary JW et al 2002 Biochim Biophys Acta 1576:316.

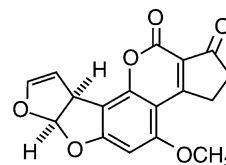


Figure A34. Aflatoxin

AFLP (anonymous fragment length polymorphism, amplified fragment length polymorphism): DNA fingerprinting technique involving restriction enzyme digestion and amplification of special fragments by PCR. It can be used for mapping genes or for the estimation of nucleotide diversity in populations. ►DNA fingerprinting, ►PCR, ►restriction enzymes, ►anonymous DNA segment, ►VNTR; Vos PR et al 1995 Nucleic Acids Res 23:4407; Saunders JA et al Crop Sci 2001 41:1596; Breyne P et al 2002 Proc Natl Acad Sci USA 99:14825.

African Green Monkey (*Cercopithecus aethiops*): Kidney cells are the best laboratory host for the propagation of SV40 (Simian virus 40). ►SV40, ►cos, ►Cercopithecidae

AFS: ►affected-sib-pair method

After Morning Pill: ►hormone receptors [RU-486]

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Agameon: A species without sexual reproduction.

Agamic: A species reproducing asexually (without gametes).

Agammaglobulinemia: Occurs as an X-chromosomal (congenital) and autosomal defect in the synthesis of γ -globulin, a component of the heavy chain of antibodies. The X-chromosome-linked (Xq21.33) is frequently called Bruton's agammaglobulinemia (XLA). The protein responsible is tyrosine kinase of 659 amino acids, encoded by 19 exons. The manifestation of XLA may differ in different families, indicating the involvement of several genes. It is conceivable that the defect is caused by rearrangement of the genes involved. Some of the individuals have truncated V regions of the antibody. In the afflicted persons the IgG and IgM content is generally no more than 1% of the normal. The absence of plasma cells from the lymph nodes, spleen, intestine and bone marrow is also a basic defect. The patients are very susceptible to pyogenic infectious bacteria (staphylococci, pneumococci, streptococci, and *Hemophilus influenzae*). Pus-forming inflammation of the sinuses, pneumonia, meningitis (inflammation of the brain), furunculosis (boils) are common but can be prevented by the use of antibiotics or raising the γ -globulin levels by regular injections. Without treatment, these infections may become fatal. The afflicted children are not more susceptible to viral, enterococcal, gram-negative bacteria, protozoan or the majority of fungal infections. Another X-chromosome linked or autosomal agammaglobulinemia causes susceptibility to bacterial, fungal and viral infections and leukemia. This is generally accompanied by lymphopenia (decrease of lymphocytes in the blood). This disease is generally detected after the discontinuation of breast-feeding of the babies or near the end of the first year of life. Agammaglobulinemia may occur also as an acquired disorder with onset at different ages, generally as a follow-up to other diseases. The prevalence is about 0.5 to 1×10^{-5} . ▶[gammaglobulin](#), ▶[immunoglobulins](#), ▶[immune system](#), ▶[antibody](#), ▶[hypogammaglobulinemia/common variable immunodeficiency](#), ▶[immunodeficiencies](#), ▶[achondroplasia](#), ▶[cancer](#), ▶[BTK](#)

Agamospecies: Reproduces by non-sexual means, e.g., parthenogenesis, apomixia. ▶[species](#), ▶[parthenogenesis](#), ▶[apomixia](#), ▶[asexual reproduction](#)

Agamospermy: Seed production without fertilization, ▶[apomixis](#), ▶[parthenogenesis](#), ▶[diplospory](#), ▶[apospory](#), ▶[adventitious embryos](#), ▶[apomixis](#)

Aganglionosis: Congenital lack of intestinal ganglions. ▶[Hirschsprung disease](#)

Agar: Gelling agent produced from marine algae with various degrees of purification (bacteriological agar,

noble agar) and used for microbial and plant cell culture media. ▶[gellan gum](#), ▶[agarose](#)

Agarose: A purified linear galactan hydrocolloid isolated from marine algae. In the crude form, it is generally contaminated with salts and other substances, polysaccharides, proteins. Some commercial products are highly purified. It is used for electrophoretic separation of oligo and polynucleotides from 0.1- to 60-kb range, depending on the concentration of this matrix. The higher concentration (2%) separates the smallest molecules whereas the lowest concentration (0.3%) permits the separation of the largest fragments. 0.9–1.2% are the most commonly used concentration ranges separating 0.4- to 7-kb fragments. Contaminations of the agarose may interfere with further enzymatic handling of the eluted DNA. ▶[electrophoresis](#), ▶[gel electrophoresis](#)

Agave (sisal): Basic chromosome number $x = 30$ and the various plant species may be diploid, triploid or pentaploid. The plant has been used for medicinal purposes as laxative; and its juice may cause abortion.

Advanced-glycation end product (AGE): A sugar-derived carbonyl group added to a free amine that forms an adduct after rearrangement producing AGEs. Age may cross-link amino groups in macromolecules and thus may promote aging, accelerate diabetes and may participate in other reactions. The cross-links may be broken by *N*-phenacylthiazolium bromide and may have therapeutic application. ▶[Alzheimer disease](#), ▶[aging](#), ▶[diabetes](#), ▶[adduct](#); Pushkarsky T et al 1997 Mol Med 3:740.

Age: The time since the birth of an individual. Prenatal age is more difficult to determine. Ultrasonic measurements are frequently compared with tables obtained by empirical data.

Age and Mutation in Human Populations: Expressed by the formula $\mu_t = \alpha t + \mu_0$ where mutation rate at a given time is μ_t , α is the mutation rate per cell divisions and μ_0 the initial frequency of mutation. It is expected that mutation rate increases as the number of cell divisions increases in the spermatogonia and oogonia. The available data indicate that chondrodystrophy (achondroplasia, a dominant dwarfness) and acrocephalosyndactyly (Apert's syndrome, pointed top of the head and syndactyly [webbing in between or attachment of the fingers and toes]) increases at birth by about 2–4 fold with paternal age from 25 to 45 years. Other dominant mutations show similar tendencies but with much less clear differences. The human eggs may be different because new egg cells are not formed in the female babies after birth; the oogenesis is almost complete in the newborn. Nevertheless, some age differences are still expected.

Chromosomal aberrations (trisomy) in the eggs may increase, however, from 1/2300 at age 20 to 1/46 after 45, probably because of the prolonged meiotic dictyotene stage (diakinesis). Some of the eggs complete meiosis before each ovulation, a period extending over 30–40 years. Trisomy in sperm is much less common, partly because it is the product of new divisions, partly because the disomic sperm may be at a disadvantage in competition for fertilization. A normal human ejaculate may contain 25–40 million sperm cells. The increase of mitochondrial mutation rate by aging is equivocal. Accumulation of mutations by aging is organ-specific in mice. ▶mutation rate, ▶gonads, ▶Apert syndrome, ▶syndactyly, ▶gametogenesis, ▶trisomy, ▶longevity; Dollé MET et al 2002 Nucleic Acids Res 30:545.

Age Correlation between Mates: Much higher in consanguineous marriages than in unrelated mates. On an average, age correlation makes first-cousin marriages about twice, second cousin marriages about 1.7 times and third cousin marriages about 1.4 times as frequent as if there would be no correlation between the ages at marriage. Since some of the human hereditary diseases have late onset, the greater the age at marriage may reduce the reproduction of genes with late manifestation also the afflicted persons may not marry or chose not to have children if they marry. ▶consanguinity

Age of Onset of Disease: The probability can be calculated: $(1 - \varphi_1)(1 - \varphi_2) \dots (1 - \varphi_{x-1})$ where φ_x = the probability of onset between ages x and $x + 1$ the probability of surviving to age x before onset is $l_x = (1 - q_1)(1 - q_2) \dots (1 - q_{x-1})$ where q_x = the probability of dying at age x before the onset of the condition. ▶aging

Age of Parents and Secondary Sex Ratio: Slightly decreasing from 0.517 to 0.516 at parental age group 15–19 to 0.512–0.511 at parental age 45–49. Based on very large samples examined, the age gap between parents does not affect significantly the sex ratio. ▶sex ratio

Age-Specific Birth and Death Rates: The probability that an individual of a certain age dies (or gives birth) within the following year is determined by population projection matrices. The numbers of giving birth and death rates in a time interval can be determined by 1-B/N for birth per women extracted from available census figures. One such study in (1966) found that among women in the age group of 15–30 and 30–45 the mean number of children born per women was 1.37 and 0.465, respectively. The studies found that the average survival of age groups 0–15, 15–30 and 30–45 were 0.992, 0.988, and 0.964, respectively. Thus, if one takes a sample of 30 woman of age group

0–15 they will give birth to $30 \times 1.37 = 41.1$ children. In the age group 30–45, dealing with 20 human females, the prediction will be $20 \times 0.465 = 9.3$, etc. Similarly, the survivors expected in the age group 0–15 will be $40 \times 0.992 = 39.68$, in the age group 15–30 the expectation is $30 \times 0.988 = 29.64$, by the end of the respective periods, etc. The natural logarithm of the annual growth rate is called the *intrinsic rate of natural increase of the population*, and it means that once a stable equilibrium is reached for the various age groups it will increase by this intrinsic rate per year. Example: if the population growth at equilibrium at 15 years cycles is 1.307 then the annual $r = \ln(1.307)^{1/15} \cong 0.0178$. The age-specific birth and death rates and r must be determined for each population because considerable variations may exist from time to time even in the same group, depending on cultural and economic conditions. A statistical survey indicates that women with later onset of menopause live longer. At the present period the estimated maximal human life span is about 120 years. ▶human population growth, ▶menopause, ▶longevity, ▶mortality; Bongaarts J, Feeney G 2003 Proc Natl Acad Sci USA 100:13127.

Agent Orange ($\text{Cl}_3\text{C}_6\text{H}_2\text{OCH}_2\text{COOH}$): Herbicide containing mainly the synthetic auxin 2,4,5-trichlorophenoxy acetic acid (2,4,5-T). It had been used as a defoliating agent and brush killer. The LD_{50} of 2,4,5-T for mammals is 500 mg/kg, however, there are reports of much lower doses of high toxicity particularly at subcutaneous injection. It is frequently contaminated by dioxin, a carcinogen. The symptoms of Agent Orange exposure can be anorexia, hepatotoxicity, chloracne, gastric ulcers, porphyrinuria, porphyria, teratogenesis, leukemia, etc. Genes in the plasmids derived from *Pseudomonas ceparia* may degrade 2,4,5-T. ▶ LD_{50} , ▶anorexia, ▶hepatotoxicity, ▶acne, ▶chloracne, ▶ulcer, ▶porphyria, ▶teratogenesis; Ngo AD et al 2006 Int J Epidemiol 35:1220.

AGGA Box: An upstream transcriptional regulatory site. ▶transcription factors, ▶promoter

Agglutination: Also known as clumping occurs when two different blood types are mixed or when bacteria are exposed to specific antisera. The basis of this phenomenon is a component of the complement on the antibody (C1_q) protein that binds to the Fc region of the IgG heavy chain and that is followed by a change in conformation of the antibody. The binding of the epitope to the antibody triggers this process. ▶immunoglobulins, ▶antibody, ▶epitope, ▶complement

Agglutinin: An antibody that causes agglutination of cognate antigen. ▶abrin

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Aggrecan: A chondroitin sulfate proteoglycan of the cartilage (Schwartz NB et al 1999 *Progr Nucleic Acid Res Mol Biol* 62:177).

Aggrecanase: ►arthritis

Aggregation: Aggregation of proteins/fragments of proteins may impair the ubiquitin-proteasome degradatory system. ►ubiquitin

Aggregation Chimera: Produced in vitro by the assembly of genotypically different early (8-cell) embryonic cells. ►chimera, ►allophenic, ►multiparental

Aggregation, Familial: The increased incidence of genetically determined traits among relatives, e.g., among natural children and parents compared with unrelated adoptive children. ►heritability, ►recurrence risk

Aggregulon: A protein complex involved in activation and repression of genes; the term re-glomerate was used in the same sense.

Aggresome: An aggregate sink of insoluble misfolded proteins in the endoplasmic reticulum or close to the microtubule organizing center (MTOC) containing chaperones, proteasome and proteasome activator complexes. Some viruses generate aggresomes-like structures for replication. These virus factories are assembled in the vicinity of MTOCs and recruit vimentin, chaperones, ubiquitin and mitochondria similarly to regular aggresomes. Some viruses form nuclear aggresomes others replicate in cytoplasmic aggresomes. Cells with aggresomes can undergo normal mitosis. The aggregated proteins are asymmetrically distributed to one of the eukaryotic daughter cells, leaving the other daughter (the one that divides further) free of accumulated protein damage (Rujano MA et al 2006 *PloS Biol* 4:e417). ►endoplasmic reticulum, ►proteasome, ►chaperone, ►ataxin, ►virioplasm, ►autophagy; Kopito RR 2000 *Trends Cell Biol* 10:524; Kolodziejaska KE et al 2005 *Proc Natl Acad Sci USA* 102:4854; Wileman T 2006 *Science* 312:875.

Aggression: A behavioral trait with great variance in animal and human populations; it may be an expression of innate self-assertion, frustration or a response to antisocial behavior encountered. It may be the consequence of affective disorders and mental illness (paranoia). Evolutionists attribute aggression to the means of survival in the struggle for life, and it is observable among the majority of animals. Accordingly, in subhuman beings it is instinctive and largely depends on the species concerned. Among humans, it has an animal component but it is determined also by the ethical and cultural factors of the individual and the standards of the population. While animals are not credited with conscientious value judgments, in human societies, the moral, ethical, religious and cultural

principles may predominate. All normal human ethnic groups appear to have a condemning attitude toward violence. Yet mainly humans display violent aggression within species. It has been suggested that the human species lack the ability of submission, a widely common ability among other mammals. In the male, vole antidiuretic hormone (vasopressin) may be responsible for aggression. The genetic basis of aggressive behavior is generally not understood although it is known that a deficiency, e.g., in hypoxanthine-guanine phosphoribosyl transferase may result in hostile and self-mutilating behavior. The major problem is concerned with the large non-biological but cultural component of aggression. Unfortunately, human societies treat the cultural problem with double standards: killing and violent behavior is condemned yet major religions approve patriotic or holy wars with the weapons of mass destruction. The questions remain unsettled whether capital punishment is appropriate for killers, is induced abortion an act of aggression, is euthanasia a merciful act or just another form of taking life? To what extent are criminals predestined by their genetic endowment to aggression and how much is the role of the social environment, and the free will? Obviously, some of the answers are beyond the scope of genetics. Mice deficient in α -calcium-calmodulin kinase II displayed reduced levels of serotonin and aggressive behavior. Mice with knocked-out adenosine receptor ($A_{2a}R$) display high blood pressure and aggressiveness. ►behavior genetics, ►submission signal, ►ethics, ►morality, ►instinct, ►Lesch-Nyhan syndrome, ►nitric oxide, ►calmodulin, ►serotonin, ►behavior in humans, ►personality, ►mental illness, ►paranoia, ►adenosine receptors, ►antidiuretic hormone.

Aggressiveness: Aggressiveness of a plant pathogen is measured by the evocation of a disease phenotype, depending on the genotype of the pathogen, that of the host and environmental factors.

Aging: An exponential increase in mortality as a function of time or cell divisions. Some type of irreversible alterations in the DNA may determine aging. In older cells, the chromosomal telomeres are shortened. Cloning by nuclear transfer can reverse this cellular aging (Hayflick limit), yet the aging pattern of the nuclear donor cell lines is genetically determined and it is conserved by nuclear transfer (Clark AJ et al 2003 *Nature Cell Biol* 5:535). In skeletal muscle stem cells, regeneration is impaired due to loss of Notch signaling. In liver cells, the decline is due to a complex of C/EBP and Brahma (chromatin remodeling factor). In aged mouse progenitor cells young serum restored the aforementioned functions (Conboy IM et al 2005 *Nature [Lond]* 433:760). In the aging heart tissue of the mouse there is a stochastic down-regulation of

gene expression compared to young hearts (Bahar R et al 2006 Nature [Lond] 441:1011).

The frequency of nondisjunction dramatically increases by age, e.g., the incidence of Down syndrome may increase 200 fold in the offspring of just pre-menopausal mothers. The autosomal recessive Werner syndrome (gene frequency 1 to 5×10^{-3}) involves premature aging (graying of hair, atrophy of skin, osteoporosis, decreased libido, and increased risk of cancer) is characterized also by non-ketotic hyperglycinemia. Progeria (Hutchinson-Gilford syndrome), another autosomal recessive trait, also causes very early senescence. The Rothmund-Thomson, Cockayne, and Down syndromes, trichothiodystrophy and ataxia telangiectasia, all involved with defects in maintaining DNA integrity, display progeroid symptoms (Hasty P et al 2003 Science 299:1355). Severe mutation in the xeroderma pigmentosum F gene (*XPF*) can lead to profound crosslinking sensitivity and progeroid symptoms. This gene encodes an endonuclease, similar to that encoded by RAD1 in yeast. Expression data from XPF-ERCC1-deficient mice indicate increased cell death and anti-oxidant defenses, a shift towards anabolism and reduced growth hormone/insulin-like growth factor 1 (IGF1) signaling (Niedernhofer LJ et al 2006 Nature [Lond] 444:1038).

Aging has been attributed to defects of the immune system and to diminished activity of superoxide dismutase, an enzyme normally destroying the highly reactive radicals that arise due to irradiation and aerobic metabolism. During aging of healthy individuals, the rate of loss or organ function is variable but with some exceptions (endocrine, thermoregulatory and gastrointestinal systems, which lose faster) it is generally between 0 to 2% annually (Sehl ME, Yates FE 2001 J Geront A Biol Sci Med Sci 56:B198). Aging increases the potentials for cancer by some partly understood processes (Finkel T et al 2007 Nature [Lond] 448:767).

It has been suggested that aging is the result of degenerative changes in the mitochondria, the formation of aberrant DNA circles. Recent information fails to support increased point mutation rate in the control region of cultured fibroblast mitochondrial DNA among normal individuals or persons with neurodegenerative diseases (Chinnery PF et al 2001 Am J Hum Genet 68:529). Defective mitochondrial DNA polymerase γ results in premature aging in mice (Trifunovic A et al 2004 Nature [Lond] 429:417). It seems that premature aging in mutable mtDNA is caused by the mutator activity without affecting the production of ROS, reactive oxygen species (Trifunovic A et al 2005 Proc Natl Acad Sci USA 102:17993). Aging mitochondria frequently show deletions (Bodyak N et al 2001 Hum Mol Biol 10:17).

Some genes are silenced by methylation and others are activated by demethylation during aging. By-products of oxidative phosphorylation, hydrogen peroxide and superoxide may accumulate during senescence. Over-expression of catalase in the mitochondria of transgenic mice extended life span (Schriner SE et al 2005 Science 308:1909). Aging causes primarily functional losses in the neurons rather than large-scale losses of the neurons. Atrophy, decrease of receptors, accumulation of fluorescent pigments and cytoskeletal abnormalities in the brain occur in aging mammals (see Fig. A35).



Figure A35. Progeria. (From Bergsma, D. ed. 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

Microarray hybridization of aging neocortex and cerebellar tissues of mouse, involving (6347) genes, indicated inflammatory responses, oxidative stress and reduced neurotrophic support. Caloric limitations retarded some of the symptoms by decreasing glucose and insulin-like growth factor level in the plasma (Longo VD, Finch CE 2003 Science 299:1342). Caloric restriction limits aging, probably by reducing oxidative stress and promotes proliferation of mitochondria through a peroxisome proliferation-activated receptor coactivator 1α signaling (López-Lluch G et al 2006 Proc Natl Acad Sci USA 103:1768). Reduced body temperature in mice also increased life span (Conti B et al 2006 Science 314:825). Insulin/insulin-like growth factor signaling promotes growth, energy storage and shorten life cycle. Transcription factor FOXO (regulator of pro-apoptotic and cell cycle genes) and June-N-terminal kinase (JNK, a stress factor) may prolong life span (Wang MC et al 2005 Cell 121:115). Mouse with 5-adenylylcyclase knocked out (*AC5* KO) is resistant to cardiac stress and have increased median lifespan of 30%. *AC5* KO mice are protected from reduced bone density and susceptibility to fractures of aging. Old *AC5* KO mice are also protected from aging-induced cardiomyopathy, e.g., hypertrophy, apoptosis, fibrosis, and reduced cardiac function. Significant activation of the Raf/MEK/ERK

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signaling pathway and upregulation of cell protective molecules, including superoxide dismutase were detected. Fibroblasts isolated from *AC5* KO mice exhibited ERK-dependent resistance to oxidative stress (Yan L et al 2007 Cell 130:247).

An analysis of gene expression of humans indicates that a set of genes display reduced expression after age 40. These genes involve synaptic plasticity, vesicular transport and mitochondrial function. In contrast, genes concerned with stress response, anti-oxidation and DNA repair are induced. The promoters are damaged in the aged cortex of the brain due to reduced DNA base excision (Lu T et al 2004 Nature [Lond] 429:883). Aging is not caused by the activation of specific genes rather it is the consequence of decline in maintenance factors and the accumulation of damage (Kirkwood BL 2005 Cell 120:437). Mutations in genes affecting endocrine signaling, stress responses, metabolism and telomeres can increase the life span as well as changes delaying age-related disease pathways (Kenyon C 2005 Cell 120:449). In *Caenorhabditis* superoxide dismutase and catalase reduced aging significantly. This causes delays in mitochondrial replication. The slow replication leaves unprotected the D loop of mtDNA, possibly increasing the chances for deletions and mutations (see Fig. A36).

During normal aging the same lamin A cryptic splice site and histone modifications take place as in Hutchinson-Gilford progeria (Scaffidi P, Misteli T 2006 Science 312:1059). Anticonvulsant drugs (ethosuximide) prolonged life of *Caenorhabditis* (Evason K et al 2005 Science 307:258). Misregulation of mitosis caused by gradual defects in cell cycle control proteins, chromosomal movement, etc. may also be players in aging. Voltage-activated Ca^{2+} influx into the brain neurons is accelerated during aging.

Hereditary premature aging is also known in animals. The mouse autosomal recessive gene *klotho*—encoding β -glucuronidase (Chang Q et al 2005 Science 310:490)—seems to be a regulator of several symptoms of aging and represses insulin-like growth factor (IGF) signaling (Kurosu H et al 2005 Science 307:1829). A *klotho* allele in humans, KL-VS (13q12) potentially increases the susceptibility to coronary artery disease (Arking DE et al 2003 Am J Hum Genet 72:1154). *Klotho* regulates the transient receptor potential ion channel (TRPV5) by hydrolyzing extracellular sugar residues on TRPV5 and regulates calcium concentration in the blood. Calcium deposits can cause arterial disease. *Klotho* converts the fibroblast growth factor to a kidney special FGF23 receptor (Urakawa I et al 2006 Nature [Lond] 444:770).

The product of this gene shares sequence similarities with β -glucosidase proteins. In *klotho*^{-/-} mouse

the level of μ -calpain is specifically activated and it leads to degradation of the cytoskeletal protein α -spectrin (Manya H et al 2002 J Biol Chem 277:35503). In *Caenorhabditis*, mutations are known that in combination may extend the life of the nematodes through two different pathways up to five fold. Mutation in succinate dehydrogenase cytochrome b causes oxidative stress and premature aging in the nematodes. In *Drosophila* the *mth* (*methuselah*) mutant line, encoding apparently a protein with homology to GTP-binding proteins with seven-transmembrane domain receptors, extends the life by about 1/3.

In yeast, activated GTPase (RAS), inactivation of the *LAG1* gene (encoding a membrane-spanning protein) and the *SIR* silencing complex extend life span (Hekimi S, Guarente L 2003 Science 299:1351). Aging in mammals seems to be associated with aging of the lymphocytes and their function. DNA microarrays can detect gene expression changes during development/aging and it seems that the processes show great similarities between *Caenorhabditis* and *Drosophila* (McCarroll SA et al 2004 Nature Genet 36:197). The telomerase enzyme has also been implicated in aging. Since aging usually occurs after the reproductive period, it is no longer the object of natural selection (antagonistic pleiotropy). Population geneticists entertain two genetic mechanisms for aging: the accumulation of deleterious mutations and increase in antagonistic pleiotropy among gene loci. Some population display *altruistic aging*, i.e., aging becomes beneficial for the younger groups of individuals. In rodents, calorie restricted (CR) diet has substantial anti-aging effect. In yeast, the replicative lifespan is increased by deleting *TOR*, *SCH9* (limiting caloric uptake) and deletion of *FOB1* genes (limiting ribosomal DNA replication). Several other deletions are also increasing lifespan of yeast (Kaeberlein M et al 2005 Science 310:1193). Mammalian cell survival is promoted by caloric restriction through the induction of the SIRT1 deacetylase. SIRT1 (Sir2) deacetylates the repair factor Ku70, which moves away the pro-apoptotic Bax protein from the mitochondria and thus inhibits apoptosis, which is associated with aging. Mitochondrial mutations due to proof-reading deficiency of DNA polymerase γ caused various mutations in mouse mitochondria but only an increase in apoptotic markers furthered aging (Kujoth GC et al 2005 Science 309:481).

Insulin and insulin-like growth factor attenuate the SIRT effect (Cohen HY et al 2004 Science 305:390). Aging has been attributed also to the gradual loss of the telomeric DNA repeats. It has been suggested that the secretion of inflammatory cytokines may be a contributing factor. The life expectancy in years in the USA changed from 47 to 76 from (1900) to 2000.

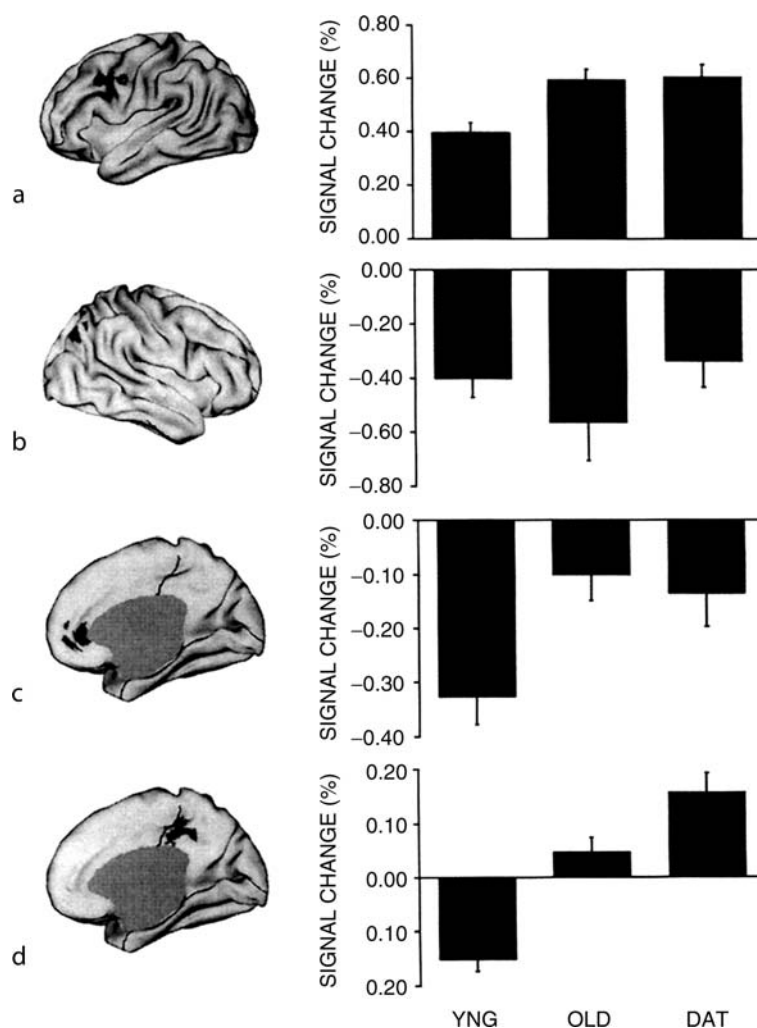


Figure A36. Brain activity in aging and Alzheimer disease. The brain was scanned by magnetic resonance imaging in four angles of the cortex. (a) left frontal, (b) right lateral parietal, (c) medial frontal and (d) medial parietal/posterior cingulate. The relative activity in each region is shown by bars and standard error for young adults (yng), healthy old (old) and older adults with early-stage alzheimer type dementia (dat). Noteworthy is that young adults deactivate specific brain regions during active task performance. The deactivated regions overlap with those that show reduced resting metabolic activity in aging and dementia. The most critical difference between healthy and alzheimer dementia is shown at (d). (Courtesy of Lustig C et al 2003 Proc Natl Acad Sci USA 100:14504 by permission. Copyright National Academy of Sciences USA, 2003). In mice the metaproteinase Zmpste24 is essential for lamin A of the nuclear envelope and its deficiency results in senescence by activation of p53 (Varela I et al 2005 Nature [Lond] 437:564)

In Sweden, the maximum life expectancy increase between (1861) and (1999) was 0.44 year per decade. The heritability of aging based on twins of humans is about or less than 0.35. The evidence for the role of mitochondria in aging has been questioned. Age-associated decline of cognitive abilities seem to be correlated to neuronal atrophy in the subcortical regions of the brain and the process may be prevented by neurotrophin or neurotrophin gene therapy. Somatic transfer of CREB gene into the hippocampal region of the brain of 15 months old rats reduced

memory loss (Mouravlev A et al 2006 Proc Natl Acad Sci USA 103:4750). ▶senescence, ▶Hayflick's limit, ▶longevity, ▶killer plasmids, ▶chromosome breakage, ▶DNA repair, ▶Werner syndrome, ▶progeria, ▶Hutchinson-Gilford syndrome, ▶Cockayne syndrome, ▶Bloom syndrome, ▶Alzheimer disease, ▶xeroderma pigmentosum, ▶ERCC, ▶longevity, ▶superoxide dismutase, ▶ion channels, ▶RAS, ▶lymphocytes, ▶telomere, ▶telomerase, ▶cytokines, ▶selection, ▶silencer, ▶RAS, ▶mating type determination in yeast, ▶mortality, ▶apoptosis,

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►heritability, ►pleiotropy, ►ROS, ►disposable soma, ►MARS model, ►mitochondrial mutations, ►substantia nigra, ►insulin, ►Ku70, ►sirtuin, ►Bax, ►control region of mitochondrial DNA, ►estradiol, ►neurotrophins, ►gene therapy, ►lamins, ►p53, ►CDC42, ►apoptosis, ►phenoptosis, ►CREB, ►brain human; Cortopassi GA, Wong A 1999 Biochim Biophys Acta 1410:183; Jazwinski SM 2000 Trends Genet 16:506; Kenyon C 2001 Cell 105:165; Finch CE, Rivkun G 2001 Annu Rev Genomics Hum Genet 2:435; Pletcher SD et al 2002 Current Biol 12:712; Holzenberger M et al 2003 Nature [Lond] 421:182; Longo VD et al 2005 Nature Rev Genet 6:866; Wallace DC 2005 Annu Rev Genet 39:359; factors and theories of aging review: Hekimi S 2006 Nature Genet 38:985; genomic resources of human aging: <http://www.senescence.info/>, microarray resources on aging: <http://gan.usc.edu>.

Aglycon: Protein or lipid linked to a polysaccharide.

α-1,4-Glucosidase Deficiency: ►acid maltase

Agonadism, Familial: Absence of gonadal tissue; usually part of a syndrome. ►azoospermia

Agonescence: Telomere-shortening dependent cell senescence and may be abrogated by telomerase. ►senescence

Agonist: Activates a receptor. *Inverse agonists* are antagonists of overexpressed receptors.

Agonistic Behavior: Combative behavior. ►aggression

Agoraphobia: A psychological disorder of fear from certain conditions or venues.

Agouti: Alternating light and dark bands on individual hairs of the fur in mammals such as mouse, rat, rabbit (see Fig. A37). The genes *agouti* and *extension* determine the relative amounts of eumelanin (brown-black) and pheomelanin (yellow-red) pigments. *Extension* encodes the receptor of the melanocyte-stimulating hormone (MSH) and *agouti* is a signal sequence in the hair follicle, inhibiting eumelanin production and the melanocortin receptor, an MSH receptor. Agouti has been cloned and sequenced; it contains 5 exons but two of them are not translated. The secreted protein products have 131 amino acid residues. The alleles that produce increased amounts of pheomelanin makes the mice more prone to late-onset obesity and diabetes. An agouti-related protein (AGRP), a neuropeptide, may increase several fold in obese mice. A^y and A^{vy} increase the liability to neoplasias and others cause embryonic lethality. ►pigmentation of animals, melanin, ►melanocyte-stimulating hormone, ►melanocortin, ►ghrelin; Dinulescu D, Cone RD 2000 J Biol Chem 275:6695.

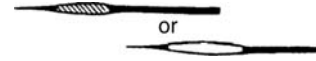


Figure A37. Agouti hair pattern

Agrelope: The part of an antigen that interacts with a deselope (antigen-binding site) of a MHC (major histocompatibility) molecule. ►deselope, ►epitope, ►histotop, ►antigen

Agricultural Measures: ►measurement units

1 hectare (ha) = 10 m⁴ = 2.47109 acres; 1 acre = 0.40469 hectare; 1 square kilometer = 100 hectares; 1 square mile = 640 acres = 259 ha.

1 bushel (bu) = 35.2393 liters = [approximate values]; *wheat* = 60 lb = 27.215 kg, *paddy rice* = 45 lb = 20.412 kg, *corn* (maize) = 56 lb = 25.401 kg, *soybeans* = 60 lb = 27.215 kg, *rye* = 56 lb = 25.401 kg, *sorghum* = 56 lb = 25.401 kg, *barley* = 48 lb = 21.772 kg, *potatoes* = 60 lb = 27.215 kg, *oats* = 32 lb = 14.515 kg, *apples* = 48 lb = 21.772 kg.

1 box of oranges (California, Arizona) = 77 lb = 34.926 kg, (Florida, Texas, Louisiana) = 90 lb = 40.823 kg, 1 box of *lemons* = 79 lb = 35.843 kg.

1 bale of cotton (U.S.) = 480 lb = 217.723 kg.

100 kg per hectare = 1.49 bushel (60 lb) per acre; 1 bushel (60 lb) per acre = 67.3 kg per hectare.

1 metric ton = 0.98421 long tons = 1.10231 short tons = 10 metric quintals.

Agricultural Productivity: Affected by genetic improvement of plants and animals and improved husbanding and cultural practices. Between the years (1951) and (1980) the overall plant productivity in the USA increased 166% and that of animals to 144%. The yield of maize after the introduction of hybrids increased to about 500%. ►heterosis, ►QTL

Agrin: A natural glycoprotein (200 kDa) causing the aggregation of acetylcholine receptors on muscle cells in vitro and in vivo is used for the formation of neuromuscular junctions and the T lymphocytes. The process also requires a muscle-specific protein kinase (MuSK). $\alpha 3Na^+/K^+$ -ATPase is the neural receptor for agrin (Hilgenberg, LGW et al. 2006 Cell 125:359). Agrin deficient mutant mouse is inviable. Agrin may restore function in muscular dystrophies caused by mutation in laminin. ►acetylcholine receptors, ►laminin, ►neuregulins; Trautmann A, Vivier E 2001 Science 292:1667; Moll J et al 2001 Nature [Lond] 413:302; Misgeld T et al 2005 Proc Natl Acad Sci USA 102:11088.

Agrobacterial Vectors: ►cointegrate vectors, ►binary vectors, ►transcriptional gene fusion vector, ►translational gene fusion vectors

Agrobacterium Mini-Plasmid: Carries the T-DNA, including its borders, but it is free of other segments, including the *vir* genes. *Agrobacterium tumefaciens*, ►T-DNA

Agrobacterium rhizogenes: A bacterium closely related to *A. tumefaciens*. It induces hairy roots rather than crown gall on the host plants. The genes responsible for the formation of hairy roots reside in the *Ri* plasmid. The hairy root tissues, unlike crown gall, readily regenerate into plants. The *Ri* plasmid has been used similarly to the *Ti* plasmid to construct plant transformation vectors. In *Nicotiana glauca* DNA sequences (*Ngrol*) homologous to the left segment of the T-DNA of the *Ri* plasmid have been detected. This observation indicates horizontal interspecific gene transfer. (►*Agrobacterium tumefaciens*, ►*Ri* ►plasmid, ►crown gall Moriguchi K et al 2001 J Mol Biol 307:771).

Agrobacterium tumefaciens: A soil born plant pathogenic microorganism of the family of *Rhizobiaceae*. It is responsible for the crown gall disease (tumor) of the majority of wounded dicotyledonous plants and it also infects a few monocots (*Liliaceae*, *Amaryllidaceae*). Several of its characteristics are similar to *Rhizobium*, *Bradyrhizobium* and *Phyllobacterium* species (see Fig. A38). The pathogenicity is coded in genes within the T-DNA of its *Ti* (tumor-inducing plasmid). T-DNA containing plasmids are the most important transformation vectors of plants. The T-DNA (transferred DNA) is an about 21 kb segment of the *Ti* plasmid with two direct repeat flanks bordering the oncogenes (responsible for tumorigenesis in the wild type plasmids), and some of the opine genes. Molecular biologists most widely use the *Agrobacterium* strains A6 and C58, containing octopine and nopaline encoding *Ti* plasmids, respectively. Certain *Agrobacteria* strains have *limited host range* (LHR) caused by an altered *virA* gene in the *Ti* plasmid. The *supervirulent* strains on the other hand overproduce the *VirG* protein. The infection of some species of plants is limited. Inhibition of purine synthesis leads to supersensitivity to infection in yeast, *Arabidopsis*, tobacco and *Ageratum* plants (Roberts RL et al 2003 Proc Natl Acad Sci USA 100:6634).



Figure A38. Crown gall

For the transfer of the T-DNA to other cells, including plant cells, requires the formation of a conjugation tube (pilus) controlled by virulence genes *virA*, *virG*, *virB1* to *virB11*. Altogether about 12 genes are involved in the transfer. *Agrobacterium tumefaciens* C58 has one ~2.1-Mb linear chromosome and three circular DNA plasmids (~2.8 Mb, ~0.54 Mb, ~0.21 Mb). Its total genome is ~5.67 Mb. The total number of assigned protein-coding genes is 1286, 1715, 333 and 141, respectively. The T-DNA is located in the 0.21 Mb plasmid. *Agrobacteria* can transfer DNA also to yeast and some other fungi. The T-DNA can integrate from binary vectors also into human HeLa cells (Kunik T et al 2001 Proc Natl Acad Sci USA 98:1871). Transferring the T-DNA into plant symbiotic bacteria such as *Rhizobia* enables these bacteria to transfer genes into plants (Broothaerts W et al 2005 Nature [Lond] 433:629). (►*Ti* plasmid, ►T-DNA, ►virulence genes of *Agrobacterium*, ►transformation [plants], ►host-pathogen relation, ►BIBAC, ►transformation genetic; Koncz C et al 1992 Methods in Arabidopsis Research, In: Koncz C et al (eds) World Scientific Publ. Co., Singapore, p. 284; Tzfira T et al 2000 Annu Rev Microbiol 54:187; Kunik T et al 2001 Proc Natl Acad Sci USA 98:1871; Wood DW et al 2001 Science 294:2317).

Agrocin 84: The non-plant-pathogenic *Agrobacterium radiobacter* synthesizes this compound and it is taken up by *A. tumefaciens* carrying agrocinopine. Agrocin associated with a toxin moiety is toxic to *A. tumefaciens* because it inhibits leucyl-tRNA synthetase. ►*Agrobacterium tumefaciens*, ►crown gall; Reader JS et al 2005 Science 309:1533; Kim J-G et al 2006 Proc Natl Acad Sci USA 103:8846.

Agrocinopine: A phosphorylated sugar, an opine, produced in octopine plasmids from mannopine by the enzyme agrocinopine synthase. ►*Agrobacterium*, ►opines, ►octopine

Agroinfection: A method of plant transformation. More than one genome of the double-stranded DNA of Cauliflower Mosaic Virus is inserted in tandem within the T-DNA of *Agrobacterium tumefaciens*. Such a construction permits the escape of the viral DNA from the bacterial plasmid once it was introduced into plants. Gemini viruses can be introduced into plants in a similar way. ►cauliflower mosaic virus, ►gemini-viruses, ►transformation genetic; Grimsley N et al 1989 Mol Gen Genet 217:309.

Agropine: Bicyclic phosphorylated sugar derivative of glutamic acid; it is synthesized by *Agrobacterium* strain Ach5. opines.

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Agropyron ($x = 7$): A genus of grasses; their chromosomes are homoeologous to that of several species within the genus of wheat and can be substituted to introduce agronomically useful genes (e.g., disease resistance). Some hybrids are known as perennial wheat, a forage crop. ▶[chromosome substitution](#), ▶[alien transfer](#), ▶[homoeologous chromosomes](#)

α GT (glucosyltransferase uridine 5'-diphosphate galactose β -D galactosyl-1,4-*N*-acetyl-D-glucosaminide α (1-3)galactosyltransferase, E.C.2.4.1.151): Synthesizes the carbohydrate epitope Gal α 1-3Gal β 1-4GlcNAc-R, which reacts with natural antibodies forming a barrier to xenotransplantation. Murine bone marrow cells transgenic for α GT may overcome the production of xenoreactive antibodies. This principle may facilitate the development of techniques to facilitate organ transfer between animals and humans. ▶[epitope](#), ▶[xenograft](#), ▶[transgenic](#), ▶[antibodies](#), ▶[epitope](#)

AGRP (agouti-related protein): ▶[agouti](#), ▶[obesity](#)

α -Helix: A secondary structure of polypeptides with maximal intrachain hydrogen bonding. A most common conformation, when after 5.4 Å high, five right turns of an amino acid chain, every 18th amino acids occupy the same line as the first. ▶[pitch](#), ▶[protein structure](#)

Ahonen Blood Group: A rare type, distinct from ABO, MNS, P, Rh, Duffy, Kidd and Dembrock. ▶[blood groups](#)

AHR: ▶[arylhydrocarbon receptor](#)

AIB: A steroid receptor implicated in breast cancer. ▶[breast cancer](#), ▶[steroid hormones](#); Anzick SL et al 1997 Science 277:965.

Aicardi-Goutières Syndrome (AGS1 3p21; AGS2 13q14.3, AGS3 11q13.2, AGS4 19p13.13): A heterogeneous disease, a progressive encephalopathy with calcification of the basal ganglia, excessive number of lymphocytes in the cerebrospinal fluid (lymphocytosis), brain atrophy and early death after birth. Elevated level of interferon α in the brain fluids—in the absence of infection—is a marker for the disorder. AGS1 is caused by mutation of TREX1, a DNA repair exonuclease. AGS2 is due to mutation of endoribonuclease H β -subunit. AGS3 involves mutation in the C subunit of ribonuclease H and AGS4 is mutant in ribonuclease H A subunit. ▶[ribonuclease H](#); Crow YJ et al 2000 Am J Hum Genet 67:213; Crow YH et al 2006 Nature Genet 38:910.

AICD: ▶[memory immunological](#)

AID: Artificial insemination by donor. artificial insemination, ▶[AIH](#), ▶[ART](#), ▶[acquired immunodeficiency](#)

AID (activation-induced deaminase): The main cause of somatic hypermutation (10^{-3} to 10^{-4} per base) and its deficiency obliterates somatic hypermutation and class switching in the development of the secondary repertoire of antibody molecules, the last step in the generation of functional antibodies. The main targets of AID are cytidines in single-stranded DNA or in double-stranded DNA during transcription. It erases methyl marks during development. Although immunoglobulins are the main targets of AID, other genes and bases besides C are also affected primarily in a binding motif of the enhancer/promoter region (Kotani A et al 2005 Proc Natl Acad Sci USA 102:4506). Protein kinase A (PKA) mediated phosphorylation is a critical factor in B cell antibody diversification (Basu U et al 2005 Nature [Lond] 438:508). ▶[immunoglobulins](#), ▶[antibody](#), ▶[antibody gene switching](#), ▶[class switching](#), ▶[immune system](#), ▶[epigenetics](#), ▶[APOBEC](#), ▶[UNG](#); Martin A et al 2002 Nature [Lond] 415:802; Conticello SG et al 2005 Mol Biol Evol 22:367)

AIDS: ▶[acquired immunodeficiency syndrome](#)

AIF (apoptosis-inducing factor): A mammalian mitochondrial flavoprotein (M_r 57K) with homology to prokaryotic oxidoreductases. The encoding gene was located to human chromosome Xq25-q26. From purified mitochondria AIF liberates—by increasing membrane permeability—cytochrome-c and caspase-9 and when injected into the nuclei it causes DNA breakage and thus promotes apoptosis. ▶[apoptosis](#), ▶[APAF](#), ▶[mitochondrial diseases in humans](#), ▶[mtPTP](#), ▶[CAD](#), ▶[ACINUS](#), ▶[L-DNase II](#); Wang X et al 2002 Science 298:1587.

AIG (anchorage independent growth): Normal mammalian cells grow in monolayer anchored to a solid surface. Tumor cells grow independently of anchorage. ▶[anchorage](#), ▶[tumor](#), ▶[cancer](#), ▶[CATR1](#), ▶[onco-genes](#)

AIH: Artificial insemination by husband. AID, ▶[artificial insemination](#), ▶[ART](#)

AIMS: *Arabidopsis* information database at Michigan State University. ▶[Arabidopsis thaliana](#)

AIR: Mitotic kinase acting on histone.

AIRE: An autoimmune regulatory protein of ~545 amino acids; when defective it is responsible for the autoimmune polyendocrine syndrome. ▶[APECED](#), ▶[autoimmune disease](#), ▶[autoimmune polyendocrinopathy](#)

Air Pollution: A probable cause of alterations in the genetic material. It appears that expansion of tandem repeats in the DNA increased about twofold by particulate material in the air compared to the gaseous material (Somers CM et al 2004 Science 304:1008). ▶environmental mutagens, ▶tandem repeat, ▶unequal crossing-over

AKAPs (A kinase anchoring protein): Cytoplasmic proteins, binding to cyclic adenosine 3',5' monophosphate (cAMP-dependent protein kinase PKA, calcineurin [phosphatase 2B]) and protein kinase C [PKC] and appears to have a regulatory role as a scaffold for the cellular signaling system. signal transduction, ▶T cell, ▶condensin; Colledge M, Scott JD 1999 Trends Cell Biol 9:216.

AKI: Adenylate kinase.

A-Kinases: cAMP-dependent protein phosphorylating enzymes; the phosphorylation is dependent on sufficiently high level of cAMP. ▶cAMP

Akinesia (akinesia): Lack of movement or poor movement or paralysis. Several types of fetal akinesia are parts of several syndromes. ▶Pena-Shokeir syndrome

AKR Mice: A long-inbred albino, specially selected strain of the animals containing the genes *Akv-1* and *Akv-2* that code for ecotropic retroviruses causing thymic lymphosarcoma (leukemia). Ecotropic viruses replicate only in cells from what they have been isolated originally. AKR strains have relatively short life span, are sensitive to ionizing radiation and highly susceptible to the carcinogenic effect, but resistant to the teratogenic effect of ethylnitrosourea. ▶replicase, ▶ecotropic retrovirus, ▶ENU

AKT Oncogene (PKB, serine/threonine protein kinase B): Isolated from thymomas (cancer of the thymus) of AKR mice transformed by an ecotropic virus. In the mouse genome, it is located in chromosome 12. A homolog of it is found in human chromosome 14q32.3 and it is frequently associated with chromosomal breakage. The Akt protein is a threonine/serine protein kinase (protein kinase B/PKB) and targeted by PI3-kinase-generated signals. Akt is involved in the regulation of cellular proliferation/apoptosis, glycogen synthase kinase (GSK3), endothelial nitric oxide synthase and protein synthesis. The interplay of Akt and Tor is frequently observed in cancer progression (Hay N 2005 Cancer Cell 8:179). AKT is activated by loss of PTEN in several types of tumors. Akt is regulated also by an insulin-like growth factor (IGF) and the nerve growth factor (NGF). AKT2 defect results in insulin resistance and diabetes (George S et al 2004 Science 304:1325). Akt is often called a cell survival kinase, activated by phosphoinositide kinase,

PIK and down-regulated by the RAS oncoprotein or by a phosphatase. Akt reduces apoptosis by phosphorylating protein BAD and inhibiting Bcl and caspase-9 in human cells. AKT inhibits cytochrome C release from mitochondria and thus inhibits apoptosis even when BAX and BAK are inactive (Majewski N et al. 2004 Mol Cell 16:819). The level of Akt1 was found 68% lower in schizophrenia than in normal tissues (Emamian ES et al 2004 Nature Genet 36:131). Akt regulates NF-κB that promotes the expression of anti-apoptotic genes. When Akt phosphorylates Raf the Raf-MEK-ERK signaling pathway is inhibited and cellular proliferation is initiated. The antiapoptotic PDGF also seems to be under Akt influence. TNF-α may or may not be involved through IKK in the regulation of NF-κB. The apoptotic FAS protein synthesis is apparently limited through blocking the FKK protein by Akt. *Akt1* governs mammary epithelial tumor cell (MEC) polarity, migratory directionality and breast cancer onset induced by ErbB2 in vivo (Ju X et al 2007 Proc Natl Acad Sci USA 104:7438). ▶AKR, ▶insulin-like growth factor, ▶nerve growth factor, ▶PKB, ▶phosphoinositides, ▶ecotropic retrovirus, ▶apoptosis, ▶glycogen, ▶hexokinase, ▶GSK3, ▶mice, ▶oncogenes, ▶nitric oxide, ▶BAD, ▶Bcl, ▶BAX, ▶BAK, ▶caspase, ▶NK-κB, ▶PDGF, ▶IKK, ▶FKK, ▶PDK, ▶ERBB1, ▶signal transduction, ▶TOR, ▶epiloia, ▶prostate cancer, ▶PML, ▶Parkinson disease; Datta SR et al 1999 Genes and Development 13:2905; Madrid LV et al 2001 J Biol Chem 276:18934).

ALA: Aminolevulinic acid, a first compound in the synthesis of porphyrins from glycine and succinyl CoA. ▶heme

α-Lactose: Milk sugar is converted into allolactose by the β-galactosidase gene of the *Lac* operon of *E. coli* and the latter then becomes the inducer of the operon. ▶Lac operon

Aladin (AAAS, triple-A syndrome): A neurological disorder resulting in alacrima (lack of tears), achalasia (failure of the smooth muscles to relax), and adrenal insufficiency because of defect in a WD-repeat family of regulatory proteins encoded at 12q13.1. ▶WD-40

Alagille Syndrome: Autosomal dominant (human chromosome 20p11.2) involving obstruction of the bile duct (cholestasis) and jaundice, lung anomalies (pulmonary stenosis), deformed vertebrae, arterial narrowness, deformed iris, altered eye pigmentation, facial anomalies (see Fig. A38), etc. The biochemical defect is in the Notch-ligand, Jagged-1. In some cases translocations or deletions of the region accompany it.

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Figure A39. Alagille syndrome. By adulthood prominent chin develops in Alagille syndrome

The multiplicity of the symptoms has been considered as a contiguous gene syndrome. The incidence is $\sim 4 \times 10^{-4}$. ▶contiguous gene syndrome, ▶face/heart defects, ▶cholestasis, ▶Byler disease, ▶BRIC, ▶Fallot's tetralogy, ▶Notch; Spinner NB et al 2001 Hum Mutat 17:18.

Aland Island Eye Disease: ▶albinism ocular

Alanine: L-alanine [$\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}$] is a non-essential amino acid for mammals. The enantiomorph D-alanine may not be metabolized by some organisms and may even inhibit their growth. β -Alanine [$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{COOH}$] is synthesized by several microorganisms from aspartate but it occurs only in trace amounts in animal tissues, possibly through the action of intestinal microorganisms; γ -butyric acid [$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{COOH}$] is structurally related. Its dipeptides with histidine are carnosine, homocarnosine and anserine. ▶alaninuria, ▶alanine aminotransferase, ▶carnosinemia

Alanine Aminotransferase (glutamate-pyruvate transaminase, GPT): Autosomal dominant gene (8q24.2-qter) encodes the enzyme that catalyzes the reversible transamination of pyruvate and α -ketoglutarate to alanine. This enzyme exists in cytosolic and mitochondrial forms. ▶amino acid metabolism, alaninuria, ▶glutamate pyruvate transaminase, ▶alanine

Alanine-Scanning Mutagenesis: ▶homologue-scanning mutagenesis

Alaninuria (with microcephaly, dwarfism, enamel hypoplasia and diabetes mellitus): The autosomal recessive condition is accompanied by the clinically demonstrable excessive amounts of alanine, pyruvate and lactate in the blood and urine. Both lactate and alanine are derived from pyruvate. ▶alanine aminotransferase, ▶amino acid metabolism, ▶alanine, ▶hypoplasia, ▶diabetes

Alarmones: Signal molecules (commonly modified nucleotides such as ppGpp) in response to stress. ppGpp interferes with IF2-dependent initiation

complex formation, severely inhibits initiation dipeptide formation, and blocks the initiation step of translation. IF2 has the properties of a cellular metabolic sensor and regulator that oscillates between an active GTP-bound form under conditions allowing active protein syntheses and an inactive ppGpp-bound form when there is a shortage of nutrients (Milon P et al. 2006 Proc Natl Acad. Sci USA 103:13962). ▶discriminator region, ▶IF2

Albers-Schönberg Disease: ▶osteopetrosis type II

Albinism: A pigment-free condition in plants and animals (see Fig. A40). The absence of skin and hair pigmentation in mammals is generally determined by homozygosity of recessive genes controlling melanin synthesis. Melanocytes are the cells specialized for melanin synthesis. During embryonal development melanoblasts, precursor cells of melanocytes move to surface areas. Melanin is synthesized in special cytoplasmic organelles, melanosomes.



Figure A40. Tyrosinase (Tyr, chromosome 7–44.0) alleles of mouse (left *c/c*, right *c/c<ch> p/p*). Courtesy of Dr. Paul Szauter, <http://www.informatics.jax.org/mgihome/other/citation.shtml>

The precursor of melanin is the amino acid tyrosine and the conversion is catalyzed by the aerobic oxidase, tyrosinase (polyphenol oxydase). In one type of albinism tyrosinase activity in the hair follicle is still present. Albinism may involve the entire melanocyte system of the body or it may be limited to the eye (11q14-q21). In this case, a pigment-specific integral glycoprotein product of the (oculocutaneous) OCA1 gene is specially targeted to the intracellular melanosomes. OCA2 was assigned to 15q11.2-q12. OCA3 is at 6q13-q15. Albinism of the eye may occur in a sectorial manner in females heterozygous for the Xp22.3-p22.2-linked recessive gene (OA1). Albinism of the eye may involve problems of vision, involuntary eye movements (nystagmus), and head nodding. OA2 (Xp11.4-p11–23) males may be partially color blind (protanomalous). Albinism is controlled by numerous single genes.



Figure A41. Cuna Indian Albinos (Courtesy of Dr. C Keeler)

The prevalence of albinism varies from 1/14,000 to 1/60,000 depending on the gene, and the ethnicity of the population; it is generally more frequent among negroids than among caucasoids. Ocular albinism may occur very frequently among some Indian tribes (1/150). Albinism involves hypersensitivity to light and increased susceptibility to some forms of cancer. The absence of hair pigmentation may be locally corrected by gene therapy using the normal tyrosinase gene. Albinism may be a component of complex syndromes and may be associated with deafness, neuropathy and bleeding disorders. Albina condition occurs with very high frequency in progenies of plants exposed to ionizing radiation (see Fig. A41). In plants over 100 genes can cause albinism when mutated. ▶Himalayan rabbit, ▶piebaldism,

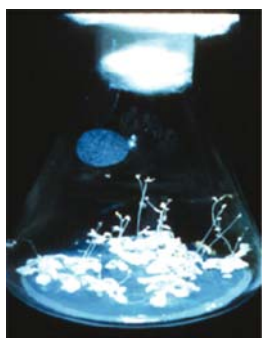


Figure A42. Albina plant

▶pigmentation of animals, ▶Chédiak-Higashi syndrome, ▶Hermansky-Pudlak syndrome, ▶xeroderma pigmentosum, ▶light-sensitivity diseases, ▶color blindness, ▶tyrosinase, ▶eye color, ▶hair color, ▶motor proteins, ▶oculocutaneous albinism; Toyofuku K et al 2001 Biochem J 355(pt2):259.

Albino: Animals defective in melanin synthesis. More commonly in plants, *albina* is the designation of leaf-pigment-free individuals (because the Latin word *planta* is of feminine gender).

Albizzin (L-2-amino-ureidopropionic acid): A glutamine analog. ▶asparagine synthetase

Albomaculata (or status albomaculatus): A green-yellow-white variegation caused by mutation in extranuclear genes in plants. ▶chloroplast genetics

Albright Hereditary Osteodystrophy (pseudohypoparathyroidism, PHP1A, PHP1B, 20q13.2): Autosomal recessive pseudoparathyroidism is based on a defect in a G-protein mutation. The locus actually encodes two G protein subunits, Gs and XL α_s . Gs is expressed from both parents, XL α_s is expressed only from the paternal chromosome. There is a third maternal transcript of the gene that encodes the neurosecretory NESP55 protein. The three transcripts share exons 2 to 11 but have different first exons. The NESP55 coding region is within exon 1 and the rest of the exons remain untranslated. An X-linked dominant form is based on a defect in the parathormone-adenylate cyclase-G $_s$ -protein complex. It displays imprinting. ▶hyperparathyroidism, ▶parathormone, ▶G-protein, ▶McCune-Albright syndrome, ▶imprinting, ▶epigenesis; Bastepe M et al 2005 Nature Genet 37:25.

Albumins: Include different proteins soluble in water and in dilute salt solutions, such as bovine serum albumin (BSA) used in chemical analyses. In the fetal serum of mammals, the predominant protein is the albumin α -fetoprotein, transcribed from two genes in humans, and they have about 35% homology and are immunologically cross-reactive despite their substantial divergence. Both serum albumin and α -fetoprotein, products of the same gene family, are synthesized in the liver and gut. After birth, the production of the latter drops dramatically whereas the former is produced throughout life. Their tissue-specificity of expression resides within 150 bp from the beginning of transcription. The α -fetoprotein gene carries three enhancer elements 6.5, 5 and 2.5 kbp upstream that may increase the level of transcription up to 50-fold. The liver-specificity for the serum albumin gene is controlled by the PE (proximal element), which is most important for promoter activity. It is located between the TATA and CCAAT

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boxes. The distal element (DE I [around -100 base from the initiation of translation] is most important for liver-specificity. There are also DE II [around -116], DE III around about -158]). The PE element (5'-GTTAATGATCTAC-3') is quite similar to sequences in the promoters of other liver-expressed genes. The PE binding protein is HNF-1 (88 kDa) is also shared by other liver genes, including the hepatitis virus promoter. The binding proteins associated with the DEs do not appear liver-specific inasmuch as they are used by a variety of other genes of ubiquitous expression, or the specificity is modified by so far unknown co-factors. ►serum, ►fetoprotein, ►transcription, ►enhancer, ►promoter, ►TATA box, ►CCAAT box, ►HNF

Alcaptonuria: ►alkaptonuria

Alcohol: An organic molecule formed from hydrocarbons by substituting -OH for H. The simplest representative is ethanol (ethylalcohol, $\text{CH}_3\text{—CH}_2\text{—OH}$, MW 46.07, boiling point 78.3°C). Ethanol usually contains 5% water; the absolute ethanol is very hygroscopic; for disinfection the 60–80% solutions are most effective. Moderate alcohol consumption may protect against ischemic heart disease. This protection was attributed to modulation of blood lipoproteins, reduced activation of platelets and thrombosis. Protein kinase C(ϵ) signals may also be involved in the protection at physiological levels of blood alcohol (>10mM). ►ischemia, ►thrombosis, ►protein kinases, ►ethanol

Alcohol Dehydrogenase: ►ADH, ►mutation detection

Alcohol Fermentation: The conversion of sugar into alcohol in the absence of air by glycolysis. ►glycolysis

Alcoholism: A chronic and addictive use of the chemical is a behavioral trait with some hereditary component of the manifestation. Alcoholism may involve fatal or very serious consequences in certain diseases, in pregnancy, and when certain types of medicines or drugs are used. The *fetal alcohol syndrome* includes microcephaly (small head), folded skin at the side of the nose, defective eyelids, upturned nose, etc. In adults, it may cause cirrhosis of the liver leading to further (fatal) complications. The maternal alcohol blocks in the fetus the NMDA glutamate receptors and activates the GABA_A receptors resulting in long-lasting process of neurodegeneration. Unfortunately, no association between alcoholism and any particular gene or chromosomal segment has been firmly established; it is apparently under polygenic control. Alcohol abuse during pregnancy may expose the fetus and the newborn to serious developmental harm (fetal alcohol syndrome, FAS) including physical and

mental retardation that may seriously affect lifelong the health and function of the individuals. FAS is an increasingly serious social problem along with other abuses of drugs. About 0.001–0.002 fraction of the children are suffering from it. In mice, the higher alcohol consumption appeared to be associated with defects in the 5-HT_{1b} serotonin receptor and genetic variations (Lys487Glu) of the aldehyde dehydrogenase 1 locus. The (ADH1 and 2) aldehyde dehydrogenases are present in some far-East human populations and may increase the proclivity to alcohol consumption by a factor of 5 to 10. In some other populations low in ADH1 the alcohol consumption is moderate because of the poor tolerance. ADH actually has a protective effect against alcoholism. In *Caenorhabditis*, the neuropeptide Y receptor-like protein allelic variants can account for variations in alcohol tolerance (Davies AG et al 2004 Neuron 42:731). In *Drosophila*, a single inebriation by alcohol may start the development of alcohol tolerance. The tolerance requires the catecholamine octopamine (functional analog of noradrenaline of mammals (see Fig. A43)), and a nuclearly encoded (*Hang*) DNA-binding zinc-finger protein (Scholz H et al 2005 Nature [Lond] 436:845).

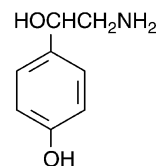


Figure A43. Octopamine

In mice the *Alp1* locus may be responsible for 14% and the *Alcp2* for 18% of the total alcohol preference. Interestingly the former gene is acting only in males and the latter only in females. Other loci-controlling alcohol withdrawal sensitivity (chromosome 1), alcohol-induced hypothermia and amphetamine-induced hyperthermia, and other hyperthermia loci seem to be in chromosome 9 of mouse. These loci do not appear to be controlling general tendencies for substance abuse. Alcohol preference appears to be a quantitative trait with ~0.39 heritability and ~60% concordance between monozygotic twins. Sensitivity to the effects of alcohol may be affected by a GABA_A type receptor and mediated by protein kinase C ϵ . Synuclein- α gene seems to be expressed at more than 2-fold rate in the brain of rats, which prefer alcohol compared to those which do not care for the substance (Liang T et al 2003 Proc Natl Acad Sci USA 100:4690). Moderate alcohol consumption may be beneficial to some individuals but alcohol

consumption in general is undesirable for health and social consequences (Pearson H 2004 Nature [Lond] 428:598). ▶**Dubowitz syndrome**, ▶**polygenic inheritance**, ▶**teratogenesis**, ▶**serotonin**, ▶**neurotransmitter**, ▶**substance abuse**, ▶**mortality**, ▶**QTL**, ▶**behavior in humans**, ▶**aldehyde dehydrogenase**, ▶**Flynn**, ▶**NMDA**, ▶**GABA**, ▶**glutamate receptor**, ▶**protein kinases**, ▶**addiction**, ▶**synuclein**, ▶**rheumatic fever**; Almasry L 2001 Am J Hum Genet 68:128; Sillaber I et al 2002 Science 296:931; Weiss F, Porrino LJ 2002 J Neurosci 22:3332; Yao L et al 2002 Cell 109:733.

Aldehyde Dehydrogenase (ALDH, acetaldehyde dehydrogenase): Form ALDH1 is encoded in human chromosome 9q21. Low level of this form of the enzyme is responsible for poor alcohol tolerance. An ALDH2 functions in the liver and it is encoded in 12q24.2 and ALDH3 is coded in human chromosome 17. Oxidizes also cyclophosphamide-derivative aldophosphamide to non-toxic carboxyphosphamide (see Fig. A44). ▶**alcohol dehydrogenase**, ▶**cyclophosphamide**

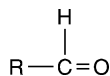


Figure A44. Aldehyde

Aldolase-1 (fructose-1,6-bisphosphate aldolase): The ALDOA isozyme has been mapped to human chromosome 16q22-q24, ALDOB (fructose intolerance) in chromosome 9q22, ALDOC in human chromosome 17cen-q12. There is also a deoxyribose-5-phosphate aldolase but its deficiency is apparently harmless. ALDOA deficiency may be involved in a form of hemolytic anemia (γ-glutamylcysteine synthetase deficiency). ▶**fructose intolerance**, ▶**anemia**

Aldose: A sugar that ends with a carbonyl group (=C=O).

Aldosterone (18-aldosterone): The main electrolyte-regulating steroid hormone of the kidney cortex. It activates a sodium channel I ATP-dependent manner. steroid hormones, ▶**aldosteronism**, ▶**ion channel**; Gorelik J et al 2005 Proc Natl Acad Sci USA 102:15000.

Aldosteronism (hyperaldosteronism, glucocorticoid-remediable aldosteronism [GRA]): Aldosteronism is controlled by two autosomal dominant genes. It is due to the excessive activity of aldosterone synthase (ADOS) and steroid 11β-hydroxylase (CYP11B2), coded in human chromosome 8q21. These two genes are quite similar in structure and also frequently form somatic recombinants. Their activity results in increased aldosterone production and hypertension.

This hyperaldosteronism is suppressible by glucocorticoids and dexamethasone. The chimeric genes are under adrenocorticotrophic hormone control. Consequently, aldosterone is secreted and causes water and salt reabsorption and high blood pressure. ▶**hypertension**, ▶**aldosterone**, ▶**glucocorticoid**, ▶**dexamethasone**, ▶**hypoaldosteronism**, ▶**pseudo-hypoaldosteronism**, ▶**mineral corticoid syndrome**

Aleurone: A protein-rich outer layer of the endosperm of monocotyledonous kernels. There is only a one-cell-thick layer of aleurone in wheat and maize, three-cell-thick layer in barley, and a layer of variable cell-thickness in rice. There are about 250,000 cells in the aleurone in maize and about 100,000 in barley. Aleurone color genes have proven to be very useful chromosomal markers (such as loci *A*, *C*, *R*, *Bz*, *B* in maize and some of the functional homologs in other cereals). The dominant alleles can be identified already in the seeds of the heterozygotes, and in case of maize, they can be classified on the cob in immobilized condition and in large numbers. ▶**maize**

Alexander's Disease: An autosomal recessive anomaly of lipid metabolism accompanied by a megaencephaly (synonym: macroencephaly), a pathological enlargement of the brain. Astrocyte fibers and small heat-shock proteins may be involved. Defects in NDUFV may be responsible for the symptoms. ▶**NDUFV**; Brenner M et al 2001 Nature Genet 27:117.)

Alfalfa (*Medicago sativa*): A leguminous forage plant (see Fig. A45). Its closest wild relatives are *M. coerulea* (2n = 16) and the somewhat more distant *M. falcata* (2n = 16). *M. sativa* is autotetraploid (2n = 4x = 32). *M. truncatula* (~454–526 bp) has only about half the genome size of *M. sativa*; it is also diploid and its circular chloroplast genome is 124,039 bp. Alfalfa is also called lucerne. By antisense technology, the lignin content of the plant tissue has been reduced and its digestibility improved (Srinivasa Reddy MS et al 2005 Proc Natl Acad Sci USA 102:16573). ▶**gene index**; *M. truncatula* database <http://www.tigr.org/tldb/e2k1/mta1/>.



Figure A45. *Medicago sativa*

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Alfalfa Mosaic Virus: The genetic material of this virus consists of four RNAs of 1.3, 1.0, 0.7 and 0.34×10^6 Da.

Alga: Alga can be prokaryotic such as blue-green algae, or eukaryotic such as *Chlamydomonas reinhardtii*, *Ch. eugametos*, *Euglena gracilis*, seaweeds etc.; they are photosynthetic microorganisms. The unicellular red alga *Cyanidioschyzon merolae* has 16,520,305 base pairs in its 20 chromosomes, with at least 5,331 genes. The single mitochondrion is 32,211 bp with 34 protein genes. The single plastid is 149,987 bp encoding 208 intron-less protein genes. (Matsuzaki M et al 2004 Nature [Lond] 428:653). ▶ *Chlamydomonas*, ▶ *Euglena*

Algeny: The genetic alteration of an organism by non-natural means such as ▶ *genetic engineering*, ▶ *gene therapy*, ▶ *genetic surgery*, and ▶ *transformation*

Algesia: Increased sensitivity to pain.

Alginate: A polymer of mannuronic acid and guluronate; it is found in the cell wall of brown algae. ▶ *biofilm*; Wong TY et al 2000 Annu Rev Microbiol 54:289.

Algol (algorithmic oriented language): A computer language set by international procedure. ▶ *algorithm*

Algorithm: A set of rules and procedures for solving problems in a finite number of sets; usually the repetitive calculation aims to find the greatest common divisor for two members. Computer programs include algorithms.

Algorithm, Genetic: Genetic algorithm uses a computational program to interpret evolutionary changes of mutation, recombination, and selection. ▶ *algorithm*, ▶ *darwinism*

Alien Addition: Addition of the chromosome(s) of another species to the genome of polyploids without seriously disturbing genic balance, in contrast to the case with diploids, where even small duplications or deletions may become quite deleterious. The procedure of addition involves crossing the higher chromosome number species as pistillate parent with the lower chromosome number pollen donor (see Fig. A46). The F_1 is generally sterile but by doubling their number (with colchicine) may result in a fertile amphiploid. Upon the recurrent back crossing of the amphiploid with the recipient parent, monosomy results for the donor's chromosomes. The F_1 is generally sterile but doubling their number (with colchicine) may result in a fertile amphiploid. After repeated backcrossing in large populations, one may obtain plants with single monosomes for all chromosomes of the donor. These are called single monosomic addition lines. Disomic additions are obtained by selfing such monosomics. These carry an

extra pair of chromosomes. The purpose of addition is that occasionally the added chromosome, containing agronomically useful genes, may get substituted for its homoeolog and lead to a substitution line. ▶ *addition line*, ▶ *pistillate*, ▶ *pollen*, ▶ *amphidiploid*, ▶ *monosome*, ▶ *disomic*, ▶ *homoeologue*, ▶ *substitution line*, ▶ *transchromosomic*; Sears ER 1953 Am J Bot 40:168.

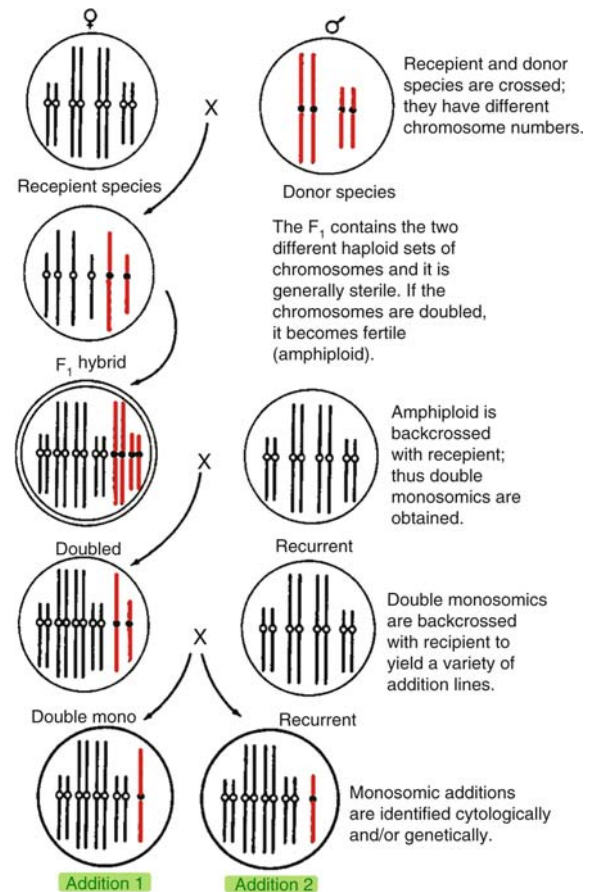


Figure A46. The general scheme for the generation of alien addition lines in wheat. The same procedure is applicable to other polyploid plant species

Alien Substitution: Alien Substitution takes place when chromosome(s) of another species replace the own chromosome(s) of a species. Alien substitutions may be obtained from alien addition lines. However, monosomic lines are used most commonly. Monosomic lines can be maintained without too many difficulties in polyploids, because the genomes are better balanced. Monosomic plants produce some eggs that are nullisomic. These recipients are then crossed with a donor species. In the F_1 the chromosome absent in the parent nullisomic will appear as a monosome of

the donor. These monosomic individuals are repeatedly backcrossed (6–8 times) with the recipient, until in some individuals all the chromosomes of the donor are eliminated, except that particular monosome. Selfing this monosomic substitution line results in a disomic substitution that has the same chromosome number as the euploid line from which the nullisomic arose, but one pair of the chromosomes will represent the donor. ►alien addition, ►monosomic, ►nullisomic, ►back-cross, ►selfing, ►euploid, ►alien transfer lines, ►chromosome substitution; Sears ER 1972 Stadler Symp 4:23.

Alien Transfer Lines: Alien substitution lines are interesting to the geneticist, but the plant-breeder is rarely satisfied with the substitution of an entire chromosome because the new chromosome may contain, in addition to the desirable gene(s), some that are undesirable. Homologous pairing and crossing over, on the other hand can borrow short segments or even single genes from the alien chromosome. This goal can also be achieved by induced translocations, and the resulting line is called a transfer line. ►alien ►substitution, ►alien transfer, ►transchromosomic, ►translocation; Sears ER 1956 Brookhaven Symp Biol 9:1.

AlifoldZ: Consensus structures of aligned sequences can be useful measures in detecting functional RNAs. One method is to test multiple sequence alignments for the existence of an unusually structured and conserved fold. An energy score consisting of free energy and a covariation term significantly improves sensitivity, as compared to a single sequence prediction (Washietl S, Hofacker IL 2004 J Mol Biol 342:19). ►RNAz, ►EvoFold, ►RNA structural

Alignment: Alignment finds nucleotide and amino acid linear sequence matches in nucleic acids and polypeptides, respectively. High alignment scores indicate great similarity between sequences. Free downloads of aligning software are available on the internet. Alignment scores estimates similarities versus dissimilarities in sequences, as well as gaps in the sequence of macromolecules. homology, CLUSTAL W, also BLAST, genomics, PFAM, human–mouse genomes: Schwartz S et al 2003 Genome Res 13:103; Higgins GD et al 2005 Proc Natl Acad Sci USA 102:104511, pairwise sequence alignment: <http://genome.cs.mtu.edu/align/align.html>, protein sequence alignment: <http://compbio.mds.qmw.ac.uk/S4.html>, genome alignment, annotation: <http://www.bx.psu.edu/>, multiple alignment of structure: <http://bioinformatics.albany.edu/~dmaps/>, binding motif alignment: <http://www.benoslab.pitt.edu/stamp/>, multiple sequence alignment with medical and microbial relevance: <http://genome.lbl.gov/vista/>

index.shtml, multiple sequence alignment: <http://prodata.swmed.edu/compass/compass.php>.

AlignACE: AlignACE is a computer program that locates upstream regions of regulons. It helps identify genes in a functional pathway, or genes homologous to known regulons, or a group of genes derived from conserved operons. ►regulon; McGuire AM et al 2000 Genome Res 10:744.

Aliphatic Molecules: The carbon atoms occur in an open chain (non-aromatic) that is bound by single or multiple bonds.

ALK: ►anaplastic lymphoma

Alkaline Chromatography: Is used for the rapid separation of less than 150 bases long DNA probes on Sepharose CL-4B (a beaded [60–14 mm pore size], cross-linked agarose). ►Sepharose

Alkaline Lysis: Alkaline Lysis is a procedure to extract plasmid DNA from bacterial cells, using 0.2 N NaOH and 1% SDS. The plasmids may be further purified by CsCl-ethidium bromide gradient ultracentrifugation, or by polyethylene glycol precipitation at 10,000 rpm. ►SDS

Alkaline Phosphatase: Alkaline Phosphatase cleaves phosphates at a pH optimum about 9; it is present in microorganisms and animal cells but absent from plant tissues. The alkaline phosphatase of *E. coli* is 86-kDA and contains 2 subunits. The human intestinal alkaline phosphatase (ALP1) is encoded in chromosome 2q37, as are the placental enzymes (ALPPP/PLAP); the liver enzyme is coded by ALPL in chromosome 1p36.1-p34. Enzyme levels that are higher or lower than normal may have deleterious consequences. Hypophosphatasia for ALP may be dangerous or even lethal for infants. ►acrodermatitis enteropathica, ►acid phosphatase

Alkaloids: Alkaloids are diverse (more than 2500), mainly heterocyclic, organic compounds containing nitrogen. They are generally alkalic in nature and are secondary metabolites of plants; frequently effecting strong biological activity at higher concentrations (examples are nicotine, caffeine, cocaine, morphine, strychnine, quinine, papaverine, atropine, hyosciamine, scopolamine codeine, capsaicine, lupinin, etc.). Of particular interest is colchicine (obtained from the lily, *Colchicum autumnale*) that blocks the microtubules of cells, causing the doubling of the chromosome number. Vincristine and vinblastine (from *Vinca rosea*) are antineoplastic drugs. The “animal alkaloid,” ptomaine, found in decomposing cadavers, is actually a microbial product. ►nicotine, ►caffeine, ►Datura ►alkaloids, ►cocaine, ►morphine,

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►capsaicine, ►lupine, ►colchicine, ►vinblastine; Facchini PJ 2001 Annu Rev Plant Physiol Mol Biol 52:29.

Alkalosis: Alkalosis is the diminished buffering capacity of tissues that leads to higher pH.

Alkane: An alkane is a aliphatic molecule joined by a single covalent bond, e.g., $\text{CH}_3\text{—CH}_3$. ►alkene

Alkaptonuria (alcaptonuria, AKU): Alkaptonuria is a recessive metabolic disorder (prevalence about 1/40,000) in which a defect in the enzyme homogentisate 1,2-deoxygenase prevents homogentisic acid from being metabolized into maleyl- and fumaryl-acetoacetic acids. The degradation of the aromatic amino acids normally follows the pathway (see Fig. A47):

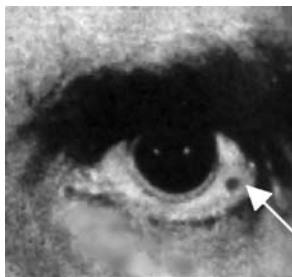


Figure A47. Alkaptonuria

The accumulated homogentisic acid in AKU is excreted in urine and is readily oxidized into a dark compound (see on the cornea: see Fig. A48), alkapton, staining dark already the diapers of affected newborns. Alkapton also causes dark pigmented spots in the connective tissues and bones, and with the ageing of the patient may lead too arthritis. This human hereditary biochemical defect was first recognized in 1859 and its genetic control identified by Sir Archibald Garrod in 1902. The gene (AKU) was located inhuman chromosome 3q21-q23. ►tyrosine, ►phenylketonuria, ►amino acid metabolism, ►tyrosinemia

Alkene: Alkenes are hydrocarbons with one or more double bonds, e.g., $\text{H}_2\text{C=CH}_2$. ►alkane

Alkylating Agent: An alkylating agent alkylates other molecules; many chemical mutagens and carcinogens are alkylating agents. The mutationally most effective alkylation site in DNA is the O^6 site of guanine. O^6 -alkylguanine can pair with either cytosine, or thymine, resulting in a substitution mutation in case of the latter. The alkyl may be removed from the DNA

in *E. coli* by an alkyltransferase enzyme. The acceptor may be a cysteine residue of that protein.

The natural compounds yatakemycin and duocarmycin SA (see Fig. A50) can alkylate nucleosomal DNA in the highly shielded minor groove and are potentially effective anti-tumor agents (Trzupek JD et al 2006 Nature Chem Biol 2:79).

►mutagens-carcinogens, ►mutagenic potency, ►environmental mutagens, ►carcinogen, ►chemical mutagens, ►alkyltransferase; see Fig. A49.

Alkylation: Alkylation is the addition of a CH_3 group (or other member of the alkane series) to a molecule. Alkylation of DNA bases may lead to mutation through mispairing and base substitution. Also, alkylation may lead to disruption of the sugar-phosphate backbone of the DNA through depurination by AP nucleases. Thymine is alkylated at the O^4 position and adenine at the N3 position. ►base pairing, ►hydrogen pairing, ►tautomeric shift, ►AP endonuclease, ►chemical mutagens, ►alkyltransferases, ►methyltransferase; Bautz E, Freese E 1960 Proc Natl Acad Sci USA 46:1585.

Alkyltransferases: Alkyltransferases protect the DNA against alkyl adducts by transferring the methyl or ethyl (alkyl) groups to cysteine and repairing the damage. These enzymes, present in different organisms, display an active site consensus V(I)PCHRV(I). If the level of these enzymes is reduced either by inhibitors, e.g., O^6 -benzylguanine, or by mutation, the efficiency of alkylating agents for treatment of cancer increases. DNA repair; Reese JS et al 2001 Oncogene 20:5258.

Allantois: The allantois is a tubular part of the hindgut, later forming the umbilical cord of the fetus and it fuses with the chorion. It also participates in the formation of the placenta. amnion, ►chorion

Allegro: Allegro is a computer program for multipoint linkage, free at allegro@decode.is.

Allele: Alleles are alternative states of a gene (e.g., a^1 and a^2). Hybrids of a^1/a^2 are commonly of mutant phenotype, although they may show incomplete (allelic) complementation. Two alleles are identical if their base sequences are identical, even though one or both of these may be different from the sequence of the wild type. *Non-identical alleles* are still in the same gene (and are non-complementary) yet their expression may be distinguishable. *Homoalleles* are effected in the same codon but a different nucleotide occurs at the same site in each, and therefore the alleles cannot be separated by recombination in a

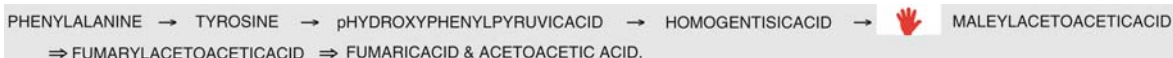


Figure A48. Degradation of aromatic amino acids

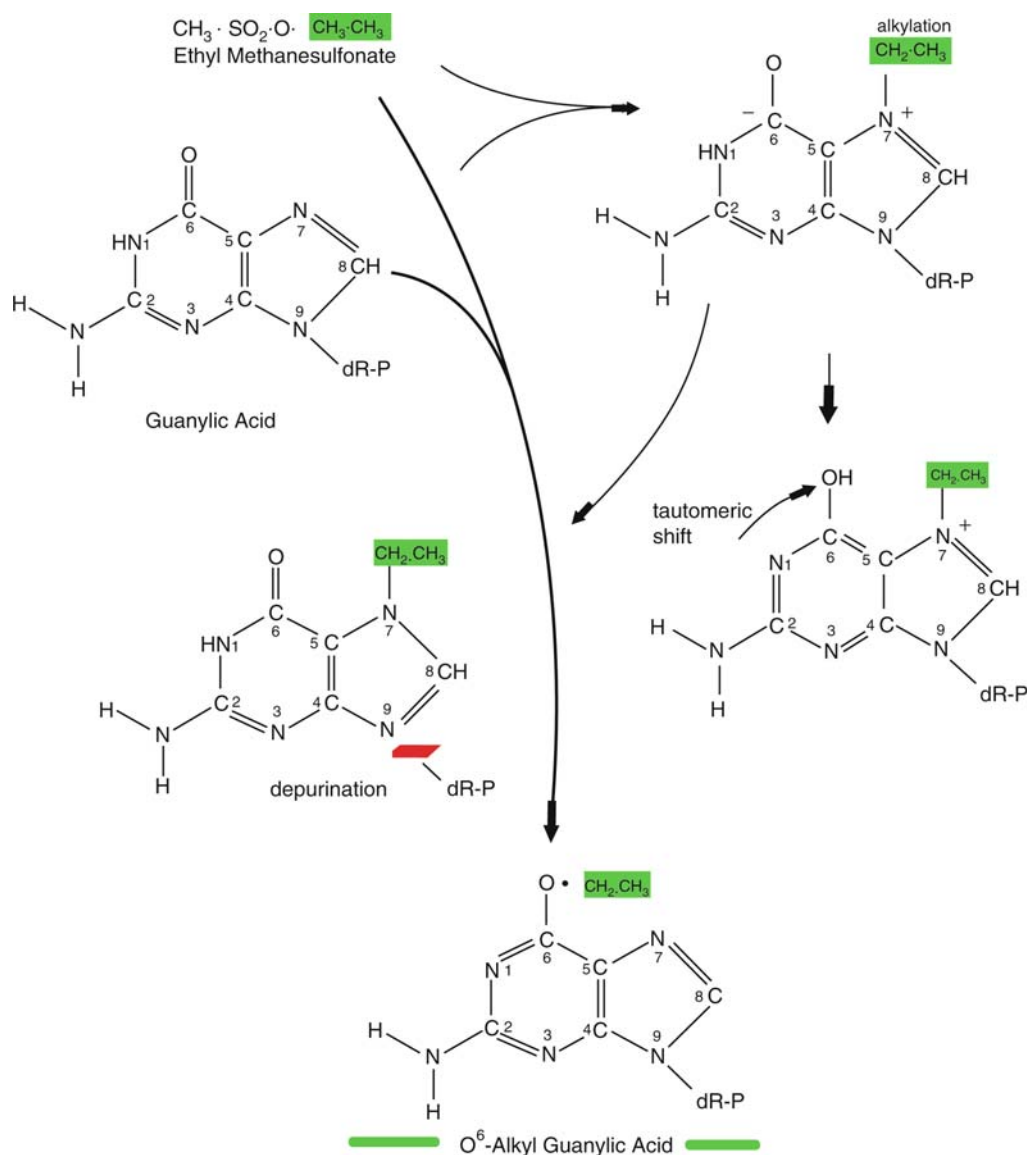


Figure A49. Most common reactions of the alkylating agent, ethylmethane sulfonate with guanine

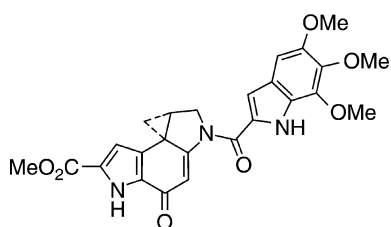


Figure A50. Duocarmycin

heterozygote for the locus. The differences between *heteroalleles* are located at non-identical sites within the codon, or in another codon altogether, and the alleles can therefore be separated by recombination. *Isoalleles* convey wild phenotype, yet under special circumstances can be recognized by appearance. *Multiple alleles* are more than two alternative alleles

of the same locus. *Super alleles* are additional mutations in cis to an allele within a gene that reinforces their expression. *Codominant alleles* both are expressed in the heterozygotes. In some organisms alleles of the *a1* locus are symbolized as *a1-1*, *a1-2*, etc. Molecular geneticists involved in physical mapping of the DNA use this term for any DNA difference (e.g., restriction fragment) that displays Mendelian inheritance and occupies the same chromosomal site (see Fig. A51). Allelic variation is widespread within a species and knowledge of the nature of these alleles is not just important in biology, but may also be relevant in applied fields such as disease susceptibility, forensic identifications, etc. In yeast, by hybridizing two different strains and through conduction microarray analysis, the frequency of such variation (single-feature polymorphism) can be ~1% (Winzeler EA et al 1998

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Science 281:1194; Gresham D et al 2006 Science 311:1932). ▶gene symbols, ▶RFLP, ▶RAPD, ▶Mendelian ▶segregation, ▶coalescent, ▶mutation ▶age ▶of, ▶SNIPS; Slatkin M, Rannala B 2000 Annu Rev Genomics Hum Genet 1:225.

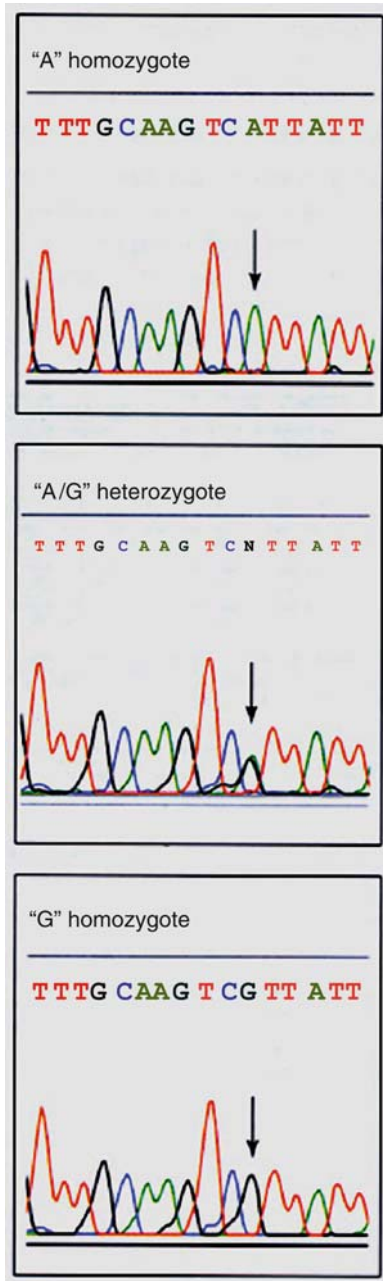


Figure A51. Mutation in a gene results in an allelic change from A (adenine) to G (guanine). Nucleotide substitution is identified by sequencing of the PCR amplified segment of the DNA. In the heterozygote for the site reduced amounts of both A and G is shown. (Courtesy of Amersham Biosciences, GE Healthcare Biodirectory 2005, p. 310.)

Allele Calling: Allele calling refers to the identification of an allele on the basis of chemical/molecular information.

Allele Dropout: When small DNA samples are multiplied too many times during forensic or ancient DNA analysis, certain alleles of a heterozygous individual may be lost to the process. ▶forensic ▶genetics, ▶DNA ▶fingerprinting; Gill P et al 2000 Forensic Sci Int 112:17.

Allele-Sharing Methods: Allele-sharing methods detect linkage by examining pedigrees for whether a particular genetic locus (chromosomal fragment) is more common among individuals in a pedigree than expected by random segregation. It is basically a non-parametric method. The probability of allele-sharing may be denoted by Y and the probability that R alleles are shared among $2N = \binom{2N}{R} Y^R (1-Y)^{2N-R}$. For R shared alleles the maximum lod score = $R \log_{10} R + (2N-R) \log_{10} (2N-R) - 2N \log_{10} N$.

An allele-sharing study of 1,592 DZ twin pairs from two independent Australian cohorts, of which 1,561 pairs were informative for linkage on chromosome 6, and 336 DZ twin pairs from the Netherlands, showed no evidence of excess allele sharing, either at the HLA locus or in the rest of the genome. One Australian group indicated a small yet significant deficit of allele-sharing (Montgomery GW et al 2006 Amer J Hum Genet 79:1052). ▶non-▶parametric ▶tests, ▶lod ▶score; Nyholt DR 2000 Am J Hum Genet 67:282.

Allele-Specific Probe For Mutation (ASP): In principle, this would detect single base change mutations because under very high stringency of hybridization oligonucleotide probes (ASO) would hybridize only to that sequence, which is exactly matching but not to another that has one base pair substitution. This would also identify heterozygotes because they would hybridize to both types of probes, mutant and normal. This procedure requires high skills but can be semi-automated. ▶hybridization, ▶mutation ▶detection, ▶probe, ▶SNIP, ▶ASO; Prince JA et al 2001 Genome Res 11:152.

Allelic Association: ▶linkage, ▶disequilibrium

Allelic Combinations: Allelic combinations in gametes (at independent loci) can be predicted by $2n$ where n is the number of different allelic pairs, and it produces $4n$ gametic combinations and $3n$ genotypes. If the number of loci is n and each has a number of alleles, the number of zygotic genotypes at one locus can be calculated as $[a \times (a + 1)]/2$ and for n loci: $\left[\frac{a \times (a+1)}{2} \right]^n$

Thus e.g., for 100 loci, each with three alleles $[(3 \times 4)/2]^{100} \geq 6.53 \times 10^{77}$ zygotic genotypes are

possible. ▶multiple alleles, ▶gametic array, ▶Mendelian segregation

Allelic Complementation: Allelic complementation is partial or incomplete complementation among mutant alleles of a gene, representing different cistrons (see Fig. A52).



Figure A52. Allelic complementation of py^5 (top row), py^4 (bottom row) temperature-sensitive mutants requiring 2-methyl-4-amino-5-aminomethyl-pyrimidine grown in test tubes. their hybrids are in the middle. (From SL Li and GP Rédei, unpublished)

If the alleles are defective when homozygous, they do not contribute to the synthesis of functional proteins. Each of the two alleles in a heterozygote has another non-overlapping defective polypeptide product. The correct polypeptide chains in the cytoplasm may combine in the heterodimeric or heteropolymeric proteins, and due to right assembly, the function of these proteins may be restored. Since the available correct polypeptide chains are reduced in number relative to that in the wild type, only a reduced number of good protein molecules can be formed. Therefore, allelic complementation is incomplete. The beneficial effect from the non-defective peptide chains may be brought about also by conformation correction, i.e., the conformation of defective chains is brought into line as an effect of the other polypeptide chain, as long as there is no defect at the active site. The extent of allelic complementation can be best determined by in vitro enzyme assays when regulatory genes cannot modify the functions by higher intensity or prolonged transcription of the relevant cistrons. ▶step allelomorphism, ▶conformation, ▶complementation mapping, ▶allelism test, ▶non-allelic, ▶non-complementation; Li SL, Rédei GP 1969 Genetics 62:281.

Allelic Dropout: Allelic dropout occurs during amplification (by PCR) when a microsatellite locus is not replicated by the DNA polymerase. ▶PCR; Miller CR et al 2002 Genetics 160:357.

Allelic Exclusion: Allelic exclusion refers to the phenomenon when only one of the two alleles at a locus is expressed or only one type of chain rearrangement is functional. Such conditions are found in immunoglobulins, various receptors, interleukin-2, and imprinted genes. Protein kinase C (PKC) modulates both differentiation and allelic exclusion during thymocyte differentiation. ▶immunoglobulins, ▶monoallelic ▶expression, ▶interleukin, ▶imprinting, ▶PKC, ▶thymocytes; Michie AM et al 2001 Proc Natl Acad Sci USA 98:609; Borst P 2002 Cell 109:5; Mostovslavsky R et al 2004 Cell 118:539.

Allelic Fixation: Allelic fixation takes place in a random mating population when one allele completely replaces another. The process depends on the coefficient of selection and the size of the populations (see Fig. A53). The time that has elapsed since the fixation of a beneficial allele is estimated on the basis of nucleotide variation at linked loci. (Przeworski M 2003 Genetics 164:1667).

Allelic Frequencies: Allelic frequencies can be determined on the basis of the Hardy-Weinberg theorem, according to which, the genotypic composition of a random mating population is $p^2 + 2pq + q^2$, where p^2 and q^2 are the frequencies of the homozygous dominants and recessives, respectively. Thus, if we consider a single allelic pair, A and a , and diploidy, the frequency of the A allele = double the number of homozygous dominants plus the number of heterozygotes. The frequency of the a allele = double the number of homozygotes plus the heterozygotes, because the homozygotes have two copies of the same allele whereas the heterozygotes have only one of each kind (see Fig. A53).

The frequency of the recessive alleles in an equilibrium population is simply $1 - p$ ($= q$). The heterozygotes may not be directly recognized in case of dominance, therefore this equation may not be applicable there. However, in case the population is at equilibrium and the mating is at random, the frequency of the recessive alleles is $q = \sqrt{q^2}$. If the size of the homozygous recessive class is very small, the vast majority of recessive alleles occur in the heterozygotes. In case of sex-linkage, the male carries one dose (XY) whereas the female is XX. Thus, males display recessive traits more frequently than do females, who express it only when homozygous. Therefore, if the expression of an X-linked recessive allele is 0.10 in males, in females it is expected to show up at $(0.10)^2 = 0.01$. The frequency of alleles in a population may change by selection, mutation, random drift, and migration. At random mating the total variance of allelic frequency with two alleles of $2n$ genes is computed from the Weir

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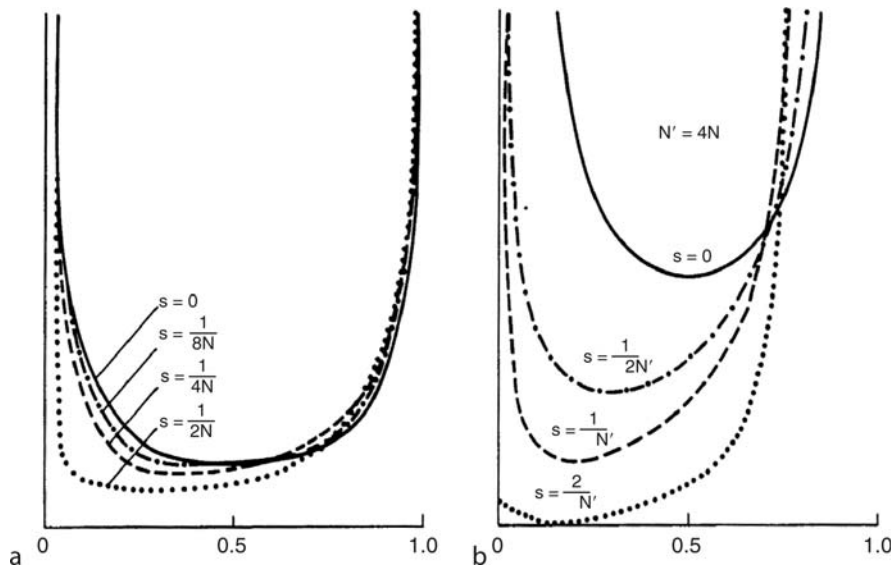


Figure A53. In very small populations only high selection coefficients can bring about changes in allelic distribution (a). When the size of the population increases fourfold, relatively small selection coefficients effectively modify the direction of fixation (b). The ordinate represents allelic densities, the abscissa shows allelic frequencies from loss, (0) to complete fixation (1.0); s = selection coefficient, N = population size. (From Wright S 1931 Genetics 16:97)

formula: $V(p) = \frac{p(1-p)}{2n} [F_{ST}(2n-1) + 1]$ and $F_{ST} = \frac{\sigma^2 - 1}{2n-1}$. ▶Hardy - Weinberg theorem, ▶selection, ▶mutation, ▶random genetic drift; Hung S-P, Weir BS 2001 Genetics 159:1365, <http://info.med.yale.edu/genetics/kkidd>; <http://alfred.med.yale.edu/alfred/AboutALFRED.asp>.

Allelic Interaction: ▶overdominance

Allelic Recombination: Allelic recombination takes place between the same sites of the homologous chromosomes. ▶ectopic recombination, ▶homologous recombination

Allelic Rescue: Allelic rescue is a procedure for cloning a mutant allele. A vector carrying the wild type allele, which has, however, an internal deletion overlapping the mutant site, transforms the mutant cell. When the cellular (gap) repair system fills in the deleted sequences using the mutant template, the plasmid vector carrying a copy of the mutant gene can be isolated, and along with it the gene itself. ▶DNA repair, ▶transformation, ▶marker rescue

Allelism Test: An allelism test is carried out by a complementation test. If two recessive genes are allelic, they fail to complement each other in the F_1 hybrids (i.e., the hybrid is of mutant phenotype). In case the hybrid of two recessive individuals is of wild phenotype (i.e., they complement each other) the two genes are not allelic. Thus, the number of

complementation groups reveal the number of different loci. In practice, the term complementation groups is understood as different complementation groups. However, allelic genes at the same multicistronic locus may show partial or allelic complementation. allelic complementation, non-allelic non-complementation; Demerec M, Ozeki H 1959 Genetics 44:269.

Allelomorph: Allelomorph is a historical term for an allele. ▶allele

Allelopathy: Allelopathy refers to the release of repellent or toxic compounds by plants to suppress neighboring species or to defend against insects or other parasites. (See Pickett JA et al 2003 Biochem Soc Trans 31 [1]:123)

Allelotyping: Allelotyping is the determination of the spectrum and frequency of allelic variations in a population. Polymorphism may be determined by restriction fragment length, SNIPS, LOH, PCR, etc. genotyping, ▶RFLP, ▶SNIPS, ▶PCR, ▶LOH; Girard L et al 2000 Cancer Res 60:4894; Yan H et al 2002 Science 297:1143.

Allergen: An allergen is any substance that causes an allergy. ▶allergy, allergenicity assessment: <http://bioinformatics.bmc.uu.se/evaler.html>.

Allergy: Sensitivity to a particular antigen(s); an allergy is the evidence of an immunological reaction. Common forms are the hay fever after exposure to

pollen (ragweed), drug, food, bacteria, cold, etc. The allergic reaction may be a hereditary property (atopy). In asthma, hay fever, and various other allergic reactions the regulatory *Re* gene is implicated in the decrease of immunoglobulin E level, and in *re/re* individuals it seems to be higher. The frequency of the *re* gene is estimated to be about 0.49. The IgE response in about 60% of the atopy cases is assigned to chromosome 11q13-q12, the site of the high-affinity IgE receptor (FcεRI-β) gene. The IgE response is apparently controlled by IgE receptor (FcεRI) and regulated by interleukin 4 (IL-4). It also appears that the IgG Fc receptor, FcγRIII, affects FcεRI assembly. Ragweed sensitivity is assigned to the HLA complex in human chromosome 6. Elevated levels of immunoglobulin E, controlled by an autosomal dominant gene with incomplete penetrance, have been detected in the neutrophil chemotaxis defect, characterized by chronic eczema, repeated infections by staphylococci and eosinophilia (cytological structures readily stained with eosin stains). Asthma and other allergies are apparently under the control of multiple genetic loci. Allergies may be alleviated by desensitization, which involves exposure to increasing amounts of the allergen in order to regulate IgE production. DNA immunization may stimulate Th1 immunity, either by producing IgG2a and IFN-γ, or by Th2 response along with the production of IgE and IgG and an increase in interleukins (IL-4, -5, -10). Actually Th1 cells antagonize the inflammatory reaction whereas Th2 cells, with the aid of IL-3, IL-5 and GM-CSF, stimulate eosinophils through IL-3, IL-4, IL-6 and IL-9 and regulate mast cells and inflammation. Dendritic cells negatively regulate Th2 cells with the aid of IL-12, and Th2 cells in turn, helped by IL-10, lower the response of dendritic cells to allergens. Bacteria and viruses promote the production of IL-12 and thus stimulate Th1 cells. Th1 cells boost the body's defense against intracellular pathogens (bacteria and viruses) by increased production of IFN-γ and synthesis IgG2a. Th2 cells, IgE, and IgG1 mediate defense against larger extracellular pathogens. The allergens of fungi and other parasites boost the level of Th2 cells and elevate IgE level in the serum. IL-4 and IL-13 enhance IgE production by B-lymphocytes and thus evoke inflammatory responses. The CD23 receptor of IgE may promote or hinder antibody presentation depending on the circumstances. In grass hay fever, CD4⁺CD30⁺ Th2 cells react to the allergen. Glucocorticoids and IL-4 enhance Th2 activity, whereas dihydroepiandrosterol favors Th1 cells. IFNα, IL-12 and TGF-β expand Th1, while IL-10, IL-6 and IL-4 skew the balance toward Th2. Allergen recognition through MHC class II peptides, organ localization, and response to allergens

all have clear genetic components. Environmental factors play very important roles as well, considering how the overall incidence of allergy and asthma is on the rise. ▶atopy, ▶ragweed, ▶HLA, ▶immunoglobulins, ▶asthma, ▶anaphylaxis, ▶eczema, ▶hypersensitive reaction, ▶γδT cell, ▶interleukin, ▶immunization ▶genetic, ▶CD4⁺, ▶CD30⁺, ▶CD23, ▶IFN, ▶TGF, ▶IL-▶10, ▶IL-3, IL-5, ▶IL-6, ▶IL-4, ▶IL-12, ▶IL-13, ▶glucocorticoid, ▶histamine, ▶interferons; Nature [Lond] 402[6760] Suppl.; oral allergy vaccine: Ma S, Jevnikar AM 2005 Proc Natl Acad Sci USA 102:17255.

<http://www.nlm.nih.gov/medlineplus/allergy.html>, allergen prediction: <http://www.imtech.res.in/raghava/allgpred/>.

Alligator (giant lizards): The two most commonly known species are *Alligator mississippiensis*, 2n = 36, *Crocodylus niloticus* 2n = 32.

Allium (onion, garlic): *Allium* is a monocot genus, 2n = 16 or 32, and is well suited for cytological analysis.

Alloantibody (isoantibody): An alloantibody is produced by an individual of a species, against alloantigens within the species. This may be due to preceding transfusions or pregnancies and may cause hyperacute rejection in case of transplantation in another individual of the same species. ▶alloantigen

Alloantigen: An alloantigen is a genetically determined antigen variant within the species. It may also be called neoantigen when the epitope appears the first time. Alloantigens are recognized within the same species by lymphocytes with different haplotype. ▶antigen, ▶epitope, ▶lymphocyte, ▶haplotype, ▶isoallogen, ▶alloantibody

Alloantisera: Alloantisera are antibodies that can recognize a certain protein in a different individual.

Allocatalasia: Allocatalasia is characterized by the condition when the catalase activity and stability is normal yet the protein is a different variant. ▶catalase

Allocation: Allocation refers to the differential distribution of cellular resources to specific structures and organs in an individual organism.

Allochronic Species: Allochronic species do not exist during the same time period in evolution.

Allocyclus: Chromosomal regions, chromosomes, or genomes may show cyclic variation in coiling and heteropycnosis. ▶heterochromatin, ▶heteropycnosis, ▶Lyonization, ▶Barr body

Allodiploid: An allodiploid is a polyploid that has chromosome sets (genomes) derived from more than

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one ancestral organism, e.g., hexaploid bread wheat has A, B, and D genomes. ►autotetraploid, ►*Triticum*

Allodynia: Allodynia is pain hypersensitivity evoked by innocuous stimuli. ►pain sensitivity; Tsuda M et al 2003 *Nature [Lond]* 424:778.

Allogamous: Allogamous individuals do not pollinate the pistils of the same plant, crosspollinating, and are also called exogamous species.

Allogamy: Allogamy is fertilization between gametes from different individual(s). ►autogamy

Allogeneic: Antigenic difference exists between two cells (in a chimera). ►antigen, ►allograft, ►autologous, ►xenogeneic

Allogeneic Inhibition: Allogeneic inhibition is found in mice; in this condition parental cells do not accept a graft from the F1, but the reciprocal graft may be successful. grafting in medicine; Mathew JM et al 2000 *Transplantation* 70:1752.

Allogenic: ►allogeneic

Allograft: The transplantation of tissues carrying cell surface antigens not present in the recipient leads to a graft that may be rejected and destroyed, and the process itself may harm the recipient. ►HLA, ►graft, ►isograft, ►heterograft, ►complement, ►grafting in medicine, ►xenotransplantation

Allohaploid: An allohaploid is a haploid cell derived from an allodiploid. ►allodiploid

Allolactose: The inducer of the *Lac* operon; it is the intermediate product of lactose (a di-saccharide) digestion by β -galactosidase, and is further converted to galactose and glucose by the same enzyme. ►galactosidase, ►lactose, ►*Lac* operon

Allolysis: ►fratricide

Allometric Development: Allometric development refers to the different growth (development) rate of one part of the body relative to other parts.

Allometry: Allometry is the study of growth of organs in different dimensions of space and time within an individual, or populations, or during evolution (Frankino WA et al 2005 *Science* 307:718; Kodric-Brown A et al 2006 *Proc Natl Acad Sci USA* 103:8733).

Allomixis: ►cross fertilization, ►allogamy

Allomone: ►kairomones

Allopatric Speciation: Allopatric speciation is involved in geographic adaptation and sexual isolation of species living in non-identical habitats. ►speciation, ►postzygotic isolation

Allophenic: Originally, allophenic genes refer to those genes that may not be expressed in one cell type but act as gene activators in other tissues. It also refers to the expression of genes in chimeric tissues of an embryo or adult that has been produced through in vitro fusion of two or more genetically different (chimeric) blastomeres. These blastomeres develop upon the fusion of the gametes of two parents, each, and several different blastomeres can be fused, resulting in (tri-, quadri-, hexa-parental, etc.) multiparental offspring. The fused blastomeres are implanted into the uterus of pseudopregnant animals, who carry the developing mosaic embryos to term. The procedure opposite to the formation of allophenic chimeras is splitting up 8-cell embryos, in two steps, into separate blastomeres and insertion of four such cells into an empty zona pellucida. Subsequently, these “quadruplets” can be transferred into the uterus of a rhesus monkey, which has produced a viable, normal offspring by this procedure (Chan AWS et al 2000 *Science* 287:317). This type of cloning offers the means for producing progeny identical in both its nuclear and cytoplasmic hereditary components. biparental, chimera, blastomere, photo at multiparental; LoCascio NJ et al 1987 *Dev Biol* 124:291; Petters RM, Markert CL 1980 *J Hered* 71:70.

Allophycocyanin: Allophycocyanin is a fluorochrome; it is excited at wavelengths 610 and 640 nm and emits bright red light at 650 nm. It is used in flow cytometry. ►fluorochromes, ►flow cytometry, ►phycobilins

Alloplasmic: An alloplasmic cell is a cell in which the cytoplasm and the nucleus are of different origins. ►nuclear transplantation, ►cell genetics

Allopolyploid: An allopolyploid species contains two or more types of genomes from different species, e.g., *Triticum turgidum* (macaroni wheat), an allotetraploid containing the AABB genomes, *Triticum aestivum* (bread wheat), an allohexaploid with AABBDD genomes, and *Triticum crassum* (a wild grass), a hexaploid DDDMM. *Nicotiana tabacum* is an allotetraploid ($2n=48$) containing the genomes of *N. tomentosiformis* ($2n=24$) and *N. sylvestris* ($2n=24$). When *N. tabacum* is crossed with either of the parents, the F1 will have 12 bivalent (12") and 12 univalent (12') chromosomes. The degree of homology between genomes can cytologically be determined in meiosis on the basis of chromosome pairing and chiasma frequency. Allopolyploids generally acquire during evolution genes that suppress multivalent pairing of chromosomes, therefore the gene segregation pattern resembles that of diploids with more than one pairs of alleles. A duplex autotetraploid may segregate in a range between 35:1 and 19.3:1 (depending on the distance between gene and centromere), while an

allotetraploid is expected to display a 15:1 ratio and an allohexaploid a 63:1 proportion if there are 4 and 6 copies of the genes, respectively. However, some genes (which have only two alleles) in hexaploids may display a 3:1 segregation. ▶duplex, ▶sesquidiploid, ▶allopolyploid segmental, ▶autopolyploid

Allopolyploid, Segmental: Here, participating genomes have partial (segmental) homology yet are sufficiently different to cause some sterility. ▶allopolyploid

Alloproteins: Alloproteins contain non-natural amino acids. ▶genetic ▶code, ▶peptidomimetics; Kiga D et al 2002 Proc Natl Acad Sci USA 99:9715.

Allopurinol (hydroxypyrazole pyrimidine): Allopurinol is an inhibitor of de novo pyrimidine synthesis and xanthine oxidase activity (see Fig. A54). It is used as a medicine to treat gout and hyperuricemia, but can also cause severe skin disease (epidermal necrolysis). ▶xanthine, ▶gout, ▶uric acid, ▶Stevens-Johnson syndrome

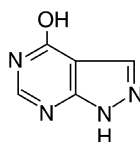


Figure A54. Allopurinol

Alloreactive (allorestrictive): An alloreactive cell is a T cell that recognizes a foreign antigen and mobilizes cellular defense against it, e.g., graft rejection. ▶T cell, ▶antigen

All-Or-None Trait: Such a trait is either present or absent, and there are no intermediates.

Allospecific: Its specificity is different from the standard normal.

Allostasis: Allostasis is a stage or state of homeostasis beyond the normal range. It may be evoked by environmental stress. homeostasis.

Allostatis: Allostatis are juvenile hormone inhibitors in insects. They have highly conserved six C-terminal amino acids. juvenile hormone.

Allosteric Control: Allosteric control is the modification of the activity of an enzyme by alteration at a site different from the active site by another molecule affecting its conformation without a covalent attachment. ▶active ▶site, ▶conformation, ▶intrasteric regulation; Süel GM et al 2003 Nature Struct Biol 10:59; signal transduction models: Changeux J-P, Edelstein SJ 2005 Science 308:1424.

Allosteric Effector: An allosteric effector is a molecule that is involved in bringing about allosteric control. ▶allosteric control, ▶allostery

Allostery: Allostery is a conformational change in a protein (ribozyme) through the effect of a ligand molecule; the process is often called allosteric shift. ▶allosteric ▶control; Monod J et al 1963 J Mol Biol 6:306.

Allosyndesis: Allosyndesis is the synapsis between non-entirely homologous chromosomes in an allopolyploid. ▶homoeologous chromosomes, ▶chromosome pairing

Allotetraploid: ▶amphidiploid

Allotopic Expression: Allotopic expression takes place when a gene, which is not organellar (mitochondrial or plastidic by origin), is targeted and expressed in an organelle. ▶ectopic expression

Allotype: Allotype refers to the difference in antibody (or antigen) caused presumably by allelic substitution mutation in the same constant region genes. ▶isotype, ▶immunoglobulins, ▶antibody

Allozygote: Allozygote refers to an individual that at one or more loci possesses alleles that were not derived from the same common ancestor, i.e., are not identical by descent. ▶inbreeding, ▶coancestry, ▶autozygous

Allozymes: Allozymes are different forms of an enzyme, occurring due to allelic differences in the genes.

All-Walking Approach: All-walking approach is a program used in the physical mapping of DNA in connection with YACs. The STS (sequence-tagged sites) are derived from the ends of YAC inserts. The three main advantages of this program are: the position of the STS here is defined vis-à-vis cases where the STS is internal; the program identifies chimeric YACs; and uses end-STS YACs that tend to be larger than others. ▶YAC, ▶STS

Allyl Alcohol: Allyl alcohol is a liquid eye-irritant that permits positive selection of alcohol dehydrogenase mutations because the wild type cells (*adh*⁺) behave in a suicidal manner to convert this compound to acrylaldehyde, as a result of which, only the *adh*⁻ cells can survive. ▶mutant isolation

Almond (*Prunus amygdalus*): The basic chromosome number $x = 7$ and $2x$ to $6x$ forms are known.

Alopecia: Alopecia is hair loss or baldness caused probably by an autoimmune condition occurring in different forms. In some cases it is accompanied by psychomotor epilepsy (involuntary movements), palm and sole keratosis (callosity), nail dysfunction, and lower mental capacity. In humans it appears as autosomal dominant. A recessive mutation (ACA, [Thr]→GCA, [Ala]) in human chromosome 8p12,

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causing total baldness (alopecia universalis), may be based on a defect in a zinc finger transcription factor. One form is caused by mutation in the Hfh11^{nu} (forkhead/winged helix) transcription factor family. In mice, asebia (rudimentary sebaceous glands) and alopecia may be caused by mutation in two genes: *Scd1* encoding stearoyl-CoA desaturase 1 and *Scd2* coding for stearoyl-CoA desaturase 2. Some cancer chemotherapies induce alopecia, which can be mitigated by topically applied inhibitors of CDK2, such as the analogs of 3-(benzylidene)indolin-2-ones, etoposides, and cyclophosphamide-doxorubicin. ▶baldness, ▶hair, ▶autoimmune disease, ▶keratosis, ▶zinc finger, ▶nude mouse, ▶connective tissue disorders, ▶hypotrichosis, ▶etoposide, ▶cyclophosphamide, ▶doxorubicin

Alpers Progressive Infantile Poliodystrophy: This condition involves degeneration of the gray matter of the brain and cirrhosis of the liver. POLG (15q25) mutations affecting the catalytic subunit of mitochondrial DNA polymerase- γ A are responsible (Nguyen KV et al 2005 Neurology 65:1493). ▶mitochondrial DNA depletion syndromes

Alpert Disease (AFP) AFP is alpha-fetoprotein deficiency, encoded at human chromosome 4q11-q13. ▶fetoprotein; Greenberg F et al 1992 Am J Obstet Gynec 167: 509.

Alpert Syndrome 10q26 Alpert Syndrome is acrocephalosyndactylia, a disease characterized by a pointed skull and fused fingers and toes. This autosomal dominant or recessive human disease involves the fibroblast growth factor receptor (FGFR2), which is defective in the Pfeiffer syndrome as well. Its estimated mutation rate is $3-4 \times 10^{-6}$. ▶Pfeiffer syndrome; Moloney DM et al 1995 Nature Genet 13:48.

Alpha Accessory Factor: The alpha accessory factor enhances the affinity of pol α and primase for the DNA template. ▶pol α , ▶primase, ▶Okazaki fragment

Alpha Complex: The translocation complex of chromosomes (see Fig. A55), it transmits only through the female, whereas the beta complex is transmitted only through the male (in *Oenothera*). ▶translocation complex, complex heterozygotes; Cleland RE 1972 *Oenothera*: Cytogenetics and Evolution. Academic Press, New York.

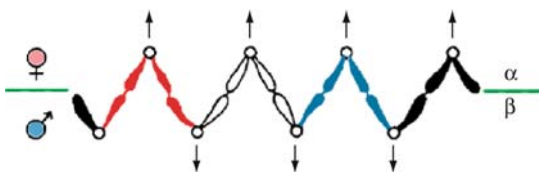


Figure A55. Alternate distribution of a four-translocation complex at anaphase I (α and β)

Alpha-Fetoprotein: ▶fetoprotein

Alpha Helix: The alpha helix is a hydrogen-bonded secondary structure of polypeptides, where the polypeptide backbone is tightly wound around the longitudinal axis of peptide bonds and the groups of amino acids protrude along this generally right-handed helical structure (see Fig. A56). Commonly, 3.6 amino acids form each turn. It is often represented as a cylinder as well. protein ▶structure, ▶pitch



Figure A56. Two representations of alpha helix

Alphameric: Alphameric symbols use alphabetical notations, and possibly other characters, such as numbers.

Alpha Parameter: The alpha parameter provides a combined estimate of the frequency of quadrivalent association (q), meiotic exchange (e), and favorable anaphase distributions (a), and from these it predicts the frequency of double reduction, i.e., the production of *aa* gametes when the parental constitution is *AAAA* (see diagram of chromosome mechanics). In a triplex the cytogenetic constitutions can be represented as shown. The letters W, X, Y and Z stand for the centromeres, the chromatids are symbolized by the gray lines, and the dominant and recessive alleles are numbered from *A1* to *A6* and *a1* to *a2*, respectively (see diagram).

(i) In the absence of recombination the association of chromatids, alleles, and centromeres are: *A1-A2*, *A3-A4*, *A5-A6*, and *a1-a2*.

(ii) In case of recombination between gene and centromere the following arrays are formed:

A1-A3, *A1-A5*, *A3-A5*. These are the possible recombinant associations of dominant alleles, which were originally attached to different centromeres.

(iii) *A1-a1*, *A3-a1*, and *A5-a1* are the three possible dominant-recessive recombinant associations, when only one chromatid originally attached to a centromere is considered in the quadrivalent.

The total frequency of the gametes is 1 and the frequency of group (i) is designated as α , and the chance of each of the 4 types of associations within this group is $\alpha/4$.

The combined frequency of recombinant group (ii) and (iii) associations is $1 - \alpha$. Since groups (ii) and (iii) have 3 representatives each, and combined 6, the frequency of each of the recombinant associations is $(1 - \alpha)/6$.

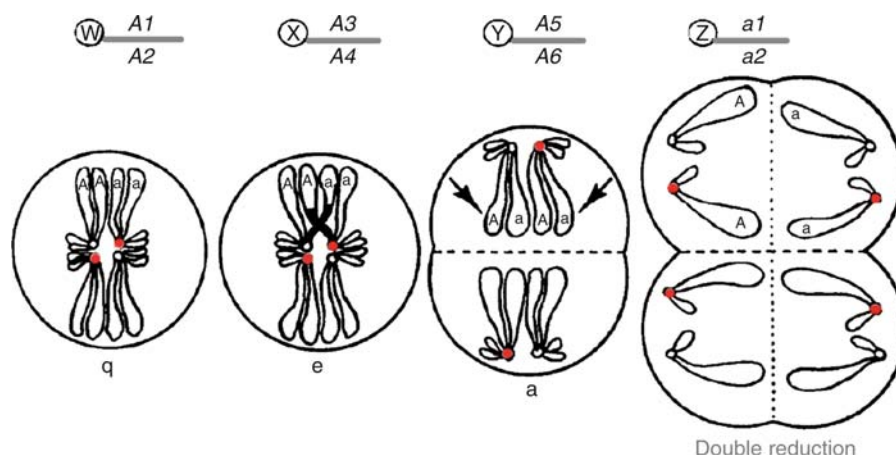


Figure A57. Chromosome mechanics (double reduction) are represented by the diagram; empty arms carry the A (dominant) allele

Group (i) has 3 double dominants ($A1-A2$, $A3-A4$, and $A5-A6$) among 4, each with a frequency of $\alpha/4$. The combined frequency of the group is $3 \times (\alpha/4)$. Group (ii) also has 3 double dominants ($A1-A3$, $A1-A5$, $A3-A5$) with individual frequencies of $(1 - \alpha)/6$ each, and a combined group frequency of $3 \times (1 - \alpha)/6$. Thus the total frequency of gametes with a dominant allele in both chromatids is $[3 \times (\alpha/4)] + [3 \times (1 - \alpha)/6] = [3\alpha/4] + [(3 - 3\alpha)/6]$. After dividing both the numerator and denominator of the second term by 1.5, we obtain the formula: $[3\alpha/4] + [(2 - 2\alpha)/4] = (2 + \alpha)/4$ = the frequency of AA gametes. The frequency of the Aa gametes is obtained similarly. Group (iii) has 3 Aa gametes with individual frequencies of $(1 - \alpha)/6$, and their combined frequency upon dividing numerator and denominator by 1.5 becomes $3 \times (1 - \alpha)/6 = (3 - 3\alpha)/6 = (2 - 2\alpha)/4$. The frequency of the double recessive gametes (aa) as shown above is $\alpha/4$. Thus the total gametic output of the triplex is $\frac{2+\alpha}{4}$ AA : $\frac{2-2\alpha}{4}$ Aa : $\alpha/4$ aa . The practical meaning of the α parameter is best illustrated by an example. Let us assume that the cytological analysis indicates the value of $q = 0.7$, $e = 0.25$, and $a = 0.333$. Thus $\alpha = 0.7 \times 0.25 \times 0.333 \times 0.5 = 0.02914$. This value can then be substituted into the formulas in the table (see Table A3).

Accordingly, for the simplex (line 3 at tetrasomy) AA becomes $\alpha/4 = 0.02914/4 = 0.007285$, Aa is obtained in frequency $2(1 - \alpha)/4 = 0.48543$, and $aa = (2 + \alpha)/4 = 0.507285$. Thus the double dominant gametes are expected to occur at a frequency below 1%, while Aa and aa at a near equal frequency of around 50%.

The proportion of the double reduction (aa gametes) indicates to some extent the relative distance of the gene from the centromere, albeit not in precise units directly convertible to map distance,

but approximating it. Theoretically, these calculations are elegant, but unfortunately the determination of the variable components of α requires great experimental skills and very favorable conditions. Therefore the analysis of segregation in polyploids is very difficult. ▶autopolyploids, ▶centromere ▶mapping; Mather K 1935 J Genet 30:53; Mather K 1936 J Genet 32:287.

Alpha Particles: Alpha particles are helium nuclei (contain 2 protons and 2 neutrons) emitted by radioactive decay. They release their excessive energy in a very short track; even in air they move only for a few centimeters. They have minimal penetration in living material, yet are very destructive (can break chromosomes) because of their short track and high ionizing energy.). Mean number of lethal lesions/per cell: α rays: 0.01, γ rays: 0.001, 10 MeVB neutrons: 0.005. ▶ionizing radiation, ▶linear energy transfer

Alpha Tocopherol (vitamin E): Tocopherols are plant products but are required in mammals for the maintenance of fertility and for the prevention of muscle degeneration. They appear to be antioxidants for unsaturated lipids. Lipid peroxidation may result in cross-linking of proteins and may cause mutation, the appearance of age pigments (lipofuscin), etc. ▶unsaturated fatty acids, ▶fatty acids

Alphavirus: An alphavirus is a single, negative-strand RNA virus with a 240 molecule basic capsid protein, surrounded by a lipid bilayer of 240 glycoprotein heteromeric envelope. It can infect a variety of cells and its genomic RNA is translated into non-structural proteins to begin the replication of the viral RNA. Although it is a cytotoxic virus it may be engineered

A

Table A3. Alpha parameter

| ZYGOTES | | GAMETES | | | |
|------------|---------------|-----------------|---------------|---------------|---------|
| | | TETRASOMY | | | DIVISOR |
| | AA | Aa | aa | | |
| Triplex | $2 + \alpha$ | $2(1 - \alpha)$ | α | | 4 |
| Duplex | $1 + 2\alpha$ | $4(1 - \alpha)$ | $1 + 2\alpha$ | | 6 |
| Simplex | α | $2(1 - \alpha)$ | $2 + \alpha$ | | 4 |
| | | HEXASOMY | | | |
| | AAA | Aaa | Aaa | aaa | DIVISOR |
| Pentaplex | $3 + \alpha$ | $3 - 2\alpha$ | α | 0 | 6 |
| Quadruplex | $3 + 3\alpha$ | $9 - 5\alpha$ | $3 + 3\alpha$ | α | 15 |
| Triplex | $1 + 3\alpha$ | $9 - 3\alpha$ | $9 - 3\alpha$ | $1 + 3\alpha$ | 20 |
| Duplex | α | $3 - \alpha$ | $9 - 5\alpha$ | $3 + 3\alpha$ | 15 |
| Simplex | 0 | α | $3 - 2\alpha$ | $3 + \alpha$ | 6 |

Simplex : 1 A

Duplex : 2 A

Triplex : 3 A

Quadruplex : 4 A

Pentaplex : 5 A

Nulliplex : no A

The A value indicates the number of dominant alleles in the zygotes

The expected gametic frequencies of polyploids. Each term on the corresponding line has to be divided by the *Divisor* • shown at the right column. (After Fisher RA, Mather, K, 1943 Annals of Eugenics 12:1)

into a vector for transient gene therapy or used for vaccination. This group of viruses includes the Sendai virus and the Simliki forest virus. ►Sendai virus

Alphoid DNA: ► α satellite

Alport's Disease: Alport's Disease exists in different forms of which, autosomal dominant, recessive, and X-linked types are described. The phenotypes vary but most common symptoms are inflammation of the kidney(s), and deafness. Most probably the primary defect involves the basement membrane of the kidney glomerules and the Goodpasture antigen leading to kidney failure and hypertension. Bone marrow-derived stem cells may repair basement membrane defects and may prove therapeutically useful for treatment of Alport patients (Sugimoto H et al 2006 Proc Natl Acad Sci USA 103:7321). The basement membrane defect is an Xq22 coded collagen α -chain anomaly. Essentially, the Alport syndrome is the same as the Epstein syndrome. The autosomal dominant Alport syndrome with leukocyte inclusions and macrothrombocytopenia (also called Fechtner syndrome) is assigned to 22q11-q13. ►Goodpasture syndrome, ►collagen, ►basement membrane, ►kidney diseases, ►thrombocytopenia, ►May-Hegglin anomaly, ►stem cells

ALPS-1, ALPS-2 (autoimmune lymphoproliferative syndrome): ALPS-1 (10q24) is caused by malfunction (mutation in Fas or FASL [1q23]) and ALPS-2 by mutation in caspase-10 (2q33-q34). In either case the apoptotic process is interfered with, causing neurodegeneration, tumorigenesis, and other disorders. The disease is rare and occurs in childhood.

T cells accumulate but carry no CD4 or CD8 and the immune system turns against the red blood cells or the platelets. ►autoimmune ►diseases, ►FAS, ►FasL, ►apoptosis, ►CD4, ►CD8, ►T cells; Chun HJ et al 2002 Nature [Lond] 419:395.

ALS: ►amyotrophic lateral sclerosis

Alström Syndrome (ALMS, 2p13): The Alstrom Syndrome is an autosomal recessive human defect involving obesity, retinitis pigmentosa, deafness, and diabetes. Its frequency is elevated in some Louisiana and Nova Scotia populations of French origin. The ALMS1 protein contains 4,169 amino acids. ►obesity, ►Bardet-Biedl syndrome

ALT: ALT is a mechanism alternative to telomerase for the maintenance of telomere length integrity. ALT relies on recombination and depends on the Rad52 protein mediating homologous recombination. In order to prevent the restoration of telomere length during cancer therapy, perhaps both telomerase and ALT need to be targeted. ►telomerase; Grobely JV et al 2001 Hum Mol Genet 10:1953.

AlterMap: The AlterMap is a computer program replacing sections of the Kohara map of *E. coli* with the MapSearch alignments of DNA fragments. ►Kohara map

Alternate Disjunction: Alternative disjunction takes place in a translocation heterozygote when each pole receives a complete set of the genetic material, and consequently the zygote is genetically stable. ►adjacent distribution, ►translocations chromosomal, ►translocation complex

Alternate Paternity: Alternative paternity is the situation where the biological father is different from the legal father. ►paternity exclosure

Alternation of Generations: Alternation of generations refers to the cycles of haploid and diploid generations such as the gametophytic and sporophytic generations of plants. It also refers to the cycles of sexual and asexual generations that coexist in some species. ►life cycles, ►meiosis, ►mitosis, ►apomixis, ►parthenogenesis, ►fission, ►gametophyte, ►sporophyte

Alternative Splicing: Alternative splicing of mRNAs generates different protein molecules from the same genes after eliminating introns (see Fig. A58). Tissue-specific expression of many human genes is based on alternative splicing and the extent of the global operation can be studied by microarrays (Pan Q et al 2004 Mol Cell 16:929). Splicing factors such as the hnRNP and a serine-arginine protein are used to carry out these functions. hnRNP A1 normally favors a distal 5' splice site, but under the influence of p38 protein kinase signals, splicing may be switched to a proximal 5' splice site. Typically, alternative splicing occurs in immunoglobulin synthesis (among other mechanisms) and T cell receptors to generate a greater repertory of antibodies from a fewer number of genes (Wang J et al 2002 Science 297:108). A survey of 528 human genes indicated 22% alternative splicing, while others indicated 40–60% alternative splicing. (Modrek B, Lee C 2002 Nature Genet 30:13). (Estimates indicated transcripts between 2.5 and 5.4 per human gene.). The average in human chromosome 12 was 2.89 transcripts per gene but for UBC (ubiquitin C, 12q24.3) 20 transcripts were found for each gene (Scherer SE et al 2006 Nature 440:346). A study of 1% of the human genome indicated that 86% of the genes are alternatively spliced (Harrow J et al 2006 Genome Biol 7[Suppl.1]:S4.1). Also it was found that in 1% of the human genome there are tissue-specific and often unannotated set of exons outside the current boundaries of

the annotated genes (Denoeud F et al 2007 Genome Res 17:746). Alternative splicing displays great similarities between the human and mouse genomes (Modrek B, Lee CJ 2003 Nature Genet 34:177). However, Yeo GW et al 2005 (Proc Natl Acad Sci USA 102:2850) found much less correspondence in alternative splicing between humans and mice. The *Drosophila* axon guidance receptor *Dscam* (Down syndrome cell adhesion molecule) gene has the potential to generate 38,000 alternative transcripts (Schmucker D et al 2000 Cell 101:671). Thus alternative splicing requires fewer genes to carry out different functions. Alternative splicing has similar incidence in humans and other higher eukaryotes but it is rare or non-existent in unicellular eukaryotes. In general, about one-third of the alternative splice isoforms contain premature termination codons and although they may persist, eventually they are degraded by nonsense-mediated mRNA decay (Lewis BP et al 2003 Proc Natl Acad Sci USA 100:189). Aberrant alternative splicing is a common cause of human genetic disease (Cáceres JF, Kornblihtt AR 2002 Trends Genet 18:186). Exons duplicated in tandem (occurring in about 10% of eukaryotic genes) may be responsible for alternative splicing. Computational methods identified 245 mammalian genes in which, the exons in the DNA are not linear with the order in the mRNA. Exons in the RNA can be duplicated leading to a potential increase in phenotypic variations (Dixon RJ et al 2005 Nucleic Acids Res 33:5904). Alternative splicing is common in cancer and most of the cDNA sequences (~70%) in databases are derived from cancer cells. Therefore, these do not represent normal conditions (Roy M et al 2005 Nucleic Acids Res 33:5026). In vitro study indicates that in *Drosophila*, exons flanked by long introns have 90-fold higher chances of being alternatively spliced. The length of upstream introns in *Drosophila* is more influential than the length of downstream introns. In humans, the architecture has a similar consequence. (Fox-Walsh KL et al 2005 Proc Natl Acad Sci USA 102:16176). In *Arabidopsis* and rice plants, more than 21% of the genes display over 8% alternative splicing; more than half result in intron retention (Wang B-B, Brendel V 2006 Proc Natl Acad Sci USA 103:7175). ►splicing, ►spliceosome, ►introns, ►mRNA ►surveillance, ►hnRNA, ►p38, ►microarray ►hybridization, ►tissue ►specificity, ►exon ►skipping, ►K_A/K_S, ►DEGEST; Lopez AJ 1998 Annu Rev Genet 32:279; Tollervey D, Cáceres JF 2000 Cell 103:703; Standiford DM et al 2001 Genetics 157:259; Modrek B et al 2001 Nucleic Acids Res 29:2850; Hu GK et al 2001 Genome Res

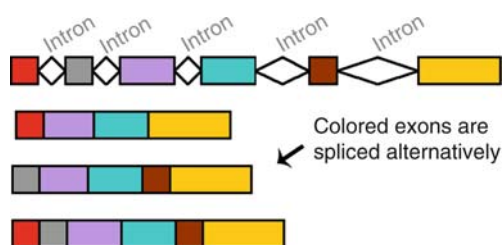


Figure A58. Alternative splicing

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11:1237; Gravely BR 2001 Trends Genet 17:100; Brett D et al 2002 Nature Genet 30:29; Kadener S et al 2002 Proc Natl Acad Sci USA 99:8185; Letunic I et al 2002 Hum Mol Genet 11:1561; Gravely BR 2002 Cell 109:409; Maniatis T, Tasic B 2002 Nature [Lond] 418:236; Zhu J et al 2003 Science 301:836; Matlin AJ et al 2005 Nature Rev Mol Cell Biol 6:386; alternative splicing and protein structure: Wang P et al 2005 Proc Natl Acad Sci USA 102:18920; alternative splicing and evolution: Xing Y, Lee C 2006 Nature Rev Genet 7:499; Biencowe BJ 2006 Cell 126:37; <http://cbcg.nersec.gov/asdb/>; <http://isis.bit.uq.edu.au>, annotation of alternatively spliced genes: <http://genome.ewha.ac.kr/ECgene/>, alternative splicing of human genes: <http://SpliceInfo.mbc.NCTU.edu.tw>; <http://prosplicer.mbc.nctu.edu.tw>, human alternative splicing database: <http://jbirc.jbic.or.jp/h-dbas/>, alternative tandem splice sites: <http://helios.informatik.uni-freiburg.de/TassDB/>; <http://www.ebi.ac.uk/asd/>; <http://hollywood.mit.edu/Login.php>, prediction of alternative splicing: <http://augustus.gobics.de/>; <http://t.caspuir.it/ASPIC/>, alternative splicing in 15 animal species: <http://www.bioinformatics.ucla.edu/ASAP2>, alternative splicing services: <http://bip.umiacs.umd.edu:8080/>, alternative splicing for entire transcripts and individual genes: <http://genome.imim.es/astalavista/>.

Altosomes: Altosomes are structurally altered dinucleosomes composed of two histone octamers, and bear an asymmetrically located region of nuclease-accessible DNA. Altosomes can be formed on chromatin that contains the abundant mammalian linker histone H1 and has a unique micrococcal nuclease digestion footprint that helps measure the position and abundance of altosomes on any DNA sequence. Over time, altosomes spontaneously revert to structurally normal but improperly positioned nucleosomes, suggesting a novel mechanism for transcriptional attenuation as well as transcriptional memory, following human SWI/SNF action (Ulyanova NP, Schnitzler GR 2005 Mol Cell Biol 25:11156). ► **nucleosome**, ► **SWI/SNF**

Altruistic Behavior: Altruistic behavior is an evolutionary feature in animals where members of the species protect other members, especially the young, even at their own peril. Altruism (helping others without expecting benefits) is genetically controlled; however, cultural inheritance also plays an important role. Human infants as young as 18 months can already show altruism, but chimpanzees at the same development stage are much less motivated for this behavior (Warneken F, Tomasello M 2006 Science 311:1301).

Altruism can promote the survival of the population. Altruism may also be manifested in mating behavior. In a pride of animals some males may refrain from reproduction to allow more powerful kin to mate with available females. Apoptosis involves some elements of altruism of single cells that turn suicidal in order to ensure differentiation of a tissue or defend the organism against mechanical or biological injuries or attacks. ► **kin selection**, ► **inclusive fitness**, ► **apoptosis**, ► **behavior genetics**, ► **aggression**, ► **group selection**, and ► **“green beard effect”**; Agrawal AF 2001 Proc Roy Soc Lond B Biol Sci 268:1099; Abbot P et al 2001 Proc Natl Acad Sci USA 98:12068; group selection and cooperation: Traulsen A, Nowak MA 2006 Proc Natl Acad Sci USA 103:10952

Alu Family: Alu family refers to 150–300-bp long nucleotide sequence monomers associated head-to-tail, and repeated about 300,000–500,000 times or more in the primate genome. RNA polymerase III transcribes Alu sequences. These nucleotide sequences are cut by the Alu I restriction enzyme (recognition site AG↓CT) and hence the name of these gene families. Members of this family are also considered to be transposable elements, which depend on other elements for transposition. The Alu sequences are specific for the human genomes but homologs appear in other mammals. The Alu sequences appear to have evolved from the 7SL RNA genes throughout the human genome by retrotransposition, to reach the present number of more than one million copies. Several lines of evidence demonstrate that these elements modulate gene expression at the post-transcriptional level (Häsler J, Strub K 2006 Nucleic Acids Res 34:5491; corrigendum: double bond error in Fig 3 [Nucleic Acids Res 35:5491]).

Alu insertional mutations have been identified in the genes involved in antihemophilic factor IX, neurofibromatosis, Apert syndrome, adenomatous polyposis cancer, X-linked immunodeficiency, and breast cancer. It is most likely that many more such sequences will be identified in the completely sequenced human genome. Alu elements may be inserted into RNA transcripts and may convert introns into new exons by a process of *exonization* (Lev-Maor G et al 2003 Science 300:1288). Alu sequences as well as other repeats, by recombination increase the instability of the genome. Alu elements can be used to trace evolutionary paths and human migration (Salem A-H et al 2003 Proc Natl Acad Sci USA 100:12787). ► **SINE**, ► **LINE**, ► **7SL RNA**, ► **selfish DNA**, ► **Myr**, ► **see the diseases listed under separate entries**; Stenger JE et al 2001 Genome Res 11:12; Roy-Engel AM et al 2001 Genetics 159:279;

Batzer MA, Deininger PL 2002 Nature Rev Genet 3:370, Alu in the human genome: McGuire DJ et al 2006 Adv Exp Med Biol: 578:73.

Alu-Equivalent: Alu-equivalent are a group of genomic sequences similar to the Alu family. ► [Alu family](#)

Aluminum Tolerance: Aluminum tolerance can be bred into plants by expression of the transgene of *Pseudomonas aeruginosa* citrate synthase. The transgenic plants exude citrate or malate by the roots and lower the pH of the soil. Aluminum induces from the roots of tolerant plants the release of organic acids and chelate Al^{3+} into the rhizosphere; the complexes so formed are less toxic. Several plant genes (QTLs) are involved in the resistance (Hoekenga OA et al 2006 Proc Natl Acad Sci USA 103:9738). Aluminum in alkalic or neutral soil is toxic to many crop plants. The *stop1* mutation (involved in the zinc finger domain in a predicted Cys2His2-type zinc finger protein encoded in chromosome 1 of *Arabidopsis*) had no effect on cadmium, copper, lanthanum, manganese, and sodium chloride sensitivity, but it caused hypersensitivity to Al^{3+} root-toxicity (Iuchi S et al 2007 Proc Natl Acad Sci USA 104:9900). (See Ma JF et al 2001 Trends Plant Sci 6:273)

Alzheimer's Disease (AD, FAD): Is a presenile/senile dementia (loss of memory and ability of judgment as well as general physical impairment) involving the accumulation of amyloid protein plaques in the brain, and resulting in degeneration of neurons and build-up of neurofibril tangles. At an early (prodromal) stage of AD, memory loss is not yet associated with dementia. In this condition there is atrophy in the hippocampus and the region near the hippocampus (parahippocampal region) (Soub TR et al 2006 Proc Natl Acad Sci USA 103:10041). The amyloid fibers form antiparallel β -sheets in a cross arrangement and are bound together between phenylalanine rings and salt bridges that exist between charged pairs (glutamic acid–lysine). These fibers stabilize the structure of the plaques. (Makin OS et al 2005 Proc Natl Acad Sci USA 102:315). Four major genes are responsible for AD. The amyloid- β peptide ($A\beta$, of 40–42 amino acids) comes from a larger amyloid precursor protein (β APP) that is synthesized in the normal brain, is processed in a number of ways, and is encoded in chromosome 21q21.3–q22.05 as a rare early onset dominant (AD1). Duplications of 0.58 to 6.37 Mb segments involve increase in deposits of amyloid- β (Rovelet-Lecrux A et al 2006 Nature Genet 38:24). The $A\beta$ -42 fragment has more deleterious effects; its three-dimensional structure has been determined (Lührs T et al 2005 Proc Natl Acad Sci USA 102:17342). The largest protein spans the cell

membrane (AD3, 14q24.3). One of the extracellular domains is a protease inhibitor. This domain may be released in normal cells, but in diseased cells the amyloid protein is processed incorrectly. Regulation of K^+ ion channels, calcium homeostasis, and protein kinase C (PKC) gene activation (by bryostatin) promote the solubility and secretion of the amyloid protein APP α obtained from transgenic mouse brain cells. Thus, it may alleviate the human condition as well (Etcheberrygaray R et al 2004 Proc Natl Acad Sci USA 101:11141).

Synaptic acetylcholinesterase (AChE-S) seems to promote fibril formation of insoluble $A\beta$. The homologous synthetic butyrylcholinesterase (BchE) that has a tryptophan residue in the polar side of the C terminus of the enzyme, co-localizes with AChE and attenuates fibril and tangle formation of amyloids (Diamant S et al 2006 Proc Natl Acad Sci USA 103:8628).

Genes responsible for the amyloid protein synthesis have been cloned and others mapped to human chromosomes 1q31–42 encoding STM2/AD4, a seven-transmembrane integral protein [presenilin 2], and to chromosome 14q24.3 encoding protein S182/AD3 (presenilin 1), which is 67% homologous to STM2. Human chromosome 19q13.2 encodes (AD2) apolipoprotein E (APOE) that controls the late onset of Alzheimer's disease. In late-onset AD (LOAD) Bace1 protease cleaves APP to generate the N terminus of $A\beta$. This protease is more active in patients with LOAD. Some results indicate that compounds antagonizing the apoE/ $A\beta$ interaction constitute an effective therapeutic approach for AD (Sadowski MJ et al 2006 Proc Natl Acad Sci USA 103:18787). A Bace-linked leucine-rich repeat transmembrane 3 (*LRRTM3*) neuronal gene promotes APP processing by BACE1 (Majercak J et al 2006 Proc Natl Acad Sci USA 103:17967). Expression of the β -site β -amyloid precursor protein (APP) cleavage enzyme gene *BACE1* is tightly controlled at both the transcriptional and translational levels. A functional hypoxia-responsive element in the *BACE1* gene promoter up-regulates β -secretase cleavage of APP and production of amyloid- β protein, by increasing *BACE1* gene transcription and expression both in vitro and in vivo. Thus, hypoxia facilitates onset of AD (Sun X et al 2006 Proc Natl Acad Sci USA 103:18727). APP overexpression leads to postsynaptic silencing through a selective reduction of AMPA receptor-mediated currents. $A\beta$ likely mediates this effect because expression of mutant APP incapable of producing $A\beta$ was found not to depress transmission (Ting JT et al 2007 Proc Natl Acad Sci USA 104:353).

Homozygosity for the APOE-4 allele (frequency ~16%) increases the chances of onset of the disease

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about 20 times, while a single copy of the APOE-2 (frequency ~7%) only doubles this chance. Chromosome 21q21.3-q22.05 (AD1) encodes β APP (early onset, dominant) and seems to be involved with the disease. $A\beta$ is the major component of the brain plaques and its ligand is a protein with a relative molecular weight ~50K, identical to RAGE (receptor for advanced glycation endproduct) or AGE/ β APP and for amphoterin controlling neurite outgrowth (an inflammatory process). RAGE/AGER receptor (6p21.3) mediates the interaction of $A\beta$ with endothelial cells and neurons, causing oxidative stress. Its interaction with microglia results in cytokine production, chemotaxis and binding movements. A spurious, unconfirmed interaction among AD1/APP, AD2/APOE, A2M (α -macroglobulin, encoded at 12p13.3-p12.3), and a low-density lipoprotein related protein (LRP, encoded at 12q13.1-q13.3) have been reported. The PAR-4/PRKC (prostate apoptosis response) mutations in the gene encoding 342 amino acids, that include a leucine zipper and a death domain, mediate neuronal degeneration and mitochondrial dysfunction in case of defects in presenilin 1. $A\beta$, in the mitochondria of AD patients, interacts with an alcohol dehydrogenase (ABAD). Reactive oxygen species are leaked consequently and lead to mitochondrial toxicity and impairment of hippocampal function. The latter causes memory impairment (Lustbader JW et al 2004 Science 304:448). Mutations in the control region of the brain mtDNA interfere with mitochondrial replication and transcription in AD (Coskun PE et al 2004 Proc Natl Acad Sci USA 101:10726). Sporadic AD may be associated with the very low-density lipoprotein (VLDL) receptor gene. The sortilin-related protein (SORL1; 11q23.2-q24.2) is a member of both the vacuolar sorting protein-10 domain receptor and the low-density lipoprotein receptor. Inherited variants in the SORL1 neuronal sorting receptor are associated with late-onset AD. These variants occur in at least two different clusters of intronic sequences within the *SORL1* gene (also known as *LR11* or *SORLA*) and may regulate tissue-specific expression of *SORL1*. SORL1 directs trafficking of APP into recycling pathways, and under-expression of SORL1 causes sorting of APP into $A\beta$ -generating compartments and results in AD (Rogaeva E et al 2007 Nature Genet 39:168).

AD is common among individuals with Down's syndrome (that occurs due to chromosome 21 trisomy where β APP is located). Some psychotropic drugs (drugs affecting the nervous system) may alleviate certain symptoms. The incidence of Alzheimer disease (AD) increases from 0.1% below 70 to double or may even reach 2% after age 80. The risk for first-degree relatives varies from 24 to 50% by age 90. Aberrant aggregation of $A\beta^{42}$ fragments and aging, are slowed when there is a decrease in insulin/insulin-like growth

factor-1 signaling. (Cohen E et al 2006 Science 313:1604). The concordance rate of AD among monozygotic twins is 40–50% and among dizygotic twins 10–50%. Genetic screening for the disease is not considered appropriate. In 2005, the estimated number of people afflicted was 4.5 million and by (2050) this number may increase to 11.3–16 million. The sporadic (apparently non-genetic) cases of this disease may be caused by frameshift mutation in the RNA during transcription or after transcription, in the β amyloid precursor and/or in ubiquitin-B. The identification of AD is difficult without an autopsy or biopsy detecting the brain plaques. Biopsies generally reveal shrinkage of gyri in the lobes of the brain involved in processing learning and memory, namely the temporal and the frontal. Pet scans (positron emission tomography) of living brains reveal reduced energy metabolism in these regions in case of AD (Mattson MP 2004 Nature [Lond] 430:631). The aggregation of $A\beta$ can be detected by fluorescence correlation spectroscopy, provided the polymerization is promoted by “seeding” with synthetic $A\beta$ probe in femtoliter samples of the cerebrospinal fluid and Cy2 fluorophore is used. The difference between afflicted and healthy individuals is clear and the procedure may be of potential value for diagnosis. It is highly desirable that AD be detected before the onset of clinical symptoms. Magnetic resonance imaging of the brain of a mouse into whose basal ganglia or blood stream E,E-1-fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB) has been precisely injected, clearly labels the early deposits of amyloids (see Fig. A59). The toxicity of the procedure seems negligible although much improvement is required before it could be used clinically for humans (Higuchi M et al 2005 Nature Neurosci 8:527; this paper is also the source of the formula of FSB adopted).

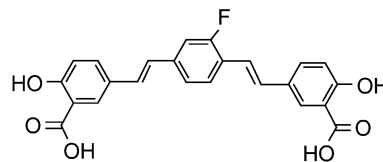


Figure A59. FSB

Mice transgenic for a mutant (Val⁷¹⁷→Phe⁷¹⁷) human APP, when immunized with $A\beta^{42}$, either prevented, or reduced the neuropathological symptoms. Unfortunately this type of vaccination resulted in meningoencephalitis in some patients and clinical trials were halted. Immunotherapy for AD so far has resulted in beneficial as well as undesirable, effects (Monsonogo A, Weiner HL 2003 Science 302:834). A non-viral $A\beta$ vaccine in mice is shown to have, beneficial prophylactic effects and ~50% reduction

in amyloids after the onset of amyloid deposition, without serious side effects (Okura Y et al 2006 Proc Natl Acad Sci USA 103:9619).

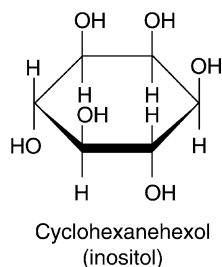


Figure A60. Cyclohexanehexol

The most likely time-course of the development of AD is: mutations in the amyloid and presenilin genes → production of Aβ⁴² fragments → formation of plaques in the brain cortex → hyperphosphorylation of tau, oxidative stress, and the formation of tangled fibers → neuronal dysfunction and neuronal death → mental deterioration. Tau reduction can block Aβ- and excitotoxin-induced neuronal dysfunction and may represent an effective strategy for treating AD and related conditions (Robertson ED et al 2007 Science 316:750). There is evidence that the formation of plaques and fibrillar tangle is preceded by the appearance of 2.7 to 4.2 nm diameter soluble oligomers (see Fig. A60). The structure of the oligomers, rather than their amino acid composition, may be responsible for the toxicity (Kayed R et al 2003 Science 300:486). Early in the disease axonal swelling may occur due to deficit in microtubule-associated transport of proteins, organelles and vesicles (Stokin GB et al 2005 Science 307:1283). The hyperphosphorylation of tau, a microtubule-associated protein, is mediated by the cyclin-dependent kinase, Cdk5. Phosphorylation gets enhanced and tau binds less efficiently to microtubules, when the p35 regulatory subunit of Cdk5 is cleaved into a truncated p25 fragment. Also, Cdk5/p25 promotes apoptotic cell death of neurons. AD involves the inflammation of the brain, as well. β-Amyloid seems to stimulate CD40-CD40L interaction causing the activation of microglia. Microglial cells are important players in AD pathogenesis by promoting the degeneration of neurons. Although AD is generally attributed to the accumulation of pathological levels of Aβ¹⁻⁴², it is possible that the other cause of the disease is the lack of clearance of the plaques by the neprilysin-like neutral endopeptidase (NEP) and related enzymes. Insulin-degrading enzyme (IDE, 10q23-q25) in neurons and microglia degrades Aβ. Protein kinase PKCε upregulates endothelin-converting enzyme ECE and reduces the number of amyloid plaques, in transgenic mice (Choi

D-S et al 2006 Proc Natl Acad Sci USA 103:8215). In a mouse model, Aβ immunization appears to reduce plaques and fibrils in the brain and improves cognitive functions and memory. In transgenic mice models of AD, oral administration of cyclohexanehexol stereoisomers (before or after the onset of the symptoms), inhibits the aggregation of Aβ amyloid peptides into high molecular weight oligomers, ameliorates cognition, synaptic physiology, and cerebral pathology and reduces early mortality (McLaurin J et al 2006 Nature Med 12:801).

In LOAD the Aβ₄₂ level is elevated by genetic factors in human chromosome 10q (Myers A et al 2002 Am J Med Genet 114:235). Although at the moment there is no cure for AD, some environmental factors may exert beneficial effects. Increased cognitive/mental activity, consumption of a low-calorie diet rich in vitamins C and E, and physical exercise may delay or reduce somewhat the onset of AD. In a mouse model of AD, a diet rich in omega-3-fatty acids was found to protect against synaptic protein loss and memory deficits (Calon F et al 2004 Neuron 43:633). The APP cleavage product by α-secretase is neuroprotective due to the increased expression of transthyretin and an insulin-like growth factor (Stein TD et al 2004 J Neurosci 24:7707). Procedures of blocking the activities of β and γ secretases, chelation of copper and iron in the brain and immunization with Aβ₄₂, are currently being studied. A transgenic mouse model suggests that an “enriched environment,” i.e., exercise, elevates the level of the Aβ-degrading endopeptidase, neprilysin, and thus reduces the amyloid burden, selectively upgrading transcripts associated with learning, memory, vasculogenesis, neurogenesis and cell survival (Lazarov O et al 2005 Cell 120:701). A mouse model is available for early-onset behavior and synaptic deficits of AD (Jacobsen JS et al 2006 Proc Natl Acad Sci USA 103:5161). Intracerebral injection of dilute human Aβ or cerebral extract from Alzheimer patients, into an APP transgenic mouse induced β amyloidogenesis depending on the agent used or the recipient host (Meyer-Luehmann M et al 2006 Science 313:1781). This phenomenon bears some similarity to prion action, although this is not very clear.

The nematode *Caenorhabditis elegans* has a single APP-related gene, *apl-1*, that is expressed in multiple tissues. Loss of *apl-1* disrupts several developmental processes, including molting and morphogenesis, and results in larval lethality. *Apl-1* lethality can be rescued by neuronal expression of the extracellular domain of APL-1. These data highlight the importance of the extracellular domain of an APP family member and suggest that APL-1 acts in a non-cell-autonomous manner during development. Overexpression of APL-1 also causes several defects, including a high level of larval lethality. Decreased

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activity of *sel-12*, a *C. elegans* homologue of the human γ -secretase component presenilin 1, partially rescues the lethality associated with APL-1 overexpression, suggesting that SEL-12 activity regulates APL-1 activity either directly or indirectly (Hornsten A et al 2007 Proc Natl Acad Sci USA 104:1971).

Serum response factor (SRF) and myocardin (MYOCD), two interacting transcription factors, orchestrate the vascular smooth muscle cells (VSMC)-differentiated phenotype. SRF-MYOCD overexpression in small cerebral arteries appears to initiate independently of A β , a pathogenic pathway mediating arterial hypercontractility, and cerebral blood flow dysregulation, which are both associated with Alzheimer's dementia (Chow N et al 2007 Proc Natl Acad Sci USA 104:823). ▶b-amyloid, ▶AMPA, ▶behavior human, ▶prion, ▶Creutzfeldt-Jakob disease, ▶scrapie, ▶encephalopathy, ▶sirtuin, ▶mental retardation, ▶Down's syndrome, ▶corticotropin releasing factor, ▶presenilins, ▶memory, ▶AGE, ▶microglia, ▶NF- κ B, ▶LDL, ▶VLDL, ▶ERAB, ▶frameshift, ▶ubiquitin, ▶tau, ▶excitotoxicity, ▶CDK, ▶p35, ▶secretase, ▶statins, ▶transthyretin, ▶BACE, ▶GSK, ▶ β sheet breaker peptides, ▶humanin, ▶fluorophore, ▶mitochondrial disease in humans, ▶microglia, ▶CD40, ▶CD40 ligand, ▶neprilysin, ▶endothelin, ▶protein kinase, ▶tomography, ▶sterols, ▶macular degeneration; Chapman PF et al 2001 Trends Genet 17:254; Wiltfang J et al 2001 Gerontology 47:65; Selkoe DJ 2001 Physiol Rev 81:741; Baekelandt V et al 2000 Curr Opin Mol Ther 2:540; Selkoe DJ, Podlisny MB 2002 Annu Rev Genomics Hum Genet 3:67, mouse model: Wong PC et al 2002 Nature Neurosci 5:633; Aguzzi A, Haass C 2003 Science 302:814; Cummings JL 2004 New England J Med 351:56, history of Alzheimer disease: Goedert M, Spillantini MG 2006 Science 314:777, potential approaches to treatment: Roberson ED, Mucker L 2006 Science 314:781, <http://www.alzforum.org/>.

Amacrine Cell: Amacrine cells are retinal neurons with short axons. ▶axon, ▶neurogenesis, ▶retina

Amanitin (C₃₉H₅₄N₁₀O₁₃S): ▶ α -amanitin

Amaranth: Amaranths are subtropical or tropical American seed plants with $2n = 2x = 32$.

Amastigote: ▶*Trypanosoma*

Amatoxins: Amatoxins are bicyclic octapeptides (e.g., α -amanitin) produced by the fungus *Amanita phalloides*. They inhibit the function of RNA polymerase II (occasionally pol III) of eukaryotes but do not affect the transcriptases of the prokaryotic type, e.g., transcriptases in the cytoplasmic organelles of eukaryotes. ▶RNA polymerase, ▶RNA replication, ▶transcription, ▶pol III

Amauris: *Amauris* is an African species of butterfly that is mimicked by the species *Papilio dardanus*. *Amauris* is distasteful to predators; hence the mimicking species improves its survival. ▶Batesian mimicry

Amaurosis Congenita (Leber congenital amaurosis, LCA): LCA refers to a group of autosomal recessive conditions of whole or partial blindness caused by a defect of the cornea (keratoconus). About 10% of the visually impaired suffer from LCA. LCA may also be caused by mutations in the photoreceptor guanylate cyclase (RETGC) or the retinal pigment epithelium (RPE), and in genes responsible for phototransduction and photoreceptor maintenance. Autosomal dominant photoreceptor-specific homeodomain gene (CRX), is responsible for cone-rod dystrophy of the retina. Activation of sensory transduction by opsin apoprotein in a light-independent manner may be one of the causes of LCA (Woodruff ML et al 2003 Nature Genet 35:158). LCA has been mapped to human chromosome 17p13.1. Another mutation was mapped to a retinitis pigmentosa locus (RET3C11) at 1q321-q32.1. This locus is called Crumbs Homolog 1 (CRB1) of a *Drosophila* gene. The cause of Type 1 amaurosis is located in chromosome 14 (Heilig R et al 2003 Nature [Lond] 421:601. Chromosome 6q14 encodes the ciliary protein, lebercillin, which interacts with 24 proteins and is associated with LCA (I den Hollander A et al 2007 Nature Genet 39:889). ▶eye diseases, ▶nephrolithiasis, ▶cilia; Seeliger MW et al 2001 Nature Genet 29:70; Cremers FPM et al 2002 Hum Mol Genet 11:1169

Amaurotic Familial Idiocy (AFI): Is the old name for Tay-Sachs disease. ▶Tay-Sachs disease, ▶Batten disease

Amber: Amber is a fossil tree resin up to millions of years old. It is hardened and resistant to most environmental factors. Frequently it contains microbes, plants or animals, or organic residue in a well preserved state, and thus may provide very valuable information on old organismal specimens, including genetic material. ▶ancient DNA

Amber: Amber also refers to a chain-terminator codon (UAG).

Amber Mutation: Amber mutation generates a chain-termination polar effect (the name has nothing to do with function; rather it was named after Felix Bernstein whose German family name translates into amber). ▶code genetic, ▶polar mutation; Epstein RH et al 1963 Cold Spring Harbor Symp Quant Biol 28:375.

Amber Suppressor: Amber Suppressor is a mutation in the anticodon triplet (3'-AUC-5') of a tRNA so that

the amber mutation (5'-UAG-3') may be read as a tyrosine codon and thus the translation not be terminated. *supC*, *supD*, *supE*, *supF*, *supG*, *supU*; Kiga D et al 2001 Eur J Biochem 268:6207.

Ambidextrous: ►handedness

Ambient Signals: The position of a particular cell determines its response to particular environmental stimuli.

Ambiguity In Translation (mistranslation, miscoding): Ambiguity may be brought about by antibiotics, or modification of the tRNA or the ribosomes (16S subunit). Consequently, an amino acid different from the original is incorporated into the nascent polypeptide. It seems the cognate tRNAs have ca. four orders of magnitude higher recognition rate than the non-cognate ones, measured on the basis of GTPase action rate in the EF-Tu-GDP ternary complex. Under normal circumstances, the estimated error per amino acid is 10^{-4} . ►error in aminoacylation, ►RAN, ►protein synthesis, ►EF-TU:GTP; Dong H, Kurland CG 1995 J Mol Biol 248:551; Ardell DH, Sella G 2001 J Mol Evol 53:269; Ogle JM, Ramakrishnan V 2005 Annu Rev Biochem 74:129.

Ambiguity of Restriction Enzymes: Such enzymes can cut more than a single sequence, although with varying efficiency, e.g., Hind I: GTT↓GAC, GTT↓AAC, GTC↓GAC.

Ambisense Virus (e.g., some bunyaviruses, arenaviruses) Ambisense viruses are transcribed into the mRNA, and also into the 5'-end of the RNA genome functioning as mRNA.

AMD: AMD is ARE- (AU-rich sequence) mediated mRNA decay. ►mRNA degradation, ►RNA surveillance, ►non-stop decay, ►RNAi, ►HuR

Ameiotic Recombination: ►parasexual mechanism, ►asexual

Amelia: ►limb defects in humans. ►thalidomide, ►phocomelia

Amelioration of Genes: DNA sequences incorporated into a genome by horizontal transfer, tend to adapt during evolution to the codon usage of recipient organisms. ►transmission, ►codon usage

Amelogenesis Imperfecta (AI): The autosomal dominant forms of this disease (ameloblastin and enamelin encoded within 4q11-q21) lead to softness of the tooth enamel caused by lack of calcium. Calcium deposits in the kidneys and variant symptoms indicate autosomal recessive inheritance as well. Two Xp22.3-p22.1- and Xq22-q28-linked forms are distinguished, one of which, is very similar in phenotype to the autosomal dominant form. The

enamel is softer than usual and of normal thickness in one these cases; while in the other, the enamel is hard but very thin. The combined prevalence of the two forms in Sweden is $\sim 1.4 \times 10^{-3}$. Various mouse mutants are available (Masuya H et al 2005 Hum Mol Genet 14:575). (►See entries under tooth; Rajpar MH et al 2001 Hum Mol Genet 10:1673)

Amelogenin Test: Amelogenin test is a forensic and archeological sex typing tissue test. The X chromosome- and the Y chromosome-derived amelogenin sizes are different and thus the test indicates sex of the specimen. In rare instances the AMELY gene (Yp11, Xp22.3-p22.1) is missing from the Y and in such a case, a male sample is indistinguishable from a female sample, unless other markers (e.g., the SRY gene) are involved in the test. Amelogenin is a dental enamel protein. (►SRY, ►sex determination; Buel E et al 1995 J Forensic Sci 40:641).

Amenorrhea: The absence of menstruation that may be caused by physiological factors (obesity or malnourishment, pregnancy), hormonal imbalance, age-related factors, disease-related factors, or genetic causes such as pseudo-hermaphroditism, Turner syndrome, absence of ovaries, uterus or vagina, etc. In the absence of structural deficiencies, selective estrogen-receptor modulating (SERM) drugs may be beneficial. Secondary amenorrhea occurs when menstruation is suspended or ceased after a period of time. In such cases hormone replacement therapy may be indicated. ►hermaphroditism, ►Turner syndrome

Amensalism: A condition in which one organism is inhibited by another, which is unaffected by this relationship.

American Type Culture Collection (ATCC): The ATCC maintains and catalogues microbial stocks, viruses, and cultured cells. <http://www.atcc.org/>.

Amerind (American Indians): Amerind refers to the ethnically diverse groups of people, which migrated 30–10 thousand years ago in several waves, apparently through the Behring Strait from Asia to North America, and eventually spread South. Anthropological and linguistic studies and DNA (mtDNA, Y chromosome) analysis permits the study of their origin, migration, and diversity. (►mtDNA, ►Y chromosome; Bortolini MC et al 2003 Am J Hum Genet 73:524).

Ames Test: Ames test is a bacterial assay based on backmutation of different histidine-requiring strains of *Salmonella typhimurium* (see Fig. A61). Reversions are capable of detecting various types of base substitutions and frameshift. A single plate generally detects mutations in 100,000 or more cells.

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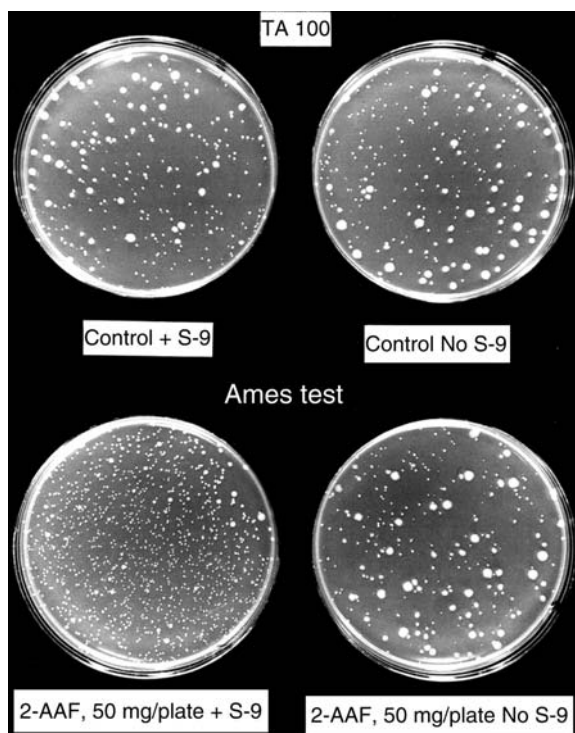


Figure A61. The Ames test with and without the use of the microsomal (S-9) fraction. It is clear that the microsomal enzymes do not affect the frequency of reversions without 2-AAF (2-acetylaminofluorene). Also 2-AAF without activation is not mutagenic. The S-9 fraction is prepared, usually, from rodent liver homogenate and in its presence, the promutagens can also be assayed. The bacteria lack the activating enzyme component. (Courtesy of Dr. D.M. Zimmer)

In some strains the *his*⁻ genes are present in multicopy plasmids to enhance the targets of the strains. Bacteria also carry mutations that interfere with genetic repair. The testing medium includes microsomal fractions of mammalian liver that can activate promutagens into ultimate mutagen. Thus the mutagenic effectiveness of a majority of chemicals may be increased by three orders of magnitude. The results of this assay are highly correlated with the carcinogenicity of the compounds being evaluated, yet its administration requires only two days compared with the several months that evaluations of rodent tests need. AMES is also inexpensive and permits the evaluation of a large number of compounds at low cost. ▶[bioassays in genetic toxicology](#), reversion studies in *Salmonella* and *E. coli* in ▶[genetic toxicology](#), ▶[microsomes](#), ▶[base substitution mutation](#), ▶[frameshift mutation](#), ▶[activation of mutagens](#); for statistical evaluations: Kim BS, Margolin BH 1999

Mutation Res 436:113; Maron DM, Ames BN 1983 Mutation Res 113:173, see Fig. A61.

Amethopterin: Amethopterin is an inhibitor of dihydrofolate reductase, an important enzyme in the de novo biosynthetic pathway of purine and pyrimidine nucleotides. Synonymous with methotrexate, amethopterin is used as an antitumor drug and as a selective agent in genetic transformation. It has also been used to treat rheumatoid arthritis and psoriasis. It is extremely toxic in concentrations of 10^{-8} to 10^{-9} , at which it may shut down the biosynthesis of nucleotides (see Fig. A62). It may also cause headaches, rashes, diarrhea, and cirrhosis of the liver. ▶[aminopterin](#), ▶[methotrexate](#), psoriasis.

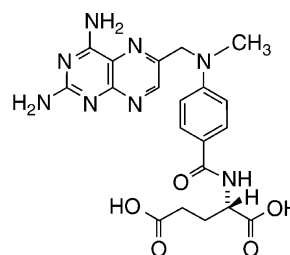


Figure A62. Amethopterin

Amide Bond: An amide bond is formed when a carbonyl group is linked to an amine (see Fig. A63). (See box, ▶[peptide bond](#)).

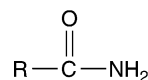


Figure A63. Amide bond

Amidotransferase: Amidotransferase enzymes are involved in charging cognate tRNAs with amino acids and in several other reactions with amid transfer. ▶[aminoacylation](#); Ibba M et al 1997 Trends Biochem Sci 22:39.

Amifostin (C₅H₁₅N₂O₃P S): Amifostin is a biological radioprotector. ▶[radioprotectors](#)

Amiloride (C₆H₈ClN₇O): Amiloride is a potassium-sparing diuretic, regulating K⁺ and Na⁺ balance in the cells. ▶[ion channels](#)

Amino Acid: An amino acid is the building blocks of a protein. There are approximately 20 naturally occurring amino acids. amino acids.

Amino Acid Activation: ▶[aminoacylation](#)

Amino Acid Analyzer: The amino acid analyzer is an automated equipment, similar to a high-pressure liquid chromatography apparatus, that separates and

quantifies the amino acid composition of protein digests. ►chromatography

Amino Acid Index: The amino acid index reveals the physico-chemical properties of amino acids and sheds light on proteins. <http://www.genome.ad.jp/dbget/aaindex.html>.

Amino Acid Metabolism: Amino acids are derived from compounds in the glycolytic-, the citric acid-, and the pentose phosphate pathways. Biosynthetic systems in different evolutionary categories may vary. Bacteria and plants are normally able to synthesize all the 20 primary amino acids, whereas animals depend primarily on diet for the *essential amino acids* (Boudko DY et al 2005 Proc Natl Acad Sci USA 102: 1360). Genetics of microorganisms plays an important role in elucidating their pathways. Single gene mutations generate special requirement for all amino acids, which can be met by feeding the amino acid or the appropriate precursor. In higher plants, auxotrophy exists only for very few amino acids, probably because amino acids may be synthesized by parallel pathways or functionally duplicated genes. In humans and other mammals, certain genetic defects may affect in different ways all the natural amino acids and many of their derivatives, and thus cause inborn errors of metabolism. ►argininemia, ►citrullinemia, ►ornithine decarboxylase, ►ornithine aminotransferase, ►ornithine transcarbamylase, ►alanine aminotransferase [glutamate-pyruvate transaminase], ►alaninuria, ►aspartate aminotransferase [glutamate oxaloacetate transaminase], ►asparagine synthetase, ►aspartoacylase deficiency, ►cystinuria, ►cystinosis, ►cystathionuria, ►homocystinuria, ►cystin-lysinuria, ►glutamate synthesis, ►glutamate decarboxylase, ►glutamate dehydrogenase, ►glutamate formiminotransferase deficiency, ►glutamate pyruvate transaminase, ►glutamate oxaloacetate transaminase, ►glutaminase, ►glycine biosynthesis, ►glycinemia, ►methylmalonicaciduria, ►vitamin B₁₂ defects, ►histidine operon, ►histidase, ►histidinemia, ►isoleucine–valine biosynthetic pathway, ►isovalericacidemia, ►3-hydroxy-3-methylglutaryl CoA lyase deficiency, ►leucine metabolism,

►methylcrotonyl-glycinemia, ►methylglutaconicaciduria, ►hydroxymethyl-glutaricaciduria, ►lysine biosynthesis, ►hyperlysinemia, ►dibasicaminoaciduria, ►methionine bio-synthesis, ►methionine adenosyl transferase deficiency, ►methionine malabsorption, ►phenylalanine, ►phenylketonuria, ►proline biosynthesis, ►hyperprolinemia, ►serine, ►threonine, ►tryptophan, ►tyrosine, ►alkaptonuria, ►valine, ►hypervalinemia, ►urea cycle, ►sarcosinemia, ►carnosinemia

Amino Acid Regulation: Amino acids and hormones, e.g., insulin, may regulate the translation of a specific amino acid mRNA or global protein synthesis, through an integrated pathway of signals.

Amino Acid Replacements: Amino acid replacements take place by base substitution in the codons, e.g., a glutamic acid (GAA) residue may be replaced by glutamine (CAA), lysine (AAA), glycine (GGA), valine (GTA), alanine, (GCA), aspartic acid (GAT), and so on. The rate of amino acid substitution per site in a protein has been estimated to average 10^{-9} /year during evolution. This average may vary by 3–4 orders of magnitude among different proteins, while the rate of substitution among genes may vary by three orders of magnitude (Wilson AC et al 1977 Annu Rev Biochem 46:573). In the enzyme 3-methyladenine DNA glycosylase (AAG), ~34% of the replacements lead to inactivation (Guo HH et al 2004 Proc Natl Acad Sci USA 101:9205).

In human disease, drastic changes in amino acid substitutions, e.g., deletions versus replacement by a similar amino acid (according to the Grantham classification), generally occur in more severe forms of the disease (Gillard EF et al 1989 Am J Hum Genet, 45:507; Miller MP, Kumar S 2001 Human Mol Genet 10:2319). ►PAM, ►mutation rate; Akanuma S et al 2002 Proc Natl Acad Sci USA 99:13549; Grantham's classification, amino acid replacement in human disease: Vitkup D et al 2003 Genome Biol 4:R72; prediction of substitutions: Ng PC, Henikoff S 2006 Annu Rev Genomics Hum Genet 7:61; <http://www.genome.ad.jp/aaindex/>; sorting intolerant from tolerant amino acid

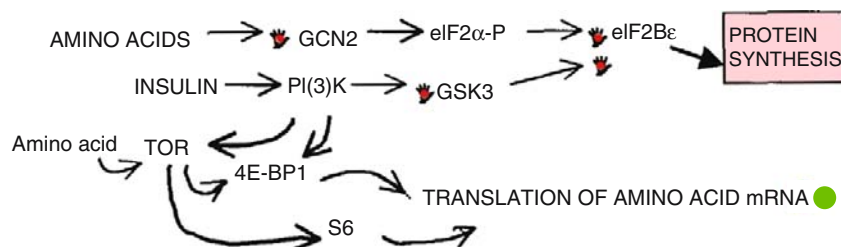


Figure A64. Regulation of Protein and amino acid synthesis under the control of amino acids and insulin

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substitutions in proteins: <http://blocks.fhcrc.org/sift/SIFT.html>.

Amino Acid Sequencing: Amino acid sequencing can be carried out in different ways. At present, the most commonly used method deduces the putative amino acid sequence indirectly from the codon sequences in DNA. Direct estimates can be obtained from polypeptides cleaved by proteolytic enzymes (trypsin, chymotrypsin, pepsin, other proteases, and cyanogen bromide) to obtain manageable smaller fragments of proteins. These agents prefer certain points of cleavage, represented by specific amino acids. Direct cleavage also utilizes the chemical breakage of disulphide bonds. This is followed by the Edman degradation, which uses end labeling and removes one amino acid at a time. Eventually, the sequenced fragments must be ordered on the basis of overlapping ends. ▶[Edman degradation](#), ▶[amino acid analyzer](#), ▶[sequenator](#), ▶[DNA sequencing](#), ▶[databases](#); Rajagopal I, Ahern K 2001 Science 294:2571; key amino acid positions in structurally similar proteins: <http://ckaaps.sdsc.edu>; sequencing aligning; structure tools: <http://toolkit.tuebingen.mpg.de/>.

Amino Acid Starvation: ▶[stringent response](#), ▶[stringent control](#)

Amino Acid Substitution: ▶[amino acid replacement](#)

Amino Acid Symbols in Protein Sequences: These are as follows: alanine A, aspartic acid or asparagine B, cysteine C, aspartic acid D, glutamic acid E, phenylalanine F, glycine G, histidine H, isoleucine I, lysine K, leucine L, methionine M, asparagine N, proline P, glutamine Q, arginine R, serine S, threonine T, valine V, tryptophan W, unknown X, tyrosine Y, glutamic acid or glutamine Z. ▶[amino acids](#)

Amino Acids: Amino acids are relatively simple yet diverse chemical compounds that all have at least one NH_2 group (see Fig. A65). **R** (see box) can be a *non-polar aliphatic* group: glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), *aromatic*: phenyl alanine (Phe), tyrosine (Tyr), tryptophan (Trp), *polar uncharged*: serine (Ser), threonine (Thr), cysteine (Cys), methionine (Met), asparagine (Asn), glutamine (Gln), *negatively charged*: aspartic acid (Asp), glutamic (Glu), *positively charged*: lysine (Lys), arginine (Arg), histidine (His). The 20 naturally occurring amino acids are known as the building blocks of proteins. Archaea and eubacteria encode, in addition, pyrrolysine (UAG) and selenocysteine (UGA, the latter also in animals). Some amino acids are modified in certain types of proteins. Cysteine and methionine always contain sulphur. In α -amino acids both the amino and carboxyl group(s) are attached to the same C atom.

The common natural amino acids in living organisms occur as the L enantiomorphs. The astrocytes in the brain, however, upon glutamate stimulation enzymatically synthesize D-serine, which facilitates synapsis between neurons by stimulation of the NMDA receptors. The amber suppressor, tRNA, aminoacylated with certain unnatural amino acids (fluoro-tyrosine, branched, and hydrophobic amino acids) can be incorporated into proteins and may be used to study the impact on hydrogen bonding, hydrophobic packing, and protein stability (Mendel D et al 1995 Annu Rev Biophys Biomol Struct 24:435). ▶[amino acid symbols in protein sequences](#), ▶[essential amino acids](#), ▶[nonessential amino acids](#), ▶[aminoacylation](#), ▶[amber suppressor](#), ▶[enantiomorph](#), ▶[unnatural amino acids](#), ▶[NMDA receptor](#), ▶[astrocyte](#), ▶[selenocysteine](#), ▶[pyrrolysine](#), ▶[genetic code](#), ▶[evolutionary clock](#)

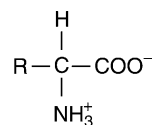


Figure A65. Amino acids general formula

Amino Group: The amino group is derived from ammonia (NH_3) by replacing one of the hydrogens by another atom ($\text{H}_2\text{N}-$).

Aminoacidurias: Aminoacidurias are diverse groups of hereditary diseases characterized by the urinal excretion of cystine (in cystinosis), tyrosine (in tyrosinemia), all kinds of amino acids (in fructose intolerance), very large quantities of primarily threonine, tyrosine, and histidine (in Hartnup disease), hypervalinemia. Many diseases of the kidneys show excessive amino acid excretion. Dicarboxylic aminoaciduria is a defect of glutamate/aspartate transport at 9p24. Dibasic aminoaciduria is a defect of cystinuria and the failure of normal transportation of dibasic amino acids at 9q13.1. ▶[homocystinuria](#), ▶[Fanconi renal tubular syndrome](#), ▶[Hartnup disease](#), ▶[neuromuscular diseases](#), ▶[Rowley-Rosenberg syndrome](#), ▶[blue diaper syndrome](#), ▶[iminoglycinuria](#), ▶[tyrosinemia](#)

Aminoacylation: An ATP-dependent enzymatic process attaches an amino acid by its NH_2 end to the acceptor arm (CCA-OH) of tRNA. The rate of mischarging is 3×10^{-3} in prokaryotes and may be higher in yeast or higher eukaryotes. Although this reaction requires a protein enzyme, a ribozyme may also be adapted to carry out aminoacylating function in a manner analogous to the ribozyme, peptidyl transferase. Certain aminoacyl-tRNA synthetases have a particular site where the misactivated amino acid tRNA

complex is destroyed to maintain the correct protein structure. Aminoacylation takes place within the eukaryotic nucleus before the correct tRNA is released to the cytosol. A single defective editing domain generates global errors in translation (Bacher JM et al 2005 Proc Natl Acad Sci USA 102:1697). For the crystal structure of an editing domain see Dock-Bergeon AC et al 2004 Mol Cell 16:375. ▶tRNA, ▶amino acid-tRNA synthetase, ▶ribozyme, ▶aminoacyl-tRNA synthetase, ▶EF-TU·GTP, ▶error in aminoacylation, ▶operational RNA code, ▶suppressor tRNA, ▶unnatural amino acids; Rodnina MV, Wintermeyer W 2001 Annu Rev Biochem 70:415; Hendrickson TL et al 2002 Mol Cell 9:353; Fahlman RP et al 2004 Mol Cell 16:799.

Aminoacyl-tRNA: Aminoacyl-tRNA is an amino acid-charged tRNA at the 3' end. ▶tRNA, ▶protein synthesis, ▶aminoacyl-tRNA synthetase, ▶amino acylation

Aminoacyl-tRNA Synthetases: These enzymes carry out the aminoacylation of tRNA (see Fig. A66). First, the amino acid is attached to the α -phosphate group of an ATP molecule. This step is accompanied by the removal of an inorganic pyrophosphate group. The aminoacyl adenylate is then bound to the active site of one of the two types of aminoacyl-tRNA synthetase enzymes. Class I, mainly monomeric (except*), enzymes handle Arg, Cys, Gln, Glu, Ile, Leu, Met, Trp*, Tyr*, and Val. Class II dimeric enzymes are involved with Ala, Asn, Asp, Gly, His, Lys, Phe, Pro, Ser, and Thr (for these abbreviations see amino acids). Class I synthetase first attaches the aminoacyl-A to the 2'-OH of the terminal A of the amino arm of tRNA. Subsequently this is shifted to the 3'-OH by transesterification. The class II enzymes bypass the 2'-OH transfer step. Enzymes recognize, among the 40–80 or more tRNAs, the appropriate acid; and this rather complex recognition process is directed by the so-called *second genetic code*. Several sites on the tRNA determine the recognition of the appropriate tRNAs, most importantly by the anticodon. In *Drosophila*, there is a Glutamic acid-Proline tRNA synthetase (GluProRS). The amino-terminal domain is active for Glu, while the C-terminal fragment is functional for Pro. In some bacteria there are three types of glutamyl-tRNA synthetases. Their substrate could be either tRNA^{Glu} and tRNA^{Gln} singly, or both. The three tRNA species have two common elements, the augmented D-helix and the deletion of nucleotide 47 (Salazar JC et al 2003 Proc Natl Acad Sci USA 100:13863).

In some Archaea, e.g., *Methanococcus janaschii*, a single aminoacyl tRNA synthetase, ProCysRS, exists for both proline and cysteine. However, this synthetase never makes ProtRNA^{Cys} or CystRNA^{Pro}

(Stathopolous C et al 2000 Science 287:479). In *E. coli* the anticodon is crucial for the recognition of 17 of the 20 amino acids. For many of the isoaccepting tRNAs, the 73 position of the amino acid-accepting arm is very important along with the anticodon. The enzyme also capable of correcting errors in recognition, e.g., isoleucyl-tRNA, cannot entirely prevent valine from attaching to its binding site and may form a valyl-adenylate. This activated valine cannot, however, attach to either tRNA^{Val} or tRNA^{Ile}; rather it is hydrolyzed by tRNA^{Ile}, so no erroneous valyl-tRNA^{Ile} is formed. Another way to eliminate translational errors is to modify the amino acids attached to the wrong tRNA; thus, rarely can these misacylated tRNA be used for peptide elongation. Actually, misacylation may occur as an intermediate step but the mentioned quality control prevents most of the stated ambiguities and errors. Misacylation of amino acids is subjected to correction by an editing complex of the tRNA (Bishop AC et al 2002 Proc Natl Acad Sci USA 99:585). tRNA-dependent amino acid modifications are the only means for the formation of formylmethionyl-tRNA and others (Asp-tRNA^{Asn}, Glu-tRNA^{Gln}) in some bacteria, archaea, and organelles. The majority of the aminoacyl-tRNA synthetases either discriminate against the D-enantiomers at activation, or use, e.g., D-Tyr-tRNA^{Tyr} deacylase, to prevent the D form from being incorporated into protein. The elongation factors (EF-Tu, EF-1 α) also prefer the L enantiomorphs. The C-terminal domain of the tyrosyl-tRNA synthetase has ~49% homology with a cytokine (endothelial monocyte-activating polypeptide II [EMAPII]). This cytokine causes phagocytotic cells to express *tissue factor* and TNF α , and migrates to the sites of inflammations. The average error in amino acid incorporation is about 1/3,000 to 1/10,000. Nuclear genes encode the aminoacyl-tRNA synthetases of organelles; however, the enzymes are organelle-specific. Some nuclear genes may encode both types of enzymes by differential transcription and processing. A reactive RNA can also catalyze this reaction, normally catalyzed by aminoacyl-tRNA synthetase. The aminoacyl-tRNA synthetases of higher eukaryotes form multiprotein complexes. Incorporation of unnatural amino acids into protein can be achieved by screening for mutant aminoacyl-tRNA synthetase genes (Link AJ et al 2006 Proc Natl Acad Sci USA 103:10180). arginyl t-RNA synthetase, ▶glutamyl-tRNA synthetase, ▶histidyl tRNA synthetase, ▶leucine t-RNA synthetase, ▶threonyl tRNA synthetase, ▶methionyl tRNA synthetase, ▶tryptophanyl tRNA synthetase, ▶valyl tRNA synthetase, ▶ribozyme, ▶EF-TU·GTP, ▶ribosomes, ▶protein synthesis, ▶tRNA, ▶missing genes, ▶cytokines, ▶EMAPII, ▶wobble, ▶tmRNA,

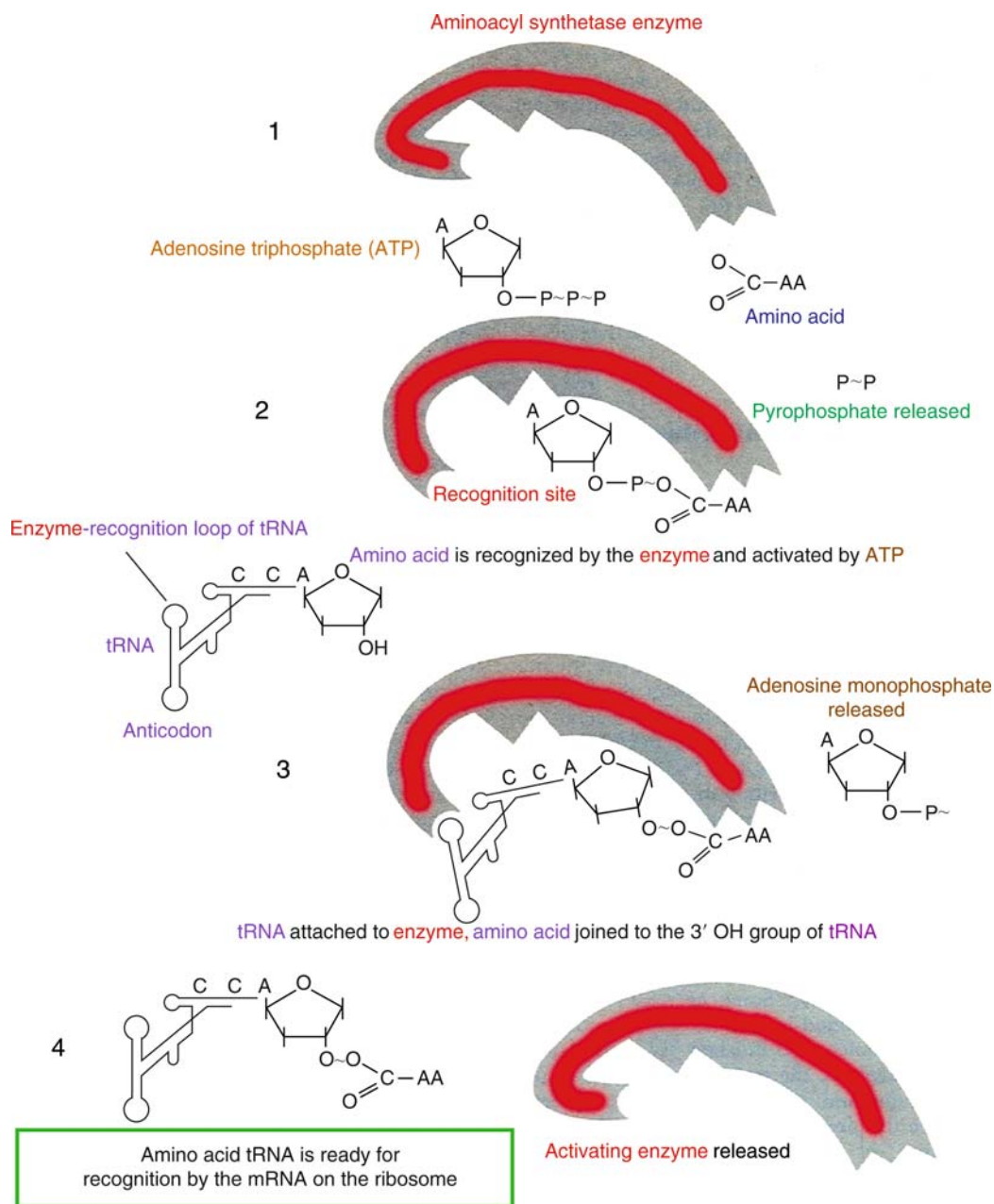


Figure A66. Amino acyl tRNA synthetases

►operational RNA code, ►unnatural amino acids; Jakubowski H, Goldman E 1992 Microbiol Rev 56:412; Carter CW Jr 1993 Annu Rev Biochem 62:715; Ibba M, Söll D 2000 Annu Rev Biochem 69:617; Ribas de Pouplana L, Schimmel P 2001 Cell 98:191; Bishop AC et al 2003 Proc Natl Acad Sci USA 100:490, <http://rose.man.poznan.pl/aars/>.

Aminobenzyloxymethyl Paper: This is a diazotized (using 1-[(m-nitrobenzyloxy)-methyl] pyridinium chloride [NBPC]) Whatman 540 or other comparable paper, used for Northern blotting. ►Northern blotting

Amino-End: The amino end of a protein marks where the synthesis began on the ribosome. It is commonly a methionine residue, although during processing of the protein the first amino acid(s) may be removed. The amino end of the polypeptide corresponds to the 5' end of the mRNA. ►amino terminus, ►protein synthesis

Aminoglycoside Phosphotransferases (NPTII, aph(3')II): NPT II phosphorylates aminoglycoside antibiotics and causes resistance against these antibiotics. The

genes for the two related enzymes were isolated from Tn5 and Tn60 bacterial transposons, respectively, and are used as dominant selectable markers (with appropriate promoters) in transformation of animal and plant cells. ▶kanamycine resistance, ▶geneticin resistance, ▶neo^R, ▶neomycin phosphotransferase; Wright GD et al 1998 Adv Exp Med Biol 456:27; Boehr DD et al 2001 J Biol Chem 276:23929.

Aminoglycosides: Aminoglycosides form a group of antibiotics in which, a cyclic alcohol occurs in a glycosidic linkage with amino-substituted sugars. They (streptomycin, kanamycin, neomycin, gentamycin, paromomycin, etc.) affect the A site (16S rRNA in the 30S ribosomal subunit) of the prokaryotic/organelle ribosomes, where the codon-anticodon interact, and thus interfere with initiation of translation, fidelity of decoding of the codon, peptidyl transfer, and peptide translocation. Inhibition of eukaryotic ribosome function requires a higher-than-approximately-20-fold concentration of the antibiotic. Resistance,—which is widespread, may be accounted for by the ability of the cells to expel antibiotics, or by enzymatic modification either of the antibiotic or the cellular target. ▶ribosome, ▶kanamycin, ▶neomycin, ▶gentamycin, ▶A site, ▶protein synthesis, ▶phenotypic reversion; Ryu H, Rando RR 2001 Bioorg Med Chem 9:2601.

Aminolevulinic Acid: (ALA): ALA is a precursor of porphyrin, required for the production of hemoglobin and chlorophylls (see Fig. A67). The ALA dehydratase (ALAD) is coded in human chromosome 9q34. ▶chlorophyll, ▶hemoglobin, ▶porphyrin



Figure A67. Aminolevulinic acid

Aminopeptidases: Aminopeptidases are generally membrane ectoenzymes involved in the processing of proteins and hormones, in controlling cell adhesion, and in signal transduction.

Aminopterin: Aminopterin inhibits the activity of dihydrofolate reductase at concentrations of 10^{-8} to 10^{-9} . This enzyme is required for the biosynthetic pathway of both pyrimidines and purines, and is also used as a drug in the HAT medium to shut down the de novo synthetic pathway of nucleotides, when thymine-, kinase-, and hypoxanthine-guanine phosphoribosyl transferase mutations are screened for in mammalian cell cultures. ▶amethopterin, ▶HAT medium, ▶DHFR

2-Aminopurine (AP): AP is an adenine analog that may incorporate into DNA in place of adenine, and can form normal hydrogen bonds with thymine. It is prone to mispairing with cytosine, either with a single hydrogen bond in its normal state, or after tautomeric shift with two hydrogen bonds (see Fig. A68). The mispairing may result in a replacement of an AT pair by a GC pair and thus, in mutation. AP may be highly mutagenic in some prokaryotes but not in eukaryotes. base analogs, ▶base substitution, ▶hydrogen pairing

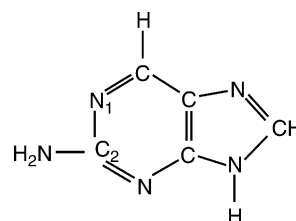


Figure A68. 2-Aminopurine

Aminoterminal: An aminoterminal is the only amino acid in a polypeptide chain with a free α -amino group; it occurs at the end of the chain. ▶amino end

Aminotransferase: Aminotransferases are transaminase enzymes that transfer α -amino groups from amino acids to α -keto acids.

3-Amino-1,2,4-Triazole: is a carcinogenic standard (non-mutagenic in the Ames test); it is now a banned herbicide. ▶Ames test

Amish: Amish refers to a Mennonite religious group that follow strict and conservative principles and lifestyle. Their communities are relatively isolated from surrounding populations. Actually, the Amish population in the USA in the 1960s, was organized in three approximately equal groups of ~14,000 people. Gene frequencies distinguish the three related groups. Incidence of endogamy and consanguineous marriage is higher, and certain genetically determined conditions more frequent, in these populations. The recessive Ellis-Van Creveld syndrome, pyruvate kinase deficiency, cartilage-hair hypoplasia, limb-girdle muscular dystrophy, and Christmas disease, are relatively common. The Amish brittle hair syndrome (also recessive) involving short stature, somewhat lower intelligence, brittle hair and reduced fertility, and low sulfur content of the nails was first recognized in such a population. ▶Ellis-Van Creveld syndrome, ▶Christmas disease, ▶cartilage-hair hypoplasia, ▶endogamy, ▶consanguinity, ▶ethnicity; McKusick VA 1980 Endeavour 42–52.

Amitochondriate: Amitochondriate organisms lack mitochondria, e.g., some microsporidian eukaryotic parasites of mammals with genomes of less than 3 Mb. More current evidence, however, indicates that these organisms may not be amitochondriate, but merely

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containing mitochondria. ▶mitosome, ▶hydrogenosome, ▶mitochondria

Amitosis: Amitosis refers to nuclear division without the characteristic features of the mitotic apparatus, and involving the small (21 to 1,500 kb) and acentric chromosomes, in the macronucleus of some *Protists*. No mitotic spindle is evident and the nuclear membrane seems intact during the entire division. The distribution of the chromatin is nevertheless, not entirely random. ▶mitosis, ▶*Paramecia*, ▶fission, ▶acentric, ▶chromatin; Prescott DM 1994 Microbiol Rev 58:233.

Amixis: Amixis is the term fungal genetics uses for apomixis. ▶apomixis

Aml1: AML1 is an acute myeloid leukemia oncogene, a DNA-binding protein, encoded in human chromosome 21q22. ▶leukemias

Ammonification: Ammonification refers to the release of ammonia upon decomposition of compounds such as amino acids.

Ammunition: Ammunition refers to gene tagging with non-autonomous P elements of *Drosophila*, which remains in place even after the removal of the helper (complete) element. ▶hybrid dysgenesis, ▶smart ammunition

Amniocentesis: Amniocentesis is a prenatal diagnosis of the genetic constitution of a fetus by withdrawing fluid or cells from the abdomen (amniotic sac) of a pregnant woman. This procedure is applicable after about 16 weeks of the pregnancy by which time the amount of the amniotic fluid is sufficient. The tests can be cytological, enzymological, immunological, or molecular, and may involve cell cultures to amplify the material. Amniocentesis can also be used for genetic counseling. Normally it entails minimal risk to either the fetus or the mother, yet should be used only in cases when it is warranted by other parts of the diagnoses. Newer procedures are aimed at the very frequency ($\sim 10^{-6}$) of fetal cells, or at fetal DNA in maternal blood. ▶risk, ▶counseling genetic, ▶prenatal diagnosis, ▶PCR, ▶polymerase chain reaction, ▶maternal contamination; Trent RJ (ed) 1995 Handbook of prenatal diagnosis, Cambridge University Press, New York; Special Advances in Fetal Evaluation; <http://www.healthscout.com/ency/1/541/main.html>.

Amnion: Amnion is the strong membrane enveloping the mammalian fetus. It contains the amniotic fluid that protects the fetus during the entire pregnancy. A similar membrane is found in other animals too. The amnion is the layer closest to the embryo, followed by the allantoic mesoderm, while the chorion is the outer layer. ▶chorion, ▶allantois

Amoeba: Amoebas are free-living or parasitic single-cell eukaryotes (see Fig. A69). Some amoebas crawl by forming pseudopodia (leg-like extensions of the single). *Amoeba dubia* has a genome size (bp) of 6.7×10^{11} in n = several hundred chromosomes. ▶nuclear transplantation



Figure A69. Ameoba

Amorph Allele: Amorph alleles are inactive; they may also be deletions. ▶allele

Amova: AMOVA refers to the analysis of molecular variance. ▶ANOVA; Excoffier L et al 1992 Genetics 131:479.

Amoxicillin: Amoxicillin is an inhibitor of cell wall-crosslinking transpeptidase; thus it enhances the effect of β -lactam antibiotics (see Fig. A70). ▶clavulanate

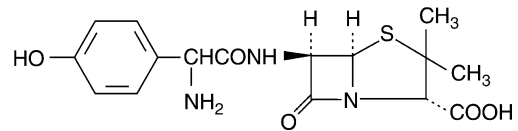


Figure A70. Amoxicillin

Amp (ampicillin, 6-[D(-)a aminophenylacetamid]-penicillanic acid): AMP is a member of the penicillin family antibiotics. The *Amp^R* genes are common in genetic vectors (see Fig. A71). ▶antibiotics, ▶vectors genetic

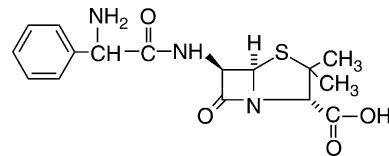


Figure A71. Ampicillin

AMP: AMP refers to adenosine 5'-monophosphate (adenylic acid); when additional 2 phosphates are added to AMP, ATP is formed. ▶cAMP

AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolpropionate): AMPA is a member of the glutamate receptor family of proteins and it mediates the excitatory synaptic transmissions in the brain and the spinal cord. It also controls post-synaptic influx of Ca^{2+} , further

regulating synapse. The AMPA receptors are built from four variable subunits having large extracellular amino ends, three transmembrane domains, and an intracellular COOH end. PDZ domains mediate the cell targeting. AMPA channels are linked to elevated Ca^{2+} influx and to progressive decline and degeneration of spinal motor neurons. The channels may also be involved in the sporadic development of amyotrophic lateral sclerosis, when aided by $\text{Cu}^{2+}/\text{Zn}^{2+}$ superoxide dismutase (Kuner R et al 2005 Proc Natl Acad Sci USA 102:5826). The GRIP (glutamate receptor interacting protein) contains seven PDZ domains, interacts with C end, and links AMPA to other proteins. ▶[synaps](#), ▶[excitatory neurotransmitters](#), ▶[PDZ domains](#), ▶[NMDA](#), ▶[MAGUK](#), ▶[kainate](#), ▶[superoxide dismutase](#), ▶[amyotrophic lateral sclerosis](#), ▶[fragile X](#); Posser RA 2001 J Neurosci 21:7815; structure, conformation of AMPA receptors: Nakagawa T et al 2005 Nature [Lond] 433:545; Tomita S et al 2005 Nature [Lond] 435:1052; Nicoll RA et al 2006 Science 311:1253.

5'-AMP-Activated Protein Kinase: This kinase regulates energy balance (Kahn BB et al 2005 Cell Metabolism 1:15).

Ampere (A): Ampere is a electric unit. 1 A = 1 C/sec. 1C (Coulomb) = 1 As (Amperesecond). ▶[Volt](#), ▶[Watt](#)

Amphibolic Path: The amphibolic path of metabolism involves both anabolic and catabolic reactions.

Amphid: Amphid is a chemoreceptor in nematodes, e.g., in *Caenorhabditis*. ▶[Caenorhabditis](#)

Amphidiploid: A cell that contains 2 genomes from at least two different species; it is obtained by doubling the number of chromosomes of amphiploids. ▶[amphiploid](#), ▶[chromosome doubling](#); Kashkush K et al 2002 Genetics 160:1651.

Amphigamy: In the usual type of fertilization the gametic nuclei fuse. ▶[dikaryon](#)

Amphihaploid: Amphihaploid refers to the haploid cell of an amphidiploid, an allohaploid. ▶[haploid](#), ▶[amphidiploid](#), ▶[allohaploid](#)

Amphimeric Genomes: In amphimeric genomes, the inverted repeats are separated by wide sequences. They may be generated in the mitochondrial DNA of yeast. Their origin appears to be due to illegitimate recombination between a pair of short inverted repeats. In amplified genomes they are relatively common, and are presumably advantageous for DNA replication. (See Royko E, Goursot R 1999 Curr Genet 35:14)

Amphimixis: Amphimixis is another term for sexual reproduction. ▶[apomixis](#)

Amphipathic: An amphipathic compound has both a charged and neutral face (e.g., some proteins forming amphipathic helix), structures that have hydrophilic (polar) and hydrophobic (non-polar) surfaces, e.g., lipids. Generally, molecular surfaces tend to be hydrophilic whereas the inner residues are hydrophobic.

Amphiphile: Amphiphile refers to a nanomolecule with a peptide and a hydrocarbon tail. Amino acid sequences inserted into the peptide, may stimulate neural growth, tend to form connections with neighboring neurons, and can possibly repair neural cord injury when inserted into a defective spinal cord. ▶[nanotechnology](#), amphiphile for bone regeneration: Hosseinkhani H et al 2007 Tissue Eng 13:11.

Amphiphysin: Amphiphysin is a nerve protein of the synaptic vesicle bound to synaptotagmin, clathrin, and dynamin. It also participates in general endocytosis and in membrane remodeling. ▶[synaptotagmin](#), ▶[BIN1](#), ▶[endocytosis](#); Peter BJ et al 2004 Science 303:495.

Amphiploid: An amphiploid cell contains at least two genomes from more than one species. ▶[amphidiploid](#), ▶[allopolyploid](#)

Amphiprotic: An amphiprotic compound can donate or accept protons and thus can behave as a weak acid or alkali, e.g., water or amino acids. ▶[proton](#), ▶[amino acids](#)

Amphiregulin: Amphiregulin is a regulator with both positive and negative effects. It regulates the proliferation of keratocytes and some fibroblasts, and inhibits the proliferation of various tumor cells. It competes for the epidermal growth factor (EGF) receptor, is required for normal implantation of blastocytes and is regulated by progesterone. Amphiregulin is the unique EGF family member, which is transcriptionally induced by estrogen in the mammary glands of sexually maturing (pubertal) mice at the time of exponential expansion of the ductal system (Ciarloni L et al 2007 Proc Natl Acad Sci USA 104:5455). ▶[EGFR](#), ▶[keratosis](#), ▶[progesterone](#), ▶[embryogenesis](#); Akatsu N et al 2001 Biochem Biophys Res Commun 281:1051.

Amphistomatous: Amphistomatous leaves bear stomata on both surfaces. ▶[stoma](#)

Amphithallism: Amphithallism refers to homoheteromixis, i.e., both self-fertilization and outcrossing; it occurs in fungi.

Amphitropic Molecule: An amphitropic molecule carries out different functions at different sites.

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Ampholine: Ampholine is an ampholyte used in polyacrylamide, agarose, and dextran gels, for density gradient stabilization in analytical and preparative electrofocusing. ► [isoelectric focusing](#)

Ampholyte: Ampholyte is an amphoteric electrolyte. ► [amphoteric](#), ► [electrolyte](#)

Amphoteric: An amphoteric substance has dual, opposing characteristics, such as behaving both as an acid and a base.

AMPHOTERINE: ► [Alzheimer's Disease](#)

Amphotropic Retrovirus (polytropic retrovirus) The polytropic retrovirus replicates both in the cells from where it was isolated, as well as in other types of cells. ► [ecotropic and xenotropic retroviruses](#)

Ampicillin: Ampicillin is an antibiotic that binds to the bacterial cell membranes and inhibits the synthesis of the cell wall. The ampicillin resistance gene (*amp^r*) codes for a β -lactamase enzyme that detoxifies this antibiotic; the *Amp^r* gene is used also as marker for insertional inactivation and concomitant ampicillin susceptibility. ► [antibiotics](#), ► [insertional mutation](#), ► [pBR322](#), ► [amp](#), ► [\$\beta\$ -lactamase](#), ► [see formula at AMP](#)

AMPK: AMPK refers to 5'-AMP-activated protein kinase.

Amplicon: Amplicon is a DNA fragment produced by polymerase chain reaction (PCR) amplification. It also refers to the amount of DNA present in an amplified gene, a chromosomal segment, or a reduced size viral construct used for genetic transformation. ► [PCR](#)

Ampliconic Region: The ampliconic region covers about half the extent of the euchromatin region of the Y chromosome and includes large palindromes. Gene conversion is frequent in these tracts. (See Rozen S et al 2003 Nature [Lond] 423:873; ► [euchromatin](#), ► [palindrome](#), ► [gene conversion](#), ► [Y chromosome](#))

Amplification: Amplification is the temporary synthesis of extra, functional copies of some genes, in vivo or in vitro, by some forms of the polymerase chain reaction. Bacteriophage λ can be amplified by a series of nitrocellulose filter transfers after in situ hybridization. The addition of chloramphenicol (10–20 $\mu\text{g/mL}$) to pBR322 and pBR327 may amplify plasmid yield, if the synthesis of protein is not completely prevented. Cosmid libraries may be amplified by starting on solid plates followed by liquid cultures. Replica-plating can amplify animal cell cultures. Approximately 5×10^4 colonies can be accommodated on a 138-mm filter, and this way about 30 filters are required to obtain a representative

library of overlapping fragments. DNA amplification can occur in a *genetically programmed and pre-determined* manner in eukaryotes. For example, in the ovarian follicle of *Drosophila*, large quantities of an egg-shell protein is needed during oogenesis. The need is met by a disproportionately favorable replication of the chorion gene clusters in the X-chromosome and chromosome 3. DNA replication is initiated bidirectionally at a replicational origin, and generates multiple copies of the genes needed. The replication tapers off after a distance and the flanking regions are amplified less and less in proportion to the distance from the origin. Similar programmed amplification takes place in the ribosomal genes of amphibia during intense periods of protein synthesis in embryogenesis. The approximately 500–600 genomic copies of rRNA genes may thus be increased by a factor of 1000. The replication of detached DNA sequences follows a rolling circle type process, and the new DNAs (in about 100 rDNA repeats) are separately localized in micronuclei. The replicates of these nuclei are structurally similar, indicating that they are the clonal products of a single replicating unit; but the new micronuclei generated in different cells may not be the same as judged by the differences in length in the intergenic spacers. Ribosomal DNA amplification takes place during the amitotic divisions of the protozoon, *Tetrahymena*. Here again, the macronuclear rDNA copies may be selectively amplified in the 10^4 range, whereas the micronuclear DNA contains only a single rDNA gene. A *genetically non-programmed amplification* takes place in several mutant cell lines to correct mutational defects. Producing multiple copies of gene-controlling low-efficiency enzymes may compensate for enzyme deficiencies. Transfection of ADA genes to mammalian cells may be amplified in the presence of dCF (see adenosine deaminase). Mammalian cells can be amplified if they are co-transfected with the *dhfr* (conveying methotrexate resistance) gene and other desired sequences. In the presence of methotrexate, the *dhfr* genes, as well as the flanking DNA, may be amplified (1000) fold. The amplified DNA, in stable lines, is integrated into the chromosome in *homogeneously stained regions* (HSRs). In unstable cell lines, *dhfr* occurs in autonomously replicating elements, called double-minute chromosomes (DMs), which have no centromeres and can be maintained only in cultures that contain methotrexate. Amplification may generate fragile sites in the chromosomes by integration of DMs sequences. Hypoxia may be a factor inducing such integration. Some general features of amplification are: (i) expansion of a particular locus and flanking regions, or the generation of small supernumerary chromosomes called double minutes that

contain the critical gene, (ii) possible rearrangements of the amplified unit (iii) the amplified sequences are not all identical and may change, but these changes are somewhat unusual because a larger number of copies may be altered simultaneously in an identical manner. In vivo amplification of genes during evolution may account for the presence of gene families. Some amplified genes, in which production of a larger number of copies was no longer advantageous, may have acquired new functions without entirely losing their structural similarity to the ancestral sequences. Other members of the amplified group lost their function(s) through deletions and mutations and became pseudogenes. Carcinogenesis commonly involves amplification of some oncogenes and genes involved with the cell cycle (cyclins). Fragile sites in some chromosomes aid amplification. ►PCR, ►MDA, ►nitrocellulose filter, ►in situ hybridization, ►chloramphenicol, ►pBR322, ►cosmid library, ►oogenesis, ►chorion, ►bidirectional replication, ►rolling circle, ►micro-nucleus, ►ADA, ►HSR, ►methotrexate, ►fragile sites, ►pseudogene, ►unequal crossing over, ►DM chromosome, ►adaptive amplification, ►breakage-bridge-fusion cycles, ►translocation heterozygote; Romero D, Palacios R 1997 Annu Rev Genet 31:91; Monni O et al 2001 Proc Natl Acad Sci USA 98:5711; Dean FB et al 2002 Proc Natl Acad Sci USA 99:5261; Tower J 2004 Annu Rev Genet 38:273.

Amplification Control Elements: Amplification of genes in chromosome 3 and the X-chromosome of *Drosophila*, are determined by DNA sequences measuring less than 5 kbp, which normally occur in the vicinity of the genes that are amplified under natural conditions of the genome (e.g., the chorion protein gene). If these control elements are isolated, inserted into genetic vectors (P-elements), and reintroduced at random sites into the *Drosophila* genome, they may amplify other sequences in their new neighborhood. ►amplification, ►hybrid dysgenesis

Amplified Fragment Length Polymorphism: ►AFLP

Amplitaq: Amplitaq is a taq DNA polymerase, a single polypeptide chain enzyme with minimal secondary structure. It is isolated from the bacterium *Thermus aquaticus*. Its temperature optimum is about 75 °C but it can withstand ≤95 °C without great loss of activity. It lacks intrinsic nuclease function but has a polymerization-dependent 5' → 3' exonuclease activity. It is a preferred enzyme for PCR. ►PCR, ►DNA polymerase, ►exonuclease, ►Taq DNA polymerase

Amplitype: ►DNA fingerprinting

Amputations: ►ADAM complex, ►limb defects

Amsterdam Criteria: Amsterdam criteria were established in (1990) at a meeting in Amsterdam for ascertaining the hereditary nature of non-polyposis colorectal cancer. The criteria are: 1. at least three family members, of which two are first degree relatives, are affected, 2. at least two generations are represented, and 3. at least one family member is below age 50 at the time of onset. ►hereditary non-polyposis colorectal cancer, relatedness, degree of, http://www.medscape.com/viewarticle/468147_4.

Amusia: Amusia is a deficit of music perception caused by a genetic or acquired brain anomaly. It may not affect any other brain function or intelligence. In some case it is associated with limitation of prosody, rhythm and pitch of speech. ►musical talent

AMV Oncogen (*v-amv*): ►MYB

α-Amylase: α-amylase hydrolyzes α-1-4 glucosidic linkages of amylose, amylopectin, and other carbohydrates and yields maltose, α-dextrin, and maltotriose. β-Amylase hydrolyzes starch into maltose. The human AMY genes are located in chromosome 1p21.

Amyloid Angiopathy: ►amyloidosis type VI

Amyloidosis: Amyloidosis involves extracellular deposition of variable amounts of amyloids. Amyloids are special fibrous glycoproteins of connective tissues, and are caused by protein misfolding. Some of the familial nephropathies (kidney diseases), heart diseases, and neoplasias involve amyloidosis. Heparanase overproduction digests heparans that are also essential for amyloid deposition (Li JP et al 2005 Proc Natl Acad Sci USA 102:6473). Genetically these are inhomogeneous groups of diseases mainly with dominant, but some with recessive, patterns of inheritance. Amyloidosis in some aging individuals manifests symptoms similar to the symptoms of Alzheimer's disease. The dominant genes were mapped to the same region of chromosome 21 as the genes behind AD, and also to 20p12, the site of the prion gene. The Swedish and Portuguese Amyloidosis I is a dominant polyneuropathy encoded near the centromere in the long arm of human chromosome 18. The Finnish Amyloidosis type V is apparently due to an autosomal dominant defect in gelsolin. The Icelandic Amyloidosis type VI involves high incidence of hemorrhages due to accumulation of amyloids. The afflicted individuals (dominant) are low in cysteine proteinase inhibitor, cystatin C, encoded in the region of human chromosome 20q13. The Ohio type Amyloidosis VII involves ocular and mental affliction. The German Amyloidosis type VIII is a visceral and renal disease. Amyloidosis IX is a skin disorder. The familial British dementia is a dominant, late onset brain degenerative

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condition caused by the BRI gene in human chromosome 13q14. There are recessive amyloidoses affecting the gingiva (gum), eyelids, cornea (eyeball), and mental health. Amyloid formation may occur in a number of pathogenic conditions, but can also occur as a rather general feature of polypeptide chains. Under some conditions, there may be a cycle of dissociation re-association. (Carulla N et al 2005 Nature [Lond] 436:554) The gelatinous drop-like corneal dystrophy (GDLD, human chromosome 1p) is an amyloidosis caused by mutation in a gastrointestinal tumor-associated antigen. The small molecules of transthyretin (thyroxin-binding prealbumin) interfere with the misfolding of the protein, and may be considered for therapeutic use. Some mutations in the human lysozyme promote fibril and plaque formation, but a heavy chain domain of the camelid antibody raised against the wild type lysozyme may inhibit this deleterious aggregation (Dumoulin M et al 2003 Nature [Lond] 424:783). ▶cold hypersensitivity, ▶Mediterranean fever, ▶ β -amyloid, ▶Alzheimer disease, ▶scrapie, ▶prion, ▶encephalopathies, ▶gel-solin, ▶amyotrophic lateral sclerosis, ▶sterols; Pepys MB et al 2002 Nature [Lond] 417:254; Hammarström P et al 2003 Science 299:713.

Amyloids: Amyloids are fibrillar poorly soluble/insoluble proteins forming β sheets, e.g., apolipoproteins. Positional scanning mutagenesis reveals tolerant and restrictive sites in the peptide for fibril formation. Mutations that accelerate β -sheet polymerization do not necessarily increase amyloid formation. Some abundant mutant fibrils polymerize slowly, and some amino acid combinations disrupt aggregating capabilities (López de la Plaz M, Serrano L 2004 Proc Natl Acad Sci USA 101:87). Potent inhibitors of amyloid aggregation may involve synthetic molecules that can bind to chaperones (of the FK506 family), and can interact with amyloids by their increased size, required for interaction with proteins (Gestwicki JE et al 2004 Science 306:865). Proteoglycan-amyloid complexes are protected from proteolysis. Several neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, prions) are caused by amyloid formation. Recent information indicates that it is not fibrillar amyloids, but rather their globular aggregation, which form ion channel-like structures, that act as the major pathological agents (Quist A 2005 Proc Natl Acad Sci USA 102:10427). According to the *amyloid stretch hypothesis* the tendency to form amyloids is localized in short stretches of the proteins in question (Esstera-Chopo A et al 2005 Proc Natl Acad Sci USA 102:16672). In addition, atomic structures, common to various amyloid proteins, have been determined (Sawaya MR et al 2007 Nature [Lond] 447:453).

Certain starch-like substances are also called amyloids. The amyloid Pml17 of melanosomes, promotes the polymerization of smaller molecules into melanin. Melanins, unlike many amyloid proteins, are beneficial molecules important in protecting against ultraviolet light and other oxidative damage. Pml17 protects cells against adverse effects of excessive melanin (Fowler DM et al 2006 PLoS Biol 4(1):e6). ▶amyloidosis, ▶Alzheimer's disease, ▶proteoglycan, ▶ β sheet, ▶protein structure, ▶FK506, ▶chaperone, ▶homolog-scanning mutagenesis, ▶melanin, ▶glaucoma

Amylopectin: Amylopectin is normally a minor variant of common starch. While starch (amylose) is an unbranched chain of D-glucose units of α 1–4 glycosidic linkages, amylopectin contains, in addition, at every 24 to 30 residues branch points in α 1–6 linkages (see Fig. A72).

Amylose is synthesized by an active granule-bound starch synthase; starch-branching enzymes SBEI and SBEII synthesize amylopectin. In monocots there are two isoforms of SBEII (a and b). In maize, deficiency of SBEIIb is the consequence of the *ae* (amylose extender) gene. Increased amounts of amylose vis-a-vis those of amylopectin lead to dietary and health-related advantages. Transgenic technology (RNAi) Can help reduce SBE enzyme levels, resulting in more than 70% amylose in wheat. (Regina A et al 2006 Proc Natl Acad Sci USA 103:3546). Cereal grains commonly contain amylose as the principal storage polysaccharide, but recessive mutations may cause the predominance of amylopectin (dextrin). Several genes of maize (*ae*, *du*) may substantially increase the amylose content relative to that of amylopectin.

These two types of starches are easily distinguished in situ by a drop of iodine solution (I_2 0.12 g + KI 0.4 g in 100 mL H_2O); amylose stains blue-black, while amylopectin appears red-brown. The amylose content of corn is desirable also to the film and fiber-manufacturing industry.



Figure A72. Stained sorghum pollen displays segregation for starch and amylopectin. (Courtesy of Dr. JR Quinby. See Karper RE (1933) J Hered 24:257)

Amyloplasts: Amyloplasts are plastids whose primary function is starch storage.

Amylose: ► amylopectin

Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig disease): ALS is characterized by the hardening of the lateral columns of the spinal cord with concomitant muscular atrophy. This may spread and may cause death in a few years after onset. According to a mouse model, it is probably caused by a defect in the enzyme Cu/Zinc Superoxide Dismutase (SOD) in about 20% of the familial cases. The expression of mSOD1G93A results in activated and neurotoxic microglia, and suggests that the lack of mSOD1G93A expression in microglia may contribute to motor neuron protection (Beers DR et al 2006 Proc Natl Acad Sci USA 103:16021). SOD breaks down superoxide radicals (highly reactive compounds) to less reactive products; it may also form other types of free radicals. Under normal conditions, SOD exists in a dimerized state. Mutations may either destabilize the precursor monomers, or weaken the dimer interface, or both. In any case, the difference between various abnormal foldings of the protein leads to differing severity of the disease (Lindberg MJ et al 2005 Proc Natl Acad Sci USA 102:9754). In ALS, frontotemporal lobe degeneration occurs in the brain, displaying tau and synuclein inclusions. Ubiquitin is also present and cleaves the C-terminal fragment of the TDP-43/TARDBP protein that is detectable in the hippocampus, neocortex, and the spinal cord (Neumann M et al 2006 Science 314:130).

Not all cases of SOD dismutase apoprotein mutations are involved in reduced stability (Rodriguez JA et al 2005 Proc Natl Acad Sci USA 103:10516). Aggregation of the molecules results in ALS. SOD1 apparently causes neural death by acting on caspases that mediate apoptosis. The *Bcl-1* gene inhibiting apoptosis prolongs the life of mice affected by SOD. A subsequent study found, however, that neither the elimination, nor elevation of SOD activity in mice influenced the expression of ALS. Current research indicates that Zinc-deficient SOD, plays a role in nitric oxide-dependent apoptosis of some motor neurons. The SOD transgene effect can be restrained by N-benzoyloxycarbonyl-Val-Asp-fluoromethyl-ketone (zVAD-fmk), an inhibitor of caspases. This, in turn delays the onset of ALS in mice, and increases life expectancy. Mutations in SOD1 may cause aberrant decrease of *S*-nitrosothiol level and may be remedied by *S*-nitrosocysteine (Schonhoff CM et al 2006 Proc Natl Acad Sci USA 103:2404).

In G37R *SOD1* mice, administration of repeated injections of adjuvant/SOD1 mouse mutant with a final booster injection before symptoms manifested at 6 months of age, were effective in delaying disease

onset and extending the life span by >4 weeks. Western blot analysis with a monoclonal antibody specific to mutant *SOD1* forms provided evidence of clearance of *SOD1* species in the spinal cord of vaccinated animals. This vaccination failed to confer significant protection in G93A *SOD1* mice that showed extreme and excessive expression of mutant *SOD1*. Nonetheless, a passive immunization, in which an intraventricular infusion of purified anti-human *SOD1* antibody was administered through an osmotic minipump, succeeded in alleviating disease symptoms and in prolonging the life span of G93A *SOD1* mice (Urushitani M et al 2007 Proc Natl Acad Sci USA 104:2495). Adult motor neurons collected by laser microdissection from mice expressing dismutase active ALS-linked mutants were found to undergo an age-dependent mRNA change that developed presymptotically. In This change occurs due to the dysregulation of the D/L-serine biosynthetic pathway, previously linked to both excitotoxic and neurotrophic effects. An unexpected dysregulation, common to motor neurons expressing mutants that were either dismutase active, or inactive, comprised of the induction of neuronally derived components of the classic complement system, and the regenerative/injury response (Lobsiger CS et al 2007 Proc Natl Acad Sci USA 104:7319).

The gene leading to ALS symptoms is a dominant “gain-of-function” mutation within the area 21q22.1-q22.2 (*SOD1*, Cu/Zn superoxide dismutase). The syndrome, in different forms, occurs at a frequency of about 1×10^{-5} . About 10% of the cases are hereditary and 90% are sporadic. It is also called LGD after baseball infielder Henry Louis (Lou) Gehrig. Gehrig, who was elected to the US National Hall of Fame in 1939, suffered from this condition. ALS is sometimes associated with phenotypes like those in Parkinson’s disease and Alzheimer’s disease. This form may be caused or aggravated by nutritional factors (neurotoxins in the food, low calcium and magnesium uptake). Other dominant loci were assigned to 18q21 and 16q12.1-q12.2. The dominant juvenile form (ALS4) has been mapped to 9q34; a similar gene is located at 15q15-q22. A recessive autosomal type of ALS, with an early onset between the ages of 3 and 20, is assigned to human chromosome 2q33. The protein encoded, alsin, may directly affect motor neuron degeneration and may signal to GEFs. Copaxone (Cop-1), a synthetic copolymer of tyrosine, glutamate, alanine and lysine, may protect motor neurons against acute and chronic degeneration (Kipnis J, Schwartz M 2002 Trends Mol Med, 8:319). Retrograde transport of insulin growth factor 1 with the aid of adeno-associated vector, from axon terminal receptors to motor neurons of the spinal cord, appears very beneficial in animal models

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(Kaspar BK et al 2003 Science 3001:839). VEGF mutations may increase the risk of developing ALS; in a mouse model a single injection of VEGF-expressing vector improved the host's condition and prolonged its survival (Azzouz M et al 2004 Nature [Lond] 429:413). It appears that mRNA editing in the GluR2 subunit of the AMPA receptor in the motor neurons may be critical for the disease (Kawahara Y et al 2004 Nature [Lond] 427:801). The pancreatic ribonuclease A family protein ANG (angiogenesis, 124 amino acid residues encoded at 14q11.2) can mutate at several sites. In addition to the catalytic center, it has a site for translocation to the nucleolus. ANG and VEGF variations in hypoxia-inducible genes increase ALS susceptibility, particularly in Irish and Scottish populations (Greenway MJ et al 2006 Nature Genet 38:411). Molecular evidence suggests common pathogenesis for sporadic and familial ALS, but no evidence suggests this commonality between ALS and normal or disease-affected tissues from other neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases, and spinal muscular atrophy, a non-ALS motor neuron disease. This fact permits the use of ALS as a biomarker (Gruzman A et al 2007 Proc Natl Acad Sci USA 104:12524). ▶neuromuscular diseases, ▶Alzheimer disease, ▶Parkinson disease, ▶tau, ▶apoptosis, ▶filament, ▶SOD, ▶gain-of-function, ▶hypoxia, ▶GEF, ▶VEGF, ▶dynein, ▶VEGF, ▶AMPA, ▶TARDP; Julien J-P 2001 Cell 104:581; Yang Y et al 2001 Nature Genet 29:160; Giess R et al 2002 Am J Hum Genet 70:1277; SOD mutations: Selverstone J et al 2005 Annu Rev Biochem 74:563.

Amyotrophy, Hereditary, Neuralgic (HNA, 17q25): Amyotrophy is a recurrent muscle weakness affecting the neck and arms; it occurs due to defects in cervical and thoracic spinal nerves. It is generally triggered by stress, such as infection, immunization, or labor at childbirth. The mutation apparently occurs in the septin gene (SEPT9) involved in the formation of the cytoskeleton, in cell division, and in tumorigenesis. (See Kühlenbäumer G et al 2005 Nature Genet 37:1044; Parsonage-Turner syndrome, Guillain-Barré syndrome)

Anabasine (neonicotine): Anabasine is an alkaloid occurring in chenopods and solanaceous plants; it is highly toxic (LD₅₀ orally 5 mg/kg for humans). ▶LD₅₀

Anabolic Steroids: Anabolic steroids are androgens that promote protein synthesis, general growth, and the development of muscles and bones. Some synthetic forms (methyltestosterone, oxymetholone, norethandrolone) show higher anabolic than testosterone-related activity and are used illegally by athletes to

boost performance; literally, these steroids are “body builders.” Some androgenic and anabolic steroids are used as drugs in the treatment of impotence, anemias, and bone marrow aplasia. These compounds may cause liver adenomas that in rare cases may become cancerous. ▶steroid hormones, ▶adenoma, ▶impotence, ▶anemia, ▶aplasia, ▶steroid doping

Anabolism: Anabolism comprises the energy-requiring synthetic processes of cellular metabolism.

Anaerob: Anaerobs are organisms that live without atmospheric (free) oxygen.

Anaerobic: Anaerobic a processes take place in the absence of (air) oxygen.

Anagenesis: Anagenesis is an evolutionary change within a line of descent. ▶cladogenesis

Analbunimemia: Analbunimemia is a human chromosome 4 recessive absence or reduction of albumin from the blood serum. It does not lead to very serious ailments, although fatigue, mild anemia, and mild diarrhea may be associated with it. ▶albumins

Analgesic: An analgesic is a medication that alleviates pain without inducing loss of consciousness. Endocannabinoids mediate analgesic action; stress can mediate the response (Hohmann AG et al 2005 Nature [Lond] 435:1108). TRPM8 cold receptor and its central downstream mediators are elements of endogenous-cooling-induced analgesia, and they represent a novel analgesic pathway that can be exploited in chronic sensitized pain of nerves in rats (Proudfoot CJ et al 2006 Current Biol 16:1591). ▶nociceptor, ▶cannabinoid

Analogous Genes: Analogous genes have similar function without common evolutionary descent. ▶homologous genes

Analogue (analog): Analogue is a chemical counterpart to a natural compound, but it may or may not function in metabolism. It may even block the function of a normal metabolite or enzyme.

Analogy: Analogy is a similarity not based on common origin. ▶homology, ▶convergent evolution

Analysis of Variance: Analysis of variance is a statistical method that detects the components of variance. It is used for the evaluation of differences between experimental data from different treatments. The square root of the quotient of the sum of squares of the variants and the mean square of the error variance is equal to t , and the corresponding probability, at each degree of freedom, can be read from a t -distribution table. The results are usually presented in a table form such as shown (see Table A4).

Table A4. Analysis of variance

| Variance Source | Degree of Freedom | Sum of Squares (SS) | Mean Square (MS) | Mean Square Ratio (MSR) |
|-----------------|-------------------|---------------------|------------------|-------------------------------|
| Between Groups | k-1 | SSB | SSB/(k-1) | $\frac{SSB/(k-1)}{SSW/(N-k)}$ |
| Within Groups | N-k | SSW | SSW/(N-k) | |
| Total | N-1 | | | |

The MSR (mean square root) permits testing the significance of the data, also with the aid of an F table. Analysis of variance is also used in calculating heritability by intraclass correlation. ▶ [variance intraclass correlation](#), ▶ [F distribution](#), ▶ [t-distribution](#); Sokal RR, Rohlf FJ 1969 Biometry, Freeman, San Francisco, California.

Analyte: An analyte is a substance subjected to analysis. It frequently reveals the basis (by deficiency or overproduction) of a genetically determined disease.

Anandamide (*N*-arachidonylethanolamine): Anandamide is an endocannabinoid and vanilloid receptor that plays different roles in healthy and cancerous cells. It is a ligand for G proteins. It is produced at higher levels in the uterus before implantation of embryo, and is regulated to lower levels afterwards. G protein, ▶ [cannabinoid](#), ▶ [vanillin](#); Wang H et al 2003 Proc Natl Acad Sci USA 100:14914; biosynthetic pathway: Liu J et al 2006 Proc Natl Acad Sci USA 103:13345.

Anaphase: During *mitosis*, the centromere of the chromosomes splits at anaphase; this is what enables spindle fibers to pull the two identical chromatids towards opposite poles. This process ensures the daughter cells are identical. In *meiotic* anaphase I, the centromere does not split and the chromatids are held together as they move toward the poles. Thus, it is the means for the reduction of chromosome number. Anaphase II of meiosis essentially resembles anaphase in mitosis. Microtubules and special motor proteins mediate the movement of chromosomes. The molecular mechanism of the process is only partly known. In yeast, the *MAD* (mitotic arrest deficient) and *BUB* (budding inhibited by benzimidazole) gene products seem to be the sensors of those kinetochores, which have not yet tackled the spindle fibers. Before the sister-chromatids can separate, the anaphase-promoting complex (APC) degrades the inhibitors of the process (Pds1/Cut2). Proteins Cdc20/Slp1 and Hct1/Cdh1 digest other inhibitory proteins (Cib2 and Ase1). ▶ [meiosis](#), ▶ [mitosis](#), ▶ [microtubules](#), ▶ [motor protein](#), ▶ [APC](#), ▶ [cell cycle](#), ▶ [spindle](#), ▶ [sister chromatid cohesion](#), ▶ [cohesin](#), ▶ [separins](#); Nasmyth K 2005 Cell 120:739.

Anaphase-Promoting Complex: ▶ [APC](#)

Anaphora: Originally anaphora is a rhetorical device of repeating a word or phrase in successive clause(s) or sentences. In science writing, the name of a compound, gene, or protein is generally referred to, after first instance, with the word “it” or with a previously given abbreviation.

Anaphylactic Shock: Anaphylactic shock refers to immediate hypersensitivity to specific antigens or haptens, resulting in dangerous loss of respiratory function. ▶ [anaphylatoxins](#), ▶ [anaphylaxis](#)

Anaphylatoxins: Anaphylatoxins are fragments released during activation of the serum complement C proteins of antibodies. C3a, C4a, and C5a (each ~10 kDa) anaphylatoxins are proteolytically cleaved from the corresponding complement components. These activation peptides are called anaphylatoxins because they may elicit reactions similar to anaphylactic shock (violent reaction to antibodies and/or haptens that may be fatal). These fragments enhance vascular permeability, cause contraction of the smooth muscles, and trigger the release of histamine, other vasoactive amines, and lysosomal enzymes. ▶ [antibody](#), ▶ [complement](#), ▶ [histamine](#), ▶ [lysozymes](#); Gerard C, Gerard NP 1994 Annu Rev Immunol 12:775; Sunyer JO et al 2005 Vet Immunol Immunopathol 108:77.

Anaphylaxis: Anaphylaxis is a rapid serological (antigen-antibody) reaction of an organism to a foreign protein. Either the crystalline fragment of the antibody (Fc), or its complement is involved. Prior sensitization may turn the reaction quite violent and even lead to death. Anaphylaxis may be treated with adrenaline. ▶ [immune system](#), ▶ [antibody](#), ▶ [complement](#), ▶ [allergy](#)

Anaplasia: Anaplasia is another term for dedifferentiation.

Anaplasma marginale: *Anaplasma marginale* causes tick-borne rickettsia of livestock. The genome of the sequenced strain has 1,197,687 bp. ▶ [rickettsia](#); Brayton KA et al 2005 Proc Natl Acad Sci USA 102:844.

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Anaplastic Lymphoma (large-cell non-Hodgkin lymphoma): Anaplastic lymphoma is a lymphoma in children, and is caused by a 2p23:5q35 chromosomal translocation fusing a protein tyrosine kinase gene, ALK, to the nucleolar phosphoprotein genes (NPM, nucleophosmin). The resulting anomaly affects the small intestine, testis, and brain, but not the lymphocytes. ALK is related to the insulin receptor tyrosine kinases and may eventually cause malignancies. Translocations involving 1q21-q23, the site of the IgG Fc receptor (FcγRIIB), are also responsible for this malignant lymphoma. ►leukemias, ►lymphoma, ►Duncan syndrome, ►Hodgkin disease, ►antibody, ►immunoglobulins; Pulford K et al 2001 Curr Opin Hematol 8(4):231.

Anaplerosis: Anaplerosis is biological repair or replacement.

Anastomosis: Anastomosis refers to formation of a reticulate arrangement, fusion between vessels.

Anastral Spindle: Anastral spindle is a mitotic spindle without asters, such as in higher plants. ►aster

Anatomy: Anatomy is the biological discipline dealing with body structure. For functional anatomy see: <http://bodymap.jp/>.

Anautogenous Control: The organism requires an external factor for the completion of a developmental process, e.g., the mosquito *Aedes aegypti* requires a meal of blood to activate its reproductive cycle. ►autogenous, ►mosquito

Ancestral: Ancestral is a trait inherited from a remote forebear or derived from a precursor molecule. Modern ancestry inferences are based on multilocus genotypes and allelic frequencies. Various statistical tools make inferences meaningful (Rosenberg NA et al 2003 Am J Hum Genet 73:1402).

Ancestral inheritance as a theory based on the false assumptions of a non-particulate genetic material, was developed by Francis Galton (1897), but lost meaning after Mendelism.

Ancestral Repeats (AR): The origin of ancestral repeats predates the separation of two species, e.g., mice and humans. ARs can be exploited for the estimation of neutral substitutions in the genomes.

Ancestry Markers: Ancestry markers can provide information on the descent of a population or an individual, because certain alleles occur in characteristic frequencies in some populations.

Anchor Cell: An anchor cell is a gonadal cell of *Caenorhabditis* that in the vulval opening induces the development of its neighboring cell. ►Caenorhabditis, organizer, ►morphogenesis

Anchor Locus: Anchor locus is a gene with well-known map position and can be used as a reference point for mapping new genes. ►anchoring

Anchor Residues: Anchor residues are amino acids of those peptides that attach to MHC molecules. ►MHC

Anchorage Dependence: Normal mammalian cells grow in culture in a monolayer attached to a solid surface; cancer cells are not contact-inhibited and pile upon each other. It appears that the suppression of cyclin E-CDK2 activity is required for cell anchorage. In transformed fibroblasts, the cyclin E-CDK2 complex is active regardless of anchorage. The surface of the cell substrate has an impact on differentiation, development, regeneration, and disease of cells (Discher DE et al 2005 Science 310:1139). ►CATR1, ►AIG, ►cyclins, ►cancer cells, ►anoikis, ►CAM, ►RGD, ►tissue engineering

Anchored Periplasmic Expression (APEX): APEX permits the isolation of ligand-binding proteins from combinatorial libraries anchored to the inner periplasmic face of *E. coli*. The procedure serves the same purpose as phage display, but the larger bacterial (or yeast) cells allow screening by flow cytometry of labeled proteins and antibodies. ►periplasma, ►phage display; Harvey BR et al 2004 Proc Natl Acad Sci USA 101:9193.

Anchoring: DNA fragments obtained during the initial stages of physical mapping must be tied together by contigs. Large capacity YACs are used for the establishment of contigs. These YACs must be correlated with molecular markers (anchors) along the length of the chromosome. RFLPs, RAPDs, STSs, and even the recombination maps obtained by strictly genetic methods may be used as anchors. The relative position of two YACs is revealed when a YAC is found to bridge two anchors to each of which, one of the two YACs each is attached (see Fig. A73).

Anchoring may provide the means for correlating genetic linkage maps with physical maps that are based on nucleotide sequencing. The principle of the procedure is diagrammed. (See also Matallana E et al 1992 In: Koncz C et al (eds) Methods in Arabidopsis Research, World Scientific, Singapore, p. 144)

Ancient DNA: DNA from ancient bones, older than 50,000–100,000 years or even more, may still be analyzed. Clear family lines between parents and children could be ascertained among bone samples collected from cemeteries in Mongolia that are older than (2000) years. This was done on the basis of the autosomal short tandem repeat of mtDNA and Y chromosomal DNA (Keyser-Tracqui C et al 2003 Am J Hum Genet 73:247). Obtained from hair and wool,

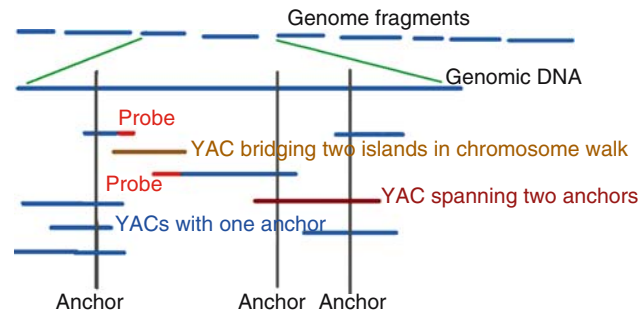


Figure A73. Anchoring

mtDNA has been successfully analyzed in samples ranging from 100– to 9,400 years old (Gilbert MTP et al 2004 *Current Biol* 14:R463). From the more-than-40,000-years-old Australian remains of the now extinct cave bear (*Ursus spelaeus*), 26,861 bp sequences of its genome have been sequenced. This revealed the extinct species' evolutionary relationship to the extant bear species (Noonan JP et al 2005 *Science* 309:597).

Samples preserved in amber may last longer. Mitochondrial DNA extracted 80 million years and amplified by PCR has shown sequences different from all known sequences. The validity of reports on very old DNA samples have thus seriously been questioned and contamination may not be ruled out. The condition of preservation is critical in DNA analysis. Often, the washed fossil bones stored in museums do not permit any DNA amplification; all recently excavated bones, however, are shown to yield authentic aurochs sequences. During the 57 years when the aurochs bones were stored in a collection, at least as much amplifiable DNA was lost as during the previous 3,200 years of burial (Pruvost M et al 2007 *Proc Natl Acad Sci USA* 104:739). It is very important that the greatest caution is exercised to avoid contamination during PCR analysis. It is advisable to test not just the sample but its immediate environment and the reagents themselves, and verify that the sample conforms to that of a species. Fragments that are too long are suspicious. Statistical tests have been developed for compensation for the miscoding (C→U, G→A) changes due to degradation and contamination with DNA of more recent origin (Helgason A et al 2007 *J Mol Evol* 65:92). In case a protein is present, the high ratio between D and L aspartic acid indicates that most likely the DNA has been degraded. The purposes of the analysis of ancient DNA are to obtain information on individuals and groups and to assess evolutionary relations. The mtDNA (~17,000 bp) of two kinds of moa birds extinct for 400 years has been fully recovered. Analysis of ancient DNA has some limitations yet it may be the only means of inquiry

into some problems of speciation, history of pathogens, human evolution, and migration. Some of the problems encountered with degradation of ancient fossil samples (~2,000–10,000 years old) of animal and human bones have been overcome by using crystal aggregates, which preserve DNA much better than they preserve entire bone samples. Sodium hypochlorite washing also removes all contaminations of recent DNA samples. Using these techniques, fossils yielded upon PCR procedures longer sequences of intact DNA (Salamon M et al 2005 *Proc Natl Acad Sci USA* 102:13783). Cross-linking is a more important cause of deterioration of ancient DNA than single- or double-strand breaks (Hansen AJ et al 2006 *Genetics* 173:1175). Ancient DNA can shed some light on the diet of ancient animals and humans, domestication of plants and animals, etc. (Pääbo S et al 2004 *Annu Rev Genet* 38:645). Ancient mitochondrial DNA may show C/G→T/A transitions upon amplification (Stiller M et al 2006 *Proc Natl Acad Sci USA* 103:13578), yet new methods facilitate to some extent, the reconstruction of at least the mtDNA. ▶ancient organisms, ▶Neanderthal people, ▶mammoth, ▶PCR, ▶ice man, ▶mummies, ▶coproscopy, ▶Romanovs, ▶hominidae, ▶out of Africa; Hofreiter M et al 2001 *Nature Rev Genet* 2:353; Lambert DM et al 2002 *Science* 295:2270; Gilbert MTP et al 2003 *Am J Hum Genet* 72:32; Jones M 2002 *The Molecule Hunt*. Arcade Publishing, New York)

Ancient Organisms: Extinct species recognized as paleontological relics are difficult to study even by the most modern research techniques because the organic material has decayed. A 25–40 million-years-old bacterial spore, discovered in the digestive tract of an extinct bee species, preserved in amber, was reported to be revived. It was found that its 16S ribosomal RNA was quite similar to that of the living *Bacillus sphericus*. Actually, the calculated rate of nucleotide substitution in the 16S RNA encoding DNA segment appeared to be 1.8 to 2.4×10^{-9} per site per year. Although the isolation of the spore from

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the amber was carried out with extreme caution, some questions regarding possible contamination may be raised and newer studies failed to confirm DNA in amber. More recently (in 2000), 250 million-years-old spore-forming bacilli have been revived, and the authenticity of their age confirmed (Science 308:603). ▶[ancient DNA](#), ▶[mummies](#), ▶[ice man](#), ▶[amber](#), ▶[mammoth](#); Hofreiter M et al 2001 Nature Rev Genet, 2:353.

Ancient RNA: Ancient RNA is retrieved from extinct or very old specimens. ▶[ancient organisms](#)

ANCOVA: ANCOVA is the abbreviation for analysis of covariance. ▶[correlation](#)

Ancylostoma: ▶[AcAP](#), ▶[hookworm](#)

Andalusian Fowl: The Andalusian fowl is frequently used as an example for co-dominant segregation. When a black fowl is crossed with a white fowl, in the F₂ 1 black: 2 blue: 1 white individuals are found; the “blue” has black and white (white-splashed) feathers (see Fig. A74). ▶[codominance](#)



Figure A74. Andalusian fowl

Andersen's Disease 3p12: Andersen's disease is an autosomal recessive deficiency of amylotrans glucosidase(s) that causes liver, heart, and muscular disease because of the defect in glycogen storage. ▶[glycogen storage disease](#) [▶[Type IV](#)].

Andersen's Syndrome (KCJN2, 17q23): Andersen's syndrome is a periodic paralysis accompanied by heart arrhythmia and deformations. The basic defect is in an inwardly rectifying potassium channel (KCJN2). ▶[ion channels](#); Plaster NM et al 2001 Cell 105:511.

Anderson's Disease: Anderson's disease involves lipid transport defects of the intestines and the retention of chylomicrons. ▶[lipids](#), ▶[chylomicron](#)

Anderson-Fabry Disease: Anderson-Fabry disease is a human X-chromosome linked deficiency of α -galactosidase resulting in angiokeratoma (red or pink skin or mucous membrane lesions caused by dilation of veins). The relevant gene is 12 kb with 7

exons encoding a 427 amino acid protein. ▶[galactosidase- \$\beta\$](#) , ▶[angiokeratoma](#).

ANDi (inserted DNA [in reverse]): ANDi was the name given to the first transgenic (rhesus) monkey.

Androdioecy: Androdioecy is the phenomenon in which male and hermaphrodite flowers are found in separate plants like in some maples, ash trees, and others. This breeding system also occurs in *Caenorhabditis elegans*, fresh water shrimps (*Eulimnada texana*), and other invertebrates. The only vertebrate capable of self-fertilization (see Fig. A75), killifish (*Kryptolebias marmoratus*), can display androdioecy and extensive outcrossing (Mackiewicz M et al 2006 Proc Natl Acad Sci USA 103:9924). ▶[hermaphrodite](#), ▶[dioecy](#); Wolf DE et al 2001 Genetics 159:1243.

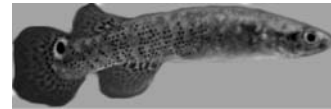


Figure A75. Killifish

Androecium: Androecium is the male part of a flower (the stamens). ▶[stamen](#)

Androgen: Androgen refers to a hormone that promotes virility, but is also present in lower concentrations in females. Androgens are formed by hydroxylation of progesterone. The most important androsterone is testosterone. Androgen has important roles in the development of the male and in prostate cancer. ▶[animal hormones](#), ▶[testosterone](#), ▶[estrogen](#), ▶[FGF](#), ▶[aromatase](#), ▶[steroid hormones](#), ▶[probasin](#), ▶[sex differences](#), ▶[prostate cancer](#); Cifuentes E et al 2004 Proc Natl Acad Sci USA 101:464.

Androgen Receptor: Androgen receptors in muscle cells are activated by a 205-kDa actin-binding protein, supervillin. ▶[hormone response elements \(HRE\)](#), ▶[Kennedy disease](#), ▶[gynecomastia](#), ▶[testicular feminization](#), ▶[histone demethylation](#); Reid KJ et al 2001 J Biol Chem 276:2943; Ting H-J et al 2002 Proc Natl Acad Sci USA 99:661.

Androgen-Insensitivity (Xq11-q12): Androgen insensitivity is caused by a defect in the dihydrotestosterone receptor. ▶[testicular feminization](#), ▶[Kennedy disease](#), ▶[Reifenstein syndrome](#)

Androgenesis: Androgenesis is the development of the male gamete into a paternal haploid or diploid embryo under natural conditions; it can be obtained by in vitro culturing and regeneration of plants from microspores. In vitro androgenesis can be *direct* when the microspores develop directly into plantlets, or *indirect* when the microspores form first a callus,

which then regenerate plantlets. Androgenesis may also arise when all the chromosomes of the female are lost in a fertilized egg, and only male chromosomes remain. Androgenesis occurs in both plants and animals. ▶apomixis, ▶embryo culture, ▶anther culture, ▶microspore culture, ▶hydatidiform mole, ▶gynogenesis, ▶hemiclinal, ▶hybridogenetic; Kermicle JL 1969 Science 166:1422; Corley-Smith GE et al 1996 Genetics 142:1265.

Androgenital Syndrome: ▶pseudohermaphroditism

Androgenote: An androgenote is a diploid embryo with only the paternal sets of chromosomes. ▶androgenesis

Androgenous: Androgenous describes a pseudo- or true hermaphroditic stage in mammals or plants. ▶hermaphrodite

Andromerogony: Andromerogony is the development of an egg (or its part) containing only the male pronucleus; the egg's own nucleus was removed prior to fusion with the male nucleus. ▶androgenesis, ▶pronucleus

Andropause: Andropause is the period of decline of the free testosterone level in human males after its peak at age 30, yet at 60 the testosterone level is still comparable to that at 20. Muscle strength may be increased by replacement therapy but impotence is usually not cured. ▶menopause

Androsome: An androsome is a chromosome, which normally occurs only in males. ▶sex chromosomes

Androstanes: Androstanes are androstanol and androstenol steroids.

Androstanol (5 α -androstan-3 α -ol): Androstanol is a mammalian pheromone, inhibitory to constitutive CAR- β . ▶CAR- β , ▶androstane, ▶androstenol

Androstenol (5 α -androsten-16-en-3 α -ol) Androstenol is a mammalian pheromone, inhibitory to constitutive CAR- β . ▶CAR- β , ▶androstane, ▶androstanol

ANE Genes: ANE genes stand for annotated non-expressed genes. ▶annotation, ▶AE genes, ▶NAE genes

Anemia: Anemia is a reduction of the red blood cells and hemoglobin below the normal level. It occurs when the production of erythrocytes does not keep up with losses. Several human diseases involve anemia, including some that are hereditary, such as thalassemias, sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, etc. Some anemias appear under autosomal dominant, autosomal recessive, or X-linked control. ▶Cooley's anemia, ▶Fanconi's anemia, ▶elliptocytosis, ▶hemolytic anemia, ▶sickle cell anemia, ▶pyruvate kinase deficiency,

▶pyrimidine 5-nucleotidase deficiency, ▶glutathione synthetase deficiency, ▶thalassemia, ▶siderocyte anemia, ▶transcobalamin deficiency, ▶magaloblastic anemia, ▶atransferrinemia, ▶acculoplasminemia, ▶hemochromatosis, ▶diphosphoglycerate mutase deficiency, ▶adenylate kinase deficiency, ▶IRE

Anemophily: Anemophily is pollination by wind.

Anencephaly (spina bifida): Anencephaly is a perinatal disorder of fetuses and newborns where the brain is absent (cerebrum and cerebellum); many of the afflicted die before birth, 1/16 of all cases survive birth but rarely live beyond a week. Anencephaly may be due to a recessive mutation but some cases can be attributed to non-genetic causes. Its prevalence is less than 1/1000. Prenatal test may be carried out if family history indicates genetic causes. Microhydranencephaly maps to 16p13.3-p12.1. Porencephaly is encoded in human chromosome 13q34. ▶neural tube defects, ▶prenatal diagnosis, ▶genetic screening, ▶MSAPF, ▶Arnold-Chiari malformation, ▶hydrocephalus MDM2

Anergy: Anergy is a lymphocyte's non-responsiveness to an antigen because, e.g., a slightly modified peptide-MHC is attached to the T cell receptor, or some inductive factors are not functioning adequately. Anergized CD4⁺ T cells are not completely idle but have some regulatory function. ▶T cell, ▶HLA, ▶MHC; Jooss K et al 2001 Proc Natl Acad Sci USA 98:8738; Schwartz RH 2003 Annu Rev Immunol 21:305.

Anesthetics: Anesthetics numb the nerve receptors; they generally affect the ligand-gated ion channels, and lipids and proteins in cell membranes. In mammals, stomatin and degenerin, and in *Caenorhabditis* the product of the *UNC-1* gene, may affect the critical ion channels. ▶ion channels, ▶stomatin, ▶degenerin; Humphrey JA et al 2002 Hum Mol Genet 11:1241.

Aneugamy: In case of aneugamy the chromosome number of the two gametes involved in fertilization is different. ▶anisogamy, ▶isogamy, ▶heterogamet-ic, ▶homogamet-ic

Aneuhaploid: is a haploid, which has incomplete set(s) of chromosomes. ▶aneuploidy, ▶haploid

Aneuploidy: Chromosome numbers in case of aneuploidy are either more or less than $2n \pm 1$ or ± 2 or ± 3 , etc. Aneuploids are trisomics or monosomics, single or multiple (see Fig. A76).

Aneuploidy is frequent in cultured cells and in cancer cells. Hamerton (1971), after surveying 1291 spontaneous human abortions, found 5%

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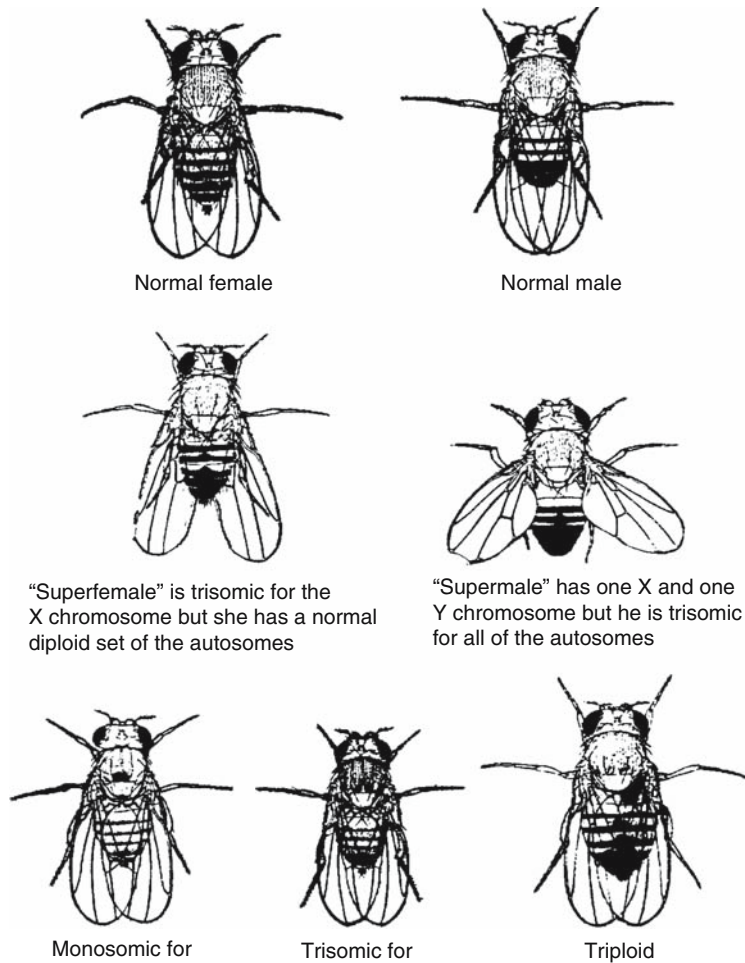


Figure A76. Normal female, normal male and various aneuploids of *Drosophila*. (From Morgan TH et al 1925 Bibl Genet 2:3)

monosomics, 11.9% trisomics, 4.1% triploids, and 1.2% tetraploids (note that the triploids and tetraploids are polyploids but not aneuploids, whose frequency is included only for comparison.). Among live human births chromosomal anomalies are close to 1%. Aneuploids are usually very deleterious yet sex-chromosomal aneuploidy e.g., Turner syndrome XO, Klinefelter syndrome XXY, etc. are not generally lethal in humans or other animals. In the 47 XXY individuals the anomaly in the majority of cases is due to nondisjunction of the XY bivalent. This high frequency may be attributed to the fact that usually even under normal conditions only a single chiasma occurs between the X and the Y (in the pseudo-autosomal region), and if this chiasma fails to materialize, nondisjunction takes place. A clinical test based on cytology and quantitative fluorescent polymerase chain reaction on X, Y, 21, 13, and 18 chromosomes is commercially available to test human aneuploidy. Monosomics ($2n-1$) have been

very skillfully exploited for mapping genes to chromosomes in polyploid plants (wheat, oats, etc.).

Microarray hybridization profiles reveal aneuploidy without cytological analysis because the expressions of large tracts of genes are detectable. Aneuploidy may lead to cancerous growth. Increased rate of aneuploidy drives an elevated level of spontaneous lymphomas and lung tumors in aged animals. Remarkably, however, in examples of chemically- or genetically-induced tumor formation, an increased rate of aneuploidy is a more effective inhibitor than initiator of tumorigenesis, probably because the aneuploid cells have diminished selective value. These findings reveal the additional role of aneuploidy and chromosomal instability in preventing tumorigenesis (Weaver BAA et al 2007 Cancer Cell 11:25). A cause of aneuploidy is probably the abnormal organization of the centrosome of animals. Animal histones are deacetylated during meiosis in the female, and it has been suggested that decreased

deacetylation can be a cause of aneuploidy and embryonic death in mice (Akyama T et al 2006 Proc Natl Acad Sci USA 103:7339). (See ►[illustration](#), ►[hypoploid](#), ►[hyperploid](#), ►[triploid](#), ►[pentaploid](#), ►[monosomic analysis](#), ►[MSAFP](#), ►[pseudoautosomal](#), ►[chiasma](#), ►[microarray hybridization](#), ►[centrosome](#), ►[polymerase chain reaction](#), ►[mosaic variegated aneuploidy](#); Jacobs PA, Hassold TJ 1995 Adv Genet 33:101; Hassold T, Hunt P 2001 Nature Rev Genet 2:280; Yuan L et al 2002 Science 296:1115; cancer: Rajagopalan H, Lengauer C 2004 Nature [Lond] 432:338)

Aneurysm: Aneurysm refers to the formation of small sacs of blood caused by the dilation of veins. Both abdominal aneurysms (more common in females) and brain aneurysms are under autosomal dominant control. Aortic aneurysm (15q21) is a heart disease involving fibrillin. Apparent linkage to 5q22-q31, 7q11 and 14q22 have also been reported. Thoracic aneurysm/aortic dissection (splitting of the arterial wall resulting in hemorrhage, TAAD) and patent ductus arteriosus is located to human chromosome 16p12.2-p13.3. It is caused by mutation in myosin 11-heavy chain (Zhu L et al 2006 Nature Genet 38:343). ►[collagen](#), ►[fibrillin](#), ►[patent ductus](#), ►[myosin](#), ►[Marfan syndrome](#), ►[Loeys-Dietz syndrome](#); Onda H et al 2001 Am J Hum Genet 69:804.

Aneusomatic: Aneusomatic describes the condition in which the somatic chromosome number varies among cells because of the presence of supernumerary chromosomes and because of their frequent somatic nondisjunction. Aneusomy is one of the most common causes of cancer. ►[supernumerary chromosomes](#), ►[nondisjunction](#), ►[aneuploidy](#); Fabarius A et al 2002 Proc Natl Acad Sci USA 99:6778.

Aneusomy, Segmental: ►[contiguous gene syndrome](#)

Angelman Syndrome (Happy Puppet Syndrome): Angelman syndrome is apparently an autosomal recessive human defect with somewhat irregular inheritance. Cytologically and molecularly detectable deletion in the 15q11-q13 region (similar to the Prader-Willi syndrome) has been observed. The unusual feature of this condition is that it is transmitted only through the mother whereas, in the Prader-Willi syndrome the transmission is via the father, the gene on the maternal chromosome being inactive. Imprinting has been suggested for the phenomenon. It has been suggested that in the female germline the so-named BD RNA transcripts induce methylation in the promoter of snRNP genes. Affected individuals have motor function defects (see Fig. A77), mental retardation, epilepsy, speech defect or absence, and a frequently

protruding tongue accompanied by excessive laughter (hence the name HPS). It appears that the syndrome is effected by abnormal ubiquitin-mediated degradation of a brain ligase (UBE3A, Xq28) of the E6-AP class. ►[disomic](#), ►[Prader-Willi syndrome](#), ►[mental retardation](#), ►[imprinting](#), ►[epigenesis](#), ►[head/face/brain defects](#), ►[snRNP](#), ►[ubiquitin](#), ►[Ube3](#), ►[E3](#), ►[imprinting box](#), ►[Rett syndrome](#); Jiang Y-H et al 1999 Am J Hum Genet 65:1.



Figure A77. Angelman syndrome

Angina Pectoris: Angina pectoris is characterized by spasmodic chest pain that may radiate to the arms (primarily the left) and breathing difficulties. It is caused by arterial ischemia and heart disease. It is a symptom also of several hereditary syndromes. ►[ischemia](#)

Angioectasis: Angioectasis is the excessive dilation of blood vessels.

Angioedema: Angioedema is the dilation of the subcutaneous capillary veins leading to skin, respiratory tract, and gastrointestinal fluid accumulations. The hereditary dominant form has been attributed to mutations in a serpin gene or to complement inhibitory factor deficiency (C1-INH). The condition may be haplo-insufficient. ►[serpin](#), ►[complement](#), ►[haplo-insufficient](#)

Angiogenesis: Angiogenesis refers to the formation of blood vessels and chronic inflammation. The vascular endothelial growth factor and its two receptors Flt-1 and Flk-1/KDR are required in rodents for angiogenesis. Vasculogenesis factor (VEGF) peptide hormones, secreted by tumors, increase blood supply and ensure neoplasias and their further growth. There are two angiogenesis pathways. Actually some pro-angiogenesis factors (FGF family) can eventually restore blood supply even after blocking VEGF receptors (Casanovas O et al 2005 Cancer Cell 8:299). The fibroblast growth factor- or tumor necrosis factor- α initiated path depends on integrin $\alpha_v\beta_3$, whereas angiogenesis initiated by vascular endothelial growth factor, transforming growth factor- α , or phorbol ester uses the $\alpha_v\beta_5$ path.

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Disruption of the matrix metalloproteinase 2 binding to integrin inhibits angiogenesis, and it may be relevant to tumor control. The tumor necrosis factor- α induced angiogenesis uses the B61 cytokine-inducible ligand for the Eck protein tyrosine kinase receptor (RPTK).

VEGF dynamically regulates tumor endothelial expression of Delta-like ligand 4 (Dll4), which was shown to be essential to normal embryonic vascular development. Blocking of Dll4 resulted in markedly increased tumor vascularization, associated with enhanced angiogenic sprouting and branching. Paradoxically, this increased vascularization was non-productive—as shown by poor perfusion and increased hypoxia, and most importantly, by decreased tumor growth—even for tumors resistant to anti-VEGF therapy. Thus, VEGF-induced Dll4 acts as a negative regulator of tumor angiogenesis; its blockade results in a striking uncoupling of tumor growth from vessel density, and may offer a novel therapeutic approach even for tumors resistant to anti-VEGF therapies (Noguera-Troise I et al 2006 Nature [Lond] 444:1032).

Angiogenesis also promotes the proliferation of tumors, but the process can be restricted by the antibiotic minocycline, AGM, interferon $\alpha/\beta/\gamma$, angiostatin, endostatin, interferons, etc. Antiangiogenic therapy may destroy the vasculature of the solid tumors and neutralize VEGF signaling. Normalization can occur by recruiting pericytes (flexible cells, which wrap around the pre-capillary vessels and stabilize them transiently). The normalization is mediated by angiopoietin-1 and metalloproteinases, and provides an opportunity for radiation and chemotherapy (Lin M Ii, Sessa WC 2004 Cancer Cell 6:529).

The combined action of the three classes of angiostatic compounds, each targeting different aspects of the angiogenic process, was tested using a VEGF aptamer chemically identical to Macugen, recently approved for the treatment of neovascular eye diseases. The small-molecules $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin antagonists targeted the extracellular matrix-mediated endothelial cell survival. To block endothelial intracellular adhesion and lumen formation, T2-TrpRS (T2) was used. This is a proteolytic fragment of tryptophan tRNA synthetase that exhibits angiostatic activity, which is linked to its ability to block vascular endothelial-cadherin-mediated adhesion. The combination angiostatic therapy significantly reduced the compensatory upregulation possible in case a component of the blocking system had been used. The synergistic antiangiogenic activity appeared effective for the treatment of neovascular disease (Dorrell MI et al 2007 Proc Natl Acad Sci USA 104:967).

Tilted (or oblique-oriented) peptides are short peptides known to destabilize membranes and lipid cores. They are characterized by an asymmetric distribution of hydrophobic residues along the axis when helical, and are antiangiogenic. 16-kDa fragments of the members of the human prolactin/growth hormone (PRL/GH) family are potent angiogenesis inhibitors. All these fragments possess a 14-amino acid sequence having the characteristics of a tilted peptide. Tilted human peptides induce endothelial cell apoptosis, inhibit endothelial cell proliferation, and inhibit capillary formation both in vitro and in vivo. These antiangiogenic effects are abolished when the peptides' hydrophobicity gradient is altered by mutation. Well-known tilted peptides of simian immunodeficiency virus gp32 and Alzheimer's disease amyloid peptide are also angiogenesis inhibitors (Nguyen N-Q-N et al 2006 Proc Natl Acad Sci USA 103:14319).

Promoters of angiogenesis include cytokines (EGF, TGF, TNF), various carbohydrates, angiogenin, and several other molecules. The ligands of the Tie receptors, Angi1 and Angi 4, regulate angiogenesis positively, whereas Angi3 is a negative regulator. MicroRNA (miR-17-92) is an important factor for adenocarcinomas because it regulates vascular endothelial growth factor (VEGF). miR-17-92 represses anti-angiogenic factors thrombospondin-1 and connective tissue growth factor (CTGF), which are upregulated by KRAS and cMyc protooncogenes and are involved in tumorigenesis (Dews M et al 2006 Nature Genet 38:1060).

Gene *ING4* is known to control angiogenesis. In the presence of the *ING4* gene transcript, angiogenic vasculature is repressed (see Fig. A78) relative to the control, whereas when the transcript is reduced by antisense RNA (*as-ANG4*) angiogenesis and glioma growth are enhanced. *ING4* physically interacts with RelA subunit of NF- κ B. These images were obtained from human glioblastoma (U87MG) grafted into the brain of a mouse. Several new drugs are now available to fight angiogenesis, such as Avastin, an antibody that blocks VEGF, and Sutent and Sorafenib that block angiogenesis indirectly by inhibiting tyrosine kinases and appear effective against cancer.

Although inhibition of angiogenesis deprives tumors of the blood supply essential for proliferation, it also hinders the targeted delivery of therapeutic chemicals; furthermore hypoxia-inducible factor (HIF1- α) accumulates and leads to an increase in metastasis. A nanoparticle has been designed to target tumors, to overcome these problems. The outer envelope of the nanocell releases temporally an anti-angiogenesis agent combretastatin at first, and then a doxorubicin-PGLA (poly-(1-lactic-co-glycolic) acid, a biodegradable, non-bioactive polymer)

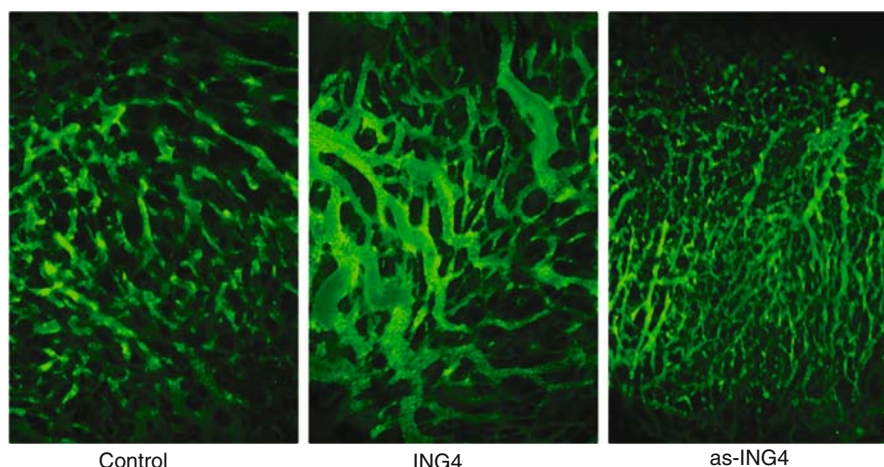


Figure A78. Angiogenesis. (Courtesy of Dr. Igor Gardatsev; see also Garkatse, I. *et al.* 2004 Nature [Lond] 428, 328)

conjugate is slowly released inside the tumor. The nanocell prefers tumor cells. This targeted approach hurts the tumor, and also comparatively reduces toxicity for normal cells (Sengupta S *et al* 2005 Nature [Lond] 436:568).

►tumor, ►cancer, ►glioma, ►VEGF [vascular endothelial growth factor], ►wound healing, ►fibroblast growth factor [FGF], ►Flk, ►Flt, ►angiopoietin, ►integrin, ►phorbol esters, ►metalloproteinases, ►tumor necrosis factor [TNF], ►neuropilin, ►neutrophil, ►angiostatin, ►Avastin, ►endostatin, ►hemangioblast, ►CXCR, ►leptin, ►EGF, ►TGF, ►TNF, ►PTEN, ►Id proteins, ►maspin, ►NF-κB, ►HIF, ►doxorubicin, ►PLGA, ►combretastin, ►KRAS, ►MYC, ►thrombospondin, ►connective tissue growth factor; Carmeliet P, Jain RK 2000 Nature [Lond] 407:249; Folkman J 2001 Proc Natl Acad Sci USA 98:398; Kuo CJ *et al* 2001 Proc Natl Acad Sci USA 98:4605; Jones N *et al* 2001 Nature Rev Mol Cell Biol 2:257; Isner JM 2002 Nature [Lond] 415:234; Grunewald M *et al* 2006 Cell 124:175; antiangiogenic therapies; Kerbel RS 2006 Science 312:1171, <http://angiodb.snu.ac.kr>.

Angiogenins: Angiogenins are RNases stimulating blood vessel formation. ►ribonucleases

Angiokeratoma: Angiokeratoma is a recessive X-chromosome linked skin disease involving dilation of the small veins, warty growth, and thickening of the epidermis primarily on fingers, toes, and the scrotum. ►Anderson-Fabry disease, ►Kanzaki disease, ►fucosidosis

Angioma: Angioma is a tumor of the blood or lymph vessels or a neoplasia, which forms blood and lymph vessels. Many forms exist in humans; they are controlled by dominant genes at chromosomes

7q11.2-q21 (CCM1), 7p15-p13 (CCM2), and 3q25.2-q27 (CCM3). The CCM1 locus encodes RAP1A interacting KRIT1 protein. ►hemangioma, ►RAP1

Angioneurotic Edema: Angioneurotic edema is a dominant chromosome 11q11-q13.1 deficiency of complement C1 inhibitor, causing edema of the air passageway. The reduced level of the inhibitor leads to excesses of the C4 and C2 kinin fragments. Angioneurotic edema is a hereditary disease. ►complement, ►angioedema, ►kinin

Angioplasty: Angioplasty corrects narrowed blood vessels. One procedure involves inflation of a balloon inside an artery to break up plaque(s) in order to restore free blood flow.

Angiopoietin: Angiopoietin-1 is a blood-vessel differentiation factor that promotes tissue vascularization. Angiopoietin-2 is an antagonist of angiogenesis. ►VEGF, ►angiogenesis

Angiosperm: Angiosperms are plants that bear seeds within an ovary; the majority of higher plants belong to this taxonomic category. Fossil evidence points to their presence in the Jurassic period (137–190 Mya). ►Mya, ►geological time periods

Angiostatin: Angiostatin is a 38-kDa protein with some homology to plasminogen. It is an anticancer agent with the twin advantages that it can deprive cancer cells from developing new blood vessels and that resistance mutations against it (common to most anticancer drugs) have not yet been observed. The therapeutic effectiveness in the cure of human cancer has not been completely accepted, although some positive results have been obtained, especially in combination with radiation treatment. Angiostatin

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may act by inhibiting endothelial ATP synthase, possibly required for supplying the energy for tumorigenesis. ►endostatin, ►cancer, ►angiogenesis, ►plasminogen, ►cancer therapy; Moser TL et al 2001 Proc Natl Acad Sci USA 98:6656.

Angiotensin: Asp - Arg - Val - Tyr - Ile - His - Pro - Phe peptides stimulate the smooth muscles of the blood vessels, reduce the blood flow through the kidneys and decrease the excretion of fluid and salts, increase the secretion of aldosterone, and stimulate the reabsorption of sodium. These peptides are known as angiotensins. They are involved in the hereditary disorders of adrenocortical steroid biogenesis (see Fig. A79). Angiotensin I receptor AT₁ mediates the enhancer (higher blood pressure) and angiotensin II receptor AT has the opposite (depressor) effect. The drugs Lisinopril and Losartan, frequently prescribed against high blood pressure, are inhibitors of the ACE enzyme and reduce hypertension. Angiotensin II cell surface receptor is directly stimulated by the Jak/STAT signal transduction pathway. The angiotensin converting enzyme (ACE, 17q23) is a dipeptidyl carboxypeptidase (kininase) that catalyzes the conversion of angiotensin I to angiotensin II. ACE2 was located to human Xp22; angiotensinogen (AGT) is at 1q42-q43. aldosterone, ►hypertension, ►eclampsia, ►signal transduction, ►tachykinin, ►pseudoaldosteronism, ►angiostatin, ►SARS, ►BBB, ►DCP1, ►rennin, ►Marfan syndrome, Zhu X et al 2001 Am J Hum Genet 68:1139; Morimoto S et al 2002 Physiol Genomics 9:113, review: Keidar S et al 2007 Cardiovasc Res 73:463.

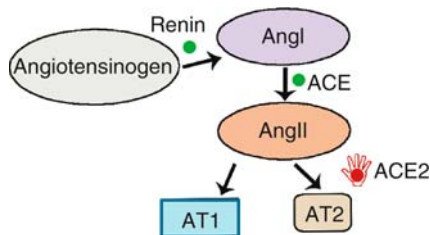


Figure A79. Renin protease cleaves angiotensinogen into the inactive decaemic angiotensin I (AngI) and the angiotensin converting enzyme (ACE) cleaves it into the active octamer angiotensin II (AngII). This can promote hypertension and renal Na reabsorption. ACE2 inactivates AngII and protects against acute lung injury by receptor AT1 with the aid of AT2. Imai, Y. et al. 2005 Nature 436:112; Danilczyk, U. et al. 2006 Nature 444: 1088

Ångström (Å): Angstrom is a unit in measurement. 1 Å = 1/10 nanometer (nm).

Angular Transformation (arcsine transformation): Angular transformation is used with percentages and proportions. In a binomial distribution the variance is a function of the mean. The arcsine transformation prevents that $\theta = \arcsin \sqrt{p}$, where p is a proportion which stands for an angle whose sine is the given quantity. The transformation stretches out both ends of a distribution of percentages and compresses the middle. It may be usefully applied to genetic data when the figures fall outside the 30% and 70% ranges. ►arcsine, sine.

Anhidrosis: Anhidrosis is reduction or lack of sweating. An X-linked hypo- or anhidrotic ectodermal dysplasia is caused by mutation in a transmembrane protein. Ectodermal dysplasia is a part of about 150 syndromes. ►ectodermal dysplasia, ►pain-insensitivity

Anhidrotic Ectodermal Dysplasia: ectodermal dysplasia.

Anhydride: An anhydride is a compound that results from a condensation reaction where water was eliminated (between carboxyl and phosphate groups).

Animal Genetics: ►individual animal species, ►OMIA, ►breeding value, ►heritability, ►QTL, ►GOBASE; Fadiel A et al 2005 Nucleic Acids Res 33:6308.

Animal Genome Size: <http://www.genomesize.com>.

Animal Hormones: Hormones are the first chemical messengers secreted by certain tissues to be carried by the bloodstream to the specific sites of action where regulatory functions are enacted. Hormones regulate either the synthesis or activity of enzymes, or affect membrane transport in cooperation with the second messengers, cyclic adenosine monophosphate and cGMP. There are of three major types of hormones, which are detailed as follows. **PEPTIDE HORMONES:** secreted by the hypophysis of the pituitary gland, are somatotropin (general growth hormone, GH), corticotropin (adrenocorticotropin, ACTH in the kidneys), thyrotropin (thyroid-stimulating hormone, TSH), follitropin (FSH, in gonads), lutotropin (luteinizing hormone, LH, in gonads), and prolactin (in mammary glands). Secreted by the neurohypophysis are: oxytocin (controls uterine contractions and milk production), vasopressin (antidiuretic hormone that controls water reabsorption of the kidneys and blood pressure). Secreted by the middle section of the hypophysis are Melanotropins (control melanin pigments). The pancreas secretes insulin (controls carbohydrate, fatty acid, and cholesterol metabolism), and glucagon (stimulates glucose production by the liver). The ovary produces relaxin (controls pelvic ligaments, the uterine cervix, thereby labor), the thyroid gland is the source of parathyrin (involved in calcium and phosphorus metabolism), the kidneys release

erythropoietin (a glucoprotein involved in erythrocyte production by the bone marrow), and renin (causes constriction of the blood vessels). The digestive tract secretes gastrin (promotes digestive enzymes), enterogastrone (controls the gastric secretion), cholecystokinin (regulates gall bladder), secretin (controls pancreatic fluids and bile production), and pancreaticozym (of duodenal origin, stimulates pancreatic functions). **AMINO ACID HORMONES:** thyroxine and triiodothyronine are secreted by the thyroid gland and affect many functions in the body. The kidney tissues secrete epinephrine (adrenaline) and norepinephrine (triiodothyronine) that regulate blood pressure and heart rate, while the pineal gland (a cone-shaped epithelial body at the base of the brain) produces melatonin, which affects the pigment producing melanophore cells. The nerve cells produce serotonin (5-hydroxytryptamine) affecting contraction of the blood vessels and nerve function. Serotonin controls the central nervous system and therefore, alertness, sleep, mood, aggressiveness, etc. **STEROID HORMONES:** are produced in the testes (testosterone, regulates male reproductive capacities), in the ovaries (estrogen [estradiol-17 β], involved in female reproductive functions), in the corpus luteum of the ovary. Progesterone is produced in the Schwann cells of the peripheral nervous system. It functions during menstrual cycles, pregnancy, and in myelin formation. In the kidney cortex cortisol (corticosterone) is synthesized affecting glucose utilization and glucose levels in the blood. Although estrogen is typically a female hormone, yet extremely high concentrations occur in the fluids of the testis, and it is important for male fertility. Progesterone is necessary for the maintenance of pregnancy. It binds to the oxytocin receptor (OTR) and prevents uterine contractions. **EICOSANOID (HORMONELIKE) SUBSTANCES:** include prostaglandins (trigger smooth muscle contraction, control fever and inflammations), leukotrienes (secreted by the white blood cells and affect hypersensitivity reactions and pulmonary functions), and thromboxanes (produced by the blood platelets and other cells, involved in blood clotting, blood vessel constriction, etc.) A large number of other hormones also exist, and perform important functions. ►hormones, ►hormone receptors, ►hormone response elements, ►opiocortin, ►oxytocin

Animal Host Cells: Host cells are used for genetic transformation. *Xenopus* oocytes are well suited for such studies because they can propagate foreign genes in appropriate vectors quite efficiently. Similarly, COS cells of mice and other somatic cells have been used effectively. Recently available techniques for the transformation of animal zygotes and embryos

have enabled that genetic information be added or replaced in the germline, and transmitted to the sexual progeny. ►transformation of animal cells, ►COS, ►vectors genetic, ►germline

Animal Models: Certain biological phenomena cannot be studied in humans because mutants are not available and cannot be produced or manipulated effectively. In such cases animals such as *Caenorhabditis*, *Drosophila*, and mice are used for the experimentation (in behavioral genetics, neurobiology, various diseases, etc.). Animal models may have an important role in improving the techniques of gene therapy. The “shiverer” deletion in mice, resulting in convulsions because of the loss of a gene coding for a myelin protein, has been genetically cured by transfection of the wild type allele into the gamete. Similarly, the size of mice could be genetically increased by transformation using the rat somatotropin (RGH, growth hormone) gene fused to and regulated by a metallothionein promoter. The following monogenic human genetic disorders have models in mouse [abbreviations h. chr. = human chromosome, m. chr. mouse chromosome]: *adenomatous polyposis* (protrusive growth in the mucous membranes, h. chr. 5q21-q22, mouse homolog *Apc*^{Min}, chr. 18), *androgen insensitivity* (sterility, h. chr. Xq11.2-q12, mouse gene *AR*^{Tfm}, m. chr. X), *X-linked agammaglobulinemia* (deficiency of γ globulin in blood, h. chr. Xq21.33-q22, mouse gene *Btk*^{Xid}, m. chr. X), *Duchenne muscular dystrophy* (an early muscular disability), h. chr. Xp21.3-p21.2, mouse *Dmd*^{mdx}, m. chr. X), *Greig cephalopolysyndactyly* (multiple fusion of digits, h. chr. 7p13, mouse gene *Gli3*^{Xt}, m. chr. 13), *mucopolysaccharidosis type VII* (a type of lysosomal storage disease, h. chr. 7q22, mouse gene *Gus*^{m^{ps}}, m. chr. 5), *α -thalassemia* (defect in the hemoglobin α chain, h. chr. 16p13.3, mouse gene *Hba*th, m. chr. 11), *β -thalassemia* (defect in the β -chain of hemoglobin, h. chr. 11p15.5, mouse gene *Hbb*th, m. chr. 7), *piebaldism* (color patches on the body, h. chr. 4p11-q22, mouse gene *Kit*^W, m. chr. 5), *ornithine transcarbamylase* (defect in the transfer of a carbamoyl group, H₂N - C = O, from ornithine to citrulline, h. chr. Xp21.1, mouse gene *Otc*^{Spf}, m. chr. X), *tyrosinase-positive type II* (oculocutaneous albinism, h. chr. 15q11-q12, mouse gene *p*^p, m. chr. 7), *phenylketonuria* (phenylalanine hydroxylase deficiency, h. chr. 12q22-q24.2, mouse gene *Pah*^{enu2}, m. chr. 10), *Waardenburg syndrome type I* (h. chr. 2q35-q37, mouse gene *Pax3*^{Sp}, m. chr. 1), *aniridia* (absence of the iris, h. chr. 11p13, mouse gene *Pax6*^{Sey}, m. chr. 2), *pituitary hormone deficiency* (h. chr. 3q, mouse gene *Pit1*^{dw}, m. chr. 16), *Pelizaeus-Merzbacher disease* (central brain sclerosis, h. chr. Xq21.33-q22, mouse gene *Plp*^{ilp}, m. chr. X),

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Charcot-Marie-Tooth disease type 1A (a progressive neuropathic muscular atrophy, h. chr. 17p12-p11.2, mouse gene *Pmp22^{Tf}*, m. chr. 11), *retinitis pigmentosa* (sclerosis and pigmentation of the retina, h. chr. 6p21.2-cen, mouse gene *RD2^{Rd2}*, m. chr. 17), *gonadal dysgenesis* (underdeveloped germ cells in the testes) h. chr. Y11.2-pter, mouse gene *Sry^{Sxr}*, m. chr. Y), *tyrosinase negative oculocutaneous albinism* albinism, h. chr. 11q14-q21, mouse gene *Tyr^c*, m. chr. 7. By disruption of hexosaminidase α subunit, a model for the Tay-Sachs disease has been generated in mice. Interestingly, these animals suffered no obvious behavioral or neurological deficit. Disrupting the hexosaminidase β subunit (Sandhoff disease model) resulted in massive depletion of spinal cord axons and neuronal storage of ganglioside G_{M2}. The two latter examples indicate possible complications with animal models (see Fig. A80).

Mouse polygenic disorders with similarities to human conditions [human problem - mouse strain]: alcoholism and opiate drug addictions - C57BL/6J, asthma - A/J, atherosclerosis - C57BL, audiogenic (sound-induced) seizures - DBA, cleft palate (fissure in the mouth) - A, deafness - LP, dental disease - C57BL, BALB/c, diabetes - NOD, epilepsy - EL, SWXL-4, granulosa cell tumors in the ovary - SWR, germ cell tumors in the ovary - LT, germ cell tumors in the testes - 129, hemolytic.

Anemia - NZB, hepatitis - BALB/c, Hodgkin disease (pre-B cell lymphoma - SJL, hypertension - MA/My, kidney adenocarcinoma - BALB/c Cd, leprosy (*Mycobacterium leprae*) - BALB/c, leukemia - AKR/J, C58/J, P/J, lung tumors - A, Ma/My, measles - BALB/c, osteoporosis - DBA, polygenic obesity - NZB, NZW, pulmonary tumors - A/J, rheumatoid arthritis - MRL/Mp, spina bifida (defect of the bones of the spinal cord) - CT, systemic lupus erythematosus

(a skin degeneration) - NZB, NZW, whooping cough - BALB/c. Some of the diseases (e.g., various types of cancer) occur sporadically because of mutations occurring during the course of the development of animals/humans. The introduction of a functional oncogene into the germline or into the soma line of a person cannot appropriately represent the conditions emerging in sporadic cases. Usually in cancer the sporadic occurrence of mutation is predominant. Normal cells generally surround the mutation in the soma and through bystander effect these may modify the expression of the mutant cell and its clonal derivatives, unlike the cases when the mutation has occurred in the male/female germline before fertilization. The former condition can be simulated in a genetic model, if, e.g., through recombination between one of the wild type RAS oncogene and its mutant a potentially proliferative allele is activated. The construction of such a model may be represented graphically.

Despite their usefulness for the study of human diseases, animal models may not always represent completely the human condition. For instance, mice deficient for both copies of the insulin receptor are born with normal weight but die from ketoacidosis soon after birth. The analogous null mutant humans are small at birth but rarely develop ketoacidosis. Human mutants of PPAR γ Pro467Leu develop extreme insulin resistance, diabetes mellitus, and hypertension. Mice with the same mutation are also hypertensive but display normal insulin-sensitivity and glucose homeostasis (O'Rahilly S et al 2005 Science 307:370). (See terms and diseases under separate entries).

Animal Pole: The animal pole is the dorsal end of the (animal) egg opposite the lower end, the vegetal pole, and the site of the entry of the sperm. After the entry,

WILD TYPE PROTOONCOGENE



MUTATIONALLY ACTIVATED AND GENETICALLY ENGINEERED ONCOGENE CONTAINS THE SELECTABLE MARKER INTO THE WILD TYPE LOCUS



SUCH A CONSTRUCT MAY RECOMBINE WITH THE WILD TYPE LOCUS AND PRODUCE A FUNCTIONAL TUMOR SUPPRESSOR:



OR AN ACTIVE ONCOGENE:



Figure A80. A genetic construct simulating the sporadic occurrence of oncogenic mutations. (See Johnson L et al (2001) Nature (Lond) 410:1111)

the egg cortex rotates slightly and in some species at the side opposite the entry a *gray crescent* is formed.

►vegetal pole

Animal Species Hybrids: The most familiar examples are the hybrids of the mare (*Equus caballus*, $2n = 64$) and the jackass (*Equus asinus*, $2n = 62$), and the stallion and the she-ass (see Fig. A81).



Figure A81. Hybrid of the male Grant's zebra and the female black Arabian ass, Gloucester zoo. (From Gray, A.P. Mammalian Hybrids. Commonwealth Agric. Bureau. Farnham Roal, Slough, UK)

Hybrid males do not produce viable sperm although they may show normal libido. The females may have a uterus and ovulate but there is no proven case of fertility. Zebras ($2n = 44$) also may form hybrids with both donkeys and horses. Buffalo (*Bison bison*, $2n = 60$) may be crossed reciprocally with cattle (*Bos taurus*, $2n = 60$) but their offspring (cattalo) has reduced fertility. The domesticated pig (*Sus crofa*, $2n = 38$) forms fertile hybrids with several wild pigs with the same number of chromosomes. The sheep (*Ovis aries*, $2n = 54$) interbreeds with the wild mouflons but the sheep x goat (*Capra hircus*, $2n = 60$) hybrid embryo rarely survives. Some monkeys can be interbred but primates are generally sexually isolated.

There is no sexual barrier among various human races, indicating close relationship, but no hybrids are known between humans and other species. These general rules do not hold for somatic cell hybrids because human cells can be fused with rodent or plant cells but they cannot be regenerated or even maintained successfully for indefinite periods of time. somatic cell hybrids, ►goat ►x sheep hybrids, ►transformation genetics

Animal Transformation Vectors: Most commonly used transformation vectors in animals are Simian virus 40

(SV40) and Bovine papilloma virus (BPV) based vectors. The BPV vectors can be used for the synthesis of large amounts of proteins specified by the gene(s) carried by the expression vectors. In addition, the BPV vectors can be maintained for long periods of time in cell cultures and may yield 10 mg of specific protein(s) per liter of culture/24 hr. The SV40 vectors can also be used for gene amplification in COS cells. Both these vectors can serve as shuttles between animal and prokaryotic cells. ►BPV and SV40 ►constructs, ►adenovirus, ►adenoassociated virus, ►retroviral vectors, ►lentivirus, ►vaccinia virus, ►COS cells, ►gene therapy

Animal Viruses: Animal viruses include viruses found in both invertebrates and vertebrates. The Rhabdoviridae and the Bunyoviridae may also infect plants. The double-stranded DNA viruses that may have been *enveloped* include Baculoviridae, Poxviridae, Herpesviridae, Hepadnaviridae, and Polydnaviridae. Double-stranded DNA viruses *without envelope* comprise Iridoviridae, Adenoviridae, and Papovaviridae. Parvoviridae have single-stranded DNA and do not have an envelope. The single-stranded RNA and *enveloped* group includes the Togaviridae, Bunyaviridae, Rhabdoviridae, Coronaviridae, Paramixoviridae, Toroviridae, Orthomyxoviridae, Arenaviridae, Flaviviridae, Retroviridae, and Filoviridae. The single-stranded RNA and *non-enveloped* viruses are: Picornaviridae, Tetraviridae, Nodaviridae, and Caliciviridae. The double-stranded RNA and *non-enveloped* viruses are Reoviridae and Birnaviridae. Their genetic material varies in size from 5 kb in the Parvoviridae to 375 kbp in the Poxviridae. The Polydnaviridae may have several copies of double-stranded circular DNAs. The Papovaviridae have only a single double-stranded DNA genetic material. The others may have two or more segments of linear nucleic acid genetic material. ►viruses, <http://www.ncbi.nlm.nih.gov/ICTVdb/ictvdb.htm>.

Animal Welfare: Animal welfare is a serious societal concern that seeks to balance the interest and need of medical research with the humane treatment of animals. Among the goals are Refinement, Reduction, and Replacement of animals as much as possible in experiments. The idea is to limit their use to the minimal and most indispensable experimentation that is in the best interest of humans as well as animals.

Animalcules: The pioneer microscopist Anthony Leuwenhoek (17th century) believed he could see small encapsulated animals in the sperm of various animals and this apparent observation supported his view that inheritance travels only through the sperm and the females serve only as incubators. His observations lead

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to the notion of preformation, rather than epigenesis (see Fig. A82). ►preformation, ►epigenesis, ►sperm



Figure A82. Animalcule

Animation: The condition of being alive and maintaining at least limited metabolic activity (suspended animation). Nitric oxide may favor *Drosophila* survival under hypoxia. ►hypoxia, ►nitric oxide; Teodoro RO, O'Farrell PH 2003 EMBO J 22:580)

Anion Exchange Resin: A polymer with cationic groups, the anion exchange resin traps anionic groups and thus can be used in chromatographic separation.

Anions: Anions are negatively charged ions.

Aniridia: Aniridia refers to the absence or reduction of the iris of the eye (see Fig. A83). It is frequently accompanied by cataract (opacity of the eye[s]), glaucoma (increased intraocular pressure causing deformation of the optic disk), nystagmus (involuntary movement of the eyeball), etc.

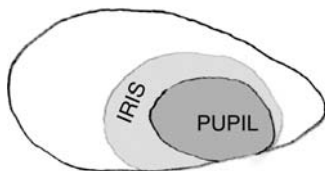


Figure A83. Hypoplastic iris and enlarged excentric pupil in adult aniridia

The condition is caused by dominant defects in human chromosomes 2 and 11. In a sample population from Michigan, the rate of mutation was 4×10^{-6} . Aniridia may involve Wilms tumors and genital abnormalities due a deletion in human chromosome 11p13 (PAX6). Aniridia may be haplo-insufficient. The *Drosophila* locus *eyeless* and the mouse *Sey/Pax-6* are the corresponding homologs. ►Wilms tumor, ►WAGR, ►deletion, ►eyeless, ►haplo-insufficient

Anisogamy: the gametes are not identical, e.g., male and female (+ or -) are distinguishable. ►isogamy

Anisomycin: Anisomycin is an antibiotic isolated from *Streptomyces griseolus*. It inhibits peptidyl transferase during protein synthesis on the ribosomes. It also inhibits pathogenic fungi (e.g., mildew) in plants and it was found to be useful against infection by various species of the parasitic flagellate, *Trichomonas*, causing inflammation of the gums, diarrhea, vaginal discharge, and irritation in humans and animals (particularly poultry and pigeons). ►antibiotics, ►protein synthesis

Anisotropic: Anisotropic describes the condition in which the material varies in different directions, responds differently to external effects depending on direction.

Anj1: A heat and other stress-inducible membrane-associated chaperone of higher plants. The Cys-Ala-Gln-Gln C-terminus may be subject to farnesylation. ►heat-shock proteins, ►chaperones, ►DnaK, ►prenylation

Ankyloblepharon: Ankyloblepharon describes fused eyelids. ►Hay-Wells syndrome

Ankylosing Spondylitis (AS): AS is an autosomal dominant rheumatism-type disease with reduced penetration. The greatest susceptibility to AS is associated with MHC (HLA B27), but spurious or fair linkage was observed with chromosomes 1p, 2q, 6p, 9q, 10q, 16q and 19q. The onset of AS occurs after age 20. ►HLA, ►immunodeficiency, ►connective tissue disorders, ►autoimmune disease, ►penetrance; Laval SH et al 2001 Am J Hum Genet 68:918.

Ankyrin: Ankyrins are protein motifs capable of binding fibrous proteins (e.g., spectrin) of the cytoskeleton, and thus may be involved in some polar transports within the cell. Several ankyrin and ankyrin-like proteins are encoded in different human chromosomes (8p11.2, 4q25-q27, 10q21, etc.). Ankyrin B mutations may be involved in type 4 LQT cardiac arrhythmia. Ankyrin repeats may form superhelical spirals and have spring-like function in *Drosophila* hairs and bristles, among others (Lee G et al 2006 Nature [Lond] 440:246). ►LQT, ►cytoskeleton, ►spectrin, ►elliptocytosis, ►poikilocytosis, ►IkB, ►spherocytosis, ►tankyrase, ►Wolbachia; Hayashi T, Su T-S 2001 Proc Natl Acad Sci USA 98:491.

Anlage: Anlagen are a group of cells of the embryo that initiate specific biological structures. ►primordium

Annealing: Annealing is the formation of double-stranded nucleic acid when two complementary single stranded chains meet (nucleic acid hybridization, attachment of a primer). Used to estimate DNA complexity, the process identifies the presence of homologous sequences in the genome with the help

of radioactively labeled or fluorescent homologous and heterologous probes. ►*c₀t* curve, ►probe, ►chromosome painting, ►FISH, ►DNA hybridization, ►primer

Annexins: Annexins are proteins composed of four or eight conserved 70-amino acid domains with variations mainly at the amino end. In mammals, there are at least 10 annexins; others exist in lower eukaryotes. Annexins bind to negatively charged phospholipids in the membranes. Annexins V and VI form voltage-regulated ion channels for different cations, whereas VII is specific for Ca²⁺. Annexin V can reveal apoptosis in imaging technology. Annexins II may assist exo- and endocytosis. An annexin-like protein may be involved in mitigating H₂O₂ stress. Annexin 7 (ANX7, 10q21) is a tumor suppressor. ►ion channels, ►endocytosis, ►exocytosis, ►imaging; Bendorowicz-Pikula J et al 2001 *Bioessays* 23:170.

Annotation of the Genome: The identification of the function of open-reading frames and other elements. This is also called *one-dimensional annotation*. When the annotation extends also to the interaction of components identified in one dimension, *two-dimensional annotation* results. *Three-dimensional annotation* identifies the spatial positions within the chromosome and *four-dimensional annotation* considers the genome changes during adaptive evolution (Reed JL et al 2006 *Nat. Rev Genet* 7:130). During recent years many of the early sequenced genomes required re-annotation because the original procedures were loaded with substantial errors (Haas BJ et al 2005 *BMC Biology* 3:7).

In microbial genomes, when an annotated gene is linked to an unclassified one either by genetic linkage in a related species or microarray profile or protein-protein interaction, there is a high probability that they are members of the same functional category. Silencing the expression of a gene may also reveal its function. The expansion of annotations will be the task of the proteome projects. Comparative sequencing of many (16) eutherian mammals may greatly facilitate the identification of evolutionarily preserved sequences (Margulies EH et al 2005 *Proc Natl Acad Sci USA* 102:4795). A precisely annotated human genome is of great significance for medicine (Bentley DR 2004 *Nature [Lond]* 429:440; Cobb JP et al 2005 *Proc Natl Acad Sci USA* 102:4801). and for basic research (<http://www.ncbi.nlm.nih.gov/projects/CCDS>). ►proteome, ►gene prediction, ►DAS, ►silencer, ►insertional inactivation, ►RNAi, ►degron, ►RefSeq, ►VEGA, ►genome annotation, ►Recon; Marcotte EM et al 1999 *Science* 285:751; Mount SM 2000 *Am J Hum Genet* 67:788; Karlin S et al 2001 *Nature [Lond]* 411:259; Auburg S, Rouze P 2001 *Plant Physiol Biochem* 39:181; Stein L

2001 *Nature Rev Genet* 2:493; Yanai I et al 2001 *Proc Natl Acad Sci USA* 98:7940; Gaasterland T, Oprea M 2001 *Curr Opin Struct Biol* 11:377; Ashurst JL, Collins JE 2003 *Annu Rev Genomics Hum Genet* 4:69; Miller W et al 2004 *Annu Rev Genomics Hum Genet* 5:15; noncoding RNA: Griffith-Jones S 2007 *Annu Rev Genomics Hum Genet* 8:279, <http://gen100.imb-jena.de/~baumgart/runmage/register.html>, annotations for 130 genomes available by 2004: <http://cbcsrv.watson.ibm.com/Annotations/home.html>; <http://vega.sanger.ac.uk/>; <http://www.sanger.ac.uk/HGP/havana/hawk.shtml>; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>, Argo Genome Browser, released every 6–8 weeks and displays annotation tracks from FASTA, GenBank, GFF, BLAST and Genscan files: <http://www.broad.mit.edu/annotation/ago>; <http://pedant.gsf.de>, genome browser for 32 species: <http://genome.ucsc.edu/>, condensation of large gene lists into gene functional groups, convert between gene/protein identifiers, visualize many-genes-to-many-terms relationships, cluster redundant and heterogeneous terms into groups, search for interesting and related genes or terms, dynamically view genes from their lists on bio-pathways: <http://david.niaid.nih.gov>, automatic annotation: <http://www.genome.jp/kegg/kaas/>.

Annulus (a ring): For example, specialized cells in a sporangium involved in opening.

Anodontia: ►tooth agenesis, ►hypodontia, ►Rieger syndrome

Anoikis: Anoikis is the loss of cell anchorage to a substrate that may lead to apoptosis and may be the requisite for metastasis. Some cell lines resistant to anoikis display increased metastasis because the probability of apoptosis is reduced. Rac GTP-ase may protect against anoikis. Neurotrophic tyrosine receptor kinase receptor (TrkB) suppresses anoikis and promotes metastasis (Douma S et al 2004 *Nature [Lond]* 430:1034). ►apoptosis, ►metastasis, ►anchorage dependence, ►receptor tyrosine kinase Coniglio S et al 2001 *J Biol Chem* 276:28113.

Anomalous Genetic Ratios: Genetic ratios that are caused by many different mechanisms. Defective chromosomes or chromosomes carrying deleterious genes are transmitted at lower than normal frequencies and reduce the expression (transmission) of the genes residing in that chromosome (conversely the other allele may appear in excess). Monosomy and trisomy also modify segregation ratios. The genetic ratios may be altered by preferential segregation of certain chromosomes in meiosis. Similarly, segregation distorter genes can cause dysfunction of the sperm carrying them. Meiotic drive in a population

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can work against the more fit alleles. ► **Mendelian segregation**, ► **chromosomal breakage**, ► **aneuploidy**, ► **deletion**, ► **segregation distorter**, ► **gametophyte factor**, ► **certation**, ► **meiotic drive**, ► **preferential segregation**, ► **monosomic analysis**, ► **trisomic analysis**, ► **gene conversion**, ► **drift genetic**, ► **penetrance**, ► **Muller's ratchet**

Anomalous Killer Cell (AK): A T cell grown in the presence of IL-2 and which acquires natural killer cell (NK)-like properties. ► **killer cell**, ► *Paramecium*

Anomer: Stereoisomers of sugar, differing only in the configuration of the carbonyl residue, e.g., α -D-(+)-glucose and β -D-(+)-glucose.

Anonychia/Hyponychia Congenita: A human chromosome 20p13 recessive condition involving no or incomplete finger and toenail development controlled by R-spondin 4 (encoding a receptor of Frizzled in the Wnt pathway. (Blaydon DC et al 2006 Nature Genet 38:1245). ► **wingless**

Anonymous DNA Segment: Mapped DNA fragment without known gene content.

Anonymous Gene: A mapped gene without information about its molecular mechanisms but known to affect the expression of a quantitative response such as a behavioral trait. If it displays two allelic states it can be used for (DNA) mapping. ► **behavior**, ► **behavior genetics**

Anonymous Probe: A DNA probe with no known gene(s) and unknown function. Nevertheless, it provides information on the presence of sequences homologous to it and thus may be useful for taxonomic or evolutionary studies. ► **physical mapping**, ► **microsatellites**

Anopheles Mosquito: The host and vector of the protozoan *Plasmodium falciparum*, the cause of malaria. *Anopheles gambiae* (278,244,063 bp) carries one major and two minor genes that control the formation of melanin-rich capsules in the midgut, thus disarming the *Plasmodium*. *Plasmodium* resistance in *Anopheles* is regulated by a leucine-rich repeat protein, similar to the role of leucine-rich repeats in plant and animal resistance to pathogens (Riehle MM et al 2006 Science 312:577). *Anopheles* control may be a major objective of fighting malaria. ► **thalassemia**, ► **sickle cell anemia**, ► *Wolbachia*, ► **leucine-rich repeats**, Atkinson PW, Michel K 2002 Genesis 32:42, ► *Aedes aegypti*, *Anopheles gambiae* genome sequence: Holt RH et al 2002 Science 298:129, systematics: Krzywinski J, Besansky NJ 2003 Annu Rev Entomol 48:11, *Anopheles* database: <http://www.anobase.org/>.

Anophthalmia: Anophthalmia is the lack of rudimentary eyes. It is caused by deletions or chromosome breakage at 3q27, the location of the SOX2 transcription factor gene involved in the control in eye, eye lens and the nervous system. Terminal deletion of chromosome 6p also causes anophthalmia among many craniofacial abnormalities (Bogani D et al 2005 Proc Natl Acad Sci USA 102:12477). The Pax6 may also be involved. ► **eye diseases**, ► **eyeless**, Fantes J et al 2003 Nature Genet 33:461.

Anophthalmos: An autosomal recessive bilateral defect in the formation of the optic pit. It has been reported also as an Xq27-encoded fusion of the eyelids and other complications. ► **microphthalmos**, ► **eye diseases**

Anorexia: Lack of appetite or *anorexia nervosa* is a psychological disturbance of adolescents (primarily females) caused by an abnormal fear of gaining weight and therefore refusal to eat. It is characterized by habitual self-induced vomiting, unnecessary use of laxatives leading to emaciation, irregular or lack of ovulation, reduced interest in sex, and other anomalies. Medical treatment may be required. Ciliary neurotrophic factor (CNTF) shows anorectic effect by overcoming leptin resistance through activation of hypothalamic neurons. This effect of CNTF could be abolished by knocking out pro-opiomelanocortin-specific glycoprotein 130 (gp130) in mice (Janoschek R et al 2006 Proc Natl Acad Sci USA 103:10707). The melanocyte-stimulating hormone, α -MSH, and analogs may be responsible for anorexia and weight loss. Oleyethanolamide may be a regulator of feeding. Susceptibility loci appear to be in chromosomes 1, 2 and 13. ► **obesity**, ► **leptin**, ► **bulimia**, ► **ciliary neurotrophic factor**, ► **melanocyte stimulating hormone**; Rodríguez de Fonseca F et al 2001 Nature [Lond] 414:209; Adan RA, Vink T 2001 Eur Neuropsychopharmacol 11[6]:483; Devlin B et al 2002 Hum Mol Genet 11:689.

Anosmia: Anosmia is the inability to smell.

ANOVA: Abbreviation for analysis of variance. ► **analysis of variance**, ► **AMOVA**

Anoxia: Absence or deficiency of oxygen; it reduces chromosomal damage during irradiation. ► **radiation effects**, ► **ARE**

Anserine (β -alanine-1-methylhistidine): A dipeptide occurring in birds and some mammals but not in humans. ► **carnosinemia**

Ant (*Formica sanguinea*): $2n = 48$. The family of ants includes about 11,000 species ~2% of the total insect fauna. Ants generally follow the pattern of reproduction of other Hymenoptera. The females are the

products of sexual reproduction and are diploid whereas the males hatch from unfertilized eggs and are haploid. The workers are also diploid, like the queen, but due to developmental control they do not develop into functional female queens. In five species of ants, unmated workers may reproduce by thelytokous parthenogenesis and produce females from unfertilized eggs. *Cataglyphis cursor* females (queens) without mating may have parthenogenetic offspring by the fusion of four products of meiosis; such offspring develops into a queen. ▶[parthenogenesis](#), ▶[thelytoky](#), ▶[honeybee](#), ▶[social insects](#); Percy M et al 2004 Science 306:1780; phylogeny: Wilson EO, Hölldobler B 2005 Proc Natl Acad Sci USA 102:7411.

Antagomirs: Short RNAs, which antagonize micro-RNAs. Their silencing effect—after injecting them into mice—is very specific and long lasting. They appear promising for therapeutic silencing (Krützfeldt J et al 2005 Nature [Lond] 438:685). Antagomirs harbor optimized phosphorothioate modifications and require > 19-nt length for highest efficiency and can discriminate between single nucleotide mismatches of the targeted miRNA. Degradation is independent of the RNA interference (RNAi) pathway (Krützfeldt J et al 2007 Nucleic Acids Res 35:2885). ▶[microRNA](#)

Antagonist: An antagonist blocks biological receptor activation. ▶[agonist](#)

Antecedent: precursor, forerunner

Anteater (*Tamandua tetradactyla*): $2n = 54$.

Antelope: (*Antilocapra americana*): $2n = 58$.

Antenatal Diagnosis: The determination of a particular condition before birth by amniocentesis or blood samplings or by other means. amniocentesis, ▶[prenatal diagnosis](#), ▶[fetoscopy](#)

Antenna: Feeler organ on the head of insects. ▶[Drosophila](#) (see Fig. A84).



Figure A84. Antenna

Antenna Pigments: Present in chloroplasts, they collect light energy that is transmitted to the reaction centers for photochemical use. ▶[chloroplasts](#), ▶[chlorophyll](#), ▶[photosynthesis](#)

Antennapedia: *Drosophila* gene (*Antp*; map location 3–47.5, salivary bands 84B1-2) with numerous alleles. The null alleles result in embryonic lethality. Initially the locus was recognized by mutations that transform the antennae into mesothoracic legs. Numerous other homeotic changes may accompany the mutations. The different alleles may involve various types at the locus. The gene occupies about 100 kb, containing eight exons. These exons are transcribed from promoters P1 or P2 or from both. The transcripts may undergo alternate splicing. The homeobox motif is in exon 8. Actually *Ant* promotes leg differentiation by suppressing antenna-determining genes *extradenticle* (*exd*, 1–54) and *homothorax* (*hth*, 3–48). ▶[homeotic genes](#), ▶[morphogenesis](#), ▶[Polycomb](#)

Anterior: Indicates a direction in front of something or towards the head.

Anterior-Posterior Polarity: Head to tail anatomical direction.

Anterograde: Ahead or forward moving. ▶[retrograde](#)

Anther: The pollen-containing parts of the male flowers (see Fig. A85). ▶[gametogenesis](#)



Figure A85. Anther

Anther Culture: Used for the isolation of haploid plants. The culture may start with microspores that are directly regenerated into plantlets (without an intermediate callus stage) or from anthers. Haploid tissues are isolated and first a callus is formed, then the calli are regenerated into plants. Both procedures use tissue culture methods under aseptic conditions. The haploid cells may diploidize spontaneously or by induction and that results in perfect homozygosis of the plants. ▶[androgenesis](#), ▶[Asparagus](#), ▶[gametogenesis](#), ▶[embryo culture](#), ▶[YY plants](#); Jahne-Gartner A, Lörz H 1999 Methods Mol Biol 111:269.

Antheridium: The male sex organ (gametangium) of lower plants and fungi.

Anthesis: The time of pollen-shedding or receptivity of a flowering plant.

Anthocyanin: Plant flower pigments (delphinidin, cyanidin, pelargonidin, peonidin, petunidin, malvidin, etc.) are synthesized from phenylalanine via

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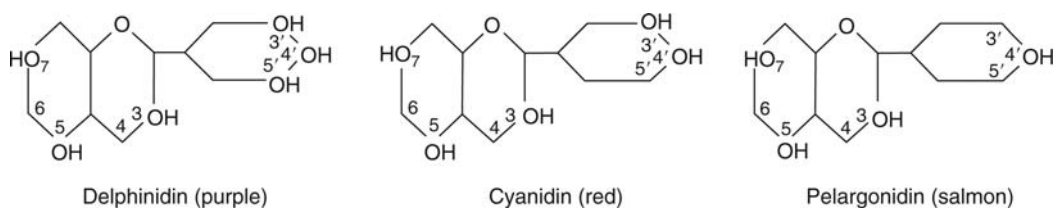


Figure A86. Pelargonidin displays an OH group at position 4', cyanidin has two OH groups at 3' and 4', delphinidin has three OH groups (3', 4' and 5'). Peonidin (not shown) has 3' OCH₃ and 4' OH. Petunidin: 3' OCH₃, and 5' OH. Malvidin: 3' and 5' OCH₃ and 4' OH. Further color variations may be brought about by glycosylation and acetylations of the A ring(s) [at left]

trans-cinnamic acid and cinnamoyl-CoA, chalcones and flavonones (see Fig. A86). CH₃ and OH groups on the B ring determine the color produced; glycosylation (hexose or pentose) at the 3 and 5 positions (or at both) on the A ring increases stability of the pigments, and these glycosides are called anthocyanidins. In the petals of roses, a single glucosyltransferase adds a glucosyl group to both the 5 and 3 positions of the A ring of anthocyanidin (Ogata J et al 2005 Nature [Lond] 435:757). Each enzymatic step is controlled by different genes and these original discoveries, beginning in the early twentieth century, prepared the way for biochemical genetics. The color is affected also by the pH of the vacuoles and those too are under genetic control. By the use of antisense constructs of the gene chalcone synthase (CHS), the activity of this enzyme and chalcone flavonone isomerase (CHI) could be reduced indicating that CHS regulates also the expression of CHI. ▶[chalcone](#), ▶[grape](#); Markham KR et al 2000 Phytochemistry 55:327; Rasusher MD et al 1999 Mol Biol Evol 16:266; van Houwelingen A et al 1998 Plant J 13:39.

Anthranilic Acid: Synthesis begins with the condensation of erythrose-4-phosphate + phosphoenolpyruvate, and from this shikimate and then chorismate are formed. Chorismate through prephenate contributes to phenylalanine and tyrosine and through another path is a precursor of the amino acid tryptophan (actually indole-3-glycerol phosphate ® indole and serine are converted to this amino acid). ▶[tyrosine](#), ▶[phenylalanine](#)

Anthrax: A toxin produced by *Bacillus anthracis*, an endospore-forming bacterium of $\sim 5.23 \times 10^6$ bp sequenced genome with two plasmids, pXO1 (181 bp) and pXO2 (94,829 bp), that carry virulence genes; but the large chromosome also has virulence factors (Read TD et al 2003 Nature [Lond] 423:81). The toxin affects, primarily, herbivorous animals but it may spread to carnivorous predators and also to humans through the skin, by ingestion or inhalation of dust

contaminated by the bacterial spores (see Fig. A87). Inhaling the spore of the most virulent strains may be lethal in 80–90% of the cases. The toxin consists of three proteins: (i) protective antigen (PA) facilitates the formation of a membrane channel for the (ii) edema factor (EF, an adenylate cyclase) and (iii) lethal factor (LF, a zinc-dependent metalloprotease and selective inhibitor of MAPK and MAPKK). For the manifestation of the toxic effects of anthrax the presence of low-density lipoprotein receptor LRP6 must be present. LRP6 enables internalization of the toxin by interacting with PA receptors TEM8/ATR (tumor endothelial marker) and/or CMG2 (capillary morphogenesis gene 2), which is a transmembrane cellular receptor. LRP6 appears to be a good candidate target for anti-anthrax therapy (Wei W et al 2006 Cell 124:1141).

The LF and the EF have a similar effect on *Drosophila* as in mammals and can be used to test the toxic functions in vivo in a much simpler system (Guichards A et al 2006 Proc Natl Acad Sci USA 103:3244). Although LF targets mainly MAPKK, apparently it hydrolyzes also a number of peptide hormones: granuloliberin R, dynorphin A (a 17-amino acid neuropeptide), kinetensin and angiotension-1 (brain peptides). The toxin represses the glucocorticoid receptor. The chemical PD09859 is also a MAPKK inhibitor but it acts differently from LF. Mutation in PA may prevent the uptake of EF and LF and thus in a dominant negative manner may become a potential tool in preventing the toxic effects. Another preventive approach is to block the formation of the heptameric cell-binding subunit of the toxin by a synthetic polyvalent inhibitor (Mourez M et al 2001 Nature Biotechnol 19:958). The bacteriolysin PlyG produced by the γ phage of *B. anthracis*, a monomeric protein of M_r of $\sim 27K$, detects and kills the anthrax bacterial spores. The antimicrobial peptide defensin and human neutrophil protein HNP-1 protects against the lethal toxin of this bacterium (Kim C et al 2005 Proc Natl Acad Sci. USA 102:4830). Ciprofloxacin antibiotic provides effective protection. A complex molecule of

a hydroxamate (2R)-[4(fluoro-3-methylphenyl)sulfonylamino]-*N*-hydroxy-2-[-2H-pyran-4-yl) acetamide interacts with LF and may provide up to 100% protection against the bacterium, especially in combination with ciprofloxacin (Shoop WL et al 2005 Proc Natl Acad Sci USA 102:7958). In case of inhalational exposure, vaccination and ciprofloxacin have synergistic protection (Vietri NJ et al 2006 Proc Natl Acad Sci. USA 103:7813).

The virulence genes are borne by the pXO1 plasmid and are regulated by temperature and carbon dioxide as well as by bacterial chromosomal genes encoding surface proteins of the semi-crystalline S-layer. A wide range of cancer cells exhibit increased surface urokinase activity. An engineered anthrax toxin equipped with urokinase plasminogen activator within the furin protease selectively increases the toxicity for cancer cells but not for normal cells. Furin and other proteases destroy the protective antigen of the toxin. The modified toxin thus can destroy cancer cells (Liu S et al 2003 Proc Natl Acad Sci 100:657). ▶adenylate cyclase, ▶metalloproteases, ▶toxins, ▶furin, ▶urokinase, ▶MAPKK, ▶bioterrorism, ▶microfluidics, ▶ciprofloxacin, ▶*Bacillus cereus*; Sellman BR et al 2001 Science 292:695; Mock M, Fouet A 2001 Annu Rev Microbiol 55:647; Bhatnagar R, Batra S 2001 Crit Rev Microbiol 27(3):167; Schuch R et al 2002 Nature [Lond] 418:884; danger as a weapon: Webb GF 2003 Proc Natl Acad Sci USA 100:4355; synthetic inhibitors of LF; Forino M et al 2005 Proc Natl Acad Sci USA 102:9499; anthrax inhalation risks based on the Sverdlovsk/Yekaterinburg, Russia accident: Wilkening DA 2006 Proc Natl Acad Sci USA 103:7589; toxin receptor binding: Young JAT, Collier RJ 2007 Annu Rev Biochem 76:243; *B. anthracis* database: [http://cmr.tigr.org/tigr-scripts/CMR/GenomePage.cgi?database=gba](http://cmr.tigr.org/tigr-scripts/CMR/GenomePage.cgi?database=gba;); <http://www.fda.gov/cder/drug/infopage/cipro/>.

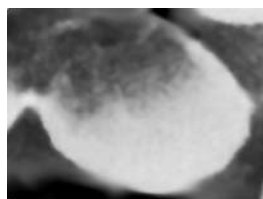


Figure A87. *Bacillus anthracis* spore

Anthropology: The science of human evolution, diversity, development and distribution, including the various human races. The database ALFRED (allele frequency database, <http://alfred.med.yale.edu/alfred/>) provides comprehensive information on human variation.

Anthropometric Traits: Those physical or physiological characters of humans (such as weight, head circumference, hair color, protein differences, behavior, etc.) that may be used for the characterization of human populations. ▶anthropology

Anthropomorphism: The study of behavior assuming that animals share many traits resembling the conscience, cognition and feelings of human beings.

Anti: A conformation of nucleotides, the CO and NH groups in the 2 and 3 positions of the pyrimidine ring (1, 2, 6 positions in the purine ring) are away from the glycosidic ring, while in the SYN conformation they lie over the ring. The anti conformation is most common in nucleic acids and free nucleotides. Kornberg A 1982 DNA replication, Freeman, San Francisco, California.

Antiauxin: Interferes with the action of auxins, e.g., 2,3,5-triiodobenzoic acid inhibits the growth promoting action of 2,4-D (dichlorophenoxyacetic acid) or the indoleacetic acid (IAA) analog 5'-azido-indole-3-acetic acid interferes with enzymes involved with IAA. ▶plant hormones

Anti-4-1BB Monoclonal Antibody: A co-stimulatory receptor expressed on activated T cells; it may be effective in amplifying T-cell-mediated immunity in cancer therapy. When used for intra-tumoral adenoviral gene transfer, it improved survival rate and reduced metastasis substantially. ▶cancer gene therapy; Martinet O et al 2002 Gene Ther 9:786.

Antibiotic Resistance: Resistance to antibiotics is brought about either by enzymatic inactivation of the antibiotic, or modification of the target, or active efflux of the substance or sequestration by binding to special proteins. Today, antibiotic resistance in the major infectious agents may be up to 98%, depending on the agent and the antibiotic used. Genes in bacterial plasmids and transposons generally determine it. The antibiotic producing organisms have some special means (proteins) to protect themselves against their products. The mechanisms of resistance vary: penicillins and cephalosporins (β-lactamase hydrolysis); chloramphenicol (detoxification by chloramphenicol transacetylase that acetylates the hydroxyl groups or interferes with uptake); tetracyclines (interference with uptake or maintenance of the molecules); aminoglycosides (streptomycin, kanamycin, etc. enzymatic modification of the drug [phosphorylation] interferes with uptake or action); erythromycin, lincomycin (methylation of the small ribosomal subunit). Tetracycline pactamycin and hygromycin B modify, in special ways, the 30S ribosomal subunit and affect the decoding of mRNAs. In the 16S rRNA subunit, 53 sites were

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identified that are, potentially, sites for inhibition of protein synthesis. The majority of these sites affect either protein synthesis or the assembly of the small subunit of the ribosome (Yassin A et al 2005 Proc Natl Acad Sci USA 102:16620). The SOS response (error-prone repair) facilitates the horizontal spread of antibiotic resistance genes (Beaber JW et al 2004 Nature [Lond] 427:72).

Mutations in DNA topoisomerase and genes affecting cell permeability may result in resistance to ciprofloxacin. Ciprofloxacin-caused DNA damage can be corrected by nucleotide excision repair or by homologous recombination. Upon autoprotoleolysis, the SOS repair repressor *lexA* gene is sufficiently weakened so it no longer suppresses prokaryotic DNA polymerases Pol II, Pol IV, Pol V, which are accessory or conditional repair genes. Blocking autoprotoleolysis may be one way to interfere with the development of resistance to ciprofloxacin and rifampicin type antibiotics (Cirz RT et al 2005 PLoS Biol 3(6):e176). The use of antibiotics can contribute to bacterial competence and antibiotic stress can facilitate the acquisition of resistance to different antibiotics. In *Streptococcus pneumoniae*, kanamycin, streptomycin and mitomycin C triggered competence, but erythromycin, tetracycline, novobiocin, rifampicin, vancomycin, and cefotaxime did not. Mitomycin C and fluoroquinolones also induced SOS repair and competence in *E. coli*, but streptomycin and kanamycin did not. This indicates that stress responses are processed differently in these two bacteria (Prudhomme M et al 2006 Science 313:89).

Switching to another antibiotic if failure of effectiveness is encountered may minimize antibiotic resistance. Never switching to a new drug always minimizes the occurrence of a resistant strain but maximizes the failure in the treatment. Immediate switching usually maximizes resistance and minimizes failure. Thus, in most circumstances, the early use of a new drug enhances the effectiveness of the treatment while promoting the rise of high-level resistance in later generations of the bacteria (Wang YC, Lipsitch M 2006 Proc Natl Acad Sci USA 103:9655).

Antibiotic resistance acquired through conjugative transfer of the resistance factors or mutation pose serious problems to medicine, e.g., the recent resistance of *Mycobacterium tuberculosis* to all known antibiotics. Antibiotic resistance genes are used generally to assure the removal (by carbenicillin or claphoran [cefotaxime]) of the carrier *Agrobacteria* after infection with plant transformation vectors. Also, the transformed bacterial, fungal, animal and plant cells are selectively isolated on the basis of antibiotic resistance. Insertional mutagenesis in bacteria is monitored by the inactivation of the

resistance genes upon integration. Various antibiotics are used all over the world in animal feed to increase animal productivity by 4–5%. Unfortunately, some of the antibiotic resistance genes may become incorporated into (facultative) human pathogens through animal products and waste and may pose a threat to human health. The soil seems to be an inexhaustible source of antibiotic resistance (D'Costa VM et al 2006 Science 311:374). The advantages gained by antibiotics in the feed may be partially compensated for by improved animal hygiene. ▶antibiotics, ▶pBR322, ▶lactamase, ▶aminoglycoside phosphotransferases, ▶clavulanate, ▶amoxicillin, ▶vancomycin, ▶tetracycline, ▶decoding on ribosomes, ▶LexA, ▶DNA polymerases, ▶biofilm, ▶fratricide, ▶SOS repair; Witte W 1998 Science 279:996 Walsh C 2000 Nature [Lond]: 407:775; Walker ES, Levy F 2001 Evolution 55:1110; Schlünzen F et al 2001 Nature [Lond] 413:814; Hughes D 2003 Nature Rev Genet 4:432; Miesel L et al 2003 Nature Rev Genet 4:442; Heymann DL 2006 Cell 124:671.

Antibiotics: A wide variety of chemicals produced by microorganisms and plants (also now by organic laboratory synthesis) that are toxic to other organisms. The major types of antibiotics are penicillins, ampicillin and cephalosporins (interfere with bacterial cell wall biosynthesis). Chloramphenicol binds to the 50S ribosomal subunit and blocks the peptidyl transferase ribozyme function during protein synthesis of prokaryotes. Tetracyclines inhibit the entry of the charged tRNA to the A site of the ribosome in prokaryotes. Streptomycin blocks the process of prokaryotic peptide chain elongation, and this as well as paromomycin, can also cause reading errors during translation. Spectinomycin inhibits the function of the 30S ribosomal subunit and reduces ribosomal translocation along with hygromycin B, edeine and pactamycin. Edeine has wide effectiveness but because of its toxicity is not useful as an antibiotic. Kanamycin, geneticin (G418), neomycin, gentamycin, and hygromycin bind to 30S and 50S ribosomal subunits and prevent protein synthesis or cause misreading. Erythromycin inhibits the translocation of the nascent peptide chain on the prokaryotic ribosomes. Lincomycin inhibits chain elongation on the prokaryotic ribosome by its effect on peptidyl transferase but not in eukaryotes. Rifampicin interacts with the β subunits of the prokaryotic RNA polymerase. Fusidic acid interferes with the binding of aminoacylated tRNAs to the ribosomal A site by inhibiting the release of prokaryotic elongation factor EF-G and also eukaryotic elongation factor eEF-2. Kasugamycin blocks the attachment of tRNA^{fMet} to the P site of the prokaryotic ribosome. Kirromycin actually promotes the binding

of elongation factor EF-TU-GTP complex to the prokaryotic ribosome but then inhibits the release of the elongation factor. Thiostrepton, from *Streptomyces azureus*, blocks prokaryotic peptide elongation from both prokaryotic and eukaryotic ribosomes. Cycloheximide interferes with peptide translocation on the eukaryotic ribosome. Anisomycin blocks the peptidyl transferase on the eukaryotic ribosomes and is comparable in effect to that of chloramphenicol in prokaryotes. Streptolydigin does not block RNA initiation but interfere with the elongation of the RNA chain in prokaryotes. Ciprofloxacin interacts with DNA gyrase. Actinomycin D inhibits, primarily, RNA polymerase II and to a lesser extent the other RNA polymerases but not DNA polymerase in either prokaryotes or eukaryotes; α -amanitin also inhibits eukaryotic RNA polymerase II and in very high concentration Pol III but not Pol I. Pactamycin blocks the eukaryotic initiator tRNA^{Met} to attach to the P site of the ribosome. Showdownmycin interferes with the formation of the eukaryotic eEF-tRNA^{Met} complex. Sparsomycin is a eukaryotic peptide chain translocation blocker; it is not very effective against microbes but works as an anticarcinogen. Cefotaxime (synonym claforan), carbenicillin, and vancomycin are more effective as antibacterial agents than their toxicity to eukaryotic cells and are frequently used in plant tissue culture to prevent bacterial growth. Macrolide antibiotics block the exit tunnel of the peptides on the ribosome. Antibiotics, which interfere with protein synthesis on prokaryotic ribosomes, cause similar damage to the ribosomes of eukaryotic organelles (mitochondria, plastids). The availability of antibiotics in the 1940s opened a new era in medicine and they became, in the 1970s, the most important selectable markers for the construction of vectors for genetic engineering. Antibiotics are used for selective isolation of various genetic constructs in microbial, plant and animal cell genetics. The number of antibiotics is continuously increasing because of the need for effective new drugs since microorganisms develop resistance to the old antibiotics. *Staphylococcus aureus* bacteria are resistant to all antibiotics except vancomycin and it will only be a matter of time when resistance mutations will develop to this too. Actually, fosfomycin (see Fig. A88) is effective against methicillin and vancomycin resistant *S. aureus* (Higgins LJ et al 2005 Nature [Lond] 437:838). There are already

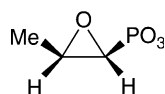


Figure A88. Fosfomycin

Enterococcus faecium strains that are resistant to vancomycin. The development of new antibiotics is becoming increasingly more difficult. A large fraction of the bacterial enzymes are not essential for infection because the metabolites they produce are available in the host cells. The existing antibiotics mostly target the enzymes that are essential for the pathogens and even a most comprehensive survey of the proteome of bacteria will probably reveal only few new targets (Becker D et al 2006 Nature [Lond] 440:303). Recently, a new class of antibiotics (platensimycin; see Fig. A89) was discovered that targets lipid biosynthesis and blocks the membrane system of a wide range of Gram-positive bacteria (Wang J et al 2006 Nature [Lond] 441:358).
 ▶antibiotic resistance, ▶protein synthesis, ▶selectable marker, ▶cell genetics, ▶vectors, ▶bleomycin, ▶antimicrobial peptides, ▶ciprofloxacin, ▶GE81112; Walsh C 2000 Nature [Lond]:407:775; Palumbi SR 2001 Science 293:1786; Béhal V 2002 Biotechnol Annu Rev 8:227; ribosomal antibiotics: Auerbach T et al 2004 Trends Biotechnol 22:570; structural bases of selectivity synergism, resistance: Yonath A 2005 Annu Rev Biochem 74:649, <http://www.hopkins-abxguide.org/>.

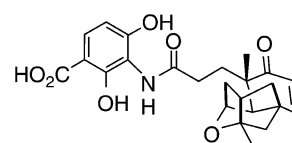


Figure A89. Platensimycin

Antibodies: Specific immunoglobulins that react—as a cellular defense—with foreign antigens. Antibodies contain two light chains, either κ or λ and one of the five heavy-chains (μ , δ , γ , ϵ , α) and their variants. Both light and heavy-chains contain variable and constant regions. The specificity resides in the variable regions. Antibodies have specificities to about a million different antigens. This specificity is achieved with the aid of a much smaller number of antibody genes by differential processing of the transcripts, mutation, recombination, gene conversion, and transposition within the families of immunoglobulin genes (see Fig. A90). Antibodies are made by the lymphocytes and may be attached to their membrane or may become humoral antibodies (secreted into the blood stream by the B lymphocytes). One particular B cell synthesizes only one type of antibody molecules. Each B cell deposits the first 100,000 antibodies it makes in its plasma membrane and serves there for antigen receptors.

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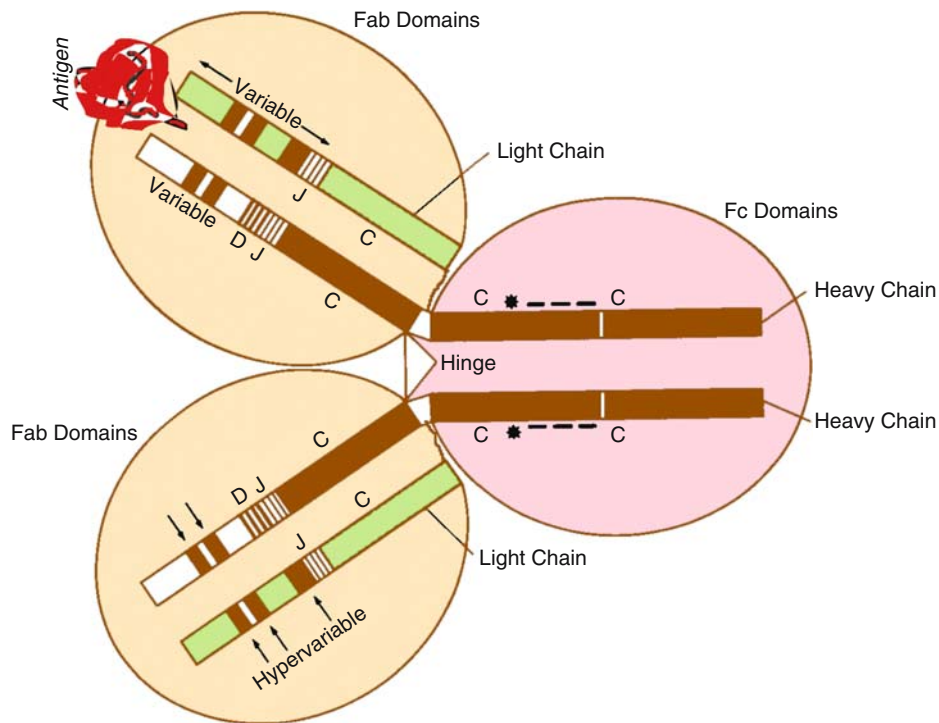


Figure A90. Antibodies have three main domains, the two Fab domains (Fragment antigen binding), including the light chains and parts of the heavy-chains and one Fc (Fragment crystalline) domain. The light chains have a size of about 23 kDa, the heavy-chains vary from 53 to 70 kDa. X-ray crystallography revealed the domains as 2×4 nm, oval or cylindrical in shape, and the polypeptide chain in each domain is folded in pleated β -sheets. Disulfide bonds hold the dimeric structure of the light and heavy-chains together in variable numbers, depending on the particular molecules. The inter- and intra-chain disulfide bonds are not shown, except at the proline-rich hinge area that provides the molecules with some flexibility. The IgM and the IgE antibody monomers lack hinges but have an additional C-terminal heavy-chain domain. At the amino end of the light and heavy-chains are the variable and hyper variable regions that determine the specificity of the antibody. This region includes approximately 100 to 115 amino acids. The specificity is determined by complementarity between antibody and antigen in the antigen-binding "pocket" arms of the antigen around the area. Induced mutagenesis of the complementarity region may substantially increase the effectiveness of the antibody (Thom G et al 2006 Proc Natl Acad Sci USA 103:7619). The various specificities are determined by combinations of the variable (V), diversity (D) and junction (J) genes that account for about 25% of the amino acid residues, and the remaining 75% are considered the framework. CDR1, CDR2 and CDR3 (shown by the dark bands) generally identify the complementarity determining regions. The variable regions in the light and heavy-chains are homologous. The constant regions (C) show very little variability within a species. There is a glycosylation site in the constant heavy-chain region within the Fc domain (*). Also, in the constant heavy-chains there are sites for binding the activator of the complement (- - -). The complement consists of about 30 different proteins of catabolic functions that are activated in a cascading manner after the binding of the antigen to the antibody and carry out the destruction of the foreign antigen

When a particular antigen binds to the B cell, it stimulates its clonal division and the production of more antibodies. These series of the antibody are then made at the amazing rate of about 2,000 molecules/second and then secreted into the blood plasma. An individual can make about 10,000 different heavy-chain variants and about 1,000 different light chain variants. Since these chains can combine freely,

the total number of different antibodies can be $10^4 \times 10^3 = 10^7$. IgM type antibodies (containing gamma immunoglobulin chains) occur at the largest concentration in the blood serum and their half-life is the longest. The general structure of the antibody molecules is diagramed here. Each antibody molecule has two identical antigen-binding sites (see diagram). The majority of the antigens have, however, several

to many antigenic determinants (epitopes). Some of these antigens may be built of repeating units and in these cases they are *multivalent* because they have multiple copies of the epitope. The binding between epitopes (e) and antibody (a) is a concentration-dependent, reversible process: $(a + e) \rightleftharpoons (ae)$. When the concentration of the epitope increases, the binding to the antibody is increasing and the intensity of the reaction is expressed by the *affinity constant*: $(k) = (ae)/(a)(e)$. When half of the (a) sites are filled $k = 1/e$, the values of (k) range from 5×10^4 to 10^{12} moles. Conformational diversity of the same antibody may result in affinity for multiple, distinct antigens (James LC et al 2003 Science 299:1362).

The *avidity* of an antibody for an antigenic determinant depends also on how many binding sites are available. The affinity is increasing with time after immunization (affinity maturation). Antibodies are involved in the destruction of invaders, either through stimulating the macrophage cells to phagocytosis, or by ions, using the complement enzymes or activating the killer cells. It was recently discovered that antibodies could generate H_2O_2 by oxidation of water with the aid of singlet oxygen ($^1O_2^*$). This ability adds a chemical to their repertoire of defense (Wentworth P et al 2001 Science 293:1806). Usually their turnover is rapid; the half-life of antibodies is days to a few weeks. By chemical modifications antibody/ligand complexes can be generated that do not dissociate and do not cross-react appreciably with other ligands (Chmura AJ et al 2001 Proc Natl Acad USA 98:8480). About 20% of the total plasma proteins represent a diverse set of antibodies. After the B lymphocytes respond to an antigen and differentiate into plasma cells, their rate of antibody production may reach 1,000 molecules/second after immunization (affinity maturation). Receptors (FcRn) of the Fc domain (see diagram) contribute toward the phagocytotic functions, cytotoxicity and to neonate immunity. In the maternal uterus, FcRn/IgG has been detected. The FcRn receptors transfer maternal humoral immunoglobulins to the newborn before the immune system of the progeny is activated. During nursing, the FcRn class receptors mediate the transfer of the IgG/FcRn complex through the milk. Antibody genes can be expressed not just in lymphoid cells but also ectopically, e.g., in bacterial cells when introduced by transformation. In such a system they may form inclusion bodies either in the cytoplasm or in the periplasmic space or may be present as soluble proteins secreted into the cytoplasm. In the periplasmic space disulphide isomerase-like and proline cis-trans isomerase (rotamase) proteins may exist that mediate folding of the antibodies or fragments. The prokaryotic chaperones may also participate in

the folding. In the *Camelidae* (camels and llamas), the antibodies contain only heavy-chain (Hamers-Casterman C et al 1993 Nature [Lond] 363:446) and the first domain of the constant region is absent although it is present in the genome (see Fig. A91); but it is not retained during mRNA processing (Nguyen VK et al 1999 Mol Immunol 36:515; Nguyen VK et al 2002 Immunogenet 54:39). The antibody-based immune system is restricted to vertebrates and is present in all gnathostomes (jawed vertebrates); but it is apparently absent from agnathans (jawless vertebrates), such as lamprey and hagfish (Klein J, Nikolaidis N 2005 Proc Natl Acad Sci USA 102:169). ▶immunoglobulins, ▶immune system, ▶complement, ▶monoclonal antibodies, ▶single-chain Fv fragment, ▶hybridoma, ▶antibody polyclonal, ▶recombinant antibody, ▶HLA, ▶lymphocytes, ▶T cell, ▶TCR, ▶B lymphocyte receptor, ▶killer cell, ▶antigen, ▶antigen presenting cell, ▶MHC, ▶neutralizing antibody, ▶immunization alloantibody, ▶natural antibody, ▶periplasm, ▶rotamase, ▶chaperone, ▶antibody engineering, ▶anti-idiotypic antibody, ▶anti-DNA antibody, ▶internal image antibody, ▶catalytic antibody, ▶plantibody, ▶antibody gene switching; Heyman B 2000 Annu Rev Immunol 18:709; Ravetch JV, Bolland S 2001 Annu Rev Immunol 19:275; antibody evolution by conformation selection and mutation: Zimmermann J et al 2006 Proc Natl Acad Sci USA 103:13722, <http://www.antibodyresource.com/onlineData.html>.

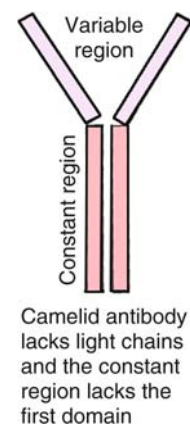


Figure A91. Camelid Antibody

Antibody Antigenization: The modification of the hypervariable region of an antibody by protein engineering in order to enhance the recognition of the new antibody to foreign epitopes by the B and T lymphocytes. ▶antibody, ▶antigen, ▶epitope, ▶B lymphocyte, ▶T cells

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Antibody, Bispecific: A bispecific antibody has affinity to two different antigens. Such an antibody may not exist.

Antibody, Bivalent: A bivalent antibody has two antigen-binding sites.

Antibody, Chemically Programmed (cpAB): A small molecule is covalently added to an antibody and providing an extension for its effective range (Guo F et al 2006 Proc Natl Acad Sci USA 103:11009)

Antibody, Chimeric: Can be produced with the aid of genetic engineering by fusing the variable regions of one type to the constant region of another antibody. It can also be produced in vivo by homologous recombination in hybridoma cells or by using the *Cre-loxP* system. hybridoma, ►*Cre/loxP*, ►HAMA, ►primatized antibody; Presta LG 2006 Adv Drug Deliv Rev 58:640.

Antibody Detection: Antibody detection is possible through several procedures: antibodies bound to proteins expressed in *E. coli* are detected by I^{125} (isotope)-labeled antibodies that react to the species-specific determinants of the primary antibodies. Protein A labeled with I^{125} second antibody, conjugated to horseradish peroxidase (HRP) or HRP coupled to avidin, may be used to detect a second antibody coupled to biotin or by a second antibody conjugated to alkaline phosphatase, using radio-labeled ligands. Antibodies can also be detected by agglutination and complement fixation. In agglutination, a precipitate is formed upon the reaction. One of the procedures is the *Ouchterlony assay* where the antibody and the antigen are placed in the neighboring wells of agar plates; upon diffusion a visible precipitate is formed about midway between the two wells if the antigen (e) and antibody (a) recognize each other (see Fig. A92).

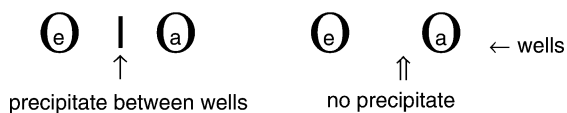


Figure A92. Ouchterlony test

The complement fixing procedure has a unique feature inasmuch as the complement binds only to the antibody that is complexed with the antigen. If the complement is fixed, adding red blood cells and a cognate antibody to the reaction mix, resulting in no hemolysis, it is proof of fixation of the complement and the procedure can be quantitated by employing a series of dilutions. ►antibodies, ►complement, ►immunostaining, ►antibody microarray

Antibody Effector Functions: These functions are carried out by activation of the complement system and by interactions of the antigen through the Fc domain receptors (e.g., FcγR) leading to ADCC. ►antibody, ►complement, ►FcγR, ►ADCC

Antibody Engineering: Antibody Engineering involves genetic modification of the immunoglobulin genes, particularly the complementarity determining regions of the antibody. ►antibody, ►humanized antibody, ►plantibody, ►phage display, ►immunotoxin, ►monoclonal ►antibody, ►transgenic, ►bispecific monoclonal antibody, ►Fv, ►gene fusion, ►antibody polymers, CDR; Maynard J, Georgiou G 2000 Annu Rev Biomed Eng 2:339.

Antibody Fusion: Antibody fusion constitutes gene fusions, which most commonly involve the antibody heavy-chain and enzyme-coding sequences (nuclease, glucuronidase, etc.) or toxins (e.g., angiogenin toxin, neurotoxin), cytokinins (interleukin 2, TNF, IGF), and labeling proteins (aequorin, avidin).

Antibody Gene Switching: is preceded by the pairing between members of the antibody constant heavy-chain gene families and the formation of loops that are then cut off at the stem. This cutting off/deletion produces different heavy-chain elements in the vicinity of the J (junction) genes. The site-specific switch then permits the expression of the genes that are moved to the vicinity of the J genes after the stem of the loop is cut off and the DNA strands are religated. The transcript is further processed by the removal of the introns. This is one of the mechanisms to generate greater diversity in the heavy-chain antibody proteins. The switching is stimulated by cytokines secreted by the T_H lymphocytes. In mouse cells, the IL-4 induces the switch from IgM to IgG1 or IgE. Interferon-γ causes switching from IgM to IgG2a and TGF-β mediates the switch from IgM to IgG2b or IgA or IgE. A defect in switching may result in Hyper-IgM syndrome and the patients thus become susceptible to infections because of low concentrations of IgG and IgA. The murine heavy-chain constant region has eight different genes. A switch region flanks each constant gene, except C_γ . The mammalian switch regions vary substantially yet they are highly repetitive, especially in Gs in the non-template strand. The switch repeats include AGCT and GGGGT subrepeats.

Upon transcription, the RNA:DNA hybrid forms in the switch region, in vitro, and the non-template strand remains single-stranded. At the switch regions, S γ 3 and S γ 2b loops form in the lipopolysaccharide (LPS)-stimulated B cells (see Fig. A93). Most of the recombination (>90–95%) occurs in these two switch

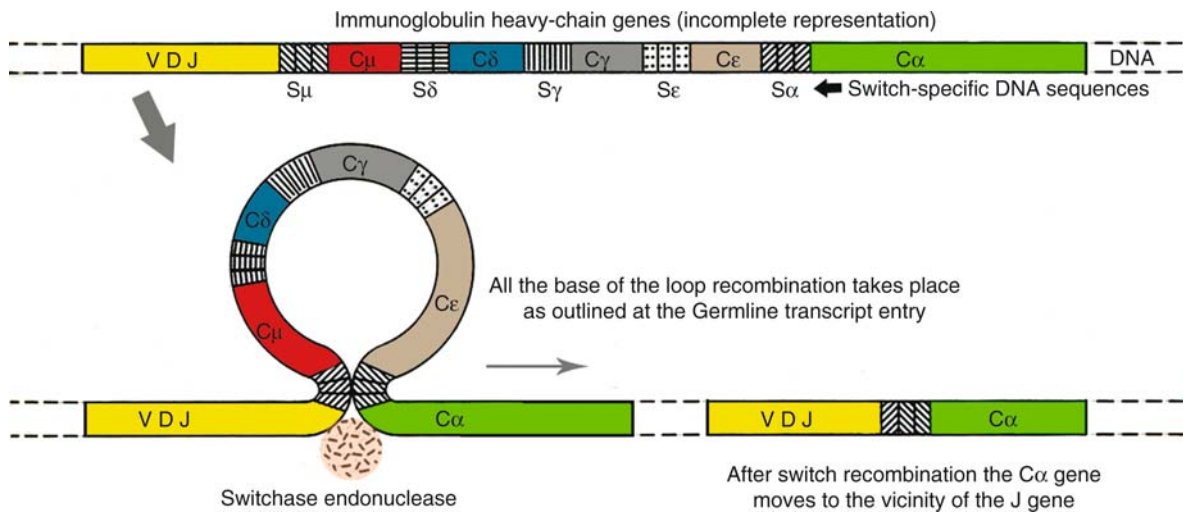


Figure A93. Antibody gene switching

regions respectively (Huang F-T et al. 2006 Proc Natl Acad Sci USA 103:5030).

The basic leucine zipper proteins of the Maf family and Bach transcription factors (Bach2, 6q15; Bach1 21q22.1) regulate the switching from IgM to other immunoglobulins in B cells and are critical for somatic hypermutation (Muto A et al 2004 Nature [Lond] 429:566). Activation-induced cytidine deaminase (AID) seems to be involved in the mediation of switching (Rush JS et al 2005 Proc Natl Acad Sci USA 102:13242). The deamination contributes to the formation of dU:dG lesions, and their resolution leads to class-switch recombination and somatic hypermutation (Rada C et al 2004 Mol Cell 16:163). Switching is different from the V(D)J recombination process. In the jawless (agnathan) fish, the lamprey variable lymphocyte receptors, composed of highly diverse leucine-rich repeats, are sandwiched between the amino- and carboxy-terminal of the receptors. This arrangement can generate large diversity when recombined for the anticipatory (adaptive/acquired) immune reaction (Pancer Z et al 2004 Nature [Lond] 430:174). Translocation between c-myc and IgH is also regulated by AID and uracil glycosylase (Ramiro AR et al 2006 Nature 440:105), a frequent cause of B lymphocyte malignancies. ▶immunoglobulins, ▶antibodies, ▶V(D)J, ▶RAG, ▶T_H, ▶immune system, ▶germline transcript, ▶somatic hypermutation, ▶hypermutation, ▶ectodermal dysplasia, ▶class switching, ▶MSH5, ▶acquired immunity, ▶AID (activation induced deaminase), ▶myc, ▶glycosylases; Kataoka T et al 1981 Cell 23:357; Revy P et al 2000 Cell 102:565; Stavnezer J 2000 Science 288:984; Honjo T et al 2002 Annu Rev Immunol 20:165; AID mechanisms: Honjo T et al 2004 Immunity 20:659.

Antibody, Intracellular: By introducing specific antibody genes into a cell and if the transgene is expressed, various processes, interactions between macromolecules, fixing enzymes in active or inactive states, modifying (binding) ligands, targeting intracellular signals, etc., can be explored. Tissue targeting vectors can be constructed for the introduction of genes to specific locations. In these systems, antibodies are coupled to viral vectors, liposomes, or directly to the passenger DNA. Antibodies can be targeted to T cell receptors (TCRs). Bispecific antibodies can be used to re-target effector cells to tumors. ▶KDEL, ▶monoclonal antibody therapies, ▶immune system, ▶viral vectors, ▶liposome, ▶T cell receptor, ▶monoclonal antibody therapies; Brekke OH & Sandlie I 2003 Nature Rev Drug Discov 2:52.

Antibody, Isomeric: Isomeric antibodies may exist in two conformational state and thus can bind two structurally distinct antigens. antibody, ▶antigen, ▶isomers

Antibody Lattice: An antibody lattice or alternating antigen-antibody complex is formed when the cognate antibody is in excess of the antigen, between the Fc domain of the IgG and the antigen. ▶antibody, ▶antigen

Antibody Microarray: An antibody microarray is the high-throughput profiling of a relatively smaller number of proteins (compared to mass spectrometry). Antibodies are spotted on solid surface and a complex mixture of cell lysates or serum labeled by a fluorescence tag are allowed to recognize the antibodies. Similarly, antigens can be spotted on glass and reacted with cognate antibodies. Allergens, glycans

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and other molecules can be studied in an analogous manner. This procedure is well suited to various biological purposes. ▶protein profiling; Huang RP et al 2001 Anal Biochem 294:55; Sreekumar A et al 2001 Cancer Res 61:7585.

Antibody Mimic: An antibody mimic is a small synthetic polypeptide with specificity for a particular natural or synthetic epitope. ▶epitope, ▶antibody

Antibody, Monoclonal: ▶monoclonal antibody

Antibody, Monovalent: A monovalent antibody has only a single binding site for an antigen. Normally the antibody is divalent, i.e., it has antigen-binding sites at both of the light and heavy-chain variability regions. By linking together multiple binding sites the avidity of the antibody increases. ▶antibody, ▶antibody bispecific

Antibody, Neutralizing: It results in the loss of infectivity, which ensues when antibody molecule(s) bind to a virus particle, and usually occurs without the involvement of any other agency. As such this is unusual of an antibody and is paralleled only by the inhibition of toxins and enzymes (Dimmock NJ 1995 Rev Med Virol 5:165; Finke D et al 2003 Proc Natl Acad Sci USA 100:199). HIV-1 may escape from the neutralizing antibody by N-linked glycosylation of the viral *env* gene (Wei X et al 2003 Nature [Lond] 422:307). ▶acquired immunodeficiency

Antibody, Polyclonal: A polyclonal antibody is a collection of antibodies secreted by different B lymphocytes in response to the epitopes of the same antigen and are therefore not entirely identical. Human polyclonal antibodies can be obtained by transferring them into bovine embryonic cells and thus into calves both the heavy and the lambda-chains of immunoglobulin gamma genes on a human artificial chromosome vector. ▶epitope, ▶antigen, ▶monoclonal antibody, ▶recombinant antibody, ▶human artificial chromosome, ▶nuclear transplantation; Kuroiwa Y et al 2002 Nature Biotechnol 20:889.

Antibody Polymers: Antibody polymers are formed by fusion of immunoglobulin chains. In this process, the immunoglobulin μ chain tailpiece fuses to the C-end of the γ chain which may increase, by two orders of magnitude, the activity of the complement system. Also, simple IgM, IgG tetramers are more effective than dimers. ▶antibody, ▶immunoglobulins, ▶tailpiece, ▶complement, ▶pIgR

Antibody Preparation: Antibody preparation involves injecting an animal with a pure antigenic molecule. After 2 to 3 weeks the animal develops antibodies against the epitope. The animal is then bled and the antibody removed from the serum by precipitation

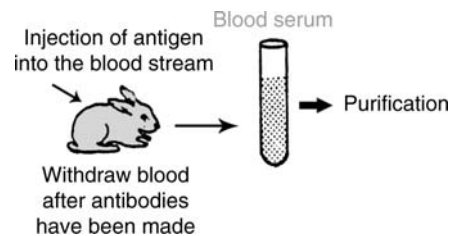


Figure A94. Antibody preparation

with the cognate antigen and further purified. Hundreds of different antibody preparations are commercially available from biochemical supply companies.

Antibody Purification: There are different methods of purifying antibodies. The protein antigen may be coupled to a cyanogen-bromide-activated Sepharose. The epitope then retains the cognate antibodies while all other antibodies flow through. Breaking the complex (with potassium thiocyanate, low-pH buffers, etc.) can then retrieve the antibody. The methods must be adapted to the different proteins. Another procedure is to adsorb antibodies to protein antigens immobilized on diazotized paper or nitrocellulose filters following electrophoresis by SDS-polyacrylamide gels. The antibodies are then eluted with a suitable buffer. Antibodies can be used for qualitative and quantitative assays of antigens, including immunoprecipitation, western blotting and solid-phase radioimmunoassays (RIA). ▶Sepharose, ▶epitope, ▶cyanogen bromide, ▶diazotized paper, ▶nitrocellulose filter, electrophoresis, ▶SDS-polyacrylamide gels, ▶immunoprecipitation, ▶radioimmunoassay

Antibody, Secondary: A molecule, cell, or tissue may be labeled with the cognate antibody (primary antibody). In order to boost the level of recognition, the primary antibody is reacted with another antibody (secondary antibody), labeled with an isotope (e.g., I^{125}) or a fluorochrome to obtain a stronger signal. ▶antibody, ▶fluorochromes

Antibody, Single Chain: ▶single-chain fragment Fv, ▶scFv

Antibody Valency: Specifies the number of antigen-binding sites. ▶antibody monovalent

Anticancer Agents: Include alkylating agents, cytotoxic and cytostatic agents, antibiotics (bleomycin, chlorambucil), topoisomerase inhibitors (etoposide, podophyllotoxin), ionizing radiation, etc. ▶chemotherapy, ▶cancer therapy, ▶cancer gene therapy, ▶ionizing radiation

Anticarcinogen: ▶antimutagens

Antichaperone: Antichaperone is a protein factor promoting aggregation of other proteins. ▶ [chaperone](#)

Antichromatin: Antichromatin is a state of the chromatin not conducive for active transcription. ▶ [chromatin](#), ▶ [pro-chromatin](#)

Anticipation: In successive generations it may appear as if the genetic trait (disease) would have occurred with an earlier onset in the more recent generations. Frequently this is, however, an artifact because when the investigator knows what is expected, the recognition becomes easier. There is also the possibility that individuals with early onset of the disease died early or failed to leave offspring. In the cases of diseases based on expansion of trinucleotide repeats there is a possibility of increased severity and earlier onset if the patients leave offspring. ▶ [ascertainment test](#), ▶ [trinucleotide repeats](#); Kovach MJ et al 2002 Amer J Med Genet 108:295.

Anticlinical Selection: An anticlinical selection is the selection that takes different directions in different environments compared to the *synclinal selection* when the direction is the same. ▶ [cline](#)

Anticoagulation: Blood coagulation is positively regulated by antihemophilic factors. Negative regulation (shutting down the coagulation pathway) is mediated by thrombomodulin, which binds thrombin and activates protein C, which in turn binds protein S and causes factors Va and VIIIa to be degraded. Thrombomodulin (an epidermal growth-factor like molecule) works by binding to thrombin at an exosite where otherwise thrombin would bind fibrinogen. Coumarin impairs the pro-coagulants thrombin, antihemophilic factors Xa, IXa and VIIa and the anticoagulant proteins C and S. Heparin enhances the inhibition of thrombin and factor Xa by antithrombin III. ▶ [blood clotting pathways](#), ▶ [antihemophilic factors](#), ▶ [thrombin](#), ▶ [exosite](#), ▶ [protein C](#), ▶ [protein S](#), ▶ [antithrombin](#), ▶ [vitamin K](#)

Anticoding Strand: An anticoding strand is the transcribed strand of DNA. ▶ [antisense RNA](#), ▶ [coding strand](#), ▶ [template strand](#), ▶ [sense strand](#), ▶ [plus strand](#)

Anticodon: An anticodon is part of the tRNA, which recognizes an mRNA code word by complementarity. It is one of the means of tRNA identity (see Fig. A95).

In the mitochondria the “universal” genetic code does not entirely prevail but different eukaryotic mitochondria (except higher plants) use a somewhat different codon dictionary. In these systems the anticodons are also different inasmuch as there are no separate tRNAs for each of the synonymous codons.

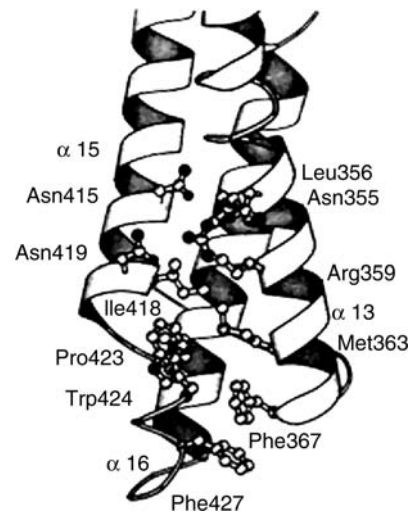


Figure A95. The Anticodon–Binding α -Helix Bundle of Bacterium tRNA^{Met} Synthetase. The Stick-and-Ball Structure shows the exposed side chains of the Amino acids (Courtesy of professor M. Konno. See also Sugiyama I et al 2000 Structure 8: 197)

Rather, the mtDNA codons are recognized in pairs or in four-member sets of codons, and the anticodon–codon interaction is by G•U pairing or the 5'-terminal U of the anticodon of the four-member set can pair with any of the four bases in the mRNA codon. Although there are 61 different sense codons in eukaryotes, there are only 54 anticodons in the universal code and 46 species of tRNAs and anticodons are sufficient for protein synthesis on the ribosomes. ▶ [tRNA](#), ▶ [genetic code](#), ▶ [wobble](#); Jukes TH 1984 Adv Space Res 4 (12):177.

Anticorrelation Genes: Have similar (analogous) function and can complement each other without substantial structural homology. Morett E et al 2003 Nature Biotechnol 21:790.

Antideterminant: Ribonuclease III, which processes about 20-bp double-stranded RNAs may not cut at any position because some Watson-Crick pairs interfere with scission and serve as an antideterminant. Such an antideterminant is, e.g., a 3-bp sequence from the selenocysteine-accepting tRNA (tRNA^{Sec}) and is an antideterminant for EF-Tu binding to this tRNA. ▶ [ribonuclease III](#), ▶ [selenocysteine](#), ▶ [EF-TU-GTP](#); Evguenieva-Hackenberg E, Klug G 2000 J Bacteriol 182:4719; Mohan A et al 1999 RNA 5:245.

Antidiuretic Hormone (vasopressin): Vasopressin is a small peptide hormone (ADH, M_r 1040) which increases water reabsorption in the kidneys and also blood pressure; it affects a variety of functions, including learning and behavior (aggression).

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Nephrogenic diabetes insipidus an X-chromosomal human disease, with problems of maintaining water balance, fails to respond to ADH and is very similar to oxytocin; only two amino acid difference exists between the two. The structure of vasopressin is (see Fig. A96):

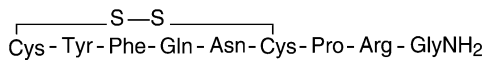


Figure A96. Antidiuretic hormone

It binds to receptor molecules in the plasma membrane in the kidneys and blood vessels and activates a specific membrane, phospholipase. The phospholipase then breaks the bond between glycerol and phosphate in phosphatidylinositol-4,5-bisphosphate and releases inositol-1,4,5-triphosphate and diacylglycerol. Vasopressin is encoded in the short arm of the human chromosome 20 along with oxytocin. [▶oxytocin](#), [▶diabetes insipidus](#), [▶phospholipase](#), [▶diacylglycerol](#), [▶inositol](#), [▶phosphoinositids](#), [▶nocturnal enuresis](#)

Anti-DNA Antibody: DNA is a poor antigen although in the autoimmune disease lupus erythematosus antibodies bind to DNA. Most DNA antibodies are not entirely specific because they bind to repetitive sequences. DNA tracts with stably bound proteins can, however, be used as antigens to specific sequences. [▶autoimmune disease](#), [▶antibody](#), [▶antigen](#); Stollar BD1986 CRC Crit Rev Biochem 20:1; Cerutti ML et al 2001 J Biol Chem 276:12769.

Antidote: Antidotes may be specific for reversing the toxic effect of a compound or nonspecific, e.g., an emetic, which induces vomiting.

Antiestrogen: Antiestrogens bind to the estrogen receptors and antagonize the effects of the hormones. Some, however, may have various levels of agonist activity. [▶tamoxifen](#), [▶raloxifene](#)

Antifreeze Protein: Antifreeze protein is present in several species of fishes living in the northern regions. The glycoprotein binds, through free OH groups of amino acids, to the first ice crystals and thus prevents the expansion of the ice and thus the fish is protected. In fishes there are more than eight forms of antifreeze protein, encoded as different proteins, yet they all contain tripeptide (Thr-Ala-Ala/Pro-Ala-) repeats. Mainly, Leu/Phe-Ile/Asn-Phe spacers link the monomers into a large polypeptide. The antifreeze glycoprotein (AFGP) genes usually contain two exons (the small for a signal peptide and the large for the antifreeze) separated by a single intron. Somewhat similar proteins may play a role in other organisms too. A very efficient antifreeze protein was

isolated from the insect *Tenebrio monitor*. A 36-kDa glycoprotein isolated from cold-acclimated carrot taproots is similar in sequence to polygalacturonase inhibitor proteins. The antifreeze protein in perennial ryegrass (*Lolium perenne*) appears to control more ice crystal growth than preventing freezing *per se*. [▶hysteresis](#), [▶cold hypersensitivity](#), [▶thermo-tolerance](#), [▶mealworm](#); Miao M et al 2000 Eur J Biochem 267:7237; Tomczak MM et al 2001 Biochim Biophys Acta 1511:255; Haymet AD et al 2001 FEBS Lett 491:285; Fairly K et al 2002 J Biol Chem 277:24073.

Antifungal Response: Insects defend themselves against fungi and microorganisms by the production of proteolytic enzymes, phagocytosis and by the production of antimicrobial peptides. In *Drosophila*, antifungal drosomycin and several antimicrobial/antibacterial peptides, cecropins, diptericin, drosocin, attacin and defensin are produced. The *spätzle*, *Toll*, *cactus*, and *dorsal* dorsoventral regulatory genes (corresponding to the mammalian NF-κB cascade) and the immunodeficiency gene, *imd*, mediate these responses. Several species of yeasts also exert antifungal action. [▶antimicrobial peptides](#), [▶morphogenesis in Drosophila](#), [▶host-pathogen relationship](#), [▶NF-κB](#)

Antigen: An antigen is a substance (usually a protein) which, either alone or in combination with a protein, elicits antibody formation. The protein antigen may be a large molecule with more than a single specificity due to its different subunits. A particular specificity of the antigen is determined by the epitope or a hapten conjugated with the protein molecule to form an antigen that reacts with the paratope of the antibody. The antigen is usually chopped into small fragments to be effectively presented to the lymphocytes. In some cases, internal sequences of the peptides are deleted by a proteasome system and, e.g., the originally 16 residues are spliced into a 9-residue antigen (Vigneron N et al 2004 Science 304:587). [▶antibody](#), [▶antigen presenting cell](#), [▶epitope](#), [▶paratope](#), [▶superantigen](#), [▶TI antigens](#), [▶lipid antigen](#); Kurosaki T 1999 Annu Rev Immunol 17:555; Zinkernagel RM, Hengartner H 2001 Science 293:251.

Antigen, Male Specific: [▶grafting in medicine](#), [▶H-Y antigen](#)

Antigen mimic: An antigen mimic is a short polypeptide used for screening specific paratope sites. [▶paratope](#), [▶antibody mimic](#)

Antigen Presenting Cell (APC): APC binds antigens, internalizes, processes and expresses them on their surface in conjunction with class II type molecules (one of the two type of molecules coded for by the

MHC genes). T cells recognize the presented antigen through their receptors. Helper T cells can be activated only in the presence of APC cells. Macrophages, dendritic (branched) cells and B lymphocyte cells express class II antigens and can thus serve as APC in vitro and in vivo macrophages and dendritic cells are apparently most important as APC (see Fig. A97).

The activation of helper T cells requires that the T cells and the APC be derived from animals (mice) syngeneic in region *I* of the MHC, and the production of the lymphokine, interleukin-1 (IL-1) and also family member, CD80. Macrophages are rich in lysosomes and can therefore rapidly break up antigens, whereas dendritic cells are poor in lysosome activity and have a more limited capacity for degradation. ▶antigen, ▶immune system, ▶T cell, ▶T cell receptor, ▶cytotoxic T cell, ▶clonal selection, ▶CD40, ▶HLA, ▶syngeneic, ▶lymphokines, ▶interleukins, ▶affinity maturation, ▶CD80, ▶CD1, ▶proteasomes, ▶MHC, ▶cross presentation; Jenkins MK et al 2001 Annu Rev Immunol 19:23; Guernonprez P et al 2002 Annu Rev Immunol 20:621.

Antigen Processing and Presentation: Antigen-presenting cells mediate the association of the native antigen with an MHC molecule and thereby the antigen is recognized by the T lymphocytes. The antigenic protein must be degraded to some extent by immunoproteasomes and processed for presentation to the MHC molecules. The processing takes place either within endosomal compartments of the cell or by the proteases secreted onto the surface of the immature dendritic cells. The final step in sizing the antigen is mediated by the enzyme ERAAP (endoplasmic reticulum aminopeptidase), which is upregulated by interferon γ (Serwold T et al 2002 Nature [Lond] 419:480). The MHC I associated peptides are generally shorter (9 ± 1 amino acids) than those associated with MHC II molecules that are derived from excreted proteins or other external proteins. Protein disulfide isomerase play a critical role in selecting MHC I molecules (Park B et al 2006 Cell 127:369). Usually the peptides enter the endoplasmic reticulum before their epitope is presented to the MHC molecules. If the

proteins lack the signal peptide to be transferred to the endoplasmic reticulum, their epitope may still be presented to the MHC molecules. The MHC Class II molecules are associated with the invariant I_i polypeptide that mediates the folding of the MHC II molecules in the endoplasmic reticulum and compartmentalizing the MHC II molecules for special peptide binding in the endosomes. The processing is mediated by cathepsins but an asparagine-specific cysteine endopeptidase may also be involved in degrading microbial antigens. ▶antigen presenting cell, ▶HLA, ▶lymphocytes, ▶immunoproteasomes, ▶endosome, ▶CLIP, ▶major histocompatibility complex, ▶TAP, ▶T cell, ▶cathepsins; York IA, Rock KL 1996 Annu Rev Immunol 14:369; Watts C 1997 Annu Rev Immunol 15:821.

Antigen Receptors: Antigen receptors are molecules on lymphocytes, responsible for the recognition and binding of antigens and antigen-MHC. ▶lymphocytes, ▶HLA, ▶receptor editing, ▶LFA, ▶CD2, ▶CD4, ▶CD8, ▶CD28, ▶CD45, ▶CTLA-4, ▶ICAM; Davis MM et al 2003 Annu Rev Biochem 72:717.

Antigene Technology: Antigene technology is used for triple helix formation. ▶triple helix formation

Antigenic Determinant: ▶epitope, ▶antibody

Antigenic Distance: The antigenic distance indicates the degree of similarity between/among antigens.

Antigenic Drift: Antigenic drift is the process by which the surface antigens of a pathogen may change by mutation. ▶antigenic variation, ▶phase variation, ▶*Borrelia*, ▶*Trypanosoma*

Antigenic Shift: Antigenic shift is a rearrangement in the genetic material of a virus resulting in an escape of the normal immune reaction. ▶antigenic drift, ▶antigenic variation

Antigenic Sin: Propensity of individuals who had been previously exposed to one virus and later encountered another virus variant of the same subtype, can make antibodies against the original viral hemagglutinin (HA) and also to the new one. This happens because

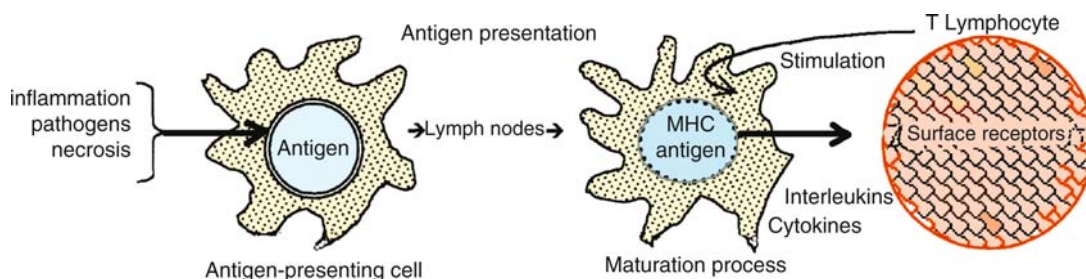


Figure A97. Antigen presenting cell

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the memory B cells or the T cells were activated in a way specific for the progenitor virus. In some instances the variant virus may escape the immune defense of the host because the lymphocyte receptor is altered by mutation although the histocompatibility class I molecules may bind normally. ▶**hemagglutinin**, ▶**immune system**, ▶**antigen**, ▶**HLA**; Good MF et al 1993 *Parasite Immunol* 15:187.

Antigenic Variation: Antigenic variation is the property of prokaryotic and eukaryotic microorganisms to switch on the synthesis of different surface proteins to escape the immunological defense system of the host organisms. This goal is reached generally by transposition of genes relative to the promoter. In *Plasmodium falciparum*—the malaria parasite—the PfEMP1 (erythrocyte membrane protein family), encoded by ~60 *var* genes determine virulence by immune evasion and intravascular sequestration of the parasite in the host. The PfEMP1 molecules adhere to the surface of the red blood cells and evade detection by the immune system at this place of hiding. By multiplying in the capillaries, clogging and malaria develops. Evasion of the host immune system takes place by switching on one or another member of the PfEMP1 family members while the other alleles are excluded from function. The expression of the *var* genes is controlled by one or another of the upstream promoters (*upsA*, *upsB*, *upsC*). The telomeric *var* gene promoters have expression sites near the periphery of the nucleus where they move by an unknown epigenetic mechanism of chromatin remodeling. The A and B promoters are subtelomeric and interact with DNA-binding proteins whereas the C interacts with a *var* intron and controls silencing by using a silent information regulator, PfSIR2 (Voss TS et al 2006 *Nature [Lond]* 439:1004).

In *Borrelia hermsii*, a bacterium responsible for tick-borne relapsing fever, unexpressed loci of variant antigens copy into a single expression site at rates determined by extragenic features of silent loci rather than similarity between coding sequences of variants at silent sites and the single expression site. Two elements, in particular, determine switch rates. One set of elements overlaps the 5' ends of the expressed gene and the silent loci; greater sequence identity between elements was associated with a higher switch rate. The second set of elements flanks the expression site on the 3' side and occurs at variable distances downstream from the silent loci; the nearer an element is to a silent locus, the greater the switch rate of that locus into the expression site (Barbour AG et al 2006 *Proc Natl Acad Sci USA* 103:18290).

The bacterium *Neisseria gonorrhoeae* (responsible for a venereal disease—manifested primarily in males but transmitted through both sexes—and for the

various complications affecting both genders) relies on gene conversion for the purpose. ▶**phase variation**, ▶*Borrelia*, ▶*Trypanosoma brucei*, ▶**cassette model** of ▶**yeast**, ▶**gene conversion**, ▶**serotype**, ▶**epigenetic memory**; Barry JD, McCulloch R 2001 *Adv Parasitol* 40:1; Brayton KA et al 2001 *Proc Natl Acad Sci USA* 98:4130.

Antigenome: An antigenome in the replicative form of the viral genetic material it serves as a template for the synthesis of the genome. The term “Antigenome of a pathogen” is used to denote the array of antibody-binding epitope array. ▶**RF**, ▶**epitope**

Antihemophilic Factors: Blood coagulation requires the formation of complexes between serine protease coagulation factors and membrane-bound cofactors. Tissue thromboplastin, an integral membrane glycoprotein (Factor III, encoded at 1p22-p21) and proconvertin (VII, encoded at 13q34) are required to activate Factors IX and X. Mouse embryonic stem cells stimulated by fibroblast growth factor gave some evidence for correction of Factor IX deficiency (Fair JH et al 2005 *Proc Natl Acad Sci USA* 102:2958). Factor VIIa is a trypsin-like serine protease that also plays a key role in blood coagulation after binding γ -carboxyglutamic acid-containing domain. A plasma thromboplastin antecedent (XI, 4q35) activates Factor IX. Blood coagulation factor (VIII, Xq28), a 293-kDa plasma glycoprotein, acts in concert with Factor IXa, a proteolytic enzyme, to activate Factor X (Stuart Factor, 13q34). The latter, in turn, activates prothrombin (II, 11p11-q12) to thrombin that acts on fibrinogen (I, 4q28) to convert it to fibrin (responsible for loose clot). The fibrin-stabilizing factors (XIII, α -chain 6p25-p24; β -chain 1q31-q32.1) then generate the firm clots required for blood clotting. The Hageman factor (XII, 5q33-qter) activates thromboplastin antecedent (XI, 4q35). Accelerin (V, 1q23) stimulates the activation of prothrombin (II, 11p11-q12). In classic recessive X-chromosomal hemophilia, Factor VIII is defective. Factor IX (454 amino acid, Xq27.1-q27.2) deficiency, a partially dominant disorder of hemostasis (arrest of blood flow), is involved in Christmas disease. Blood clotting requires, in addition, calcium and thromboplastin (lipoprotein released into blood from injured tissues). A thromboplastin antecedent (XI, 4q35) deficiency is responsible for hemophilia C. The level of Factor IX increases as a normal condition with the advancing age and may be responsible for the increase in cardiovascular and thrombotic disorders among the aged. Bleeding disorders may be the consequence of mutations at the LMANN1/ERGIC-53 (18q21.3-q22) gene, encoding the lectin, mannose-binding protein, or the simultaneous defects of Factors V and VIII

(2p21-p16.3 and 18q21.3-q22). In the latter case the two proteins may not be folded properly and cannot be moved by the endocytotic vesicles (Zhang B et al 2003 Nature Genet 34:220). A similar condition arises by mutation in MCFD2 (multiple coagulation factor deficiency-2, 2p21p16.3). ▶hemophilia, ▶Hageman trait, ▶PTA deficiency, ▶prothrombin deficiency, ▶Stuart disease, ▶vitamin K-dependent clotting factors, blood clotting pathways, ▶coumarin-like drug resistance, ▶parahemophilia, ▶afibrinogenemia, ▶dysfibrinogenemia, ▶fibrin-stabilizing factor, ▶hypoproconvertinemia, ▶von Willebrand's disease, ▶platelet abnormalities, ▶hemostasis, ▶APC, ▶LINE, ▶tissue factor, ▶anticoagulation, ▶thrombopoietin, ▶warfarin; Bajaj SP et al 2001 J Biol Chem 276:16302; Hockin MF et al 2002 J Biol Chem 277:18322; Tuddenham E 2002 Nature [Lond] 419:23, <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a694027.html>.

Antihormones: Antihormones are antagonists of hormones which alter the conformation of the hormones or bind to the hormone receptor sites and thus prevent the attachment of hormones to the hormone responsive elements (HRE) in the DNA and thus block the transcription of the hormone-responsive genes. ▶hormone responsive element, ▶conformation

Anti-Idiotypic Antibody: An anti-idiotypic antibody is a specific antibody that recognizes a particular paratope (idiotype) of an antibody and binds to it rather than to the epitope of the antigen. Homologous anti-idiotypic antibodies are produced within the species, whereas in different species heterologous anti-idiotypic antibodies are produced. The anti-idiotypic antibody may be generated in the laboratory by first exposing the cell to the epitope, an antigen. This specific antibody so obtained may give rise to another antibody, a mimic of the original. Also, other antibodies may arise in a similar manner, which may respond to the original and also to a mutant antigen. These antibodies may be capable of stimulation of B lymphocytes and T cells and thus both humoral and cellular immunity can be generated. Thus, anti-idiotypic vaccine production may become feasible for particular cases, e.g., against the poorly antigenic bacterial polysaccharides or mutant p53 proteins that do not suppress tumor formation. ▶antibody, ▶idiotype, ▶paratope, ▶internal image immunoglobulin, ▶epitope, ▶p53; Birebent B et al 2001 Crit Rev Oncol Hematol 39:117; Bhattacharya-Chatterjee M et al 2001 Curr Opin Mol Ther 3:63.

Antilog: An antilog is the inverse logarithm and it is obtained if the base is raised to the power of the logarithm. The antilogarithm for $\log_{10} x$ is 10^x and for $\ln(x)$ the antilogarithm is e^x . ▶logarithm

Antelope (blackbuck, *Antelope cervicapra*): the male is $2n = 31-33$, the female $2n = 30-32$. ▶antelope

Antimetabolite: Antimetabolite is a compound that binds to an enzyme but is not generally utilized as a substrate, and thus interferes with normal metabolism. ▶metabolism, ▶metabolite

Antimicrobial Peptides (AMP, RAMP): Antimicrobial peptides occur on, or in, animals and plants as a defense system. They can be linear molecules such as *cecropin* (moths, pig, *Drosophila*), making pores by lysis, *magainin* (frog skin) forming pores, or *bactenein* (bovine neutrophils) affecting membrane permeability. They include disulphides: *defensins* (in several organisms, Hoover DM et al 2001 J Biol Chem 276:39021) making pores, *tachyplesins* (in horseshoe crab), affecting potassium efflux, *protegrins* (pig leukocytes). Many of these peptide genes contain attachment sites for transcriptional activators related to NF- κ B, *Rel/Dorsal* oncogene. *Serprocidins* that are high molecular weight protease-like molecules: *protease 3* and *azurocidin* in mammals and *cathepsin G* in human neutrophils that inhibit metabolism. Lipopolysaccharide-binding proteins and bactericidal/permeability-increasing proteins, collectins are components of the mammalian defense system. A defensin-like peptide is expressed exclusively in the epididymis of rats. Plectasin, a defensin family peptide, was discovered in saprophytic ascomycete fungus *Pseudoplectania nigrella* and is highly effective against *Streptococcus pneumoniae* (Mygind PH et al 2005 Nature [Lond] 437:975). Most cells respond to invaders by the mediation of Toll receptors, which initiate and activate the production of antimicrobial peptides against Gram-positive bacterial infection through the peptidoglycan recognition protein (Gobert V et al 2003 Science 302:2126). *Mycobacterium tuberculosis* susceptibility in humans depends on the Toll-like receptor that triggers the upregulation of the vitamin D receptor leading to the induction of the cathelicidine antibacterial peptide (Liu. PT et al 2006 Science 311:1770). A synthetic library of linear peptide-like sequences consisting of alternating acyl chains and cationic amino acids prevents the formation of a stable secondary structure and appears promising as antibiotics (Radzishhevsky IS et al 2007 Nature Biotechnol 25:657). ▶antifungal response, ▶antibiotics, ▶opsonins, ▶nisin, ▶Toll, ▶*Mycobacterium*; Hoffmann JA et al 1999 Science 284:1313; Khush RS, Lemaitre B 2000 Trends Genet 16:442; Zasloff M 2002 Nature [Lond] 415:389; molecular pathways of *Drosophila* immunity: Hoffmann JA 2003 Nature [Lond] 426:33; degradation resistance by folding: Raimondo D et al 2005 Proc Natl Acad Sci USA 102:6309; insect antimicrobial systems: Uvell H, Engström Y 2007

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Trends Genet 23:342; defensins database: <http://defensins.bii.a-star.edu.sg/>; http://nar.oxfordjournals.org/cgi/content/full/32/suppl_1/D590.

Antimitotic Agents: Antimitotic agents block or inhibit mitosis through ionizing radiation, radiomimetic chemicals and inhibitors of the cell cycle. ▶[radiation effects](#), ▶[cancer therapy](#), ▶[cytostatic](#)

Antimongolism Chromosome: A chromosome 21 deletion in humans that compensates in some respects for the syndrome accompanied by the trisomy of complete chromosomes 21 (Down's syndrome; by old name mongoloid idiocy). This deletion, G I, causes the formation of large ears, prominent nasal bridges, an antimongoloid slant of the eyelids, long fingers and toes, micro- or dolicephaly and hypo- γ -globulinemia (rather than an excess as in Down's syndrome). ▶[Down's syndrome](#), ▶[dolicephaly](#), ▶[microcephaly](#), ▶[agammaglobulinemia](#)

Antimorph: A (dominant) mutation, which antagonizes the function of the wild type allele (by competing for the substrate). dominant negative, ▶[killer genes](#)

Anti-Müllerian Hormone (AMH/AMS): The anti-Müllerian hormone is produced by the Sertoli cells. It masculinizes XX rodents whereas males deficient in AMH become pseudohermaphrodites. SF-1, SOX9 and WT1 regulate AMH. ▶[Sertoli cells](#), ▶[gonads](#), ▶[pseudohermaphrodite](#), SF-1, ▶[SOX](#), ▶[Wilms tumor](#)

Antimutagen: An antimutagen protects against the mutagenic effect(s) of other agents. Generally, hypoxia-reducing agents (such as dithiothreitol) lower the damaging effects of ionizing radiation. Inhibitors of microsomal mutagen activating enzymes (such as 9-hydroxyellipticine, gallic and tannic acids, carbon monoxide, selenium, etc.) may reduce the mutagenic effectiveness of chemicals. ▶[antimutator](#), ▶[mutagen](#), ▶[caffeic acid](#), ▶[polyphenols](#), ▶[methylguanine-O⁶-methyltransferase](#); Novick A 1955 Brookhaven Symp Biol 8:201.

Antimutator: An antimutator lowers mutation rate. An increased level of nuclease activity (editing function) and all other genetic repair mechanisms may act this way. Compounds that inactivate microsomal enzymes involved in conversion of promutagens into mutagens are also antimutagens, or mutations, which reduce oxidative stress. ▶[AP nucleases](#), ▶[ABC excinucleases](#), ▶[DNA repair](#), ▶[mismatch repair](#), ▶[mutator](#), ▶[proofreading](#); Reha-Kranz LJ 1998 Genetics 148:1551.

Antioncogenes: Antioncogenes are the normal alleles of some genes that, in the mutant state, incite tumors. For example, the cloned normal allele of the human retinoblastoma gene codes for a DNA-binding protein

and the cancer cells transformed by this gene are suppressed in proliferation. ▶[tumor suppressor genes](#)

Antipain: Antipain is a protease inhibitor (1–2 $\mu\text{g/mL}$) and is effective against cathepsin A and B, papain and trypsin protease enzymes.

Antiparallel Pairing: Antiparallel pairing of polynucleotide chains means that at the same end of the double helix one has 5' and the other has 3' ends of the paired nucleotides (see Fig. A98).



Figure A98. Antiparallel

Antiphospholipid Syndrome: Antiphospholipid syndrome is the endocytosis defect which involves greater risk of thrombosis, thrombocytopenia, and recurrent and spontaneous abortions. The antibodies may attack phospholipids, or the protein-phospholipid complex or proteins like $\beta 2\text{q}$ glycoprotein. ▶[endocytosis](#)

Antipodal: Refers to haploid cells (nuclei) located in the plant embryosac at the end opposite to the place of the egg and the micropyle. ▶[embryosac](#)

Antipyretic: An antipyretic is a fever reducing drug.

Antiport: Antiport is the membrane transport of substances in opposite directions. A substance could also be sequestered through the antiport within another compartment. The Na^+/H^+ antiporters in different organisms (bacteria/plants/humans) determine the sodium/proton balance in the cells and are keys to adaptation to high salinity or extreme pH. It is supposed that the ion exchange is regulated by a conformational change elicited by pH at the entry site (Hunte C et al 2005 Nature [Lond] 435:1197)

Antirecombination: Antirecombination prevents recombination between not entirely homologous DNA strands, i.e., between homeologous DNA.

Antidepression: Refers to the situation when transcription factors bound to the DNA upstream of the promoters interfere with the binding of unspecific DNA binding proteins, which normally exert repression. ▶[insulator](#)

Antirestriction Mechanisms: Antirestriction mechanisms are those which prevent the cleavage of the DNA by different mechanisms, e.g., methylation of critical bases (e.g., phages T2, T4, SP β), inhibition of the endonuclease (e.g., T3, T7 phages), enhancing host-encoded methylase (phage λ), carrying hydroxymethyl cytosine in place of cytosine (T-even phages), 5-hydroxymethyluracil substitution for thymine (SPO1, SP8, $\phi 25$), reducing certain vulnerable

restriction sites in their DNA (f29), etc. ▶restriction endonucleases, ▶restriction-methylation; King G, Murray NE 1995 Mol Microbiol 16:769.

Antiridge: ▶ridge

Antirrhinum majus (snapdragon): Is a higher plant of the *Scrophulariaceae* family ($2n = 16$). It is an attractive autogamous flowering plant and a favorite in genetic and cytogenetic studies. A large collection of mutants and transposable elements are available (see Fig. A99). ▶TAM, ▶snapdragon, ▶peloric; <http://www.antirrhinum.net/>; <http://www.mpiz-koeln.mpg.de/english/research/saedlerGroup/schwarzSommer/index.html>.

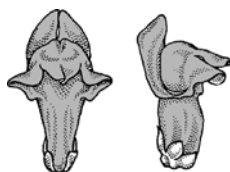


Figure A99. Antirrhinum

Antisense DNA: library can be used for transformation and isolation of mutations or for other purposes of preventing gene expression. The 25-base oligodeoxyribonucleotide phosphorothioate (TCTTCCTCTC TCTACCCACGCTCTC, Hybridon, Inc., trade name GEM 91) binds to the translation initiation site of the *gag* gene of the HIV-1 pathogen of acquired immunodeficiency and may inhibit the production of new infectious particles because of the defect in packaging. The human L1 (LINE) retrotransposon has two promoters, a sense promoter that directs the transcription of the full-length L1 tract and an antisense promoter that drives in the opposite direction and into adjacent sequences and thus generates chimeric transcripts. Both promoters are situated within the 5' non-translated region of L1 (Nigumann P et al 2002 Genomics 79:628). Antisense transcripts occur not only in tumors but also in normal cells. In the mouse, 72% of the transcriptional units (TU) overlap with some transcripts of the opposite strand. From all Tus, (4520) are full-length sense/antisense pair transcripts. Antisense transcription is different in different chromosomes; it is lower in the X chromosome than in the autosomes (RIKEN 2005 Science 2005 309:1564). Antisense transcripts have a regulatory and evolutionary role to play and do not appear to be due to accidental leakage (Dahary D et al 2005 Genome Res 15:364). ▶OL(1)p53, ▶Bcl, ▶antisense RNA, ▶aptamer, ▶peptide nucleic acid, ▶antisense technologies, ▶cancer gene therapy, ▶G3139, ▶acquired immunodeficiency, ▶HIV,

▶phosphorothioate, ▶antisense technologies, ▶L1; Zhang YM et al 2001 J Nucl Med 42:1660; Lehner B et al 2002 Trends Genet 18:63.

Antisense Oligodeoxynucleotide (AS ODN): ▶antisense DNA, ▶antisense RNA, ▶selection and design: <http://www.bioit.org.cn/ao/aobase/>.

Antisense RNA: Is a transcript of a gene or transposon that may inhibit translation by pairing with the 5' end of the correct (sense) mRNA and thus prevent its ribosome binding and expression. In several bacterial plasmids, by inhibiting the synthesis of the replication initiator protein, the antisense RNA limits copy number. Some synthetic oligonucleotide analogs may block replication and transcription, interfere with splicing of exons, disrupt RNA structure, destabilize mRNA by interfering with 5' capping of mRNA, inhibit polyadenylation, activate ribonuclease H. When coupled to alkylating agents they can cross-link nucleic acids at the recognized sequences, can be used as vehicles for targeted DNA cleavage, may inhibit receptors, etc. The various functions require a large variety of specific antisense constructs. Usually, the antisense oligonucleotides are 12–50-nucleotide long. According to calculations in the human genome, any 17-base sequence occurs only once, and in the mRNA populations, 13mer residues are unique. Shorter sequences do not have sufficient specificity. Long antisense sequences may have self-binding tracts that may cause lowered affinity for their target. Natural antisense RNA transcripts (NATs) occur in all types of biological systems, from viruses to higher eukaryotes. This fact indicates that in eukaryotes both strands of the DNA may be transcribed. In the human genome, 2,667 loci were reported as showing transcripts of the complementary strands (Yelin R et al 2003 Nature Biotechnol 21:379). In *Arabidopsis* ~30% of the annotated genes displayed significant antisense RNA expression (Yamada K et al 2003 Science 302:842). The cis-NATs are transcribed at the same locus but from the opposite strand of the DNA. The trans-NATs are transcribed at sites different from that where encoding of the sense transcript takes place. The trans-NATs can regulate the expression of several genes like the microRNAs (Wang, X.-J. et al. 2005 Genome Biol 6: R30). Among five species of fungi, the number of genes involved with antisense transcripts is variable (Steigle S, Nieselt K 2005 Nucleic Acids Res 33:5034).

Antisense RNA (or DNA) was expected to become an important therapeutic tool for fighting infections and cancer. This technology is still under development for finding cures against cytomegaloviruses, HIV1, Papilloma virus, autoimmune diseases (arthritis, etc.), leukemia (CMV) and blocking the immune

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system in case of organ transplants. Surprisingly, the antisense RNA may trigger an immune reaction because the CpG blocks are unmethylated and the animal immune system responds to them as to bacterial molecules. In bacteria these bases are largely unmethylated in contrast to eukaryotes where a substantial fraction of the DNA is methylated. The phosphorothioate oligodeoxynucleotides or oligoribonucleotides are taken up by a variety of cell types, including some prokaryotes (*Vibrio*), and bind either to DNA, RNA or protein. Phosphorothioate LD₅₀ is about 750 mg/kg. Antisense RNAs may block embryonic development and can be used to inhibit gene expression at defined stages. Although antisense RNA is supposed to be very specifically for the intended target, it may affect several genes that have short or long sequences homologous to the target. A deletion in the hemoglobin gene cluster juxtaposes another gene (LUC7L, an U1Snrp component) to the HBA2 gene, which normally is situated 335–337 bp downstream from the polyA addition site of HBA2 and transcribed in the opposite direction of the hemoglobin gene. The LUC7L is also truncated by the deletion and thus lacks the termination signals and consequently its transcript fuses with the CpG island of HBA2. This condition generates an antisense RNA, which causes complete methylation of the island and silencing of the intact HBA2 and thereby α -thalassemia (Tufarelli C et al 2003 Nature Genet 34:157). In addition, the antisense RNA may bind and affect different proteins as an aptamer. Furthermore, the nucleic acid degradation products concomitant or following the administration of the antisense RNA may also result in unspecific inhibition in the cells.

►host-pathogen relations, ►triplex, ►aptamer, ►pseudoknot, ►peptide nucleic acid, ►phosphorothioates, ►methylphosphonates, ►cap, ►fruit ripening, ►anthocyanin, ►co-suppression, ►RIP, ►Cytomegalovirus, ►Papilloma virus, ►autoimmune disease, ►leukemia, ►transplantation antigens, ►antisense technologies, ►sense strand, ►AS ODN, ►anticoding strand, ►coding strand, ►triple strand formation, ►RNA double-stranded, ►hybrid arrested translation, ►RNAi, ►G quartet, ►U1 RNA, ►thalassemia, ►Xist, ►microRNA, ►TUF; Helene C, Toulme JJ 1990 Biochim Biophys Acta 1049:99; Matveeva OV et al 2000 Nucleic Acids Res

28:2862; Sohail M et al 2001 Nucleic Acids Res 29:2041; <http://www.prl.msu.edu/PLANTncRNAs/database.html>, natural antisense RNA: <http://natsdb.cbi.pku.edu.cn/>.

Antisense Strand of DNA: An antisense DNA strand is the template strand of DNA from which the mRNA or other functional, natural RNAs, are replicated as complementary copies. ►antisense RNA

Antisense Technologies: Use RNA and DNA targets for the suppression or modification of gene expression. The antisense molecule then blocks the synthesis of RNA and protein (see Fig. A100). Various forms of antisense molecules have been used (see antisense RNA); for antisense DNA technology, the nucleotides are ligated, for example, e.g., by phosphorothioate linkage and not by the normal phosphodiesterase linkage in order to protect the antisense strand from nuclease attack. For the production of antisense nucleic acids, the oligonucleotides are modified either in the base of the sugar or through changes in the sugar phosphate background. The good antisense molecules are expected to allow for RNase H activity to remove the natural target (preventing its translation) and then bind stably to DNA, blocking protein synthesis. The modification usually prevents enzymatic disposal of the antisense constructs. The antisense sequences may have side effects. Guanine-rich antisense sequences may have an undesirable affect on the telomerase enzyme, may form quadruplex structures, interfere with replication of the chromosomes, and may bind to proteins and may modify their function. In order to minimize these deleterious consequences various alterations have been attempted. The number of phosphorothioates is reduced or in a five base sequence the terminals (“wings”) are modified whereas, in-between, an RNase H-competent 2'-deoxy-oligodeoxynucleotide “window” is preserved. This approach basically is the generation of an “artificial restriction endonuclease” site. Another possibility involves targeting a mutant, activated oncogene by a single mismatch antisense RNA. The mismatch is expected to reduce the chance of cleavage at the heteroduplex site, but increase the chance of cleavage by RNase H at the oncogenic mutation and the perfectly matched mutant mRNA,

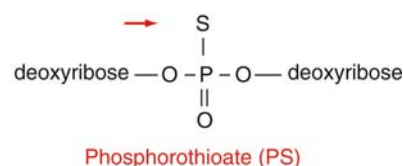
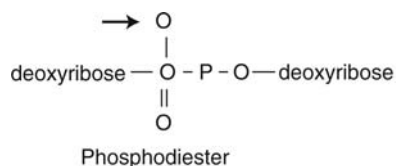


Figure A100. Antisense technologies

thus achieving suppression of malignancy. Antisense oligonucleotides also have therapeutic applications by correcting for defects in mRNA splicing, to induce exon skipping and restoring normal reading frames in cases when deletion or nonsense mutation cause the disease (Aartsma-Rus A et al 2004 *Am J Hum Genet* 74:74). A two exon skipping may change the more serious symptoms of Duchenne muscular dystrophy to the milder Becker type. Besides these changes, good uptake should be secured, e.g., by the use of cationic lipids and by assuring membrane permeabilization with the stability of the internalized oligonucleotides. The nerve cells apparently take up oligonucleotides more readily than other type of tissues if introduced by injection. There however is a blood/neuron barrier after intravenous or intraperitoneal applications. Antisense constructs readily target the liver and kidneys, but the degradation and excretion are most rapid in and from these tissues. Endocytosis and pinocytosis can take up antisense oligonucleotides but then they are usually locked up in the vesicles within the cells. When injection or electroporation introduces the antisense molecules, they may reach the nucleus. The half-life may be less than 5 min and within 10 h half the antisense oligonucleotides are lost. The antisense construct may have a variety of effects on the cells and the observed consequences may be the result of non-antisense type of action. The antisense DNA oligonucleotides usually target the AUG initiator codon, the 5' cap, the first splice acceptor, the polyadenylation, or the translocation breakage point site in cancer. The actively transcribed RNA is a superior target. At the proper dosage the AO have minimal or no effect on normal cells but may be quite effective. (►antisense RNA, ►fruit ripening, ►peptide nucleic acid, ►triple helix formation, ►methylphosphonates, ►phosphoramidate, ►phosphorothioates, ►cancer gene therapy, ►ribonuclease H, ►TFD, ►PKA, ►mixed backbone oligonucleotides, ►aptamer, ►G3139, ►BCL, ►fomivirsen, ►cationic lipid, ►tricyclo-DNA, ►muscular dystrophy; Galderisi U et al 1999 *J Cell Physiol* 181:251; Cotter FE et al 1999 *Biochim Biophys Acta* 1489:97; Kushner DM, Silverman RH 2000 *Curr Oncol Rep* 21:23; Astriab Fisher A et al 2002 *J Biol Chem* 277:22980; Fu C et al 2002 *Anal Biochem* 306:135; Sazani P et al 2002 *Nature Biotechnol* 20:1228.

Antisense Transcript: ►antisense RNA

Antiserum: An antiserum is a blood serum that contains specific antibodies obtained from an animal after natural or artificial exposure to an antigen. Antisera are collected from the blood of fasted animals by centrifugation and allowed to clot at room temperature. The clot is then discarded and the straw-colored

serum may be preserved either by lyophilization and stored at room temperature or at 4° with 0.02% sodium azide or deep frozen at -20° to -70°C. The antisera generally contain polyclonal antibodies.

►antibody polyclonal, ►monoclonal antibody

Antiserum Purification: Of polyclonal antibodies by affinity chromatography on protein A-Sepharose columns. Protein A binds the Fc domain of IgG of various sources but not with equal intensity. Further purification may be obtained by affinity chromatography with an immobilized antigen of high purity. ►antibody purification, ►antibody, ►immunoglobulins

Anti-Shine-Dalgarno Sequence: CCUCC is complementary to the GGAGG Shine-Dalgarno consensus near the 3'-end of the 16S rRNA molecule. ►Shine-Dalgarno

Antisuppression: Inactivates suppressor genes. ►suppressor gene, ►suppressor tRNA

Antitermination: Antitermination permits the RNA polymerase to ignore transcription termination instructions such as bacterial rho and thus proceed through the termination signal. In phage λ , after the transcription of two *immediate early genes*, the RNA polymerase should stop. The switch to transcribe the next set of genes is controlled by gene N, transcribed from the left promoter (PL) and terminated by the rho-dependent tL1 terminator and cro, transcribed from the right promoter (PR) and terminated by the rho-dependent tR1 terminator. The product of the N gene is protein N (pN), an antiterminator that permits readthrough to the delayed early genes in both tL1 and tR1. Although pN has a half-life of about 5 min, transcription is maintained because N is part of the delayed early transcript. Gene Q is also part of the delayed early transcript and its product pQ is also an antitermination protein that allows, by readthrough, the transcription at the late promoter PR. The recognition site for pN is upstream at the N utilization sites, NutL and NutR; the former is near the promoter but the latter is near the terminator. pN can act on both rho-dependent and rho-independent systems. Different phages have different nut sites, yet all these work in a similar manner. The nut elements include boxA and boxB; the former is required for binding the bacterial antitermination proteins, used by phages as well as by bacteria. The boxB is a phage-specific element.

Mutations in bacteria (rpoB) interact with pN. The nus loci (A, B, G) are involved with transcription termination; nus E codes for a protein in the 30S ribosomal subunit (p10). The product of nusA is a general transcription factor interacting with p10 and it affects termination by binding to boxA. Gene nusG organizes the various Nus proteins that together

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control rho-dependent termination, whereas the nusA product combined with pN may interfere with termination where it normally is supposed to take place. In *E. coli* antitermination involves also the ribosomal *rm* genes. This operon has in its leader sequence a boxA where the NusB-S10 protein dimer binds to the RNA polymerase as it passes through. This binding enables pol to continue transcription through the rho-dependent terminators of the transcript. Protein NusA does not bind to the bacterial RNA polymerase when it is associated with the σ factor but after pol attaches to the promoter, σ may be released and that provides an opportunity for transcription and for the formation of the core polymerase-Nus complex. After termination of transcription the pol complex is released from the DNA and the separation of Nus from pol takes place. Thus, the polymerase core enzyme may be in two alternative states, one with σ for transcription and another with Nus with the potential for termination of transcription. Antitermination may then be mediated through pN after the polymerase binds Nus. Gene Q of phage λ also has a role to play in antitermination by permitting, through its product, the passage over the terminator signals. Transcription is modulated by preventing termination of transcription at T-rich sequences that occur at random within the gene, but they dissociate the RNA polymerase from the DNA when it arrives at the T-rich region at the end of the gene and where termination of transcription is expected. Other antitermination (attenuation) proteins act in the amino acid operons of bacteria, and allow the expression of the operon only after the protein that mediates attenuation of transcription is made. Thus, attenuation is not always dependent on the presence of an excess of charged specific tRNAs that slow down transcription when the supply of this particular amino acid is sufficient. In eukaryotes the Pol II-transcribed U1-RNA is involved in proper processing of the 3'-ends of the RNA used for reinitiation of transcript elongation. ▶attenuation, ▶RNA polymerases, ▶rho, ▶lambda phage, ▶half-life, ▶rm, ▶transcription, ▶ σ transcription termination in prokaryotes, ▶T box, ▶terminator, ▶transcription termination in eukaryotes, ▶rho factors, ▶tryptophan operon, ▶hut ▶operon; Mason SW, Greenblatt 1992 J Biol Chem 267:19418; Yarnell WS, Roberts JW 1999 Science 284:611, Grundy FJ et al 2002 Proc Natl Acad Sci USA 99:11121.

Antithrombin (AT-III, 1q23-q25): Is an α -globulin, neutralizing the blood clotting contribution of thrombin. Antithrombin—especially when cleaved at the COOH-terminal loop—blocks angiogenesis and tumor development. ▶thrombin, ▶blood clotting pathways, ▶antihemophilic factors, ▶protein C,

▶protein S, ▶dysfibrinogenemia, ▶angiogenesis, ▶anticoagulation

Antitoxin: ▶immunization

Antitrypsin Gene (AAT or PI): In the human chromosome 14q32.1 prevents the activity of the protease trypsin and elastase. The α -antitrypsin gene is supposed to be involved in pulmonary emphysema (increase of lung size because dilatation of the alveoli [the small sacs] of the lung) and liver disease. Different mutations may lead to one or the other, or to both of these diseases. The so-called Z mutant group prevents the exit of the AAT protein from the liver, where it is synthesized, and as a consequence the liver disease (cirrhosis) appears. Smoking may increase the chances of the development of cirrhosis in the individuals of ZZ genotype by 3 orders of magnitude. The incidence of AAT deficiency is about 8×10^{-4} in the white population of the USA. The total length of the α -antitrypsin gene is 10.2 kb with coding sequences of 1,434 bp. Oral administration of 4-phenylbutyric acid facilitates the release of AAT from the endoplasmic reticulum and as a “chemical chaperone,” may prevent the injuries resulting from AAT deficiency. The 14q32 chromosomal site includes the serpin gene encoding the corticosteroid-binding globulin (CBG) and a DNase-1 hypersensitive site. The AAT gene can be inserted into sheep eggs and under favorable conditions the milk may contain the protein it encodes. ▶emphysema, ▶cirrhosis of the liver, ▶liver cancer, ▶endoplasmic reticulum, ▶serpin, ▶corticosteroid, ▶DNase hypersensitive site, ▶acquired immunodeficiency; Crystal RG 1989 Trends Genet 5:411; Brigham KL et al 2000 Hum Gene Ther 11:1023.

Antivector Cellular Immunity: Antivector cellular immunity in a vaccination may cause a serious problem if the vector, e.g., adenovirus, occurs in the population and if the animal/human cells have already developed antibodies against a particular serotype, thereby diminishing the effectiveness of such a vector. Antivector immunity can be circumvented by the use of a chimeric vector. In a novel vector the hypervariable region of the rare adenovirus serotype Ad48 replaced, in a rAd5 adenovirus-derived vector, the seven short hypervariable regions of the Ad5 hexon protein. The engineered vector expressed well the simian HIV Gag protein in naïve mice and rhesus monkeys and it did not show neutralizing suppression. Such a construct may open a new approach to vaccination and gene therapy (Roberts DM et al 2006 Nature [Lond] 441:239). ▶human gene transfer, ▶gene therapy, ▶HIV, ▶acquired immunodeficiency, ▶hexon

Antiviral Antibodies: Result when immunization against some viral diseases is not fully successful. Monoclonal (or enriched polyclonal) antibody therapies have been considered against human respiratory syncytial virus (RSV), rabies, hepatitis B and C, herpes simplex viruses, cytomegalovirus and acquired human immunodeficiency (HIV). These preparations may be administered intramuscularly. ► **monoclonal antibody therapies**

Antiviral Protein: Zinc-finger anti-viral protein (ZAP) is a host antiviral factor that specifically inhibits the infection of cells by Moloney murine leukemia and multiple members of the alphavirus family, including Sindbis virus (SIN). An overexpression of ZAP prevents the accumulation of the viral RNA in the cytoplasm. The N terminus of ZAP contains four CCCH-type zinc-finger motifs. ZAP binds directly to specific viral RNA sequences through these zinc-finger motifs. The target sequence of ZAP in MLV was mapped to the 3'-LTR, and the target sequences in SIN were mapped to multiple fragments, but no obvious common motifs have been found in these sequences yet. Particularly, ZAP does not target ARE-containing mRNAs. Despite the lack of primary sequence homology, ZAP shares considerable similarities with tristetraproline (TTP). Both ZAP and TTP directly bind to their cognate target RNAs, and the zinc-finger motifs are required for the binding. ZAP directly interacts with the exosome, and it seems that ZAP destabilizes RNA by directly binding to the target RNA and recruiting the exosome to degrade the target RNA. Type I interferons (IFNs) play an essential role in the host response to viral infection through the induction of numerous IFN-stimulated genes. IFN-stimulated gene 15 (ISG15) is an ubiquitin homolog that is rapidly up-regulated after viral infection, and it conjugates to a wide array of host proteins. It appears to be a novel antiviral molecule with activity against both RNA and DNA viruses and can provide a target for the development of therapies against important human pathogens

(Lenschow DJ et al 2007 Proc Natl Acad Sci USA 104:1371). ARE, ► **exosome**, ► **tristetraproline**, ► **zinc finger**; (Guo X et al 2007 Proc Natl Acad Sci USA 104:151).

Antiviral siRNA Design Tool: ► **RNAi**; <http://sivirus.mai.jp/>.

Antizymes: Antizymes are proteins that bind to enzymes and direct their degradation by proteasomes without ubiquitin (see Fig. A101). The proximal or distal products of the enzymes they inhibit induce their synthesis. Antizymes regulate polyamine enzymes such as ornithine decarboxylase. Antizyme (AZ) ornithine decarboxylase (ODC) fusion proteins provide the means of targeted protein destruction by proteasomes without prior ubiquitination (Matsuzawa S-i et al 2005 Proc Natl Acad Sci USA 102:14982; see diagram redrawn). ► **proteasome**, ► **polyamines**, ► **ubiquitin**; Coffino P 2000 Proc Natl Acad Sci USA 97:4421; Chattopadhyay MK et al 2001 J Biol Chem 276:21235.

Antley-Bixler Syndrome (trapezoidocephaly-synostosis syndrome): Is a defect in bone formation, abnormality of the face and other developmental anomalies due to mutation in the fibroblast growth factor receptor 2 (FGFR2) gene. ► **craniosynostosis syndromes**, ► **fibroblast growth factor**, ► **Apert or Apert-Crouzon syndrome**

Anucleate: Is a cell after the nucleus has been removed. ► **cytochalasins**, ► **cytoplasm**, ► **nuclear transplantation**

Anus: Is the end opening of the intestinal tract.

Anxiety: In mice, glyoxylase 1 and glutathione reductase 1 seem to regulate this condition (Hovatta I et al 2005 Nature [Lond] 438:662). ► **stress**, ► **phobia**, ► **panic disorder**, ► **panic obsessive disorder**, ► **BDF**

Aorta: Is the main arterial vein (carrying blood away from the heart) originating in the left heart ventricle

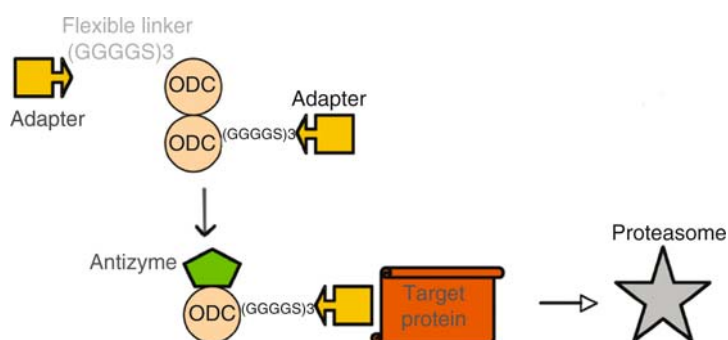


Figure A101. Antizyme

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and passing through the chest and abdomen.
 ►coarctation of the aorta

Aortic Stenosis: ►coarctation of the aorta

Aotus: owl monkey ►cebidæ

AP: ►amino purine, ►base analog mutagen

AP1, AP2, AP3, AP4, AP5 (activated protein): Is a group of transcription factors. AP1 is similar to the one coded for by the chicken virus, oncogene *v-jun*. The human gene at chromosomal location 1p32-p31 shows 80% homology to the avian viral protein gene; their binding is greatly enhanced by the *fos* oncogene. AP1 generally appears as a heterodimer of Jun and FOS and Fra1n yeast AP1 has a homolog, GCN4, and the mammalian homolog is TFIID. The yeast and their mammalian factors can substitute for each other. This family of genes encodes the AP transcription factors where the binding motif is well conserved but other sequences may vary. These proteins bind to 5'-TGANTCA-3' consensus in DNA. AP2 binds only to TC-II but not to TC-I of the two identical and adjacent TC motifs (5'-TCCCCAG-3') upstream in the promoter of eukaryotic genes. AP2 binding affects enhancer activity. AP2 is an essential morphogenetic factor; in its deficiency head development is impaired. AP2 seems to have negative control on the cell cycle possibly by activation of p21 protein. AP3 binds to TC-II and to the adjacent GT-I motif (5'-G[C/G]TGTGGA[A/T]TGT-3') and also to the so-called core enhancer sequence (5' -GTGG[A/T][A/T][A/T]G-3') that is similar to parts of viral and prokaryotic enhancers but does not function by itself alone. AP4 binds to the 5'-CAGCTGTGG sequence that partially overlaps the GT-II motif (that is identical to GT-I, except two bases). AP5 binds to GT-II and adjacent sequences (5'-CTGTGGAATGT-3') and it is present in some cell types but not in others. The mouse Jun genes (chromosomes 4 and 8) are inducible by serum and the phorbol ester, 12-o-tetradecanoyl phorbol 13-acetate (TPA). The AP loci of *Arabidopsis* are completely different and mean apetala, a defective flower type.
 ►oncogenes, ►transcription factors, ►adaplin, ►ep-sin, ►endocytosis, ►Jun, ►Fos, ►Fra, ►PC4; Shaulian E, Karin M 2002 Nature Cell Biol 4:E131.

AP180 (assembly protein): Mediates the assembly of clathrin for endocytosis. It is built of four adaptin proteins (100, 100, 50, 25 kDa, respectively).
 ►endocytosis

AP Endonucleases (APE): APE are basically repair enzymes, in both prokaryotes (2 enzymes) and eukaryotes (encoded in humans by HAP1m BAP1, APE/APEX) that cut DNA 5' or 3' to modified (alkylated or otherwise mutated) DNA bases or at apurinic and apyrimidinic sites from where

glycosylases have already removed damaged purines or pyrimidines. Usually the first step is the recognition of the altered bases and the DNA sequence is cut in the vicinity. Then the exonuclease activity removes the damaged section and creates a gap. After that a repair synthesis adds the correct bases to the 3'-OH ends, using the undamaged strand of the double helix as a template. Ligation by covalent bonds restores the integrity of the DNA. The glycosylases have some specificity for deaminated cytosine residues; the uracil-*N*-glycosylase removes uracil residues and the hypoxanthine-*N*-glycosylase removes hypoxanthines formed by deamination of adenine. These endonucleases have thus antimutator activities. The eukaryotic DNA uses pol β or pol δ and pol ϵ for filling the gap. ►antimutator, ►DNA repair, ►glycosylases, ►DNA polymerases, ►AP site; Sobol RW, Wilson SH 2001 Progr Nucleic Acid Res Mol Biol 68:57.

AP lyase: Releases apurinic and apyrimidinic sites from the DNA. ►apurinic site, ►apyrimidinic site, ►DNA repair

AP Site: ►apurinic site, ►apyrimidinic site

Apaf-1 (apoptotic protease activating factor/CED4): Interacts with caspase-9 after being activated by a cytochrome c and dATP. Then caspase-3 triggers the process of apoptosis. Somehow, the caspase-3 is linked to an endonuclease that cuts up chromosomal DNA in the cells destined for apoptosis. The Apaf gene (and some others) may be disabled by methylation and then apoptosis is interfered with and the road opens up to carcinogenesis, as it happens in chemotherapy-resistant metastatic melanoma. ►caspase, ►apoptosis, ►AIF, ►melanoma, ►Crohn disease, ►Huntington's disease; Bratton SB et al 2001 EMBO J 20:998; Soengas MS et al 2001 Nature [Lond] 409:207; molecular structure; Riedl SJ et al 2005 Nature [Lond] 434:926.

Apandry: Is the development of a diploid fruiting body of fungi by the fusion of two female nuclei, without the involvement of any male gamete.

APC: ►antigen presenting cell, ►Gardner syndrome, ASE1

APC: (anaphase-promoting complex; also called cyclo-some): It is a ~13-subunit, ~1700-kDa ubiquitin ligase protein complex containing CDC27, CDC16, CDC23, CDC26, Apc1p, Apc2p, Apc4p, Apc5p, APC9, APC10/DOC, Apc11p, Apc13 and bimE. APC is required for the progression from metaphase to anaphase. It is regulated by CDC20 and CDH1 in humans, *fzy* and *fzr* in *Drosophila* and the APC complex mediates ubiquitination of the superfluous cyclins and anaphase-inhibitory proteins such as

securin. Securin is required for the prevention of the separation of sister-chromatids until there is a firm association with the mitotic spindle fibers. Premature separation may result in aneuploidy. Protein Rael–Nup98 complex regulates securing degradation (Jeganathan KB et al 2005 Nature [Lond] 438:1036). This degradation is a requisite for exiting from each phase of the cell cycle and for entry into the next one. APC recognizes a 9 amino acid destruction box at the N-terminus of cyclins and some other proteins such as Pds1p/Cut2p anaphase inhibitors of yeasts or the spindle protein Ase1. ▶cell cycle, ▶CDCs, ▶bimE, ▶CDC20, ▶CDH1, ▶PDS, ▶ubiquitin, ▶E2, ▶Rbx1, ▶mitotic exit, ▶SCF, ▶tetra-trico sequences, ▶cullin, ▶SIC1, ▶PDS, ▶CDH, ▶D box, ▶sister chromatid cohesion, ▶securin, ▶separin, ▶nucleoporin, ▶Mnd2, ▶MPF, ▶substrate ordering, ▶Evi oncogene; Page AM, Hieter P 1999 Annu Rev Biochem 68:583; Schwab M et al 2001 EMBO J 20:5165; Peters J-M 2002 Mol Cell 9:931; Burton JL et al 2005 Mol Cell 18:533.

APC (activated protein C): Mediates cleavage and inactivation of antihemophilic factors Va and VIIIa with the cooperation of protein S. Its mutation which conveys resistance to blood coagulation may increase the risk of thrombosis by 5–10 fold and is the most common genetic cause of thrombosis. ▶protein C, ▶protein S, ▶antihemophilic factors, ▶thrombosis

APC: ▶adenomatous polyposis coli

APE: A apurinic/apyrimidinic endonuclease which recognizes these sites and cleaves the nucleic acid backbone as part of the repair function. APE activity is essential for cellular viability (Fung H, Demple B 2005 Mol Cell 17:463). ▶excision repair; Gros L et al 2004 Nucleic Acids Res 32:73.

APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy): Is a human autoimmunity syndrome involving a Zn-finger-like protein (a transcription factor) encoded in chromosome 21q22.3 by the gene called AIRE (autoimmune regulator). It also affects diabetes. ▶autoimmune disease, ▶Zinc fingers

Aperiodic Crystal: Is the term used for the chromosome by the physicist Erwin Schrödinger in 1944. (See Stent GS 1995 Ann NY Acad Sci 758:25)

Apert or Apert-Crouzon Syndrome: Involves acrocephaly (top of the head pointed), syndactyly (fingers fused) and mental retardation, although some individuals have near normal intelligence (see Fig. A102). The symptoms vary. Many of the cases are sporadic, in others, autosomal dominant inheritance is most likely; chromosomal rearrangement may also



Figure A102. Syndactyly. (From Bergsma, D. 1973 Birth Defects. By permission of the March of Dimes Foundation)

be present in some cases. This condition may also be caused by a defect in FGFR2 (fibroblast growth factor receptor), a protein tyrosine kinase, encoded at 10q25-q26. An insertion of an Alu element in the gene results in an alternately spliced keratinocyte growth factor receptor (KGFR). It is allelic to the Crouzon and Pfeiffer syndromes. ▶syndactyly, ▶mental retardation, ▶craniosynostosis syndromes, ▶Crouzon syndrome, ▶Pfeiffer syndrome, ▶Jackson-Weiss syndrome, ▶tyrosine kinase receptor

Apes: Closest to humans among animals. The human non-repetitive DNA sequences appear 98.7% identical to that of chimpanzees and 98.38% to that of gorillas. ▶primates, ▶chimpanzee; Hacia JG 2001 Trends Genet 17:637.

Apex: Refers to the top part of a cell, organ or any structure. The shoot apex of plants gives rise to the leaves, stem and inflorescence. The topless (*tpl-1*) dominant negative mutation of *Arabidopsis* transforms the apex into a root pole by suppressing transcription (Long JA et al 2006 Science 312:1520). ▶apical, ▶meristem

Apex: ▶arrayed primer extension

APH: Aminoglycoside phosphotransferases are enzymes phosphorylating aminoglycoside antibiotics, resulting in resistance to the antibiotics when the enzyme is present (introduced by transformation). ▶APH[3']II, ▶antibiotics, ▶aminoglycosides

APH(3')II: The aminoglycoside phosphotransferase enzyme inactivates kanamycin, neomycin and geneticin, commonly used antibiotic resistance markers for

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transformation in tissue culture; synonymous with NPTII. ►aminoglycoside, ►antibiotics

Aphakia: A rare abnormality of the development of the embryonal lens caused by homozygosity of the human gene (1p32) FOXE3 (Valleix S et al 2006 Amer J Hum Genet 79:358). ►eye diseases

Aphasia: Aphasia is a form of brain injury resulting in the partial or complete inability to speak/understand language. About two-dozen human gene loci in several chromosomes may be responsible for aphasia. ►MASA syndrome

Apheresis: The separation of certain component(s) of a patient's blood and reinfusion of the remainder.

Aphidicolin: A tetracyclic diterpene of fungal (*Cephalosporium*) origin capable of blocking cell division and of antiviral activity; it is an inhibitor of DNA polymerase α , δ and ϵ (see Fig. A103) (Wright GE et al 1994 FEBS Lett 341:128). ►pol, ►terpenes

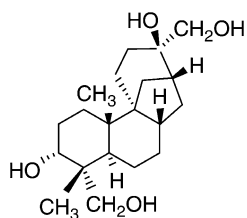


Figure A103. Aphidicolin

Aphids (*Aphididae*, homoptera): Aphids are small sucking insects and parasites of almost all plant species (see Fig. A104). At the site of the infestation the plants secrete honeydew that may attract other types of insects. They reproduce sexually at the end of the growing season after the males have differentiated. During the rest of the year only the females are found. The females reproduce parthenogenetically and their ca. 20 generations produce daily three to seven nymphs. Thus, the progeny of a single individual may run into billions during the year. Besides the direct damage by sucking, they spread viral diseases of plants. They can be controlled by contact or systemic insecticides. Aphids harbor 60–80 large cells (bacteriocytes), which contain the symbiotic *Buchnera* bacteria with ~100 copies of a genome of 640,681 bp. The bacteria supply essential amino acids to the aphids and rely on the host for cell-surface molecules, regulator genes and defense. The genotype of the symbiotic bacterium *Hamiltonella defensa* determines the degree of resistance of pea aphids (*Acyrtosiphon pisum*) to parasitoid wasp *Aphidius ervi* (Oliver KM et al 2005 Proc Natl Acad Sci USA 102:12795). In addition to the most common *Buchnera*, several other

bacterial species may cohabit with aphids and some are transmitted to the female by copulation and subsequently transmitted by the females during parthenogenetic reproduction (Moran NA, Dunbar HE 2006 Proc Natl Acad Sci USA 103:12803). ►parthenogenesis, ►parasitoid, ►biological control; Abbot P et al 2001 Proc Natl Acad Sci USA 98:12068.

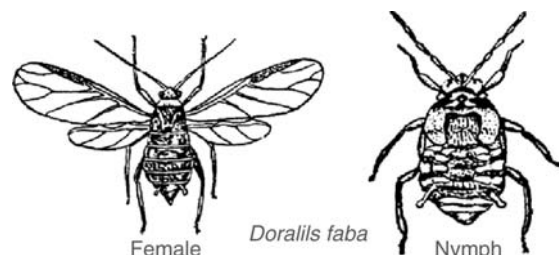


Figure A104. Aphids

Aphrodisiac: Aphrodisiacs are compounds that stimulate sexual interest. ►yohimbine

Apical: Indicates top position. ►apex

Apical Dominance: Apical dominance is the phenomenon whereby the main central stem of the plant is dominant over (i.e., grows more strongly than) other side stems, and on a branch, the main stem of the branch is further dominant over its own side branchlets. The terminal bud of the main stem of a plant prevents or suppresses the formation of lateral buds or branches by auxin although auxin does not enter the lateral bud. In *Arabidopsis* the flavonoid pathway represses lateral outgrowth by diminishing the expression of auxin transporters in the stem and bud (Lazar G, Goodman HM 2006 Proc Natl Acad Sci USA 103:472).

Apical Ectodermal Ridge (AER): AER refers to the group of cells at the tip of the limb bud, involved in the differentiation of the limbs of animals. ►ZPA, ►morphogenesis, ►organizer

Apicomplexan Plastid: ►apicoplast

Apicoplast (apicomplexan plastid): An apicoplast is an acquired ~35 kb DNA-containing plastid type body (from endosymbiosis by green algae) in several parasites (e.g., *Toxoplasma*, *Plasmodium*). The *Plasmodium falciparum* apicoplast contains about 466 proteins, which are mainly nuclear encoded and imported with the aid of signal peptides and transit peptides. The apicoplast has an as yet undefined essential role in the survival of the parasite and can be targeted by antibiotics as a measure of defense. The 9.1 Mbp *Cryptosporidium parvum* genome (3,807 genes) has been sequenced. This intestinal parasite

has no apicoplast and its degenerate mitochondria has lost its genome (Abrahamsen MS et al 2004 Science 304:441). ▶[signal peptide](#), ▶[transit peptide](#), ▶[toxoplasmosis](#), ▶[microneme](#), ▶[rhoptry](#); Wilson RJM 2002 J Mol Biol 319:257; Foth BJ et al 2003 Science 299:705; Ross DS 2005 Science 309:72. *Cryptosporidium*, *Plasmodium* and *Toxoplasma* database: <http://ApiDB.org>.

Apigenin: A flavone plant pigment.

Apis mellifera (honeybee): The *Apis mellifera* refers to social insects with three types of individuals: diploid egg-laying queen ($2n = 32$), haploid drones, and sexually undifferentiated diploid workers. The drones hatch from unfertilized eggs. The difference between the queen and the workers is due to different nutrition of the larvae. ▶[arrhenotoky](#), ▶[honey bee](#); Robinson GE et al 1997 Bioessays 19:1099; mapping: Solignac M et al 2007 Genome Biol 8(4):R66; HGS 2006 Nature [Lond] 443:931.

Aplasia: Failure of the development of an organ or a type of tissue.

Aplastic Anemia: Aplastic anemia is a condition of several blood diseases where the bone marrow may not produce the cellular elements of the blood. ▶[anemia](#), ▶[Duncan syndrome](#)

Aplysia: Refers to a sea mollusc, an invertebrate small animal, frequently used for behavioral and memory studies. Hawkins RD et al 2006 Biol Bull 210:174.

APM: Affected—pedigree-member or APM is used in determining identity by descent and as a non-parametric method to detect linkage. ▶[IBD](#)

Apnea (familial obstructive sleep, snoring): Apnea is a breathing disorder of any age; it is also responsible for sudden infant death. The genetic basis for apnea is unclear. The composer Johannes Brahms might have been afflicted by it. ▶[narcolepsy](#); Palmer LJ et al 2003 Am J Hum Genet 72:340.

AP01: ▶[Fas](#)

Apo-2: ▶[TRAIL](#)

Apoaequorin: ▶[aequorin](#)

ApoBec1: Developmentally active, tissue-specifically distributed deaminase of 5-methyl-cytosine into uracil. ▶[AID](#)

APOBEC (apolipoprotein B mRNA-editing complex, CEM15): A cellular protein in defense against infection by single-strand RNA viruses (HIV, MLV, etc.). The eight genes are in human chromosome 22q12-q13. The protein packaged into the virion has a deaminase activity and changes the viral code

by converting C residues to U during reverse transcription. It also increases mutation of C/G → T/A (Schumacher AJ et al 2005 Proc Natl Acad Sci USA 102:9854). HIV fights this defense by suppressing its synthesis with the help of the Vif viral proteins. APOBEC3G deaminase is encapsulated by the HIV virion and facilitates restriction of HIV-1 infection in T cells (see Fig. A105). It binds at random to single-strand DNA and then jumps and slides processively to deaminate the CCC target motif. Sliding is lost when it encounters double-strand DNA but it continues jumping. Deamination is mainly in 3'→5' direction (Chelico L et al 2006 Nature Struct Mol Biol 13:392). Apobec also inhibits retrotransposition of endogenous retroviruses, LINE-1 elements and Alu sequences, which would still have the ability to move in the mouse genome (Esnault C et al 2005 Nature [Lond] 433:430; Bogerd HP et al 2006 Proc Natl Acad Sci USA 103:8780). The crystal structure of APOBEC-2 has been determined (Prochnow C et al 2007 Nature [Lond] 445:447). ▶[HIV](#), ▶[MLV](#), ▶[reverse transcription](#), ▶[retroviruses](#), ▶[LINE](#), ▶[retroviral restriction factors](#), ▶[AID](#); Gu Y, Sundquist WI 2003 Nature [Lond] 424:21; Zhang H et al 2003 Nature [Lond] 424:94; Harris RS, Liddament MT 2004 Nature Rev Immunol 4:868; Ribeiro AC et al 2005 J Virol 79:823; Turelli P, Trono D 2005 Science 307:1061.

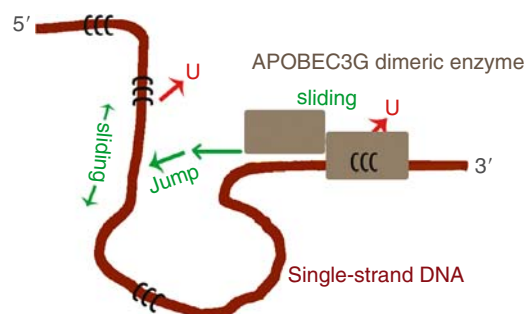


Figure A105. APOBEC3G jumping and sliding during deamination

Apocrine Gland: The tip of the secreting organ is cast off with the secretion.

Apocytochrome B Gene (cob): Located in mitochondrial DNA of yeast; cytochromes are heme-containing proteins involved in electron transport. ▶[mitochondrial genetics](#), ▶[mtDNA](#)

ApoE: ▶[apolipoprotein](#)

Apoenzyme: The enzyme protein without the co-factors required for activity.

A

Apoferritin: The protein part (M_r 460,000) of ferritin, it contains ferric hydroxide clusters. About 20–24% of it is iron. Ferritin is the most readily available iron storage facility in the body. ► [ferritin](#)

Apogamety (apogamy): Embryo formation without fertilization from a cell of the embryo sac, other than the egg cell. ► [apomixis](#)

Apoinducer: DNA binding protein that stimulates transcription. ► [transcription](#)

Apolar: Molecules are generally insoluble in water because they do not have symmetrical positive and negative charges.

Apolipoproteins: Lipid-binding proteins in the blood that transport triglycerols, phospholipids, cholesterol and cholesteryl esters within the body. Apolipoproteins are not only the most important parts of the high-density lipoprotein (HDL), but are also preferred in order to lower the risk of coronary heart disease. Different classes are distinguished (APOA1, human chromosome 11q23.2-qter and mouse chromosome 9), APOA2 (1q21-q23), APOC2 (19q13.2), APOC3 and APOA4 are in the same region. APOA1 protects against cardiovascular disease by combination with high-density lipoproteins. Its crystal structure is known (Ajee AA et al 2006 Proc Natl Acad Sci USA 103:2126). Apolipoprotein B (human chromosome 2p24) exists in two lengths due to different editing of the transcript. APOC cluster is in human chromosome 19q13.2 and APOE appears to be linked to it. APOE deficiency causes hyperlipidemia and atherosclerosis. APOE isoform E4 is involved in dementia associated with HIV infection and Alzheimer's disease. ApoE ϵ 4 allele increases the risk of Alzheimer's disease whereas allele ϵ 2 lowers the risk (Dodart J-C et al 2005 Proc Natl Acad Sci USA 102:1211). Some other apolipoproteins are genetically less well defined. Apolipoprotein A-IV may protect against atherosclerosis without an increase of HDL levels. Apolipoprotein B deficiency lowers male fertility in knockout mice. Apolipoprotein L-1 is a high-density apolipoprotein bound particle that kills *Trypanosoma brucei brucei*, except subspecies *T. b. rhodesiense* and *T. b. gambiense*. Its killing effect is based on M60-W265 region, which is homologous to bacterial colicins and it lyses holes in lysosomal membranes (Pérez-Morgan D et al 2005 Science 309:469). ► [cholesterols](#), ► [fatty acids](#), ► [atherosclerosis](#), ► [arteriosclerosis](#), ► [HDL](#), ► [hyperlipidemia](#), ► [hypobetalipoproteinemia](#), ► [hyperlipoproteinemia](#), ► [abetalipoproteinemia](#), ► [lipoprotein lipase](#), ► [cholesterol](#), ► [megalin](#), ► [Alzheimer's disease](#), ► [AIDS](#), ► [Tangier disease](#), ► [hypo- \$\alpha\$ -lipoproteinemia](#), ► [Trypanosomatids](#); Mahley RW, Rall SC Jr 2000 Annu Rev Genomics Hum Genet 1:507;

Pennachio LA et al 2001 Science 294:169; Davidson WS, Thompson TB 2007 J Biol Chem 282:22249.

Apomeiosis: Gamete development without a meiotic process. ► [meiosis](#), ► [apomixis](#)

Apomict: A plant which reproduces by apomixis. ► [apomixis](#), ► [Rosa canina](#)

Apomixia: Parthenogenesis, common in *Caenorhabditis elegans*, bees, wasps, aphids, in some crustacea, lizards, isopoda, lepidoptera, etc.; it does not occur in humans. ► [parthenogenesis](#), ► [apomixis](#)

Apomixis: Embryo (zygote) development without fertilization in plants and fungi. It occurs regularly in certain species, e.g., in the polyploid *Festuca*, hawkweeds (*Hieracium*), etc. Some apomicts reproduce sexually after doubling the chromosome number. Apomicts may make possible the fixation of heterozygous condition. Apomixis may be genetically very different from somatic embryogenesis. If apomixis is preceded by meiosis, and the egg parent was heterozygous, segregation may occur among the apomictic progeny. In aposporous apomixes, the megagametophyte develops from a somatic cell of the ovule. ► [parthenogenesis](#), ► [apomixia](#), ► [apogamety](#), ► [agamospermy](#), ► [androgenesis](#), ► [Hieracium](#); Koltunov AM 1993 Plant Cell 5:1425; van Dijk O, van Damme J 2000 Trends Plant Sci 5:81; Grimanelli D et al 2001 Trends Genet 17:597.

Apomorphic: A species trait evolved from a more primitive state of the same. ► [plesiomorphic](#), ► [symplesiomorphic](#), ► [synapomorphic](#), ► [autapomorphy](#)

Apopain (caspase 3, human chromosome 4q35): ► [apoptosis](#)

Apoplast: Intercellular material of plants. (Sattelmacher B, Horst W (eds) 2007 Springer Berlin, D.)

Apoptosis (programmed cell death, PCD): The cells and the nuclei shrink and are generally absorbed after fragmentation. Apoptosis is an indispensable process for the majority of organisms. Unneeded cells are disposed of, room is made for differentiated cells and it is a safeguard against cancerous growth. A generalized outline of the apoptotic cell death pathway is presented here. Ceramide is one of the regulatory molecules of the process. Tumor necrosis factor (TNF) is an inducer of apoptosis. The metabolites of ceramides, sphingosine and sphingosine-1-phosphate prevent the symptoms of apoptosis. These two molecules are supposedly second messengers for cell proliferation mediated by platelet-derived growth factor. The activation of protein kinase C brought about by sphingosine kinase and the increase of the level of sphingosine-1-phosphate inhibits the ceramide-mediated apoptosis. The latter molecules also stimulate the ERK-controlled

reactions and inhibit the stress-activated kinases SAPK/JNK. In *Caenorhabditis* more than a dozen *ced* (cell death) genes have been identified. Ced3 protein is an interleukin-1 converting (ICE) cysteine protease enzyme, involved in ceramide production. Ced9 is a suppressor of cell death and EGL-1 releases the suppression and CED-tetramer facilitates the conversion of the CED-3 zymogen (enzyme precursor) to an active CED-3, which brings about cell death. The apoptotic pathway mediated by CED-3 is illustrated after Yan N et al 2005 Nature [Lond] 437:831. CED-9 has 23% identity to the human oncogene BCL-2, controlling follicular lymphoma. If this human gene is transfected to the nematode it suppresses apoptosis, indicating that the same function is controlled over a wide evolutionary range (see Fig. A106).

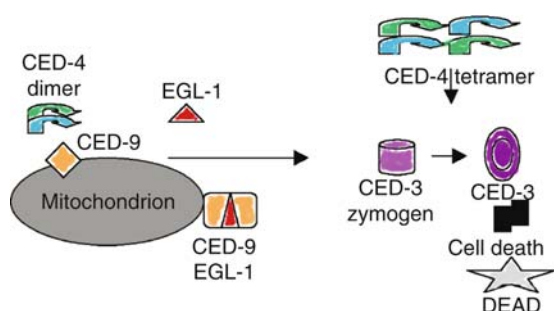


Figure A106. Death pathway CED-3

The *reaper* gene (*rpr*) of *Drosophila* is an activator of apoptosis and it is homologous to *ced-3* of *Caenorhabditis*. Another *Drosophila* gene, *hid* (*head-involution defective*), is linked to *reaper*. The 65-amino acid RPR protein has similarity to the “death domain” of the tumor necrosis factor receptor (TNFR) family. TNFR1 and Fas induce cell death when activated by ligand binding or when over-expressed. Other death receptors are DR3 (Ws1, Apo3, TRAMP, Lard) and Dr4. They may directly connect to the Fas-associated death domain (FADD/MORT1) or to the tumor necrosis factor-associated death domain receptor (TRADD). FADD recruits procaspase 8. TRAIL is another killer protein for which DR3 and Dr4 serve as receptors. Curiously, the latter receptors are present in non-apoptotic cells. The lack of killing effect in these cells is explained by other TRAIL receptors TRID (TRAIL receptor without an intracellular domain) or DcR1 (decoy receptor 1). These receptors have glycopospholipid anchored cell surface portions that trap TRAIL but do not allow the transfer of the death signal to FADD and actually function as a decoy preventing the death signal transduction even for Dra3 and Dra4. The dead cells are disposed of generally by the macrophages without producing inflammation in the tissue. The

apoptotic cells are recognized generally by the altered sugar groups or phosphatidylserine on their surface. The phagocytes recognize apoptotic cells by their phosphatidylserine receptors (PSR). The absence of PSR during early mammalian organogenesis results in respiratory and brain anomalies (Li MO et al 2003 Science 302:1569; Wang X et al 2003 Science 302:1563). The macrophage secretes an extracellular protein, thrombospondin, which recognizes apoptotic cells. The *Alg-2* (apoptosis-linked gene) encodes a Ca^{2+} -binding protein that is required for T cell receptor-, Fas- and glucocorticoid-induced apoptosis. *Alg-3* is a homolog of Alzheimer’s disease gene, which is basically a senescence gene. Apoptosis may be a very natural response of the cells to be disposed when no longer needed. In some cancers the proliferation is not under control because regulators of the process go awry. The baculovirus apoptosis inhibitor proteins (Cp-IAP and Op-IAP) as well as neuronal apoptosis inhibitor proteins (NAIP), located in human chromosome 5q13.1, are defective or deleted in spinal muscular atrophy. BAX is a heterodimeric protein that works in the opposite direction as BCL2 (chronic lymphocytic leukemia, B cell). The gain of function BAX mutations, knockouts were viable but in the lymphocyte cell lineages apoptosis was induced. In other cell lineages hyperplasia was observed. Thus, the BAX expression depends on the cellular context. The wild type BCL2 gene functions similarly to *Ced-9* of *Caenorhabditis*, i.e., it suppresses apoptosis. The enzyme apopain, cleaving poly(ADP-ribose) polymerase (PAR) is also necessary for apoptosis to proceed. Apopain is generated from the proenzyme called CPP32, a protein related to ICE and CED-3. Lymphocyte apoptosis may be mediated by Type 3 inositol 1,4,5-trisphosphate receptor in the plasma membrane by promoting the influx of calcium. Apoptosis of neurons is mediated by the activation of JNK (JUN [oncogene] NH2-terminal kinase) in a process opposing the effect ERK (extracellular signal-activated kinase) in the absence of the nerve growth factor (NGF). The p35 protein of the baculovirus *Autographa californica* has similar antiapoptotic property for insects as well as for mammals as the *Ced-9* gene product of *Caenorhabditis*. *Ced-9/Bcl-2* gene product inhibits both the apoptosis promoting and protecting effects of the *Ced-4/Apaf-1* products. CED-4 interacts with CED-3 and they oligomerize. Their oligomers may associate with BCL and this results in processing (in the presence of ATP) of CED-3 leading to cell death. In order to activate the death pathway the EGL-1 protein stops the interaction of CED4-CED3 with BCL. CED-10/RAC1 mediates the removal of apoptosed cells through actin reorganization (see Fig. A107). (Kinchin JM et al 2005 Nature [Lond] 434:93).

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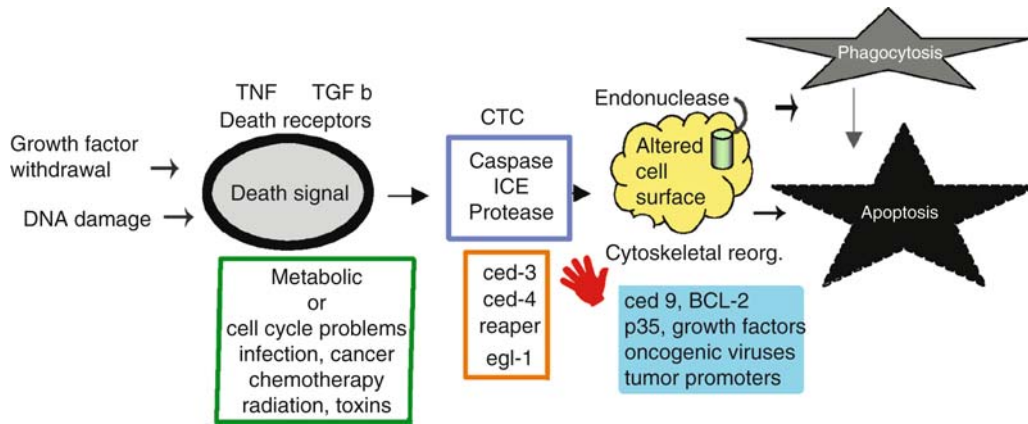


Figure A107. Pathway to apoptosis and its inhibition

Ced-9 is homologous to the mammalian BCL-2. *Ced-3* and *Ced-4* are considered to be promoters of apoptosis. Actually, *Ced-4* has two transcripts; the short transcript promotes apoptosis whereas the long transcript is somewhat protective. Excessive manifestation of *ced-4L* can actually prevent programmed cell death. It is interesting to note that the structurally unrelated *BCL-x* and *Ich-1* genes are also involved in apoptosis, similarly to *Ced-4*, all have two alternative transcripts. This indicates that RNA splicing may have an important role in programmed cell death.

Before caspase could be fully functional *ced-4* moves from the mitochondrion to a perinuclear location. The basic leucine zipper proteins (bZIP) PAR (proline and acid rich) and other members of the protein family can also control apoptosis. PAR mediates cytochrome c release during apoptosis by remodeling mitochondrial cristae with the aid of the dynamin-related protein OPA1 (Cipolat S et al 2006 Cell 126:163; Frezza C et al 2006 Cell 126:177).

Inappropriate activation of apoptosis may be involved in diseases such as AIDS, degeneration of the nervous system (Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, retinitis pigmentosa), constriction or obstruction of the blood vessels (ischemic stroke), anemias, liver diseases, autoimmune diseases, etc. The diagram given here is modified after Thompson CB 1995 Science 267:1456.

Recently, the generic name CASPASE has been suggested (c for cysteine protease, aspase for cleaving at aspartate) for the ICE-*ced* protease enzyme system. The individual enzymes would also be designated by numbers. After the initiation of the apoptotic pathway cytochrome c is released from the mitochondria by the action of the BAX protein and this in turn leads to the activation of the caspases by Apaf-1. The mitochondrial route of apoptosis is initiated by the facilitation of the permeability of the outer membrane of the mitochondria. The permeability enables the

leakage of mitochondrial proteins involved in the activation of caspases (Green DR, Kroemer G 2004 Science 305:626). According to some, there are two pathways of apoptosis, one through the Fas and another through the Apaf/mitochondrial route. Protein BAR (member of the BCL family) may coordinate these two pathways. BCL-2/CED-9 protein blocks caspase activation. "BH-Only" proteins of the Bcl family (Bad, Bil Blk, Hrk/Dp5, Bid, Bim, Noxa, EGL-1) share 9–6 amino acids and are initiators of apoptosis. The X-chromosome-linked IAP (inhibitor of apoptosis) directly inhibits caspase-3 and 7 proteases. Another protease inhibitor is known by the synonyms FLIP, Casper, Flame, Cash and I-FLICE. The CED-3 enzymes are cysteine proteases, accompanied by nucleases that cut the DNA to approximately 180–200 bp fragments, the size of a nucleosomal unit (hence the name caspase-activated DNase [CAD]). There is a closely associated other protein inhibitor of CAD (ICAD or DFF45 in humans). ICAD releases CAD after caspase-3 cut and its role is that of a chaperone. CAD is produced as a complex with ICAD and the action of caspase-3 permits CAD to move into the nucleus from the cytoplasm. The site of cutting is between two nucleosomes by the 343 amino acid nuclease, a basic protein. Actually the whole complex process involves a number of other proteins that interact and affect the outcome of cell death or proliferation (see Fig. A108).

Apoptosis is used for multiple purposes besides aging. Differentiation, homeostasis, cellular defense mandate this process of suicide for damaged or unnecessary cells. The purpose of the apoptotic process is to free the system from unwanted cells and stop proliferation (e.g., prevent cancer and autoimmune disease) and maintain healthy conditions. Glucocorticoids are effective stimulators of apoptosis. After a stroke or Alzheimer's disease overactive



Figure A108. Apoptosis can be imaged by introducing into the cell the firefly luciferase gene (*Luc*) attached to the regulatory domain of a silencer estrogen receptor (ER) domain. In between *Luc* and ER there is A DEVD cleavage site for caspase-3. When caspase is activated at apoptosis the DEVD link is severed and the silencing effect of ER is removed and luciferase is expressed. This is a non-invasive real-time monitoring procedure. (Modified after Laxman B et al 2002 Proc Natl Acad Sci USA 99:16551)

apoptosis may, however, damage the brain. Low level of apoptosis may be the cause of follicular B cell lymphoma. Tumor formation may be caused by the overexpression of *Bcl-2* suppressor of apoptosis. The suppression of *Bcl-2* may, however, promote apoptotic death of cancer cells. The suppression of survivin, an apoptosis inhibitor may also cause death of cancer cells. TRAIL, caspases and caspase inhibitors, respectively have also been considered for cancer therapy. p53 tumor suppressor may channel damaged cells to an apoptotic path.

It has been estimated that in the human body 10 billion cells suffer apoptosis daily and about the same number of cells arise again by mitosis. Humans have more than 200 genes that are involved with apoptosis and their manipulation has therapeutic significance (Schwerk C, Schultze-Osthoff K 2005 Mol Cell 19:1).

Programmed cell death also occurs in plants during the differentiation of the vascular system (xylem), fruit ripening and senescence, the hypersensitive defense reaction against pathogens. Although plants do not have caspases, the vacuolar processing enzyme, a protease has a similar function in controlling virus infection by hypersensitive reaction (Htsugai N et al 2004 Science 305:855).

►aging, ►Hayflick's limit, ►necrosis, ►ceramides, ►sphingosine, ►ERK, ►SAPK, ►T ►cell, ►signal transduction, ►TNF, ►TNFR, ►Fas, ►DISC, ►TGF, ►p53, ►TRF2, ►interleukins, ►leukemia, ►lymphoma, ►cysteine proteases, ►fragmentin-2, ►perforin, ►ICE, ►FADD/►MORT-►1, ►FLICE, ►granzymes, ►Down's syndrome, ►acquired immunodeficiency, ►Alzheimer's disease, ►amyotrophic lateral sclerosis, ►retinitis pigmentosa, ►aplastic anemia, ►CTC, ►apopain, ►addiction module, ►altruism, ►DAP kinase, ►Myc, ►TRAIL, ►DR, ►chaperone, ►p35, ►phagocytosis, ►macrophage, ►Apaf, ►Smac, ►ARF, ►PAK, ►BCL, ►BID, ►BAK, ►RAC,

►IEX, ►nur77, ►transmission, ►IAP, ►survival factor, ►survivin, ►necrosis, ►APAF, ►AIF, ►L-DNase I/mtPTP, ►dynamin, ►mitochondrial ►diseases in humans, ►porin, ►acinus, ►glucocorticoid, ►T cell receptors, ►anoikis, ►death ►signaling, ►hypersensitive reaction, ►addiction ►module, ►Endonuclease G, ►paraptosis, ►phenoptosis, ►*Caenorhabditis*; Nature [Lond] 407:769 ff; Huang DCS, Strasser A 2000 Cell 103:839; Vousden KH 2000 Cell 103:691; Fesik SW 2000 Cell 103:273; Strasser A et al 2000 Annu Rev Biochem 69:217; Engelberg-Kulka H, Glaser G 1999 Annu Rev Microbiol 53:43; Aravind L et al 2001 Science 291:1279; Joza N et al 2001 Nature [Lond] 410:549; Wei MC et al 2001 Science 292:727; Hunot S, Flavell RA 2001 Science 292:865; Nature Cell Biol 2002 June issue for several papers, Igney FH, Krammer PH 2002 Nature Rev Cancer 2:277, <http://www.apoptosis-db.org/welcome.html>.

Apoptosis Inhibitors: These are viral (baculovirus) proteins aimed at overcoming the host defense against viral infection by cell death. Similar proteins targeting primarily caspase-9 and apoptotic mitochondrial cytochrome c occur in insects, mammals as well as in humans.

Apoptosome: A complex of apoptosis proteins including caspases, Apaf, etc. ►apoptosis, ►caspase, ►Apaf; Acehan D et al 2002 Mol Cell 9:423; review: Schafer ZT, Kornbluth S 2006 Developmental Cell 10:549.

Aporepressor: Repressor proteins that require another molecule, the co-repressor (frequently a late product of the metabolic pathway) to be active in controlling transcription. ►transcription, ►tryptophan operon, ►tryptophan repressor

Aposematic Coloration: Warning display of animals and plants against invaders, e.g., bright color of poisonous snakes or poisonous mushrooms or plants. ►Batesian mimicry, ►Müllerian mimicry; Brodie ED III, Agrawal AF 2001 Proc Natl Acad Sci USA 98:7884.

Apospory: Seed formation without fertilization from diploid cells of the nucellus or integumentum. ►apomixis, ►agamospermy diplosperry, ►adventitious embryo, ►amixia

Apostatic Selection: Predators often prefer the most abundant types of prey and thus maintain the polymorphism of the prey population. Polymorphism in populations is maintained by frequency-dependent selection that seems to be paradoxical to the principle of natural selection but under experimental conditions some rare phenotypes have the unexpected advantage of survival (Olendorf R et al 2006 Nature

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[Lond] 441:6330; ►selection types, ►frequency-dependent selection; Bond AB, Kamil AC 2002 Nature [Lond] 415:609.

Aposymbiotic: An organism cured from the symbiotic partner. ►symbionts

Apothecium: An open fruiting body of fungi on which the asci develop; it is similar to perithecium but the latter is a closed fruiting body. Among the genetically widely used organisms *Ascobolus* develops apothecia (see Fig. A109). ►perithecium

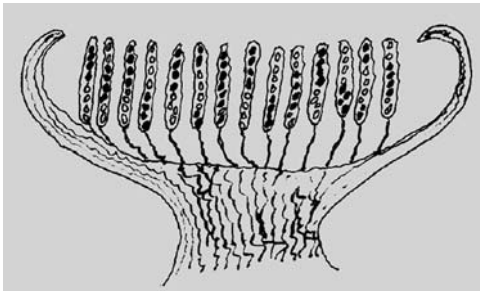


Figure A109. Apothecium. (After Weier TE et al 1973 Botany. Wiley & Sons, New York)

Apotransferrin: A transport protein without its ligand. ►transporters, ►ligand

apo-VLDL: ►apolipoprotein

AP-PCR: Arbitrarily primed PCR. ►polymerase chain reaction, ►methylation-specific PCR

APP (amyloid precursor protein): ►Alzheimer's disease, ►amyloids, ►secretase, ►memory

Apple (*Malus* spp.): About 25 species all with $x = 17$, most of them are diploid although tetraploid and triploid varieties also occur. Apples are frequently self-incompatible but cross-fertilize with other apples. They do not easily hybridize with pears (*Pyrus*), but they hybridize with *Sorbus* (mountain ash). ►pears

Application Programs (computer): Programs serving special purposes such as word processing, graphics, telecommunication, DNA sequencing, data management, etc.

Appressor: Cylindrical or globular fungal organs at the end of the hyphae with a rigid wall. It serves for infection by rupturing the cell wall of plants and invasion of the tissues with the aid of the penetration peg. The process may rely on cutinase, cellulase and other enzymes but it may utilize high turgor mechanical pressure.

Appressorium: An enlarged fungal structure at the point of invasion of the host tissue (see Fig. A110).

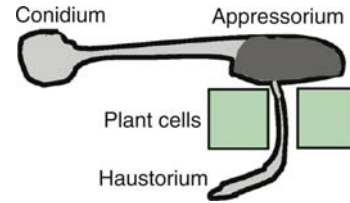


Figure A110. Appressorium

APRF (acute-phase response factor, 17q21): A transcription factor related to the p91 subunit of the interferon-stimulated gene factor-3 α (ISGF-3 α). It is phosphorylated by the mediation of cytokines, and along with Jak1 kinase, it is associated with gp130. Interleukin-6, leukemia inhibitory factor (LIF), oncostatin M (OSM, 252 amino acids, encoded at human chromosome 22q12.1-q12.2 at the same general location as LIF) and ciliary neurotrophic factor (CNTF, 11q12.2), cytokines, neurokines and neuronal differentiation factors are also involved. LIF and OSM may promote atherosclerosis by inhibiting the replacement of defective endothelial cells. ►gp130, ►signal ►transduction, ►cytokines, ►embryogenesis, ►leukemia inhibitory factor, ►ciliary neurotrophic factor, ►atherosclerosis

Apricot (*Prunus armeniaca*): $x = 7$; 2x and 3x forms are known.

APRIL (a proliferation-inducing ligand): A member of the TNF ligand family with homology to CD95. The tumor necrosis factor ligand 13B (encoded at 13q32-q34) is also called TNFSF-13B and April. ►TNF, ►CD95, ►BAFF; Stein JV et al 2002 J Clin Invest 109:1587.

Aprotinin: Inhibitor (at concentrations 1–2 mg/mL) of proteases kallikrein, trypsin, chymotrypsin, plasmin but not of papain. ►protease, ►kallikrein, ►trypsin, ►chymotrypsin, ►plasmin, ►papain

APSES (present in ASM-1-Phd1-StuA-EFGTF1-Sok2 proteins [among others]): A helix-loop-helix-like structure regulating developmental processes. ►DNA binding protein domains

Aptamer: An oligo-RNA, oligo-DNA or a protein—oligo-RNA complex that can bind specifically a particular protein or other molecule (see Fig. A111). E. G., a thrombin-binding aptamer inhibits the action of thrombin in blood clotting and thus prevents the formation of blood clots. Human neutrophil elastase, fibroblast growth factors, vascular endothelial growth factor, selectin, antibodies have been successfully

isolated by the SELEX procedure. Short RNA aptamers inserted into the 5' untranslated region of a mRNA may bind various ligands including (fluorescent malachite green) and may facilitate the control of translation behind it. Cancer cell-specific aptamers can distinguish normal cells from cancer cells and may facilitate fast and effective early diagnosis (Shangguan D et al 2006 Proc Natl Acad Sci USA 103:11838). ▶antisense ▶RNA, ▶SELEX, ▶elastase, ▶FGF, ▶riboswitch, ▶selectin, ▶antibody, ▶mRNA ▶display; Hermann T, Patel DJ 2000 Science 287:820; Cerchia L et al 2002 FEBS Lett 528:12; Famulok M 2004 Nature [Lond] 430:976.

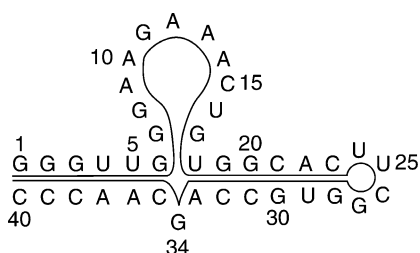


Figure A111. RNA aptamer of ATP

Aptazyme: A ribozyme with an aptamer. ▶ribozyme, ▶aptamer

Apurinic Endonuclease: ▶AP ▶endonucleases

Apurinic Site (AP): A site from where a purine has been removed from the nucleic acid. It has been estimated that mammalian cells lose about ten thousand purines daily. The apurinic sites are removed by excision repair and deoxycytidyltransferase can include deoxycytidine across the apurinic site and DNA polymerase ζ makes further repair. ▶glycosylases, ▶abasic ▶sites, ▶depurination, ▶excision repair; Lindahl T, Nyberg B 1972 Biochemistry 11:3610; Haracska L et al 2001 J Biol Chem 276:6861.

Apyrase: An acid tri- and diphosphatase enzyme that also degrades nucleotides.

Apyrimidinic Endonuclease: ▶AP endonucleases

Apyrimidinic Site: A site from where a pyrimidine has been removed from a nucleic acid.

Aquaporin (AQP2, 12q13, APQ4, 18q11.2-q12.1): Six transmembrane domain proteins (M_r 28K) and water channel in fluid absorbing and fluid secreting cells. The AQP1 monomer contains 269 amino acids, forming two tandem repeats of three membrane-spanning domains and amino and carboxy termini located on the cytoplasmic side of the membrane. The AQP family includes proteins with wide distribution in diverse species across the plant, animal and microbial world. The aquaporin channel of plants is

closed when two conserved serine residues are dephosphorylated or when a conserved histidine is protonated during anoxia by flooding. In closed conformation a D loop caps the channel from the cytoplasm. In open conformation the D loop is displaced and removes the blockade of the entrance of the channel from the cytoplasm (Törnroth-Horsfield S et al 2006 Nature [Lond] 439:688). cAMP-dependent mechanisms or PKA activate the aquaporin channel. It is important for various types of cells, diabetes, kidney function, *Drosophila* neural development, nematodal infestation of plants, etc. Aquaporin 7 deficiency activates adipose glycerol kinase and may lead to obesity (Hibuse T et al 2005 Proc Natl Acad Sci USA 102:10993). The deletion of aquaporin-4 in mice reduces brain edema. The disruption of the rodent aquaporin-1 gene (*AQP1*) impairs angiogenesis and cell migration and thus reduces tumor growth (Saadoun S et al 2005 Nature [Lond] 432:786). ▶CHIP, ▶forskolin, ▶cAMP, ▶PKA, ▶cell ▶membranes, ▶ion ▶channels; Borgnia M et al 1999 Annu Rev Biochem 68:425; Murata K et al 2000 Nature [Lond] 407:599; Sui H et al 2001 Nature [Lond] 414:872; Uehlein N et al 2003 Nature [Lond] 425:734; King LS et al 2004 Nature Rev Mol Cell Biol 5:687.

Aquaretic: Secreting bloody fluids.

Aqueous: Prepared with water (e.g., a solution) or watery in appearance.

Aquifex aeolicus: A chemolithoautotroph bacterium capable of growth at 95 °C. Its completely sequenced DNA genome is 1,551,335 bp. ▶chemolithoautotroph

Aquilegia (Columbine): 700 species have a genome size of ~400 Mb; under development for ecological and evolutionary genetic studies (see Fig. A112).



Figure A112. Columbine

Arabidopsis Mutagen Assays: In the mature embryo of plants two diploid cells represent the inflorescence. Therefore, if the seeds are exposed at such a stage to a mutagen, in the progeny of the emerging plants the

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segregation is about 7:1 for recessive mutations. This also indicates that one of the two apical cells became heterozygous for the new mutation induced. For mutagen assays it is sufficient to open up the immature fruits of the plants before the seed coat becomes opaque (about 10–14 days after fertilization) and albina or other color mutations in the cotyledons or embryo defects can be determined. Within a single fruit the segregation for recessives is 3:1 (see above). The fruits on the plants emerging from the treated seed already contain the F_2 generation. Generally, two opposite fruits next to each other are examined because the phyllotaxy index assures that these are sufficient for complete sampling. Such a test permits the identification of about 80% of the spectrum of visible mutations. Since the plants are diploid and the “germline” consists of two cells, the mutation rate on genome basis is calculated by counting all independent mutational events and dividing it by the total number of plants tested $\times 4$. *Arabidopsis* can activate many types of promutagens and therefore provides an efficient and low cost method for assessing the genotoxic effects of a wide variety of agents in a single culture (see Fig. A113). ►bioassays for genetic toxicology, ►*Arabidopsis thaliana*, ►phyllotaxy; Rédei GP, Koncz C 1992 In: Koncz C et al (eds) *Methods in Arabidopsis Research*, World Scientific, Singapore, p 16; Hays JB 2002 *DNA Repair* 1:579.



Figure A113. *Arabidopsis*.



Figure A114. Open *Arabidopsis* fruit.

***Arabidopsis thaliana*:** An autogamous plant of the crucifer family, $2n = 10$, the genome size has been estimated to be 9×10^7 to 1.5×10^8 bp (the current best estimate is ~ 121 – 125 Mbp). Its life cycle may be as short as 5–6 weeks. Its seed output may exceed

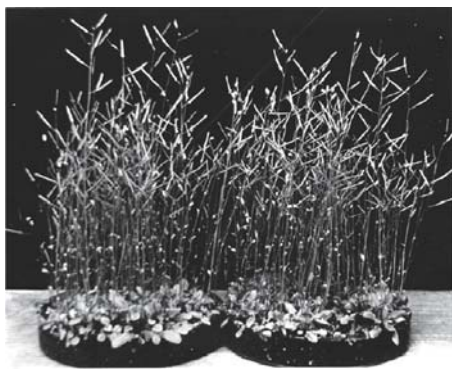
50,000 per plant. Its mitochondrial DNA is 366,924 bp, 10% duplicated, and apparently codes for 58 genes. Because of its small size thousands of individuals may be screened even on a Petri plate or grown for the entire life cycle in test tubes where the plants may produce more than 100 seeds. Its plastid DNA is approximately 154 kbp encoding 79 proteins and 17% is duplicated. It is the first higher plant with the genome completely mapped and sequenced in 2000. Transposons constitute 14% of the nuclear DNA and 4% of the mitochondria; the plastids appear free of moving elements. Chromosome 2 and 4 sequences became available by late (1999) (Nature [Lond] 402:761 and 769).

The initial data indicate higher gene number than in *Drosophila* or *Caenorhabditis*. At present the predicted gene number of *Arabidopsis* is $\sim 30,700$ from which $\sim 25,540$ have been annotated as protein-coding whereas the remaining are pseudogenes or partial genes (Yamada K et al 2003 *Science* 302:842). Interestingly, more than two decades ago, on the basis of mutation frequency in *Arabidopsis*, the total number of genes was estimated to be about 28,000 (Rédei GP et al 1984 In: Chu EHY, Generoso WM (eds) *Mutation, Cancer, and Malformation*. Plenum, p. 306). All chromosomes display on an average ca. 60% duplication. Although many of the genes show homologies to those of other organisms, there is 38.9% identity with the human breast cancer gene (BRC2), Werner syndrome (37.4%) and the Niemann-Pick disease (42.7%). Interestingly, many genes with apparently so far unidentified function and specific for plants were revealed by the sequences.

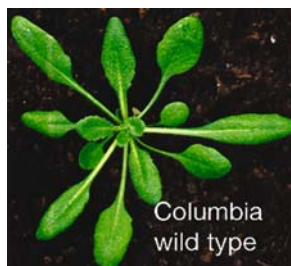
Annotation of the full-length cDNA: Seki M et al 2002 *Science* 296:141. A global gene expression map is available including from embryogenesis to seed development and senescence. The expression pattern of large gene families indicates that many families are co-opted for specific developmental processes. (Schmid M et al 2005 *Nature Genet* 37:501).

Information is available through Arabidopsis Biological Resource Center, Ohio State University, (1735) Neil Ave., Columbus, OH 43210, USA. Tel.: 614-292-1982 (Scholl, seeds), 614-292-2988 (Ware, DNA). E-mail: arabidopsis+@osu.edu. Orders: by Fax 614-292-0603. *Science* 282:6612; Marra M et al 1999 *Nature Genet* 22:265; Mozo T et al 1999 *Nature Genet* 22:271; *Nature [Lond]* 408:796 [2000]; Bennetzen JL 2001 *Nature Genet* 27:3; Allen KD 2002 *Proc Natl Acad Sci USA* 99:9568; genome-wide mutant screens: Alonso JM, Ecker JR 2006 *Nature Rev Genet* 7:524; taxonomic identities: Koch MA, Matchinger M 2007 *Proc Natl Acad Sci USA* 104: 6272;

E-mail seedstock@arabidopsis.org, dnastock@arabidopsis.org,



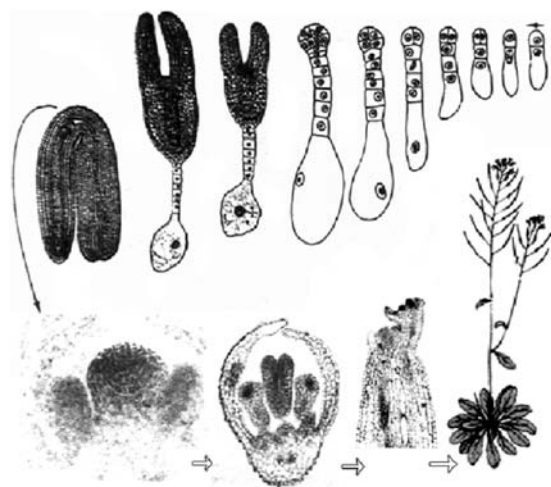
Hundreds of Columbia wild type *Arabidopsis* plants can be raised to maturity in 9 cm diameter Petri plates on commercial Promix soil-substitute medium under long-day illumination in greenhouse (Redei, unpublished).



Columbia
wild type



er mutant



Developmental Cycle of *Arabidopsis*



Figure A115–118 Features of *Arabidopsis*

NASC <http://nasc.nott.ac.uk>; <http://arabidopsis.info/>,

TAIR: <http://arabidopsis.org>; <http://mips.gsf.de/proj/thal/db>,

Arabidopsis Genome Encyclopedia: <http://rarge.gsc.riken.jp/>,

cis-acting elements, T-DNA, regulation: <http://arabidopsis.med.ohio-state.edu/>,

interactions: http://www.ptools.ua.ac.be/at_idb,
EMB-EBI bioinformatics protein index; <http://www.ebi.ac.uk/IPI/IPIarabidopsis.html>,

genetics, genetics, genomics; <http://bioresearch.ac.uk/browse/mesh/D017360.html>,

nucleolar markers: <http://bioinf.scri.sari.ac.uk/cgi-bin/atnodb/home>,

small RNAs: <http://asrp.cgrb.oregonstate.edu/mitochondria>; <http://www.plantenergy.uwa.edu.au/applications/ampdb/index.html>,

gene co-expression data mining tool: <http://www.arabidopsis.leeds.ac.uk/act/>.

Arabinose Operon: Consists of three juxtapositioned structural genes *araB* (l-ribulokinase), *araA* (L-arabinose isomerase) and *araD* (L-ribulose-4-epimerase) transcribed in this order into a polycistronic *araBAD* mRNA starting at the O^{BAD} operator and

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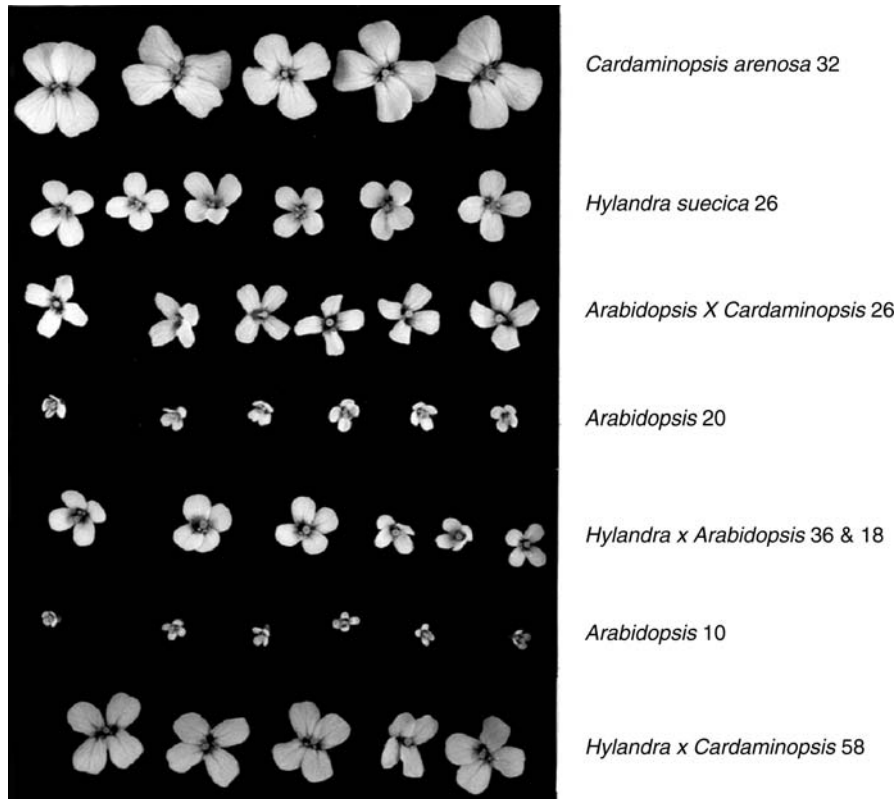


Figure A119 *Arabidopsis*, related species and hybrids with somatic chromosome numbers. (Rédei GP 1960 unpublished)

initiated by the P^{BAD} promoter. The repressor-activator site functions by positive or negative control and it is transcribed in the opposite direction from the O_C operator and uses the P_C promoter. These genes are near the beginning of the *E. coli* map, while another gene *araF* is located near map position 45. They form a common regulatory system: a regulon. The activation of the *ara* operon not only requires the presence of the substrate arabinose, but also that the catabolite activating protein cyclic adenosine monophosphate complex be attached to the promoter. This operon is subject to catabolite suppression and as long as glucose is present in the medium (even when arabinose is also available) its transcription cannot begin. ▶operon, ▶polycistronic, ▶operator, ▶catabolite activating protein, ▶cAMP, ▶negative control; Schleif R 2000 Trends Genet 16:559.

Arabinosuria: An early name of pentosuria but it was subsequently found that L-xylulose was misidentified as arabinose; the current name of the recessive disorder is (essential) pentosuria. ▶pentosuria, ▶xylulose

Arachidonic Acid (arachidate): An unsaturated fatty acid, which, is known as arachidonate when there are four double bonds in the molecule (it is synonymous with eicosatetraenoate). It occurs in lipids and plays a role in mediating signal transduction. Cyclooxygenase

mediates the formation of prostaglandins, prostacyclins and thromboxanes whereas lipoxxygenase catalyzes the synthesis of leukotrienes from arachidonic acid.

▶fatty acids, ▶cyclooxygenase, ▶lipoxxygenase signal transduction, ▶atherosclerosis

Arachnodactyly (5q23-q31): A characteristic of the Marfan syndrome involving unusually long fingers and toes. Unlike the Marfan syndrome (FBN1), here the mutation involves the fibrillin gene FBN2 (see Fig. A120 for a photograph). ▶Marfan syndrome, ▶fibrillin; Belleh S et al 2000 Am J Med Genet 92:7.

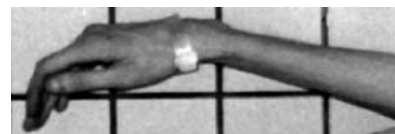


Figure A120. Arachnodactyly

Aracne (algorithm for the reconstruction of accurate cellular networks): From phenotypic and biochemical information scale-free networks of interconnected gene hubs are determined (Basso K et al 2005 Nature Genet 37:382). ▶networks, ▶genetic networks

ARAF Oncogenes: Have been assigned to the mouse X-chromosome whereas in humans ARAF 1 is in chromosome Xp11-p11-2 and ARAF 2 was localized to either 7p11.4-q21 or 7p12-q11.21. These oncogenes are homologous to the RAF1 oncogene and are supposed to encode a serine/threonine kinase. ►**RAF1**

Aragorn: A computer program for the detection of tRNA and tmRNA genes. (Laslett D, Canback B 2004 Nucleic Acids Res 32:11)

Arboviruses: Parasites of blood-sucking insects and vertebrates, their genetic material is RNA.

Arbuscular Mycorrhiza: The hyphae of the fungus actually penetrate the roots of the plants and form their branching structures. ►**mycorrhiza**

ARC: ►**DRIP**

Archaea: The third major group of living systems besides bacteria and eukarya. *Methanococcus jannaschii* DNA (1.66 megabase) has been sequenced in (1996) and 1,738 predicted protein-coding genes have been identified. The organism has two, 58-kb and 16-kb, extrachromosomal elements. Only 38% of its genes appear similar to genes (by nucleotide sequences) of other fully sequenced bacteria or budding yeast. The metabolic genes bear similarities to bacterial genes whereas its genes involved in transcription, translation and replication bear greater resemblance to eukaryotic genes. Their genome displays nucleosomal structures. For a complete nucleotide sequence see World Wide Web at <http://www.tigr.org/tdb>. In halobacteria the genes are in linkage equilibrium, which is an indication of frequent genetic recombination (Papke RT et al 2004 Science 306:1928). Archaea in the rhizosphere of rice plants are responsible for an estimated 10 to 25% of the global methane emission. The genome of 3,179,916 bp of the methanogenic strains contains 3,103 coding sequences (Erkel C et al 2006 Science 313:370). ►**life form domains**, ►**evolution of eukaryotes**, ►**linkage disequilibrium**; Whitman WB et al 1999 Genetics 152:1245; Podani J et al 2001 Nature Genet 29:54.

Archaeobacteria: Groups of prokaryotes that appear to have some similarities to eukaryotes in as much as displaying nucleosome-like structures in their DNA, introns in their genes, unlinked 5S RNA genes and their transcriptase enzyme are somewhat related antigenically to similar enzymes in lower eukaryotes. ►**archaea**

Archaeogenetics: Studies the descent of humans mainly on the basis of mitochondrial and Y-chromosomal population information.

Archegonium: Female sexual organ (gametangium) of lower plants where the eggs develop.

Archeogenetics: The application of molecular genetics techniques to ancient populations, their bone remains or otherwise preserved biological samples and their evolving descendants. The studies are based on mitochondrial DNA that can reveal the pattern(s) of human/animal evolution and migration of females and the analysis of Y chromosomal makeup provides comparable information on the male lineages. ►**Eve foremother of mtDNA**, ►**Y chromosome**

Archeozoic: Geological period 400 to 100 million years ago when protists (unicellular organisms) evolved.

Archespore: The ancestral, enlarged cell that develops into the megasporocyte (megaspore mother cell) in plants. ►**megagametophyte**

Archezoa: ►**microsporidia**

Architectural Editing: Proteins from the endoplasmic reticulum are selectively transported. The new proteins are retained until properly folded and the misfolded chains are degraded. ►**endoplasmic reticulum**

Architectural Proteins: Modulate DNA structure in such a way that transcription factors gain better access to the promoter area. ►**UBF**, ►**high-mobility group proteins**

Archival DNA: Stored in museum, herbarium or other preserved samples of long dead cells; can be amplified with PCR techniques for analysis and for obtaining information on old populations or on extinct species. ►**PCR**, ►**ancient DNA**

Archtype: A hypothetical ancestral form in evolution.

Arcsine: The inverse of sine (\sin^{-1}), it denotes the angle of whose sine is given. ►**sine**

Arcsine Transformation: ►**angular transformation**

ARE (anoxia response element): DNA sequences regulating responses to anaerobiosis. ARE responding genes represent detoxification and antioxidant defense. ►**anoxia**; Li J et al 2002 Physiol Genomics 9:137.

ARE: AU-rich elements in the 3'-untranslated region of RNA involved in the regulation of translation Cheong C-G, Tanaka-Hall TM 2006 Proc Natl Acad Sci USA 103:13635; Vasudevan S, Steitz JA 2007 Cell 128:1105; ►**AMD**, ►**HuR** [human AUY-rich elements], <http://rc.kfshrc.edu.sa/ared/>.

α-Repeat: A 171 bp abundant (up to 1,000,000) repeat in the human genome, localized primarily in the centromeric regions of the chromosomes. This and

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the Alu repeats constitute 5–10% of the human genome. ►Alu family

ARF (ADP-ribosylation factor, p14^{ARF} [human]/p19^{ARF}[mouse]): A GTP-binding protein of the monomeric Raf family of G proteins involved in the transport between the endoplasmic reticulum and the Golgi apparatus and within the Golgi complex. The ARF alters the membrane lipid composition. It is also required for the physiological effect of cholera and pertussis toxins. p^{ARF} regulates tumor suppressors p53 and RB through the E2F-1 transcription factor. A novel nuclear protein NIAM (nuclear interactor of ARF and MDM2) binds both the ARF and the p53 antagonist MDM2). NIAM protein is normally expressed at low to undetectable levels in cells partly because of, MDM2-mediated ubiquitination and proteasomal degradation. When reintroduced into cells, NIAM activated p53, caused a G1 phase cell cycle arrest, and collaborated with the ARF in an additive fashion to suppress proliferation. Notably, NIAM retains growth inhibitory activity in cells lacking ARF and/or p53, and knockdown experiments revealed that it is not essential for ARF-mediated growth inhibition. Thus, NIAM and ARF act in separate anti-proliferative pathways that intersect mechanistically and suppress growth more effectively when jointly activated. Intriguingly, silencing of *NIAM* accelerated chromosomal instability, and microarray analyses revealed reduced *NIAM* mRNA expression in numerous primary human tumors (Tompkins VS et al 2007 J Biol Chem 282:1322).

When c-Myc oncoprotein level increases, the ARF blocks c-Myc and its ability to induce hyperproliferation. Also, the ARF does not affect the transcription of Myc and enhances apoptosis independently from p53 (Qi Y et al 2004 Nature [Lond] 431:712). The short mitochondrial form of p19^{ARF} induces autophagy and caspase-independent cell death (Reef S et al Mol Cell 22:463). The ARF is turned on by Sec7 guanine nucleotide exchange factor domain proteins, which are inhibited by brefeldin. ►signal transduction, ►cholera toxin, ►pertussis toxin, ►GTPase, ►SecA, ►SecB, ►translocase, ►translocon, ►ARNO, ►Golgi, ►G proteins, ►raf, ►tumor suppressor, ►p53, ►retinoblastoma, ►E2F1, ►p16^{INK4}, ►guanine nucleotide exchange factor, ►brefeldin, ►cytohesins, ►MDM2, ►Myc, ►Sirtuin, ►RNAs polymerase III, ►Pokemon, ►MDM2, ►ABA; Sherr CJ 1998 Genes Dev 12:2984; Randle DH et al 2001 Proc Natl Acad Sci USA 98:9654.

ARF1: A GTPase protein activating phospholipase D. It is activated by PtdIns (phosphatidyl inositol), and participates in the recruitment of coatomer and trans-Golgi network (TGN) clathrin. ►coatomer,

►phosphoinositols, ►trans-Golgi network, ►clathrin, ►GEF, ►Sec, ►Ypt, ►COP ►transport ►vehicles

ARF1 (auxin response factor): Modulates the action of auxin response elements (AuxRE, TGTCTC) in combination with transcription factors. auxins, ►plant ►hormones

Arfaptin: An adaptor mediating cross-talk between the ARF and small G-proteins Rac, RHO and RAS in signal transduction. signal ►transduction, ►ARF, ►cross-►talk, ►G-proteins; Peters PJ et al 2002 Nature Cell Biol 4:240.

ARG: An oncogene related to ABL in human chromosome 1q24-q25 and in mouse chromosome 1. It encodes a tyrosine kinase, different from that of the ABL product. ►oncogenes, ►ABL

Arg: Abbreviation for arginine.

Arginase: ►argininemia

Arginine (2-amino-5-guanidinovaleric acid): A positively-charged essential amino acid. Arginine methylation and demethylation play an important role in the regulation of gene expression. ►urea cycle, ►nucleosome, ►nuclear receptors; Lee Y-H et al 2005 Proc Natl Acad Sci USA 102:3611.

Argininemia (hyperargininemia): The accumulation of high levels of arginine in the blood and urine caused by autosomal recessive arginase deficiency (ARG1 and ARG2 genes). ARG1 (6q23) coded enzyme represents 98% of the arginase activity in the liver and its deficiencies the common argininemia. Arginine accumulates in the blood because it is not degraded. It is a relatively rare disease. Treatment with benzoate and restriction of arginine intake may ameliorate the condition. Shope virus infection may restore arginase activity in the cells. ►amino acid metabolism, ►citrullinemia, ►citrullinuria, ►urea cycle

Argininosuccinic Aciduria: A rare hereditary disorder (human chromosome 7cen-q11.2) involving mental retardation, seizures, hepatomegaly (enlargement of the liver that may become cancerous), intermittent ataxia, brittle and tufted hair, and accumulation of large quantities of argininosuccinic acid (an intermediate in the arginine-citrulline [urea] cycle) in the blood, urine, and the cerebrospinal (brain and spinal cord) fluid. Early and late onset types have been distinguished. The basic defect is argininosuccinase or argininosuccinate lyase deficiency. ►urea cycle

Arginyl tRNA Synthetase: The enzyme that charges the appropriate tRNA with arginine. The encoding gene was located to human chromosome 5. ►aminoacyl tRNA synthetase

Argon Dating: Potassium (^{40}K) decays to argon (^{40}Ar) with a half-life of about 1.25 million years. The gaseous Ar is trapped in the volcanic rocks after it is formed but expelled from the molten lava before the eruption because of the intense heat. Thus, the amount of ^{40}Ar indicates the time elapsed since the volcanic deposits were formed. If any relics (e.g., human bones) are found in the layers, their age can be inferred by potassium-argon dating of the rocks in case the time exceeds the limits of carbon dating. ►radio carbon dating

Argonaute (AGO): Exists in different forms. The enzyme argonaute-2 mediates the degradation of mRNA in response to interfering dsRNA (Liu J et al 2004 Science 305:1437). This protein may also function downstream of Dicer or RNA-dependent RNA polymerase in gene silencing in eukaryotes and probably in prokaryotes. AGO mediates through siRNA the dimethylation of histone H3 lysine 9 (H3K9me2) and RNA-dependent RNA polymerase complexes (Irvine DV et al 2006 Science 313:1134). ►RNAi, ►piRNA, ►PAZ, ►RISC, ►Dicer, ►miRNP, ►rasiRNA, ►RNA-directed DNA methylation; Williams RW, Rubin GM 2002 Proc Natl Acad Sci USA 99:6889; Martinez J et al 2002 Cell 110:563; Kidner CA, Martensen RA 2004 Nature [Lond] 428:81, crystal structure: Song J-J et al 2004 Science 305:1434; minireview: Tanaka Hall TM 2005 Structure 13:1403; mammalian miRNA: <http://www.ma.uni-heidelberg.de/apps/zmf/argonaute/interface/>.

Argos: A secreted *Drosophila* protein containing a single EGF motif. It is a repressor of eye and wing determination and it acts against *Spitz*. ►Spitz, ►DER, ►EGF; Klein DE et al 2004 Nature [Lond] 430:1040.

Argosomes: Epithelial membrane vesicles that are capable of moving cargo between cells. Greco V et al 2001 Cell 106:633.

Argyrophilic Grains: May accumulate in the brain in some dementias; they are stained by bound silver salts, reduced by light or reducing compounds and appear black in post-mortem study.

Arias Syndrome: Probably the same as Gilbert syndrome or Crigler-Najjar syndrome II.

Arithmetic Mean: $\bar{x} = \frac{\sum x}{N}$ is the sum of all measurements (x) divided by the number of measurements (N). ►mean

Arithmetic Progression: A series with elements increasing by the same quantity, e.g., 1, 3, 5, 7, 9. ►geometric progression

ARK β : β -adrenergic receptor, also called GRK2. ►adrenergic receptor, ►GRK1

Arlequin: A software for the analysis of population genetics data (<http://anthro.unige.ch/software/arlequin/>).

Arm Ratio: The relative length of the two arms of a eukaryotic nuclear chromosome. ►chromosome arm, ►chromosome morphology

Armadillo: *Euphractus sexcinctus* 2n = 58; *Dasypus novemcinctus* 2n = 64; *Cabassous centralis* 2n = 62; *ChaetophRACTUS villosus* 2n = 60.

Armadillo (arm, 1–1.2): Homozygosity of the recessive allele is lethal. The normal allele of *Drosophila* is involved in embryonic differentiation in connection with other genes. Its vertebrate homolog encodes β -catenin. It is positively regulated by *Wg* (wingless) and down-regulated by axin. ►morphogenesis in *Drosophila*, ►wnt, ►axin

Armitage-Doll Model: Interprets carcinogenesis as a multistage process developed by a series of subsequent mutations. ►Knudson's two-mutation theory, ►Moolgavkar-Venzon model

ARMS (amplification refractory mutation system): Along with PCR, it may detect the strand that contains a known mutation or identify polymorphism of a particular DNA stretch. Two sets of primers are used for amplification and one of the primers has a difference at the site of the suspected mutation. The different nucleotide is inserted at the 3' end of the primers and extension of the strands follows. However, the penultimate base frequently leads to a mismatch in both mutant and wild type primers and may be difficult to find a primer suitable to obtain a sequence-specific amplification. ►PCR, ►primer, ►primer ►extension, ►mutation ►detection; Chiu RW et al 2001 Clin Chem 47:667; Carrera P et al 2001 Methods Mol Biol 163:95.

Arms of Bacteriophage λ : When the stuffer segment is removed a left and a right segment (arms) of the genome remains and these are used for vector construction. ►stuffer DNA, ►lambda phage

arRNA: Ancient RNA. ►ancient organisms, ►ancient DNA

ARNO (ARF nucleotide binding site opener): A 399 amino acid human protein involved in the $\text{GDP} \rightleftharpoons \text{DGTP}$ exchange of ARF. This and similar proteins contain an amino-terminal coiled coil, a central secretory protein domain (Sec) and a C-terminal pleckstrin domain. It is a homolog of the yeast Gea1, and both are inhibited by brefeldin. ►ARF, ►GTP, ►pleckstrin, ►brefeldin, ►endocytosis

Arnold-Chiari Malformation: Multifactorial recessive brain anomaly. The brain stem is herniated into the foramen magnum (interconnecting the brain and

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the vertebral column) resulting in hydrocephalus and anencephalus as well. ►anencephaly, ►hydrocephalus

ARNT (arylhydrocarbon-receptor nuclear translocator): A helix-loop-helix heterodimeric transcription factor with the AHR and other receptors mediating the metabolism of xenobiotics. ►aryl hydrocarbon receptor, ►xenobiotics, ►helix-loop-helix

Aromatase (ARO): A ~500 amino acid cytochrome 450 (CYP19) protein (estrogen synthetase) converting C19 androgen into C18 estrogen. It is encoded at human chromosome 15q21.1. It is present in the skin, muscle, fat, ovary, placental and nerve tissues. Its deficiency in females causes virility and pseudohermaphroditism and lowered fertility in male mice. An excess of it in human males may cause gynecomastia. ►estradiol, ►steroid hormones, ►gynecomastia, ►pseudohermaphroditism

Aromatic Molecule: A closed ring molecule with C in the ring, linked by alternating single and double bonds; they are frequently conjugated with other compounds.

ARP (autonomously replicating pieces): ►macronucleus

ARP2/3 Complex (actin-related protein complex): An actin assembly complex involved in the movement of cells and mitochondria during cell division and budding of yeast. It appears to be involved in regulating cell shape (Mathur J et al 2003 Development 130:3137). Arp4 is found in large multisubunits of the INO80 and SWR1 chromatin remodeling complexes, in the NuA4 histone acetyltransferase complex and in the assembly of the kinetochore (Ogiwara H et al 2007 Nucleic Acids Res 35:3109). ►actin; Robinson RC et al 2001 Science 294:1679; Cooper JA et al 2001 Cell 107:703.

ARPKD: ►renal-hepatic-pancreatic kidney disease, ►polycystic kidney disease

Array [V80] Hybridization: This is designed to identify single (or a small number) of nucleotide changes in genomic DNA. The procedure requires a large array of oligonucleotide probes, which are obtained by light-directed parallel chemical synthesis. Using in each oligonucleotide set four probes, which differ only in one of the four bases, A, T, G, C, whereas the flanking bases are kept identical. The complementary synthetic probes then query each sequence of the target:

The single-base different hybridization probes are distinguished on the basis of the signals provided by the differences in the fluorescence labels and hybridization intensities of the probes. The procedure also permits the identification of more than one base and deletions. A confocal device can thus scan an entire genome and its great merit lies in its rapidity

(see Fig. A121). ►light-directed parallel synthesis, ►DNA chips, ►microarray hybridization; Chee M et al 1996 Science 274:610.

| | | | |
|--------|-------------|---------------------|------------|
| Target | 5'..... TGA | ACTGTATCCGACAT...3' | |
| Probes | 3' | GACATAGGCTGTA | MATCH |
| | | GACATCGGCTGTA | |
| | | GACATGGGCTGTA | MISMATCHES |
| | | GACATTGGCTGTA | |

Figure A121. Array hybridization

Arrayed Library: Cloned DNA sequences are arranged on two-dimensional microtiter plates where they can be readily identified by row and column specifications. ►DNA library, ►microarray

Arrayed Primer Extension (APEX): An array of oligonucleotide primers is immobilized by their 5'-end on a glass surface. The DNA is amplified by PCR, digested enzymatically and annealed to the immobilized primers. A template-dependent DNA polymerase extends the sequence using fluorescent-labeled dideoxynucleotides. Mutation is revealed by a change in the color code of the primer sites. The procedure is suited for analysis of DNA polymorphism. ►primer, ►PCR, ►dideoxynucleotide; Kurg A et al 2000 Genet Test 4:1.

Arrest, Transcriptional: Transcription is stopped because the supply of one or more types of nucleotides has run out or even due to protein factors. It can usually be restarted by the missing building block. T-rich sequences in the non-template DNA strand are frequently liable for the arrest. Genes like *LexA*, *lac* repressor, CAAT-box-binding and other binding proteins may block or impede transcription. In some instances the RNA polymerase may either bypass or remove the binding proteins in its way. The nucleosomal structure may not interfere with transcription although in some cases it may retard it. The degree of interference may depend on the dissociation of the protein. Strong positive or negative supercoiling of the DNA may impede RNA elongation. Some RNA polymerases may transcribe through the gaps of a few nucleotides but the transcript will have deletions. ►pause transcriptional, ►lexA, ►lac operon, ►nucleosome, ►supercoiled DNA, ►RNA polymerase

Arrestin: A 45-kDa phosphoprotein which regulates the phototransduction and β_2 adrenergic pathways (by non-visual arrestins) in animals. It is dephosphorylated when it interacts with the trimeric

G-protein-coupled signal receptor. It may serve as a deactivator of G protein-mediated signaling path by binding to the SH³ domain of the cellular Src molecules. Arrestin may also recruit clathrin to the receptor complex, resulting in the internalization of the complex into clathrin-coated pits. In such a situation it may stimulate cross-talk with the MAP kinase pathway. β -Arrestin 2 acts as a scaffold and transducers for seven-membrane spanning receptors and can regulate development through the *Hedgehog-Smoothed* pathway (Wilbanks AM et al 2004 Science 306:2264). Sinophilin antagonizes most of the arrestin functions (Wang Q et al 2004 Science 304:1940). ►phototransduction, ►signal transduction, ►desensitization, ►adrenergic receptor, ►PDZ, ►Src, ►cross-talk, ►clathrin, ►cargo receptors, ►hedgehog, ►seven-membrane protein, ►endocytosis, ►MAP, ►retinal dystrophy, ►dopamine, ►Oguchi disease, ►adaptin, ►AP180; Krupnick JG, Benovic JL 1998 Annu Rev Pharmacol Toxicol 38:289; Lefkowitz RJ, Shenoy SK 2005 Science 308:512.

Arrhenotoky: A mechanism of sex determination. The males are haploid and the females are diploid for the sex genes (as in bees and wasps). The males develop from unfertilized eggs (a form of parthenogenesis) and display one or the other allele(s) for what the diploid females (queens) are heterozygous for. The homozygous diploid males are either sterile or lethal or destroyed by the workers in the colony. This type of sex determination is seen in nearly 20% of animals (mites, white flies, scale insects, thrips, rotifera, etc.) ►chromosomal sex determination, ►sex determination, ►complementary sex determination, ►wasp; Cowan DP, Stahlhut JK 2004 Proc Natl Acad Sci USA 101:10374.

Arrhythmia, Cardiac: ►LQT

Arrowsmith: A computer tool for identifying the links between MedLine articles. http://arrowsmith.psych.uic.edu/arrowsmith_uic/index.html.

Arrhythmogenic Right Ventricular Cardiomyopathy (RVD): Eight different dominant and one recessive (17q21) forms of the disease, involving degeneration of the myocardium (heart muscles), followed by fibrous-fatty replacement have been described. ARVD1 (14q24.3), ARVD22 (1q42), ARVD3 (14q11-q12), ARVD4 (2q32), ARVD5 (3p23), ARVD6 (10p12-p14), ARVD7 (10q22) and ARVD8 (6p24) are the known dominant mutations. In mice, mutation of a laminin receptor gene (*Lamr1*) contained in an intron-free retroposon caused RVD. The transposon may move to different chromosomes. The gene product was bound to the heterochromatin protein HP1. HP1 is a regulator of heterochromatin sites and LAMR1 protein apparently caused the degeneration

of cardiomyocytes (Asano Y et al 2004 Nature Genet 36:123). cardiomyopathy, ►heart disease, ►long QT syndrome, ►laminin; Rampazzo A et al 2002 Am J Hum Genet 71:1200.

ARS (autonomously replicating sequences): These are nearly 100 bp long origins of replication of yeast chromosomal DNAs. The different ARS sequences share a consensus of 11 base pairs (5'-[A/T]TTTAT[A/G]TTT[A/G]-3'), and there are some additional elements around it that vary in the different chromosomes from where they were derived. ARS1 contains subdomains A, B1 that are recognized by ORC. Subdomain B2 unwinds DNA, and B3 is where ABF1 binding factor is attached. Artificial yeast plasmids must contain ARS sequences to be maintained and they may remain stable as long as selective pressure exists for their maintenance, i.e., they carry essential genes for the survival of the yeast cell (missing from or inactive in the yeast nucleus). ARS elements occur also in organellar and other DNAs. ►YAC, ►yeast vectors, ►DUE, ►cell cycle, ►ORC, ►MCM, ►Abf; Marilley M 2000 Mol Gen Genet 263:854.

Arsenic (As³⁺ or As⁵⁺): Refers to common contaminants produced by burning coal and glass manufacturing which are serious environmental poison (in impure drinking water) and human carcinogen (although not for rodents) (see Fig. A122). It may cause chromosomal deletions in rodents and humans by the generation of oxyradicals. Arsenic trioxide (As₂O₃) is an activator of the MAP kinases. Chronic arsenic poisoning may cause melanotic spots on the palm. Arsenic chaperone, ArsD, is encoded by the *arsRDABC* operon of *Escherichia coli* and it transfers trivalent metalloids to ArsA, the catalytic subunit of an As(III)/Sb(III) efflux pump. Interaction with ArsD increases the affinity of ArsA for arsenite, thus increasing its ATPase activity at lower concentrations of arsenite and enhancing the rate of arsenite efflux. Cells thus become resistant to environmental concentrations of arsenic and toxicity (Lin Y-F et al 2006 Proc Natl Acad Sci USA 103: 15617). Arsenic trioxide is an anticancer agent (Lu J et al 2007 Proc Natl Acad Sci USA 104:12288). ►MAP, ►soil remediation; Basu A et al 2001 Mutation Res 488:171; Oremland RS, Stolz JF 2003 Science 300:939; Croal LR et al 2004 Annu Rev Genet 38:175.



Figure A122. Arsenic spots

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ART (assisted reproductive technology): This may benefit about 15% of infertile couples. Various techniques are available to assist in conception. Although most of these technologies appear safe, some concerns have been raised (Powell K 2003 Nature [Lond] 422:656). More recent evidence, however, indicates that the concerns are unwarranted and the offspring from intracytoplasmic sperm injection does not suffer any detectable harm (see Fig. A123) (Rosenwaks Z, Bendikson K 2007 Proc Natl Acad Sci USA 104:5709). ▶artificial insemination, ▶intrauterine insemination, ▶in vitro fertilization, ▶ROSI, ▶oocyte donation, ▶GIFT, ▶intrafallopian transfer of gamete and zygote, ▶surrogate mother, ▶sperm bank, ▶insemination by donor, ▶preimplantation, ▶genetics [▶PGD], ▶sex selection, ▶micromanipulation of the oocyte, ▶ICSI, ▶IUGTE, ▶counseling genetic; Baritt JA et al 2001 Human Reprod 16:513; Trounson A, Gardner D (eds) 2000 Handbook of In Vitro Fertilization. CRC Press, Boca Raton, Florida.



Figure A123. Qing dynasty enameled porcelain

Art in Science: Artworks and ancient relics provide much information about anthropology, evolution of species, diseases and technology. ▶Lascaux, ▶mammoth, ▶body mass index in humans, ▶inbreeding depression, ▶Toulouse Lautrec, ▶depression, ▶chimera, ▶gynecomastia, ▶Native Americans, ▶Van Gogh, ▶Poliovirus, ▶obesity, ▶gout, ▶musical ▶talent, ▶Mondrian

Artemis: A single-strand-specific 5'→3' exonuclease, which upon activation by a protein kinase (DNA-PK_{CS}) gains endonuclease function for 5' and 3' overhangs and hairpins. Its mutations render DNA hypersensitive to double-strand breaks and the loss of B and T lymphocytes results in severe combined immune deficiency. This exonuclease is required along with ATM and other proteins for the repair of radiation-induced double-strand breaks (Riballo E et al. 2004 Mol Cell 16:715). ARTEMIS is also required for plant cell and chloroplast division. ▶ATM, ▶endonuclease, ▶exonuclease, ▶lymphocyte, ▶severe combined immunodeficiency, V(D)J; Ma Y et al 2002 Cell 108:781; Fulgosi H et al 2002 Proc Natl Acad Sci USA 99:11501.

Artemis: DNA sequence viewer and annotation tool. ▶ACT; <http://www.sanger.ac.uk/Software/Artemis>.

Arterial Calcification of Infancy (occlusive infantile calcification, 6q dominant): Calcification of the internal lamina of the arteria due to defective ectonucleotide pyrophosphatase/phosphodiesterase 1. Normally the pyrophosphate generated by the enzyme prevents calcification. Rutsch F et al 2003 Nature Genet 34:379.

Arterial Tortuosity Syndrome (20q13.1): A disease of the arterial wall due to disruption of the elastic fibers which produces twists, elongation and aneurysm (sac formation). In one of the genes (SLC2A10), glucose transporter (GLUT10) deficiency upregulated TGF-β (Coucke PJ et al 2006 Nature Genet 38:452). ▶Loeys-Dietz syndrome, ▶Marfan syndrome

Arteriosclerosis: This refers to thickening and hardening of the walls of arterial veins, a common form of heart disease. ▶atherosclerosis

Arthritis: An inflammation and erosion of the major component (aggrecan) of cartilage in the joints is caused by several factors with incomplete penetrance and expressivity. It is a common occurrence in familial gout, a hyperuricemia (excessive uric acid production). Rheumatoid arthritis is generally described as an autoimmune disease. About one-third of the cases involve the HLA-DRB1 *04 alleles in the presence of this condition. The telomeres in CD4⁺ T lymphocytes are eroded during the first two decades of life followed by reduced homeostasis in T cell proliferation later (Schönland SO et al 2003 Proc Natl Acad Sci USA 100:13471). It appears to be autosomal dominant but the genetic control is not entirely clear. The erosion is mediated by aggrecanase (a metalloproteinase with thrombospondin, glycoprotein secreted by the endothelium). ADAMTS5 (a disintegrin and metalloprotease with thrombospondin-like repeats) destroys aggrecan, and its knockout is a promising therapeutic measure

for arthritis in mouse (Glasson SS et al. 2005 Nature [Lond] 434:644; Stanton H et al 2005 Nature [Lond] 434:648). IL-6, IL-8, GM-CSF promote inflammation whereas IL-10, IL-1ra, soluble TNF-R reduce inflammation in rheumatoid arthritis. Anti-TNF- α antibody treatment may offer some promise. In some forms the basic problem is that the lymphocytes target the cell's glucose-6-phosphate isomerase. Its prevalence is about 1% in the general population. ►rheumatic arthritis, ►arthropathy, ►arthropathy-camptodactyly, ►connective tissue disorders, ►cartilage, ►TNF, ►IFN, ►IL, ►NF- κ B, ►*Borrelia*, ►metalloproteinase, ►ADAM, ►osteoarthritis, ►IL-6, ►IL-8, ►IL-10, ►IL-1, ►IL-17, ►GM-CSF, ►TNF-R, ►ZAP-70, ►telomeres, ►T cell; Ota M et al 2001 Genomics 71:263; Feldmann M, Maini RN 2001 Annu Rev Immunol 19:163; Firestein GS 2003 Nature [Lond] 423:356.

Arthroconidiation: A process of fungal conidiation involving germination of conidia, forming hyphae with coupled septation and nuclear division. ►conidia, ►hypha, ►septate

Arthrogryposis: There is unclear (autosomal) genetic determination of this malformation of low recurrence which causes deformation of limbs, hip dislocation, scoliosis (crooked spine), frequently short stature, amyoplasia (poor muscle formation), etc. Distal arthrogryposis (DA1, 9p13.2-p13.1, 9p21-q21) is responsible for dominant club foot and encodes tropomyosin. The DA2B locus (11p15.5) encodes a mutant isoform of troponin (Sung SS et al 2003 Am J Hum Genet 72:681). A neurogenic type is in chromosome 5q35; it is a non-progressive multiple joint contracture disease that is not lethal. *Arthrogryposis-renal dysfunction-cholestasis syndrome* is caused by *VPS33B* mutations, in chromosome 15q26 is neurogenic, with renal tubular dysfunction and neonatal cholestasis that leads to death during the first year of life. X-linked forms have also been described. Severe forms are the *lethal congenital contractural syndrome* (LCCS) in 9q34, 12q13 and 19p13; it is likely that they involve mutation in PIP5K1C encoding phosphatidylinositol-4-phosphate 5-kinase, type I, gamma (PIPKI), an enzyme that phosphorylates phosphatidylinositol 4-phosphate to generate phosphatidylinositol-4,5-bisphosphate, PIP₂ (Narkis G et al 2007 Am J Hum Genet 81:530). *Lethal congenital contractural syndrome type 2* (LCCS2, 12q13) is an autosomal recessive neurogenic form of arthrogryposis that is associated with atrophy of the anterior horn of the spinal cord (Narkis G et al 2007 Am J Hum Genet 81:589). ►limb defects, ►connective tissue disorders, ►Freeman-Sheldon syndrome, ►clubfoot, ►tropomyosin, ►troponin, ►phosphoinositides

Arthroptalmopathy: ►Stickler syndrome

Arthropod: An invertebrate animal with a segmented body like insects, spiders, crustaceans, etc.

Arthropathy: Any disease that affects the joints.

Arthropathy-Camptodactyly (synovitis): This is based on autosomal recessive inheritance. It involves inflammation of the joints (synovial membranes) resembling arthritis. It may have an onset in early childhood. ►connective tissue disorders

Arthus Reaction: An inflammatory immunological reaction to antigen introduced into sensitized animals. The lesion causes activation of the complement and the large number of infiltrating neutrophils release lysosomal enzymes that lead to tissue destruction. ►antigen, ►antibody, ►immune response, ►complement, ►neutrophil, ►lysosomes

Artichoke (*Cynara scolymus*): Vegetable crop; $2n = 2x = 34$.

Artifact: Refers to something that is man-made or a result of human handling of the object, rather than due to entirely natural causes.

Artificial Chromosome: ►YAC, ►BAC, ►PAC, ►human artificial chromosome

Artificial Insemination: This method may be used to overcome the consequences of male infertility in humans or to obtain a larger number of offspring of male animals with economically desirable characters and high productivity. Generally, the sperm is obtained from sperm banks where the semen is preserved at very low temperatures. The cryopreservation may protect against sexually transmitted disease. ►sperm bank, ►ART, ►intrauterine insemination, ►surrogate mother, ►AID, ►AIH, ►ART, ►bioethics

Artificial Intelligence: A device (computer) with the ability to function similarly to human intelligence, i.e., capability of learning, reasoning and self-improvement. ►robot scientist

Artificial Seed (synthetic seed): This is formed usually from somatic embryos that are enclosed by a Na-alginate (polymer of mixed mannuronic and glucuronic acids) capsule in the presence of a calcium salt (CaNO₃ or CaCl₂). Within the capsule an "artificial endosperm" of nutrients may be included. Partially dehydrated embryos may also be used as artificial seed. Artificial seeds may be used for studying the physiology of such constructs and also for micropropagation of some plants. ►micropropagation

Artificial Selection: This process may alter the structure of the population in a way similar to natural selection. When the selection is relaxed or reversed due to

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genetic homeostasis the selection may still be effective for various traits (e.g., bristle number in *Drosophila*, oil or protein content in plants, etc.) that are under polygenic control (see Fig. A124). ▶selection, ▶selection conditions, ▶selection index, ▶gain, ▶homeostasis

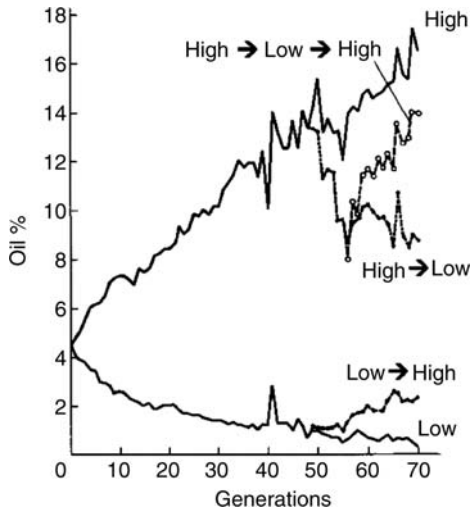


Figure A124. Artificial selection. Selection and reversed selection of oil content in maize. (After Dudley JW (1973) Rep. 28th Annu. Corn Sorghum Res. Conf. Am. Seed Trade Assoc. Washington, DC, p. 126)

Arts Syndrome: ▶ataxia

Arylesterase (ESA, paraoxonase): Encoded in human chromosome 7q22, this enzyme breaks down parathion and related insecticides. ▶cholinesterase, ▶pseudocholinesterase

Aryl Hydrocarbon Receptor (ARH): Mediates the carcinogenic and teratogenic, immunosuppressive, etc. responses to arylhydrocarbons present in many environmental toxins (dioxin, benzo(a)pyrene, cigarette smoke, polychlorinated and polybrominated biphenyls, etc.). ARH regulated genes include cytochromes P450, uridine diphosphate-glucuronosyl transferase, growth factors and proteins. In yeast 54/4507 genes examined modify the ARH signal transduction in five modules involving receptor folding, nuclear translocation, transcriptional activation, receptor level and the PAS complex. (Yao G et al 2004 PloS Biol 2:355). ▶ARNT, ▶PAS, ▶genetic networks, ▶networks, ▶items under separate entries

Arylsulfates: These are aromatic molecules with bound sulfate. Arylsulfatases deficiency is observed in the lipidosis group of diseases, collectively designated as metachromatic leukodystrophy. ▶lipidoses, ▶Krabbe's leukodystrophy, ▶metachromatic leukodystrophy

α-Satellite DNA This refers to centromeric repetitive DNA. ▶repetitious DNA, ▶satellite DNA

AS: ▶asparagine synthetase

AS ODN (antisense oligodeoxynucleotide): This may bind oncogene mRNA and may inhibit cancer growth and regulate the formation of megakaryocytes. It may be used in gene therapy. ▶antisense technologies, ▶cytofectin, ▶megakaryocytes, ▶gene therapy, ▶cancer gene therapy

ASAP: Cell adhesion molecule of the ARF family of proteins. ASAP1 is a regulator of protein sorting through membranes, it activates GTPase and regulates the cytoskeleton. ▶ARF, ▶protein sorting, ▶cytoskeleton, ▶polycystic kidney disease

ASAP: Aster associated protein binds microtubules at the COOH end. Over manifestation or under manifestation of ASAP results in aberrant spindle, delays in mitotic progression and causes cell death because of defects in cytokinesis (Saffin J-M et al 2005 Proc Natl Acad Sci USA 102:11302). ▶aster, ▶spindle, ▶cytokinesis

Asbestos: Mineral silicate fibers are carcinogenic supposedly by being phagocytized and then accumulate around the cell nucleus where they may interfere with chromosome segregation. The mechanical irritation may contribute to mesothelial (lung) cancer. The cells with asbestos release TNF-α and other cytokines. In vitro, asbestos is lethal to mesothelial cells. The treatment of human mesothelial cells with TNF-α considerably reduces toxicity by activating the NF-κB signaling pathway thereby constituting a potential therapy for asbestos damage (Yang H et al 2006 Proc Natl Acad Sci USA 103:10397). ▶TNS, ▶NF-κB; Tweedale G 2002 Nature Rev Cancer 2:311.

Ascaris megalocephala (horse threadworm): It shows very unusual chromosome behavior (see Fig. A125). It has only one pair of large chromosomes in the germline but during somatic cell divisions these large chromosomes are fragmented into numerous small chromosomes. On the basis of this organism Van Beneden discovered in (1883) reductional division in meiosis, a cornerstone of the cytological basis of Mendelian segregation.

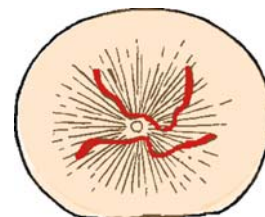


Figure A125. *Ascaris megalocephala univalens*. (Boveri, T.)

A. megalcephala univalens has $2n = 2$, *A. megalcephala bivalens* $2n = 4$, and *A. lumbricoides* $2n = 43$ chromosomes. ▶chromosome breakage programmed

Ascertainment Test: This is generally required in larger mammals with few offspring to determine the segregation ratios on the basis of pooled data of several families. The problem involved in biased sampling (because those families where the parents are heterozygous for the recessive gene escape identification if no homozygotes are observed among the progeny) can be corrected for. The solution is mathematical. According to Mendelian expectation, 3/4 of single-child families has no affected children. Among the two-child families $(3/4)^2 = 9/16$ is the probability that neither will be of recessive phenotype. Of the remaining 7/16 of the families, 6/7 will have one recessive and one dominant and 1/7 should have 2 recessives. Thus, the average expectation is $(1) \times (6/7) + (2) \times (1/7) = 8/7 = 1.143$. In three-child families 27/64 will have no affected offspring, 9/37 will have 2, and 1/37 are expected to have 3 recessives. Therefore, the average expected is $(1) \times (27/37) + (2) \times (9/37) + (3) \times (1/37) = 1.294$. In the same manner the average expectation of recessives for various sizes of families can be determined (see Table A5):

Using this information the number of observed and expected data for affected and unaffected families of varying sizes can be analyzed with the chi square procedure and the goodness of fit can be evaluated:

$$\chi^2 = \frac{(25 - 26.9)^2}{26.9} + \frac{(24 - 22.1)^2}{22.1} = 0.298;$$

The degree of freedom = 1, and the probability of fit is >0.5 (for χ^2 only, values below 0.05 would have some

ground for doubting the fit). A simpler (and less reliable) procedure for determining the average number of recessives (\hat{q})

$$\hat{q} = \frac{R - N}{T - N}$$

where R is the number of recessive segregants observed, N is the number of families showing recessives, and T is the total number of children of these families.

The *ascertainment bias* (the correction for truncated/ incomplete selection of families on the basis of probands) can also be estimated by the Bernstein formula: Expected number of affected recessives $E_r = n_s(p/1 - q^s)$ where s = number of sibs per family, n_s = number of families with s number of sibs, p = segregation ratio, $q = 1 - p$. The results of the ascertainment may not be valid for populations which were not part of the samplings in complex cases. Using DNA sequence information the ascertainment bias may be eliminated because penetrance or expressivity does not affect the correct molecular information. ▶chi square, ▶sib, ▶proband, ▶penetrance, ▶expressivity, ▶segregation ratio; Burton PR et al 2000 Am J Hum Genet 67:1505; Lake SL et al 2000 Am J Hum Genet 67:1515; Haghighi F, Hodge SE 2002 Am J Hum Genet 70:142; Epstein MP et al 2002 Am J Hum Genet 70:886.

Aschheim-Zondek Test (AZT): Uses subcutaneous injection of the urine of human females into immature female mice to test for early pregnancy. Swelling, congestion and hemorrhages of the ovaries and precocious maturation of the follicles in the mice are positive indicators of pregnancy of the tested person. Today, a hemagglutination test or a chorionic gonadotropin test is used. Pregnancy immediately

Table A5. Ascertainment test

| Number of Children | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Average Homozygotes | 1.000 | 1.143 | 1.297 | 1.463 | 1.639 | 1.825 | 2.020 | 2.223 |

| Number of Sibs/Family | Families | Number of Affected Sibs | | Number of Unaffected Sibs | |
|-----------------------|----------|-------------------------|---------------------------|---------------------------|----------|
| | | Observed | Expected | Expected | Observed |
| 1 | 7 | 7 | $7 \times 1 = 7.00$ | 0 | 0 |
| 2 | 10 | 8 | $10 \times 1.143 = 11.43$ | 12 | 8.57 |
| 3 | 4 | 6 | $4 \times 1.297 = 5.19$ | 6 | 6.81 |
| 5 | 2 | 4 | $2 \times 1.639 = 3.28$ | 6 | 6.72 |
| Total 25 | | | 26.90 | 24 | 22.10 |

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raises dramatically the level of this hormone.
 ►hemagglutinin, ►gonadotropin

Asci: Is the plural of ascus. ►ascus

Ascidians: Invertebrate (chordate) sea animals with sexual and asexual reproduction. ►*Ciona intestinalis*; Davidson B, Christiaen L 2006 Cell 124:247, <http://www.ascidians.com/>; <http://crfb.univ-mrs.fr/aniseed/index.php>.

Ascites: In this condition the abdominal fluid (may contain also cells) is excreted in response to cell proliferation in the abdominal cavity because of a neoplasia. The fluid is serum, containing polyclonal antibodies. Cirrhosis or hypoalbuminemia, and experimental injections may also cause ascites.
 ►cirrhosis of the liver, ►albumin

Ascobolus: This fungal genus is advantageously exploited for tetrad analysis. ►tetrad analysis

Ascobolus immersus: An ascomycete where the dissection of the ascospores is very simple, the spores spring off when touched and can be captured on microscope slides. This fungus has been extensively used in studies of recombination and gene conversion; x = 12, 16, 18.

Ascomycetes: Refer to those sites in fungi where the perithecia and apothecia (fruiting bodies) develop.

Ascogenous Hyphae: These diploid or bikaryotic hyphae lead to the formation of fruiting bodies in fungi. ►fruiting body, ►hypha

Ascogonium: This refers to the gametangium (oogonium), the female sexual organ of fungi (also called protoperithecium).

Ascomycete: A large group of different fungi producing either asexual conidiospores and/or ascospores within asci as a consequence of meiosis. ►tetrad analysis

Ascorbic Acid (vitamin C): This anti-scurvy (antiscorbutic) substance is required for proper hydroxylation of collagen and its deficiency causes skin lesions and damages the blood vessels, i.e., symptoms of scurvy. It is also a reducing compound and upon oxidation it is converted into dehydroascorbic acid (see Fig. A126). Together with Fe(II) and O₂ it is a hydroxylating agent for aromatics. In the process H₂O₂ is formed. It has been claimed that high daily

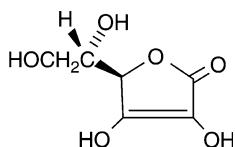


Figure A126. Ascorbic acid

doses of ascorbic acid lower the risks of common cold and other ailments. Further, it has been found to be weakly mutagenic, probably because of its ability to generate free radicals. Most primates and guinea pigs cannot synthesize this vitamin because of numerous alterations in the gene (human chromosome 8p21) encoding L-gluconolactone oxidase and depend on dietary supplies (Nishikimi M et al 1994 J Biol Chem 269:13685). There is a need for an ascorbic acid transporter SLC23a1 (Sotiriou S et al 2002 Nature Med 8:514). The biosynthetic pathway in plants differs from that in animals, algae or fungi. Over expression of a NADPH-dependent D-galacturonate reductase may substantially increase ascorbate production in plants (Agius F et al 2003 Nature Biotechnol 21:177). Vitamin C degradation in plant material can take place enzymatically (via hydrolysis of 4-oxalyl-L-threonate) or during cooking (Green MA, Fry SC 2005 Nature [Lond] 433:83). The therapeutic applications of ascorbate against flu or cancer are controversial although high intravenous doses may have anticancer effects because of H₂O₂ effects (Chen Q et al 2005 Proc Natl Acad Sci USA 102:23604). In the presence of ascorbate low 0.2–2 μM doses of chromate caused 10–15 times more chromosomal breakage in primary human bronchial epithelial cells or lung fibroblasts (Reynolds M et al 2007 Nucleic Acids Res 35:465). ►vitamin C, ►Charcot-Marie-Tooth disease; Lee SH et al 2001 Science 292:2083; Smirnov N et al 2001 Annu Rev Plant Physiol Plant Mol Biol 52:437.

Ascospores: Haploid products of meiosis formed within an ascus (see Fig. A127). ►ascus, ►tetrad analysis



Figure A127. Ascospores

ASCT1: This is a zwitterionic amino acid transporter.
 ►transporters, ►zwitterion

Ascus: A sac-like structure in the *Ascomycete* fungi, containing the four products of meiosis (spores). In many fungi the number of ascospores may increase to eight due to a mitotic division following meiosis. The spores in the asci may be arranged in the same linear order as in the linear tetrad of meiosis (ordered tetrads such as *Neurospora*, *Ascobolus*, *Aspergillus*, etc.) or may be scrambled (unordered tetrad such as in yeast). Asci have been used very effectively to study the mechanics of recombination because the results of single meiotic events could be analyzed separately.
 ►tetrad analysis

Ascus-Dominant: A mutation or even a deletion affects (prevents) the expression of the dominant allele within an ascospore. It has been attributed to reduced dosage, defects in inter-nuclear communication and transvection. ▶ [transvection](#)

ASE1 (anaphase spindle elongation): This is a gene encoding MAP, required for elongation of the mitotic spindle and separation of the spindle poles. The anaphase-promoting complex (APC) degrades it. ▶ [MAP](#), ▶ [spindle](#), ▶ [cell cycle](#), ▶ [centriole](#)

Aseptic: This means that the culture is free from contaminating microorganisms. ▶ [axenic](#), ▶ [pasteurization](#), ▶ [autoclaving](#), ▶ [filter sterilization](#)

Asexual Reproduction: This does not involve fusion of gametes of opposite sex or mating type. Yet, genetic changes in asexual or mainly asexual crustacean *Daphnia* lines genotyped at 126 microsatellite loci and sequencing 16 nuclear protein-coding loci showed spontaneous loss of heterozygosity resulting from ameiotic recombination at many loci (Omilian AR et al 2006 Proc Natl Acad Sci USA 103:18638). ▶ [reproduction](#), ▶ [mitotic recombination](#), ▶ [parasexual mechanism](#)

ASF1 (anti-silencing function protein, CIA/CCG1 interacting factor 1): This is a chaperone for newly synthesized histones H4 and H4 and it participates in nucleosome assembly, DNA replication and repair. ▶ [chaperones](#), ▶ [nucleosomes](#), ▶ [chromatin](#), ▶ [RCAF](#), ▶ [NHEJ](#), ▶ [histone acetyltransferases](#); Mousson F et al 2005 Proc Natl Acad Sci USA 102:5975; English CM et al 2006 Cell 127:495, SR motif, structure: Natsume R et al 2007 Nature [Lond] 446:338.

AS-Fish (antisense fluorescent in situ hybridization): The probe labels the sense strand of the DNA and thus it may make possible to label differentially the transcribed and non-transcribed heterologous DNA, introduced by transformation in the cell. ▶ [FISH](#), ▶ [antisense strand](#)

Ash: The mineral residue of tissues left after igniting the organic material.

Ash Tree: Forest and ornamental trees (*Fraxinus excelsior*, 2n = 46; *F. americana*, 2n = 46, 92, 138).

Ashkenazi: Refers to Jews who lived during the Middle Ages in German lands although they migrated from there to Eastern Europe and other parts of the world. They preserved their ethnic identity and a special gene pool. Therefore, certain hereditary conditions such as Tay-Sachs disease, Gaucher disease, Niemann-Pick's disease, Bloom's syndrome, higher I.Q, etc. occur at increased frequencies in the population compared to some other ethnic groups. The haplotype spectrum based on the non-recombining

part of the Y chromosome and microsatellite haplotypes indicate some significant differences from the Sephardic Jews and similarities to some Eastern European Slavic and Turcic (Khazar) ethnic groups. Some likely Khazar introgression appeared among Hungarian Jews because among the invaders of the Carpathian basin the tribe of chieftain Taksony was of Turcic ethnicity and embraced Jewish religion during the seventh-eighth century. ▶ [Sephardic](#), ▶ [Jews and genetic diseases](#), ▶ [introgression](#); Behar DM et al 2003 Am J Hum Genet 73:768.

Asialoglycoprotein Receptor: Normally many soluble glycoproteins have sialic acid residues attached to their end. The sialic acid residues determine whether or not the glycoprotein is circulated in the bloodstream. If the sialic acid is lost the glycoprotein may bind to the plasma membrane of the liver cells (hepatocytes) and become asialoglycoprotein receptors. Glycoproteins attached to these receptors are generally degraded by the lysosomes of the liver. ▶ [sialic acid](#)

Asilomar Conference: In 1975, when recombinant DNA was beginning to be widely used, scientists convened at this place in California to prepare voluntary guidelines for protection against the potential hazards of the application of new techniques. ▶ [containment](#); Berg P et al 1975 Proc Natl Acad Sci USA 72:1981.

ASK1 (apoptosis signal regulating kinase): This member of the mitogen-activated MAP protein family is activated by TNF- α . It induces apoptosis but it may inhibit TNF- α -induced apoptosis. It stimulates JNK activation, and also interacts with the TRAF family especially with TRAF2- induced JNK activation. ▶ [apoptosis](#), ▶ [MAP](#), ▶ [TNF](#), ▶ [JNK](#), ▶ [TRAF](#)

ASLV (avian sarcoma-leukosis virus): ▶ [retroviruses](#)

ASMD (anterior segment mesenchymal dysgenesis): This is encoded by the dominant PTX3 gene (10q25) affecting the development of cataract and later midbrain, tongue, incisors, breastbone (sternum), vertebrae and limbs. ▶ [cataract](#), ▶ [Rieger syndrome](#), ▶ [eye diseases](#)

ASN.1 (Abstract Syntax Notation): Describes the format in sequence databases to which all other files correspond; asn.all describes the formats of both literature and genetic sequence messages. ▶ [Bioseq](#), ▶ [gi](#), ▶ [accession](#); <http://asn1.elibel.tm.fr/>.

Asn-Pro-X-Tyr: An amino acid sequence responsible for the internalization of low-density lipoproteins (LDL) of the membranes. LDL.

ASO: Refers to allele-specific oligonucleotide probe. Screening can be carried by semi-automated procedures. ▶ [allele-specific probe](#)

A

ASP Analysis: This analysis is used to estimate linkage in cases when a particular trait is under polygenic control. The co-segregation of multiple markers is followed in individuals who manifest the particular trait and determine which of the markers are most consistently present in these individuals. The analysis still requires the MAPMAKER/SIBS computer program, which evaluates multiple segregating families. ► [MAPMAKER](#), ► [QTL](#), ► [interval analysis](#)

Asparagine (α -aminosuccinamic acid): $\text{NH}_2\text{COCH}_2\text{CH}(\text{NH}_2)\text{COOH}$; its RNA codons are AAU, AAC.

Asparagine Synthetase (AS): Asparagine synthetase of bacteria uses ammonia as an amide donor, rather than glutamine as the mammalian enzyme. Cells expressing the bacterial AS will grow in asparagine-free medium if the glutamine analog, albizzin is present. In AS transfected mammalian cells the gene can be amplified in the presence of β -aspartyl hydroxamate, an analog of aspartate, and thus AS can be used as a dominant amplifiable marker in mammalian cell cultures. The mammalian genes are present in human chromosomes 7q21-q31, 8pter-q21, 21pter-q22. The AS genes do not have TATA and CAAT boxes in the promoter. They are homologous to the hamster *tsII* gene that is required for passing the cell cycle through the G1 stage. ► [amino acid metabolism](#), ► [cell cycle](#), ► [house keeping genes](#), ► [CAAT box](#), ► [TATA box](#), ► [AS in leukemia chemotherapy](#); Richards NGJ, Kilberg MS 2006 Annu Rev Biochem 75:629.

Asparaginyl tRNA Synthetase (ASNRS): This charges the appropriate tRNA with asparagine. In human cells it has been located in chromosome 18. ► [aminoacyl tRNA synthetase](#)

Asparagus officinalis (a dioecious monocot, $2n = 20$): Refers to sex determination by XX pistillate and XY staminate plants (see Fig. A128). By anther culture YY plants can be obtained that can be vegetatively propagated or by pollination they produce exclusively male progeny. The male plants are of special economic value because their yield/area of edible spears is substantially higher. Almost half of the human populations excrete methanethiol in their urine after consuming this vegetable. The excreter trait appears to be autosomal dominant. The ability to smell this particular odor may also be under dominant control. ► [YY asparagus](#), ► [olfactory genetics](#)



Figure A128. Asparagus

Aspartame (Nutra-Sweet): Refers to *N*-L- α -aspartyl-L-phenylalanine-1-methyl ester, an artificial low-calorie food and beverage sweetener; about 160 times as sweet as sucrose. It is not recommended for phenylketonurics because it contains phenylalanine. ► [saccharine](#), ► [fructose](#), ► [phenylketonuria](#)

Aspartate Aminotransferase (glutamate oxaloacetate transaminase, GOT1, GOT2): One of the functional forms of this enzyme GOT1, is encoded in human chromosome 10q24.1-q25.1 and it is expressed in the cytosol. A homolog GOT2 is encoded in human chromosome 16q12-q21 and it is expressed in the mitochondria. Pseudogenes of the latter have been located at 12p13.2-p13.1, 1p33-p32 and 1q25-q31. In the liver, the mitochondrial enzyme is largely present whereas the cytosolic enzyme is mainly located in the serum. ► [amino acid metabolism](#), ► [asparagine synthetase](#)

Aspartate Phosphatase: ► [two-component regulatory systems](#)

Aspartate Proteases: The opening up of DNA for the integration of retrotransposable elements. Their protein generally shares the motif D,D45E (aspartic acid, aspartic acid, 35 amino acids, glutamic acid). ► [transposase](#), ► [retrotransposons](#)

Aspartic Acid ($\text{HOOCCH}_2\text{CH}[\text{NH}_2]\text{COOH}$): This is a negatively charged amino acid. ► [amino acids](#), ► [aspartate aminotransferase](#), ► [ancient DNA](#)

Aspartic Acid Racemization: ► [ancient DNA](#)

Aspartoacylase Deficiency (aminoacylase-2 deficiency, Canavan disease, ACY2): This enzyme cleaves acylated amino L-acids into an acyl and amino acid group, whereas amino-acylase-1 (ACY-1) similarly cleaves all acylated L-amino acids, except L-aspartate. The autosomal recessive disorder has an early or late onset resulting in debilitating muscle, eye defects, mental retardation and spongy degeneration of the white matter of the brain. A defect in myelin synthesis is the major cause of the frequently fatal diseases (Madhavarao C et al 2005 Proc Natl Acad Sci USA 102:5221). There may be a 200-fold increase of *N*-acetylaspargic acid in the urine. Its incidence is increased among Jews of Ashkenazi descent and in Saudi Arabic populations. The chromosomal location is 17pter-p13. The catalytic site of aspartoacylase reveals close structural similarity to those of carboxypeptidases despite only 10–13% sequence identity between these proteins. Around 100 C-terminal residues of aspartoacylase form a globular domain with a two-strand β -sheet linker that wraps around the N-terminal domain. The long channel leading to the active site is formed by the interface of the N- and C-terminal domains. The

C-terminal domain is positioned in a way that prevents productive binding of polypeptides in the active site. The structures revealed that residues 158–164 may undergo a conformational change that results in the opening and partial closing of the channel entrance (Bitto E et al 2007 Proc Natl Acad Sci USA 104:456). ▶amino acid metabolism, ▶neuromuscular defects, ▶mental retardation, ▶eye diseases, ▶Jews and genetic diseases, ▶carboxypeptidase

Aspartylglucosaminuria (AGA): A chromosome 4 recessive defect of the enzyme aspartylglucosaminidase (4q32-q33) may eliminate an important S—S bridge of the protein resulting in neurological-mental and other defects. Its frequency is higher ($\sim 4 \times 10^{-5}$) in populations of Finnish descent. ▶amino acid metabolism, ▶disulphide bridge, ▶sialidosis; Saarela J et al 2001 Hum Mol Genet 10:983.

AS-PCR: Refers to allele-specific PCR. polymerase ▶chain reaction

ASPD (Artificially Selected Proteins/Peptides Database): ▶phage display

Asperger Syndrome (Xq22.3, Xq13-q21): This is a form of childhood autism with less severe expression than the adult forms encoded at several autosomal locations. Susceptibility genes have been located to 3q25-q27, 3q24-q21, 17p13, 1q21-q22 and to TBX1 (T-box protein) transcription factor at 22q11.2. ▶autism

Aspergillus: Numbering nearly ~185 species, including 20 human pathogens of ascomycetes, *Aspergillus nidulans* ($n=8$, $\sim 3 \times 10^7$ bp, 9,541 protein-coding genes) is a favorite organism for studies of recombination (see Fig. A129). One meiotic map unit is about 5–10 kbp. It has been extensively used for mitotic recombination. Asexual reproduction is by conidiospores (3–3.5 μm). This is a homothallic fungus and thus does not have different mating types. In the cleistothecium there are up to 10,000 binucleate ascospores in 8-cell linear, ordered asci. Transformation systems



Figure A129. *Aspergillus nidulans* conidiophore and conidia

are available. It yields about 5×10^3 transformants/ μg DNA. *A. flavus* is responsible for the production of aflatoxin, an extremely poisonous toxin that is found on infected plant residues, seeds, etc. *A. fumigatus* ($\sim 2.8 \times 10^7$ bp, 9,926 protein-coding genes) is a soil-born fungus, which causes ear, nose, lung and other infections in humans and animals. *A. oryzae* (3.7×10^7 bp, 12,074 protein-coding genes) is important for food technology (sake, soy sauce and miso [a fermented Japanese soy paste]). The size of protein-coding genes varies from 1,547 (*nidulans*) to 1,389 (*fumigatus*) and 1,1529 (*oryzae*). *A. nidulans* is more closely related to *A. fumigatus* than to *A. oryzae*. *A. nidulans* has a known sexual cycle whereas the other two species generally reproduce asexually. All three species display homology of 5000 non-coding regions. The homothallic *A. nidulans* has both the MAT locus and a HMG (high-mobility group) gene. The heterothallic *A. fumigatus* conserved through evolution only HMG but no MAT and the heterothallic *A. oryzae* has only the MAT locus but no HMG. The latter two species have, however, highly homologous sequence to the flanking sequences sex-determination loci of *A. nidulans*. The industrially important *A. nigr*a genome has also been sequenced (Pel HJ et al 2007 Nature Biotechnol 25:221). ▶aflatoxins, ▶mitotic recombination, ▶recombination, ▶cleistothecium, ▶conidia, ▶tetrad analysis, ▶mating type determination in yeast, ▶high-mobility group of proteins, ▶nuclear membrane, comparative genomic sequences of *Aspergilli*: Galagan JE et al 2005 Nature [Lond] 438:1105; Nierman WC et al 2005 Nature [Lond] 438:1151; <http://www.ncbi.nlm.nih.gov/genome/guide/aspergillus/>, scientific and medical information: <http://www.fgsc.net/aspergenome.htm>.

Aspermia: Refers to the lack of ejaculating ability of the male.

Asphyxiating Thoracic Dystrophy (Jeune syndrome, 15q13): This is a recessive chondrodysplasia causing constricted thorax and respiratory difficulties and possibly different malformations; it is frequently lethal in the case of infants. It bears similarity to Ellis-van Creveld syndrome. ▶Ellis-van Creveld ▶syndrome

Aspirin (salicylic acid acetate): An analgesic, anti-fever, anti-inflammatory and anti-coagulant drug (blood thinner) (see Fig. A130).

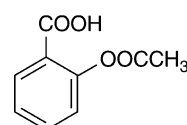


Figure A130. Aspirin

A

It inhibits cyclooxygenases, IKK and JNK. The aspirin metabolite salicylic acid inactivates staphylococcal virulence factors and thus acts directly on the bacteria rather than on the host organism (Kupferwasser LI et al 2003 J Clin Invest 112:2221). Aspirin reduces the risk of major cardiovascular disease in both men and women (Ridker PM et al 2005 New England J Med 352:1293). Nitroaspirin increases the function of tumor-antigen-specific T lymphocytes and aids the anti-tumor effect of cancer vaccines (De Santo C et al 2005 Proc Natl Acad Sci USA 102:4185). Some individuals may show hypersensitivity to aspirin and precautions are required in the case of some hearing deficits, gout, hyperthyroidism, some kidney and liver problems, anemia, glucose-6-phosphate deficiency and Hodgkin's disease. Contraindication is warranted for hemophilia, other bleeding diseases, pregnancy, nursing, chickenpox and Rye syndrome. ▶salicylic acid, ▶cyclooxygenases, ▶IKK, ▶JNK, ▶host-pathogen relations; Kurumbail RG et al 1996 Nature [Lond] 384:644.

Asplenia: One form (Ivemark syndrome) of asplenia is usually sporadic or autosomal recessive and it is associated with the absence or enlargement of the spleen or multiple accessory spleens and cardiac and other organ malformations. Another form of asplenia involves most conspicuously cystic livers, kidneys and pancreas. ▶spleen; Nikawa N et al 1983 Am J Med Genet 16:43.

ASPP (apoptosis stimulatory proteins of p53): These are specific activators of tumor suppressor p53. iASPP is an inhibitor of p53 and is thus an oncoprotein. ▶p53, ▶oncoprotein; Bergmaschi D et al 2003 Nature Genet 33:162.

Assay: Refers to a test for mutagenic effectiveness or efficiency or the velocity of a chemical reaction catalyzed by enzymes or the test of function of any biological process.

Assembly Initiation Complex: The minimal elements required for the completion of the assembly of the viral components. ▶bacteriophages

Assignment Test: ▶somatic cell hybrids

Assimilation: This is a process for converting nutrients into the cell constituents and also, for blending of an initially different ethnic (cultural) group into the general population. ▶genetic assimilation

Association: The joint occurrence of pathological symptoms, which do not have an expected common functional basis. Some of the associated genetic factors may indicate, however, disease risk. ▶syndrome, ▶PAF; Lohmueller KE et al 2003 Nature Genet 33:177.

Association Constant (K_a): Indicates the association between the components of a complex. The larger the K_a the stronger is the association.

Association Mapping: Identifies chromosomal regions containing disease-susceptibility or other genes on the basis of their association (linkage) with other marker(s) in a population rather than in a pedigree. The association may not necessarily indicate a linkage because selective forces may bias the observations in small populations. Moreover, recent migration or other admixture may lead to a bias. A transmission disequilibrium test may provide a remedy for the spurious association. With the availability of SNP and microsatellite markers genome-wide association between a number of genetic factors and complex disease traits can be attempted (Hirschhorn JN, Daly MJ 2005 Nature Rev Genet 6:95). ▶transmission disequilibrium test, ▶linkage disequilibrium, ▶haplotype block, ▶family-based association tests [▶FBAT], ▶QTL, ▶SNIPs, ▶triad ▶test; Sham PC 2000 Am J Hum Genet 66:1616; Wang WYS et al 2005 Nature Rev Genet 6:109, power and efficiency: de Bakker PIW et al 2005 Nature Genet 37:1217; Yu J et al 2006 Nature Genet 38:203; Laird NM, Lange C 2006 Nature Rev Genet, 7:385.

Association Phase: Refers to the coupling phase in a linkage, a term used in fungal genetics. ▶coupling phase, ▶repulsion, ▶crossing over, ▶linkage

Association Site: Periodically distributed, microscopically detectable multiple interstitial association points are also called nodules. The distance between the paired chromosomes is about 0.4 μm . ▶zygotene stage, ▶meiosis, ▶synaptonemal complex, ▶recombinational node

Association Test: This is basically a 2×2 contingency chi square test based on a panel:

where a, b, c, d represent the number of observations (+ +), (+ -), (- +) and (- -), respectively; n = the total number of observations. If b = c = 0, there is no association. The significance of the association is tested $\chi^2 = \frac{n(ad-bc-0.5)^2}{(a+c)(a+b)(b+d)(c+d)}$ chi square, and the probability of a greater chi square can be determined by a χ^2 table or χ^2 chart for 1 degree of freedom. The association test is most useful for studying a homogeneous population. A particular association may not be an indication of a genetic linkage, a physiological or cause-effect relationship but may provide useful information on the relation between two diseases or whether or not the reciprocal crosses are identical. A family-based association test for QTLs has similarity to the linkage disequilibrium approaches (Lange C et al 2002 Am J Hum Genet 71:1330). Single nucleotide polymorphism can be exploited for genome-wide search of SNP and disease

susceptibility association (Van Steen K et al 2005 Nature Genet 37:683). In the direct approach the candidate genes are sequenced and non-synonymous codon changes (SNPs) are most likely to be associated with disease (Cohen JC et al 2004 Science 305:869) although some non-synonymous substitution are neutral regarding function; the structural effect of SNPs may be more critical for disease and 26–32% of the non-synonymous natural SNPs affect function in a deleterious manner (Chaseman D, Adams RM 2001 J Mol Biol 307:683). The SIFT (sorting tolerant from intolerant) computer program can distinguish between neutral and deleterious amino acid changes in a protein sequence (Ng PC, Henikoff S 2003 Nucleic Acids Res 31:381, <http://blocks.fhcrc.org/sift.SIFT.html>). In the indirect approach, whole-genome associations are sought (Carlson CS et al 2004 Nature [Lond] 429:446). Such studies may rely on heritability estimates, which include the effect of several gene loci as well as the effects of the environment. The variations, however, can be partitioned to components by appropriate experimental design and statistics (see Table A6) (Mountain JL, Risch N 2004 Nature Genet 36:S48). ▶linkage disequilibrium, ▶association mapping, ▶chi square, ▶SNIPS, ▶heritability, ▶partitioning, ▶Odds ratio; Lange C, Laird NM 2002 Am J Hum Genet 71:575; Lange C et al 2003 Am J Hum Genet 73:801; Balding DJ 2006 Nature Rev Genet 7:781.

Table A6. Association test

| Association test | First Variable | | |
|------------------|----------------|---|---|
| | + | – | |
| Second variable | + | a | b |
| | – | c | d |

Assortative Mating: Mates are chosen on the basis of preference or avoidance (positive or negative assortative mating), rather than at random, e.g., tall people frequently chose tall spouses; educated, higher economic or social status individuals usually marry within their group. Traits unknown to the majority, like blood groups, usually do not come into consideration in mate selection. Assortative mating may contribute only slightly to the average coefficient of inbreeding (f) in human populations: $\bar{f} = \frac{r}{2n_e(1-r)+r}$ where r = correlation coefficient, n_e = an equivalent number of genes ($n_e = \frac{\sum_{ij} \sigma_i \sigma_j}{\sum_i \sigma_i^2}$). Assortative mating may have some effect on the expression of a quantitative trait and the heritability becomes $h^2 = \hat{h}^2 [1 - (1 - \hat{h}^2)A]$ where A is the product of the

average heritability and the phenotypic correlation, i.e., $r \hat{h}^2$. ▶controlled mating, ▶mating system, ▶inbreeding, ▶correlation; Rice TK, Borecki IB 2001 Adv Genet 42:35.

Astacin: This is a zinc-metalloprotease. ▶bone morphogenetic protein

Aster: Radiating structures around the two (round) centrosomes are visible in some animal cells (see Fig. A131). ▶centrosome, ▶centrioles, ▶ASAP; figure is redrawn after Cleveland LR 1938 Biol Bull 74:41.

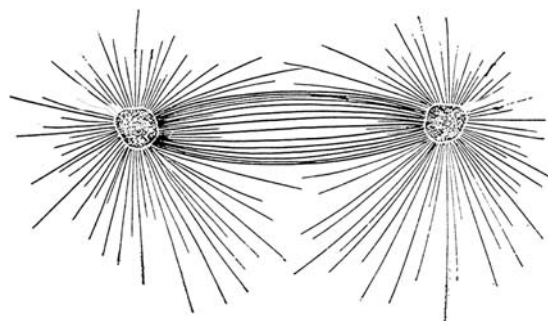


Figure A131. Aster

Asthenozoospermia: Less than 25–50% of the spermatozoa show forward motility. It appears that reduced OXPHOS activity in the mitochondria affects them. Defects in dynein axonemal heavy chain (DNAH1, 3p21.3) may also be concerned. ▶OXPHOS, ▶dynein, ▶cytoplasmic male sterility; Ruiz-Pesini E et al 2000 Am J Hum Genet 67:682; Neesen J et al 2001 Hum Mol Genet 10:1117.

Asthma: This is a respiratory disease due to multiple causes affecting ~155 million people worldwide. Nasal polyps or elevated level of immunoglobulin A (IgA) or IgE may cause some autosomal recessive forms. Key players in the development of asthma are interleukin-13 (IL-13), IL-10 because they guide immature T cells into the development of T_H2 lymphocytes. IL-4 controls the development of B cells (that produce IgE) and IL-5, IL-3 and GM-CSF also play a role through eosinophils that are required for allergic inflammation. Transgenic mouse line genetically devoid of eosinophils lack the inflammatory response (mucus and airways hyper-responsiveness) of asthmatic animals (Lee JJ et al 2004 Science 305:1773). Mast cells and basophils affect the production of histamines, cytokines and chemokines control acute symptoms of asthma. The mast cells respond to IgE and the allergens. The interleukin gene cluster is located in human chromosome 5q31-q33. Genes in human chromosomes 1p32, 2q, 5q31, 6p21, 7p, 8p23, 11q21, 12q12, 13q, 14q24, 15q13 and perhaps other sites appear to be associated with the manifestation of asthma. In different populations different loci may play a major role. The α chain

A

of IL-4 receptor binds IL-13 to the T^H2. Susceptibility to asthma is controlled by a few genes and the heritability has been estimated as ~75%. Asthma—as well as some other anomalies of the immune system—also has a maternal effect. The risk of maternal transmission seems to be fourfold higher. This may be caused either by allelic exclusion, imprinting or by placental transfer or breastfeeding. Indeed, the IgE receptor (FCεRI-β, IL-5) has been mapped to a chromosome (11q13) that commonly affects imprinting. The metalloprotease ADAM33 (20p13) appears to be an important regulator of the disease (Van Eerdewegh P et al 2002 Nature [Lond] 418:426). Glucocorticoids are most commonly used in medication. Immunoglobulin free light chains (κ) mediate hypersensitivity response and the light chain antagonist 9-mer peptide F991 can abrogate the development of airways obstruction, hyperresponsiveness and pulmonary inflammation (Kraneveld AD et al 2005 Proc Natl Acad Sci USA 102: 1578). In asthma-sensitive mice, endogenous S-nitrosothiols (R-S-N=O) are depleted because of increased S-nitroso-glutathione reductase activity. Thus, the enzyme may be a logical target for therapeutic intervention (Que LG et al 2005 Science 308:1618). ▶immunoglobulins, ▶polyp, ▶protease ▶inhibitor, ▶allergy, ▶γδ T cell, ▶T cells, ▶IL-13, ▶IL-10, ▶IL-4, ▶IL-5, ▶IL-3, ▶imprinting, ▶allelic exclusion, ▶hypersensitive reaction [▶animals], ▶atopy, ▶platelet activating factor, ▶eczema ▶filaggrin, ADAM; Xu J et al 2001 Am J Hum Genet 68:1437; Niimi T et al 2002 Am J Hum Genet 70:718; Umetsu DT et al 2002 Nature Immunol 3:715; Laitinen T et al 2004 Science 304:300, nitrosothiol pharmacology: Hogg N 2002 Annu Rev Pharmacol Toxicol 42:585, genes; Ober C, Hoffjan S 2006 Genes Immunol 7:95, <http://cooke.gsfc.de/asthmagen/main.cfm>.

ASTRAL: This is a compendium of protein structures, protein structure, structural classification of proteins, SCOP; <http://astral.berkeley.edu/>.

Astrobiology: This is the study of the possibility of biology in the stars. ▶exobiology, ▶extraterrestrial life

Astrocyte: Refers to a type of branching cell that supports the nervous system. glial cells (see Fig. A132).



Figure A132. Astrocyte

Astrocytosis: Denotes an increase in astrocyte number because of neuronal loss.

ASV: The avian sarcoma virus of birds is an oncogenic RNA virus that can induce sarcoma in rodents.

▶sarcoma

Asymbiotic Nitrogen Fixation: This proceeds by a microorganism without dependence on cohabitation with other organisms such as by members of the soil bacterial species *Azotobacter* and *Clostridium*. ▶nitrogen fixation, ▶symbiosis

Asymmetric Carbon: This atom has four different covalent attachments. ▶covalent bond

Asymmetric Cell Division: This is a requisite for embryonal differentiation and these divisions specify the dorso-ventral and anterior-posterior polarities of the body pattern (see Fig. A133). Several protein factors specify the process. The orientation of the spindle in *Drosophila* involves the localization of the Numb and Prospero proteins in the basal cells and the polarity instructions may come from the product of the *inscrutable* (*insc*), *partner of inscrutable* (*pins*) and other loci. Yeast (*Ash1p*) and *Caenorhabditis* (*SKN-1*) also have controls similar to Numb and Prospero and *she* and *par* genes, respectively, are analogous to *inscrutable*. In *Drosophila* epithelium the adherens junctions inhibit asymmetric divisions. Centrosomally located mRNAs may be asymmetrically transmitted during the embryonic cleavage divisions (Lambert JD, Nagy LM 2002 Nature [Lond] 420:682). Cdc2 appears to link the asymmetric division machinery and the cell cycle. In the initial determination of the left-right axis in the embryo, the leftward flow of the extraembryonic fluid propelled by the primary monocilia plays a role in vertebrates from mouse, rabbit and medakafish and probably others too (Okada Y et al 2005 Cell 121:633). Embryonic stem cells have the potential of self-renewal (symmetric development) or differentiation into various types of cells (asymmetric divisions). ▶morphogenesis in *Drosophila*, ▶polarized differentiation, ▶spindle, ▶axis of asymmetry, ▶left-right asymmetry, ▶adherens junction, ▶polarCdc2; Grill SW et al 2001 Nature [Lond] 409:630; Knoblich JA 2001 Nature Rev Mol Cell Biol 2:11. Adler PN, Taylor J 2001 Curr Biol 11:R233; Knust E 2001 Cell 107:125; Betschinger J et al 2003 Nature [Lond] 422:326, review: Betschinger J, Knoblich JA 2004 Curr Biol 14:R674; Morrison SJ, Kimble J 2006 Nature [Lond] 441:1068.

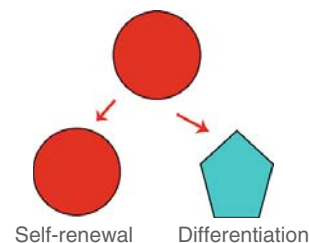


Figure A133. Asymmetric cell division

Asymmetric Heteroduplex DNA: ► Meselson-Radding model of recombination

Asymmetric Hybrid: Some of the chromosomes of one or the other parent are lost. ► somatic hybrids

Asymmetric Inheritance: ► asymmetric cell division

Asymmetric Mutation: ► mutation asymmetry

Asymmetric Replication: At the replication fork DNA synthesis on the leading and lagging strands proceeds in an opposite direction relative to the base of the fork. ► replication, ► replication fork

Asynapsis: Refers to the failure of chromosome pairing. ► desynapsis, ► synapsis

Asymptomatic: This is a disease without any symptoms.

Asymptotic Distribution: This type of distribution is observed in a sample or population when the n becomes very large. *Asymptotic relative efficiency* indicates the ratio of sample sizes required to obtain the same accuracy. An *asymptote* is a curve steadily approaching but never intersecting a straight line.

At Hooks: These are DNA minor groove-binding peptides, common in chromatin-associated proteins. The AT hooks generally contain a conserved GRP (glycine-arginine-proline) core surrounded by basic amino acids. They assist other proteins in binding to DNA.

At Least One Hypothesis: Every NK cell in an individual expresses at least one inhibitory receptor molecule specific for one or another self-MHC class I molecule. Consequently, self-tolerance is increased since many NK cells would be capable of destroying any autologous cells that have down-regulated MHC class I molecules. ► killer cells, ► MHC, ► self-tolerance, Valiante NM et al 1997 Immunity 7:739.

Atabrine: This is a preparation of quinacrine, an antimalaria and antihelminthic (intestinal tapeworm) drug. The quinacrine mustard (ICR-100) is a radiomimetic mutagen. ► quinacrine, ► radiomimetic

ATase: ► UTase

Atavism: Refers to the recurrence of expression of traits of ancestors beyond great grandparents. It is based on either recessive, complementary recessive or recombination of genes or special environmental conditions. For some time in the twentieth century it was no longer used in genetic literature. Atavism may, however, have a real basis in the genetic material and may represent in an altered form of ancient genetic sequences that are expressed in an "atavistic"

manner if appropriately activated by a developmental program shift. Under such circumstances, from the rudimentary limb buds of the whales occasionally hind limb bones may develop. Hypertrichosis in humans, encoded in chromosome Xq24-q27.1, also represents such an atavistic reprogramming. These atavistic changes may not be basically very different from the expression of homeotic genes. (Atavus in Latin means great great grandfather). ► hypertrichosis, ► homeotic genes, ► non-Mendelian inheritance, ► paramutation; Verhulst J 1996 Acta Biotheor 44:59.

Ataxia Telangiectasia (AT): This is one of almost a dozen human ailments involving ataxias: poor coordination of the muscles because of dilations in the brain blood vessels, reduced immunity, elevated level of α -fetoprotein, DNA repair, etc. Its appearance in human diseases is attributed to instability and breakdown of chromosomes 14, 7, 2, 11 and 12 although the major locus (150 kb genomic DNA and 66 exons transcribed into 13 kb RNA) appears to be at chromosome 11q22-q23. Leukemias and other malignancies are very common among these patients. Cultured cells of the affected individuals are highly sensitive to both X-ray and UV damage. Further, standard radiation therapy for malignant tumors may prove fatal in such cases. The basic defect in AT is either in a DNA-dependent phosphatidylinositol protein kinase (M_r 350K) that controls progression of the cell cycle (p53) or in DNA repair and recombination (its homologs are MEC1, SAD3, ESR1). Alternatively, it has been found that an inositol 1,4,5-trisphosphate receptor (IP^3R1) deficient mouse mutants either die in utero or when born display severe ataxia and die shortly thereafter. The normal allele of AT stabilizes double-strand DNA breaks and promotes apoptosis and the deficiency of this function can explain the symptoms caused by its (ATM) mutation (Bredemeyer AL et al 2006 Nature [Lond] 442:466). It now appears that the mutant AT protein (ATM, 11q22.3) interacts with c-Abl oncogene resulting in radiation-sensitivity and in the arrest of the cell cycle at the G1 phase. An SH3 domain of c-ABL interacts with a DPAPNPPHFP amino acid sequence in ATM. As a consequence of radiation the tyrosine kinase activity of c-Abl is reduced in the ATM cells. Homozygosity of this recessive human gene has a frequency about 5×10^{-5} and the frequency of the carriers, prone to breast cancer and other malignancies, is about 1%. All mutations, which cause ataxia telangiectasia in homozygotes involve ~2.4 increased risk for breast cancer in the heterozygotes (Renwick A et al 2006 Nature Genet 38:873). The *spinocerebellar ataxia* (SCA5) of human chromosome 11 is caused by instability of the CAG trinucleotide repeats. SCAs include more

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than 16 genetically distinct neurodegenerative anomalies. SCA6 involves defects in the α subunits of Ca^{2+} ion channel. SCA1 is in chromosome 6p23.5-p24.2 and has CAG instability resulting in polyglutamine protein misfolding. SCA2 maps to 12q23-q24.1, SCA3 in 14q24.3-qter, SCA4 in 16q. The autosomal dominant cerebellar ataxia type III (SCA11) maps to 15q14-21.3 region. SCA10 is in human chromosome 22. The *autosomal dominant cerebellar ataxia* (ADCA type II) with pigmentary muscular dystrophy is coded in human chromosome 3p12-p21.1, and ADCA-like recessive gene is at 9q14. A nonepisodic dominant form (19q13.4) is due to mutation in protein kinase $\text{C}\gamma$ (Chen D-H et al 2003 *Am J Hum Genet* 72:839). *Episodic ataxia* is associated with defects in potassium ion channel or in the α subunits of Ca^{2+} channel functions. Ataxia with oculomotor apraxia (AOA2, 9q34) is a recessive ataxia telangiectasia-like disease, characterized by difficulty in moving the eyes and elevated levels of α -fetoprotein. The basic defect is in DEAXQ-box helicase (senataxin) involved in RNA maturation (Moreira M-C et al 2004 *Nature Genet* 36:225). X-linked ataxia with deafness and vision loss (*Arts syndrome*, Xq22.1-q24) also involves mental retardation and is apparently caused by mutation in phosphoribosyl pyrophosphate synthetase 1 gene (PRPS1) and impaired purine biosynthesis (de Bouwer APM et al 2007 *Amer J Hum Genet* 81:507). ▶Friedreich ataxia, ▶Nijmegen breakage syndrome, ▶DNA repair, ▶DNA replication in eukaryotes, ▶excision repair, ▶carcinogenesis, and a number of genetic diseases, which may have ataxic symptoms such as neuromuscular diseases, ▶gangliosidosis, ▶ β -galactosidase, ▶Niemann-Pick disease, ▶metachromatic leukodystrophy, ▶neurofibromatosis, ▶olivopontocerebellar atrophies, ▶Refsum diseases, ▶Usher syndrome, ▶Hartnup disease, ▶light-sensitivity diseases, ▶myotonia, ▶cancer, ▶cell cycle, ▶DNA repair, ▶trinucleotide repeats, ▶AVED, ▶RAD3, ▶abl, ▶SH3, ▶phosphoinositides, ▶ion channels, ▶p53, ▶breast cancer, ▶Mre11, ▶Mantle cell lymphoma, ▶telangiectasia, ▶DEAD-box proteins, ▶fetoprotein- α ; Taroni F, DiDonato S 2004 *Nature Rev Neurosci* 5:641; Paulson HL et al 2005 *Neuron* 46:845, autophosphorylation of Atm protein-activation: Pellegrini M et al 2006 *Nature [Lond]* 443:222, Gros-Louis F et al 2007 *Nature Genet* 39:80.

Ataxin: The protein responsible for SCA1 ataxia associates with a cerebellar leucine-rich acidic protein and alters the nuclear matrix. The expression of the neurodegenerative disease depends on the phosphorylation of ataxin-1 containing expanded polyglutamine tract by Akt and then its association

with protein 14-3-3. Ataxin 3 is involved in deubiquitylation as well as in aggresome formation (Burnett BG, Pittman RN 2005 *Proc Natl Acad Sci USA* 102:4330). ▶ataxia, ▶spinocerebellar ataxia, ▶trinucleotide repeats, ▶Akt, ▶protein 14-3-3, ▶SCA, ▶aggresome, ▶ubiquitin; Emamian EE et al 2003 *Neuron*, 38:375; Chen HK et al 2003 *Cell* 2003 113:457.

ATCC: American Type Culture Collection maintains cell cultures of prokaryotes and lower and higher eukaryotes.

Ateles (spider monkey): ▶cebidæ

Atelosteogenesis (5q32-q33.1): Refers to fetal defect in the formation/elongation of fetal skeletal bones due to a defect in the diastrophic dysplasia sulfate transporter. ▶diastrophic dysplasia

ATF2 (activating transcription factor): A family of proteins containing homologous basic/leucine-zipper (bZIP) binding domains; it is regulated by the JNK signal transduction pathway. Mutations in ATF2 interfere with the retinoblastoma and E1A oncogene's transcription suppressing activities. ATF6 is a membrane-bound transcription factor, which activates genes of the endoplasmic reticulum (ER). ATF4 is a suppressor of CREB-mediated long-term potentiation. When unfolded proteins accumulate in the ER ATF6 is released by Site-1 and Site-2 proteases. These two enzymes are required for the stress response of ER, lipid biosynthesis and for the processing of SREBPs in response to cholesterol deprivation (Ye J et al 2000 *Mol Cell* 6:1355). ATF3 is induced by lipopolysaccharide and it is a negative regulator of IL-6 and IL-12b by altering the chromatin structure. It also seems to regulate the Toll-like receptor 4 and thereby inflammatory responses (Gilchrist M et al 2006 *Nature [Lond]* 441:173). ▶retinoblastoma, ▶CREB, ▶long-term potentiation, ▶osteoblast, ▶bZIP, ▶JNK, ▶adenovirus [▶E1A], ▶SREBP, ▶Coffin-Lowry syndrome, ▶IL-▶6, ▶IL-▶12, ▶Toll; Fuchs SY et al 2000 *J Biol Chem* 275:12560; Bhoomik A et al 2002 *J Clin Invest* 110:643.

Athanogene: This generates an anti-apoptotic function. ▶BAG1, ▶apoptosis

Atherosclerosis: This condition is characterized by hardening and then degeneration of the walls of arteries because of the deposition of fatty acid nodules on the inner walls and obstruction of blood circulation (see Fig. A134).

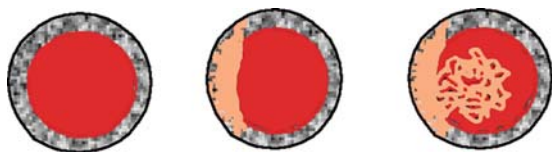


Figure A134. Cross section of an artery with blood (red) at center. Normal artery (at left), foamy plaques accumulate within the smooth muscles of the arterial wall and reduce blood flow because of the constriction of the lumen (in the middle), ruptured plaque may eventually block the blood flow to the heart (right).

In the first phase lipid-filled foam cells (macrophages) appear. In the next phase, fibrous plaques are formed of lipids and necrotic cells, covered by smooth muscle cells and collagen. The final phase lesion involves platelet and fibrous clots (thrombus). This group of vascular diseases is one of the most common causes of heart diseases. The number of deaths annually due to coronary heart disease and stroke are 490,000 and 150,000 respectively in the USA. The underlying genetic mechanisms vary and non-genetic factors play a substantial role. In human atherosclerotic lesions CD40 and its ligand CD40L are expressed. Susceptibility is controlled by 10 to 13 genes in human chromosome 1q24.3-1q25.1 and by 11 gene at the *Ath* locus of mice (Wang X et al 2005 Nature Genet 37:365).

By blocking the latter signaling molecules, atherosclerosis and some autoimmune symptoms may be mitigated. Atherosclerosis develops at a high level of the enzyme ACAT (acylcoenzyme cholesterol acyltransferase). In the case of apolipoprotein E (APOE) deficiency in mouse atherosclerosis, caused by oxidation of arachidonic acid, symptoms can be reduced by oral administration of vitamin E. Monocyte chemoattractant protein (MCP-1), a chemokine, and low-density lipoprotein (LDL) deficiency, and substantially reduced lipid deposition in the arteries are some of the characteristics. MCP-1 apparently recruits monocytes to the arterial epithelium during the earliest stages of the disease. A number of different hereditary and environmental factors contribute to the development of atherosclerosis. The heritability of the genetic factors (high cholesterol, triglycerides, diabetes) may vary from 40 to 80%. High lipoprotein (A) level controlled by several genes has over 90% heritability. Bone marrow-derived vascular progenitor cells can alleviate the symptoms upon injection into mice. Apparently, due to aging the repair capacity of the bone

marrow decreases (Karra R et al 2005 Proc Natl Acad Sci USA 102:16789). The immunomicelles provide excellent, validated in vivo enhancement of atherosclerotic plaques. The enhancement seen is related to the macrophage content of the atherosclerotic vessel areas imaged by MRI. The immunomicelles may aid in the detection of high macrophage content associated with plaques vulnerable to rupture (Amirbekian V et al 2007 Proc Natl Acad Sci USA 104:961). The immunomicelles have an average mean hydrated size of 107.3 ± 0.21 nm and average concentration of gadolinium 2.23 mM. Gadolinium is a rare earth metal providing high resolution in magnetic resonance imaging. ▶cardiovascular diseases, ▶myocardial infarction, ▶heart disease, ▶sterol, ▶HDL, ▶LDL, ▶CETPL, ▶CD40, ▶arachidonic acid, ▶apolipoproteins, ▶vitamin E, ▶T-bet, ▶monocytes, ▶MCP, ▶APRF, ▶osteoarthritis, ▶MRI; Lusis AJ 2000 Nature [Lond] 407:233; Welch CL et al 2001 Proc Natl Acad Sci USA 98:7946; Glass CK, Witztum JL 2001 Cell 104:503; Lusis AJ et al 2004 Annu Rev Genomics Hum Genet 5:189.

α-Thiophosphate-dNTP: Refer to point mutagens when incorporated into gapped DNA by DNA polymerase I. The thiophosphates are not effectively removed by the 3' → 5' editing function of the DNA pol I enzyme. ▶pol

Atlas Human cDNA: This contains commercially available arrays of cDNAs (Clontech, Palo Alto, CA) on membranes in several quadrants, each specific for 96 genes of different specificity of expression. The membranes can be used for hybridization probes for the identification of genes with unknown function in different tissues or in healthy and diseased conditions. ▶microarray hybridization; Sehgal A et al 1998 J Surgical Oncol 67:234, protein atlas: <http://www.proteinatlas.org/>.

ATM (ataxia telangiectasia mutated, 370 kDa): It involves an altered phosphatidylinositol kinase. ATM kinase may activate p53 in response to radiation stress but if ATM is defective p53 does not respond to e.g., ionizing radiation and in the absence of apoptosis the chances of cancer may increase. ATM or loss of AT increases the chances of oxidative damage to the cell. It is homologous to *MEC1* and *rad53* of yeast and *mei-41* of *Drosophila*. ▶PIK, ataxia ▶telangiectasia, ▶ATR, ▶BID, ▶p53, ▶apoptosis, ▶Chk2, ▶breast cancer, ▶double-strand break, ▶X-ray ▶repair, ▶telangiectasia; Pincheira J et al 2001 Mutagenesis 16:419.

Atom Microscopy: This technique is being developed for imaging atomic structures. The equipment uses

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mono-energetic sodium atoms ejected into a vacuum chamber and carried by noble gases such as argon. The beam is broken up into sub-components on a silicon nitride grid. The phase shift generated by the two beams is then measured.

Atomic Coordinate File: Lists molecular coordinates of macromolecules in three dimensions. ►[coordinate](#)

Atomic Force Microscope (AFM): An instrument that can image the surfaces of conductor and non-conductor molecules even in aqueous media. It can reveal molecular structure of surfaces, adhesion forces between ligands and receptors, and other biological processes in real time. It can also be adopted for DNA sequencing. ►[STM](#), ►[nanotechnology](#); Ljubchenko YL et al 1995 *Scanning Microsc* 9:705; Lyubchenko YL et al 2001 *Methods Mol Biol* 148:569; Müller DJ et al 2002 *Progr Biophys Mol Biol* 79:1.

Atomic Radiations: Killed 100,000 and injured 60,000 in Hiroshima (6 August, 1945) and Nagasaki (9 August, 1945) at the end of World War II, and caused substantial increase (about 4 fold or more at the epicenter) of cancer but showed no significant increase in human mutation. The incidence of cancer varied depending on a number of factors such as distance from the epicenter, age, sex (higher in females), by the type of cancers and some unexplained factors (such as geographic location of Hiroshima or Nagasaki).

The cause of the scarcity of mutations is not that these radiations were genetically ineffective rather the human breeding system, avoiding marriage between relatives, did not favor homozygosity of the recessive mutations resulting in lethality. Recent studies of the populations exposed to the radiation caused by the failure of the Chernobyl nuclear power plant (26 April 1986) indicate an increase not only in cancer but also of mutation (see Fig. [A135](#)).

Most likely, some of the mutations induced will be maintained in the exposed populations and may contribute to an increase of the genetic load. The total radiation from natural sources (cosmic radiation, disintegration of terrestrial isotopes [uranium, thorium, potassium], etc.), reaching the human gonads was estimated to be 100–125 millirads per year. The atomic bomb tests conducted during the years (1956) to (1965) contributed an average of about 76 millirads and expected to have exerted their effect mainly up to the year (2000) through the short half-life radioactive elements (Cesium¹³⁷, Strontium⁹⁰) and have substantially decayed by then. The long half-life Carbon¹⁴ will continue to pollute by an additional estimated 167 millirads even after year 2000.

The meltdown of the Chernobyl power plant in the Ukraine near the Byelorussian border, in the spring of 1986, exposed nearby populations up to 75 rem, whereas the whole of Byelorussia received about 3.3 rem.

In 1986, in that country, the total number of thyroid cancer in children was 2, and by (1992) it reached to about 60 cases. By (1999) more than 800 children who drank milk from cows exposed to the radiation developed thyroid cancer. The figures are still increasing. The thyroid cancer has been attributed to iodine¹³¹ released during the fallout. In the human minisatellite DNA the mutation rate doubled and in the feral populations of voles (*Microtus*) the base pair substitution frequency in the mitochondrial DNA was found to be in excess of 10^{-4} , over two orders of magnitude increase above the appropriate control groups. Nevertheless, the rodent populations appeared in good condition and their fertility was also good. This report of 1996, about the high mutation rate at Chernobyl, was retracted by the authors in (1997) (*Nature* 390:100). In barn swallows an increase of mutations at two microsatellite loci was observed (*Nature* 389:593). The Hanford Nuclear Reservation, in the state of Washington, exposed nearby populations in excess of 33 rads over a period of three years. The official estimates place 0.025 rads per year as safe for airborne pollution by nuclear weapon plants for the civilians living in the neighboring area and 5 rads for the workers in those plants for the entire body per year. According to some estimates based on irradiation of mice 20–40 rad is the doubling dose of mutation for ionizing radiation. It was estimated that the radioactive fallout from weapon testing may have increased the genetic risks by 2% over the natural background effects and by 8% for leukemia. The effects of atomic radiation on mutation rates in the minisatellite DNA remains controversial because of the difficulties of finding appropriate (concurrent) controls. The mutation rate in these very sensitive DNA sequences is much affected by environmental factors (pollution), age, etc.

When considering the harmful effects of radiation potentially released by atomic power plants, one must consider the harmful pollution generated by the coal-fired industry and the carcinogenic hydrocarbons released by the combustion in wood fireplaces, etc. Also, the shortage of energy may directly or indirectly cause substantial suffering and even death to the genetically more vulnerable part of the population, especially children.

Estimation of the risk is very complicated because of the many modifying factors (angle of the radiation, age, sex, length of exposure, genetic susceptibility to

cancer, life style [smoking, drug use, etc.]) involved. One simple formula for assessing the excess relative risk (ERR) is $1 + \beta z$, where β = ERR and z = radiation dose. Some variations of the following formula based on least squares regression models have also been developed for the estimation of excess risk: (Cases. $\text{PYR}_d = \alpha + \beta d + \epsilon$ where PYR is the dose-specific person years, α denotes the intercept of the regression term, β stands for the contribution of the doses of the radiation as an excess risk and ϵ is the error [formula after D.A. Pierce]. ▶cosmic radiation, ▶isotopes, ▶radiation hazard assessment, ▶doubling dose, ▶plutonium, ▶nuclear reactors, ▶mutation in human populations, ▶mutation detection, ▶rad, ▶rem, ▶control, ▶correlation, ▶public opinion; Dubrova YE et al 2002 Science 295:1037; Williams D 2002 Nature Rev Cancer 2:543; Dubrova YE et al 2002 Am J Hum Genet 71:801; Awa A 2003 Mutation Res 543:1.

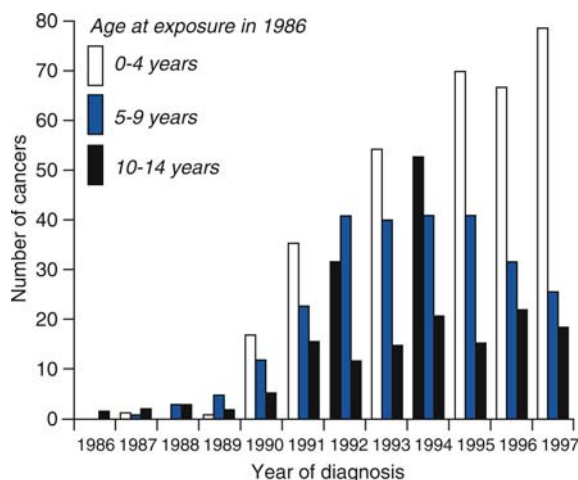


Figure A135. The incidence of thyroid cancer in Belarus following the Chernobyl accident in 1986. (From *Sources and Effects of Ionizing Radiation*. United Nations Scientific Committee Report 2000. vol. II. New York.)

Atopy: A familial allergy, including asthma, hay fever and eczema. The blood serum carries an increased level of immunoglobulin E (IgE). An IgE responsiveness locus was assigned to 11q12-q13. Human chromosome 5q31-q33 harbors an asthma susceptibility region. Atopy is controlled also by epithelial barrier determined by the 370-kDa filaggrin protein, encoded at human chromosome 1q21; semidominant and dominant mutations or loss of this protein predisposes to dermatitis and/or asthma or to

both. In about 9% European populations, filaggrin variants occur (Palmer CNA et al 2006 Nature Genet 38:441). ▶allergy, ▶asthma, ▶immunoglobulins, ▶ichthyosis, ▶Netherton syndrome; Wheatley AP et al 2002 Hum Mol Genet 11:2143.

ATP: Adenosine-5'-triphosphate is a universal carrier of metabolic energy by transferring the terminal phosphate to various acceptors and resulting in ADP (adenosine diphosphate) that is recycled to ATP by either the chemical energy of oxidative phosphorylation or the solar energy of photosynthesis. Besides the thermodynamic role, ATP has also catalytic activity e.g., in nitrogen fixation. ATP provides also binding energy through non-covalent interactions with various molecules in order to lower activation energy. It provides energy for charging tRNA with amino acids, for DNA synthesis, for bioluminescence mediated by the firefly luciferase, it is indispensable in carbohydrate metabolism, it serves as a precursor of cyclic AMP that has major role in signal transduction and protein phosphorylation, etc. The major catabolic pathways (glycolysis, citric acid cycle, fatty acid and amino acid oxidation and oxidative phosphorylation) are coordinately regulated in the production of ATP. The relative abundance of ATP and ADP controls electron transfers in the cell. ATP is generated in the mitochondria and chloroplasts. ATP is the major link between anabolic and catabolic reactions mediated by enzymes. UTP (uridine triphosphate), GTP (guanosine triphosphate) and CTP (cytidine triphosphate) are also important in similar processes but have relatively minor role compared to ATP. ▶ATP synthase, ▶ATPase, ▶cAMP; Pfeiffer T et al 2001 Science 292:504.

ATP Synthase: A ~500 kDa multisubunit protein complex forming ATP from ADP and phosphate (oxidative phosphorylation) on plasma membranes (bacterial, mitochondrial, chloroplast); it is also a motor protein. ▶ATP, ▶ATPases; Boyer PD 1997 Annu Rev Biochem 66:717; Yoshida M et al 2001 Nature Rev Mol Cell Biol 2:669.

ATPase: Enzymes are required for active transport of chemicals and other functions in the cells. The *P-type* ATPases maintain low Na^+ , low Ca^{2+} and high K^+ levels inside the cells, generate low pH within cellular compartments and activate proteases and other hydrolytic enzymes of eukaryotes and generate transmembrane electric potentials. Na^+ , K^+ -ATPase has binding sites for cardiac glycosides such as ouabain, digoxin and digitoxin and mediates adrenocorticotrophic hormone (ACTH) induced hypertension

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in mice and presumably in humans (Dostanic-Larson I et al 2005 Proc Natl Acad Sci USA 102:15845). The *V-type* (vacuolar) ATPases secure low pH inside lysosomes and vacuoles of eukaryotes. The *F type* ATPases (energy coupling factors, F_1 - F_0 -ATPase) are located in the plasma of prokaryotes. In the mitochondrial and thylakoid membranes of eukaryotes the *F type* ATPases are actually ATP synthase enzymes generating ATP from ADP and inorganic phosphate. The *DNA-dependent* ATPases are type I restriction endonucleases that depend on Mg^{2+} , ATP and SAM for cutting of DNA strands. After cleavage they function only as ATPases. ▶ATP, ▶SAM, ▶ACTH, ▶ouabain, ▶digoxigenin, ▶digitoxin; Palmgren MG 2001 Annu Rev Plant Physiol Plant Mol Biol 52:817; V-type Na^+ -ATPase structure: Murata T et al 2005 Science 308:654; F-type Na^+ -ATPase structure: Meier T et al 2005 Science 308:659.

A-Tract: Includes four or more AT base pairs in the DNA without a 5'-TA-3' step. Such elements cause curvature at the helix axis and influence nucleosome packaging and base pair opening due to the C⁵ methyl of thymine. Such structures modulate sequence-specific ligand binding and gene expression. (See Wärmländer S et al 2002 J Biol Chem 277:28491).

ATR (ATM - Rad3-related): Is a phosphatidylinositol kinase related to ATM and yeast gene product RAD3. It controls cell cycle checkpoints and double-strand breaks. Phosphorylation of its substrates inhibits DNA replication fork, mitosis and promotes repair, recombination or apoptosis. ▶ATM, ▶checkpoint, ▶PIK, ▶RAD3, ▶sex body; Cortez D et al 2001 Science 294:1713; Zou L, Elledge SJ 2003 Science 300:1542.

Atransferrinemia (3q21): A defect in the synthesis of the iron-regulatory protein transferrin, resulting in hypochromic anemia. ▶transferrin, ▶anemia

Atrazine (Lasso): ▶herbicides, ▶photogenes

Atresia: Closure of an organ (e.g., vagina, and it can be surgically corrected to permit procreation), parts of the digestive tract (pyloric atresia), closure of the bile duct (biliary atresia), etc. pyloric stenosis.

Atresia: Mediates the elimination—by apoptosis—of oocytes with mutant mitochondria. Although the primordial germ cells produce millions of oocytes in humans, only a small fraction of them reach the stage of ovulation. Thus, atresia serves as a genetic quality control. In the male germ cells (which do not transmit mitochondria) atresia was not observed. ▶apoptosis, ▶mtDNA; Krakauer DC, Mira A 1999 Nature [Lond] 400:125.

Atresia, Congenital Aural: A narrowing or closure of the auditory channel due to deletion of human chromosome 18q21–q23 region. Its prevalence is 1×10^{-4} per live birth. (See Veltman JA et al 2003 Am J Hum Genet 72:1578).

Atrial: Adjectivization of atrium. ▶atrium

Atrial Septal Defect: An autosomal recessive type developmental heart disease that displays increased recurrence when transmitted through the males although the prevalence is greater in the females. The dominant form encoding a transcription factor is in human chromosome 6. Dominant defects in the NXX2-5 gene (encoded at 5q35) affects cardiac septation and is responsible for congenital heart disease. Gene TBX5 (12q24) is responsible for ventricular septal defects. ▶heart diseases

AT-Rich DNA: Common in the repetitive sequences, and is generally not transcribed. Some of the petite colony mutants of yeast mitochondrial DNA contain mainly AT sequences. ▶mitochondrial genetics, ▶mtDNA

ATRIP: ATR-interacting protein. ▶ATR; Cortez D et al 2001 Science 294:1713; Zou L, Elledge SJ 2003 Science 300:1542.

AT-Risk-Motifs (ARM): Increase instability of the genome such as inverted repeats, palindromes, and insertion elements either by illegitimate or homologous recombination or rearrangements. ▶repeat inverted, ▶palindrome RecA-independent recombination, ▶Alu family, ▶instability genetic; Gordenin DA, Resnik MA 1998 Mutat Res 400:45.

Atrium: The entrance to an organ. ▶atrial

Atropa belladonna: A plant of the *Solanaceae* family (n = 50, 72) is a source of alkaloids. ▶henbane

Atrophine-1: Protein is encoded by the human gene DRPLA and affects other trinucleotide repeat genes. ▶dentatorubral-pallidoluyian atrophy, ▶Huntington's chorea

Atrophy: Under-nutrition or lack of nutrition; wasting away of cells and tissues. ▶Kugelberg-Welander syndrome, ▶Kennedy disease, ▶dystrophy, ▶muscular dystrophy, ▶neuromuscular diseases, ▶spinal muscular atrophy

Atropine: A highly toxic alkaloid. ▶henbane

ATRX: A helicase protein encoded at human chromosome Xq13 (>220 kb). It is similar to the RAD54 and the SWI/SNF proteins. It is implicated in psychomotor functions, DNA methylation, regulation of transcription, DNA repair and chromosome segregation. Mutations have been found in cases of

The phage (POP') sequence is:
the bacterial (BOB') sequence is:

GCTTTTTTATACTAA
CGAAAAAATATGATT
GCTTTTTTATACTAA
CGAAAAAATATGATT

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Figure A136. att sites

thalassemia/mental retardation and in the Juberg-Marsidi syndrome. See separate entries for the terms mentioned.

att SITES: At the position where site-specific integration and excision takes place, lysogenic bacteria and temperate phage have consensus sequences (see Fig. A136). The att sites are about 150 nucleotides long in l and 25 bp in the bacterium. 15 bp sequences are identical in both.

The underscored sequences (see figure) are then reciprocally recombined and POB' and BOP' sequences are generated from the left (attL) and right (attR) sequences. The integration requires the phage-coded INT and the bacterial coded HF proteins. The excision requires an additional protein XIS to be coded by the bacterial gene *xis*. This is probably because it is not exactly the reverse type of process since the original attP and attB elements were not identical except the 15 bps. ▶lambda phage, ▶integrase; Williams KP 2002 Nucleic Acids Res 30:866.

Attached X Chromosomes: Two X chromosomes fused at the centromere (see Fig. A137). They have been exploited for cytogenetics. Among others, they were first used to carry out half-tetrad analysis in *Drosophila*. Females with attached-X produce eggs but half of them have only autosomes and no X-chromosome. If the attached X-chromosomes carry different alleles of a locus, double dose of the same allele in the eggs can be achieved only if there is a recombination between that gene and the centromere. This is because the first meiotic division is reductional and the second is equational. ▶half-tetrad analysis, ▶compound X chromosomes; Anderson EG, 1925 Genetics 10:403.



Figure A137. Attached X-chromosomes (→) in the oögonium of an XXY *Drosophila*. (After a drawing by Curt Stern in the 1920s)

Attachment Point (ap): A mappable site in the chromosome of the chloroplast of *Chlamydomonas reinhardtii* green alga, representing a hypothetical centromere-like element. It is called *ap* because it attaches to the chloroplast membrane and assists the disjunction of the ring DNA during division. In genetic recombination this is taken as the 0 coordinate of marker segregation. ▶chloroplast genetics, ▶mapping of chloroplast genes

Attachment Site: ▶att site

Attention Deficit-Hyperactivity (ADHD): A condition observed in 2 to 5% of elementary school children that causes learning disabilities and emotional problems. Boys have about 5-fold higher chance to be affected than girls. It frequently goes into remission as age progresses but some personality disorders (hyperactivity, antisocial behavior, alcoholism, hysteria) may persist even in adulthood. About 25 to 30% of the parents of affected children had some of the symptoms in childhood. The genetic basis is unclear. The dopamine receptor 4 encoded in human chromosome 11p15.5 may be responsible for the behavioral anomalies but not necessarily for the attention deficit. The heritability is 0.75–0.91. Chromosomal locations 17p11, 15q, 7p and 9q have been implicated (Bakker SC et al 2003 Am J Hum Genet 72:1251). Childhood asthma is strongly associated with ORMDL3, a member of a gene family that encodes transmembrane proteins anchored in the endoplasmic reticulum in human chromosome 17q21 (Moffatt MF et al 2007 Nature [Lond] 448:470). ▶affective disorders, ▶dyslexia, ▶autism, ▶behavior genetics; Fisher SE et al 2002 Am J Hum Genet 70:1183; Wilens TE et al 2002 Annu Rev Med 53:113.

Attenuate: Tapered appearance.

Attenuation: A regulatory process in bacteria. ▶attenuator region, ▶host-pathogen relations, ▶tryptophan operon, ▶antitermination

Attenuation, Viral: A reduction in virulence achieved by subculturing in a new cell population. In this process, numerous adaptive mutations occur after a period of

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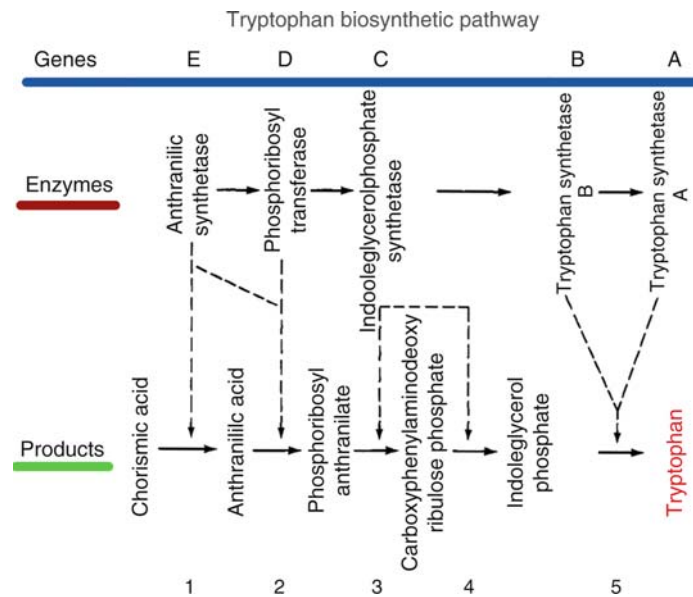


Figure A138. The biosynthesis of tryptophan from chorismic acid in *E. coli* bacteria requires five steps, mediated by five enzymes. The sequence of the encoding genes in the bacterial genetic map corresponds to the sequence of the metabolic steps. This was the first case of recognition of such a [co-ordinate](#) regulation in bacteria. Primarily, a repressor controls the five genes, and attenuation provides an additional fine-tuning. Some of the enzymes are composed from more than a single functional unit. Indoleglycerolphosphate synthetase catalyzes two synthetic steps as shown in figure

time that permit them to grow well in the original cells but with diminished virulence. These mutations generally occur in the 5'-non-translated region and modify the translation of the viral RNA although attenuating mutations may occur all over the viral RNA genome. attenuator region.

Attenuation, Vaccines: The virus is immunogenic but not pathogenic in the vaccine.

Attenuator Region: Region where RNA polymerase may stop transcription when all the cognate tRNAs are charged. Then the mRNA assumes a special secondary structure and this leads to a temporary cessation of transcription, leading to a reduction of transcription by a factor of 8–10. It is one of the regulatory mechanisms of bacterial amino acid operons. A type of attenuation also regulates the pyrimidine operon of *E. coli*. The operon is induced by low concentration uridine triphosphate. (see Fig. A138; tryptophan biosynthetic pathway).

When the UTP level increases, slippage occurs at the promoter incorporating long stretches of uridylic acid and the RNA polymerase cannot escape the promoter. The cytosine deaminase/cytosine transport locus behaves similarly. The histidine operon does not even use the more common type of operator repressor/inducer system.

Sucrose, β -glucoside, β -glucan utilization enzymes in bacteria use RNA-binding proteins that inactivate transcription termination and thus promote transcription. The elongation of some lipid biosynthesis RNAs may be also negatively controlled. Attenuation appears to be a widely used mechanism of regulation in bacteria (see Fig. A139) (Merino E, Yanofsky C 2005 Trends Genet 21:260).

(See diagrams of the [tryptophan operon](#), [TRAP](#), [tryptophan](#), [tryptophan repressor](#), [antitermination](#), [slippage](#); Yanofsky C 2000 J Bacteriol 182:1).

Attractin: A human serum glycoprotein-regulating cell mediated immunity and is homologous to the *mg* locus of mouse. It is a low affinity receptor for agouti protein. [obesity](#), [agouti](#); He L et al 2001 Nature Genet 27:40.

Attrition: The cost of failure in the development of an effective drug. The cost of developing a highly successful therapeutic agent generally exceeds \$800 million and the chance of failure is over 90% either because of insufficient efficacy or unacceptable side effects. [translation](#)

Auberger Blood Group: [Lutheran blood group](#)

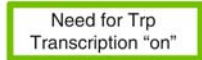
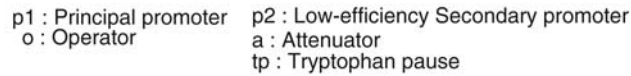


Figure A139. A genetic and molecular map of the tryptophan operon in *Escherichia coli* bacterium. Attenuation may dictate an early termination of transcription. The site of attenuation (*a*) is within the tryptophan leader sequence (*trpL*) and the site of the transcription pause (*tp*) precedes it. Transcription is primarily under the control of the promoter - operator region and the process begins at the left end of the *trpL* site. The RNA polymerase pauses at the *tp* site before proceeding further. In case most of the tryptophanyl tRNAs (tRNA^{Trp}) are charged with tryptophan and therefore there is no need for additional molecules of this amino acid, transcription is momentarily terminated at the attenuator (*a*) site. If however the tRNA^{Trp} is largely uncharged because of shortage of tryptophan and active protein synthesis, the transcriptase RNA polymerase passes through the *a* site without interference. This passage is made possible by alterations in the secondary structure of the RNA transcript of the operon. The initial segment of the leader sequence encodes a short tryptophan-rich peptide. In case there is a scarcity in tryptophan, translation on the ribosome is stalled at the tryptophan codons in the leader sequence. During the pause (*tp*), the mRNA transcript assumes a hairpin-like structure by base pairing between segments marked by (2) and (3) and thus the passage through the *attenuator* (*a*) site is facilitated. In case, however, most of the cognate tRNAs are charged, the transcript shows base pairing between segments (3) and (4), resulting in stoppage of transcription until the over-supply is exhausted by protein synthesis. The tryptophan operon also relies on suppressive transcriptional controls. See base sequences of the attenuator at the entry “tryptophan operon”. (Modified after Yanofsky C 1981 Nature (Lond.) 289:751)

AUC (area under the curve): See Fig. A140.

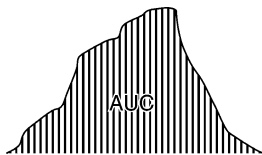


Figure A140. AUC

Auer Bodies: Clusters of granules or bundles of rods in the nuclei of acute promyelocytic leukemia cells.
▶ leukemias

AUG Codon: In mRNA, AUG is the only one codon that specifies methionine yet there are two different tRNAs for methionine. In a majority of cases in prokaryotes one of the methionine-tRNAs is formylated at the amino group by N¹⁰-formyltetrahydrofolate, and this formylmethionine tRNA initiates translation whereas the other methionine-tRNA carries methionine to all other sites in the polypeptide. In eukaryotes the *initiator methionyl-tRNA* is not formylated, the primary structure and conformation of the tRNA specify its initiator attribute. Thus, the overwhelming majority of nascent proteins that start at the NH₂ end with a methionine. In the mature

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protein this methionine may be absent because of processing. ►[genetic code](#)

Auger Emission: ^{125}I (iodine) or $^{195\text{m}}\text{Pt}$ (platinum) isotopes may emit electrons or Auger positrons (^{64}Cu) when excited by external radiation. When incorporated, these isotopes may deliver high doses within the radius of a cell and can be used to damage tumor cells.

Augmenting Genes: Facilitate viral reproduction although not absolutely essential for it.

AU-Rich Elements (ARE): ARE in the 3'-untranslated region may target the mRNAs of proto-oncogenes, cytokines and lymphokines for rapid degradation. However, these AU-rich mRNAs are stabilized by heat shock, UV, hypoxia, stimulation and oncogenic transformation. ELAV family of proteins, such as HuRs, may bind AREs. ►[ELAV](#), ►[HuR](#); Stoecklin G et al 2001 RNA 7:1578.

Auricles: Small projections at the upper part of leaf sheath in cereals (see Fig. [A141](#)). They are of importance for taxonomic characterization.

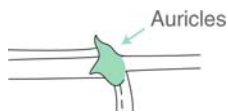


Figure A141. Auricles

Aurones: Plant flavonoids conveying yellow color to flowers. They are synthesized from chalcones by aureusidine synthase (39-kDa copper glycoprotein) and a member of polyphenol oxidases.

Auroras: Are threonine/serine protein kinase(s), regulating the mitotic spindle, chromosome segregation, cytokinesis, etc. Humans have three Aurora kinases, A, B and C. Its activator is the Ajuba protein of the LIM family. Inhibitors have relevance to cancer therapy. Loss of the mitotic checkpoint protein Chfr can ubiquitinate and regulate Aurora. It promotes chromosomal instability (Yu X et al 2005 Nature Genet 37:401). Aurora A and B are associated with and over-expressed in several types of cancer. The inhibitors target serine 10 in histone H3 and may cause tetraploidy. ►[LIM domain](#), ►[passenger proteins](#), ►[co-orientation](#), ►[infertility](#), ►[condensin](#); Taguchi S et al 2002 FEBS Lett 519:59; Keen N, Taylor S 2004 Nature Rev Cancer 4:927.

Austin Disease: ►[mucosulfatidosis](#)

Australopithecus: An extinct, fossil (5–1 million year old) of the bipedal Hominidae of the Old World. Its brain size is intermediate—between modern humans

and apes. Exact relation to existing species is unclear. (“Austral” means Southern). ►[hominidae](#)

Autapomorphy: A condition when a particular trait(s) occurs only in a particular evolutionary line and not in other related species.

Autapsis (adj. autaptic): Are synapses that cells form with themselves. ►[synaps](#)

Autism: A human behavioral anomaly involving reticent, self-centered, subjective thoughts and actions, learning and communication difficulties. Its prevalence is 0.02 to 0.05% in the general population, and the recurrence risk in families may be 6–8%. More recent estimates of the prevalence are about 0.06%. The concordance between monozygotic twins appeared 36 to 96% while between dizygotic ones none to 24% was observed. Its incidence is about 4-fold higher in males than females. Because of its behavioral nature, animal models cannot be used efficiently and directly. It is generally associated with mental retardation and other psychological disorders. Although the incidence within affected families is 50 times higher than that in the general population, no single gene could be identified as a causative agent although some role of serotonin transporter has been suspected. Actually even in humans, the diagnosis is somewhat difficult because of the complexity of the traits and differences among the alleles. Several features of the condition overlap some symptoms of other diseases. Autism may be associated with genes in several chromosomes but 7q31 or 1p or 1q23-q24, or 3q25-q27 or 17q11 appear to be the most likely locations of the major factors involved. However, other search have revealed several other putative linkage relations (Liu J et al 2001 Am J Hum Genet 69:327; Bartlett CW et al 2005 Am J Hum Genet 76:688). An aminophospholipid-transporting ATPase situated in the imprinted region 15q11-q13 near the ubiquitin ligase E3A and the Angelman syndrome genes is associated with a small percent of the autisms (Herzing LBK et al 2001 Am J Hum Genet 68:1501; Folstein SE, Rosen-Sheidley B 2001 Nature Rev Genet 2:943). Additional loci have also been identified (Yonan AL et al 2003 Am J Hum Genet 73:886). Using Affymetrix 10K SNP microarrays and 1,168 families with at least two affected individuals implicate chromosome 11p12–p13 and neurexins, respectively, among other candidate loci (The Autism Genome Project 2007 Nature Genet 39:319). De novo copy number variations (CNVs) in the genome were significantly associated with autism ($P = 0.0005$). Such CNVs were identified in 12 out of 118 (10%) patients with sporadic autism, in 2 out of 77 (3%) of patients with an affected first-degree relative, and in 2 out of 196 (1%) of controls. Most de

novo CNVs were smaller than microscopic resolution (Sebat J et al 2007 Science 316:445).

The infantile autism becomes apparent during the first year of life. Apparently it is under polygenic control. In the dominant autism with onset after an initial normalcy (Rett syndrome, RTT, prevalence 1×10^{-4}), the symptoms are shared but progressive dementia, uncoordination and deterioration of all mental functions follow. This view about autism is gradually changing as current studies reveal the other end of the condition that involves preoccupation with details and qualities of a genius. The latter type appears to be coded at Xq28 as McPqG2. The Rett syndrome affects primarily females. Earlier the short arm of the X had also been implicated. The Xp22.3 region encodes the NLGN4 neuroligin and Xq13 encodes NLGN3 neuroligins, their mutations are associated with autism (Jamain S et al 2003 Nature Genet 34:27). Neuroligins are essential factors for the formation of synapses. ▶affective disorders, ▶Asperger syndrome, ▶attention deficit-hyperactivity, ▶disorder, ▶mental retardation, ▶neurexin, ▶McPqG2; Fombonne E 1999 Psychol Med 29:769; Folstein SE, Mankoski RE 2000 Am J Hum Genet 67:278; Geschwind DH et al 2001 Am J Hum Genet 69:463; Shao Y et al 2002 Am J Hum Genet 70:1058; Yu C-E et al 2002 Am J Hum Genet 71:100; Veenstra-VanderWeele J et al 2004 Annu Rev Genomics Hum Genet 5:379.

Autoallopolyploid: A polyploid in which the genome(s) is/are duplicated from one or more species, e.g., AAAABBBB or AAAABB. ▶allopolyploid, ▶sesquidiploid

Autoantibody: An antibody formed against the body's own antigens, such as in autoimmune disease. During early B lymphocyte development 55–75% of all antibodies formed may display self-reactivity but most of them are destroyed as the B cells mature (Wardemann H et al 2003 Science 301:1374). ▶autoimmune disease, ▶B lymphocyte

Autoantigen (self-antigen): A normal cellular protein yet it may be attacked by the cellular immune system. This is similar to what happens in autoimmune disease. ▶immune system, ▶immune reaction

Autocatalytic Function: Of DNA is the process of replication; also, any reaction that is promoted by its own product. Although self-replication is the most common property of nucleotide chains, peptides and other molecules may be involved in autocatalysis and cross-catalysis (i.e., the formation of other molecules). ▶replication, ▶heterocatalysis; Paul N, Joyce GF 2002 Proc Natl Acad Sci USA 99: 12733.

Autochthonous: Located at its original site or a graft of an individual at another position within the same body.

Autoclaving: Heating under pressure (1 atmosphere above sea level) by steam, usually at 121 °C, for a minimum of 15 min to kill non-spore-forming bacteria and other cells. ▶sterilization, ▶filter sterilization

Autocorrelation, Spatial: Compares data (e.g., DNA sequences and haplogroup frequencies) within arbitrary areas in order to study diversity distribution. Measures of overall genetic similarity are evaluated in each distance class and the degree of genetic similarity at the different genetic distances determined. A variable can be autocorrelated either (+) or (–) if its value at a given point in space is associated with its measures at other locations. (Simoni L et al 2000 Amer J Hum Genet 66:262).

Autocrine: Signal production within a cell in response to external stimuli.

Autocrine Stimulation: Cells infected by proto-oncogene carrying virus secrete a growth factor that further stimulates the cell's proliferation. ▶proto-oncogenes, ▶paracrine stimulation

Autoecious: A parasite that completes its life cycle on the same host.

Autogamy: A process of self-fertilization common in hermaphroditic and monoecious plants; autogamy in the unicellular animals, *Paramecia*, is preceded by meiosis and one the four haploid products survive. This cell then divides into two cells by mitosis. These two identical cells may then fuse and a genetically homozygous diploid zygote is formed. ▶alogamy

Autogenesis: ▶Lamarckism

Autogenous Control: The own product of genes regulates the coding gene either in a positive or a negative way. In genetic networks the autogenous control appears superior to the non-autogenous system. The autogenous control better prevents false triggering due to transient fluctuations of input (Camas FM et al 2006 Proc Natl Acad Sci USA 103:12718). ▶negative control, ▶positive control, ▶genetic network

Autogenous Evolution: Structures and organelles evolved through differentiation of the cells own system. ▶exogenous evolution

Autogenous Suppression: The *Salmonella* RF2 translation termination protein occasionally fails to recognize or misreads the UGA stop codon resulting in readthrough by suppressing termination. ▶translation termination, ▶readthrough, ▶recoding, ▶stop codon

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Autograft: The tissue transplantation is within one individual. ►homograft

Autoimmune Disease: The immune system fails to recognize the cell's own antigens and attacks them. In many instances altered glycosylation is responsible for the pathogenesis. Normally the lymphocytes with defects in self-antigen recognition are eliminated by apoptosis. It has been shown that receptor tyrosine kinases (Tyro 3, Axl, Mer) plays an essential regulatory role in the development of the immune response. Normally these receptors control the function of antigen presenting cells by supplying growth-promoting and pro-survival molecules. They also seem to have negative control. Mutation of these receptors may disable the binding of gamma interferon and the inability to clear the dying cells results in overactivity of the macrophages that then attack the body's own cells (Lu Q, Lemke G 2001 Science 293:306). The regulatory CD4⁺ CD25⁺ T cells can suppress the autoreactive T cells by engaging the B7 protein molecules on the surface of the target T cells (Paust S et al 2004 Proc Natl Acad Sci USA 101:10398). Mutation in ICOS, an essential co-stimulatory receptor of follicular T cells results in overproduction of IL-21 and fails to repress autoantibody formation. A RING-type ubiquitin ligase can repress these T cells and autoimmunity (Vinueza CG et al 2005 Nature [Lond] 435:452).

Lupus erythematosus cells (a variety of skin and possibly visceral inflammations) make antibodies against their own DNA and RNA. In insulin-dependent diabetes the insulin producer β cells of the pancreas are attacked by the body's immune system, coded for by the major histocompatibility genes. The Rasmussen's encephalitis, a rare form of epilepsy, and the paraneoplastic neurodegenerative syndrome (PNS), both are caused by autoantibodies against the glutamate receptors of the nervous system. PNS is a rare sign of cancer and often the patient is unaware of the cancer. The symptoms are generally memory loss, sensory deficiency, motor dysfunction or blindness. The most common cause is breast or ovarian or small-cell lung cancer. The tumor cells express proteins that are normally only expressed in neurons. The CD8⁺ T cells are then activated and the immune lymphocytes somehow cross the blood-brain barrier and evoke neuronal degeneration (Albert ML, Darnell RB 2004 Nature Rev Cancer 4:36). Herpes Simplex virus Type 1 expresses a coat protein which recognizes autoreactive T cells targeting mouse corneal antigens and may cause stromal keratitis (inflammation of the fibrous coat of the eye). Autoimmune diseases include a series of different anomalies (p = prevalence, r = risk of siblings relative to risks in the general population): psoriasis (p: 2.8, r: 6),

rheumatoid arthritis (p:1, r: 8), goiter (p: 0.5, r: 15), insulin-dependent diabetes (p: 0.4, r: 1.6), ankylosing spondylitis (p: 0.13, r: 54), multiple sclerosis (p: 0.1, r: 20), lupus erythematosus (p: 0.1, r: 20), Crohn disease (p: 0.06, r: 20), narcolepsy (p: 0.06, r: 12), celiac disease (p: 0.05, r: 60), cirrhosis of the liver (p: 0.008, r: 100). Autoimmune diseases have been attributed to increased V(J)D recombination in a class of B (B-1) lymphocytes as a result of increased RAG activity. Several autoimmune diseases (multiple sclerosis, rheumatoid arthritis) are more prevalent in females. The cause is apparently the difference in response to hormones of the T_H1 and T_H2 lymphocytes. Low estrogen level T_H1 cells secrete IL-2, INF- γ and lymphotoxins due to which, multiple sclerosis and rheumatoid arthritis are aggravated. At high estrogen (increased progesterone, testosterone) levels, T_H2 cells promote IL-4, IL-5, IL-6, IL-10. As a consequence, during pregnancy the symptoms of multiple sclerosis and rheumatoid arthritis are mitigated but lupus erythematosus may be aggravated. Immune therapies are being sought for the cure of these diseases (Steinman L 2004 Science 305:212). Autoimmune diseases seem to be clustered in certain families because they share common environment, genes and the interaction of the two. Protein tyrosine-phosphatase (PTPN22, 1p13) is lymphoid-specific and intracellular. Fc gamma RIII receptor may mediate early neutrophil recruitment in immune complex-mediated inflammation and reduced copy number of the gene increases the susceptibility to systemic lupus erythematosus, microscopic polyangiitis and Wegener's granulomatosis (6p21.3). However, the organ-specific Graves' disease or Addison's disease did not show this association (Fanciulli M et al 2007 Nature Genet 39:721). Single nucleotide polymorphism in this gene confers four autoimmune phenotypes: Type 1 diabetes (T1D), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Hashimoto thyroiditis (HT). The Multiple Autoimmune Disease Genetics Consortium survey detected nine "core" diseases, which included at least two autoimmune phenotypes: rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, autoimmune thyroid diseases (Hashimoto thyroiditis), Graves disease, juvenile rheumatoid arthritis, inflammatory bowel disease (Crohn disease), psoriasis and primary Sjögren syndrome (Criswell LA et al 2005 Am J Hum Genet 76:561). (See named diseases under separate entries, ►immunotherapy, ►statins, ►PPAR, ►CTLA4, ►AIRE, ►IPEX, ►HLA, ►NF- κ B, ►complement, ►B7 protein, ►T cell, ►Sjögren syndrome, ►goiter, ►Hashimoto disease, ►Goodpasture syndrome, ►APECED, ►bullous pemphigoid autoimmune disease, ►hemolytic anemia, ►Borrelia, ►V(J)D, ►RAG, ►B cell, ►T helper cell, ►signal transduction, ►interferon,

►antigen presenting cell, ►ICOS, ►interleukins, ►IL-21, ►RING-finger, ►ubiquitin, ►lymphotoxins, ►TGF, ►immunoglobulins, ►monoclonal antibody therapies, ►caspase, ►ALPS, ►epitope spreading, ►apoptosis, ►stem cells, ►T cell vaccination; Marrack P et al 2001 Nature Med 7:899; Leadbetter EA et al 2002 Nature [Lond] 416:603; Malek TR, Bayer AL 2004 Nature Rev Immunol 4:665; Feldman M, Steinman L 2005 Nature [Lond] 435:612 and other articles in the same issue; Gregersen PK, Behrens TW 2006 Nature Rev Genet 7:917).

Autoimmune Lymphoproliferative Disease: ALPS.

Autoimmune Polyendocrinopathy: APECED.

Autoinduction: A type of cell-to-cell interaction in bacteria and other organisms. The cells release small extracellular signaling molecules, which are taken up again by the cells. It adjusts gene expression in the cells responding to a level appropriate for the local density of the signaling cells. The autoinducer signals may be acylated homoserine lactones, Tra proteins, amino acids, short peptides and pheromones. ►auto-regulation, ►pheromones, ►quorum sensing, ►tra, ►Tata, ►homoserine ►lactone; Tata JR 2000 Insect Biochem Mol Biol 30:645.

Autoinhibition: Inactive conformation of a receptor in quiescent cells. It is controlled by a variety of mechanisms such autophosphorylation, ligand binding, etc. Schlessinger J 2003 Science 300:750.

Autointerference: The process when defective virions may interfere with the replication of intact ones.

Autologous: Its origin is within the cell or individual; a self-made molecule.

Autologous Transplantation: Used in cancer therapy by implanting e.g., genetically modified bone marrow cells of the same individual. Thereby, the undesirable immune rejection may be avoided. ►immune system, ►gene therapy, ►cancer gene therapy

Autolysis: Is the decomposition of cells and cell content by the action of the natural enzymes of the cells. It takes place generally in injured cells.

Automaton: Is a machine that can react automatically to preset conditions. The biological system can also be considered an automaton, which maintains continuous operations in response to potentially variable conditions. An applied possibility is to devise a DNA computer, which has three main functional parts. The first measures the absence or excess of a particular nucleic acid (RNA) in the cell that indicates e.g., a particular disease. The second part identifies the mRNA and the third part then releases an antisense

RNA, which can suppress e.g., small-cell lung carcinoma or prostate cancer. Such device can work under selected laboratory conditions but its clinical applicability is still awaited. ►DNA computer, ►small cell lung carcinoma, ►prostate cancer; Benenson Y et al 2004 Nature [Lond] 429:423.

Automixis: ►Self fertilization

Automutagen: A metabolite of the organism may become mutagenic, e.g., tryptophan.

Autonomous Controlling Element: A plant transposable element carries the transposase function and controls its own movement, e.g., Ac versus Ds in maize, the latter is a defective form of Ac, incapable of moving by its own power unless the autonomous (intact) Ac is present in the cell. ►transposable elements, ►Ac - Ds, ►Spm

Autonomous Developmental Specification: Maternal information or prelocalized morphogenetic information regulates the initiation of transcription of morphogenetic genes. ►morphogen

Autonomous Parvovirus: Uses the host system for productive replication. Only strain B19 is pathogenic in humans. They display antineoplastic properties in Ehrlich ascites tumors. ►parvoviruses, ►ascites

Autonomously Replicating Pieces: ►macronucleus

Autonomously Replicating Sequences: ►ARS

Autonomy: Cells transplanted into tissues of different genotype, or forming parts of genetically different sectors, still maintain the expression encoded by their genotype, and are not, or barely, affected by the genetically different tissue environment.

Autophagy: Destruction of cytoplasmic particles within a cell by delivering dispensable structures or molecules (in autophagosome vehicles), to lysosomes or to vacuoles (see Fig. A142). Autophagosomes are large (500–100 nm) double-membrane vesicles. Autophagy, a pathway of cell elimination, is different from apoptosis. This process gets rid of and re-utilizes the molecules during adverse conditions (e.g., cell starvation). The same machinery may degrade infective microorganisms. Before autophagy, isolation membranes sequester certain molecules. In resting cells, TOR inhibits autophagy; starvation and rapamycin dephosphorylate, and inactivate TOR, and can lead to the formation of *autophagosomes*. Autophagosomes can fuse with lysosomes and non-degraded proteins and viruses can be transported to the cell surface. Degradation within the lysosomes is also called *microautophagy*. In *macro-autophagy*, the subcellular membranes are altered and part of the cytoplasm is sequestered into double-membrane-surrounded

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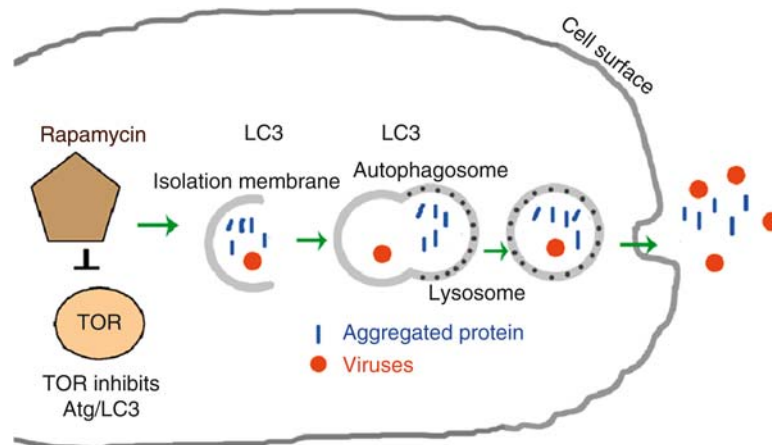


Figure A142. Autophagy

autophagic vacuoles (autophagosomes). Caspase 8 mediates autophagy through ATG7 (an ATP-dependent activator) and beclin 1 (Yu L et al 2004 Science 304:1500). Autophagy may have both advantageous (defensive) and deleterious features for health and disease (Shintani T, Klionsky DJ 2004 Science 306:990). Loss of autophagy in the central nervous system leads to neurodegeneration mice (Komatsu M et al 2006 Nature [Lond] 411:880; Hara T et al 2006 Nature [Lond] 441:885). When the proteasomes cannot handle the load, the non-degraded proteins may aggregate as *aggresomes*. Eventually the aggresomes can also be degraded (Wileman T 2006 Science 312:875). ▶lysosomes, ▶aggresome, ▶ubiquitin, ▶apoptosis, ▶beclin, ▶pexophagy, ▶dauer larva, ▶trinucleotide repeat, ▶TORs, ▶rapamycin, ▶endoplasmic reticulum-associated degradation; Klionsky DJ, Emr SD 2000 Science 290:1717; Subramani S 2001 Developmental Cell 1:6; Ohsumi Y 2001 Nat. Rev Mol Cell Biol 2:211; Khalfan W, Klionsky DJ 2002 Curr. Opin Cell Biol 14:468; yeast microautophagy; Duyboulou F et al 2005 Mol Cell 19:15, mini review: Yoshimori T 2007 Cell 128:833.

Autophene: Genetically determined trait, which is expressed independently of the position in case of transplantation. ▶allophenic

Autophosphorylation: Upon binding a ligand to a receptor it results in rapid phosphorylation of the receptor by its own subunits, e.g., by members of a dimeric molecule generally at tyrosine sites. ▶receptor tyrosine kinase

Autoploid (autopolyploid): Autoploid is the presence of more than two complete sets of identical genomes per cell. Autopolyploids may be [auto] tetraploid ($2n = 4x$), hexaploid ($2n = 6x$), octaploid ($2n = 8x$), etc. Autotetraploids in meiosis may pair as

quadrivalents, however, at a particular point only two chromosomes synapse (see Fig. A143). In autopolyploids, pairing may be also as two bivalents, one trivalent and univalent, and may form four univalents. When all chromosomes pair as bivalents, it is called selective pairing, and segregation of genes resemble that of diploids with duplicate genes. Autotetraploids

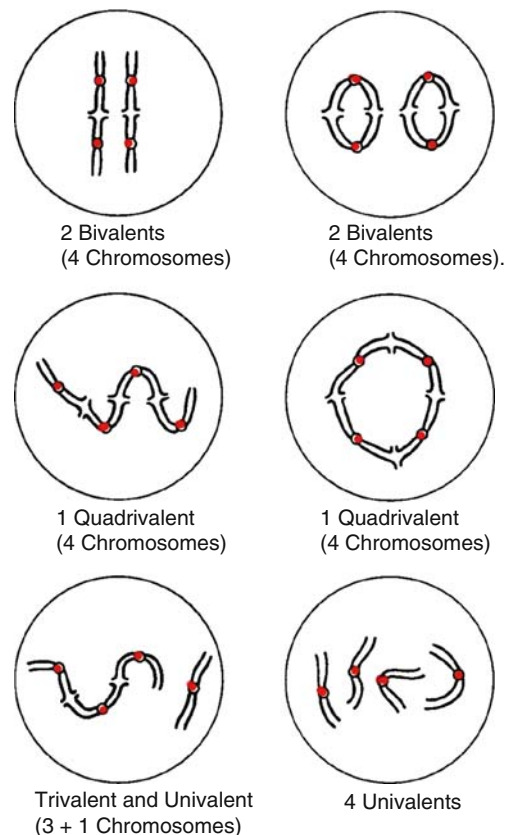


Figure A143. Association of homologs in autotetraploids

may carry a different allele in each of the four chromosomes; therefore, they can produce a larger variety of gametes than diploids. The maximal number of gametic combinations can be determined by the formula (see Table A7 and A8):

$\begin{bmatrix} n \\ x \end{bmatrix}$ where n = the total number of alleles, and x = the number of alleles in a gamete, thus in autotetraploids it becomes $\begin{bmatrix} 4 \\ 2 \end{bmatrix}$ for octaploids it is $\begin{bmatrix} 8 \\ 4 \end{bmatrix}$

and these can be rewritten as $\frac{4 \times 3}{2 \times 1} = 6$ for autotetraploids and $\frac{8 \times 7 \times 6 \times 5}{4 \times 3 \times 2 \times 1} = 70$ for autooctaploids, and this means that the number of allelic combinations possible with 4 different alleles are 6 types ($[4 \times 3] / [2 \times 1] = 6$) of gametes and in an octaploid with 8 different alleles ($[8 \times 7 \times 6 \times 5] / [4 \times 3 \times 2 \times 1] = 70$), the total number of gametic types is 70.

In case all the four alleles are dominant, AAAA, the individual is a quadruplex, AAAa = triplex, AAaa = duplex, Aaaa = simplex and aaaa = nulliplex. The segregation ratios in F_2 depend on whether there is

crossing over between the gene and the centromere, the type of pairing (as indicated above) and the type of disjunction at anaphase II (alpha parameter). The phenotypic proportions in F_2 are determined by the gametic output of the parents or selfed individuals. The gametic output and F_2 segregation of autopolyploids is very difficult to generalize because the genes are rarely linked absolutely to the centromere and the frequency of recombination may vary from 0 to 50%. There are additional variables that may be estimated by the alpha parameter. Segregation ratios at higher level of polyploidy can be predicted only theoretically, the actual results may be quite different, however. ▶synteny, ▶bivalent, ▶trivalent, ▶univalent, ▶synteny, ▶alpha parameter, ▶maximum ▶equational ▶segregation; Haldane JBS 1930 J Genet 22:359; Rédei GP 1982 Genetics, Macmillan, New York; see chromosome association diagram.

Autopodium: The skeletal portion of the hand and foot.

Autoprocessing: Occurs when a sequence of a protein (e.g., the C-terminal) is involved in its processing.

Table A7. Gametic output of autotetraploids

| Parent | Absolute Linkage* | | | Independence from Centromere [†] | | |
|--------|-------------------|----|-----------|---|----|------------|
| | AA | Aa | aa | AA | AA | aa |
| AAAA | 1 | 1 | 0 | 13 | 10 | 1 (4.2%) |
| AAaa | 1 | 4 | 1 (16.6%) | 2 | 5 | 2 (22.2%) |
| Aaaa | 0 | 1 | 1 (50.0%) | 1 | 10 | 13 (54.2%) |

Table A8. Phenotypic segregation ratios in autotetraploids in case the dominance is complete in F_2

| Mating | Absolute Linkage* | | Independence from Centromere [†] | |
|-------------|-------------------|-----------|---|-----------|
| | Dominant | Recessive | Dominant | Recessive |
| AAAA selfed | 1 | 0 | 575 | 1 |
| AAaa Selfed | 35 | 1 | 19.3 | 1 |
| Aaaa selfed | 3 | 1 | 2.4 | 1 |
| AAAA×AAaa | 1 | 0 | 107 | 1 |
| AAAA×Aaaa | 1 | 0 | 43.3 | 1 |
| AAAA×aaaa | 1 | 0 | 23 | 1 |
| AAaa×Aaaa | 11 | 1 | 7.3 | 1 |
| AAaa×aaaa | 5 | 1 | 3.5 | 1 |
| Aaaa×aaaa | 1 | 1 | 1 | 1.2 |

*No recombination between gene and centromere (chromosome segregation).

[†]The distance between gene and centromere is 50 map units or more, and therefore recombination occurs freely as if they (gene and centromere) would not be syntenic (chromatid segregation or maximum equational segregation).

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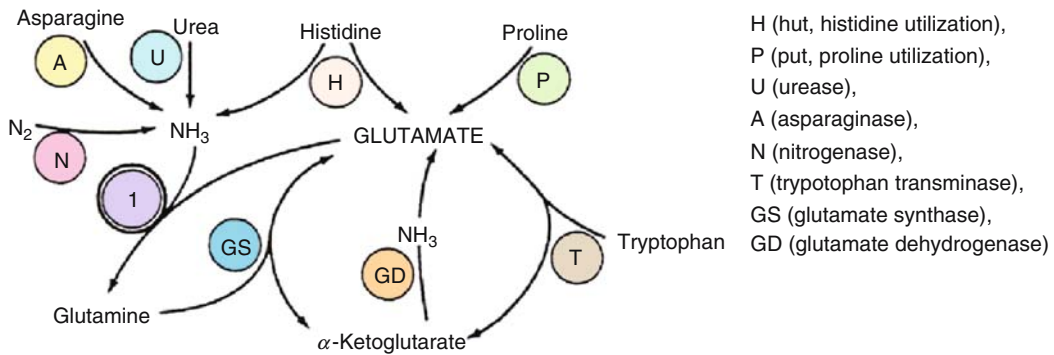


Figure A144. Metabolic steps involved in the regulation and autoregulation of Glutamine synthetase ①

Autorad: Lab slang for autoradiogram. ► [autoradiography](#)

Autoradiography: Labeling technique by which a radioactive substance reveals its own position in a cell or on a chromatogram when brought into contact with photographic film. For cytological analyses, most commonly H^3 -labeled thymidine is used because it gives the clearest resolution of chromosomal regions without serious DNA breakage, whereas in molecular genetics the much higher energy P^{32} -labeled compounds are employed usually. ► [non-radioactive labels](#), ► [immunoprobes](#); Taylor JH et al 1957 Proc Natl Acad Sci USA 43:122.

Autoreactive: When the lymphocytes recognize the individual's own molecules and develop an immune reaction to them. ► [autoimmune disease](#)

Autoreduplication: self-duplication.

Autoregulation: Occurs when a compound (or system) controls the rate of its own synthesis (see Fig. A144). For, e.g., the bacterium *Klebsiella aerogenes* uses glutamine dehydrogenase to make glutamate from α -keto-glutarate and ammonia, if the concentration of the latter exceeds 1 nM. If the concentration of ammonia is low, glutamate dehydrogenase cannot function to an appreciable extent. In this case, the ammonia + glutamate are converted into glutamine by glutamine synthetase. The active form of glutamine synthetase is non-adenylylated. In the presence of high concentration of ammonia, the enzyme is adenylylated and thus, the activity is reduced by this mechanism of autoregulation. In its non-adenylylated states it represses glutamate dehydrogenase instead. ► [regulation of gene activity](#), ► [nitrogen fixation](#), ► [genetic network](#); Magasanik B et al 1974 Curr Top Cell Reg 8:119; Chandler DS et al 2001 Nucleic Acids Res 29:3012; Isaacs FJ et al 2003 Proc Natl Acad Sci USA 100:7714.

Autosegregation: May take place in an apomictic or vegetatively multiplied organism due to chromosomal loss or somatic mutation. ► [apomixis](#), ► [mutation](#)

Autosexing: Identification of sex by genetic markers rather than by the genitalia. Silkworm breeders and poultry producers have exploited this procedure. Homozygosity for the *B* (barring) genes suppresses the appearance of colored spots on the head of the newly hatched chicks, controlled by this sex-linked gene (remember that in birds the males are homogametic). The *B* gene is dominant yet it shows clear dosage effect. In the females that are heterogametic, the spot is evident. Thus, the hens can be separated early from the roosters when the recognition of gender by anatomy is very difficult. Since most of the roosters will be used for meat production and the hens for egg production, they can be fed and managed accordingly. In the silkworm, the male cocoons (chrysalis) produce 25 to 30% more silk than the females and therefore, autosexing may have economic advantage. An electronic device may sort the silkworm eggs according to color (sex). (see Fig. A145; ► [chromosomal sex determination](#), ► [sexing](#))

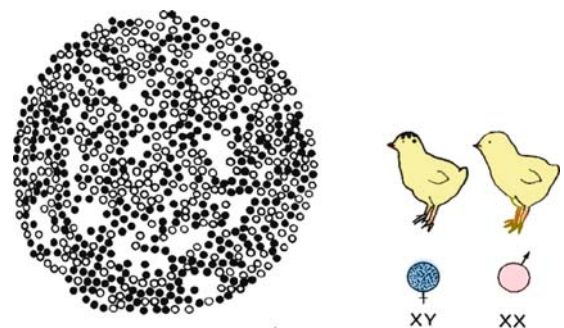


Figure A145. Left: Autosexing in the silkworm. The dominant gene in the Y chromosome permits the distinction between the eggs which will hatch to become a male (pale color) and female (dark). Right: The homozygous male (b/b) chicks are light colored while the hemizygous b/o females develop colored spots on the head. (In the Lepidoptera and birds the males are WW and the females are WZ)

Autosomal Dominant Mutation: Readily detected and identified in many instances because the novel type appears suddenly without precedence in the pedigree. Achondroplasia in humans is frequently cited as such an example. The homozygotes generally suffer perinatal death. Therefore, most of the achondroplastic dwarfs are heterozygotes and new mutants. These dwarfs are of normal and frequently of superior intelligence. One must not forget that over 70 gene loci are responsible for various types of dwarfing in humans. Autosomal dominant mutation rates (per gamete/generation) in human populations for ten diseases vary from 4 to 100×10^{-6} . ▶ [mutation rate](#), ▶ [achondroplasia](#)

Autosomal Recessive Lethal Assay: A tester stock used for the detection of recessive second chromosomal lethals in *Drosophila*. It is of the following genetic constitution: *Cy L/Pm* where *Cy* (*Curly*) *L* (*Lobe*) and *Pm* (*Plum*) are heterozygous viable but homozygous lethal dominant genes. The *Cy* chromosome generally carries three inversions to prevent the recovery of crossovers. The heterozygotes of either sex are crossed with a mate that carried no mutation in either of the two second-chromosomes before the test. Single F_1 male(s) are then backcrossed with the *Cy L/Pm* female tester. From their offspring *Cy L* individual sibs are mated. From this mating, an F_2 is obtained. If all the survivors are *Cy L*, this indicates that a new lethal mutation occurred in the grandfathers' or grandmothers' 2nd chromosome and therefore *non-Curly* and *non-Lobe* homozygous individuals could not live. The diagram does not show the genotypes in the F_2 (see Fig. A146). ▶ [sex-linked recessive lethal assays](#)

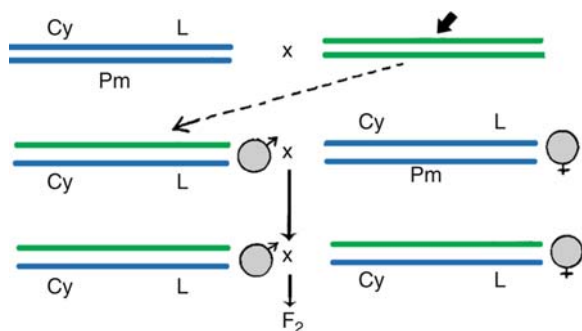


Figure A146. Autosomal recessive lethal assay

Autosome: Autosome is a chromosome that is not a sex chromosome. ▶ [chromosomal sex determination](#)

Autosynthesis: May take place between homoeologous chromosomes in the absence of homoeologous pairing-suppressor genes. ▶ [homoeologous](#), ▶ [chromosome 5B](#)

Autotoxic Enterogenous Cyanosis: An obsolete name for human familial NADH-methemoglobin deficiency. ▶ [methemoglobin](#)

Autotroph: Can synthesize cellular C- and N- containing molecules from carbon dioxide and ammonia.

Autozygous: A genotype, which is not just homozygous but the alleles at the locus are *identical by descent*. ▶ [allozygous](#), ▶ [inbreeding coefficient](#), ▶ [coancestry](#), ▶ [homozygosity](#)

Autozygosity Mapping: ▶ [homozygosity mapping](#), ▶ [inbreeding coefficient](#); Kruglyak L et al 1995 Am J Hum Genet 56:519.

Auxanography: A method for mutant selection. A minimal medium is over-layered with auxotrophic spore or cell suspension and subsequently to different segments of the plate small quantities of various substances that the cells may need for growth are added. Where growth occurs, the cells utilize the compounds added and their nutritional requirement is identified.

Auxilin: 100-kDa brain-specific chaperone with C-terminal homology to DnaJ. Auxilin-bound clathrin mediates also uncoating of clathrin-coated vesicles (Fotin A et al 2004 Nature [Lond] 432:649). ▶ [DnaJ](#), ▶ [clathrin](#)

Auxins: phytohormones (morphogens) produced by the plant metabolism such as indole-3-acetic acid or of synthetic origin such as α -naphthalene acetic acid or 2,4-dichloro-phenoxyacetic acid (see Fig. A147). They play important role in cell elongation, signal transduction and required supplements for proliferation and regeneration in tissue culture. The transport of auxins in the plant tissues is regulated by chemosmosis aided by various transporter proteins. Auxin is synthesized in the leaves of the plants and it is transported to the stem apex where it plays an important role in the generation of flowers. Auxins also regulate root development. The *pin* family of proteins controls the transport of auxin either to the shoot and/or to the root and is essential for the development/growth of these organs (Kaplinsky NJ et al 2004 Science 306:822). The (▶ [PLETHORA](#) *PLT*) genes are required for *PIN* transcription and for stabilizing auxin at the root tip (Blilou I et al 2005 Nature [Lond] 433:39). The auxin-binding protein (ABP1)—with its crystal structure known—is essential for normal function of auxin (Napier RM et al 2002 Plant Mol Biol 49:373). The auxin-response factor (ARF) and AUX/IAA proteins are involved in regulation of auxin-dependent genes. The latter binds ARF and ARF binds directly to DNA (Hagen G, Guilfoyle T 2002 Plant Mol Biol 49:373; Liscum E, Reed JW 2002 Plant Mol Biol 49:387). These proteins are considered repressor of gene expression.

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Figure A147. Pin-like mutants of *Arabidopsis* do not develop normal flowers at the tip of the stem. (Rédei, unpublished)

H⁺-pyrophosphatase (AVP1) controls auxin distribution and auxin-mediated shoot and root development (Li J et al 2005 Science 310:121). Auxin aides the interaction between the large number of AUX/IAA family of proteins and the ubiquitin ligase SCF, and the TIR1 and three other F-box proteins appear to be auxin receptors and transport inhibitors, which degrades AUX/IAA (Dharmasiri N et al 2005 Nature [Lond] 435:441; Kepinski S, Leyser O 2005 *ibid.* 446). The leucine-rich repeat domain of TIR1 of *Arabidopsis* contains an inositol hexakisphosphate co-factor and recognizes auxin and the AUX/IAA polypeptide substrate through a single surface pocket. Anchored to the base of the TIR1 pocket, auxin binds to a partially promiscuous site, which can also accommodate various auxin analogues (such as naphthalene acetic acid and 2,4-D). Docked on top of auxin, the AUX/IAA substrate peptide occupies the rest of the TIR1 pocket and completely encloses the hormone-binding site (Tan X et al 2007 Nature [Lond] 446:640). Inositol hexakisphosphate (IP6) and inositol heptakisphosphate (IP7) kinase activities generally regulate cell growth and morphology (Mulugu S et al 2007 Science 316:106).

Auxin modulates the response to gibberellin and the latter opposes the nuclear DELLA proteins, which are growth repressors (Fu X, and Harberd NP 2003 Nature [Lond] 421:740). Genes (*iaaH*, *iaaM*) in the Ti plasmid of *Agrobacterium* have instructions for their production and regulation, and these genes play a role in crown gall formation (in cooperation with cytokinins). An auxin response element first identified in the octopine synthase (*ocs*) gene of *Agrobacterium tumefaciens* (AuxRe [named *as-1* in cauliflower mosaic virus]) is an enhancer and it is present in many

genes. The *ocs/as-1* consensus consists of a more or less well-conserved 20- bp direct repeat with a 4 base spacer: TGACGTAAGCGCTGACGTAA. These elements respond to various auxins, salicylic acid, methyljasmonate and many other diverse compounds. The binding transcription factors have basic leucine zipper (bZip) motifs. Indole-3-acetic acid is biosynthesized mainly from tryptophan (aminotransferase) through indole-3-pyruvate (decarboxylase). ▶plant hormones, ▶crown gall, ▶Ti plasmid, ▶embryogenesis somatic, ▶ARF1, ▶SCF, ▶chemosmosis, ▶bZip, ▶SAUR, ▶sirtuin, ▶phosphoinositides; Guilfoyle TJ, Hagen G 1999 In: Reynolds PHS (ed) Inducible gene expression in plants. CABI, New York, p 219; Sabatini S et al 1999 Cell 1999:463; Zhao Y et al 2001 Science 291:306; Gray WM et al 2001 Nature [Lond] 414:271; Leyser O 2002 Annu Rev Plant Biol 53:377.

Axiom: Is a self-evident statement, which does not require proof; a basic tenet, e.g., nucleic acids represent genetic material.

Auxonography: ▶auxotrophy

Auxotroph: A mutant that requires nutritive(s) not needed by the wild type (prototroph) (see Fig. A148). Auxotrophic mutations have been extensively used for the study of biochemical pathways and for the identification enzymes catalyzing particular metabolic steps. In genetic analysis, auxotrophs facilitate selective techniques in backmutation, recombination, transformation, etc. A pyridoxine deficiency, causing seizure in humans, has been identified.

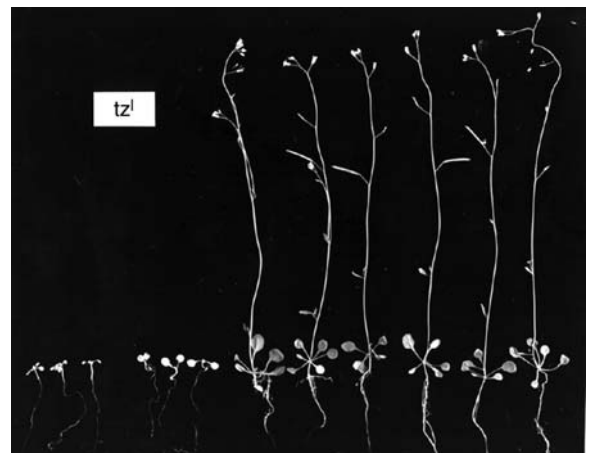


Figure A148. Left: Thiazole auxotrophs of *Arabidopsis* on basal medium; Right: on thiamine medium. (From GP Rédei, unpublished)

True auxotrophic animal mutations are exceptional and are also rare in higher plants. In *Arabidopsis*, over 200 mutations were obtained in the thiamine pathway without any obligate auxotrophy for other metabolites. The scarcity of auxotrophic mutations may be

due to redundancy of the genomes, alternative metabolic pathways and to compensatory effects in large genetic networks. ▶pyridoxine, ▶autotroph, ▶redundancy, ▶genetic network; Rédei GP 1982 Genetics, Macmillan, New York.

AuxRE (auxin response element): ▶ARF1, ▶auxin

Avastin (Bevacizumab): Avastin is a monoclonal antibody drug targeting vascular endothelial growth factor (VEGF) to reduce the blood supply (angiogenesis) for cancer cells. ▶angiogenesis, ▶VEGF, ▶monoclonal antibody, ▶biomarkers

AVED (ataxia with vitamin E deficiency): Caused by mutation in the large subunit of microsomal triglyceride transfer protein (encoded in human chromosome 8q13). Although the intestinal absorption of α -tocopherol is normal, the hepatic secretion into the blood is defective. The condition is very similar to Friedreich ataxia. ▶Friedreich ataxia

Avena: A genus of grasses (oats) with basic chromosome numbers $x = 7$ and form an allopolyploid series, $2n, 4n, 6n$.

Average: Arithmetic mean, i.e. the sum of all measurements (x) divided by the number of measurements (N): $\bar{x} = \frac{\sum x}{N}$. ▶mean, ▶median, ▶mode

Average Inbreeding Coefficient: α .

Avian: Pertaining to the taxonomic class of *Aves*. (sing. *Avis*, bird[s]). ▶chicken; <http://www.grcp.ucdavis.edu/publications/doc20/full.pdf>.

Avian Erythroblastosis (erbB): Viral oncogene (prevents maturation of the red blood cells in fowl) has its cellular homolog as a proto-oncogene in several eukaryotes. It is a protein kinase, phosphorylating primarily tyrosine residues. The normal allele specifies a plasma membrane receptor of epidermal growth factor (EGF). ▶erythroblastosis ▶fetalis

Avian Influenza Virus: ▶influenza

Avian MC29 Myelocytomatosis: A viral oncogene (*myc*, causes carcinoma, sarcoma and myelocytoma [a kind of leukemia]). It is present as a cellular proto-oncogene in vertebrates and its homologs are also present in plant cells. ▶oncogene, ▶proto-oncogene, ▶carcinoma, ▶sarcoma, ▶leukemias

Avian Myeloblastosis: ▶MYB oncogene

Avian Sarcoma Virus: ▶ASV

Avidian: A computer generated “artificial life form” useful for simulating genetics and evolutionary processes in a virtual environment of cybernetics. ▶genetics digital, ▶cybernetics

Avidin: A ca. 68,000 M_r protein of four subunits, each having strong affinity to biotin. It binds strongly to any molecule complexed with biotin such as nucleic acids, and biotin containing enzymes. It is widely used for non-isotopic labeling of nucleic acids. Originally, it was found and isolated from raw egg white. Eating raw eggs may cause biotin deficiency (cooking inactivates it). It is isolated also from *Streptomyces avidinii* under the name streptavidin. ▶biotinylation, ▶genomic subtraction

Avidity: ▶antibody

Avirulence: The lack of competence for causing pathological effects by an infectious agent.

Avogadro Number: The number of molecules ($= 6.02 \times 10^{23}$) in a gram molecular weight, a constant for all molecules.

Avoidance Learning: This is a classical test of animal behavior. In a two-compartment box one is electrically wired to provide test animals, an electric shock after a light turns on. After a learning period, some of the animals immediately move to the safe compartment when they see the light signals and learn that the shock comes from one compartment. The learning ability of inbred mice strains is genetically different. In some, about half of the individuals “learn,” in others only 10% associates the light signal with the shock. In *Drosophila* olfactory sensory neurons mediate the avoidance of CO_2 emitted by stressed flies (Suh GSB et al 2004 Nature [Lond] 431:854). ▶behavior genetics

Avuncular: Ancestral relatedness such as existing between nephews/nieces and uncles/aunts.

Awn (arista): Awn is a part of the glume present in some monocot plants (wheat). It supposedly has a role in photosynthesis, water regulation of the kernel and in seed dispersal. ▶glume; Elbaum R et al 2007 Science 316:884.

Axenic: The pure culture of organisms or cells without any contamination by other (micro) organisms. ▶aseptic culture, ▶tissue culture

Axenfeld-Rieger Anomaly (FKHL7/FOXC1, 6p25): Anterior eye segment defect and glaucoma caused by mutation in the human homolog of the *Drosophila* forkhead gene, FOXC1 (see Fig. A149). Additional loci at 4q25 (PITX2, a bicoid-related protein), 13q14, and 16q22-q24 (FOXC2 forkhead-like). ▶forkhead, ▶bicoid, ▶glaucoma; Priston M et al 2001 Hum Mol Genet 10:1631; Lines MA et al 2002 Hum Mol Genet 11:1177.

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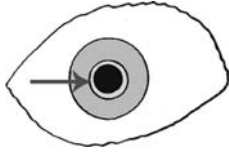


Figure A149. In the Axenfeld-Rieger syndrome with-in a reduced size iris, a light-colored ring (the sphincter muscle) is conspicuous around the pupil

Axial Elements: The lateral elements of the tripartite synaptonemal complex. ►[synaptonemal complex](#)

Axillary: Formed in the axil, the upper surface of the area between the leaf petiole and stem.

Axin: A protein-controlling body axis formation. Mutant axin may interfere with the normal developmental pathway and cause cancer, especially when the mismatch repair is defective. It is homologous to conductin. ►[conductin](#), ►[Wnt](#), ►[DNA](#) ►[repair](#)

Axis of Asymmetry: Axis through which objects or molecules form mirror images. In the body of the majority of organisms three axes are recognized: anterior–posterior (front–hind), dorsal–ventral (back–abdominal) and left–right. Recently, genes controlling asymmetry of the body have been identified. It had been known for a long time that changing the placement of internal organs has multiple deleterious consequences ►[situs inversus viscerum](#). It has been shown now in the *lefty* mouse mutant that the expression of the transforming growth factor (TGF β) family plays the role of a morphogen in controlling asymmetry by expressing only in the left half of the gastrula. This asymmetry is transient and sets on before lateral asymmetry becomes visible. Similar genetically-controlled mechanisms have also been discovered in chickens and other organisms. ►[morphogen](#), ►[TGF](#), ►[activin](#), ►[Kartagener syndrome](#), ►[asymmetric cell division](#), ►[situs inversus visceri](#); Lall S, Patel NH 2001 *Annu Rev Genet* 35:407.

Axl: A receptor tyrosine kinase, which is human myeloid leukemia transforming protein. ►[leukemias](#)

Axon: A long nerve fiber that, generally in a bundle surrounded by a myelin sheath, communicates impulses between the central and the peripheral nervous system. Organelles and molecules can be transported along the nerve axons outward from the cell or back to the cell. ►[neurogenesis](#), ►[netrin](#), ►[Slit](#), ►[Robo](#), ►[comm](#), ►[neuropilin](#), ►[axotomy](#); Kamal A et al 2000 *Neuron* 28:449; axonal transport; Stokin GB, Goldstein LSB 2006 *Annu Rev Biochem* 75:607.

Axon Guidance: Axons grow and move through the embryonal body toward their targets and allow for

synaptic connections of the neurons. Many proteins guide their advance. Some axons follow the same path, and bundle together by a process called fasciculation. Brain wiring and axon guidance can be monitored with the aid of the *PLAP* (placental alkaline phosphatase) vector equipped with an IRES site 5' to the *PLAP* gene. The vector includes another part carrying β -galactosidase and neomycin phosphotransferase (*G418*^r). This portion of it is expressed by virtue of its fusion to neural body cell-specific promoter. Transformants can be selected on neomycin media. The β -gal gene marks the cell body by blue color on X-gal medium; the *PLAP* gene is expressed exclusively in the dendritic part of the neurons. Thus, the wiring pattern of the brain can be monitored without laborious chemical purification. The Netrin, Slit, Semaphorin and Ephrine families of proteins—besides being involved with axons—contribute to the development of many other organs too by regulating transcription and translation of morphogenetic genes (Hinck L 2004 *Developmental Cell* 7:783). ►[axon](#), ►[Parkinson disease](#), ►[neuron](#), ►[IRES](#), ►[G418](#), ► [\$\beta\$ -galactosidase](#), ►[X-gal](#), ►[sema-phorin](#), ►[netrin](#); Leighton PA et al 2001 *Nature [Lond]* 410:175; Lin MZ, Greenberg ME 2000 *Cell* 101:239; Stein E, Tessier-Lavigne M 2001 *Science* 291:1928; Patel BN, Van Vactor DL 2002 *Curr. Opin Cell Biol* 14:221; Dixon BJ 2002 *Science* 298:1959; Zhu F-Q et al 2004 *Neuron* 42:897.

Axoneme: Cylindrical structures of microtubule doublets and about 250 attached polypeptides that are the major part of cilia, flagella and sperm. Two rows of the motor protein dynein are situated along the microtubules. ►[microtubule](#), ►[dynein](#), ►[cilia](#); Nicastro D et al 2006 *Science* 313:944.

Axoplasm: The cytoplasm of axons. ►[axon](#), ►[cilia](#)

Axotomy: Lesion of axons; may affect expression of genes. ►[regulation of gene activity](#)

5-Azacytidine: A pyrimidine analog (and suspected carcinogen) that interferes with methylation of DNA bases and may even restore the function of genes silenced by methylation (see Fig. A150). 5-azacytidine covalently binds cytosine methyltransferase enzymes and dramatically reduces methylation of cytosine in the DNA (Santi DV et al 1984 *Proc Natl Acad Sci [USA]* 81:6993). It may affect differentiation and development because hypomethylated genes are preferentially transcribed. It is noteworthy that some small eukaryotic genomes (yeast, *Drosophila*) do not contain methylcytosine yet their genomes are regulated during development. ►[methylation of DNA](#), ►[housekeeping genes](#), ►[fragile X](#), ►[trichostatin](#)

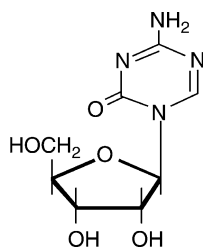


Figure A150. Azacytidine

Azaguanine: A toxic analog of guanine, it is readily incorporated into RNA or DNA (see Fig. A151).

►HAT medium

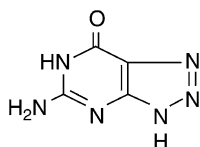


Figure A151. Azaguanine

8-Azaguanine Resistance: A commonly used marker in mammalian cell cultures; the resistance is based on a deficiency of the enzyme azaguanine-hypoxanthine phosphotransferase and therefore, this toxic purine cannot be processed by the metabolism. ►HAT medium

Azaserine (O-diazoacetyl-L-serine): An alkylating, antitumor, antifungal and mutagenic agent. The oral LD50 for rodents is 150–170 mg/kg. ►LD50

Azathiopurine (azathioprine): An anticancer, immunosuppressive drug (see Fig. A152). It is also a receptor of ultraviolet light A and increases the cells sensitivity to oxidative damage brought about by UV. Therefore, people who underwent azathioprine therapy may have increased risk for skin cancer (O'Donovan P et al 2005 Science 309:1871).

►thiopurine-S-methyltransferase [TPMT]

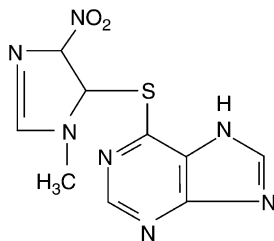


Figure A152. Azathiopurine

6-Azauracil: An antineoplastic pyrimidine analog; its nucleotide is inhibitory to orotidylic-acid decarboxylase and may repress the synthesis of orotidylic acid

pyrophosphorylase, key enzymes in the de novo pathway of nucleotide synthesis. ►TIIFS

Azide: A compound with a NH_3 ; sodium azide, a respiratory inhibitor, is a strong mutagen for certain organisms at low pH but not for others. Nitrogenase enzymes may reduce azides to N_2 and NH_4 .

►nitrogenase

Azidothymidine: ►AZT

Azoospermia: Human gene AZF (azoospermia factor) appears to be the expression of the DAZ (deleted in azoospermia) site and it has been assigned to human chromosome Yq11. At the AZF site three long palindromic sequences encoding 11 transcription units have been identified (Kuroda-Kawaguchi T et al 2001 Nature Genet 29:279). At Yq11.2, in the vicinity of AZF, is the DFFR (*Drosophila* fat-facet related), another spermatogenesis control gene. The frequency of the DAZ causes sterility is about 1.25×10^{-4} in men. There is no sperm in the ejaculate although the testes may produce sperm. This gene is substantially (42%) homologous to the *Drosophila* gene *boule* (*bol*) controlling meiotic G2 - M transition. Mouse gene *Dazla* is 33% homologous to DAZ. Both the mouse and the *Drosophila* genes are, however, autosomal yet they also involve male sterility. It has been shown recently that the human AZF gene was originally in the short arm of human chromosome 3 (where highly homologous sequences still exist), and it was transposed to the Y chromosome, amplified and pruned. The human Y chromosome encodes an RNA recognition motif, which is active particularly in the testes and the deletion of this motif may cause azoospermia. Histological analysis revealed that *Brek*^{-/-} germ cells (deficient in a brain-enriched kinase) differentiated normally until the round-spermatid stage, but failed to undergo the normal change in morphology to become elongated spermatids. Testicular somatic cells appeared normal in these mice. Expression of *Brek* in testis was restricted to the germ cells, suggesting that the maturation of germ cells in *Brek*^{-/-} mice are affected in a cell-autonomous manner. *Brek* seems to be essential for a late stage of spermatogenesis and may help to identify new targets for reproductive contraceptives and treatments against infertility (Kewa S et al 2006 Proc Natl Acad Sci USA 103:19344). ►holandric genes, ►twine, ►pelota, ►boule ►[bol], ►RBM, ►agonadism, ►oligospermia, ►CBADV, ►infertility; Hackstein JHP et al 2000 Trends Genet 16:565; Xu EY et al 2001 Proc Natl Acad Sci [USA] 98:7414.

Azorhizobium: ►nitrogen fixation

A

Azotobacter: ►nitrogen fixation

AZT (azidothymidine, also called zidovudine): A thymidine analog with an azido (N_3) substitution of the 3'-OH group (see Fig. A153); it may slow down the reverse transcriptase activity of HIV virus by

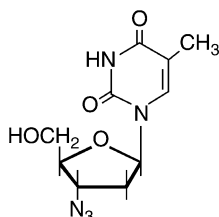


Figure A153. AZT

preferentially selecting this analog that has only minor effect on DNA polymerase of the mammalian cells. Unfortunately, some bone marrow damage is associated with the drug and this limits its usefulness in protecting against the full-scale development of AIDS. Mutations in the HIV reverse transcriptase may result in resistance against the drug by removing the AZTMP that blocks transcription. Eventually it may also debilitate the cells by the inhibition of DNA polymerase γ . It should be remembered that the Aschheim-Zondek test for pregnancy is also abbreviated as AZT. ►acquired immunodeficiency, ►AIDS, ►HIV, ►mtDNA; Lim SE, Copeland WC 2001 J Biol Chem 276:23616.

Azurocidin: ►antimicrobial peptides**Historical vignettes**

The Cambridge (Massachusetts) City Council were not the first to disapprove of recombinant DNA. Joshua Sylvester (1563–1618) answers the “New objection of Atheists, concerning the capacite of the Ark”:

“O profane mockers! if I but exclude
Out of this Vessel a vast multitude
Of since-born mongrels, that derive their birth
From monstrous medly of *Venerian* mirth:
Fantastick Mules, and spotted Leopards,
Of incest-heat ingendred afterwards:
So many sorts of Dogs, of Cocks, and Doves,
Since, dayly sprung from strange & mingled loves,
Wherein from time to time in various sort,
Dedalian Nature seems her to disport:
If plainer, yet I prove you space by space,
And foot by foot, that all this ample place,
By subtile judgement made and *Symmetrie*,
Might lodge so many creatures handsomely,
Sith every brace was *Geometricall*:
Nought resteth (*Momes*) for your reply at all;
If, who dispute with God, may be content
To take for current, Reason's argument.”

– *The Complete Works of Joshua Sylvester*,
Vol. I, ed. Rev. Alexander B Grosart, printed
for private circulation, 1880, p. 136

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“On 1 July 1858, three papers were read by the [Linnean Society] society's undersecretary, George Busk, in the order of their date of composition: Darwin's abbreviated abstract of his 230-page essay from 1844; an ‘abstract of abstract’ that Darwin had written to the American botanist Asa Gray on 5 September 1857; and Wallace's essay, ‘On the Tendency of Varieties to Depart Indefinitely from Original Type; Instability of Varieties Supposed to Prove the Permanent Distinctness of Species’ (1858; ref 10).

The papers generated little response and virtually no discussion, their significance apparently lost to those in attendance. Nor was it noticed by the president of the Linnean Society, Thomas Bell, who, in his annual address the following May, blandly stated that the past year had not been enlivened by ‘any of those striking discoveries which at once revolutionize’ a branch of science.”

B

B: Refers to back cross generation; the numbers of back crosses are indicated by subscripts, e.g., B₁. ► [back cross](#)

β: ► [Error types](#), ► [power of a test](#)

7B2 (secretogranin V, chromogranin): A 25–29 kDa pro-hormone which is processed to a 18–21 kDa neuroendocrine chaperone (distantly related to chaperonins-60/10) in the secretory pathway. It is widely found in animals, and it is encoded in human chromosome 15q13-q14 as SGNE-1. It is an inhibitor/activator of the pro-hormone convertase PC2 enzyme but not of other PCs. ► [Golgi apparatus](#), ► [chaperonins](#); Umemura S et al 2001 Pathol Int 51:667.

B104: Refers to *Drosophila* retroposon, which is similar to copia, gypsy and others. ► [Copia](#)

β Barrel: The polypeptide chain of a membrane protein forms a folded up β sheet arranged in the shape of a barrel. ► [Protein structure](#), ► [membrane proteins](#), ► [transmembrane β barrel detection in bacteria](#): <http://cubic.bioc.columbia.edu/services/proftmb/>; <http://bioinformatics.bc.edu/clotelab/transFold/>; <http://tmbeta-genome.cbrc.jp/annotation/>.

B1 B Cell: These are fetal and early infant B cells which may be found in excess in leukemias and autoimmune diseases. ► [B lymphocyte](#), ► [leukemias](#)

B Box: This refers to a part of the internal control region of tRNA and some other genes. See also A box and internal control region of pol III genes. ► [Trna](#), ► [pol III](#)

B.C.E. (before the common era): An archaeological concept for the designation of age of event(s) or artifacts based on different criteria such as carbon dating, old scriptures, etc.

B Cell: B lymphocyte, B lymphocyte receptor.

B Chromosome: This is the accessory (supernumerary) chromosome. They are generally heterochromatic and carry no major genes yet they may be present in several copies in many plants. B chromosomes have no homology to the regular chromosomal set (A chromosomes) and are prone to non-disjunction because their centromeres appear to be defective. If A-B translocations are constructed, the placement of genes to chromosomes, arms or even shorter regions may be facilitated. The principle of the use of A-B chromosome translocations is presented in the

diagram here. The A chromosome or a translocated segment carries the dominant *A* allele and the B chromosome has no counterpart to it, therefore a null phenotype (*a*) appears in its absence. In the diagram the male has the translocation and the female is homozygous recessive for the *a* allele. In case there is no B chromosomal non-disjunction—when the chromosomal constitution is as diagramed—both the endosperm and the embryo express the dominant gene. In the case of non-disjunction the phenotypic effects depend on the constitution of the sperm, which fertilizes the diploid polar nucleus of the endosperm or the embryo, respectively (see Fig. B1).

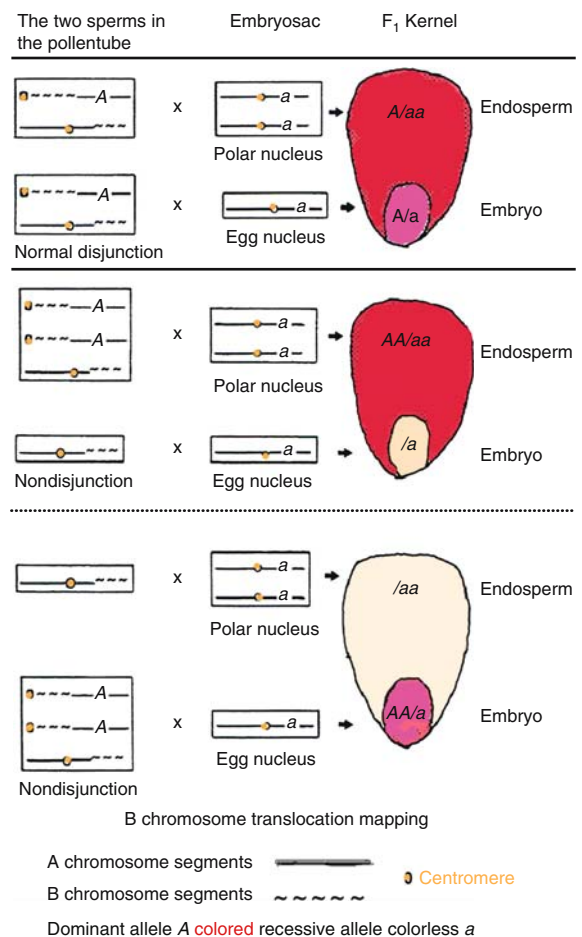


Figure B1. B chromosome translocation mapping

This type of difference reveals the approximate physical and genetic position of the locus. Had the dominant allele been outside the translocated segment, the recessive allele would not have been unmasked. The example given here describes the most favorable case when the consequence of the translocation can be identified without tissue-specificity.

B

B chromosomes have been reported in ~1300 species of plants and in ~500 species of invertebrate and vertebrate species of animals. The transmission of the B chromosomes varies in different species and it may be preferential in the female member (e.g., in grasshoppers) or in some wasps by the male. A total of 19 B chromosome sequences of maize have been isolated by microdissection and cloned and characterized according to their information content (Cheng Y-M, Lin B-Y 2003 *Genetics* 164:290). ▶**mapping genetic**, ▶**trisomic analysis**, ▶**translocation genetic**, ▶**centromere**, ▶**centromere silencing**; Beckett JB 1982 *J Hered* 73:29; Page BT et al 2001 *Genetics* 159:291; Camacho JPM et al 2000 *Philos Trans R Soc Lond B* 355:163.

B DNA: ▶**DNA type**, ▶**Z DNA**

B Lymphocyte (B cell): This is responsible for humoral antibody synthesis and secretion. Pro-apoptotic proteins, BAX and BAK, limit the number of B cells. The deletion of *Bax* and *Bak* genes leads to autoimmune disease in mice (Takeuchi O et al 2005 *Proc Natl Acad Sci USA* 102:11272). There are two types of B cells, B1 and B2. T cells activate the common B2 cells. Its differentiation from hematopoietic cells (plasma cells) depends on transcription factors (XBP-1) of the bone marrow, cytokines and antigens, T_H cells and a series of non-receptor and receptor tyrosine kinases and phosphatases, proteins mediating the pathway shown in italics (see Fig. B2) in the diagram outlining the developmental pathway of B lymphocytes. The B1 cells also employ an RNA editing system for the diversification and amplification of their antigen receptors in contrast to T cells, which rely on the V(D)J recombination system, and

appear independent of T cell activation. ▶**T cells**, ▶**apoptosis**, ▶**EBF**, ▶**CpG motifs**, ▶**CD40**, ▶**TAPA-1**, ▶**blood**, ▶**immune reactions**, ▶**germinal center**, ▶**Blimp-1**, ▶**BTK**, ▶**surrogate chains**, ▶**Pax**, ▶**immunoglobulins**, ▶**BASH**, ▶**V(D)J**, ▶**RNA editing**, ▶**XBP**; Fagarasan S, Honjo T 2000 *Science* 290:89; ▶**blood**, ▶**bone marrow**, ▶**thymus**, ▶**immune system**; Hardy RR, Hayakawa K 2001 *Annu Rev Immunol* 19:595; Reimold AM et al 2001 *Nature [Lond]* 412:300; Berland R, Wortis HH 2002 *Annu Rev Immunol* 20:253.

B Lymphocyte Receptor (B cell receptor, BCR): This is constructed from the membrane-bound immunoglobulin molecules IgM and IgD as receptors and after the attachment of the antigen they can also use IgG, IgA and IgE (see Fig. B3). The intracellularly linked IgA and IgB heterodimer that is the signaling portion of the receptor and the complex transmits the immunoglobulins recognized by the BCR. All the immunoglobulins are attached to the receptors associated with the IgA and IgB heterodimer through their heavy-chain terminal amino acids. This tail consists of 3 amino acids in IgM and IgD but it has 28 amino acids in IgG and IgE. In both, part of the A-B heterodimer includes an ITAM (immunoreceptor tyrosine-based activation motif). The latter is instrumental in activating the Sky and Lyn protein tyrosine kinases that mediate the switching to the IgG, IgA and IgE molecules when the appropriate antigen is presented. These tails are required for the endosomal targeting of the immunoglobulins. The B cell linker protein (BLNK) is also required for the normal development of B lymphocytes. ▶**B lymphocyte**, ▶**BASH**, ▶**immune system**, ▶**ITAM**, ▶**ITIM**, ▶**BAP**, ▶**endocytosis**, ▶**agammaglobulinemia**; Meffre E et al 2001 *J Clin Invest* 108:879; Vilches C, Parham P 2002 *Annu Rev Immunol* 20:217.

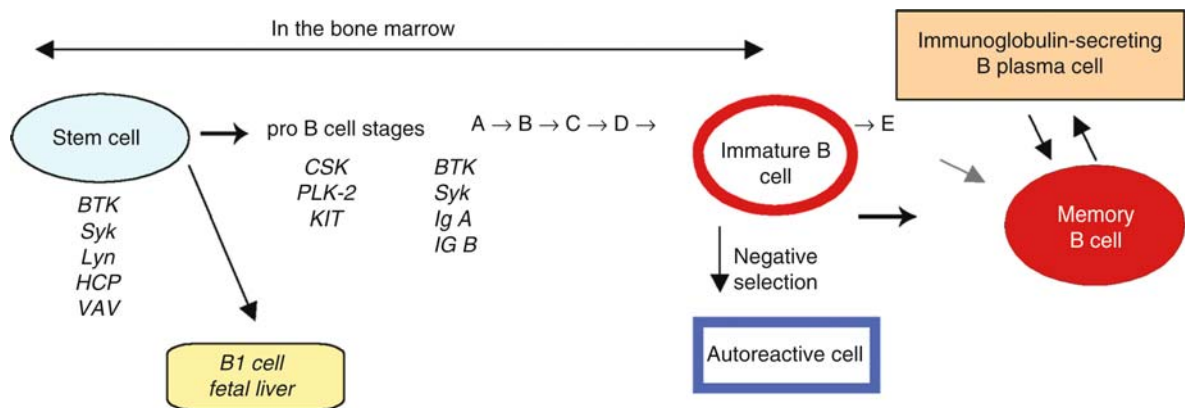


Figure B2. B lymphocyte-bone marrow. During the pro-B cell stages in the bone marrow first the IgH and then the IgL immunoglobulin chains are rearranged through signaling by the pre-BCR (B cell receptor). After expression of the BCR, some cells leave the bone marrow and mature into IgM and IgD cells that move between the peripheral lymphoid organs

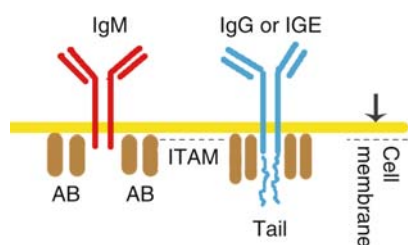


Figure B3. B lymphocyte receptor

β Oxidation: Refers to the degradation of fatty acids at the β carbon into acetyl-coenzyme A. ▶fatty acids, ▶acetyl CoA

B7 Protein: This is required for the activation of B cells. It is recognized by CD28 on the surface of the antigen-presenting cells. The other signal required for B cell activation is a foreign peptide antigen, associated with class II MHC molecule on the surface of an antigen-presenting cell. This is the same as BB 1 or CD80. ▶CD40, ▶antigen presenting cells, ▶MHC, ▶B cell, ▶co-stimulator, ▶ICOS; Yoshinaga SK et al 2000 Int Immunol 12:1439.

B1, B2 Repeats: These are highly dispersed SINE elements in the mouse genome. ▶SINE

B2 RNA: This is a small (178-nucleotide) non-coding RNA in the mouse regulating RNA polymerase III and II (Allen TA et al 2004 Nature Struct Biol 11:816). ▶RNA regulatory

β Sheet: Refers to the secondary structure of proteins where relaxed polypeptide chains run in a close parallel or an antiparallel arrangement. (See diagram on protein structure).

β Sheet Breaker Peptides (iA β 5): 4 amino acids (LVFF) in the 17–20 N-terminal domain of amyloid β protein (A β) may be substituted (particularly by proline) in this region and may alter the conformation of β sheets and reduce the formation of and disassemble the already formed amyloid fibrils characteristic of Alzheimer's disease (see Fig. B4). A charged amino acid may be added to increase solubility (Leu, Pro, Phe, Phe, Asp). Shorter or different peptides may have opposite effects. The iA β 5 molecules may provide an approach to the treatment of Alzheimer's disease. (Alzheimer's disease, Soto C et al 2000 Lancet 355:192).



Figure B4. β sheet breaker

Babelomics: This is the web server for the interpretation of microarray data as well as gene annotation and interaction networks: <http://www.fatigoplus.org>.

Baboon (*Papio*): ▶Cercopithecidae, ▶xenotransplantation

BAC (bacterial artificial chromosome): Refers to bacterial cloning vector (derived from F plasmid) that can accommodate up to 350 kb (most commonly 120–150 kb) DNA sequences and has a considerably lower error rate than the still larger capacity yeast artificial chromosome (YAC). BACs usually exist in a single copy per cell. *Random BACs* are selected at random from a genomic library and are then shotgun-sequenced. Most BAC vectors lack selectable markers suitable for mammalian cell selection but can be retrofitted by employing the Cre/loxP site-specific recombination system. ▶vectors, ▶PAC, ▶YAC, ▶BIBAC, ▶shotgun sequencing, ▶genome projects, ▶F plasmid, ▶Cre/loxP, ▶selectable marker, ▶TAC; Wang Z et al 2001 Genome Res 11:137, http://www.nih.gov/science/models/bacsequencing/end_sequencing_project.html.

BACE (beta site APP-cleaving enzyme): The amyloid precursor protein (APP) cleavage enzyme—a β -secretase [a membrane-bound aspartyl protease]—is involved in the production of brain plaques in Alzheimer's disease. The transmembrane BACE splits APP into soluble β -sAPP and a membrane-attached carboxy-terminal fragment, CTF- β . The latter is expected to be the substrate for γ -secretase. Bace1 also controls the myelination of peripheral nerves (Willem M et al 2006 Science 314:664). BACE1 deficient mice do not generate A β peptide, responsible for Alzheimer plaques and appear to be normal. BACE is encoded at human chromosome 11q23.3. Its homolog BACE2 is in chromosome 21, near the region critical in Down's syndrome trisomy. Research on drug development for the treatment of Alzheimer's disease has a likely target in BACE. ▶Alzheimer's disease, ▶secretase, ▶Down's syndrome, ▶presenilin, ▶GSK; Roberds SL et al 2001 Hum Mol Genet 10:1317, substrate binding; Gorfe AA, Catfish A 2005 Structure 13:1487.

BACH (BRCA1-associated carboxy-terminal helicase): This is a DEAH family protein. Phosphorylated BACH helicase interacts with the C-terminal domain of BRCA1 (BRCT) and in the case of DNA damage it controls the G2→M transition in the cell cycle as a checkpoint. BRCT mediates the tumor-suppressor function of BRCA1. BACH1 seems to be identical to Fanconi anemia FANCI, and is essential for homologous recombination (Litman R et al 2005 Cancer Cell 8:255). ▶breast cancer, ▶DEAH box proteins, ▶cell cycle, ▶checkpoint; Yu X et al 2003 Science 302:639.

B

Bach, Johann Sebastian: One of the greatest geniuses of classical music, Bach's (1685–1750) family included over 50 more or less renowned organists, cantors and musicians (see Fig. B5). Of the four surviving children from his first marriage to his second cousin Maria Barbara Bach, three were musicians (inbreeding coefficient 1/64 [three offspring died in infancy]). Five of the 13 children from his second marriage to unrelated singer Anna Magdalena Wilcken (assortative mating) survived and of these three were musically talented. This family tree reveals that musical ability may be controlled by relatively few genes, and the cultural environment may also play a major role. Recent studies have demonstrated that musical talent is correlated with stronger development of the left planum temporale, increased leftward asymmetry of the cortex. ▶[dysmelodia](#), ▶[musical talent](#), ▶[Mozart](#), ▶[Beethoven](#); Wolff C 2000 Johann Sebastian Bach: The learned musician, Norton, New York.



Figure B5. Bach and Bach morning prayer. Morning prayers in the family of Sebastian Bach, painted in 1870 by American artist Toby Edward Rosenthal in Europe. Members of the large family are either playing music or singing. From Music with Ease (<http://www.music-with-ease.com>); courtesy of Paul Wagner.

Bacillus: This is a rod-shape bacterium. (▶[Bacillus subtilis](#), ▶[Bacillus thuringiensis](#))



Figure B6. Bacillus

Bacillus Calmette-Guerin (BCG): This attenuated form of *Mycobacterium bovis* bacillus is used to vaccinate against the human *Mycobacterium tuberculosis* and may serve as a suitable vector for the *B. burgdorferi* and the HIV virus. BCG differs from the virulent *M.t.* by the deletion of ~91 open reading frames and several (~38) additions. BCG has also been introduced into liver cancer cells, skin tumors and other cancer cells with some beneficial effects on slowing down metastasis and/or delayed recurrence. Protection against tuberculosis has the highest correlation with the rapid accumulation of specific CD8⁺ T cells in the infected tissues of challenged mice. Specific IFN-production by CD4⁺ T cells reflected the load of *M. tuberculosis* rather than the strength of protection (Mittrücker H-W et al 2007 Proc Natl Acad Sci USA 104:12434. ▶[Borrelia](#), ▶[acquired immuno-deficiency](#), ▶[mycobacteria](#), ▶[metastasis](#), ▶[T cell](#), ▶[interferon](#); Sasseti CM et al. 2001 Proc Natl Acad Sci USA 98:12712; Hsu T et al 2003 Proc Natl Acad Sci USA 100:12420.

Bacillus cereus: This opportunistic pathogen causes diarrhea and emetic syndromes. Its 4,559,996 bp sequenced genome is closely related to that of *Bacillus anthracis* and *Bacillus thuringiensis*. (▶[anthrax](#), ▶[Bacillus thuringiensis](#); Ivanova N et al 2003 Nature [Lond] 423:87)

Bacillus subtilis: A gram-positive, rod-shaped soil bacterium that lives on decayed organic material and is therefore harmless. Under conditions of starvation, most of the cell content, particularly the DNA moves to one end of the cell. This area, constituting about 10% of the cell, is walled off and becomes a spore. Before spore formation a checkpoint protein (DisA) scans the chromosome for DNA damage and halts spore formation until the damage is repaired (Bejerano-Sagie M et al 2006 Cell 125:679). The spore is extremely resistant to various environmental effects that can destroy vegetative cells. Under favorable conditions the spore regenerates the bacterium. Before the cells form spores, half of the bacterial population exports a killer protein,

SdpcC. The killer protein destroys the non-producer cells, which are then cannibalized by the producer cells. The exporter cells produce an immunity protein SdpI that protects these cells from the killer protein. SdpC stimulates SdpI production. SdpI synthesis is under the control of a two-gene operon which is controlled by the SdpR repressor (Ellermeier CD et al 2006 Cell 124:549). The size of its cells is similar to those of *E. coli*, and its genome of 4,214,810 bp (4,100 ORF) was completely sequenced by 1997 (Nature 390:248). Among the 4,100 genes only 271 appeared indispensable for growth of the bacterium when the genes were inactivated singly (Kobayashi K et al 2003 Proc Natl Acad Sci USA 100:4678). The DNA has a different base composition from that in *E. coli*, A + T/G + C ratio is 1.38 in the former and 0.91 in the latter indicating that *B. subtilis* has more A + T than *E. coli*. The genome includes many repeats in only half of the chromosome, at both sides of the replicational origin. For transcription it uses 18 different σ factors although its major RNA polymerase is similar to that of *E. coli* ($\alpha\alpha\beta\beta'\sigma$). The 43 kDa (σ_{43}) recognizes some of the consensus sequences of *E. coli* promoters. Its best known phage is SPO1 that is transcribed either by a phage RNA polymerase or by the host. It contains 4100 protein-coding genes with an average length of 890 bp. 78% of them start with ATG. 75% of the genes are transcribed in the direction of the replication. 53% of the genes occur only once (singlets) whereas the putative ATP binding transporter family paralogues appear to be 77 (14% of the genome). The DNA is not methylated. ►*E. coli*, ►forespore, ►endospore, ►sporulation, ►paralogous, ►fratricide; Hecker M, Engelmann S 2000 Int J Med Microbiol 290:123, <http://genolist.pasteur.fr/>.

Bacillus thuringiensis: This gram-positive bacterium produces the BT toxin. The toxin (delta endotoxin) is within the crystalline inclusion bodies produced during sporulation. In an alkaline environment (such as in the midgut of insects) the crystals dissolve and release proteins of M_r 65000 to 160000 that are cleaved by the proteolytic enzymes of the insects into highly toxic peptides. These toxins are most effective against *Lepidopteran* larvae (caterpillars) but some nematodes are susceptible to one or another form of the toxin (Wei J-Z et al 2003 Proc Natl Acad Sci USA 100:2760; Cappello M et al 2006 Proc Natl Acad Sci USA 103:15154). The most economical solution is to transform plants (tobacco, cotton, maize etc.) with the *Bt2* gene, which codes for the 1,115 amino acid residue pro-toxin protein. Actually, a smaller polypeptide, Mr 60K, and even smaller fragments are still fully active. The transgenic plants kill the invading

caterpillars within a couple of days and remain practically immune to any damage. The activity of the transgene has been further enhanced by the use of high efficiency promoters in the T-DNA constructs. In some instances, however, transgenic cotton was overpowered by bollworms. There are differences in the spectra of the bacterial toxins produced by different strains of the *bacillus* and this provides an opportunity to extend the range of toxicity to other insect species. For the production of corn rootworm resistant transgenic plants, the toxin gene of *B. thuringiensis tenebrionis* has been used. Mutation in insect aminopeptidase receptors, in a cadherin superfamily gene and β -1,3-galactosyltransferase may impart resistance to the BT toxin. Glycolipids are the receptor to the BT toxin and the absence of the special glycolipid (vertebrates) or mutation in the receptor imparts resistance (Griffitts JS et al 2005 Science 307:922). *B. thuringiensis*-induced mortality depends on the presence of enteric bacteria in the gut of the target organisms (Broderick NA et al 2006 Proc Natl Acad Sci USA 103:15196).

The resistance of pests to BT is surprisingly rare under field conditions, only the diamondback moth (*Plutella xylostella* [L]) seems to be an exception (Fox JL 2003 Nature Biotechnol 21:958). The transfer of the BT toxin gene into commercial varieties may have some deleterious effects on the Monarch butterfly and other lepidopteran larvae, however under field conditions these adverse effects may not be very serious. Resistance genes to the BT toxin are located in different chromosomes of plants and experimental evidence shows that insects cannot simultaneously overcome the two-gene hurdle unless single and two-gene resistance crops are grown at the same time. In such a situation the insect can develop immunity against one than the other gene and eventually the plant resistance may be lost. However, when only two-gene resistant plants are grown the evolution of the insects may not be possible (Zhao J-Z et al 2005 Proc Natl Acad Sci USA 102:8426). The culture of the BT toxin transgenic cotton did not affect biodiversity as much as the use of broad-spectrum insecticides and secured higher yield in two years of large scale agricultural production (Cattaneo MG et al 2006 Proc Natl Acad Sci USA 103:7571). ►transformation of plants, ►promoter, ►*Photorhabdus luminescens*; pest eradication by genetic means, ►hookworm, ►Cry9C, ►cadherins, ►insect resistance in plant, ►GMO, ►*Bacillus cereus*, ►anthrax; Gahan LJ et al 2001 Science 293:857; Griffitts JS et al 2001 Science 293:860; series of articles in Proc Natl Acad Sci USA 98:11908–11937 [2001]; membrane receptor: Pérez C et al 2005 Proc Natl Acad Sci USA 102:18303.

B

Back Cross: The F1 is crossed (mated) by either of its two parents (►test cross). Each back crossing reduces by 50% the genetic contribution of the non-recurrent parent; thus after (r) back crosses it will be $(0.5)^r$. The percentage of individuals homozygous for the (n) loci of the recurrent parent in (r) number of back crosses = $[(2^r - 1)/2^r]^n$. The chance of eliminating a gene linked to a selected allele is determined by the intensity of linkage (p) and the number of back crosses (r) according to the formula $1 - (1 - p)^{r+1}$.

Back Mutation: This mutation (recessive) reverts to the wild type allele. ►reversion

Back Reaction: Refers to a property of RNA polymerase to move backward and cleave the synthesized RNA if a nucleotide needed for the forward (synthetic) reaction is not available. ►dead end complex

Backbone: An example is the sugar-phosphate chain of nucleic acids or the N–C chain of amino acids in a protein. To the backbone, side chains may be attached such as nucleotides or some other molecular groups in amino acids, except in glycine, which has no side chain. ►Watson and Crick model

Background, Genetic: Refers to the (residual) genetic constitution without considering particular loci or genes under special study. Knowledge of the genetic background may be of substantial importance because different sets of modifier genes may influence the expression of particular genes. ►modifier genes

Background Radiation: This is the natural radiation from cosmic or terrestrial sources. ►cosmic radiation, ►terrestrial radiation

Background Selection: The recurrence of deleterious mutations reduces the effective size of the population. The selection is directed against the chromosomal background carrying the particular allele(s). The balance between hitchhiking and background selection determines the extent of genetic variation in a population. ►hitchhiking, ►effective population size; Charlesworth D et al 1995 Genetics 141:1619.

Backtracking, Transcription: In this process the RNA polymerase (the elongation complex) slides backward on the DNA template by one or more nucleotides. In this case the RNAP may lose the 3'-end of the transcript and the complex may be temporarily inactivated thereby interrupting transcript elongation. Reactivation may require (prokaryote) GreA, GreB and TFIIS (eukaryote) and other protein factors (Mfd). Reinitiation may be facilitated by the use of multiple RNAP molecules. (►Gre, ►Mfd, ►TFIIS, ►reinitiation, ►Epshtein V; Nudler E 2003 Science 300:801).

Bactenein: antimicrobial peptides.

Bacteremia: Refers to bacterial infection of the blood.

Bacteria: This broad taxonomic group of microscopically visible (prokaryotic) organisms has DNA as the genetic material (nucleoid) that is not enclosed by a distinct membrane within the cell and may have various numbers of extrachromosomal elements, plasmids that constitute from about 2 to 20% of the DNA per cell. The size of the bacteria varies considerably from 0.2 to 750 µm. Bacteria are capable of protein synthesis and of independent metabolism even if they are parasitic or saprophytic. Their cell wall is mucopolysaccharide and protein. Their cells contain ribosomes (70S) but no mitochondria, plastids, endoplasmic reticulum or other compartments. They divide by fission in an exponential manner as long as nutrients and air are not in limited supply. The division rate of bacteria during exponential growth can be expressed as $N = 2^g \times N_0$ where N is the number of cells after g generation of growth and N_0 is the initial cell number. After the exponential phase, unless their increasing need is met, the growth either declines or may become stationary. The generation time of *E. coli* under standard conditions may be 20–25 minutes.

Bacteria can be classified into three main groups: *Archeobacteriales*, *Eubacteriales* and *Actinomycetales*. *Eubacteriales* includes *Pseudomonadaceae* (*Pseudomonas aeruginosa*), *Azotobacteriaceae* (*Azotobacter vinelandii*), *Rhizobiaceae* (*Rhizobia*, *Agrobacteria*), *Micrococcaceae* (*Micrococcus pyogenes*), *Parvobacteriaceae* (*Haemophilus influenzae*), *Lactobacteriaceae* (*Diplococcus pneumoniae*, *Streptococcus faecalis*), *Enterobacteriaceae*, (*Aerobacter aerogenes*, *Escherichia coli*, *Salmonella typhimurium*), *Bacillaceae* (*Bacillus subtilis*, *B. thuringiensis*). *Actinomycetales* includes *Mycobacteriaceae* (*Mycobacterium phlei*, *Mycobacterium tuberculosis*) and *Streptomycetaceae* (*Streptomyces coelicolor*, *S. griseus*). There are many other types of classification systems. It is common to identify bacteria as gram-positive (indicating that they retain the deep red color of the gram stain [crystal-violet and iodine] after treatment with ethanol) or gram-negative that fail to retain it (and may appear colorless or just slightly pinkish). These properties depend on the composition and structure of the cell wall. Gram-positive bacteria are surrounded by peptidoglycan outside of the plasma membrane, and gram-negative cells have an outer membrane enveloping the peptidoglycan wall. The peptidoglycans are polymers of sugars and peptides and are cross-linked by pentaglycines that determine the shape of the cell wall and the bacterium. There are at least 10^{30} bacteria on the planet and at least as many bacteriophages. Probably less than 1% of the bacteria can be cultured in the laboratory and that makes their study

difficult (Amann RI et al 1995 Microbiol Rev 59:143). Closely related bacteria can be distinguished—even if the difference between two 16S RNAs is in only one nucleotide—by the use of quenched autoligation probes. ►conjugation, ►bacterial recombination frequency, ►bacterial transformation, ►recombination molecular mechanisms in prokaryotes, ►bacteria counting, ►quenched autoligation probe; bacterial names and standing nomenclature: <http://www.bacterio.net>, chromosome maps of several bacteria: <http://wishart.biology.ualberta.ca/BacMap/>.

Bacteria Counting: This is done either by counting the number of colonies formed or by determining cell density in a volume, using a photometer. In the first procedure an inoculum of a great dilution of a culture is seeded on a nutrient agar plate and incubated for a period of time (e.g., 2 days). Each colony thus formed represents the progeny of a single cell and the number of colonies indicates the number of *live* bacteria in the volume of the inoculum. Optical density obtained through the second procedure indicates the cell density that becomes meaningful only if information is available on the correlation between light absorption and cell number, determined earlier by the plating technique. If the plate was seeded by 2 mL of the culture diluted 10^7 times and 100 colonies are observed then the number of live cells is $(100/2) \times 10^7 = 5 \times 10^8$ cells/mL. ►bacteria, ►lawn bacterial

Bacterial Artificial Chromosome: ►BAC

Bacterial Recombination Frequency: In the case of conjugation transfer of genes recombination frequency is determined by the time in minutes since the beginning of mating. This procedure is useful for genes that are more than 2 to 3 minutes apart. It takes about 90–100 minutes at 37 °C to transfer from a Hfr donor bacterium to an F[−] recipient cell the entire genome (more than 4 million nucleotides). The efficiency of transfer depends on the nature of the Hfr strain used. Approximately $5-6 \times 10^4$ nucleotides are transferred per minute. Bacterial recombination does not permit the recovery of the reciprocal products of recombination and all detected cross-over products are double cross-overs. If bacterial genes are closer than 2 to 3 minutes, then recombination mapping is used. For bacterial recombination, selectable (auxotrophic) markers are generally used so that the phenotypes can be easily recognized. The recipient strain carries genes, e.g., a and b^+ , and the donor strain carries the alleles a^+ and b defining the interval where recombination is studied. In order to measure the number of successful matings, the donor strain also carries the prototrophic gene (c^+) and the recipient is marked by the auxotrophy allele (c) of the same locus. The c gene does not have to be

very close to the interval studied:

$$\frac{a \quad b^+}{a^+ \quad b} \quad \frac{c^+}{c}$$

The *frequency of recombination* (p) is then calculated:

$$p = \frac{\text{number of cells } a^+ b^+ \text{ constitution}}{\text{number of } c^+ \text{ cells}}$$

The $a^+ b^+$ recombinants are the result of an exchange between a^+ and b^+ and also beyond the c^+ site as shown by the arrows: $a^+ \uparrow b^+ c^+ \downarrow$.

To determine *gene order by recombination* one must use at least three loci in a reciprocal manner (see Tables B1 and B2):

Would the gene order be $a b c$:

Table B1. Gene order determination by recombination in bacteria

| | | |
|-----------|-----------------------------------|---|
| Donor | $a \downarrow b^+ c^+ \downarrow$ | To obtain triple prototrophs double exchange is sufficient in both of the reciprocal crosses |
| Recipient | $a^+ b c$ | |
| Donor | $\downarrow a^+ \downarrow b c$ | |
| Recipient | $a b^+ c^+$ | |

Would the gene sequence be $b a c$:

| | | |
|-----------|--|---|
| Donor | $\downarrow b^+ \downarrow a c^+ \downarrow$ | In order to obtain triple prototroph recipients, the number of exchanges must be at least quadruple as shown by the arrows |
| Recipient | $b a^+ c$ | |
| Donor | $b \downarrow a^+ \downarrow c$ | In the reciprocal cross only double recombination is required to produce $b^+ a^+ c^+$ prototrophs |
| Recipient | $b^+ a c^+$ | |

Thus, depending whether the gene order is abc or bac one can tell from the frequency of prototrophs in the reciprocal crosses. The higher numbers of exchanges are less frequent.

Recombination frequency in bacteria within very short intervals, such as between alleles within a gene can also be determined by transduction. If the constitution of the donor DNA is $a^+ b^+$ and the recipient is $a b$, the *frequency of transduction* (recombination) is:

$$\frac{[a^+ b] + [ab^+]}{[a^+ b] + [ab^+] + [a^+ b^+]}$$

Gene order in bacteria can be determined by a three-point transformation test as illustrated by a hypothetical experiment described here when the donor DNA is

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$a^+ b^+ d^+$ and the recipient is $a^- b^- d^-$, and the reciprocal products of recombination are not recovered:

Table B2. Gene order determination by transformation in bacteria

| Genes | Genotypes of Transformants | | | | | | |
|-----------------|----------------------------|------|-----|-----|------|-----|------|
| <i>a</i> | + | - | - | - | + | + | + |
| <i>b</i> | + | + | - | + | - | - | + |
| <i>d</i> | + | + | + | - | - | + | - |
| Number of cells | 12000 | 3400 | 700 | 400 | 2500 | 100 | 1200 |

Recombination for a particular interval is calculated by the number of recombinants in the interval(s) divided by the total number of cells transformed in that interval. There are 7 classes of cells. Recombination is calculated in three steps: in the *ab*, *bc* and *ad* intervals.

In the *ab* interval we have here

$$\frac{[3400 + 400 + 2500 + 100]}{[1200 + 3400 + 400 + 2500 + 100 + 1200]} \approx 0.33$$

in the *bd* interval

$$\frac{[700 + 400 + 100 + 1200]}{[12000 + 3400 + 700 + 400 + 100 + 1200]} \approx 0.14$$

in the *ad* region

$$\frac{[3400 + 700 + 400 + 2500 + 100 + 1200]}{[12000 + 3400 + 700 + 400 + 2500 + 100 + 1200]} \approx 0.41$$

Although the frequency of recombination in three-point transformation test is never exactly additive, it is clear that the *a-d* distance is the longest and thus the conclusion that the gene order is *abd* appears to be reasonable. Recombination may affect the population structure and it permits evolutionary conclusion. ►physical mapping, ►crossing over, ►mapping genetic, ►conjugation, ►transduction, ►bacterial transformation, ►generalized transduction; Lederberg J 1987 Annu Rev Genet 21:23; Feil EJ, Spratt BG 2001 Annu Rev Microbiol 55:561.

Bacterial Transformation: Refers to genetic alteration brought about by the uptake and integration of exogenous DNA in the cell that is capable of expression. The exogenous DNA is generally supplied at a concentration of 5 to 10 µg/mL to transformation competent cells. Competence is a physiological state when the cells are ready to accept and integrate the

exogenous DNA. Competence is maximal in the middle of the logarithmic growth phase. The donor DNA may synapse with the recipient bacterial chromosome and naked DNA generally replaces a segment of the bacterial genetic material rather than adding to it. The entire length of the donor DNA may not be integrated into the host and the superfluous material is degraded. The integrated DNA may form a permanent part of the bacterium's chromosomal genetic material. During integration only one or both strands of the donor DNA may be integrated. Transformation may be regarded as one of the mechanisms of recombination and can be used for determining the gene order in the bacterial chromosome. The frequency of transformation in prokaryotes is generally less than 1% and it is usually within the range of 10^{-3} to 10^{-5} . Transformation of bacterial protoplasts (spheroplasts) may occur at a higher frequency. Transformation may also denote the transfer and expression of plasmid DNA in the cell. These plasmids may remain as autonomous elements within the bacteria. Transformation with the aid of plasmids is much more efficient. Moreover, competence can greatly be enhanced by some divalent cations and by other means. ►transformation genetic, ►competence of bacteria, ►bacterial recombination frequency; vectors, Hotchkiss RD, Gabor M 1970 Annu Rev Genet 4:193; Oishi M, Cosloy SD 1972 Biochem Biophys Res Commun 49:1568.

Bacteriocin: Denotes natural bacterial products that may kill sensitive bacteria. ►colicins, ►pyocin, ►pesticin; Riley MA 1998 Annu Rev Genet 32:255; bacteriocin identifying tool: http://bioinformatics.biol.rug.nl/web/software/bagel/bagel_start.php.

Bacteriocyte: Refers to special cells of eukaryotes harboring bacterial symbionts. (Spaulding AW, Dohle CD 1998 Mol Biol Evol 15:1506; Nakabachi A et al 2005 Proc Natl Acad Sci USA 102:5477).

Bacteriome: This is a cytoplasmic polyploid organ of insects harboring one or more species of bacteria. The exact function of the bacteriome is unknown; it probably synthesizes useful nutrients for the host. (Von Dohlen CD et al 2001 Nature [Lond] 412:433; Normark BB 2004 PloS Biol 2:0298).

Bacteriophages: These are viruses infecting bacteria (see Table B3). (►phage, ►phage life cycle, ►phage morphogenesis, ►filamentous phages, ►lambda phage, ►T4, ►T7, ►φX174, ►MS2, ►Mu bacteriophage, ►icosahedral, ►virulence, ►temperate phage, ►development, ►phage therapy; Knipe DM, Howley PM (eds) 2001 Fundamental Virology Lippincott Williams & Wilkins, Philadelphia, PA); Brüssow H, Hendrix RW 2002 Cell 108:13; Campbell A 2003 Nature Rev Genet 4:471, <http://www.phage.org>.

Table B3 Major types of bacteriophages

| Phage | Type | Host | Da × 10 ⁶ | Morphology |
|-----------------|--------------------|--------------------------|----------------------|------------------|
| MS2, f2, R17 | RNA, ss, virulent | <i>E. coli</i> | 1 | icosahedral |
| φ6 | RNA, ds, virulent | <i>Pseudomonas</i> | 3.3, 4.6, 7.5 | icosahedral |
| φX174, G4, St-1 | DNA, ss, virulent | <i>E. coli</i> | 1.8 | icosahedral-tail |
| M13, fd, f1 | DNA, ss, virulent | <i>E. coli</i> | 2.1 | filamentous |
| P22 | DNA, ds, temperate | <i>Salmonella</i> | 26 | icosahedral-tail |
| SPO1 | DNA, ds, virulent | <i>Bacillus subtilis</i> | 91 | icosahedral-tail |
| T7 | DNA, ds, virulent | <i>E. coli</i> | 26 | octahedral-tail |
| lambda | DNA, ds, temperate | <i>E. coli</i> | 31 | icosahedral-tail |
| P1, P7 | DNA, ds, temperate | <i>E. coli</i> | 59 | head-tail |
| T5 | DNA, ds, virulent | <i>E. coli</i> | 75 | octahedral-tail |
| T2, T4, T6 | DNA, ds, virulent | <i>E. coli</i> | 108 | oblong head-tail |

ss = single-stranded, ds = double-stranded

The major types and characteristics of bacteriophages are presented here:

Bacterioplankton: This includes prokaryotes and plays a major role in biogeochemical processes in seawater. *Silicibacter pomeroyi* represents 10–20% of bacterioplankton; it has a chromosome of 4109611 bp and a megaplasmid of 491611 bp in its sequenced genome (Moran MA et al 2004 Nature [Lond] 432:910).

Bacteriorhodopsin: This is a light receptor protein in the plasma membrane of some bacteria; it pumps protons upon illumination. ▶[rhodopsin](#)

Bacteriostasis: This prevents the reproduction of bacteria without destroying them. In the long run, however, this may lead to their destruction. Many antibiotics have such an effect. ▶[antibiotics](#)

Bacteroid: These are specialized, modified forms of bacteria such as the ones found in the root nodules where they act in the fashion of intracellular “organelles” in nitrogen fixation. ▶[nitrogen fixation](#); Li Y et al 2002 Microbiology 148:1959.

Bacteroides fragilis: This is an obligate anaerobic, opportunistic pathogen of the human colon. Its circular chromosome is 5,205,140 base pairs with an estimated 4,274 genes; it harbors a plasmid too. Its genome, like that of *B. thetaiotaomicron*, has many inversions and rearrangements, which affect gene expression. Several species of bacteroides are part of the indigenous intestinal flora and may be represented by 10¹¹ to 10¹² cells/g feces. They constitute 15–20% of gingival flora and 8–16% of dental plaques. It is somewhat of a paradox that the host does not marshal

the immune defense against them. These organisms apparently decorate their surface polysaccharides with L-fucose and mimicking host polysaccharides thus acquiring an evasive tool in their competitive environment (Coyne MJ et al 2005 Science 307:1778). The pathogenic bacteria apparently do not have this self-defense against the host. (▶[fucose](#); Cardeno-Tárraga AM et al 2005 Science 307:1463).

Bacteroides thetaiotaomicron: This is a gram-negative anaerobic bacterium with a 6.26 Mb sequenced genome. It is a predominant member of the human and mouse small intestinal and colon microbiome. It plays an important role in the metabolism of dietary polysaccharides, which are not digestible by human enzymes. (▶[microbiome](#); Kuwahara T et al 2004 Proc Natl Acad Sci USA 101:14919).

Bactigs: Contigs of BACs. (▶[contig](#), ▶[BAC](#))

Bacto Yeast Extract: This water-soluble fraction of autolyzed yeast contains vitamin B complex.

Bacto-Tryptone: A peptone, rich in indole (tryptophan), is used for bacterial cultures and the classification of bacteria on the basis of activity.

Baculoviruses: These are large (130 kbp) double-strand DNA viruses used for the construction of insect transformation vectors. Baculoviruses do not efficiently transform mammalian or plant cells. The baculovirus vectors accommodate large amounts of DNA and the foreign DNA replacing the polyhedrin gene is expressed under a powerful polyhedrin promoter. The majority of the proteins within the insect remain soluble. The extracellularly present virus particles appearing *late* in the infection are called

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non-occluded virus. The occluded virus particles occur in the cell nuclei and appear *very late* in the infection phase. The polyhedra viral protein coating is responsible for the occlusion. (►polyhedrosis, ►AcNPV, ►transformation, ►viral vectors; insect viruses, Grabherr R et al 2001 Trends Biotechnol 19[6]:231; Herniou EA et al 2003 Annu Rev Entomol 48:211).

Baculum: This is a bony structural element above the urethra in the penis of many species (e.g., rodents, carnivores, primates) but not in humans.

Bad: Refers to an apoptosis-promoting protein when phosphorylated by MAPK/RSK or Akt or a c-AMP-dependent protein kinase. When it is dephosphorylated (by calcineurin) it may interfere with the apoptosis suppression of Bcl proteins and that may lead to carcinogenesis. Also, when RSK phosphorylates CREB, cell survival is facilitated. The combined inhibition of EGFR (epidermal growth factor receptor) and PI3K (phosphatidylinositol kinase)—regulated by BAD—synergistically favors apoptosis (She Q-B et al 2005 Cancer Cell 8:287). ►apoptosis, ►survivin, ►CaM-KK, ►Bcl, ►MAPK, ►RSK, ►CREB, ►Akt; Konishi Y et al 2002 Mol Cell 9:1005; Ranger AM et al 2003 Proc Natl Acad Sci USA 100:19324.

Badger (*Taxidea taxus*): $2n = 32$.

Badnaviruses: These are double-stranded DNA viruses of plants (►pararetrovirus).

Baf Complex: This is similar to SWI/SNF proteins and it regulates chromatin remodeling. The Baf60c subunit (60-kDa, encoded by mouse gene *Smardc3*) is essential specifically for the expression of the differentiation of the heart and somites of the early embryo (Lickert H et al 2004 Nature [Lond] 432:107). ►SWI/SNF; chromatin remodeling, Liu R et al 2001 Cell 106:309.

BAFF (B cell activating factor): TNF receptor ligand, which among other proteins regulates B cell proliferation and differentiation. Autoreactive B cell survival is regulated by BAFF-dependent protein kinase, PKC δ , which phosphorylates serine 14 in histone H2B (Mecklenbräuer I et al 2004 Nature [Lond] 431:456). ►Blys, ►TNFR, ►APRIL, ►NF- κ B, Thompson JS et al 2001 Science 293:2108; Schiemann B et al 2001 Science 293:2111.

BAG1: (Bcl2-associated athanogene, 9p12): This is part of an anti-apoptotic complex and affects cell division, cell migration and differentiation. The BAG family proteins recruit molecular chaperones and thus play a role in regulating protein conformation. ►BCL, ►athanogene; Takayama S, Reed JC 2001 Nature Cell Biol 3:E237.

BAIT: ►Two-hybrid system

BAK: A member of the Bcl protein family comprising BH1, BH2 and BH3 domains that after a conformational change induced by other members of the

Bcl family of proteins containing only BH3 domain, promotes apoptosis by opening the permeability transition pore complex channel in the mitochondrial membrane. The mitochondrial outer-membrane protein VDAC2 inhibits BAK and apoptosis. ►Bcl, ►BID, ►Bim, ►apoptosis, ►porin; Wei MC et al 2000 Genes Dev 14:2060; Korsmeyer SJ et al 2000 Cell Death Differ 7:1166; Cheng EH et al 2001 Mol Cell 8:705; Cheng E H-Y et al 2003 Science 301:513.

Bal 31: The exonuclease removes simultaneously nucleotides from the 3' as well the 5' ends and thus it can be used for mapping functional sites in a DNA (see Table B4): The fragments can then be separated by electrophoresis and assayed after transformation. ►deletions unidirectional, ►exonuclease electrophoresis; Wei C-F et al 1983 J Biol Chem 258:13506.

Table B4. Bal 31 exonuclease

| | | |
|--------------------|-----------|--------------|
| 0 Time | a b c d e | Original DNA |
| After 1 time unit | b c d | Digest |
| After 2 time units | c | Digest |

Balance of Alleles: This population model assumes that at the majority of loci several different alleles are present and these are maintained in a dynamic equilibrium by the continuous but variable selective forces. ►balanced polymorphism, ►Hardy-Weinberg theorem, ►fitness, ►selection

Balanced Lethals: These are genetic stocks heterozygous for two or more non-allelic linked recessive lethal genes. Since both homozygotes die, only heterozygotes survive that are phenotypically wild type or in some cases exhibit mutant phenotype and continue to produce both types of lethals. Such stocks can be maintained indefinitely as long as recombination between the linked loci can be prevented.

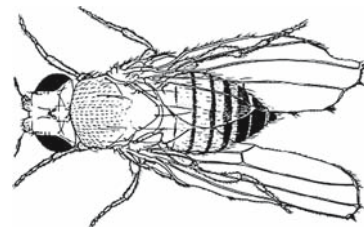


Figure B7. Beaded (From Bridges CB, Morgan TH 1923 Carnegie Inst Wash 327:152)

For balancing, generally spanning inversions are used that eliminate the cross-over gametes because of the duplications and deficiencies generated by recombination within the inverted region. The first balanced lethal of *Drosophila* contained the gene *Bd 1* (*Beaded*, incised wing in heterozygotes, lethal in

homozygotes, at map location 3–91.9 [slightly different in some other alleles]) and *l(3)a*, a spontaneous lethal mutation (map position 3–81.6) within the inversion *In(3R)C* (see Fig. B7). In the multiple translocations of plants of different *Oenothera* species, there are gametic and zygotic recessive lethal genes that are prevented from becoming homozygous and thus help to maintain these lethal genes by balanced heterozygosity. Besides the biological advantage of balanced lethals, they may be useful for various types of research. The *Bd* alleles have been extensively studied at the molecular level and the developmental functions may be revealed by the availability of heterozygotes for the mutations. ▶lethal factors, ▶lethal equivalent, ▶translocation ring; Muller HJ 1918 Genetics 3:422.

Balanced Polymorphism: When the fitness (reproductive success) of heterozygotes exceeds both homozygotes at a locus, a stable genetic equilibrium may be established and the heterozygotes may reproduce the homozygotes in equal frequencies. This type of heterozygote advantage may lead to balanced polymorphism, i.e., the population may maintain several genotypes in stable proportions even if some of the homozygotes have low adaptive value. ▶selection coefficient, ▶fitness, ▶balanced lethals, ▶autosomal recessive lethal assay, ▶balance of alleles, ▶Hardy-Weinberg theorem, ▶fitness, ▶selection, ▶Muller's ratchet; Rucknagel DL, Neel JV 1961 Progr Med Genet 1:158.

Balanced Translocation: Refers to a reciprocal translocation where each of the interchanged chromosomes has a centromere. Unbalanced translocations have an acentric piece due to the interchange. ▶translocation chromosomal

Balancer Chromosomes: These are structurally modified (by inversions, translocation) so the recombinants (because of duplications or deficiencies in the meiotic products) are not recovered in the progeny, and facilitate the maintenance of certain chromosomal constitutions without recombination. Balanced systems permit the maintenance of recessive lethal factors in a heterozygous condition. Balancer chromosomes have been developed in the past with the use of clastogenic agents. By inserting the *LoxP* gene in opposite orientations and bringing about recombination with the aid of the *Cre* recombinase, inversions can also be generated in e.g., mouse cells at particular intervals. ▶*CIB* method, ▶*Base*, ▶inversion, ▶translocation chromosomal, ▶Renner complex, ▶balanced lethals, ▶autosomal recessive lethal assay, ▶*Oenothera*, *Cre/Lox*, ▶targeting genes; Muller HJ 1918 Genetics 3:422; Yu Y, Bradley A 2001 Nature Rev Genet 2:780.

Balancing Selection: This includes heterozygote advantage (overdominance), or alleles differently selected by

sex, season and niche in the habitat or in a frequency-dependent manner. ▶selection, ▶sexual selection, ▶overdominance, frequency dependent selection; Verelli BC et al 2002 Am J Hum Genet 71:1112.

BALB/c Mice: An albino inbred laboratory strain used frequently in immunoglobulin (antibody) and cancer research (see Fig. B8). It is highly susceptible to *Salmonella*. ▶mouse

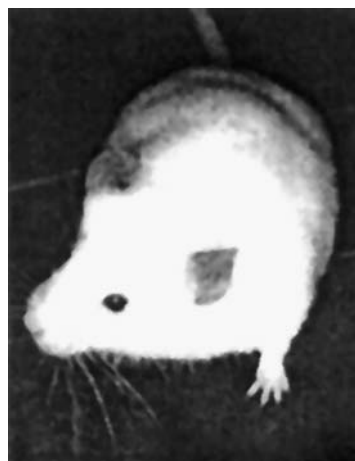


Figure B8. Albino Mouse (Courtesy of Dr. Paul Szauter, <http://www.informatics.jax.org/mgihome/other/citation.shtml>)

Balbiani Body: This is a large distinctive organelle aggregate found in developing oocytes of many species; it contains a mitochondrial “cloud” and Golgi bodies.

Balbiani Ring: Refers to a puff (bloated segment) of the polytenic chromosome indicating special activity (intense RNA transcription) at the site, it loosens up the multiple elements of the chromosome (see Fig. B9). ▶polytenic chromosomes, ▶puff, ▶BR RNP

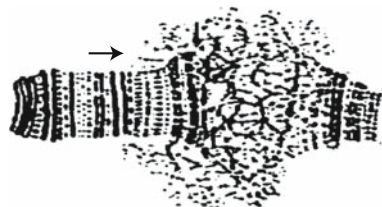


Figure B9. Balbiani ring

Baldness: This sex-influenced trait in humans is more common among males than females (particularly with later onset) and it probably depends to some extent on the level of androgen receptor.

Apparently a polyglycine-encoding GGN repeat in exon 1 of the gene in X chromosome causes

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baldness (see Fig. B10). This also explains the fact that inheritance is primarily through the maternal line (Hillmer AM et al 2005 Am J Hum Genet 77:140). In this condition a developmentally manifested pattern is seen starting from the front hairline toward the top of the head. It has a strong hereditary component but it may be caused by certain diseases (alopecia), exposure to higher doses of ionizing radiation and to certain carcinostatic drugs. Early baldness may be determined by an autosomal dominant gene (10q24) encoding steroid 17 α -hydroxylase with better penetrance in males than in females. Loss of hair on the human scalp may be controlled by a deletion in chromosome 3q27, the site of (LIPH) phospholipase (Kazantseva A et al 2006 Science 314:982). ▶alopecia, ▶hair, ▶androgen, ▶penetrance, ▶monilethrix



Figure B10. X-chromosomal baldness

Baldwin Effect: The physiological homeostasis permits the survival of a species until mutation may genetically fix the adaptive trait in an originally inhospitable environment. ▶homeostasis, ▶canalization, ▶genetic assimilation; West-Eberhard MJ 2003 Developmental Plasticity and Evolution, Oxford University Press, New York.

Ball-And-Stick Model (ball-and-spoke model): ▶stick-and-ball model

Ball-In-Urn: This is used to characterize the distribution of repeats in the genome; urns correspond to all DNA words of a given size and balls refer to the observed words in a given DNA sequence. Rare words may be the binding sites of transcription factors. Also, they may be discriminated against because of structural incompatibilities. Frequent words may be repetitive, structural and regulatory sequences as well as transposable elements. (Karlin S 2005 Proc Natl Acad Sci USA 102:13355).

BamH1: Refers to restriction enzyme with recognition sequence G↓GATCC.

BAMBE (Bayesian Analysis in Molecular Biology and Evolution): This is a free software for the analysis of phylogeny based on nucleotide sequences. ▶Bayes

theorem, ▶phylogeny; <http://www.mathcs.duq.edu/larget/bambe.html>.

β-Amyloid: This exists as extracellular deposits of the brain plaques in Alzheimer's disease (see Table B5). It is split off the amyloid precursor protein (APP) by secretase. In the neuronal tissue APP₆₉₅ is prevalent. If Ile, Phe or Gly replaces Val642, the substitutions lead to fragmentation of nucleosomal DNA in the neurons and presumably contribute to neurotoxicity. ▶Alzheimer's disease, ▶scrapie, ▶amyloidosis, ▶amino acid symbols in protein sequences, ▶secretase, ▶prion

Table B5. Amyloid fibers in Alzheimer disease

The major amyloid fibers (Aβ1-42) in Alzheimer disease are truncated at the C terminus:

Aβ1-40: DAEFRHDSGYEVHHQLVFFAEDVGSNK-GAIIGLMVGGVV

Aβ1-42: DAEFRHDSGYEVHHQLVFFAEDVGSNK-GAIIGLMVGGVVIV

Aggregation of the fibers may lead to plaque formation seen in amyloidosis. The aggregation may be initiated by "seeding" like a crystallization process.

Banana (*Musa acuminata*, x = 11): This is a fruit plant. The diploid fruits are full of seeds and have minimal edible pulp. The majority of the edible fruits are harvested from seedless triploid plants. When the triploids are crossed with diploids the progeny is partly tetraploid (2n = 44) and heptaploid (2n = 77) because of the high frequency of unreduced 3x and 6x gametes and their fruits are also seedless. Some of the related species have chromosome numbers 2n = 14, 18 and 20. ▶seedless fruits, ▶triploidy, ▶sugar beet; Simmonds NW 1966 Bananas, Longman, London.

Band: Refers to an element of the cross-striped chromosome. The banding (perpendicular to the length of the salivary gland chromosomes and continuous across the giant chromosome) may be due to condensation of the juxtapositioned chromomeres or to specific staining of the chromatin. ▶bands of polytenic chromosomes, ▶chromosome banding. The average DNA content in a single natural band of the *Drosophila melanogaster* salivary gland chromosome is 26.2 kb. The total number of salivary chromosome bands is 5,072. The number of distinguishable bands depends on the stage of condensation of the chromosome. The cytologically detectable chromomeres/bands are greater at pachytene than at the metaphase, and in the extended condition structural abnormalities are easier to identify microscopically.

Electrophoretic separation of restriction enzyme digested DNA, or pulsed field electrophoresis separated small chromosomes, as well as various proteins subjected to separation in the electric field, generate bands in the substrate (gel) when visualized either by staining or by special illumination. ▶ **chromosome banding**, ▶ **coefficient of crossing over**, ▶ **electrophoresis**, ▶ **pulsed field electrophoresis**, ▶ **FISH**

Band Cloning: Denotes amplifying DNA bands, extracted from electrophoretic gels, in genetic cloning vectors for molecular analyses. ▶ **cloning vectors**

Band-Morph Mutation: This is distinguished by electrophoretic analysis of the proteins. Mutations resulting in amino acid replacement of different charge appear as mobility difference in the electric field. Although studies of this type were very popular during the 1960s and 1970s, they have very poor resolution because they can detect only 1/4 or less of the mutations. The advantage of this type of research was that large populations could be screened for mutations that would not have necessarily other phenotypic effect. ▶ **electrophoresis**, ▶ **band**; Harada K et al 1993 Jpn J Genet 68:605.

Band III Protein: This is a transmembrane protein consisting of about 800 amino acids. ▶ **spectrin**; Low PS et al 2001 Blood Cells Mol Dis 27:81.

Band-Sharing Coefficient (S_{xy}): This denotes the proportion of shared DNA fragments separated by electrophoresis; $S_{xy} = (2n_{xy})/(n_x + n_y)$ where n_x and n_y are the number of bands in x and y samples and n_{xy} is the number of shared bands. This coefficient may be used to determine the genetic composition of populations on the basis of DNA. In multi-locus forensic tests the British legal system previously used the formula $(0.26)^k$ for calculating the match probabilities of alleles of at least 4 kb in length. 0.26 is an empirical constant and k is the average number of matching alleles. However, this latter formula lacks sufficient robustness. The single locus probes (SLP) based on the profiles of 6–8 short tandem repeat loci (STR) is more popular today. This procedure is useful with as low as 100 pg DNA samples when amplified by PCR. ▶ **DNA fingerprinting**; Zhu J et al 1996 Poultry Sci 75:25.

Band Shifting: ▶ **gel retardation assay**

Banding Pattern: Refers to the distribution of chromosome bands reflecting genetic differences or differences in the expression of genes displaying more or less loose puffs. ▶ **polytenic chromosomes**, ▶ **lampbrush chromosomes**, ▶ **chromosome banding**, ▶ **puff**

Bands of Polytenic Chromosomes: These are deeply stained prominent cross bands on the chromosomes where the chromomeres of the elementary strands are appositioned (see Fig. B11). The salivary chromosomes of *Drosophila* display about 5,000 bands and for a period of time it was assumed that each corresponds to a gene locus. It is now known that the number of genes is about 2.5 times the number of bands. In the region 2B of the X chromosome of *Drosophila* the bands may appear different and rather than being perpendicular to the axis, they may be roughly parallel to the axis. In situ hybridization with molecular probes suggests that this unusual structure is caused by inverted repeats in the DNA. ▶ **polyteny**, ▶ **band**, ▶ **salivary gland chromosomes**, ▶ **coefficient of crossing over for the tip of the X chromosome**



Figure B11. Bands, polytenic

BankIt: This is a GenBank submission form for protein coding sequences. It then generates a GenBank accession number. Its address is: <http://www.ncbi.nlm.nih.gov/BankIt/>. ▶ **GenBank**, ▶ **Sequin**

Bannayan-Riley-Ruvalcaba Syndrome: This is similar to Bannayan-Zonona Syndrome.

Bannayan-Zonona Syndrome: This condition is characterized by autosomal dominant macrocephaly with multiple lipomas and hemangiomas, as well as susceptibility to hamartomatous polyposis cancer. Haplo-insufficiency of PTEN may play a role in its manifestation. ▶ **PTEN**, ▶ **lipomatosis**, ▶ **hemangioma**, ▶ **multiple hamartomas**

BAP: Refers to 6-benzylaminopurine which is a plant hormone. ▶ **plant hormones**

BAP (B-cell receptor associated proteins): Denote three (32, 37, 41 kDa) proteins associated only with IgM membranes. The 32 and the similar 37-kDa molecules form heterodimers and seem to be inhibitors of cell division. BAP29 (240 amino acid) and BAP31 (245 amino acids) are 43% homologous and bind mainly to IgD and somewhat to IgM. ▶ **B lymphocyte receptor**

BAPG: ▶ **bullous pemphigoid autoimmune disease**

Bar: This is a regulator of the Fas- and Apaf-mediated pathways of apoptosis. ▶ **apoptosis**

B

Bar Mutation: The mutation of *Drosophila* (*B*, map position 1–57.0) reduces the eye to a vertical bar with about 90 facets in the male and around 70 in the female compared with 740 in normal males and 780 in normal females; heterozygous females have 360. The *B* mutation is actually a tandem duplication of salivary band 16A, which arises because of unequal (oblique) crossing over.

Thus, the “normal allele” has 16A, *Bar* 16A-16A, *Ultrabar* 16A-16A-16A constitution (see Fig. B12).

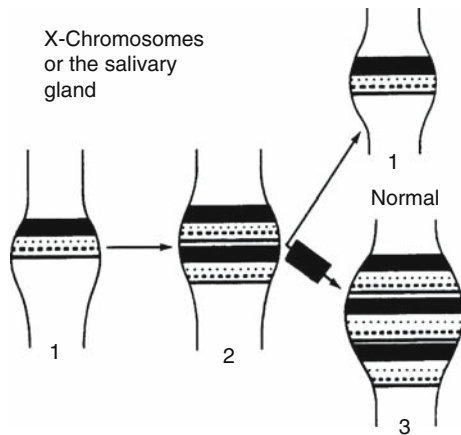


Figure B12. *Bar* mutation

The phenotype is actually a position effect and not the cause of a dosage effect as revealed by genetic analyses. The process of unequal crossing over may be repeated and as many as 9 copies of band 16A can accumulate in a single X chromosome. Also, the 16A band may be lost resulting in reversion by the loss of the *roo* transposable element. *B* mutations may also be induced by the P hybrid dysgenesis element whereas chemical mutagens have never produced this mutation. These facts indicate that the *breakage points in the duplications cause the Bar phenotype*. The *Bar* phenotype may be the result of a breakage in a regulatory element or within an intron and causes abnormal fusion of the exons. The *Bar* locus is very large, it spans at least 37 kb DNA. ▶[duplication](#), ▶[position effect](#), ▶[unequal crossing over](#), ▶[intron](#), ▶[exon](#), ▶[CIB](#); Bridges, Sturtevant AH 1925 *Genetics* 10:117; Bridges CB 1936 *Science* 83:210.

Bar-Code, Genetic (molecular): Bar-code generally represents vertical bars of varying widths (two or four) that correspond to digits 0 and 1, and which in turn specify numbers 0 to 9. An optical laser can read the bar-coded information and—through the computer—the scanner can identify various types of information, including properties of a gene, phenotypic expression, etc. Molecular bar-codes can be generated by two ~20-base (20-mer) oligonucleotides (UPTAG,

DOWNTAG) introduced by transformation into special (deletion) cells. These molecular bar-codes can be identified in the genome by microarray hybridization or by sequencing. Also, the growth rate of various deletion strains can be monitored. DNA bar-coding can be used for the identification of species. In animals, mitochondrial cytochrome oxidase I is useful for the identification of species (Hebert PD et al 2004 *PLoS Biol*, 2:e312; Hajibabaei M et al 2006 *Proc Natl Acad Sci USA* 103:968). In plants, an approximately 450-bp intergenic spacer in chloroplasts appeared to be discriminatory (Kress WJ et al 2005 *Proc Natl Acad Sci USA* 102:8369). ▶[DNA chips](#), ▶[targeting genes](#), ▶[signature-tagged mutagenesis](#); Gad S et al 2001 *Genes Chromosomes Cancer* 31:75; Eason RG et al 2004 *Proc Natl Acad Sci USA* 101:11046; identification of various organisms and for taxonomy: <http://www.barcodinglife.org>; <http://www.barcoding.si.edu>.

Bar-Code DNA Isolation Method: ▶[bar-code genetic](#), ▶[nanoparticles](#)

BARD1 (BRCA1-associated Ring domain protein): This inhibits polyadenylation of mRNA in cooperation with Cstf-50 (cleavage stimulation factor). BRCA1/BARD1 heterodimer modulates Ran-dependent assembly of the mitotic spindle (Joukov V et al 2006 *Cell* 127:539). ▶[cleavage stimulation factor](#), ▶[breast cancer](#), ▶[spindle](#), ▶[RAN](#); Joukov V et al 2001 *Proc Natl Acad Sci USA* 98:12078.

Bardet-Biedl Syndrome (BBS, MKKS): This heterogeneous recessive disease involves retinal dystrophy (retinitis pigmentosa), polydactyly, and other anomalies of the limbs, obesity, underdeveloped genitalia and kidney malfunction, diabetes. Mental retardation is also common. Six to seven chromosomal locations, including (BBS1) 11q13, (BBS5) 2q31, (BBS3) 3p12–p13, (BBS4) 15q23, (BBS2) 16q21, and (BBS6) 20p12 have been reported earlier. The BBS8 locus is at 14q32.11, the BBS10 locus is in chromosome 12. The latter involves a chaperonin (Stoetzel C et al 2006 *Nature Genet* 38:521). The BBS protein has been localized to ciliated structures and to the centrosome (see Fig. B13). The BBS11 locus was assigned to chromosome 9q33 by a high-density single nucleotide polymorphism marker and microarrays; it encodes an E3 ubiquitin ligase (Chiang A et al 2006 *Proc Natl Acad Sci USA* 103:6287). Actually, the other BBS genes seem to affect the same cellular structures (Ansley SJ et al 2003 *Nature [Lond]* 425:628). The major form of BBS shares a chromosomal position with McKusick-Kaufman (MKKS, 20p12) syndrome. One basic problem may

involve a chaperonin that folds improperly several proteins. The core complex of BBS in cooperation with the Rab8 GTPase promotes ciliary membrane biogenesis (Nachury MV et al 2007 Cell 129:1201). ▶kidney diseases, ▶eye diseases, ▶triallelic inheritance, ▶cilia, ▶RAB, ▶McKusick-Kaufman syndrome, ▶chaperonin, ▶Prader-Willi syndrome; Beales PL et al 2001 Amer J Hum Genet 68:606; Myktyyn K et al 2001 Nature Genet 28:188; Katsanis N et al 2001 Hum Mol Genet 10:2293; Badano JL et al 2003 Am J Hum Genet 72:650.

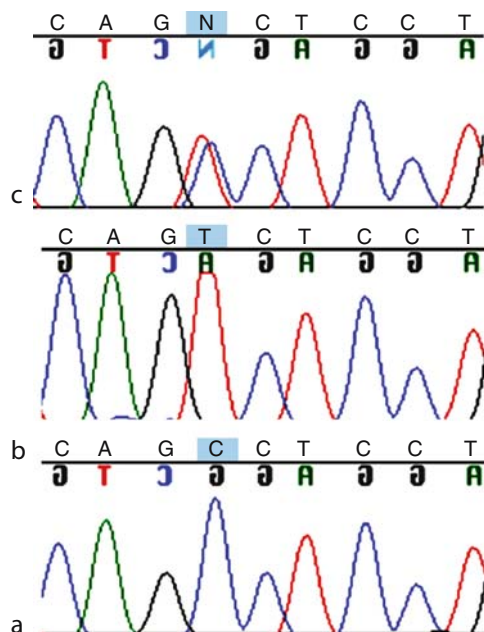


Figure B13. Bardet-Biedl. CCT (a) is normal proline, TCT (b) is homozygous for mutant serine, and (c) is heterozygous at position 130 of the TRIM32 sequence of the ubiquitin ligase gene of BBS11. Courtesy of Annie Chiang and Val Sheffield

Bare Lymphocyte Syndrome (BLS, 19p12 [RFXANK], 16p13 [MHC2TA], 1q21.1-q21.3 [RFX5], 13q14 [RFXAP]): This is a group of recessive severe immunodeficiency diseases caused by defects in the regulation of the major histocompatibility system by any of the four loci identified earlier. Some forms are due to defect(s) either in the HLA class I or class II genes involving lymphocyte differentiation. Some of the defects involve RFX proteins, which bind to the X box of the MHC2TA promoter. MHC II deficiency may also be due to mutation in MCC2TA transactivator. The MHCII molecules are heterodimeric transmembrane proteins. The current therapy is bone marrow transplantation. In future, gene therapy may be feasible. ▶immunodeficiency, ▶HLA,

▶lymphocyte, ▶MHC, ▶gene therapy, ▶RFX; Reith W, Mach B 2001 Annu Rev Immunol 19:331.

B

Barley (*Hordeum*): This cereal crop is used for feed, food and the brewery industry. The cultivated *H. sativum* is diploid $2n = 14$. Some of the varieties of wild barley are polyploids. The cultivated varieties have either two-row (see diagram; right) or four-row spike (see Fig. B14) or six-row depending on the number of florets fertilized per spikelets and bearing seeds. The diagram of the kernel arrangement (two-row and six-row) on the rachis (the axis of the spike) is presented here. The *vrs1* (*six-rowed spike 1*) gene, responsible for the six-rowed spike in barley, has been isolated by means of positional cloning. The wild type *Vrs1* allele (for two-rowed barley) encodes a transcription factor that includes a homeodomain with a closely linked leucine zipper motif. The expression of *Vrs1* was strictly localized in the lateral-spikelet primordia of immature spikes, suggesting that the VRS1 protein suppresses the development of the lateral rows. The loss of function of *Vrs1* resulted in complete conversion of the rudimentary lateral spikelets in two-rowed barley into fully developed fertile spikelets in the six-rowed phenotype (Komatsuda T et al 2007 Proc Natl Acad Sci USA 104:1424). ▶haploid [*H. bulbosum*], ▶*Hordeum*, ▶homeodomain, ▶leucine zipper, ▶positional cloning; <http://www.barleycap.org/>; <http://www.shigen.nig.ac.jp/barley/Barley.html>; <http://barleygenomics.wsu.edu/>; <http://www.barleybase.org/>.

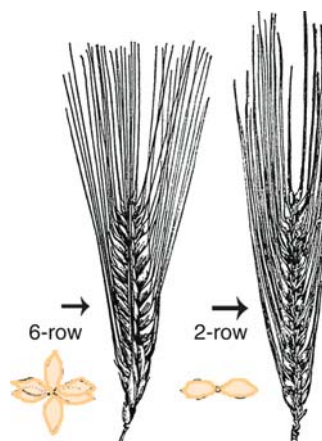


Figure B14. Barley

BARNASE (*Bacillus amyloliquefaciens* ribonuclease): This is a ribonuclease that may be associated with chaperones (see Fig. B15). ▶chaperones, ▶barstar, ▶ribonucleases, ▶RBF

B

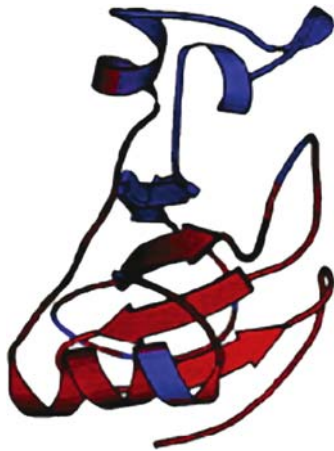


Figure B15. Barnase. Courtesy of Alm, E. & Baker, D. 1999 Proc. Natl. Acad. Sci. USA 96:11305

Barr Body: This dark-stained (heteropyknotic) structure is visible at the periphery of the interphase nuclei of cells that have more than one X chromosome. XY cells do not have a Barr body whereas normal XX female cells have one (see Fig. B16). The number of Barr bodies (named after M.L. Barr) is always one less than the number of X chromosomes, indicating that the non-active X chromosomes remain condensed (dosage compensation). Barr bodies are also present in XXY males. The Barr body is sometimes called sex chromatin. In the leukocytes the Barr body is enclosed in a special nuclear appendage called the “drum-stick” because of its shape. Methylation of CpG dinucleotides is the mechanism of inactivation. ▶[lyonization](#), ▶[methylation of DNA](#), ▶[dosage compensation](#); Heard E et al 1997 Annu Rev Genet 31:571; Hong B et al 2001 Proc Natl Acad Sci USA 98:8703.

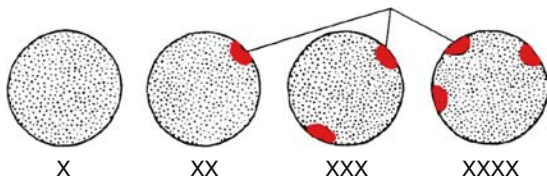


Figure B16. Barr body

Barrage: This is the sign of vegetative incompatibility in fungi. At the zone of contact between the two types of mycelia a distinguishable zone is formed as the result of antagonism between the two strains. (Rizet G 1952 Rev Cytol Biol Végét 13:51).

Barrel: Refers to protein β -sheets closing the interior and α chains on the exterior (see Fig. B17). ▶[protein structure](#)

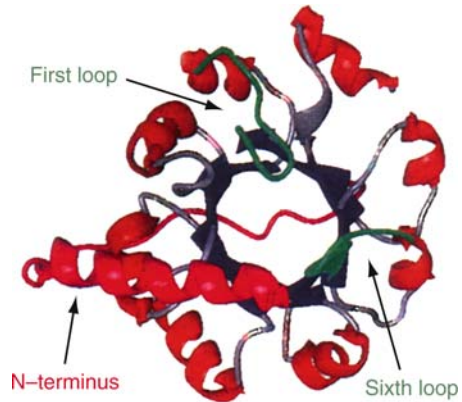


Figure B17. α/β barrel folds of phosphoribosylanthranilate isomerase. The β -sheets in the center are darker. (From Gerlt JA 2000 Nature Struct Biol 7:171)

Barren Stalk: Refers to (*ba*) maize genes (in chromosomes 3, 2 and 9) which affect the tassel or ear or both and cause partial/full sterility. The tassel is male inflorescence. ▶[tassel-seed](#); Gallavotti A et al 2004 Nature [Lond] 432:630.

Barrett Metaplasia (gastroesophageal reflux disease, 13q14): The efflux of the content of the stomach exposes the esophagus to acid and bile. This may result in ulceration and eventually adenocarcinomas of this organ. Demethylation of the CDX1 promoter is a key factor in the development of the disease (Wong NACS 2005 Proc Natl Acad Sci USA 102:7565). ▶[CDX1](#), ▶[acid reflux](#), ▶[esophagus](#)

Barring Gene (*B*): ▶[autosexing](#)

Barstar: This is an inhibitor of barnase. ▶[barnase](#), ▶[RBF](#); Hartley RW 1989 Trends Biochem Sci 14:450.

Barth Syndrome: ▶[endocardial fibroelastosis](#)

Barter Syndrome: Type 1 (15q15-q21.1) is a defect in the NaKCl transporter. Type 2 dominant, human chromosome 11q24 encoded disease is characterized by salt wasting and low blood pressure, accompanied by excessive amounts of calcium in the urine. The basic defect lies in an inward rectifier potassium ion channel. Type 3 (1p36) involves Chloride channel B. ▶[ROMK](#), ▶[Gitelman syndrome](#), ▶[Liddle syndrome](#), ▶[hypoadosteronism](#), ▶[hypertension](#), ▶[ion channels](#), ▶[hypokalemia](#)

β -ARK: β -adrenergic receptor kinase. ▶[adrenergic receptors](#)

Basal: This means at or near the base.

Basal Body: Refers to a group of microtubules and proteins at the base of cilia and flagella of eukaryotes (see Fig. B18). ▶[microtubule](#), ▶[cilia](#), ▶[flagellum](#)

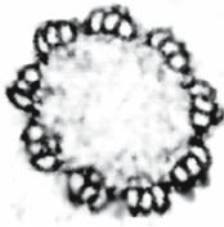


Figure B18. Basal body

Basal Cell Carcinoma: ►nevoid basal cell carcinoma

Basal Lamina: This is the same as the basement membrane. ►basement membrane

Basal Level Elements (BLE): These perform enhancer-type functions in gene regulation and can occur at several positions. ►enhancer

Basal Promoter: This is normally situated in the region –100 bp upstream of the transcription initiation site and contains various regulatory elements of transcription. ►promoter, ►transcription factors, ►core promoter

Basal Transcription Factors: ►transcription factors

BASC: This is one of several similar *Drosophila* genetic stocks, containing the dominant *Bar* (*B*), the recessive eye color allele, *apricot* (*w^a*), and several *scute* inversions. The B and w markers identify

the untreated chromosomes of untreated females and eliminate the cross overs with the treated X chromosomes of males. The mutagenic effectiveness is determined on the basis of the reduced proportion of males in F₂ if a lethal or sublethal mutation was induced in the X chromosome by the treatment. This type of analysis is called Muller-5 technique after H.J. Muller who designed the first stocks. The advantage of these stocks is that both males and homozygous females are completely fertile whereas the XO males are poorly viable and no cross overs appear along the X chromosome. Variegation may occur in some unlinked genes.

Rarely some exceptional females are also detected due to an unequal sister chromatid exchange in the inversion heterozygote females. ►CIB, ►autosomal dominant mutation, ►autosomal recessive mutation; Inoue Y 1992 *Genetica* 87:169; Forbes C 1981 *Mutation Res* 90:255, see Fig. B19.

BASC (BRCA1-associated genome surveillance complex): This includes tumor suppressors, DNA repair proteins, DNA replication factor C, etc. ►breast cancer; Wang Y et al 2000 *Genes Dev* 14:927.

Base: Refers to the lowest part of a structure or a compound or an ion which can combine with protons to yield salt. *Nitrogenous bases* such as the

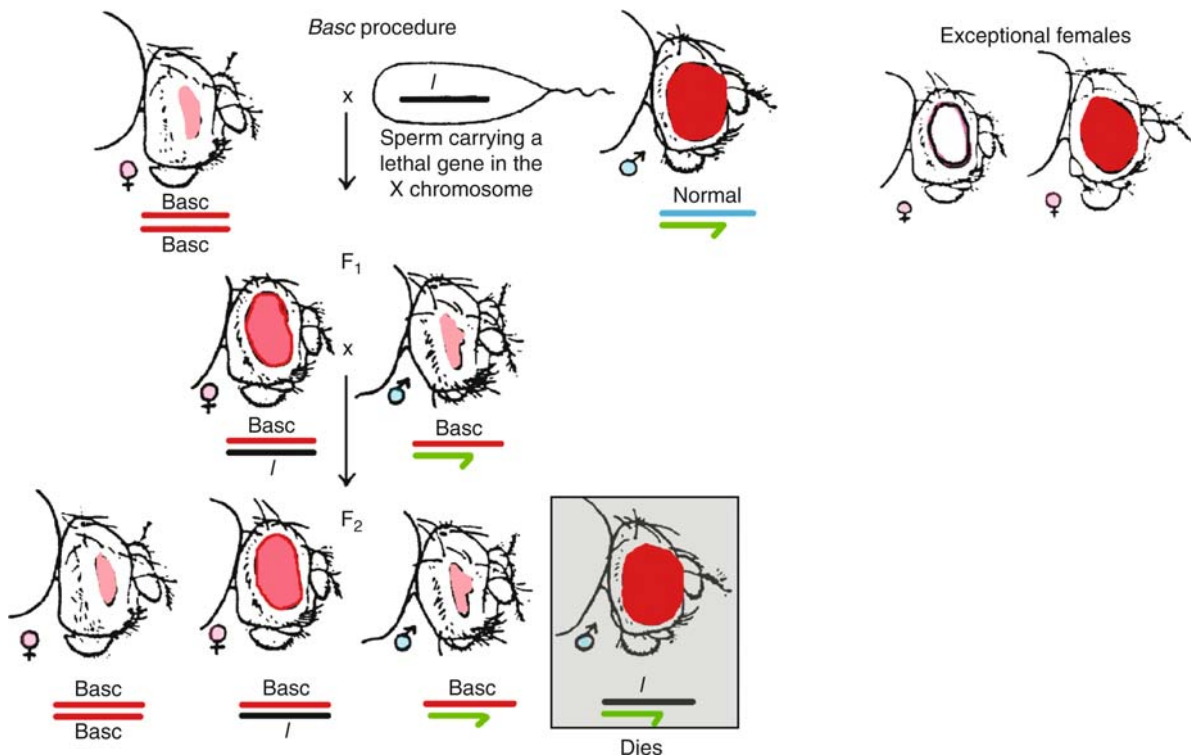


Figure B19. Basc

pyrimidines and purines of nucleic acids. ►[nucleic acid bases](#)

B

Base Analogs: These are nucleic acid bases or nucleosides similar to the normal compounds but cause mutation when incorporated into the DNA either by incorporating in the wrong place or by mispairing with the incorrect base. The most commonly used mutagenic base analogs are 5-bromouracil (thymine analog) and 2-aminopurine (adenine analog). Base analogs expanded by an intercalated benzene ring have been synthesized and the expanded xA and xT analogs form Watson–Crick pairs with the natural complementary base when incorporated into the DNA (see diagram). A single such pair decreases the stability of the double helix but longer tracts are stable. The dxA is a violet-blue fluorochrome (max. emission 389 nm). The dXT appears violet (max. emission 375 nm). When all expanded base analogs are in one strand the binding ability of the natural strand is enhanced making it potentially useful for microarrays, antisense and DNA–RNA analyses (Liu H et al 2003 *Science* 302:868). ►[hydrogen pairing](#), ►[base substitution](#), ►[point mutation](#), ►[universal base](#), ►[microarray hybridization](#), ►[antisense technologies](#), ►[isoguanine](#), ►[modified bases](#), Freeze E 1959 *J Mol Biol* 1:87.

Base Composition: Refers to the percentage of nucleotides in DNA or RNA.

Base Excision Repair (BER): ►[DNA repair](#)

Base Flipping: Some enzymes such as methyltransferases, glycosylases, T4 endonuclease V, *E. coli* phospholyase and endonuclease III must access the bases, which are inside the sugar-phosphate backbone of the B DNA double helix in order to be recognized by the active site of the protein. Some bases are swung out of the helix into an extra-helical position to meet the requirement. Base flipping is important for the hairpin processing reaction in transposition because it performs two opposite but closely related functions. It disrupts the double helix, providing the necessary strand separation and steric freedom, also the transposase appears to position the second DNA strand in the active site for cleavage using the flipped base as a handle (Bischerour J, Chalmers J 2007 *Nucleic Acids Res* 35:2584). ►[methylation of DNA](#), ►[glycosylases](#), ►[endonuclease](#), ►[DNA repair](#), ►[ABC excinucleases](#), ►[photolyase](#), ►[cyclobutane ring](#); Cheng X, Roberts RJ 2001 *Nucleic Acids Res* 29:3784; Patel PH et al 2001 *J Mol Biol* 308:823; Huang N et al 2003 *Proc Natl Acad Sci USA* 100:68; Luo J, Bruce TC 2005 *Proc Natl Acad Sci USA* 102:194.

Base Modifying Agents: Nitrous acid causes oxidative deamination, hydroxylamine converts cytosine into

hydroxylamino-cytosine (a thymine analog), and alkylating agents place alkyl groups at several possible positions to purines and pyrimidines. ►[chemical mutagens](#), ►[base substitution](#), ►[point mutation](#), ►[hydrogen bonding](#)

Base Pair (bp): Refers to hydrogen bonded A = T and G=C in DNA or A = U in double-stranded RNA. (►[mismatch](#), ►[mispairing](#), ►[hydrogen pairing](#), ►[universal bases](#), ►[Watson-Crick model](#))

Base Pair Opening (base flipping): A nucleoside unit swivels out of the DNA helix and inserts into the recognition pocket of a protein. Such nucleoside extrusion and extra-helical recognition may take place by processing the DNA by various glycosylases and endonuclease action. ►[base flipping](#)

Base-Pair Stepping: ►[nucleic acid chain growth](#)

Base Promoter: ►[core promoter](#)

Base Sequencing: ►[DNA sequencing](#)

Base Stacking: The nucleotides in parts of a polynucleotide chain may lie in such a way that the faces of the rings are appositioned (see Fig. B20). The stacking is most likely to occur by non-covalent forces near the chain termini where the bases move somewhat. It imparts some rigidity to the strand(s). The stacking is detectable by physical methods such as circular dichroism and optical rotatory dispersion. Reagents, which weaken hydrophobic reactions, eliminate the stacking, and heating reduces the stacking resulting in hyperchromicity. Destruction of hydrogen bonding also reduces the stacking in double-stranded DNA. Base stacking may occur in double-stranded molecules where the pairing is weakened by deletions or mismatches. ►[circular dichroism](#), ►[optical rotatory dispersion](#), ►[hyperchromicity](#), ►[excimer](#); Kool ET 2001 *Annu Rev Biophys Biomol Struct* 30:1.

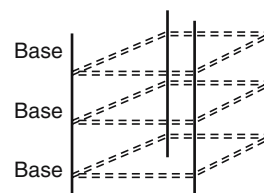


Figure B20. Base stacking

Base Substitutions: When a pyrimidine in the DNA is replaced by another pyrimidine or a purine is replaced by another purine the change is a *transition*. When a purine is replaced by a pyrimidine, or vice versa, a *transversion* takes place. These changes cause mutation in the DNA and they may also lead to amino

acid replacement in the protein if the base substitution involves a non-synonymous codon. Many mutagens cause base substitutions, e.g., hydroxylamine (NH₂OH) targets cytosine (C) and hydroxyaminocytosine is formed which is a thymine analog. As a result a C≡G base pair is replaced by a T = A bp. Similarly, 5-bromouracil may cause, through a tautomeric shift, T = A to be replaced by C≡G; and 2-aminopurine, an adenine analog, causes a tautomeric shift that may lead to the replacement of an A = T pair by a G≡C pair. Some other chemicals, e.g., nitrous acid, by deamination, changes cytosine to uracil and converts adenine into guanine. These base substitutions may also cause reversions. A hydroxylamine-induced mutation may be reverted by bromouracil, etc. It is generally assumed that base substitutions occur independently and coincidental double substitutions should be rare. Some genetic repair mechanisms may, however, bring about more than single replacements. A large-scale evolutionary study revealed that double substitutions may occur in the serine codons of primates at the high frequency of 0.1/site/billion years. (►DNA, ►hydrogen bonding, ►point mutation, ►base analogs, ►evolution and base substitutions, ►incorporation error, ►replication error, ►chemical mutagens, ►substitution mutations, ►mutation and DNA replication, ►mutation bias, Freese E 1959 Brookhaven Symp Biol 12:63, base substitution model selection tool: http://darwin.uvigo.es/software/modeltest_server.html).

Base-Call: This process evaluates the nucleotide sequence information using the PHRED program. ►base-calling, ►PHRED, ►PHRAP

Base-Calling: This means identifying the correct nucleotide in a sequence in the DNA. Also, identifying the correct base sequence on the basis of hybridization in microarrays compared to the actual direct sequencing information. Miscalls are false identifications. The multifluorescence discrimination (pulsed multiline excitation, PME) correlates a sequence of excitation pulses from four monochromatic wavelength laser sources with detector response from emission intensities of fluorescently labeled DNA fragments. For this purpose, a new set of dyes has been developed that spans with absorption maxima the entire visible spectrum. This procedure appears superior to the ones previously used (Lewis EK et al 2005 Proc Natl Acad Sci USA 102:5346). ►microarray hybridization, ►PHRAP, ►PHRED; Walther D et al 2001 Genome Res 11:875.

Basedow Disease: ►goiter

Basement Membrane (basal lamina): This is less than 500-nanometer thick laminated condensation of the extracellular matrix (including laminin, collagen IV

and other proteins) on the basal surfaces of epithelia and condensed mesenchyma. The basement membrane is an attachment platform and a barrier to cell mixing. Several human diseases involve anomalies of basement membranes and/or associated proteins. ►extracellular matrix, ►proteoglycan, ►laminin, ►collagen, ►Alport's disease, ►Goodpasture syndrome, ►fibromatosis; Quondamatteo F 2002 Histochem J 34:369; Masunaga T 2006 Connect Tissue Res 47:55.

Base-Pairing: ►hydrogen pairing

Base-Specific Reagents for DNA Single Strands:

1. Dimethylsulfate (DMS) + hydrazine the methylated cytosine is cleaved at the 3' position. 2. DMS alone methylates guanine. 3. Osmiumtetroxide or potassium permanganate oxidizes the C5-C6 double bonds in thymidine. 4. Diethylpyrocarbonate (O[CO₂C₂O₅]₂) preferentially modifies adenine at N-7 although it affects other purines as well. (►DNA sequencing [Maxam & Gilbert method])

Base-Stacking: ►base stacking

Bash (B cell-restricted adaptor protein, BLNK/SLP-64): After ligation Sly tyrosine kinase phosphorylates it and it binds various B cell signaling proteins that control B cell development. Its role is similar to that of SLP-76 for T cells. ►SLP-76, ►B lymphocyte, ►ITIM; Tsuji S et al 2001 J Exp Med 194:529.

Basic Chromosome Number: This is found in the gametes of diploid organisms and it is represented by x; in polyploids the haploid (n) number may be 2x, 3x and so on, depending on the number of genomes contained. The basic number is frequently called a genome. ►chromosome numbers, ►genome, ►polyploid

Basic Copy Gene: It is the silent copy of a *Trypanosoma* gene that is activated by transposition to an activation site in the telomeric region of the chromosome. ►Trypanosomas, ►telomere

Basic Dye: The dye stains negatively charged molecules. ►stains

Basidiomycetes: A taxonomic group of fungi bearing the meiotic products in basidia. ►basidium, ►mushroom

Basidium: This is a fungal reproductive structure generally in the shape of a club where meiosis takes place and then the haploid basidiospores are released infecting the host plants (see Fig. B21). ►stem rust



Figure B21. Basidium with four meiotic spores

B

Basonuclin: This is a cell type-specific Zinc finger protein with a nuclear localization sequence and a serine stripe (serine-rich region). It is in abundance in the human keratinocyte nuclei but in the absence of phosphorylation it is in the cytosol. Basonuclin is also found in the epidermal cells and the germ cells of the testis and the ovary. It binds to the rRNA promoter and apparently regulates rRNA transcription. ▶ [Zinc finger](#), ▶ [nuclear localization signal](#); Tian Q et al 2001 Development 128:407.

Basophil: Refers to a type of white blood cell which is well stainable with basic cytological dyes. These cells contain conspicuous secretory granules and release histamine and serotonin in some immune reactions. Any other (acidic) structure or molecule with an affinity for positive charges. ▶ [granulocytes](#), ▶ [blood](#), ▶ [immune system](#)

Basta: This is a glufosinate ammonium herbicide, pesticide and a selective agent in plant transformation. ▶ [herbicides](#), ▶ [transformation genetic \[plants\]](#); Rathore KS et al 1993 Plant Mol Biol 21:871.

Bastard: This means a hybrid [in German]; and an illegitimate or undesirable offspring [in English].

Bat: *Carollia perpicillata* 2n = 21 in males, 20 in females; *Glossophaga soricina* 2n = 32; *Desmodus rotundus murinus* 2n = 28; *Atropzous pallidus* 2n = 46; *Eptesicus fuscus* 2n = 50; *Myotis velifer incautus* 2n = 44; *Nysticeius humeralis* 2n = 46. They are useful predators of insects but constitute a reservoir of different pathogenic viruses such as SARS, Ebola, Marburg and other strains. (Dobson AP 2005 Science 310:628).

Bateman's Principle: It states that the reproductive success of males shows greater variation than that of females because of greater competition among males and larger number of male gametes.

Batesian Mimicry: This is an adaptive evolutionary device. Certain species develop phenotypic characteristics of sympatric species (models) in order to increase their chances of survival. The models are repugnant (distasteful) to certain ▶ [predators](#), which avoid them, and so the mimickers when mistaken for the models also escape destruction. Batesian mimicry is more common among females than males (butterflies) because females are more often subject to predation than males. (▶ [adaptation](#), ▶ [natural selection](#), ▶ [Müllerian mimicry](#), see Fig. B22).

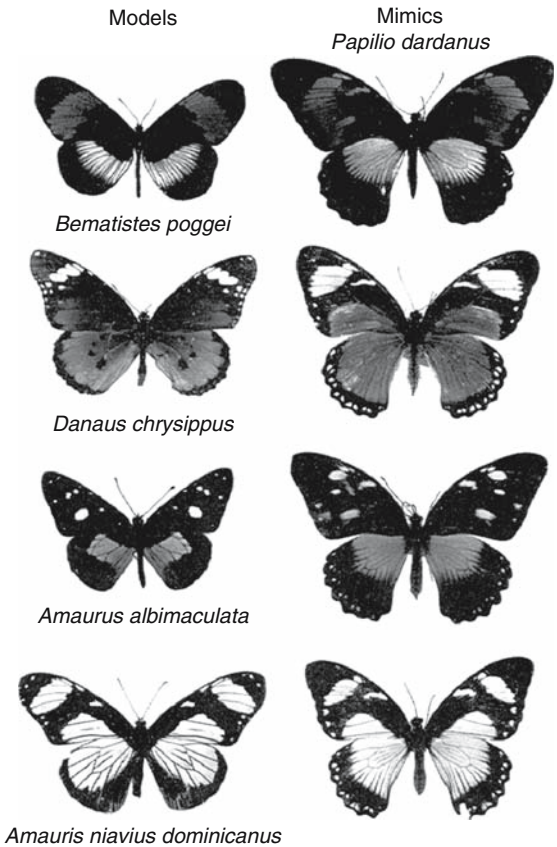


Figure B22. Batesian mimicry. Batesian mimicry in butterflies. (From Sheppard, P.M. 1959 Cold Spring Harbor Symp. Quant. Biol. 24:131)

Batten Disease: This is a recessive (human chromosome 16p12.1–p11.2) juvenile-onset familial amaurotic idiocy caused by lipid accumulation in the nerve tissues and vacuolization of the lymphocytes. Its incidence is $\sim 5 \times 10^{-5}$. The disease seems to be associated with low vacuolar pH. In the yeast *bml* defects chloroquine reverses the phenotype. ▶ [amaurotic familial idiocy](#), ▶ [ceroid lipofuscinosis](#), ▶ [chloroquine](#), ▶ [Vogt-Spielmeyer disease](#), ▶ [PPT](#); Luiro K et al 2001 Hum Mol Genet 10:2123, <http://www.ucl.ac.uk/ncl/>.

Batten-Turner Syndrome: ▶ [myopathy congenital](#), ▶ [human chromosome 16](#)

Bauplan (body plan): Refers to the pattern of body organization. ▶ [tagmosis](#)

BAX (BCL2-associated X protein): ▶ [BCL](#), ▶ [porin](#), ▶ [Puma](#), ▶ [Bid](#); Chipuk JE et al 2004 Science 303:1010.

Bayes' Theorem: The theorem permits the estimation of various conditional probabilities and is used for

decision-making processes. In the simplest general form:

$$P(A|B) = \frac{P[B|A]P[A]}{P[B|A]P[A] + P[B|A']P[A']}$$

Its application in genetics can be illustrated by assuming that there are three individuals, two homozygotes for a semi-lethal dominant factor and one heterozygote for the same semi-lethal and incompletely dominant gene. There are problems with visual classification at an early stage of the development. Assuming that the two homozygotes [A] have 60%, and the heterozygote [A'] is expected to have 80% viability. Thus $P[B|A] = 0.6$, and $P[B|A'] = 0.8$.

The chance of selecting an individual of either genotype is $P[A] = 2/3$ and $P[A'] = 1/3$. If the selected individual turns out to be very weak, and if one is uncertain about the choice, one may want to determine—in view of the information available—the probability of having selected the heterozygote:

$$P(A|B) = \frac{[0.8][0.33]}{[0.8][0.33] + [0.6][0.67]} \cong 0.4$$

Basically, the Bayesian method considers the classical population parameters as random variables with a specific *a priori* probability of distribution. Then the *conditional probability* is estimated on the basis of the *a priori* distribution. The conditional probability is thus a property of a *posteriori* distribution because the accepted or supposed *a priori* distribution is used for the estimation of an existing situation in a population. ▶probability, ▶a priori, ▶prior distribution, ▶conditional probability, ▶risk, ▶inference, ▶Bernoulli process; Shoemaker JS et al 1999 Trends Genet 15:354; Bernardo JM, Smith AFM 1994 Bayesian theory, Oxford University Press, Oxford, UK; Beaumont MA, Rannala B 2004 Nature Rev Genet 5:251.

Bayesian Mapping: This can be applied to QTL. Inferences are made on the basis of the joint posterior distribution of all unknown variables given the prior distribution of all unknowns of the observations. It uses Monte Carlo approximation to the multiple integration required. It may be useful for analyzing complex animal pedigrees. ▶QTL, ▶genetic networks, ▶BAMBE, ▶Monte Carlo method, ▶Bayes' theorem; Yi N, Xu S 2000 Genetics 155:1391.

Bayesian Network: This can represent systems with multiple interactions. It can detect direct molecular interactions and also indirect effects that have not been directly observed. ▶networks, ▶signal transduction, ▶genetic networks; Sachs K et al 2005 Science 308:523.

BB-1: This is the same as B7 or CD80.

BBB (blood-brain barrier): The mechanism seriously limits transport to the central nervous system (CNS) because of the tight junction of the endothelial cells of the brain capillaries. Molecules larger than 180 MW and viruses may be excluded. Lymphocytes may enter the central nervous system but are not retained unless foreign antigens are present. Neurons and some other cells may poorly express MHC proteins and escape the effects of cytotoxic T cells. In such a situation different viruses (rubella, measles, polyoma JC, herpes simplex, rabies, mumps) may infect the brain. In the absence of such a barrier serum may leak into the brain causing edema. Angiotensin may be required to maintain BBB. Antagonists of the hypothalamic growth hormone-releasing hormone such as JV-1-42 (a peptide analog) enter the brain and can accumulate there. Since this hormone is present in several types of cancers there may be an opportunity for the treatment of glioblastomas (Jaeger LB et al 2005 Proc Natl Acad Sci USA 102:12495). Some lipids (but not by water-soluble or protein) molecules may however overcome the barrier if the cargo protein is associated with a carrier such as transferrin (Demeule M et al 2002 J Neurochem 83:924). High doses of the enzyme β -D-glucuronidase injected into the bloodstream of mice, mutant in mucopolysaccharidosis VII, passed through the blood-brain barrier (Vogler C et al 2005 Proc Natl Acad Sci USA 102:14777). Receptors on the blood-brain barrier bind ligands to facilitate their transport to the central nervous system. The use of the lentivirus vector system can deliver the lysosomal enzyme glucocerebrosidase and a secreted form of GFP (green fluorescent protein) to the neurons and astrocytes in the CNS. Fusing the low-density lipoprotein receptor-binding domain of the apolipoprotein B to the targeted protein is useful in delivering to the CNS (Spencer BJ, Verma IM 2007 Proc Natl Acad Sci USA 104:7594). ▶angiotensin, ▶protein transduction, ▶multiple sclerosis, ▶MHC, ▶glucose transporters, ▶GH, ▶gliomas, ▶transferin, ▶enzyme replacement therapy, ▶siRNA; Asahi M et al 2001 J Neurosci 21:7724.

β -Catenin: This is a component of the cadherin-catenin cell adhesion complex. ▶adherens junction

B-Cell Differentiation Factor: ▶interferon β -2 (IFNB2)

B-Cell Growth Factor: ▶IL-4, ▶interleukins

BCG: ▶*Bacillus Calmette-Guerin*

BCGF (B cell growth factor): Refers to 12-kDa cytokine produced by activated T cells. ▶B cell, ▶T cell, ▶cytokine, ▶lymphocytes

BCIP: 5-bromo-4-chloro-3-indolyl phosphate is used in combination with nitroblue tetrazolium (NBT; it

B

reveals precipitated indoxyl groups) for the detection of antigen-antibody—antibody-AP (alkaline phosphatase) complexes. ►antigen, ►antibody

BCL1, BCL2, BCL3, BCL5, BCL6 (B cell lymphoma):

These are leukemia oncogenes but they are also upregulated in various other types of cancers. *Bcl-1* is cyclin D1 (see Fig. B23). *Bcl-2* (18q21.3) suppresses apoptosis (by phosphatase action when bound to calcineurin) as a defense against malignant tumorigenesis and suppresses signaling by NF-AT. BCL2 apparently shuts off the voltage-dependent anion channel on the mitochondrial membrane and prevents the leakage of apoptotic cytochrome c into the cytosol to guard against apoptosis. It also promotes regeneration of severed cells in the central nervous system. The *Bcl-2* protein functions as an ion channel and a docking protein. BCL-2 is located in the outer membrane of the mitochondria, nuclei and the endoplasmic reticulum. *Bcl-6* regulates STAT and cytokine signaling. *Bcl-6* suppresses p53, a pro-apoptotic and cancer suppressor protein in the germinal center B cells (Phanm RT, Dalla-Favera R 2004 Nature [Lond] 432:635). The *Bcl* protein is usually up-regulated in lymphomas, and gene therapy involving deoxyoligonucleotides (such as 5'-TCTCCCAGCGTGCGC-CAT-3') targeted to the *AUG* initiator codon has been used. There are over a dozen members of the *Bcl* family. *Bcl-2* is homologous to *Ced-9* of *Caenorhabditis*. Antimycin A, a complex of highly toxic antifungal substances, inhibitors of electron transport, bind *Bcl* and *Bcl-X* and favor apoptosis and may thus protect against cancerous growth. The *Bcl* proteins can be effectively modulated by engineered BH3 fragments and the so-activated BID protein promotes apoptosis and destroys leukemia cells (Walensky LD et al 2004 Science 305:1466). The anti-apoptotic BCL-2 favors the maintenance of blood cancer, leukemia (Letai A et al 2004 Cancer Cell 6:241). *Bcl-2* interferes with RAD51 controlled recombination that may mediate error-free repair and may thus promote cancer-prone conditions independently from its anti-apoptosis effect. The normally anti-apoptotic *Bcl-2* may interact with Nur77 orphan nuclear receptor and may promote apoptosis. The pro-apoptotic members of the BCL family, BAX and BAK, regulate the inositol triphosphate receptor (IP3R-1) and normally maintain a high calcium level in the endoplasmic reticulum (ER). Mutant BAX and BAK decrease the ER calcium level and the released Ca^{2+} increases mitochondrial permeability leading to apoptosis. BCL2 has the opposite effects (Oakes SA et al 2005 Proc Natl Acad Sci USA 102:105). ►leukemia, ►apoptosis, ►BAX, ►BAD, ►BAK, ►BID,

►IP3, ►Bim, ►malignant growth, ►cyclin, ►NF-AT, ►calcineurin, ►STAT, ►cytokine, ►G3139, ►G3854, ►lymphoma, ►nur77, ►IAP, ►germinal center; p53, Petros AM et al 2001 Proc Natl Acad Sci 98:3012; Saintigny Y et al 2001 EMBO J 20:2596; Vander Heiden MG et al 2001 J Biol Chem 276:19414; Deng X et al 2004 Proc Natl Acad Sci USA 101:153.

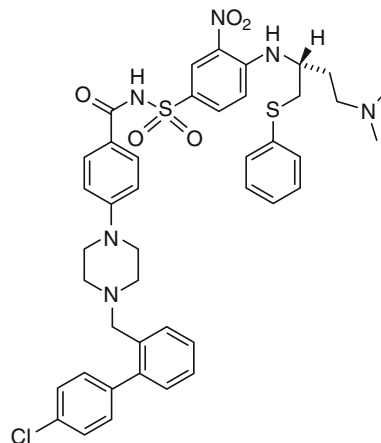


Figure B23. ABT-737 inhibits Bcl-2 family of proteins; regresses solid tumors. (Oltersdorf, T. et al. 2005 Nature 435:677)

BCMA: This is one of the B lymphocyte receptors.

►BCR, ►BAFF, ►Blys

β-Conformation: Refers to an extended conformation of a peptide chain; a type of secondary structure.

►protein structure

BCR: Refers to B-cell antigen receptor. ►B lymphocyte

BCR (bcr): The break point cluster region in the Philadelphia chromosome is an area where multiple chromosomal breakages have been observed leading to cancerous transformation (leukemia, ABL). The BCR polypeptide contains 1,271 amino acids and its normal function is a protein serine/threonine kinase.

►Philadelphia chromosome, ►leukemia, ►ABL

B-DNA: This denotes a conformation of the DNA most common in hydrated living cells. ►DNA types

BDNF (brain-derived neurotrophic factor): This is an autocrine growth substance of neurons but it is found in other organs as well. Genetic variant (Val codon 66→Met) predisposes to anxiety and depressive disorders (Chen ZY et al 2006 Science 314:140). ►autocrine, ►neuron, ►TRK, ►ovary, ►Parkinson's disease, ►Rett syndrome, ►anxiety, ►depression; Li Y et al 2005 Nature [Lond] 434:894.

Beacon, Molecular: These are hairpin-shaped single-stranded oligonucleotide genetic probes that become fluorescent after hybridization to the homologous target. One end is covalently bound to a fluorophore and the other end is attached to a non-fluorescent quencher. If the probe does not find homology there is no fluorescence because the quencher prevents it in the hairpin (see Fig. B24). If the probe locates a homologous sequence, unwinding removes the quencher from the vicinity of the fluorophore and the site lights up ✱. ▶[spectral genotyping](#), ▶[molecular beacon](#); Tyagi S, Kramer FR 1996 *Nature Biotechnol* 14:303; Heyduk T, Heyduk E 2002 *Nature Biotechnol* 20:171; Hopkins JF, Woodson SA 2005 *Nucleic Acids Res* 33:5763.

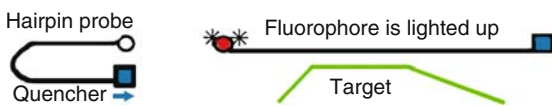


Figure B24. Molecular beacon

Beads-On-A-String: Originally this referred to the (light-microscopically visible) chromosome structure at the pachytene where the chromomeres could be seen as beads-on-a-string. In the 1920s chromomeres were equated with genes, units of function, mutation and recombination. Today, this is also used to describe the DNA strands wrapped around the eight histones (nucleosomes) as seen through an electron microscope. ▶[nucleosome](#), ▶[pachynema](#), ▶[chromomeres](#), ▶[complex locus](#)

Beagle: ▶[copia](#)

BEAMing (beads, emulsion, amplification and magnetics): This is a procedure for the quantification of variation in single DNA molecules among a large number of molecules. The purpose is the detection of SNIPS, rare mutations in genes and transcript of importance for function and disease or state of disease progression in specific tissues. Small numbers of DNA molecules that display variations are amplified by polo. Counting the attached beads on the basis of fluorescent labels using flow cytometry leads to the numbers of variants. ▶[flow cytometry](#), ▶[polo](#), ▶[SNIPS](#); Dressman D et al 2003 *Proc Natl Acad Sci USA* 100:8817.

Bean-Bag Genetics: This phrase was used for characterizing the work of Mendelian geneticists, studying/counting individual genes as they controlled the phenotypes and inheritance. It expressed the contempt of some evolutionists whose interest was in entire

organisms rather than in dissecting the mechanisms of the Mendelian factors by statistical means. With advances in physiological, biochemical and molecular genetics new terms such as “factorial genetics/formal genetic” were proposed for the classical approaches. Today, genetics research relies on the wide-reaching methods and principles based on simple and macromolecules and single molecules, networks of molecules as well as biophysics and cybernetic tools and principles of bioinformatics. The boundaries of modern genetics are unrestricted and genetics has permeated the whole field of basic and applied biology. (Haldane JBS 1964 *Persp Biol Med* 7:343).

Beans (*Phaseolus* spp): These are pulse crops, all with $2n = 2x = 22$ chromosomes, including the most common *P. vulgaris* (French or navy beans) and the *P. lunatus* ▶[Lima bean](#)

Bear: Refers to *Ursus americanus* (black bear) $2n = 74$; *Tremarctos ornatus* (spectacled bear) $2n = 52$.

Beare-Stevenson Syndrome: An autosomal dominant disorder which is characterized by furrowed, corrugated skin (cutis gyrata), head bone fusions, facial anomalies, abnormal digits, umbilical, genital malformations and early death. The basic defect lies in the fibroblast growth factor receptor 2, encoded at 10q26. Some heterogeneity exists. ▶[FGF](#)

Beaver: *Castor canadensis*, $2n = 40$. A large (>80 cm long) brown rodent.

Becker Disease: ▶[myotonia](#)

Becker Muscular Dystrophy (BMD): ▶[muscular dystrophy](#)

Beckwith-Wiedemann Syndrome (EMG syndrome): This disorder is caused by a dominant gene in human chromosome 11p15.5. The symptoms include enlarged tongue (detectable at birth), umbilical anomalies (omphalocele = herniated intestines at the belly button area), hypoglycemia, enlargement of the internal organs (visceromegaly), frequent concomitant kidney and liver anomalies, tumorous striated muscles (rhabdomyosarcoma), etc. It may be associated with trisomy for chromosome 11 and it has been suggested that it is caused by paternal or maternal disomy when the normal (most commonly paternal) chromosome is lost from the trisomic cell lineage, or imprinting. A gene encoding a cyclin-dependent kinase inhibitor ($p57^{KIP2}$) is imprinted and preferentially expressed by the maternal allele may be

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responsible for some of the cases. Insulin-like growth factor (IGF2) also has a regulatory effect. Deletion, duplication and balanced translocation have been suggested for some cases. It has been shown recently that KVLQT1 gene, encoding a putative potassium channel, and mapped to the 11p15.5 region controls imprinting not only the Beckwith-Wiedemann gene but also the Jervell and Lange-Nielsen syndrome and the LQT heart arrhythmia. ▶disomic, ▶disomic uniparental, ▶Wilms tumor, ▶cancer, ▶Jervell and Lange-Nielsen syndrome, ▶rhabdomyosarcoma, ▶Simpson-Golabi-Behmel syndrome, ▶imprinting, ▶insulin-like growth factors, ▶ion channels, ▶cyclin, p57; LQT; epigenesis; Alders M et al 2000 Am J Hum Genet 66:1473; Blik J et al 2001 Hum Mol Genet 10:467; DeBaun MR et al 2003 Am J Hum Genet 72:156.

Beclin 1 (17q21): This is a mammalian autophagy gene that is deleted in 40–75% of the sporadic ovarian and breast carcinoma cells. ▶autophagy

Becquerel: This corresponds to 1 disintegration of radioactive material/second; 1 becquerel = 2.7027×10^{-11} Curie (≈ 27 picocuries). ▶Curie

Bedwetting: ▶nocturnal enuresis

Beech (*Fagus*): This is a hardwood tree, *F. sylvestris*, $2n = 2x = 24$ (see Fig. B25).



Figure B25. Beech, *F. sylvestris*

Beethoven, Ludwig van (1770–1827): Beethoven was one of the greatest musical geniuses of the eighteenth-nineteenth century. Both his grandfather Louis and his father Johann were outstanding singers in Louvain and Liège. Later his father worked as a musical director (Kapellmeister) in Bonn. His talent was obvious from early childhood (see Fig. B26). Only three of his seven siblings survived to adulthood but none of them had any special musical ability. At the age of 22 he moved from Bonn to Vienna and rose to become a highly esteemed member of the nobility and the imperial court.

Many famous contemporaries were his friends. He was financially independent because of the generosity of his admirers. Beethoven never married because he was plagued by various minor and major illnesses, including gradual loss of hearing leading to near total deafness by the age of 40. Ironically, during this phase, he composed some of his most famous works such as the Emperor concerto, a new version of the opera Fidelio, the seventh and the ninth symphonies. Although he had a platonic relationship with several women, he became isolated



Figure B26. This is the Brunszvik mansion of Martonvásár, Hungary where Beethoven was a guest two times. His bust is in the park at the lake behind the building. Above the spruce tree is the triple window of the music room where he composed the Moonlight Sonata. By the strange fate of life, many years ago author of this book lived in the same elegant room—with beautiful inlaid wood ceiling—for about a month

because he was troubled by his hearing loss (see Fig. B27). ►musical talent, ►genius, ►Bach, ►Mozart, ►Strauss; Mai FM 2007 Diagnosing genius: The life and death of Beethoven, McGill-Queen's University Press, Montreal, Canada.



Figure B27. Beethoven in the park. Beethoven bust in the park in Martonvásár. (Courtesy of Prof. J. Kiss)

Beethoven (*Bth*): This is a mouse mutation with dominant progressive hearing loss at the locus homologous to the human gene *TMC1*, causing DFNA36. Beethoven was apparently afflicted by the same mutation. ►deafness

Begonia (*Begonia semperflorens*): This is an ornamental plant, $2n = 34$.

Behavior Genetics: This branch of genetics analyzes the genetic determination and regulation of how organisms behave. Most of the traits (courtship, bird and frog songs) are under multigenic control and they depend to a large extent on the influence of the environment. In a few cases large effects of single genes have also been observed (Hall JC 2002 *J Neurogenet* 16:135). In *Drosophila* the *fruitless* (*fru*) gene is involved in the determination of courtship. The Fru^M transcription factor protein is expressed in about 2% of the neurons of the central nervous system. When the yeast *GAL4* gene is inserted into the *fru* locus Fru^M is expressed in all the peripheral sensory systems involved in courtship. Gal4 is a positive regulatory protein of the yeast galactose gene. Inhibition of Fru^M in the olfactory system components reduces olfaction-dependent courtship. Transient inactivation of all Fru^M -expressing neurons terminates courtship behavior without affecting other behavioral traits. The expression of Fru^M in female flies results in the manifestation of male courtship ritual in females toward other females (Manoli DS et al 2005 *Nature [Lond]* 436:395). The mosquito *Toxorhynchites brevipalpis* “hears” the frequency of the wing beats and both males and females recognize

the opposite sex on this basis (Gibson G, Russell I 2006 *Current Biol* 16:1311).

The Western scrub-jay (*Aphelocoma*), a corvid bird, hides food for future consumption and adopts a very elaborate pattern for protection of the cache (see Fig. B28). The bird can remember which individual saw the cache and alters its tactics to elude potential



Figure B28. Behavior genetics-*Aphelocoma*

thieves (Dally JM et al 2006 *Science* 312:1662). In the honeybee a single gene controls the habit of uncapping the honeycombs containing dead larvae but another gene is required for the removal of the dead brood. If both genes are present the colony becomes resistant to the bacterial disease foul brood because of improved hygienic behavior.

Alcoholism, criminality, etc. in humans may be determined by several genes and by the social environment. The Lesch-Nyhan syndrome is caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase, which renders the salvage pathway of nucleic acid inoperational. As a consequence purines accumulate and uric acid is overproduced leading to gout-like symptoms but more importantly the nervous system is also affected, leading to antisocial behavior and self-mutilation. This gene has been isolated and cloned and may be transferred to the afflicted human body for gene therapy. Since behavioral traits are determined by the nervous system, neurogenetics may provide the answer to many serious conditions such as Alzheimer's disease (an amyloid accumulating presenile dementia), neurofibromatosis (a soft tumor of the nervous system affecting the entire body involving a protein resembling a GTPase activator), etc. Behavioral alteration may result from brain damage without a genetic change. A lesion in the frontal lobe of the brain may result in sociopathy in humans and in macaques (Rudebeck PH et al 2006 *Science* 313:1310).

In recent years progress has been made in the molecular analysis of memory and learning ability through studies of simple organisms such as the slug *Aplysia* and *Drosophila*. Several genes involved in the development of the nervous system of *Drosophila* have been cloned. Recent research has shown that mice without the *fos* gene fail to nurse their pups presumably because of some brain lesions.

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For genetic and developmental analysis of nerve functions, the nematode, *Caenorhabditis* is particularly well suited because its entire nervous system consists of only 302 cells. In the tobacco hornworm (*Manduca sexta*) the feeding preference depends on an acquired recognition template. The naïve larvae can feed on different plant species but once they have been exposed to a steroidal glycoside (indioside D) present in tobacco leaves, they become “addicted” to that host. Although all biological traits and attributes have some biological basis, the influence of the environment has a very substantial role in the development of behavioral traits. Frequently, for unknown reason, identical behavioral traits are expressed differently in isogenic strains maintained in different laboratories under apparently identical conditions. This fact indicates that genes cannot exonerate criminal behavior, neither should people be condemned on the basis of collective responsibility by supposed sharing of a common gene pool.

Microarray profiles of the brain are associated with behavior (Whitfield CW et al 2003 Science 302:296). Magnetic resonance imaging (MRI) of the brain distinguishes between extrovert and neuroticistic behavior on the basis of humor-driven blood oxygenation level-dependent signals in different regions of the brain (Mobbs D et al 2005 Proc Natl Acad Sci USA 102:16502). The molecular basis of a few mouse behavioral genes is now known. Deletion from the *ROR α* gene causes the *staggerer* phenotype. The *vibrator* mouse carries a retroposon in an intron of the phosphatidylinositol transfer protein. The *weaver* ataxia is a serine→glycine replacement gene in a G-protein-gated inwardly rectifying K-ion channel. The different types of estrogen receptors control mating behavior. Introduction by a viral vector the single gene of the vasopressin V1a receptor into the ventral forebrain of the polygamous species of the Vole substantially increased monogamous behavior (Lim MM et al 2004 Nature [Lond] 429:754). Oxytocin knockout male mice are afflicted by an olfactory recognition problem, a deficit in the amygdala of the brain which can be corrected by injecting oxytocin. *Trpc2* vomeronasal organ-specific neuron ion channel mutant mouse females display unique characteristics of male sexual and courtship behavior such as mounting, pelvic thrust, solicitation, anogenital olfactory investigation, and emission of complex ultrasonic vocalizations towards male and female conspecific mice. The same behavioral phenotype is observed after surgical removal of the vomeronasal organ of adult animals, and is not accompanied by disruption of the estrous cycle and sex hormone levels (Kimchi T et al 2007 Nature [Lond] 448:1009). Galanin, a neuropeptide with inhibitory action on neurotransmission and memory, causes Alzheimer’s disease-like behavior in mice. Enkephalin (opioid

peptide) knockout and/or the loss of its receptor lead to an increase in anxiety. Mutation in the dopamine receptor D2 results in Parkinsonism-like phenotype. The loss of the serotonin receptors increases anxiety. NO synthase knockout mice express greater aggressiveness. Single genes, encoding pheromone-binding protein(s) may regulate complex social behavior, such as recognition of conspecific individuals in social insects (Keller L, Parker JD 2002 Current Genet 12[5]:R180). The nursing of female rabbits and the sucking of pups seem to be regulated by the pheromone 2-methylbutenal (Schaal B et al 2003 Nature [Lond] 424:68). Mice deficient in the TRP2 gene lose their ability to distinguish between sexual types and consequently males mate with both males and females. In the carpenter ants (*Camponotus japonicus*) hydrocarbon blends produced by sensillae of the antennae are the chemical signals for the recognition of nestmates and for the aggressive behavior towards non-nestmates (Ozaki M et al 2005 Science 309:311). Behavior is subject to epigenetic modification. In rats well cared by their mothers during early life the hippocampal glucocorticoid receptor is methylated to a lesser degree than in the neglected pups. This condition persists during the later stages of development. Infusion of L-methionine, a precursor of S-adenosylmethionine and methyl donor for DNA methylation reverses the effect of the maternal behavior on DNA methylation (Weaver IC et al 2005 J Neurosci 25:11045). The higher level of maternal androgens—especially in the later phase of pregnancy—influences social rank and aggressiveness in spotted hyenas (Dloniak SM et al 2006 Nature [Lond] 440:1190). ▶courtship in *Drosophila*, ▶personality, ▶alcoholism, ▶cognitive abilities, ▶autism, ▶addiction, ▶fate mapping, ▶behavior in humans, ▶altruistic behavior, ▶aggression, ▶ethics, ▶instinct, ▶morality, ▶eugenics, ▶avoidance learning, ▶cross fostering, ▶FOS, ▶human intelligence, ▶behavior, ▶affective disorders, ▶Huntington’s chorea, ▶Alzheimer’s disease, ▶mental retardation, ▶attention deficit hyperactivity, ▶dyslexia, ▶homosexual, ▶vomeronasal organ, ▶oxytocin, ▶microsatellite, ▶antenna, ▶sensillum, ▶sex determination, ▶Gal4; Pfaff D 2001 Proc Natl Acad Sci USA 98:5957; McGuffin P et al 2001 Science 291:1232; Toyee AA, Cox R 2001 Curr Biol 2001 11:R473; Krieger MJB, Ross KG 2002 Science 295:328; Bucan M, Abel T 2002 Nature Rev Genet 2002 3:114; Stowers L et al 2002 Science 295:1493; Kucharski R, Maleszka R 2002 Genome Biol 3[2]:res.0007.1; Rankin CH 2002 Nature Rev Genet 3:622; Sokolowski MB 2002 Nature [Lond] 419:893; Sherman G, Visscher PK 2002 Nature [Lond] 419:920; chemical communication; Proc Natl Acad Sci USA 100, Suppl 2 [2003]; application in law, education, employment and insurance: Rothstein MA 2005 Nature Rev Genet 6:793.

Behavior in Humans: For long human behavior has been suspected to be genetically determined but with a few exceptions (Lesch-Nyhan syndrome, Tay-Sachs disease, Huntington's chorea, etc.). However, the genetic control is not completely understood. The majority of the behavioral traits are under the control of several genes. In such instances the tools of quantitative inheritance are needed, such as heritability, comparison of monozygotic-dizygotic twins with the general population and QTL mapping. The approximate ratios of monozygotic:dizygotic concordance are for alcoholism, females (1.1) versus males (1.7), dyslexia (1.7), Alzheimer's disease (2.1), major affective disorders (2.4), schizophrenia (2.7), autism (6.7). Heritabilities determined by intraclass correlation were 0.22 for memory, 0.22 for mental processing speed, 0.38 for scholastic achievement in adolescence, 0.40 for spatial reasoning, 0.42 for adolescent vocational interest, 0.46 for neuroticism, 0.50 for verbal reasoning and 0.52 for general intelligence. [Data based on Plomin, Owen, McGuffin 1994 *Science*:264:1733]. Cognitive abilities are also studied as part of the developmental genetic pattern (longitudinal genetic analysis). Multivariate genetic analysis determines the covariance (►correlation) among multiple traits. Although some genetic effects are specific to certain abilities, the majority of the genetic components have overlapping effects. The studies must also consider in assessing behavioral, cognitive genetic traits that form a continuum and the anomaly in a proband or several individuals may be just the extreme form of a normally existing behavioral pattern. Behavioral traits in general have about 50% or more environmental components. These effects include family relationships and changes in such relationships (e.g., divorce, death, accidents), social environment (economic status, schools, drug use, neighborhood), etc. The quantitative genetic approaches assumes that behavioral traits are complex and are the end product of cooperative action of individual genes, expressed as a phenotypic class rather than one gene-one disorder (OGOD). Some behavioral anomalies may show cosegregation with DNA markers such as those used in QTL analysis. Some mental anomalies, such as phenylketonuria (single recessive defect in phenylalanine hydroxylation) may account for about 1% of the affliction in mental asylums (►the fragile-X syndrome). Over 100 single gene determined human diseases include mental retardation as part of the syndromes. Defects in the X-chromosomally encoded gene product mitochondrial enzyme, monoamine oxidase A (MAOA) was attributed to violent behavior and also to schizophrenia. MAOA degrades serotonin, dopamine and norepinephrine. ►behavior genetics, ►cognitive abilities, ►human intelligence, ►ethology, ►self-destructive behavior, ►personality,

►MAOA, ►homosexuality, ►aggression, ►autism, ►dyslexia, ►morality, ►instinct, ►cocaine, ►serotonin, ►dopamine, ►norepinephrine, ►heritability, ►QTL, ►determinism, ►differential psychology

Behcet Syndrome (TAP): This rare disorder is characterized by mouth and genital inflammation in humans. It is probably autosomal dominant.

Behr Syndrome: The disorder leads to recessive infantile optical nerve atrophy. ►optic atrophy

BEL: ►copia

Bell Curve: ►normal distribution

Bellevia: This is a subspecies of lilies ($2n = 8$ or 16) with large and well stainable chromosomes.

Bellophage: Refers to a 1-kb RNA phage, encoding a nucleocapsid protein, a replicase component and an integrase. It has some retroviral-like properties. The small replicase binds to the host DNA polymerase and modifies it in such a way that the enzymes act as an RNA-directed DNA polymerase. Assisted by the integrase, the DNA formed is inserted into the host genome as a prophage. The nucleocapsid, because of its leucine zipper motif, can associate with its helper phage. The helper is originally the *Salmonella* phage Ω but it may recruit for this function adenovirus or influenza virus if mutation alters the leucine zipper. In chickens and some apes the provirus integrates into the mtDNA rather than into the nucleus. Thus it opens the possibilities of inserting foreign DNAs into the mitochondria and chloroplasts for genetic engineering. ►viral vectors, ►transformation of organelles, ►integrase, ►leucine zipper

BEM1: This protein with SH3 domain is involved in signal transduction. ►SH3, ►signal transduction

Bematistes pongei: This is an African butterfly mimicked by *Papilio dardanus*. ►Batesian mimicry

Bence-Jones Protein: Some immunoglobulin heavy chain diseases (HCD) such as the lymphoproliferative neoplasms may only contain the antibody heavy chains (IgM, IgG, IgA), and even those are truncated and are deficient in most parts of the variable region. The γ and α type HCD cells synthesize no light chains but the μ HCD cells secrete an almost normal light chain that is detectable in the urine and it is called Bence-Jones protein. Some of the bone marrow cancer (myeloma) patients also discharge Bence-Jones protein in their urine. These light chain immunoglobulins are generally homogeneous because they are the products of a clone of cancer cells and were historically useful to obtain information on the antibody structure. ►myeloma, ►monoclonal antibody, ►immunoglobulins, ►antibody; Beetham R 2000 *Ann Clin Biochem* 37(5):563.

B

Beneficial Mutation: The majority of new mutations are less well adapted than the prevailing wild type allele in a particular environment or at best they may be neutral. Beneficial mutations are rare because during the long history of evolution the possible mutations at a locus had been tried and the good ones preserved. Nevertheless, if a new mutation has 0.01 reproductive advantage, the odds against its survival in the first generation is $e^{-1.01} = 0.364$. Its chances to be eliminated by the 127th generation are reduced to 0.973 compared to a neutral mutation that would be eliminated by a chance of 0.985. Even mutations with an exceptionally high selective advantage may have a good chance to be lost ($e^{-2} \cong 0.1353$). Under normal conditions the selective advantage(s) is very small and the chance of ultimate survival is $(y) = 2s$ and the chance of extinction is $(l) = 1 - 2s$. In order that the mutation would have more than 50% probability of survival, the requisites must be $(1 - 2s)n < 0.5$ or $(1 - 2s) > 2$. Hence, $-n \ln((1 - 2s)) > \ln 2$ or approximately $-n(-2s) > \ln 2$, and therefore $n > (\ln 2)/2s$ or $\cong (0.6931)/2s$. If $(s) = 0.01$ and $(n) =$ number of mutations, (n) must be larger than $0.6931/(2 \times 0.01) \cong 34.66$. In other words, at least 35 mutational events must take place with at least 1% selective advantage of the mutants over the wild type that one would ultimately survive. If the rate of mutation is 10^{-6} , nearly a population of 35 million may provide such a mathematical chance. Under evolutionary conditions neutral or even deleterious mutations may make it (succeed) by random drift or chance in small populations. ►mutation neutral, ►mutation rate, ►mutation spontaneous, ►mutation in human populations; Fisher RA 1958 The genetical theory of natural selection, Dover, UK; Dobzhansky T, Spassky B 1947 Evolution 1:191; Miura T, Sonigo P 2001 J Theor Biol 209:497.

Benign Hereditary Chorea: This disorder refers to dominant childhood chorea encoded at 14q. ►chorea

Benton-Davis Plaque Hybridization: This process involves the selection of recombinant bacteriophages on the basis of DNA hybridization with ^{32}P probes on an appropriate (nitrocellulose or nylon) membrane. For the screening of a mammalian or other large library, hundreds of thousands of recombinants need to be screened. In a 150 mm Petri dish 5×10^4 plaques may be used. ►DNA hybridization, ►Grunstein-Hogness screening, ►DNA library, ►recombination molecular mechanisms prokaryotes, ►plaque, ►plaque-forming unit; Benton WD, Davis RW 1977 Science 196:180; Lewis JA et al 1983 Mol Cell Biol 3:1815.

Benzimidazoles: These are tubulin-binding/depolymerizing chemicals used as herbicides (trifluralin, oryzalin) or fungicides (benomyl). The oral dose of LD50 for mouse is ~ 2910 mg/kg. ►tubulin

Benzo(a)Pyrene: This is a highly carcinogenic polycyclic hydrocarbon generated by combustion at relatively lower temperatures by polymerization of organic material (see Fig. B29). It is present in automobile emissions, burning of coal, cigarette smoke, fried and grilled meat (in charbroiled T-bone steaks more than 50 $\mu\text{g/kg}$ has been detected, etc.). It has been estimated that 13,000 ton is annually released into the world's atmosphere by these processes. A single 0.2 mg intra-gastric dose per mouse, resulted in 14 tumors in five of the 11 animals treated. Exposure of the skin and inhalation of the fumes substantiated high and rapid carcinogenicity. It is also a promutagen requiring metabolic activation in *E. coli*, yeast, *Drosophila*, various rodents and the plant *Arabidopsis*. Benzo(a)pyrene forms adduct not only with guanine by binding to the N2 position, but also with deoxyadenosine. It also leads to sister chromatid exchange and the formation of micronuclei. Exposure to benzo(a)pyrene results in the expression of cytochrome P450 (cyp1a1) in the skin and liver of mice if the aryl hydrocarbon receptor (AhR) is active. Cyp1a2 gene expression did not need AhR. For carcinogenesis by benzo(a)pyrene AhR is a requisite. ►environmental mutagens, ►carcinogens, ►Ames test, ►bioassays in genetic toxicology, ►sister chromatid exchange, ►micronucleus formation as a bioassay, ►adduct, ►cytochromes; arylhydrocarbon receptor; Chiapperino D et al 2002 J Biol Chem 277:11765.

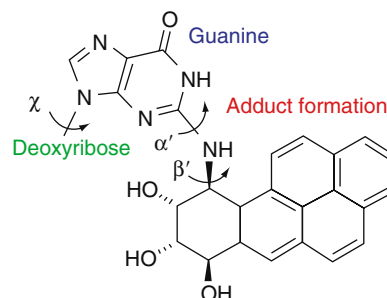


Figure B29. Benzo(a)Pyrene

Benzyladenine (6-benzylaminopurine): ►plant hormones

BER (base excision repair): ►DNA repair, ►excision repair

Berardinelli Disease: ►lipodystrophy familial

Berardinelli-Seip Congenital Lipodystrophy: This condition is characterized by recessive defects in seipin, an integral membrane protein of the endoplasmic reticulum, leading to neurodegeneration. The symptoms are somewhat similar to those of the Silver syndrome as the same region in human chromosome 11 is involved. ►spinal muscular atrophy, ►Silver syndrome, ►lipodystrophy congenital; Windpassinger C et al 2004 Nature Genet 36:271.

Bergamottin: This is one of the several structurally and functionally related derivatives of furanocoumarins affecting +/- drug transport. It is present in citrus fruits (grapefruit juice) and other natural products (see Fig. B30). ►grapefruit; Ohnishi A et al 2000 British J Pharmacol 130:1369.

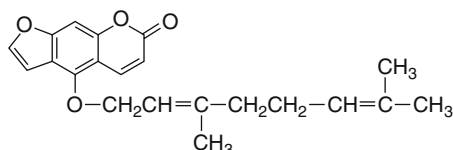


Figure B30. Bergamottin

Bermuda Standard: Refers to the 1997 agreement at the 2nd International Strategy Meeting of the human genome sequencing project that provides quality standards. The goals included accuracy at the 1×10^{-4} level of nucleotides and specifying the principles of various technical levels of operations, e.g., using the PHRED and PHRAP computer programs, and restriction enzymes. It also spells out some principles of etiquette. ►human genome projects, ►PHRAP, ►PHRED; see in AltaVista: <http://www.gene.ucl.ac.uk/hugo/bermuda2.htm>.

Bernard-Soulier Syndrome: This refers to 22q11.2 and 17pter-p12 recessive dysfunction of the platelets and thrombocytopenia. It is a potentially lethal bleeding disease. A platelet membrane receptor, glycoprotein Ib-IX-V is absent and the platelets do not agglutinate by interaction with the von Willebrand plasma factor. ►thrombocytopenia, ►platelet, ►von Willebrand disease; Ludlow LB et al 1996 J Biol Chem 271:22076.

Bernoulli Process: Independent experiments, which provide only two outcomes, yes or no, success or failure are called Bernoulli trials, and the two-event classes and their probabilities are called Bernoulli process where p = probability of success and $1 - p = q$ = probability of failure. If in a sequence of 10 trials there are 4 successes, the probability of that sequence is $p^4 q^6$; if

$p = \frac{2}{3}$ then the probability of the sequence becomes

$$\left(\frac{2}{3}\right)^4 \left(\frac{1}{3}\right)^6$$

The general formula becomes:

$$P(r \text{ success} | N, p) = \binom{N}{r} p^r q^{N-r} \quad \{1\}$$

where p = probability of success, r = the exact number of successes and N = the number of independent trials. If it is assumed that one can observe a monogenic segregation where the penetrance of the mutant class

is reduced from 25% to 20%, then the probability of finding a recessive mutant among 3 individuals will be according to $\{1\}$:

$$\begin{aligned} P(1 \text{ mutant among 3 individuals}) \\ &= \binom{3}{1} (0.20)^1 (0.80)^2 \\ &= \left(\frac{3!}{2!(2-1)!}\right) 0.2 \times 0.64 = 0.384 \end{aligned}$$

If the population is increased to say, 210, the chances of finding a mutant increase to 70.

►binomial probability, ►inference

BERT (background equivalent radiation time): If a diagnostic X-ray exam uses 360 mrem it corresponds to 1 BERT/year (approximate average in the USA). Sources contributing to the natural background (in mrem) are: radon (200), cosmic sources (100), medical treatment (39), consumer and industrial products (11), air travel (6) and nuclear industry (<1). The total may vary, however, from 100 to 600 mrem or even more at certain locations. The general public usually overestimates the risk of the nuclear industry and underestimates that from medical diagnosis and treatment. ►rem, ►radiation hazard assessment, ►cosmic radiation, ►risk

Berylliosis (CBD): This is a granulomatous (nodular inflammation) lung disease among people exposed to beryllium dust. Homozygosity of a rare major histocompatibility allele (MHC) predisposes certain individuals to this disease. ►MHC

Best Disease: ►macular dystrophy

BeT (best hit): This is a feature of orthologous sequences displaying homologies among individual genes (COGs) in different species. ►COG

Beta Barrel: ►barrel

Beta Blocker (beta adrenergic antagonist): This drug reduces blood pressure by slowing down the heart rate.

Beta Breaker Amino Acids: These disrupt beta sheets highly likely (Asp, Glu, Pro) or less frequently (Gly, Lys, Ser). ►protein structure, ►prions; Adessi C et al 2003 J Biol Chem 278:13905.

Beta Complex: Refers to one of the alternately distributed translocation complexes of the plant *Oenothera*. ►alpha complex alternative, ►multiple translocations, ►complex heterozygote

Beta Distribution: This distribution is very similar to the binomial probability function. This distribution is continuous whereas the binomial distribution is discrete. $f(x) = \frac{x^{\alpha-1}(1-x)^{\beta-1}}{B(\alpha, \beta)}$. ►binomial distribution

Beta Galactosidase: ►galactosidase; ►Lac operon

B

Beta-Lipoprotein (apolipoprotein, 2p24): This is a component of the low-density lipoprotein fraction (LDL) in the plasma. The ApoB-48 fraction is made in the gut, the ApoB-1000 in the liver by differential processing of the transcript of the same locus. [▶hypobetalipoproteinemia](#), [▶abetalipoproteinemia](#), [▶hyperbetalipoproteinemia](#)

Beta Particles: These electrons are emitted by radioactive isotopes; their mass is 1/1837 that of a proton. The negatively charged form of it is an electron whereas the positively charged is a proton. Beta particles have no independent existence; they are created at the instance of emission. In the biological laboratory the most commonly used isotopes emitting β radiation (with energy in MEV) are H3 (0.018), C14 (0.155), P32 (1.718), S35 (0.167), I131 (0.600 and 0.300 but emits also γ radiations of various energy levels). The mean length of the path of H3 is about 0.5 μ m and that of P32 is about 2600 μ m. [▶linear energy transfer](#), [▶isotopes](#)

Beta Sheets: [▶protein structure](#)

Beta vulgaris: Refers to beets (*Chenopodiaceae*) having basic chromosome number 9. Included in this group are sugar beets, fodder beets, mangold and chards which are all-important food and feed crops. Sugar beets represent a glowing example of the success of selective plant breeding by increasing the sugar content (about 2% in the mid-eighteenth century) by over 10-fold in some modern varieties. The most productive current varieties display triploid heterosis and improved disease resistance and the monogerm “seeds” facilitate mechanization of cultivation, etc. [▶heterosis](#), [▶triploid](#), [▶monogerm seed](#)

Betel Nut (*Arecia catechu*): This seed palm tree is used as a stimulant; $2n = 4x = 32$.

Bet-Hedging: Sexually mature individuals reduce their reproductive potentials due to environmental circumstances. (Menu F et al 2000 Am Nat 155:724).

Bethlem Myopathy: This is a dominant human disorder involving contractures of the joints, muscular weakness and wasting. It is associated with mutations of collagen type VII genes in human chromosomes 21q22.3 and 2q37. [▶collagen](#), [▶laminin](#)

BEV: (Baculovirus expression vector): This is a potential tool to control insect populations by biological means. [▶baculovirus](#), [▶biological control](#), [▶viral vectors](#)

bFGF: Refers to the basic fibroblast growth factor.

BFP (blue fluorescent protein): This is similar to GFP (green fluorescent protein). Excitation at 368 nm causes light emission at 445 nm, which excites the

Ser65Cis mutant of GFP and causes light emission at 509 nm. [▶aequorin](#), [▶EGFP](#)

β -Galactosidase: This enzyme (lactase) splits the disaccharide lactose into galactose and glucose. It can also act on some lactose analogs, e.g., on ONPG (o-nitrophenyl- β -D-galactopyranoside). This substrate (10–3 M or less) when exposed to active enzymes (1010 molecules/mL) yields a yellow product (that has an absorption maximum at 420 nm) and can be used to measure the activity of the enzyme. In cells grown in A medium and with Z buffer the activity of galactosidase is determined by the formula:

$$> 1000 \times \frac{OD_{420} - (1.75 \times OD_{550})}{tx(0.1 \times OD_{660})}$$

where OD is optical density at the wavelength indicated, and t is time of the reaction run in minutes. On a Petri dish the activity of β -galactosidase is detected on EMB agar (containing eosin yellow, methylene blue and lactose) and in case the sugar is fermented, a dark red color develops. Bacterial galactosidase is an inducible enzyme and induction takes place by allolactose that is formed upon the action of the residual few galactosidase molecules in the non-induced cells. A gratuitous inducer (induces synthesis although the enzyme itself is not a substrate) is isopropyl- β -D-thiogalactoside (IPTG). Constitutive mutants of the *E. coli* z gene can be identified on Xgal media containing 5-bromo-4-chloro-3-indolyl- β -D-galactoside dissolved generally in dimethylformamide (20 mg/mL). This compound is not an inducer of the enzyme but it is cleaved by it and thus a blue indolyl derivative is released. [▶Lac operon](#), [▶galactosidase](#)

BGH: [▶bovine growth hormone](#)

β -Glucuronidase: [▶GUS](#)

BH: [▶BAK](#)

BHK: This refers to the baby hamster kidney cell; cultured fibroblasts of the Syrian hamster. [▶hamster](#)

bHLH (basic helix-loop-helix protein): [▶helix-loop-helix](#)

b/HLH/Z Motif: A basic amino acid sequence at the N terminus which is probably required for DNA binding, helix-loop-helix structure, leucine zipper. This general structure is widely found in biologically active proteins involved in DNA binding. [▶binding proteins](#), [▶DNA binding protein domains](#), [▶helix-loop-helix](#)

Bialaphos: This inhibitor is a glutamine synthetase normally produced by *Streptomyces hygroscopicus*.

Upon splitting off two alanine residues it is activated into phosphinotricin. ►herbicides

Biallelic: For gene expression in diploids both alleles must be present. ►allele, Karolinska Institute human bi-allelic sequence: <http://www.kisac.ki.se>.

Bi-Armed Chromosome: This has two chromatids at the opposite sides of the centromere (see Fig. B31). ►telochromosome, ►chromosome morphology

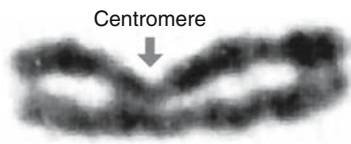


Figure B31. Bi-armed chromosome

Bias: Denotes an average error of an estimate. It is a false difference of an observation from the correct value.

BIBAC (binary bacterial artificial chromosome): This is a plant genetic expression vector that can be propagated in *Agrobacterium tumefaciens* and *E. coli* and it can deliver to plant chromosomes large (160 kb) foreign DNA sequences. ►BAC, ►Agrobacterium, ►transformation, ►vectors

bicoid (*bcd*, 3–48): This is a maternal effect mutation in *Drosophila* (see Fig. B32). The larvae lack a head, thorax, some abdominal segments and duplicate telsons. In the wild type the *bicoid* mRNA is localized in the anterior part of the egg. The mammalian homologs are Pitx1 and Pitx2. Its protein product is in the cleavage embryos in a decreasing anterior-posterior gradient. The Bcd protein—through its binding region, BBR—interacts with d4EHP (an eIF-4E related protein) binds the cap region of *cad* (*caudal*, *Drosophila* gene at 2–55) mRNA and prevents its translation (Cho PF et al 2005 Cell 121:411). Caudal mutations are homozygous lethal because of an abnormal segmentation pattern.

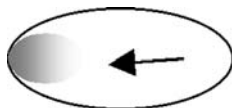


Figure B32. *bicoid*

VPS36 (a component of the ESCRT transport system) functions by binding directly and specifically to stem-loop V of the *bicoid* RNA 3' UTR through its amino-terminal GLUE domain. VPS36 localizes to the anterior of the oocyte in a *bicoid*-mRNA-dependent manner, and is required for the subsequent recruitment of Staufen (a *Drosophila* RNA-binding protein)

to the *bicoid* complex. This function of ESCRT-II as an RNA-binding complex is conserved (Irion U, Johnston D St 2007 Nature [Lond] 445:554). ►left-right asymmetry; Cha B-J et al 2001 Cell 106:36; Houchmandzadeh B et al 2002 Nature [Lond] 415:798.

BID: A pro-apoptotic protein which links proximal signals to the apoptotic pathways (FAS and TNFR). The inactive cytosolic form of BID (p22) is split into the 15-kDa fragment, tBID (truncated BID) that then moves to the mitochondria. Its BH3 domain oligomerizes with BAK and cause mitochondrial dysfunction and the release of cytochrome c. Post-proteolytic *N*-myristoylation triggers the BID-induced apoptosis. When ATM (ataxia telangiectasia mutated) and the related (ATR) kinases phosphorylate BID it can cause cell cycle arrest or by acting on BAX and BAK pro-apoptotic proteins induce apoptosis (Kastan MB 2005 Nature [Lond] 437:1103). One study concluded that Bid has no role in DNA damage or replicative stress-induced apoptosis or cell cycle arrest (Kaufmann T et al 2007 Cell 129:423). ►apoptosis, ►ATM, ►ATR, ►BAK, ►BAX, ►myristic acid, ►Bcl; Wei MC et al 2000 Genes Dev 14:2060; Zha J et al 2000 Science 290:1761.

BiDiI (isosorbide dinitrate and hydralazine): This vasodilator drug is manufactured by Nitro Med, Inc (Bedford, MA), and it is particularly effective in heart failure in the case of some Afro-American individuals with ventricular ejection problems. The label of “ethnic/racial drug” is controversial. ►race, ►ethnicity; Wolf SM 2005 Nature Genet 37:789.

Bidirectional Replication: From the replicational origin the replication moves in opposite directions in the DNA (see Fig. B33). ►replication bidirectional, ►replication fork

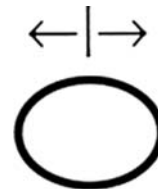


Figure B33. Bidirectional

Bidirectional Gene Organization: Genes in large genomes are not dispersed uniformly but form clusters. Among the 144 and 319 known genes of human chromosomes 21 and 22, 22% and 18%, respectively, are divergently arranged within ~1 kb from each other whereas the average spacing distance for all genes is ~85 kb. In most cases the spacing islands of the bidirectional genes carried a CpG island that

B

generally overlapped partially or entirely the first exon or rarely more than one. This organization has regulatory advantage. A study of 23,752 human genes revealed that more than 10% of the genes whose transcription start sites are separated by less than 1000 base pairs are transcribed bidirectionally (Trinklein ND et al 2004 Genome Res 14:62). ▶**operon**, ▶**clustering**; Adachi N, Lieber MR 2002 Cell 109:807.

BIDS: ▶**hair-brain syndrome**

Biennial: Refers to plants with a life span of two years yet the total period is less than two years. These plants germinate in fall and mature and die before the end of the following year.

Bifunctional Antibody: This carries an antibody variable region fragment that secures its ability to recognize certain molecules (antigen). In addition, a fused heterologous component conveys either enzyme activity or carries a toxin or a pro-drug, etc. Such a complex can home in on the cognate molecules and destroy or alter them according to the specificity of the heterologous portion. ▶**bispecific antibody**

Bifunctional Enzymes: These have apparently evolved with the potential to adapt the amino and carboxy terminal tracts to fulfill the metabolic requirements of different tissues. ▶**one gene—one enzyme theorem**; Kitzing K et al 2001 J Biol Chem 276:42658.

Bifunctional Mutagen: ▶**functionality of mutagens**

Big Blue: A commercially available mouse strain that carries the bacterial *LacI* gene (in about 40 copies) as a stably integrated lambda vector, thus it is very useful for the laboratory detection of in vivo mutagenic/carcinogenic effects. The transgene is extracted from mice and with the aid of the λ shuttle vector introduced into *E. coli* bacteria. In the presence of Xgal substrate mutations in the *LacI* gene give rise to blue plaques because of the loss of inhibition of the galactosidase gene, *LacZ*. Thus, mutations in the prokaryotic gene in the animals, activated by the animal metabolism, are screened in bacteria because of the convenience of detection in the prokaryotic system. This system permits the detection of mutation in different animal tissues, e.g., liver, brain, at different developmental stages and under different conditions. ▶ **β -galactosidase**, ▶**Xgal**, ▶**Lac operon**, ▶**Muta Mouse**, ▶**host-mediated assay**; Gossen JA et al 1989 Proc Natl Acad Sci USA 86:7971; Nohmi T et al 2000 Mutation Res 455:191.

BigSeq: A computer program with a similar purpose as Mask, it contains information on millions of contigs. ▶**contig**, ▶**physical map**

Bikont: This eukaryote has two cilium-bearing centrioles (nucleating cone of microtubules) such as plant and protozoa. Unikonts have one cilium on the centriole such as animals, fungi and amoebazoa. ▶**cilia**, ▶**centriole**; Richards TA, Cavalier-Smith T 2005 Nature [Lond] 436:1113.

Bilateral Symmetry: ▶**symmetry**, ▶**zygomorphic** (see Fig. B33), ▶**retinoic acid**



Figure B34. Bilateral symmetry

Bilayer: A bilayer of membranes consists of amphipathic lipids (and proteins) and the non-polar phase faces inward. The majority of cellular membranes are double membranes. ▶**amphipathic**

Bile Salts: These are detergent-type steroid derivatives involved in digestion and absorption of lipids. ▶**lipids**, ▶**cholesterol**; Russel DW 2003 Annu Rev Biochem 72:137.

Bilineality: More than a single locus determines a particular trait and they may segregate independently making chromosomal localization, by genetic techniques, very difficult.

Bilirubin: This bile pigment is formed by the degradation of hemoglobin and other heme containing molecules such as cytochromes. It is circulated in the blood as a complex with albumin and when deposited in the liver it forms bilirubin diglucuronide. It may arise from biliverdin, a breakdown product of heme, through reduction. Bilirubin is a strong antioxidant and may cause brain damage in neonatal jaundice. ▶**hyperbilirubinemia**, ▶**jaundice**, ▶**cholestasis**, ▶**Alagille syndrome**, ▶**Byler disease**, ▶**steroid dehydrogenase**, ▶**steroid reductase**, ▶**Gilbert syndrome**, ▶**cerebral xanthomatosis**, ▶**Crigler-Najjar syndrome**, ▶**Dubin-Johnson syndrome**; Tomaro ML, del C Battle AM 2002 Int J Biochem & Cell Biol 34:216.

Bim: This is a member of the BCL family of proteins. The proteins sharing the Bcl-2 homology domain BH3 promote apoptosis in contrast to other members of the family (e.g., Bax, Bak) that are anti-apoptotic. ▶**BCL**, ▶**BAX**, ▶**BAK**; Chen D, Zhou Q 2004 Proc Natl Acad Sci USA 101:1235.

BimC: This family of motor proteins of the kinesin group is involved in the separation of the mitotic chromosomes by the spindle. ▶motor proteins, ▶spindle, ▶monastrol, ▶mitosis

BimD: A negative regulator of the cell cycle progression in *Aspergillus*, it mediates recombination and chromosome morphology.

BimE: This is an *Aspergillus* protein subunit of the APC complex, it is homologous to APC1. ▶APC, ▶cell cycle

Bimodal Distribution: In this case when the population is represented graphically, it displays two peaks (see Fig. B35). Or, in general, the data are clustered in two modes, in two classes.



Figure B35. Bimodal distribution

BIN: A group of markers (microsatellite DNA) mapped to the same location.

BIN1 (box-dependent Myc interacting protein-1): This is a tumor-suppressor protein (human chromosome 2q14) that interacts with the Myc oncoprotein. It is related to amphiphysin that serves a similar purpose in breast cancer and to the RVS167 cell cycle control gene of yeast. ▶MYC, ▶tumor suppressor; DuHadaway JB et al 2001 Cancer Res 61:3151.

Bin2 (Cct3, TriC): This is synonymous with the CCT γ chaperonin subunit. ▶chaperonins

Bin3 (Cct2): This is synonymous with the CCT β subunit of chaperonins. ▶chaperonins

Binary: Refers to any condition, choice or selection with two possibilities or a numeration system with a radix of 2. ▶radix, ▶founder cells

Binary Variables: These variables are either yes or no (0 or 1); their analysis can be performed by logistic regression or Bernoulli process. ▶logistic regression, ▶Bernoulli process

Binary Gene Expression: The expression is full or none.

Binary Fission: This means splitting into two parts (see Fig. B36). Bacteria, chloroplasts and mitochondria that do not have a mitotic mechanism reproduce in this way after DNA replication has been completed.



Figure B36. Binary fission

Binary Vector: Refers to *Agrobacterium* carrying two plasmids, one has the T-DNA borders and other sequences (special genes, selectable markers) that will integrate into the transformed cell's chromosomes, the other is a helper plasmid carrying the Ti plasmid virulence genes, required for transfer but no part of the latter plasmid is integrated into the host genome during transformation. ▶T-DNA, ▶virulence genes of *Agrobacterium*, ▶transformation genetic, ▶cointegrate vector, ▶agrobacterial vectors; Bevan M 1984 Nucleic Acids Res 12:8711.

Binary Targeting: The specific recombinase gene (*Cre*, *Flp*) is carried by one of the mating pairs and the site-specific recombination site (*loxP*, *FRT*) is present in the other partner. ▶targeting genes, ▶Cre/LoxP, ▶Flp/FRT

Binase: This is a 12-kDa dimeric ($\alpha\beta$) endonucleolytic ribonuclease binding to N-1 of 3'-guanine monophosphate. It has 82% amino acid identity with barnase. ▶barnase; Wang L et al 2001 Proc Natl Acad Sci USA 98:7684.

BIND (Biomolecular Interaction Network Database): <http://www.xml.com/pub/r/1290>.

Bindin: An acrosomal protein that mediates the species-specific binding between gametes during fertilization. Apparently the egg surface has a species-specific bindin receptor. ▶fertilization, ▶acrosomal process, ▶sperm, ▶acrosome; Glaser RW et al 1999 Biochemistry 38:2560; Kamei N, Glabe CG 2003 Genes Dev 17:2502.

Binding Energy: This is derived from the non-covalent interaction between ligand and receptor, enzyme and substrate. ▶ligand, ▶receptor

Binding Proteins: These proteins are of a great variety and they control gene expressions at the level of transcription (transcription factors, hormones, heat-shock proteins, etc.). Most of them bind to upstream consensus sequences. The cap-binding proteins regulate the stability of the mRNA. Some of them are transcription termination factors, such as rho in bacteria or Sal I box binding proteins in the mouse. To study their position and function at the DNA level, footprinting or protein microarrays is undertaken (Ho S-W et al 2006 Proc Natl Acad Sci USA 103:9940). An in vitro method for specific and sensitive solution-phase analysis of interactions between proteins and nucleic acids in nuclear extracts is based on the proximity ligation assay. The reagent consumption is very low, and the excellent sensitivity of the assay enables analysis of as few as 1–10 cells. The method appears highly reproducible, quantitative, and in good agreement with both EMSA (electrophoretic mobility shift assay) and predictions obtained by using a motif finding software. This

B

assay can serve as a valuable tool for characterizing in depth the sequence specificity of DNA-binding proteins and for evaluating the effects of polymorphisms in known transcription factor binding sites Gustafsdottir SM 2007 Proc Natl Acad Sci USA 2104:3067.

Some proteins bind to the cellular membranes and control imports and exports, others mediate signal transduction. These proteins may have a combinatorial hierarchy and are thus capable of influencing a multitude of processes in the cell, far in excess of their individual numbers. Proteins may bind to the DNA in a non-specific manner and this property facilitates the binding to specific nucleotide sequences. Non-specific binding—by electrostatic forces—facilitates the recognition of the specific sites much faster than mere diffusion (Kalodimos CG et al 2004 Science 305:386). Gene expression is controlled primarily by proteins binding non-covalently to the DNA. In general, there is no particular specificity of recognition between amino acids and DNA bases yet some data indicate structural preferences (Mandel-Gutfreund Y et al 1995 J Mol Biol 253:370; Kono H, Sarai A 1999 Proteins 35:114). The interaction is the result of hydrogen bonding between polar atoms of the protein and nucleic acid bases. Therefore unnatural amino acid substitutions may alter the binding specificity (Maiti A, Roy S 2005 Nucleic Acids Res 33:5896). The interaction is not based on one to one relation rather a particular amino acid is more frequently distributed around a particular DNA base. Transcription factors recognize multiple genes, generally within families and this feature is conserved through evolution. Highly conserved bases seem to interact more specifically with particular protein residues. The binding may also be affected by changes in conformation due to mutation at a remote amino acid site. Through laboratory design binding proteins can be created for the regulation of gene function, which is of significance in biotechnology (Desjarlais JR, Berg JM 1994 Proc Natl Acad Sci USA 91:11099; King CA, Berg JM 1995 J Mol Biol 252:1). ▶transcription factors, ▶signal transduction, ▶DNA-binding protein domains, ▶single-strand binding protein, ▶footprinting, ▶EMSA, ▶protein arrays, ▶affinity-directed mass spectrometry, ▶UAS, ▶methyltransferase DNA, ▶protein binding, ▶threading, support vector machine based procedure for predictions: Bhardwaj N et al 2005 Nucleic Acids Res 33:6486; Ren B et al 2000 Science 290:2306; Verdine GL, Norman DPG 2003 Annu Rev Biochem 72:337; Sarai A, Kono H 2005 Annu Rev Biophys Biomol Struct 34:379; DNA and RNA binding server: <http://bioinformatics.ksu.edu/bindn/>, protein-protein binding site prediction: <http://biportal.weizmann.ac.il/promate/>.

Binet Test: ▶human intelligence

Binomial Coefficient: ▶binomial probability

Binomial Distribution: A distribution that is useful in genetics for the direct estimation of segregation ratios in the case of dominance by expansion of $(3 + 1)^n$ where n = is the number of heterozygous loci (note: $3 + 1$ must not be added). By expansion the binomial becomes:

$$1 \times 3^n + [(n!)/1!(n-1)!] \times 3^{n-1} \\ + [n!/2!(n-2)!] \times 3^{n-2} + \dots + [n!/(n-1)!] \\ \times 3^{n-(n-1)} + 1 \times 3^{n-n}$$

The *exponent* of a base gives the number of loci with the dominant phenotype, the *power* identifies the frequency of that phenotype, and the *coefficients* show how many times—quadruple, triple, etc.—dominant phenotypic classes will be expected theoretically. The solution for 4 heterozygous pairs of alleles:

$$(1 \times 3^4) + \left(\frac{4 \times 3 \times 2 \times 1}{1 \times 3 \times 2 \times 1} \times 3^{4-1} \right) \\ + \left(\frac{4 \times 3 \times 2 \times 1}{2 \times 1 \times 2 \times 1} \times 3^{4-2} \right) \\ + \left(\frac{4 \times 3 \times 2 \times 1}{3 \times 2 \times 1 \times 1} \times 3^{4-3} \right) + (1 \times 3^{4-4}) \\ = (1 \times 3^4) + \left(\frac{24}{6} \times 3^3 \right) + \left(\frac{24}{4} \times 3^2 \right) \\ + \left(\frac{24}{6} \times 3^1 \right) + (1 \times 3^0) \\ = (1 \times 81) + (4 \times 27) + (6 \times 9) \\ + (4 \times 3) + (1 \times 1)$$

Translated into genetic language in the case of an Aa Bb Cc Dd heterozygote's F₂ progeny the phenotypic classes will be:

81 ABCD, [27 ABCd, 27 ABcD, 27 AbCD, 27 aBCD], [9 ABcd, 9 AbCd, 9 AbcD, 9 aBCd, aBcD, 9 abCD], [3 Abcd, 3 aBcd, 3 abCd, 3 abcD], [1 abcd] or

81: 108 (4 × 27): 54 (6 × 9): 12 (4 × 3): 1

For the calculation of genotypic classes among the segregants see trinomials and multinomials.

▶Mendelian segregation, ▶Pascal triangle

Binomial Nomenclature: ▶taxonomy

Binomial Probability: P is the complete binomial probability function whereas the $n!/(x!(n-x)!)$ is the binomial coefficient, an integer that shows how many ways one can have x combinations of n , and $p = 0.75$ and $q = 0.25$ (because of the 3:1 segregation). In genetic experiments this shows—if we have

n = independently segregating gene loci, and the inheritance is dominant—how many ways can have x combinations of n ; e.g., if we deal with $n = 5$ loci and we wish to know the chance that at 3 ($=x$) loci the dominant phenotype would appear is then:

$$p = \binom{n}{x} p^x q^{(n-x)} \text{ and } \binom{n}{x} = \frac{n!}{x!(n-x)!}$$

$$[5!/(3!2!)] = (0.75^3)(0.25^2) \cong 0.26367$$

The binomial distribution is obtained from the expansion of the binomial terms $(p + q)^n$; its standard deviation $\sigma = \sqrt{\frac{pq}{n}}$ and $p + q = 1$; n = is the exponent.

►Pascal triangle, ►transmission disequilibrium, ►binomial distribution, ►trinomial distribution, ►Bernoulli process

Binuclear Zinc Cluster: A domain of a DNA-binding transcriptional activator containing 2 Zinc ions about 3.5 Å apart and regulated by 6 cysteines. ►Zinc finger

Bioarrays: Methods/software systems for analysis of microarray hybridization and other high throughput platforms. (Troen C et al 2006 Methods Enzymol 411:99).

Bioassays (biological assays): Used for determining the biological effect(s) of chemicals, drugs or any other factor on live animals, plants, microorganisms and cells.

Bioassays in Genetic Toxicology: Bioassays have been designed to assess mutagenic (and indirectly carcinogenic) properties of factors that human, animal, plant and microbial populations may be exposed to. Their range varies from testing chromosome breakage and point mutations in a wide variety of organisms using different endpoints. All the different procedures cannot be discussed or even enumerated here but the major types of tests include: (i) excision repair, (ii) reversion studies in *Salmonella* and *E. coli*, (iii) sister chromatid exchange, (iv) mitotic recombination, (v) host-mediated assays, (vi) specific locus mutation assays, (vii) micronuclei formation, (viii) chromosome breakage, (ix) sex-linked lethal assays, (x) unscheduled DNA synthesis, (xi) sperm morphology studies, (xii) cell transformation assays, (xiii) dominant mutation, (xiv) somatic mutation detection, (xv) *Arabidopsis* mutagen assays, (xvi) human mutagenic assays, (xvii) mitotic recombination as a bioassay in genetic toxicology, (xviii) *Tradescantia* stamen hair somatic mutation assay is popular for monitoring environmental pollution, (xix) zebrafish assay for mutagens in aquatic media, (xx) mouse lymphoma test. (see the essential features of these tests under the separate entries, ►transgene mutation assay, ►mutation

detection, ►hemiclonal, ►genotoxic chemicals, ►Big Blue ►MutaTM Mouse, ►toxicogenomics; Waters MD, Fostel JM 2004 Nature Rev Genet 5:936.

Bioavailability: The portion or fraction of drugs applied that can be accessed by living cells.

Biobank: A repository that is supposed to collect and maintain information on gene–environment relations in disease, based on large population studies.

Bio-Bar Code, Nano-Particle Based: ►nanoparticle-based bio-bar code

Biocatalysts: Enzymes mediating metabolic processes. They have numerous industrial applications and with the aid of molecular biotechnology means exist for improvement of their efficiency. (Burton SG et al 2002 Nature Biotechnol 20:37).

Biochemical Engineering: Synthesizes proteins and other new molecules in the laboratory without the direct involvement of the classical biosynthetic pathway. The products may have biological value in nutrition, therapeutics, etc. ►antibody engineering, ►nanotechnology, ►bioreactor, ►tissue engineering; unnatural amino acids.

Biochemical Genetics: Studies the genetic mechanisms involved in the determination and control of metabolic pathways. ►inborn errors of metabolism

Biochemical Mutant: The chemical basis of the mutant function is identified. ►auxotroph

Biochemical Pathway: The chemical steps involved in a biological function are represented in a sequence. Enzymes encoded by separate genes usually mediate the individual steps. ►One gene–one enzyme theorem, ►genetic networks, ►transcriptome, Rison SC, Thornton JM 2002 Current Opin Struct Biol 12:374.

Biochips: ►DNA chips, ►protein chips, ►electrical biochip

Biocoenosis (biocenosis): Different organisms living together within the same environment; some of them may be dependent on others for survival or interact in various ways.

Biocomputer: Use approaches different from the digital electronic computing. The input, output software and the hardware are biological molecules without electronic representation. This approach holds promise for the identification of disease conditions. ►DNA computer; Adar R et al Proc Natl Acad Sci USA 101:9960.

Bioconductor: Software for genome analysis (<http://www.bioconductor.org>).

Biocrystalization: DNA may be protected in prokaryotes by co-crystallization with the stress-induced protein Dps. Dps dodecamers protect against

oxidative damage (and nucleases) in a manner similar to ferritins. ► **ferritin**

B

BioCyc: A collection of a set of 160 pathway/genome databases (PGDB) based on the MetaCyc database. ► **MetaCyc**, ► **Pathway Tools**, Karp PD et al 2005 Nucleic Acids Res 33:6083; 142 databases: <http://biocyc.org>; <http://www.org/open-compounds.shtml>, pathway tools for downloading: <http://biocyc.org/download.shtml>.

Biodegradation: Decomposition, destruction of substances by bacterial or other organisms. ► **oil spills**, ► **Pseudomonas**, ► **bioremediation**; <http://umbbd.ahc.umn.edu/>.

Biodiversity: See species extant: <http://www.sp2000.org/>; <http://ip30.eti.uva.nl/BIS/index.php>.

Bioengineering: The replacement of body parts by means of mechanical or biological manufactured devices. (Science 2002 vol 295:998–1031).

Bioethics: The application of ethical principles to biotechnology, medical, genetic and related fields. (► **biotechnology**, ► **embryo research**, ► **nuclear transplantation**, ► **ethics**, ► **informed consent**, ► **human subjects**; Merz JF et al 2002 Am J Hum Genet 70:965; <http://www.bioethics.net>; <http://www.hhmi.org/bioethics>); http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml; <http://www.ornl.gov/hgmis/elsi/elsi.html>; <http://www.nhgri.nih.gov/ELSI/>.

Biofilm: A community of single-cell organisms established as a surface layer with chemical communication among the components. Bacterial aggregates of single or dozens of different species (including also fungi) surrounded by foamy substance and resistant to many types of disinfectants, antibiotics or to antibodies. Within the biofilm, the bacteria may show morphological differentiation depending on actual environment. Also in these cells, different mutations may arise (Kolter R, Greenberg EP 2006 Nature [Lond] 441:300). Aminoglycoside antibiotics can induce biofilm formation and the bacteria become resistant to antibiotics. It appears that an inner membrane phosphodiesterase with substrate for cyclic di-guanosine monophosphate regulates surface adhesiveness and guanosine triphosphate, an inhibitor of this enzyme, reduces biofilm formation (Hoffman LR et al 2005 Nature [Lond] 346:1171). Cells within the biofilm differentiate differently than free-living bacteria. Polymer production suffocates neighboring non-polymer producers and it suggests that polymer secretion provides a strong competitive advantage to cell lineages within mixed-genotype biofilms and global cooperation is not required (Xavier JB, Foster KR 2007 Proc Natl Acad Sci USA 104:876). Engineered bacteriophage T7 containing a biofilm- and *E. coli*-degrading

enzyme eliminates the bacteria ~4.5 orders of magnitude more effectively than non-enzymatic procedures (Lu TK, Collins JJ 2007 Proc Natl Acad Sci USA 104:11197). The polysaccharide (alginate) film may corrode pipes, medical equipment and may be responsible for dental plaques, lung, kidney, prostate, etc. infections and inflammation. The development of the biofilm usually requires quorum-sensing signals. Some fungi (*Candida albicans*) can also form biofilm. ► **algin**, ► **quorum-sensing**, ► **cystic fibrosis**, ► **antibiotics**, ► **antibiotic resistance**, ► **aminoglycosides**; O'Toole G et al 2000 Annu Rev Microbiol 54:49; Whitely M et al 2001 Nature [Lond] 413:860.

Bio-Gel: A commercial ion exchange chromatography medium suitable for the separation of RNA from DNA, purification of oligonucleotides, linkers, etc.

Biogenesis: The cells arise only from cells rather than from non-living organic material. ► **spontaneous generation**

Biohazards: Working with pathogenic organisms or transgenic material containing potentially dangerous genes (coding for toxins). Containment (P1 to P4, the latter the most stringent) is necessary and the appropriate safety regulations must be complied with. Transgenic plants may transmit by cross-pollination the nuclear transgene (e.g., herbicide or antibiotic resistance) to other plants, including weeds. Some of this unwanted transmission problems can be prevented by using transgenic chloroplasts or mitochondria that are only maternally transmitted (Danielle H 2007 Proc Natl Acad Sci USA 104:6879). Information for particular cases can be obtained from the local biohazard committees or from National Institute of Health, Building 31, Room A452, Bethesda, MD 20205, USA. ► **biological containment**, ► **recombinant DNA and biohazards**, ► **laboratory safety**, ► **GMO**

Bioinformatics: The use of computers for developing algorithms, information gathering, storage and analysis of molecular biological data. ► **GenBank**, ► **NCBI**, ► **GSDB**, ► **databases**, ► **image analyzer**, Basset DE Jr et al Nature Genet Suppl Vol 21; Searls DB 2000 Annu Rev Genomics Hum Genet 1:251; Jenssen TK et al 2001 Nature Genet 28:21; Letovsky S (Ed) 1999 Bioinformatics. Databases and Systems 1999 Kluwer, Boston; Davidson D, Baldock R 2001 Nature Rev Genet 2:409; Yandell MD, Majoros WH 2002 Nature Rev Genet 3:601; Kanehisa M, Bork P 2003 Nature Genet 33 (Suppl.):305, <http://www.ncbi.nlm.nih.gov/Tools/index.html>, macromolecular structure, function, taxonomy, sequences: <http://www.ebi.ac.uk/msd-srv/docs/sifts>, bioinformatics assistance: <http://www.ebi.ac.uk/2can/home.html>, HSLS On-line Bioinformatics Resources Collection (OBRC)

contains annotated information and guided links to 1542 open sources bioinformatics databases and software tools: <http://www.hsls.pitt.edu/guides/genetics/obrc>.

Biolistic Transformation: It (biological-ballistic) introduces genes into the nuclei of cells (of the germline) by shooting DNA coated particles into the target cells, propelled by high-power air or helium guns. It is a most useful procedure when other methods of transformation are not sufficiently successful. It can accomplish transformation also in terminally differentiated cells and chloroplasts and mitochondria. High efficiency mitochondrial transformation (100–250 transformants μg DNA) of *Chlamydomonas reinhardtii* with linearized plasmid DNA is feasible. Gene guns are also used for cancer gene therapy and genetic immunization. ▶ [Transformation](#), ▶ [chloroplast genetics](#), ▶ [mitochondrial genetics](#), ▶ [cancer gene therapy](#), ▶ [immunization genetic](#), ▶ [Chlamydomonas](#); Klein TM et al 1987 Nature [Lond] 327:70; Maenpaa P et al 1999 Mol Biotechnol 13:67.

Biological Clock: Frequently called circadian rhythm; it measures in various organisms daily periods and responses to alternation of daily light and dark cycles. The endogenous rhythms also influence gene activity and developmental patterns. ▶ [circadian](#); <http://www.cbt.virginia.edu>.

Biological Containment: The preventive measures to avoid the spread of potentially hazardous organism outside the laboratory. Recombinant DNA-containing organisms with unknown biological impact in the environment may be prevented from spreading accidentally, by using transformation vectors that lack the *bom* and *nic* sites facilitating plasmid mobilization. The cloning bacteria may have an absolute requirement for diaminopimelic acid (lysine precursor), deficient in excision repair (*uvrB* deletion), auxotrophic for thymidine and *rec*[−] (recombination and repair deficient). Thus even after accidental escape, assuming a mutation rate of 10^{-6} for each of the 5 loci, they would require $(10^{-6})^5 = 10^{-30}$ chance to succeed in the environment. 10^{30} *E. coli* bacterial cell number has a mass of about 10^{11} metric tons. The mass of the Earth has been estimated to be 10^{20} tons. ▶ [biohazards](#)

Biological Control: Pathogens or parasites are contained by propagation of their natural enemies or by other pathogens or parasites (e.g., *Aphelinus mali*) or genetically engineered organisms. *Colletotrichum truncatum* fungus is used as weed killer bioherbicide, *Sesbania exaltata*, in various crops such as soybeans, rice and cotton. Attack of plants by armyworm (*Spodoptera exigua*) is concomitant with the oral secretion of *N*-(17-hydroxylinolenoyl)-L-glutamine

[volicitin], which triggers the emission of chemical signals by the plants that attract parasitic wasps, predators of armyworm larvae (see Fig. B37). In some instances, the parasitic wasps are attacked by bacterial symbionts of the host and the presence of the latter may also adversely affect the host's fecundity and longevity. The parasitic wasp *Trichogramma brassicae* spies on mated *Pieris brassicae* butterflies and it is attracted to the pheromone passed from the male to the female to discourage conspecific males. The small wasp (0.5 mm long) then rides on the female and when she lays eggs, the wasp parasitizes them. It is interesting that the wasps show no interest in virgin female butterflies (Fatouros NE et al 2005 Nature [Lond] 433:704). When their roots are attacked by the weevil *Diabrotica virgifera*, wild ancestors and European varieties of maize emit the sesquiterpenoid (E)- β -caryophyllene (see Fig. B38), an attractant for the entomopathogenic nematode, *Heterorhabditis megidis* and it reduces the herbivorous insect population to about half (Rasmann S et al 2005 Nature [Lond] 434:732). Although biological control is frequently considered as the safest method of protection, some biologists worry about the general environmental impact. Some of the control organisms may adversely affect useful native species. ▶ [Bacillus thuringiensis](#), ▶ [genetic sterilization](#), ▶ [Dengue virus](#), ▶ [BEV](#), ▶ [antisense RNA](#), ▶ [conspecific](#), ▶ [parasitoid](#), ▶ [aphids](#); Howarth FG 1991 Annu Rev Entomol 36:485; Pemberton RW, Strong DR 2000 Science 290:1896; Louda SM et al 2003 Annu Rev Entomol 48:365, <http://www.nhm.ac.uk/entomology/chalcidoids>; <http://ipmworld.umn.edu/>.



Figure B37. There are many types of parasitic wasps. The female insect has a long egg depository tube used for placing their eggs into the eggs of another insect

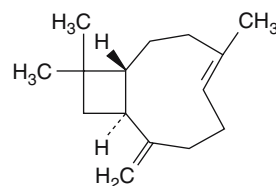


Figure B38. Caryophyllene

Biological Membranes: ►cell membranes**B**

Biological Mutagens: A large number of natural products present in different organisms may be mutagenic for others. Spontaneous mutation may be also increased by endogenous factors such as defective DNA polymerase or defects in the genetic repair system. ►mutator genes, ►transposable elements, ►transposons, ►insertional mutation, ►epigenetics

Biological Systems: ►systems biology

Biological Weapons: It may contain highly pathogenic microorganisms such as *Bacillus anthracis* (anthrax), *Corynebacterium diphtheriae* (diphtheria), *Pasteurella pestis/Yersinia pestis* (bubonic plague), *Francisella tularensis* (tularemia), and various viruses. The *Clostridium botulinum* toxin or castor bean toxin, ricin may also be very dangerous. (The Botox toxin has been used recently for the very questionable cosmetic purpose to reduce facial wrinkles by immobilizing muscles through blocking of acetylcholine at the ends of the motor nerves.) In case the genetic signature of all organisms potentially usable for biological warfare would be available, the rapid identification and effective protection may be facilitated.

The agents are categorized as A if they constitute a national hazard by their easy transmission, have major health impact, possibly increase death rates, and they potentially impacts society to a serious extent. Category B agents constitute somewhat reduced hazards, yet require enhanced surveillance and diagnostic capacities. Category C agents include new pathogens that can be modified for higher disease effectiveness and are potentially hazardous. Research on these agents requires special containment facilities. The availability of genomic sequences of the pathogens facilitates the identification of the organisms and facilitates taking effective defensive measures. ►signature of molecules, ►anthrax, ►*Yersinia*, ►tularemia, ►diphtheria toxin, ►Pox virus, ►*Clostridium botulinum*, ►ricin, ►*Francisella*, ►sarin; Stone R 2001 Science 293:414; Kortepeter MG et al 2001 J Env Health 63(6):21; Hawley RJ, Eitzen EM Jr 2001 Annu Rev Microbiol 55:235; Fraser CM 2004 Nature Rev Genet 5:23, <http://www.virology.net/garryfavwebbw.html>.

Biologics: The material is of biological nature, the processing is biological, the quality of the product is determined by biological methods.

Bioluminescence: ►luciferase, ►aequorin

Biomarker: Any product of the body (e.g., a metabolite) that may respond to adverse environmental effects (carcinogens, mutagens, etc.) or that may be specific for a biological condition, e.g., cancer, other disease,

developmental change or any other function. Biomarkers are important diagnostic and prognostic aids in health and disease. Identification of good biomarkers may facilitate the design of appropriate therapy at a particular stage of a disease. It may help to reveal effective drug targets. If good biomarkers are available, the most likely positive responses may be predicted and unresponsive individuals can be spared from the potential side effects of treatments. Biomarker availability is expected to meet the needs of personalized therapy. Unfortunately, only few effective biomarkers are available for clinical guidance. Gleevec, a tyrosine kinase inhibitor, is a very effective new class of drug against chronic myelogenous leukemia. Gefitinib, also a tyrosine kinase inhibitor capable of blocking epidermal growth factor receptor (EGFR) is used for treating non-small cell lung cancer. Japanese patients respond better to this drug because of differences in missense mutations in those populations compared to people of European descent. Trastuzumab/Herceptin is a monoclonal antibody targeting primarily a tyrosine kinase receptor encoded at 17q12 and involved in certain subtypes of breast cancer. Unfortunately, multiple genes affect the majority of cancers. Therefore only genomic analysis may provide satisfactory approach. Such studies can provide biological signatures for the disease and treatment and are in the frontline of research. The outcome of the research may be affected by genetic, developmental and environmental conditions, the methodology used (proteomics or RNA microarrays) and the statistical analysis employed (t-test or multivariate). (see Dalton WS, Friend SH 2006 Science 312:1165; ►Gleevec, ►Gefitinib, ►Iressa, ►Herceptin, ►Avastin, ►Trastuzumab, ►cancer, ►genetic medicine, ►receptor tyrosine kinases, ►Desatinib, ►Sutent, ►Lepatinib, ►biomarkers in development: http://www.imgenex.com/emarketing/083106_Tissuearray/elucidating_protein_signatures.htm).

Biomaterial: Generally synthetic substances—other than drugs—useful for biological and/or medical devices such as tissue replacement, gene delivery vehicles, diagnostic and array technologies. (see Langer R, Tirrell DA 2004 Nature [Lond] 428:487).

Biometric: An electronic code of human physical features (fingerprints, eye iris scans), and can be used for digital personal identification.

Biometry: Mathematical statistical principles applicable to the study of genetic and non-genetic variation in biology. ►quantitative genetics, ►population genetics

Biomimetic Particles: The system is based on a peptide that recognizes clotted plasma proteins and selectively homes to tumors, where it binds to vessel walls

and tumor stroma. Iron oxide nanoparticles and liposomes coated with this tumor-homing peptide accumulate in tumor vessels, where they induce additional local clotting, and thereby producing new binding sites for more particles. The system mimics platelets, which also circulate freely but accumulate at a diseased site and amplify their own accumulation at that site. The self-amplifying homing is a novel function for nanoparticles. The system enhances tumor imaging, and the addition of a drug carrier function might also be exploited (Simberg D et al 2007 Proc Natl Acad Sci USA 104:932). ►nanoparticles

Biomining: Certain bacteria obtain energy by oxidizing inorganic materials. This process may release acid, which in turn can wash out metals from ores. ►*Thiobacillus ferrooxidans* can release copper and gold, ►*Pseudomonas cepacia* may assist phosphate mining. Eventually this biotechnology may become economical, especially for low-grade ores. Some plants, e.g., Brassica spp, Impatiens spp. may accumulate gold from the soil. ►Bioremediation; Mergeay M 1991 Trends Biotechnol 9:17; Guiliani N, Jerez CA 2000 Appl Environ Microbiol 66:2318.

Biomonitoring: Surveying potential mutagens, carcinogens or other health hazards using biological means such as organismal bio-assays for mutagens, blood cells, human buccal cells, nasal mucosal cells, scalp hair follicles, sputum, detached colon cells, cervical epithelia, exfoliated bladder cells, spermatozoa, bacteria, etc. The tests may involve cytological or molecular methods. ►quantum dots

Bionics: Construction of mechanical devices with the technology of engineering and biology.

Biopanning: The selection by repeated cycles for specific peptides (phage display), interactive ligands, etc. ►phage display, ►ligand; Giordano RJ et al 2001 Nature Med 7:1249; Shadidi M, Sioud M 2004 Methods Mol Biol 252:569.

Biopharming: Producing pharmacological agents by plants and animal transgenic for special genes. ►pharming, ►plant vaccines, ►single-chain Fv fragment; Ma JK-C et al 2003 Nature Rev Genet 4:794.

Biophilia: A hypothesis suggesting an innate human tendency to focus on life and life-like processes and interest in living beings as proposed by E.O. Wilson.

Biophore: A hypothesized hereditary unit of the pre-mendelian era. ►pangenesis

Biophore: A compound or structural element of it that may exert potential biological (carcinogen) activity. ►SAR, ►CASE, ►MULTICASE

Biophysics: The theory and practice of application of physical methods for the study of biological structures (e.g., nucleic acids, proteins) and mechanisms of function (energy conversions, thermodynamics). (<http://www.biophysics.org/education/>).

Biopiracy: The use of human genomic information for commercial purposes without the informed knowledge or consent of the individuals, or the sources of the DNA. ►informed consent

Biopoesis: The evolution of living cells from chemical substances rather than from other cells. ►evolution prebiotic, ►origin of life

Bioprospecting: Searching for natural products (genes) potentially useful for pharmaceutical or agricultural applications. ►biotechnology

Biopterin: A pterin derived co-factor of enzymes functioning in oxidation-reduction processes (see Fig. B39)

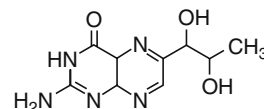


Figure B39. Biopterin

Bioreactor: A large-scale (industrial) culture of cells for the purpose of production and extraction of pharmaceuticals, enzymes, polypeptides, biodegradable plastics, etc. The use of transgenic organisms extended the range of utility of these procedures. Some constructions simulate conditions for growth in outer space. *Flow bioreactors* provide a continuous supply of fresh nutrients. In vitro operations may produce human organs, such as bones for therapeutic implantations. Skin and cartilage can already be proliferated outside the body for medical use. ►cell culture, ►chemostat, ►tissue culture, ►transgenic; Baoudreault R, Armstrong DW 1988 Trends Biotechnol 6:91.

Bioreactor: A collaborative software creation initiative for data acquisition, data management, data transformation, data modeling, combining different data sources, making use of evolving machine learning methods, and developing new modeling strategies suitable for computational biology and bioinformatics (Gentlemen RC et al 2004 Genome Biol 5:R80; <http://genomebiology.com/2004/5/10/R80>).

Bioremediation: A procedure of adding organisms to an environment for the purpose of promoting degradation of harmful or undesirable properties of that environment. Some observations indicate that 44 ±18% of polycyclic hydrocarbons of the atmosphere are captured by the vegetation and eventually

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incorporated into the soil. Many polycyclic hydrocarbons are carcinogenic and mutagenic and pose serious health hazards to people and animals. Their removal from the atmosphere is desirable, however, it is not clear what is the consequence of eating plants that absorbed these semi-volatile compounds. Several organic compounds can be degraded by sequential exposure to anaerobic and aerobic bacteria. Bacterial mercuric ion reductase gene, in a re-engineered form, has been introduced into *Arabidopsis* plants by transformation and the transgenic plants became resistant to HgCl_2 and to Au^{3+} . The transgenic plants evolved substantial amounts of Hg^0 (vapors). *Arabidopsis* plants expressing the yeast gene YCF1 accumulate greater amounts of cadmium and lead and display greater resistance to these toxic metals (Song W-Y et al 2003 Nature Biotechnol 21:914). Plants can extract toxic substances from the soil (phytoextraction) and from water (rhizofiltration), thus facilitate the cleaning up of the environment. By a technique of genetic engineering cytochrome P450 monooxygenase genes can be combined with toluene dioxygenase genes in e.g., *Pseudomonas*. Such bacteria then can degrade polyhalogenated compounds such as 1,1,1,2-tetrachloroethane (a powerful narcotic and liver poison) to 1,1-dichloroethylene and eventually to formic and glyoxylic acids, which are still irritants but occur in natural products of ants and fruits, respectively, but do not pose serious threat at low concentrations. *Dehalococcoides ethenogenes* can degrade vinyl chloride to non-toxic ethane. ►environmental mutagens, ►biomining, ►biodegradation, ►soil remediation; Lovley DR 2001 Science 293:1444; Kramer U, Chardonens AN 2001 Appl Microbiol Biotechnol 55:661; He J et al 2003 Nature [Lond] 424:62; phytoremediation: Pilon-Smits E 2005 Annu Rev Plant Biol 56:15; <http://pdg.cnb.uam.es/MetaRouter>; http://www.pdg.cnb.uam.es/bio_deg_net/MetaRouter.

Bi-Orientation: The sister kinetochores are attached to spindle fibers that connect them to the opposite spindle poles. ►coorientation, ►spindle fibers, ►microtubule, ►kinetochore; Tanaka TU 2002 Current Opin Cell Biol 14:365.

Biosemiotics: The discipline of communication within and among biological systems.

Biosensors: They analyze macromolecular interactions in real time in intact cells. Among the different systems ligand-receptor binding and signal transduction pathways may be the most sensitive, especially when coupled to fluorescent stains. ►ligand, ►signal transduction, ►fluorochromes, ►aequorin, ►surface plasmon resonance; Aravanis AM et al 2001 Biosens Bioelectron 16:571; engineered protein biosensor:

Kohn JE, Plaxco KW 2005 Proc Natl Acad Sci USA 102:10841.

Bioseq: It contains relevant information about a biological sequence beyond what is included in the ASN.1. ►ASN.1, ►gi, ►accession number

Biosphere: The range of habitat of organisms living in and on the soil, in bodies of water and the atmosphere.

Biostratigraphy: The relative dating of the succession of different evolutionary forms of organisms on the basis the paleontological relics.

Bisulfite Reaction: Sodium bisulfite is a mutagen inducing point mutations and chromosomal aberrations. The bisulfite reaction permits also the distinction between cytosine and methylcytosine. In bisulfite-treated single-stranded DNA cytosine is converted into uracil (*bisulfite conversion*) but methylated cytosine is essentially non-reactive. The chemically modified DNA tract can then be amplified by PCR and sequenced to determine the location of the methylated base. A procedure has been worked out to assess the extent of DNA methylation (involved in epigenetic modification), applicable genome-wide (Meissner A et al 2005 Nucleic Acids Res 33:5868). ►methylation-specific PCR, ►methylation of DNA, ►epigenesis; Sasaki M et al 2003 Biochem Biophys Res Commun 309:305.

Biosynthesis: Synthesis of molecules by living cells.

Biota: The community of all living organisms in an environment.

Biotechnology: The purposeful application of biological principles to industrial, medical and agricultural production such as molecular alteration of enzymes, cloned recombinant DNA and its translated products (e.g., human insulin produced by transgenic bacteria), replacement of defective genes by site-specific recombination, gene medicine (introducing transiently into cells genes capable of producing the medication required), transfer desirable genes into domestic animals and plants by genetic transformation to improve their economic value, clean up environmental pollutants by modified microorganism capable of digesting crude oil, etc. The economic importance of the biotechnology industry is indicated by their total value of \$224 billion in 2002, and it employed more than 194,000 people (Rasnick D 2003 Nature Biotechnol 21:355). ►Genetic engineering, ►tissue engineering, ►bioethics, ►bioprospecting, ►genomics, ►GMO; applications to public health: Daar AS et al 2002 Nature Genet 32:229, approval by different social groups: Gaskell G et al 2005 Science 310:1908, agricultural biotech: <http://www.cid.harvard.edu/cidbiotech/homepage.htm>.

Bioterrorism: It produces fear and harm among selected individuals or in the general population or harm plants, animals or the environment with the use of agents like bacteria, viruses, fungi or toxins derived from biological agents. Mechanical detection of explosive devices carried by suicide bombers lack sufficient sensitivity for detection beyond distances of 10 meter and are too bulky and expensive for soft targets (Kaplan EH, Kress M 2005 Proc Natl Acad Sci USA 102:10399). ▶ **Biological weapons**, ▶ **pathogen identification**; Henderson DA 1999 Science 283:1279; Atlas RM 2002 Annu Rev Microbiol 56:167; Fauci AS 2003 Nature [Lond] 421:787; mathematical modeling of food supply poisoning: Wein LM, Liu Y 2005 Proc Natl Acad Sci USA 102:9984, <http://www.health.gov/nhic/Scripts/Hitlist.cfm?Keyword=Bioterrorism>, toxins, virulence factors, antibiotics for biodefense: <http://mvirdb.lnl.gov/>.

Biotic: Related to living organisms.

Biotinidase Deficiency (same as multiple carboxylase deficiency, 21q22.1, 3p25): An autosomal recessive disease yet the heterozygotes may be identified, however, by much less obvious symptoms. The biochemical basis is a deficiency of an enzyme (multiple carboxylase) that splits biocytin (biotin—ε-lysine) and thus generates free biotin from protein linkages. The symptoms that may have late onset or appear in neonates are hypotonia (reduced tension of muscles), ataxia (reduced coordination of the muscles), neurological deficiencies (hearing, vision), alopecia (baldness), skin rash, susceptibility to infections, etc. Generally, administration of biotin alleviates the symptoms and may restore normality. The prevalence varies within the 10^{-5} range. Simple procedure is available for the testing of blood by color on filter paper, without purification. ▶ **genetic screening**, ▶ **biotin**

Biotin: A vitamin, a mobile carrier of activated CO_2 , its major biological role involves pyruvate carboxylase (see Fig. B40). It combines with avidin and thus used for non-radioactive labeling. ▶ **non-radioactive labeling**, ▶ **fluorochromes**, ▶ **biotinylation**; Mardach R et al 2002 J Clin Invest 109:1617.

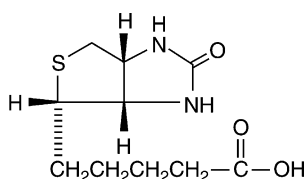


Figure B40. Biotin

Biotinylation: A very sensitive, non-radioactive labeling generated by incorporation into the DNA, with the aid of nick translation, biotinylated deoxyuridylic or deoxyadenylic acid. Biotin in the DNA has great affinity for streptavidin carrying a dye marker and the labeled DNA can thus be identified in light either cytologically or on membrane filters. ▶ **biotin**, ▶ **fluorochromes**, ▶ **labeling**, ▶ **FISH**; Demidov VV et al 2000 Curr Issues Mol Biol 2:31.

Biotope: A small, uniform ecological niche.

Biotrophic: A parasite living on live host. ▶ **saprophytic**

Biotype: Physiologically distinct race within a species.

BiP: A soluble heat-shock protein 70, a chaperone. It is an immunoglobulin-binding protein. ▶ **heat-shock proteins**, ▶ **Sps70**, ▶ **chaperone**

Biparental Inheritance: The female and male parents transmit the nuclear genes (see Fig. B41), in contrast, cytoplasmic organelles (and their genetic material) are most commonly inherited only through the egg, and therefore, the inheritance is uniparental (through the female). ▶ **allophenic**, ▶ **mtDNA**, ▶ **mitochondrial genetics**, ▶ **chloroplast genetics**, ▶ **meiotic drive**



Figure B41. Bride & groom, ceramics By Margit Kovács

Bipedal: Animals walking on two feet as an evolutionarily developed characteristic.

Bipolar Mood Disorder: A complex human disorder involving manic depression fluctuating with euphoria. Putative genetic determinants have been found in human chromosomes 1p33-p36, 2p, 2q21-q33, 3p14, 3p21, 3q26-q27, 4p15.3-p16.1, 5p15, 6q21-q22, 8q24, 8p21, 10q25-q26, 7, 13q11, 13q31-q34, 14q12-q13, 15, 16, 17q and 18, 21q22. Apparently, a major factor associated with human chromosome

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22q12 is XBP1 (X box-binding protein transcription factor controlling class II major histocompatibility complex antigens). It involves the control of a heat-shock protein (HSPA5) mediating protein folding in the endoplasmic reticulum (Kakiuchi C et al 2003 Nature Genet 35:171).

By all evidence, several genes contribute to bipolar disorders (Dick DM et al 2003 Am J Hum Genet 73:107; also corrections *ibid.* 73:979). Prevalence of the various manifestations during a lifetime is about 1%. Among artistically creative persons, Hemingway, Gogol, Strindberg, Byron, Goethe, van Gogh, Goya, Donizetti, Handel, Klemperer, Mahler, Schumann and others suffered from this illness to a variable degree (Janka Z 2004 Orvosi Hetilap [in Hungarian]: 145:1709). ▶ [affective disorders](#), ▶ [depression](#), ▶ [manic depression](#), ▶ [lithium](#), ▶ [unipolar depression](#), ▶ [psychoses](#), ▶ [HLA](#), ▶ [QTL](#), ▶ [GSMA](#), ▶ [reelin](#); Kelsoe JR et al 2001 Proc Natl Acad Sci USA 98:585; Cichon S et al 2001 Hum Mol Genet 10:2933; Mitchell PB, Malhi GS 2002 Annu Rev Med 53:173; Segurado R et al 2003 Am J Hum Genet 73:49, review: Belmaker RH 2004 New England J Med 351:476.

Bipolarity: Both strands of the DNA are transcribed in opposite \rightarrow directions.

BIR (chromosome break-induced replication): A mechanism to repair a broken single strand of a chromosome by new DNA synthesis. In haploid budding yeast, Rad51-dependent BIR induced by HO endonuclease requires the lagging strand DNA Pol α -primase complex as well as Pol δ to initiate new DNA synthesis. Pol ϵ is not required for the initial primer extension step of BIR but is required to complete 30 kb of new DNA synthesis. Initiation of BIR also requires the nonessential DNA Pol δ subunit Pol32 primarily through its interaction with another Pol δ subunit, Pol31 (Leydeard JR et al 2007 Nature [Lond] 448:820). (See Kraus E et al 2001 Proc Natl Acad Sci USA 98:8255, BIR in yeast telomere elongation: McEachern MJ, Haber JE 2006 Annu Rev Biochem 75:115).

BIR (baculoviral IAP repeats): N-terminal motifs in the IAP proteins, in one or several copies. The Bir1p protein is an inhibitor of apoptosis and in cooperation with the kinetochore proteins Ndc10p, Cep3p, Ctf13p and Skp1p controls chromosome segregation. ▶ [IAP](#), ▶ [kinetochore](#)

Birch (*Betula*): The silver birch, hardwood tree *B. pubescens* is $2n = 28$ and the *B. verrucosa* is $2n = 56$; $x = 14$ (see Fig. B42).



Figure B42. Birch

BIRN (Biomedical Informatics Research Network, <http://www.nbirn.net/>; <http://birn.ncrr.nih.gov>): Initially it was concerned with neurosciences but now it is extended to a wide range of biological projects. It provides an infrastructure for biology, computer science and statistics with the goal that in the mound of data, a pattern/patterns could be found that would suggest mechanisms of function and facilitate further experimental tests. ▶ [Internet2](#), ▶ [Abilene](#)

Birnavirus: Icosahedral double-stranded RNA virus.

Birth Control: ▶ [contraceptives](#), ▶ [hormone receptors](#), ▶ [sex hormones](#), ▶ [menstruation](#)

Birt-Hogg-Dubé Syndrome: A genodermatosis (genetic skin disease) involving tumorous hair follicles, renal neoplasia, lung cysts and pneumothorax (air accumulation in the serous membrane of the chest). It is linked to the pericentromeric region of human chromosome 17p. (See Schmidt LS et al 2001 Am J Hum Genet 69:867).

Birth Defect: A perinatal anomaly of either hereditary (~6% chromosomal, ~7–8% monogenic, ~20% polygenic) or of extraneous cause (maternal disease, infection or caused by environmental physical or chemical agents).

Birth Rates: ▶ [age-specific birth and death rates](#)

Birth Weight: It may be affected by a number of intrauterine factors such as maternal nutrition, disease, smoking and also genetic causes. Some of the initial relative differences may or may not be eliminated during subsequent development. ▶ [glucokinase](#)

Birth-and-Death Evolution: ▶ [concerted evolution](#)

Bisexuality: May be a case of hermaphroditism or just a behavioral anomaly. In the fruit fly some losses in the brain olfactory centers or receptors lead to a defect of the interpretation of pheromones causing anatomically male flies to court females as well as males. ▶ [pheromones](#), ▶ [hermaphrodite](#), ▶ [homosexual](#), ▶ [olfactory](#), ▶ [olfactogenetics](#), ▶ [sex determination](#)

Bison: American buffalo (*Bison bison*), $2n = 60$.

Bispecific Monoclonal Antibodies (diabody): One of the two arms of the antibody has the recognition site for the surface antigens of a tumor cell, the other for

the antigens of a killer lymphocyte. The bispecific antibody is thus expected to bring these two cells together and destroy the tumor cells. ►antibodies, ►monoclonal antibodies, ►antibody engineering, ►diabody, ►triabody, ►quadroma

Bisphenol: An estrogen and an industrial chemical used in manufacturing polycarbonate food and beverage containers. It can leach out and may be hazardous to developing offspring (see Fig. B43). ►estradiol, ►sex hormones

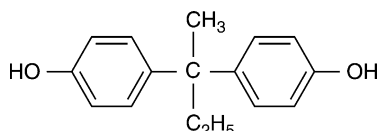


Figure B43. Bisphenol

Bistable Systems: They can toggle between two alternative steady-states but cannot rest in intermediate states. Such systems have importance for signal transduction, feedback and differentiation. ►signal transduction, ►feedback; Ferrell JE Jr 2002 Current Opin Cell Biol 14:140.

Biston betularia (peppered moth): A frequently used example for adaptive natural selection (see Fig. B44). The moth had predominantly overall grayish tones until the industrial revolution in the vicinity of Birmingham, England deposited black soot on the tree barks and favored the propagation of the dark colored (carbonaria) form of the moth that could hide better from predators. In unpolluted areas the light peppered form remained. These experiments have been subjected to criticism, mainly on ground of flawed methodology because during the decades after the publication of the Kettlewell experiments of the 1950s (Nature 175:943) the dark forms declined. The moth population is actually in a dynamic equilibrium and frequency-dependent selection affects the frequency of different types (Cook LM 2003 Quarterly Rev Biol 78:399). (Cook LM, Grant BS 2000 Heredity 85:580).



Figure B44. *Biston betularia*

Bisulfite (sodium bisulfite, HNaO_3): deaminates cytosine to uracil (Shortle D et al 1981 Annu Rev Genet 15:265).

Bit: A binary digit with a two-way choice such as a value of 1 or 0, on or off, etc. The smallest unit of information a computer recognizes. One byte = 8 bit and 1 kilobyte (K) is 1024 bytes (2^{10}); 1 megabyte (MB) = 2^{20} bytes.

Bithorax: (bx, 3–58.8) ►morphogenesis in *Drosophila* (see Fig. B45), ►Polycomb, Duncan I 1987 Annu Rev Genet 21:285.

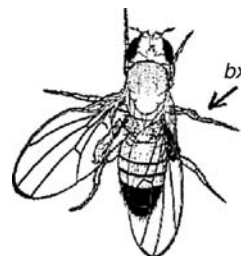


Figure B45. *Bithorax*. (From Bridges & Morgan 1923, bx)

Bitmap: Bits representing a graphic image in the memory of a computer.

Bitnote: A message communicated through the computer (e-mail) using the Bitnet system, an IBM mainframe connection to the Internet. ►Internet

BITOLA (Biomedical Discovery Support System): Directs potential relationships between biomedical concepts. The concepts are under Medical Subject Heading (MSH) that is indexed in Medline and HUGO. The system facilitates the discovery of disease–candidate gene relations. Background knowledge and chromosomal locations are included. ►Medline, ►LocusLink, ►HUGO; <http://www.mf.uni-lj.si/bitola/>.

Bitransgenic Regulation: The *A* transgene to be expressed must have its regulator transgene *R* be present in the cell. For normal function, the appropriate ligand(s) must also be available within the cell. ►transgenic, ►ligand; Yao TP et al 1992 Cell 71:63.

Bitscore: The raw quantitated sequence alignment score that indicates the statistical property of the scoring system. It is the likelihood that a query sequence is a genuine homolog of the sequence in the database. The natural logarithm of this likelihood ratio is the bits score. ►Blast, ►likelihood

Bivalent: Two homologous chromosomes, consisting of altogether of 4 chromatids, paired in meiotic prophase. ►heteromorphic bivalent, ►interlocking bivalent, ►chromatid, ►synaptonemal complex

Bivalent Promoters: In embryonic stem cells, bivalent promoters carry both trimethylated lysines at 4 and 27 position of histone 3 (H3K4me3 and H3K27me3).

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The former is conducive to transcription, the latter to silencing. This combination probably serves to poise key developmental genes for lineage-specific activation or repression, respectively.

Bivariate Distribution: The joint distribution of two random variables.

Bivariate Flow Cytometry: Sorting chromosomes tagged with two fluorochromes (Hoechst 33258), specific for A=T and chloromycin A3, specific for G=C, and excited by laser. flow cytometry, laser; Nunez R 2001 Curr Issues Mol Biol 3:67.

Bivariate Plot: Two-dimensional arrangement of data of two variables.

Bivoltinism: Insects have two generations per year.

Bixin: A pigment extracted from *Bixin orellana*, a tropical American plant and it is used in food and cosmetic industry. It is produced by several steps from lycopene and can now be synthesized in *E. coli* transformed for three genes encoding the critical enzymes. ▶lycopene; Bouvier F et al 2003 Science 300:2089.

BK Virus: It has 80% homology to Simian virus 40 with a somewhat different host range (human, monkey, hamster and other rodent cells). It may occur as an episomal element in two dozen to hundreds of copies. Its autonomous replicon may be useful for propagating DNA and genes in human cell cultures.

BKM Sequences: tetranucleotide GATA and GACA repeats in the W chromosomes (comparable to the Y chromosome) of birds and reptiles, occasionally in other eukaryotic chromosomes. ▶satellite DNA, ▶tetranucleotide repeats, ▶Y chromosome

Black Box: A slang expression for equipment that is too complicated inside to be generally understood. Figuratively, a living cell was considered to be a black box because some of its functions were observed yet all the mechanisms that drove these functions were not fully understood. Geneticists knew segregation of genes and chromosomes but the molecular mechanisms underlying these processes were largely shut inside the “black box” until the discoveries of DNA replication, transcription, translation, gene regulation, cell cycle, etc.

Black Locust (*Robinia pseudoacacia*): A leguminous tree with fragrant flowers; $2n = 20$.

Black Pepper (*Piper nigrum*): Southeast Asian spice. Basic chromosome number probably 12, 13, or 16, and $2n = 46, 52, 104$ and 128 have been reported.

Bladder Exstrophy: An apparently recessive familial disease with poor penetrance. A defect of the hindgut

(cloaca) results in open lower abdominal wall, pubis, lower urinary tract and the genitalia. The expressivity varies.

β-Lactamase: An enzyme (synonym: penicillinase) capable of cleaving the β-lactam ring of antibiotics of the penicillin family (see Fig. B46). Their activity is determined by the R-group attached to the lactam ring. The majority of the synthetic penicillins are not susceptible to penicillinase action. The coding gene was originally detected in Tn3. The ampicillin resistance gene in the pBR322 plasmid codes for 263 amino acid residue pre-protein containing a 23 amino acid leader sequence, which directs the secretion of the protein into the periplasmic space of the bacterium. The transcription of the gene starts counterclockwise at pBR322 coordinate 4146 and ends at 3297. Its mRNA in vitro contains a 5'-pppGpA terminus. The tetracycline resistance gene in pBR322 is transcribed from another promoter clockwise, starting at coordinate 244 or 245. The *Tc^R* gene encodes a polypeptide of 396 residues. Penicillinases occur naturally only in bacteria with peptidoglycan cell wall. The lack of the enzyme, in the absence of antibiotics, is inconsequential for the bacteria. The β-lactamase genes are used extensively in vector construction (to convey antibiotic resistance) and for the detection of insertional events that inactivate the enzymes. The lactamase enzyme can be used for real time monitoring gene transcription. A substrate (e.g., cephalosporin) complexed with a fluorochrome (7-hydroxy-coumarin) upon hydrolysis may generate a wavelength shift (from blue to green) in the emission of the substrate located in the plasma membrane. With aid of a cell sorter, transcription can be monitored in single cells. β-Lactamase is inhibited by clavulanic acid (an oxygen containing β-lactam). ▶antibiotics, ▶Tn3, ▶periplasma, ▶vectors, ▶cell sorter, ▶fluorochrome, ▶coumarin, ▶penicillin, ▶PBP; Daiyasu H et al 2001 FEBS Lett 503:1; Jacoby GA et al 2005 New Engl J Med 352:380.

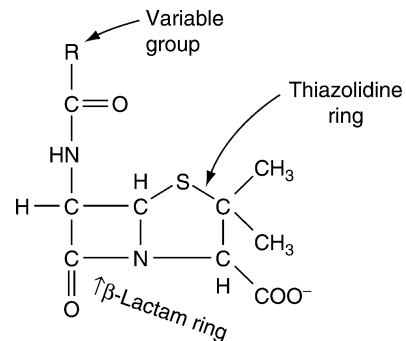


Figure B46. β-Lactamase

Blank Allele: It is not expressed.

BLAST (basic local alignment search tool): It is used for comparison of nucleotide sequences in apparently related (homologous) DNA (Altschul SF et al 1990 J Mol Biol 215:403) or for amino acid sequences in proteins (for DNA BLAST and for proteins PSI-BLAST: Altschul SF et al 1997 Nucleic Acids Res 25:3389). E-mail address blast@ncbi.nlm.nih.gov. ▶DNA sequencing, ▶MegaBLAST, ▶homology, ▶evolutionary tree, ▶FASTA, ▶BLOSUM, ▶databases; Trends Supplement [Elsevier Science] 1998; Wolfsberg TG, Madden TL 1999 In: Ausubel FM et al (eds) Short protocols in molecular biology, Wiley, New York, p.18-1, <http://www.ncbi.nlm.nih.gov/BLAST/>, WU-BLAST: <http://blast.wustl.eduftp://ftp.ncbi.nih.gov/blast/executables/LATEST/>.

Blast Cell: A cell, which may give rise to a progeny cell(s) different from itself.

BLASTP: BLAST for proteins. ▶BLAST

Blastema: A group of cells resembling stem cells in function and instrumental in tissue or organ regeneration. Hsp60 is required for regeneration of animal organs from blastema. Mutation in Hsp60 leads into mitochondrial defects and apoptosis (Makino S et al 2005 Proc Natl Acad Sci USA 102:14599). ▶chaperonin, ▶apoptosis, ▶regeneration in animals

Blastid: The site in the fertilized egg where cellular organization takes place.

Blastocoele: ▶Blastula

Blastocyst: An early embryonal stage (of about 60 cells in mammals) when the blastocoele is enveloped by a trophoblast cell layer, a pre-implantation stage of the animal zygote when the zona pellucida (the envelop of the egg) is still visible and the blastula begins to develop its inner cell mass (see Fig. B47). Before implantation the blastocysts sheds the zona pellucida. The mode of implantation is somewhat different in different mammals. ▶blastocoele, ▶trophoblast, ▶blastula, ▶stem cells, ▶uterus; Wang H, Dey SK 2006 Nature Rev Genet 7:185.

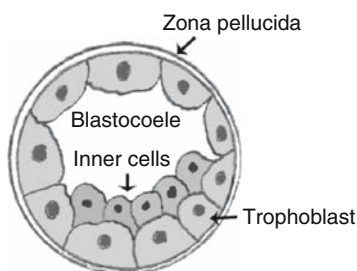


Figure B47. Blastocyst

Blastocyte: An undifferentiated cell of an early zygote.

Blastoderm: A single layer of cells at the embryonic stage of insects surrounding a fluid-containing cavity (blastocoele) at the blastula stage of cell divisions.

Blastoma: A cell in the early stage of differentiation or a neoplastic tissue containing embryonic cells.

Blastomeres: The large fertilized egg through cleavage divisions produces smaller cells, the blastomeres. These divisions are extremely fast and during the short process RNA synthesis ceases and protein synthesis depends on reserve mRNAs. Individual blastomeres of the mouse are already different at the two-cell stage as detectable by the localization of the Cdx2 transcription factor. This cell gives rise to the trophectoderm during the following divisions (Deb K et al 2006 Science 311:992). ▶blastoderm, ▶cleavage, ▶founder cells, ▶Cdx2, ▶trophectoderm, ▶oviduct, ▶morula

Blastopore: Located near the site of the gray center of the animal pole where invagination of the blastula begins and eventually encompasses the vegetal pole. The *dorsal lip* of the blastopore organizes gastrulation. ▶blastula, ▶animal pole, ▶vegetal pole, ▶gastrulation, ▶organizer

Blastula: A product of the cleavage of the early zygote when it becomes a spherical structure in which the blastoderm envelops the blastocoele cavity. ▶blastocoele

BLASTX: A computer program for gene and protein searches. (Nature Genet. 3:266 [1993]).

BLAT: A computer program for aligning nucleotide or amino acid sequences. (Ogasawara J, Morishita S 2003 J Bioinform Comput Biol 1:363).

Blattner Number: Refers to the position of genes in the sequenced genome of *E. coli* bacterium. ▶*E. coli*, Blattner FR et al 1997 Science 277:1453; Riley M, Serres MH 2000 Annu Rev Microbiol 54:341; Liang P et al 2002 Physiol Genomics 9:15; <http://genprotec.mbl.edu/>.

Blau Disease: A form of ulcerative colitis (intestinal inflammation) under the control of more than a single gene. Its symptoms overlap with those of Crohn disease. ▶Crohn disease; Miceli-Richard; C et al 2001 Nature Genet 29:19.

Blebistatin: (-)-blebistatin is an inhibitor of myosin II of mammals and thus the contraction of the cytokinesis cleavage furrow without affecting the assembly of the contractile ring. ▶cytokinesis, ▶myosin; Straight AF et al 2003 Science 299:1743.

Bleeder Disease: ▶hemophilia, ▶antihemophilic factors

bullosa the larger vesicles appear in clusters on the palms, soles, neck and around the mouth apparently due to a mutation in the keratin 14 gene. Another epidermolysis bullosa appears to be due to deficiency of galactosylhydroxyllysyl glucosyltransferase. In one form, a human chromosome 12-coded gelatin-specific metalloprotease deficiency may be involved. A mottled type (pigmented spots) displays recurrent blistering beginning at birth and premature aging. The epidermolysis bullosa with absence of skin and deformity of nails has a perfect penetrance. The autosomal recessive types: epidermolysis bullosa dystrophica (human chromosome 11q11-q13) is caused by excessive collagenase activity affecting primarily the hands, feet, elbows and knees at birth or infancy but may affect other organs too. The epidermolysis bullosa letalis may kill infants within about three weeks after birth but occasionally some survive to the first decade of life. In some forms the distal opening of the stomach (pylorus) may be constricted and atrophied and in other forms congenital deafness, muscular dystrophy may appear. X-linked epidermolysis with multiple complications (baldness, hyperpigmentation, dwarfism, microcephaly [small head], mental retardation, finger and nail malformation, and death before adult age is also known.) ►keratosis, ►ichthyosis, ►skin diseases

BLK: ►SRC oncogene family

BLM: ►Bloom syndrome

Bloch-Sulzberger Syndrome: ►incontinentia pigmenti

Block: A group of related sequences in proteins or DNA stretches between recombination sites. (Kimmel G, Shamir R 2005 Proc Natl Acad Sci USA 102:158; protein block database: <http://motif.stanford.edu/eblocks/>).

Block Design: Generally each treatment is present in every block (complete block) where the treatments may be randomized. In the incomplete block design, not all treatments are present in each block because of the large number of treatments causes technical difficulties. In the latter cases mathematics is used for compensation.

Block Mutation: It affects more than a single nucleotide in the cell, e.g., deletion; such mutations may not yield wild type recombinants if the defects overlap.

Blocked Reading Frame: Translation is interrupted by nonsense codons. ►nonsense codons

Blocking Buffer: 3% BSA (bovine serum albumin) in phosphate buffered saline containing also 0.02% sodium azide. BSA blocks the binding sites on nitrocellulose filter that are not occupied by proteins

transferred from (SDS polyacrylamide) gels. ►gel electrophoresis

Blocks: An Internet tool for the search of functional DNA motifs: blocks@howard.fhcrc.org or <http://blocks.fhcrc.org>.

Blog: Informal communication through the Internet about various topics from science to politics. The site <http://scienceblogs.com/> contains an index of blogs of possible interest to science. More information about blogging: Bonetta L 2007 Cell 129:445.

Blood: The fluid that carries nutrients and oxygen by circulating through the blood vessels in the animal body. It is composed of red (non-nucleated mature erythrocytes) and white (nucleated leukocytes) cells. The white cells include granulocytes, neutrophils, eosinophils and basophils, B and T lymphocytes and natural killer cells. The differentiation of these various types of cells from the multipotential hematopoietic stem cells is determined by a combination of growth factors, such as interleukins, stem cell factors, colony stimulating factors, etc. In the lymphoid developmental path the Pax5 gene and its product BSAP (B-cell-specific activator protein) plays a key role. The blood contains also platelets (thrombocytes) and the blood plasma, the non-corpusculate yellowish fraction. In *Drosophila* there are crystal cells (contain defense enzymes), plasmatocytes (the main phagocytotic defense cells) and lamellocytes (develop from plasmatocytes with similar functions). See these cell types, ►hemolytic disease, ►ABO blood group, ►blood groups, ►macrophages, ►dendritic cells, ►immune system, ►hematopoiesis, ►Pax, ►anti-hemophilic factors, ►B lymphocyte, ►T cell, ►erythrocyte, ►leukocyte, catalog of blood proteins relevant to disease: <http://bpb.nci.nih.gov/>; www.plasmaproteomedatabase.org, biology and disease: www.blood.interhealth.info/, blood cell development: <http://hembase.niddk.nih.gov>.

Blood Brain Barrier: ►BBB

Blood Clotting Pathways: These are the intrinsic pathway involving the successive participation of the Hagemann factor (XII), plasma thromboplastin antecedent (PTA XI), Christmas factor (IX), anti-hemophilic factor (VIII), Stuart factor (X), phospholipid and proaccelerin and the extrinsic clotting pathway requiring proconvertin (VII), Stuart factor (X), proaccelerin and calcium ions. With the aid of lentiviral vectors directed to the liver of mouse, the human Factor IX gene can be expressed and stably maintained for months. ►antihemophilic factors, ►tissue factor, ►vitamin K; Tsui LV et al 2002 Nature Biotechnol 20:53.

B

Blood Coagulation: ►blood clotting pathway, ►anti-hemophilic factors, ►aspirin

Blood Formation (hematopoiesis): During early embryonic development the yolk and the aorta-gonad-mesonephros (AGM) region are involved, later the function in the embryo is switched to the liver and after birth, the bone marrow is involved.

Blood Groups: An incomplete list of the types found in this volume: ABO, ABH, Ahonen, Colton, Diego, Dembrock, Duch, Duffy, En, Gerbich, I system, Kell-Cellano, Kidd, Lewis, Lutheran, LW, MN, Newfoundland, OK, P blood group, Radin, Rhesus, Scianna, Ss, Webb, Wright, Yt, and Xg. These are distinguished mainly by the epitopes on the erythrocytes. ►epitope, ►erythrocyte

Blood Pressure: The pressure of the blood on the blood vessels (arteries). ►hypertension

Blood Transposable Element: ►copia

Blood Typing: Identification the blood group a person belongs to. ►blood groups

Bloom Syndrome (BS, BLM): Semi-recessive human dwarfism; increases the frequency of chromosomal aberrations (particularly sister chromatid exchanges), and various forms of cancer (leukemia), sensitive to sunlight (red blotches over face) and usually shorter than normal life expectancy. It was attributed to a DNA ligase I deficiency but the cloning and sequencing of the gene indicates that this is not the primary defect rather a DNA helicase-like protein (RecQ family, homolog of budding yeast genes SGS1 and SRS2), encoded in human chromosome 15q26.1, is involved. The DRAFT protein complex is shared by Fanconi anemia and Bloom syndrome (Meetei AR et al 2003 Mol Cell Biol 23:3417). SGS1 mutations greatly enhance gross chromosomal aberrations and the rate of recombination. The wild type SGS1 represses chromosomal aberrations. The *Drosophila* homolog is Dmblm. In BS sister chromatid exchange and mitotic recombination are elevated but genetic repair seems to be normal. In Dmblm, an extra copy of Ku70 compensates for sterility. The BS helicase physically interacts with the Werner syndrome helicase. ►DNA repair, ►xeroderma pigmentosum, ►Fanconi anemia, ►Werner syndrome, ►Cockayne syndrome, ►Rothmund-Thomson syndrome, ►carcinogenesis, ►light-sensitivity diseases, ►co-suppression; Ku, Luo G et al 2000 Nature Genet 26:424; Myung K et al 2001 Nature Genet 27:113; von Kobbe C et al 2002 J Biol Chem 277:22035.

BLOSUMS: Amino acid substitution matrices used to determine evolutionary changes in proteins [Henikoff S, Henikoff JG 1992 Proc Natl Acad Sci USA

89:10915]. ►BLAST, ►FASTA, ►evolutionary clock, ►SSPA

Blotting: Macromolecules separated by electrophoresis in agarose or polyacrylamide are transferred to a cellulose or nylon membrane and immobilized there for further study. ►Southern blot, ►Northern blot, ►Western blot, ►colony hybridization, ►immunoprobe

BLOTTO (Bovine Lacto Transfer Technique Optimizer): A 5% solution of non-fat, evaporated milk in 0.02% sodium azide (NaN₃). [It may contain RNase activity]. In 25-fold dilution, it may be used for blocking background annealing in Grunstein-Hogness hybridization, Benton-Davis hybridization, dot blots, and non-single copy Southern hybridization. ►Denhardt reagent, ►heparin, ►Grunstein-Hogness screening, ►Benton-Davis plaque hybridization, ►dot blot

Blue Grass (*Poa pratensis*): Lawn and pasture plant; 2n = 36–123 in the polyploid series.

Blue Diaper Syndrome: An intestinal failure to transport tryptophan and *Pseudomonas aeruginosa* bacteria convert the amino acid into indole, which upon oxidation stains bluish. ►amino acidurias

Blue Light Response: Photomorphogenetic reaction (of plants) to illumination in the range of 400–500 nm wavelength. ►photomorphogenesis, ►cryptochromes

Blueberry (*Vaccinium* spp): A fruit shrub with x = 12; *V. corymbosum* (high-bush blueberry) is tetraploid, the *V. angustifolium* (low-bush blueberry) is diploid.

Bluescript M13: A 2.96 kb genetic vector containing the bacteriophage M13 replication origin and a polycloning insertion site flanked by T7 and T3 phage promoters in opposite orientation and useful for generation of single-stranded DNA or RNA complementary to the double-stranded DNA insert. Several variations exist (e.g., (ZAP, bluescript SK). The name comes from the bacterial Lac fragment that upon expression of (β-galactosidase in Xgal medium forms an easily detectable blue color. ►Xgal; Short JM et al 1988 Nucleic Acids Res 16:7583; Snead M et al 1988 Methods Mol Biol 81:255.

Blunt End: The blunt-end of double-stranded DNA is generated by non-staggered cut and it terminates at the same base pair across both strands of the double helix (see Fig. B50). Bacterial DNA polymerase I (Klenow fragment) or phage T4 DNA polymerase can also generate 3' blunt ends of DNA by 5'→3' exonucleolytic activity. ►blunt end ligation



Figure B50. Blunt end

Blunt-End Ligation: T4 phage DNA ligase joins non-staggered DNA ends or adds chemically synthesized duplexes to double-stranded blunt ends. ▶DNA ligases, ▶linker

BLUP (best linear unbiased prediction): A statistical procedure based on covariance analysis of gametic genetic disequilibrium of QTL and other types of markers in multibreed populations. (Wang T et al 1998 Genetics 148:507, ▶multibreed, ▶QTL)

BLYM: Chicken bursal lymphoma oncogene, located to human chromosome 1p32. It is homologous to transferrin, a glycoprotein with important role in the synthesis of ribonucleotide reductase, and thereby in DNA replication and mitosis. ▶oncogenes, ▶lymphoma, ▶transferrin

BLYS (B lymphocyte stimulator): A human chromosome 13q34-encoded protein of the tumor necrosis factor family is involved in B cell proliferation and immunoglobulin secretion. ▶B lymphocyte, ▶TNF

BMI: ▶body mass index

BMK1 (big MAP kinase): ▶ERK

BMP: ▶bone morphogenetic protein

BMT: Transformed monkey cell line expressing the T antigen of SV40, driven by a mouse metallothionein promoter. ▶SV40, ▶metallothionein

BMYC: Oncogene isolated from rat has extensive homology to the MYC oncogene but it maps to a different location than the other members of the MYC family LMYC, NMYC, PMYC, RMYC. (▶MYC and other members of the family, ▶oncogenes)

BNA: ▶locked nucleic acids

Bni: A member of the formin proteins involved in polar morphogenesis and cytokinesis of eukaryotic cells. Bni1 protein is associated with CDC42 protein, with actin, profilin and Bud6. ▶actin, ▶profilin, ▶CDC42, ▶Bud

Bob: ▶OBF

BOB': ▶att sites

BODIPY: ▶fluorochromes

Body Map (human and mouse gene expression database): Abundance of mRNAs in different tissues of the body. It reveals also the functional relatedness of genes by the similarity of expression profiles. (See Kawamoto S et al 2000 Genome Res 10:1807; <http://bodymap.ims.u-tokyo.ac.jp>; <http://bodymap.jp/>).

Body Mass Index in Humans (BMI): BMI is determined as a measure of obesity by the formula: weight in kg/height in meter². In morbid obesity BMI > 40 kg/m². Obesity (BMI>30) is detrimental to health although for centuries it was associated with fertility (see Fig. B51). The body mass index does not take into account unusually strong muscle development and in such cases does not provide good measure of obesity. Correlation of BMI between monozygotic twins is about 0.74 versus 0.32 for dizygotic twins indicating very high heritability. The correlation among parents and biological offspring were found to be 0.19 versus adopted children 0.06 indicating the major role of hereditary factors. The pro-opiomelanocortin locus in human chromosome 2p21 is a significant contributor to body mass according to some studies. Perola M et al 2001 Am J Hum Genet 69:117) failed to detect any linkage to BMI by QTL in Finnish populations. ▶obesity, ▶leptin, ▶melanocortin, ▶morbidity, Barsh GS et al 2000 Nature [Lond] 404:644.



Villendorfl Venus
ca. 15000 B.C.

Figure B51. Fertility goddess from Willendorf, Austria ~15,000 B.C. (From Gowans CS 1974 Stadler Symp 6:113)

Body Plan (bauplan): The three-dimensional organization of the body of an organism, e.g., mammals are bilaterally, incomplete symmetrical quadripeds, star fish has five-fold symmetry.

Body Size: In insects a balance between ecdysone and insulin signals determines body size. Ecdysone is produced by the prothoracic gland and its size is controlled by activated RAS or PI3K although RAF also regulates body size by activation ecdysone-dependent genes (See Caldwell PE et al 2005 Current Biol 15:1785). ▶ecdysone, ▶RAS, ▶PI3K, ▶size, ▶body mass, ▶Kleiber's rule

bol: ▶boule

Boltzmann Time Warping: ►dynamic time warping**B**

bom: A bacterial gene (basis of mobilization), required for the transfer of plasmids. ►plasmid mobilization, ►mob, ►Hfr

Bombardia lunata: An ascomycete, $n = 7$.

Bombay Blood Type: A relatively rare blood type discovered in India and subsequently on the Reunion Island in the Indian Ocean. This blood type has two main forms determined by the recessive alleles h (for H type red cell antigen). In the h/h se/se individuals also the enzyme fucosyltransferase 1 is inactive; in the h/h Se/se individuals a weak expression of the H antigen may be observed; Se is apparently coding for fucosyltransferase 2. ►ABH antigen, ►Secretor, ►Lewis blood group, ►fucose

Bombesin (protein, $C_{71}H_{110}N_{24}O_{18}S$): Bombesin modulate smooth muscle contraction, hormone traffic, metabolism, hyperglycemia, hypertension and eating behavior. ►obesity, ►ovarian cancer

Bombyx mori: ►silkworm

BONCAT (bioorthogonal noncanonical amino acid tagging): A method for detection and separation of newly synthesized proteins in response to environmental cues. The metabolic machinery incorporates azides and ketones and subsequent ligation with reactive probes facilitates their detection. Azidohomoalanine can be introduced into mammalian cells and the tagged proteome can be separated by affinity chromatography and identified by tandem mass spectrometry (Dieterich DC et al 2006 Proc Natl Acad Sci USA 103:9482). ►azide, ►ketone, ►homoalanine, ►affinity chromatography, ►tandem mass spectrometry

Bond Energy: It is required to break a chemical bond. Such bonds in the piconewton range are important in biology and are represented by protein and nucleic acids interactions, receptor-ligand pairs and covalent bonds. Measurement of the forces involved may be important for, e.g., detection of DNA base mismatches and for proteomics. ►atomic force microscope, ►newton; Albrecht C et al 2003 Science 301:367.

Bone Development: A complex process that involves signaling, molecules, growth hormones, transcription factors, etc. ►osteoblast, ►osteoclast; Kronenberg HM 2003 Nature [Lond] 423:332; Boyle WJ et al 2003 Nature [Lond] 423:337; Harada S-i, Rodan GA 2003 Nature [Lond] 423:349.

Bone Diseases: ►collagen, ►campomelic dysplasia, ►achondroplasia, ►hypochondroplasia, ►pseudoachondroplasia, ►osteogenesis imperfecta, ►SED, ►PAPS, ►osteoporosis, ►osteosarcoma, ►osteolysis, ►Paget disease, ►osteopetrosis, ►diastrophic

dysplasia, ►chondrodysplasia, ►dyssegmental dysplasia, ►dyschondrosteosis, ►dwarfism, ►adactyly, ►brachydactyly, ►polydactyly, ►syndactyly, ►exostosis, ►trichorhinophalangeal syndrome, ►ectrodactyly, ►Ellis-van Creveld syndrome, ►Holt-Oram syndrome, ►Hay-Wells syndrome, ►head/face/brain defects, ►pynodysostosis, ►osteochondromatosis, ►Larsen exostosis Alagille syndrome, ►spondylocostal dysostosis, ►spondylo-metaphyseal dysplasia, ►spondyloepiphyseal dysplasia, ►Greig's cephalopolysyndactyly syndrome, ►craniometaphyseal dysplasia, ►Pallister-Hall syndrome, ►Townes-Brocks syndrome, ►Robinow syndrome, ►acromesomelic dysplasia, ►acrodysostosis, ►acheiropodia, ►nail-patella syndrome, ►sympalangism proximal, ►radioulnar synostosis, ►synostosis, ►cleidocranial dysplasia, ►Waardenburg syndrome, ►Stickler syndrome, ►hypophosphatemia, ►Kniest dysplasia, ►Marfan syndrome, ►osteolysis, ►osteopetrosis, ►osteoporosis, ►sclerosteosis, ►scoliosis, ►Camurati-Engelmann disease, Kornak U, Mundlos S 2003 Am J Hum Genet 73:447.

Bone Marrow: The red spongy tissue inside the bones gives rise to lymphocyte stem cells and erythrocytes; the yellow bone marrow is mainly made of fat cells (see Fig. B52). Hematopoietic stem cells egress from the bone marrow by signals from the sympathetic nervous system (Katayama Y et al 2006 Cell 124:407). From the stromal cells of the bone marrow, stem cells can be isolated that can generate muscle cells at very good efficiency (89%) and suitable also for the development of neural and other types of cells under appropriate conditions and can be exploited for repairing degenerated tissue. It has the advantage that these stem cells would not be rejected if taken from the same individual and would avoid some ethical objections to the use of embryonic stem cells (Dezawa M et al 2005 Science 309:314). It has been claimed that stem cells exiting from the bone can end up in the ovaries and produce oocytes. Newer experiments challenged this claim (Powell K 2006 Nature [Lond] 441:795). ►stem cells, ►thymus, ►sympathetic nervous system, ►hematopoiesis



Figure B52. Bone marrow is in the inner cavity (light brown)

Bone Morphogenetic Protein (BMP): A maternally expressed factor in *Xenopus* embryos; in addition to bone differentiation it is involved in dorso-ventral organization of the embryo. Osteoblast differentiation

and proliferation is controlled by BMP and Smad. BMP-1 is a procollagen protease (PCP) that assembles collagen within the extracellular matrix. The other BMPs belong to the transforming growth factor (TGF- β) family. BMP-4 regulates apoptosis in neural crest cells affecting skeletal bone and muscle formation. BMP-3 is a negative regulator of bone density. The growth/differentiation factors of mouse (GDF) belong to this family and their mutation shortens the limb bones (brachypodism) without affecting the axial skeleton. The CBFA-1 gene seems to be a major factor in ossification. BMP is the vertebrate homolog of decapentaplegic (dpp) in *Drosophila*. The Sog (short gastrulation) and the Chd (chordin) proteins in vertebrates and invertebrates negatively regulate the BMP/Dpp system, respectively. The metalloprotease Xld (Xolloid)/Tld (tolloid) release the Bpm/Dpp from inactive complexes. Thus, a balance between Sog/Chd and Xld/Tld determines a morphogenetic gradient. Noggin, gremlin, chordin and follistatin inhibit BMP and dorsalize the embryo. The process is, however, more complex since that other serine protease(s) may also be involved (astacin, furin). The Kuz metalloprotease (a reprolysin) regulates the Notch cell surface receptor by proteolytic cleavage. BMP in coordination with other signal proteins regulates the specification of teeth development: $Msx-1^+$ ($Barx-1^-$) activity state leads to the development of incisors whereas $Msx-1^-$ ($Barx-1^+$) state promotes molar formation in the oral mesenchyme in mouse. ► [fibrodysplasia ossificans progressiva](#), ► [pulmonary hypertension](#), ► [decapentaplegic](#), ► [furin](#), ► [Notch](#), ► [organizer](#), ► [noggin](#), ► [GLI](#), ► [Smad](#), ► [osteoclast](#), ► [osteoblast](#), ► [collagen](#), ► [brachydactyly](#), ► [tooth](#), ► [hepcidin](#); Olsen BR et al 2000 Annu Rev Cell Dev Biol 16:191; Ray RP, Wharton KA 2001 Cell 104:801; Khokha MK et al 2003 Nature Genet 34:303.

Bonferroni Correction: Guards against type I error at some α values (false positives). In case of a small number of tests it is satisfactory and simple. It is frequently used when multiple hypotheses are tested: $p_{\text{corrected}} = 1 - (p_{\text{uncorrected}})^n$ where p is the values of the hypotheses and n is the number of hypotheses. The basic assumption is that all alternatives are equally likely and the results are tested against this hypothesis. ► [significance level](#), ► [error types](#), ► [test significant difference](#); Altman DG 1991 Practical statistics for medical research, Chapman & Hall, London; Hochberg Y 1988 Biometrika 75:800.

Bonobo (*Pan paniscus*): Pygmy chimpanzee is an ape closest to humans after chimpanzee. ► [chimpanzee](#)

Book Syndrome: An autosomal dominant defect of tooth development, high degree of sweating and premature loss of hair color. ► [hair color](#)

Bookmark: Indicates an address on the Internet or other items in the computer where you wish to return.

Bookmarking: The mechanism responsible for preventing compaction of a specific gene region during mitosis (Xing H et al 2005 Science 307:421).

Boolean Algebra: Developed by George Boole (1815–1864) for the use of formal logic. He supposed that in binary forms thinkable objects could be defined. Thus, if x = horned and y = sheep then by selecting x and y the class of horned sheep is defined. Also $1-x$ would define all things of the universe that are not horned, and $(1-x)(1-y)$ would identify all things that are neither horned nor sheep. This approach defines sets and subsets in discrete forms without intermediates, yet capable of defining mutual relationships. Using simple symbols, syllogisms could be developed in mathematical forms. Learning of concepts by humans appears to be proportional to its Boolean complexity, i.e., to the length of the shortest logically equivalent proposition. The switch-gear of the telephone systems and the modern digital computers were developed on the basis of the Boolean binary logic. Boolean logic is employed in devising cellular automaton networks and some information retrieval system, e.g., PubMed is operated on the basis of Boolean principles. DNA-based digital logic circuits have also been designed for the detection of complex enzyme-free nucleic acid circuits for the monitoring of complex gene expression patterns (Seelig G et al 2006 Science 314:1585). ► [automaton](#), ► [networks](#), ► [synthetic genetics](#), ► [PubMed](#)

Bootstrap: A statistical device that was introduced for computer operations (versus the classical type computations). The standard error by the classical method is computed as:

$$se(\bar{x}) = \left\{ \sum_{i=1}^n (x_i - \bar{x})^2 / [n(n-1)] \right\}^{1/2}$$

in comparison, with the bootstrap procedure:

$$se[t(x)] = \left\{ B [t(x^{*b}) - \bar{t}]^2 / (B-1) \right\}^{1/2}$$

where $se[t(x)]$ is the standard error of the bootstrap statistic, $t(x)$, B = bootstrap samples of size n from the data, \bar{t} is the average of the B bootstrap replications ($\bar{t}(x^{*b})$). The bootstrap algorithm can be applied to the majority of statistical problems and it is widely used for estimating the confidence level in evolutionary trees. The data points x_i need not be single numbers, they can be vectors, matrices or more general quantities, such as maps, graphs. The statistic $t(x)$ can be anything as long $t(x^*)$ can be computed for every bootstrap data set x^* . Data set x does not have to be a random sample from a single distribution.

B

Regression models, time series, or stratified samples can be accommodated by appropriate changes. For details and specific references see Efron B, Tibshirani RJ 1993 *An Introduction to the Bootstrap*. Chapman & Hall, New York. ▶jackknifing; Kerr MK, Churchill GA 2001 *Proc Natl Acad Sci USA* 98:8961; Davison AC, Hinkley DV 1997 *Bootstrap methods and their application*, Cambridge University Press, Cambridge, UK.

Bora Bora: ~220 kb centromeric sequences in *Drosophila*. ▶centromere

Border Sequences: ▶T-DNA

Borjeson Syndrome (Borjeson-Forssman-Lehman syndrome): Face, nervous system, endocrine defects, hypogonadism, assigned to human chromosome Xq26-q27. ▶RBM, ▶head/face/brain defects

Borna Virus: An enveloped negative-strand, non-segmented RNA virus with inverted terminal repeats (see Fig. B53). Its genome is replicated and transcribed in the nucleus of warm-blooded animals, including humans. Viral replication is controlled by genome trimming. From the 5' end one or four bases can be eliminated in the hairpin structure limiting genome amplification but not protein synthesis. From three transcription units it transcribes mRNA for six proteins by overlapping open reading frames, read-through transcription signals and alternative splicing of the polycistronic transcripts. Infection of the nervous system of newborn rats results in inflammation and causing mood disorders reminiscent of schizophrenia and autism of humans. In adult animals, uncoordinated movement and serious weight loss were observed. (Diagram is modified after Schneider U et al 2005 *Proc Natl Acad Sci USA* 102:3441).



Figure B53. Borna virus

Borrelia: Spirochete bacteria; about 28 species (*B. burgdorferi*, *B. hermsii*, etc.) are responsible for relapsing fever or Lyme disease and other human ailments all over the world. The *Borrelia burgdorferi* genome B31 contains 910,725 bp linear DNA and 17 linear and circular plasmids. This bacterium, like *Mycoplasma genitalium*, has no genes for cellular biosynthetic functions but there are 853 genes for transcription, translation, transport and energy metabolism. The filamentous bacteria are 8 to 16 µm long flagellate cells infectious for birds and mam-

mals. Their generation time is about 6 hours and in about 5 days within a single animal their population may exceed 10^6 cells and that coincides with the major symptoms (erythema migrans [enlarged red spots]) of the infection. Within weeks or months, the bacteria may invade all major organs of the body, primarily the joints and cause arthritic symptoms. If untreated, Lyme disease may be fatal. Intravenous injection of rocephin or other antibiotics (also orally administered doxycycline) may be the cures although some of the effects may persist for years. The vectors of the bacteria are the *Ixodes* arthropods (ticks) that live on grasses and low-growing bushes in wildlife (deer, mice, birds) frequented rural and suburban areas. The salivary protein Salp15 of *Ixodes scapularis* interacts with the surface protein of *B. burgdorferi* and protects the spirochete from the mammalian host antibodies (Ramamoorthi N et al 2005 *Nature [Lond]* 436:573). The bacterial σ^{54} , a RNA polymerase subunit deficient *Borrelia* cells can invade the tick but they are not infectious (Fisher MA et al 2005 *Proc Natl Acad Sci USA* 102:5162). The tick receptor (Trospa) that is required for spirochetal colonization (Pal H et al 2004 *Cell* 119:457). The *Bb* gene of *Borrelia* is required for the persistence of the bacteria in ticks and subsequent productive infection of the mammalian cell. The BptA a putative lipoprotein is a likely virulence factor for *Bb* (Revel AT et al 2005 *Proc Natl Acad Sci USA* 102:6972).

Identification of the disease is difficult because of the complexity of the symptoms. Serological detection encounters problems because the outer membrane of the bacteria displays variable serotypes. *Borrelia*s harbor several copies of approximately 23–50-kb linear plasmids with genes for Vmps/Vsps (variable major proteins). Transposition within and recombination between the plasmids assures great antigenic variation in these organisms. New serotypes appear at an estimated frequency of 10^{-4} to 10^{-3} per cell per generation. This fact accounts for the difficulties in developing effective immunosera and no acceptable vaccine is available (Abbott A 2006 *Nature [Lond]* 439:525). An attenuated strain of *Mycobacterium bovis*, the bacillus Calmette-Guerin (BCG) may serve as a suitable vector for the *B. burgdorferi* surface protein antigen A and may secure more than a year long protection by mucosal delivery. About 10% of Lyme disease patients appear resistant to antibiotic treatment and display arthritis symptoms long after spirochetal DNA in fluids of the joints is no longer detectable. The arthritis is an immune response to the outer surface protein A (OspA) of the bacterium. Actually, OspA-reactive type 1 T helper lymphocytes are found in the joints many years after the infection is cured. OspA has

homology to human leukocyte-function associated antigen-1 (hLA-1). Thus, it seems that the apparently antibiotic-resistant individuals have an autoimmune reaction to this major histocompatibility class peptide encoded by the dominant DRB*0401 allele. OspA is up-regulated when *Borrelia* is in its tick host and down-regulated when it is in a mammalian host. Before the bacterium enters the mammalian host, the host neuroendocrine stress hormones, epinephrine and norepinephrine, specifically bound by *B. burgdorferi*, and result in increased expression of OspA. This recognition is specific and blocked by competitive inhibitors of human adrenergic receptors. Propranolol significantly reduced uptake of *B. burgdorferi* by feeding ticks and decreased expression of OspA in the bacteria recovered from ticks that fed on propranolol (anti-hypertension drug)-treated mice (Scheckelhoff MR et al 2007 Proc Natl Acad Sci USA 104:7247). ▶serotype, ▶antigen, ▶serum, ▶mucosal immunity, ▶Ixodoidea, ▶σ, ▶BCG, ▶HLA, ▶autoimmune disease, ▶arthritis, ▶leptospirosis; Ohnishi J et al 2001 Proc Natl Acad Sci USA 98:670, Kumaran D et al 2001 EMBO J 20:971; Revel AT et al 2002 Proc Natl Acad Sci USA 99:1562.

Borromean Rings: Interlocked rings. DNA may be arranged this or more complex ways (see Fig. B54). The simplest representation.

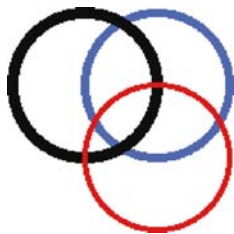


Figure B54. Borromean rings

Bos taurus (cattle): $2n = 60$. ▶cattle

Boss: A transmembrane protein product on the R8 photoreceptor in the eyes of *Drosophila*, encoded by gene boss (bride of sevenless, 3.90.5). It is the ligand and activator for the receptor tyrosine kinase, encoded by the sev (sevenless, 1–33.38) gene. ▶sevenless, ▶son-of-sevenless, ▶rhodopsin, ▶receptor tyrosine kinase, ▶daughter of sevenless

Botany: A basic scientific field concerned with plants. (See herbaria and botanists: <http://www.nybg.org/bsci/ih>; all plants: <http://plants.usda.gov/>; Plant Name Index: <http://www.ipni.org>).

Bottleneck Effects: If the size of the population is periodically reduced substantially, genetic drift may alter gene frequencies. Usually bottlenecks reduce variation. Occasionally after bottlenecks, an increase of variation has been reported, and it was attributed to dominance and epistasis. Bottleneck effect is quite common in the transmission of mtDNA because only a small portion of it is passed through the germline and the heteroplasmy may be altered. ▶genetic drift, ▶mtDNA, ▶heteroplasmy; Galtier N et al 2000 Genetics 155:981.

Bottom-Up Analysis: ▶top-down analysis

Bottom-Up Map: It relies on STS-based information. These are useful for relatively short chromosomal distances. Two STSs are “singly linked” if they share at least one YAC and “doubly linked” in case they share at least two YACs. Single linkage is generally not useful because of the high degree of chimerism among the YACs. In the first step, STS are assembled into doubly linked contigs. Then, the doubly linked contigs are ordered either on the basis of radiation hybrids or traditional genetic recombination information. Finally, single linkage can also be used to join contigs to the same short genetic region. ▶mapping genetic, ▶STS, ▶contig, ▶radiation hybrid, ▶bottom-down mapping, ▶YAC; Carrano AV et al 1989 Genome 31:1059.

Botulin (botulinum): Highly toxic product of *Clostridium* bacteria (lethal dose 1 ng kg^{-1}) and frequent cause of potentially lethal food poisoning. It is approved for treatment of strabismus and blepharospasm (a nervous eyelid problem), and it is also a cosmetic treatment of “crow’s feet” facial, signs of aging. It is also a potential biological weapon. The botulinum neurotoxin A enters neurons by binding to synaptic vesicle protein (SV2) isoforms (Dong M et al 2006 Science 312:592). Botulinum toxin also binds synaptotagmin II (Jin R et al 2006 Nature [Lond] 444:1092; Chai Q et al 2006 Nature [Lond] 444:1096). ▶strabismus, ▶synaptotagmin; Moore A 2002 EMBO Reports 3:714.

Boule (bol): An autosomal gene in *Drosophila* encoding a cell cycle protein regulating G2-M transition. It is homologous to the human Y-chromosomal gene DAZ responsible for azoospermia. Its suspected function is translation and localization of mRNA. ▶infertility, ▶fertility, ▶azoospermia, ▶cell cycle, ▶twine, ▶pelota, ▶Dazla

Boundary Element (barriers): Limits the function of cis-regulatory elements or the spread of heterochromatinization. ▶insulator, ▶heterochromatin, ▶RAP, ▶CTCF

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Bouquet (polarization): In leptotene the chromosomes are attached by their ends to a small area of the nuclear membrane (spindle pole body) while the rest of the chromosome length is looped across the nucleus (see Fig. B55). Meiotic proteins Bqt1 and Bqt2 tether the telomeres to the spindle pole body (fungal organ comparable to the centrosome). These proteins form a connecting bridge between telomere protein Rap1 and Sad1, a spindle pole protein (Chikashige Y et al 2006 Cell 125:59). ▶meiosis, ▶leptotene stage, ▶spindle pole body, ▶horsetail stage

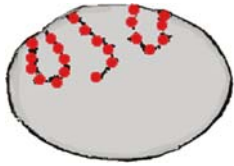


Figure B55. Bouquet

Bovine: Animals of *Bos taurus* (cattle) group. ▶*Bos taurus*, ▶cattle

Bovine Growth Hormone (BGH): A somatotropin; it has been commercially produced by genetic engineering and it boosts significantly milk production. ▶somatotropin

Bovine Papilloma Viral Vectors: By genetic manipulations and with pBR322 bacterial plasmid sequences added, they can be converted into a shuttle vector carrying genes between mouse and *E. coli*. ▶transformation genetic, ▶vectors, ▶viral vectors, ▶shuttle vector

Bovine Papilloma Virus (BPV): A papova virus (about 7.9 kbp DNA), responsible for wart in animals. The BPV69T segment of their genome (5.5 kbp) has been used as a large capacity vector, which can multiply into 10 to 200 copies. It can stay as an episome or can be integrated into the chromosomes of mammals.

Bovine Spongiform Encephalopathy (BSE): ▶encephalopathies, ▶Creutzfeldt-Jakob disease, ▶Alzheimer disease, ▶prions, ▶scrapie

Bowel Disease (chronic inflammatory bowel disease): ▶CIBD, ▶CARD15, ▶Crohn disease

Bowman-Birk Inhibitors: These are prepared from plant tissues and can bind and inhibit simultaneously or independently, trypsin and chymotrypsin. They may decrease cancer development in animals exposed to alkylating agents or displaying sporadic tumorous growth. (Witchi H, Espiritu I 2002 Cancer Lett 183[2]:141).

Bow-Tie: A system with various inputs and outputs connected by a node, resembling a bow-tie.

Box: Generally used for a consensus sequence in the DNA, such as a homeobox; domains of the internal control regions (box A, box, B, box C) that are the sequences where transcription factors bind. Sometimes protein boxes are also distinguished.

Box Genes: Clustered mutations in exons or introns (in mosaic genes of mtDNA). ▶mtDNA

β-Pleated Sheet: Extended polypeptide chains in parallel or antiparallel arrangement linked by hydrogen bonds between the amino and carboxyl groups. ▶protein structure

BP (B.P.): Before present, for archeological age.

bp: Base pair.

BPV: ▶bovine papilloma virus

BR RNP (Balbiani ring ribonucleoprotein): Transcripts of the Balbiani ring and associated with about 500 protein molecules of a total molecular size of 106 daltons. ▶Balbiani ring

Brachmann-De Lange Syndrome: ▶De Lange syndrome

Brachydactyly: Abnormally short fingers and toes controlled by autosomal dominant genes (see Fig. B56). In Type E the metacarpus and metatarsus (the bones between the wrist and the fingers of the hand and the corresponding bones in the foot) are shortened. In still other types nervous defects, hypertension, shortening the bones of the arm accompanies the hand and foot problems. The expression may vary. Most commonly the middle bones (phalanx/phalanges) are affected (Type A); in some cases not all the fingers express the gene. In type B (9q22, receptor tyrosine kinase ROR2), in addition to the middle phalanges, the terminal ones are also short or absent. In type C more than 3 phalanges may appear. Type D involves short and flat terminal phalanges of the big toe and the thumb. In Type E the metacarpus and metatarsus (the bones between the wrist and fingers of the hand and the corresponding bones in the foot) are shortened. In still other types nervous defects, hypertension, shortening the bones of the arm accompanies the hand and foot bone problems. In an autosomal recessive form the brachydactyly involves also small head (microcephaly). In another recessive form primarily the great toe is affected but the proximal (near the wrist) joints do not move. The dominant brachydactyly with severe hypertension gene has been assigned to human chromosome 12p. Brachydactyly type A-1 is due to mutation in the Indian hedgehog gene. Brachydactyly type A2 (4q21-q25) is due to mutation in bone morphogenetic protein receptor

1B (Lehmann K et al 2003 Proc Natl Acad Sci USA 100:12277). ►polydactyly, ►syndactyly, ►car-tilage, ►bone morphogenetic protein, ►Robinow syndrome, ►hedgehog; Schwabe GC et al 2000 Am J Hum Genet 67:822; Gao B et al 2001 Nature Genet 28:386.



Figure B56. Brachydactyly

Brachymeiosis: When the second meiotic division is missing. ►meiosis

Brachyury: A homozygous (*TT*) dominant lethal (after 10 days of conception) gene in mice. The *Tt* heterozygotes are viable and have reduced tail (tailless), the homozygous *tt* also dies in 5 days. The different alleles of the complex locus have different effects of the development. The anomaly (chromosome 17) involves a genetic defect in the notochord development. The somites undergo differentiation but resorbed before birth. There are defects also in the posterior parts (limbs, allantois, umbilical vessels). The *t* alleles may display meiotic drive and from the male *t*/+ heterozygotes more than 90% of the progeny may receive the *t* allele. The distortion of the transmission (TRD) is controlled by at least six loci that do not normally recombine because of the presence of inversions. The *t* complex occupies about 1/3 of chromosome 17 and generally is inherited as a block because the region includes at least four inversions. The rare recombinants are called “partial *t* haplotypes.” Females display normal transmission and fertility. In addition, there are at least 16 lethality loci within the *t* haplotype but these are not the primary causes of the distorted segregation. The *Tcd1*, *Tcd2* and *Tcd3* distorters act in response to the *Tcr* responders and can affect the transmission of any chromosome of mouse. The distorted segregation is due to the cis-acting so-called *T* complex responder (*Tcr*). The *Tcr*^f (acts only in cis) males avoid distortion and can fertilize the females but show the abnormal transmission. The distorted ratio is due to the *Smok* (sperm motility kinase) located at the C-terminus of the ribosomal *Rsk3* kinase. *Smok* apparently phosphorylates the axonemal dynein of

the microtubules. The *T* complex distorters (*Tcd*) are transacting factors, which increase transmission of the *tcr*-bearing chromosome. Despite the preferential transmission of the *t* haplotype by the heterozygous males, the populations carry only 10–25% *t* haplotypes. The brachyury transcription factor is embedded by its carboxy-terminal into the minor groove of the DNA contacting a guanine residue but it is not bending the DNA. It is an important transcription factor for mesodermal specification. The *t* haplotype carries four Rho-GTPase-activating loci (*Tapgap-1*) whereas the wild type has only one. Brachyury-like anomalies occur also among cats, dogs, sheep, cattle and pigs (see Fig. B57). ►Manx in cat, ►meiotic drive, ►killer spore, ►somite, ►notochord, ►haplotype, ►axoneme, ►dynein, ►TCP-1, ►Holt-Oram syndrome; Schimenti J 2000 Trends Genet 16:240; Lyon MF 2003 Annu Rev Genet 37:393; Bauer H et al 2005 Nature Genet 37:969.



Figure B57. Short-tail pig

Bracken Fern (*Pteridium aquilinum*): Carcinogenic plant used as food in Japan.

Bract: A small, modified leaf from which flower may develop or a leaf on the floral axis subtending the flower (see Fig. B58).



Figure B58. Bract

Bradford Method (Anal Biochem 72:248): The Bradford protein assay, for 1 to 100 µg protein. Prepare a standard solution (0.5 mg/mL) of bovine serum albumin (BSA) and make a dilution series 5 to 20 µL and dilute to 100 µL with 0.15 M NaCl. Prepare also 0.15 M NaCl blanks. Make a series of dilutions also from the unknown quantity of the protein to be

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tested. Add 1 mL Coomassie brilliant blue to all and mix thoroughly. After 2 min determine absorption at 1-cm path-length at 595-nm wavelength in a spectrophotometer and extrapolate the concentration of the sample from the standard series. ►Lowry test, ►Kjeldahl method

Bradykinin: ►kininogen

Bradytelic Evolution: Evolution at very slow pace involving species whose adaptive environment extends over very long (geological) periods. In contrast, the tachytelic evolution is progressing at a fast pace whereas the horotelic evolution appears to show an average rate. ►evolution

BRAF: A cytoplasmic serine/threonine kinase that is mutant in 66% of melanomas but it occurs at lower frequencies in other cancers. Inhibition of MEK abrogates BRAF tumor growth (Solit DB et al 2006 Nature [Lond] 439:358). BRAF mutations occur in the majority of probands with the cranio-facio-cutaneous syndrome without an apparent increased frequency of cancer. ►RAS, ►MEK, ►cranio-facio-cutaneous syndrome, ►melanoma; Davies H et al 2002 Nature [Lond] 417:949.

Brahma: A catalytic component of the SWI/SNF chromatin-remodeling complex. ►nucleosome, ►chromatin remodeling, ►meCP2, ►Rett syndrome

Brain-Derived Neurotrophic Growth Factor: ►BDNF

Brain Diseases: ►Addison-Schilder syndrome, ►epiloia, ►mental retardation, ►affective disorders, ►craniofacial synostosis syndromes, ►prions

Brain, Human: A very complex structure and here only a few major landmarks are outlined as reference to several entries dealing with the central nervous system. The seven-layered hippocampus, consisting of “gray matter” is not shown although this is the most important area at the basal-temporal region involved in memory and learning. The functional areas of the brain can be identified by the increased blood flow upon stimulation by using positron emission tomography or functional magnetic resonance imaging. Microelectrodes applied to individual nerve cells reveal electrical activity at a single cell level. Since the mammalian brain contains thousands of distinct neuronal glial cell types, their synthesis requires separate transcription factors and the study of Gray PA et al (2004 Science 306:2255) found by in situ hybridization that that 349 genes in the brain displayed restricted expression pattern reflecting the anatomical organization of the mouse brain (see Fig. B59).

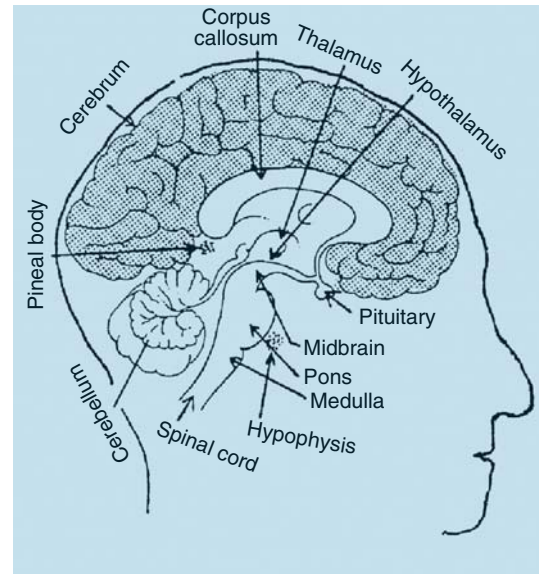


Figure B59. Major areas of the human brain

The new Allen Brain Atlas (ABA) allows one to view all the locations at which any of the more than 20000 genes in the mouse brain are activated, down to cellular-level resolution. The site allows one to search any anatomical region of the brain for any gene or combination of genes. The activated genes can be viewed with tools that can zoom from a whole-brain section down to a single cell while retrieving data at multiple levels of resolution (Markram H 2007 Nature [Lond] 445:160). The current technology visualizes the expression of single genes per cells but eventually larger the parts of the transcriptome might be visualized. Newly developed image-based informatics tools allow global genome-scale structural analysis and cross-correlation, as well as identification of regionally enriched genes. Unbiased fine-resolution analysis has identified highly specific cellular markers as well as extensive evidence of cellular heterogeneity not evident in classical neuroanatomical atlases. The new methods enable global analysis and mining for detailed expression patterns in the brain. The entire Allen Brain Atlas data set and associated informatics tools are available through an unrestricted web-based viewing application (Lein ES et al 2007 Nature [Lond] 445:168; <http://www.brain-map.org>).

The brain size of hominids (1,200–1,600 cm²) approximately tripled in less than 3 million years of evolution. Brain volume and cognitive abilities seem to be positively correlated ($r = +0.4$) yet the correlation between brain size and cognitive performance is very low within families. The heritability of brain size of humans is very high and evolutionarily it has reached a plateau because the pelvic size of the mothers is restrictive in order to assure uncomplicated

child delivery. The positive correlation may be mainly non-genetic and influenced by socioeconomic status, cultural influences, etc. (See figure; ►memory, ►cerebellum, ►EQ, ►IQ, ►nerve function, ►tomography, ►nuclear magnetic resonance spectrography, ►human intelligence, ►brain scan, ►chimpanzee ►language, ►EPH, ►blood-brain barrier, ►microcephaly, ►encephalon; Nichols MJ, Newsome WT 1999 Nature Suppl 402:C35; brain evolution: Gilbert SL et al 2005 Nature Rev Genet 6:581; computer modeling of the brain: Herz AVM et al 2006 Science 314:81; neuronal networks: Destexhe A, Contreras D 2006 Science 314:85; computational models of cognition: O'Reilly RC 2006 Science 324:91; gene expression: <http://www.loni.ucla.edu>; <http://www.loni.ucla.edu>; mouse brain: <http://www.mbl.org>; expression pattern of ~21,000 mouse genes in the brain: <http://www.brain-map.org/>; <http://www.brainatlas.org>; <http://www.trans.nih.gov/bmap>; brain maps of different vertebrates: <http://www.brainmaps.org/>).

Brain Scan: Uses various sophisticated technologies such a functional magnetic resonance imaging (fMRI) and other technologies well as statistics to monitor sensorimotor and cognitive processes to shed light on human motivation, reasoning, emotions, possibility of deceptions and social attitudes. It reveals activation in different critical regions of the brain. It is becoming also a clinical tool of neurology. Some unresolved ethical issues still remain regarding the interpretation and validity of the data so obtained. ►brain human, ►tomography, ►nuclear magnetic resonance spectrography; Illes J et al 2003 Nature Neurosci 6:205; Check E 2005 Nature [Lond] 435:254.

Brain Stem: medulla + pons + midbrain. ►See diagram of brain

B-RNA: ►cowpea mosaic virus

Branch Migration: During the process of molecular recombination the exchange point between two fixed sites of the DNA single strands can move left or right when the two single strands are separated they can simultaneously reassociate in an exchanged manner in both double helices. This strand invasion brings about heteroduplexes. In *E. coli* the RuvA (a specificity factor) and RuvB (an ATPase) proteins (induced by ultraviolet radiation damage to the DNA) bind to the Holliday junctions and increase the length of the heteroduplex. RuvA and RuvB drive helical rotation of the DNA at the rate of about 8.3 bp/second (Han Y-W et al 2006 Proc Natl Acad Sci USA 103:11544). In eukaryotes, Rad54 and Rad51 operate homologous recombination at the Holliday junctions. Mismatches in the synaptic strands may interfere with

branch migration. ►Holliday model, ►Holliday junction, ►heteroduplex, ►recombination molecular mechanisms, ►mismatch repair; Ruv ABC; Walker box; Putnam CD et al 2001 J Mol Biol 311:297; Constatinou A et al 2001 Cell 104:259; Fabisiewicz A, Worth L Jr 2001 J Biol Chem 276:9413; Karymov M et al 2005 Proc Natl Acad Sci USA 102:8186.

Branch Length: of an evolutionary tree may be determined by the least square method or by using the maximum likelihood principle. ►evolutionary tree, ►least squares, ►maximum likelihood principle

Branch Point Sequence: Short RNA tract YNCURA Y, (Y stands for pyrimidine, R for purine and N can be either) in the primary transcript near (18–38 base upstream) to the 3' end of an intron (AG) of mammals. After exon1-intron boundary is severed and the intron end is released with a 5'-GU pair at the end, it forms then a loop as it folds back by G making a 2'→5' bond with the A shown bold above. Subsequently, a cut is made at the 3' end of the intron, the intron is released, and the exon1 is attached to exon 2. ►introns; Peled-Zehavi H et al 2001 Mol Cell Biol 21:5232.

Branched Chain Amino Acids: ►isoleucine-valine biosynthetic steps

Branched RNA: An intermediate of RNA splicing. ►introns

Branchio-Otorenal Syndrome (BOR): A human chromosome 8q13.3 dominant syndrome with incomplete penetrance and expressivity. It involves defects in the appearance of the ears, underdevelopment of the middle ear structures (malleus, incus, stapes) and the inner ear (cochlea) resulting in mild to severe hearing loss. This is accompanied by under-development of the kidney and the urinary tract. A variant form without the kidney symptoms maps to 1q31. The prevalence of BOR is $\sim 4 \times 10^{-4}$. The gene bears homology to the *Drosophila* gene *eyes absent* (*eya*). The 61.2 kDa Eya protein seems to be a transcriptional coactivator. (See Kumar S et al 2000 Am J Hum Genet 66:1715).

Brassica oleracea (cabbage, kale): Vegetable crops. Basic chromosome number is controversial 5 or 6 although cabbage is $2n = 18$ (C genome) and there are some indications of being an amphidiploid. ►turnip, ►swedes, ►rapes, ►mustards, ►radish, ►watercress; Howell EC et al 2002 Genetics 161:1225; Lukens L et al 2003 Genetics 164:359; annotated genomes of the species: <http://hornbill.cspg.latrobe.edu.au>; <http://brassica.bbsrc.ac.uk>; *Brassica*, strawberry: <http://bioinformatics.pbcbasc.latrobe.edu.au/index.htm>.

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Brassica rapa: (*syn. B campestris*; mustard; genome AA; $2n = 20$): Sequence-tagged linkage map is available (Kim JS et al 2006 Genetics 174:29).

Brassinolide: ►brassinosteroids (see Fig. B60).

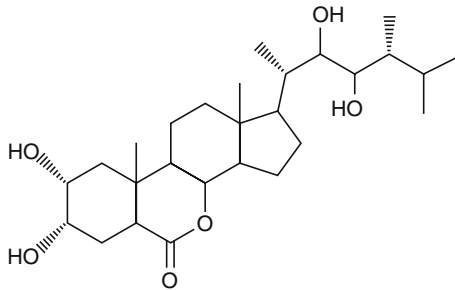


Figure B60. Brassinolide

Brassinosteroids (BR): Synthesized through the pathway campesterol→ campestanol→ cathasterone→ teasterone→ 3-dehydroteasterone→ typhasterol→ castasterone→ brassinolide. Uridine diphosphate glycosyltransferase mediates the glycosylation in the last two steps of this pathway in *Arabidopsis* (Poppenberger B et al 2005 Proc Natl Acad Sci USA 102:15253). The latter compound has been shown to remedy de-etiolation, derepression of light-induced genes, miniaturizing, male sterility and other symptoms of stress-regulated genes. These brassinosteroids bear close similarity to ecdysones, the animal molting hormones. The phytoecdysones were known for two decades in plants. All these plant hormones interact with each other in various ways and regulate signal transduction and gene activities. Unlike most animal steroid hormones, plant hormones are of small molecular size (except brassinosteroids) generally in the range of 28–350 Da. Brassinolide has a MW of about 480. A putative brassinosteroid receptor kinase shows similarities to the *ERECTA* and *CLAVATA1* gene products of *Arabidopsis* and share leucine-rich repeat with disease-resistance genes. Brassinosteroids bind to BRI1 leucine-rich receptor kinase in the outer plasma membrane (Kinoshita T et al 2005 Nature [Lond] 433:167). The *BES1* locus of *Arabidopsis* regulates the level of brassinosteroids and the response to light. BES1 interacts with the helix-loop-helix protein BIM1 and binds to an E box in some brassinosteroid gene promoters and regulates their transcription (Yin Y et al 2005 Cell 120:249). BES1 is constitutively localizes to the nucleus and its activity there is modulated by BIN2 kinase (Vert G, Chory J 2006 Nature [Lond] 441:96). Another protein BZR1—when receives the brassinosteroid signal—turns some genes off although it controls homeostasis of BR (He J-X et al 2005 Science 307: 1634). BRI1 is a serine/threonine kinase cell surface receptor of

brassinosteroids, and its coreceptor is BAK1. BKI1 (brassinosteroid receptor kinase inhibitor) is a negative regulator of signaling (Wang X, Chory J 2006 Science 313:1118). Removal of its C-terminus results in increased phosphorylation and increased activity. Ligand binding relieves inhibition of kinase activity (Wang X et al 2005 Developmental Cell 8:855). Ca^{2+} /calmodulin are important for brassinosteroid biosynthesis and growth (Du L, Pooviah BW 2005 Nature [Lond] 437:741). Brassinosteroids appear to be rate-limiting for auxin-responsive gene expression (Mouchel CF et al 2006 Nature [Lond] 443:458). ►plant hormones, ►de-etiolation, ►photomorphogenesis, ►hormones, ►steroid hormones. ►epidermis; Szekeres M et al 1996 Cell 85:171; Clouse SD, Sasse JM 1998 Annu Rev Plant Physiol Mol Biol 49:427; Neff MM et al 1999 Proc Natl Acad Sci USA 96:15316; Kang J-G et al 2001 Cell 105:625; Li J, Nam KH 2002 Science 295:1299; Yin Y et al 2002 Cell 109:181; Bishop GJ, Koncz C 2002 Plant Cell 14:S97; brassinosteroid signaling: Belkadir Y, Chory J 2006 Science 314:1410.

BRCA1 (breast cancer antigen): An exclusively nuclear located protein. ►breast cancer

BrdU: bromodeoxyuridine. ►bromouracil, ►hydrogen pairing, ►chemical mutagens

Breakage and Reunion: The broken chromatids or DNA single strands are broken at the position of chiasmata, and reunited in an exchanged manner during genetic recombination. This process is a physical event not requiring (normally) DNA replication as it was one time hypothesized with the copy choice idea. Recently, it was found that recombination takes place also by replication. ►recombination molecular models, ►recombination by replication, ►Holliday model; Creighton HB, McClintock B 1931 Proc Natl Acad Sci USA 17:492; Stern C 1931 Biol Zbl 51:547; Meselson M 1964 J Mol Biol 9:734.

Breakage–Fusion–Bridge Cycles: May cause variegation in the tissues because some of the genes may not be present in one of the daughter cells whereas the other cell receives two copies. If this dominant gene determines color, its presence is immediately recognized in the cell lineages. In telomerase-deficient and p53 mutant mice, epithelial cancer development is promoted by breakage-fusion-bridge cycles (see Fig. B61). In *Saccharomyces cerevisiae* dysfunctional telomeres may increase mutation rate ten to hundred fold. (See Fig. B62, ►Ac-Ds, ►cancer, ►telomerase, ►centromere silencing, ►p53; McClintock B 1941 Genetics 26:234; Hackett JA et al 2001 Cell 106:275).

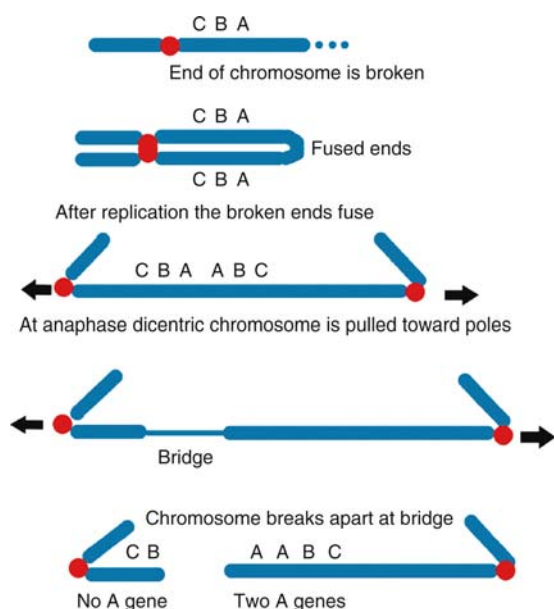


Figure B61. Breakage-fusion-bridge cycles may occur in the endosperm of maize plants if the end of the chromosomes is broken. The genetic and cytological consequences of such events are diagramed here. The relative size of the sectors (detectable when appropriate color markers are used) indicates the developmental time of the cycle. Early events involve large sectors, late events are indicated by small sectors. If the event occurs repeatedly, several sectors are observed. In case the two centromeres move toward the same pole no bridge is formed and an intact dicentric chromatid is recovered. In case double bridge is formed and both chromatids break, two monocentric (most commonly defective chromosomes) go to the poles. The breakage-fusion-bridge cycle may not continue in the tissues of the growing plants because of apparent healing of the broken ends. The healing is attributed to the acquisition of new telomeres. (Photographs by courtesy of Barbara McClintock)

Breakpoint Mapping: ► inversions

Breast Cancer (BRCA): Breast cancer is one of the most common diseases of women. The development of the disease proceeds through multiple steps. The pre-malignant stage is an atypical ductal hyperplasia. It progresses into the preinvasive stage of localized ductal carcinoma, which may change into invasive carcinoma, a potential lethal condition. Recently, for the better definition of these stages at the cell, rather than tissue level, microarray technology is combined with laser-capture microdissection. Although these different stages do not display significant differences in the pattern of gene expression, different grades of tumors are associated with distinct gene signature patterns and thus have predictive value regarding the condition of the disease (Ma X-J et al 2003 Proc Natl Acad Sci USA 100:5974). There is over 10% chance that the survivor to age 90 or over will develop breast cancer and ~5–10% of the cases are caused by mutation either in the BRCA1 or BRCA2 genes. Based on 22 studies involving 8,139 index cases, with unselected family with history of female (86%) and male (2%) breast cancers or epithelial ovarian cancers (12%) were evaluated. The average cumulative risks in BRCA1 carriers for breast cancer by age 70 were 65% and for ovarian cancer 39%. For BRCA2 the same risks were 45% and 11%, respectively (Antoniou A et al 2003 Am J Hum Genet 72:1117).

Deficiency of BRCA2 leads to impaired homologous recombination but maintains normal non-homologous end joining (Xia F et al 2001 Proc Natl Acad Sci USA 98:8644). Fusion of Replication Protein A to BCR2 repeats reduced mutagenic recombination and promoted repair (Saeki H et al 2006 Proc Natl Acad Sci USA 103:8768). Even in non-hereditary (sporadic) cases of breast cancer, the BRCA1 gene is frequently lost or is inactive or rearranged. BRCA1, actually a tumor suppressor

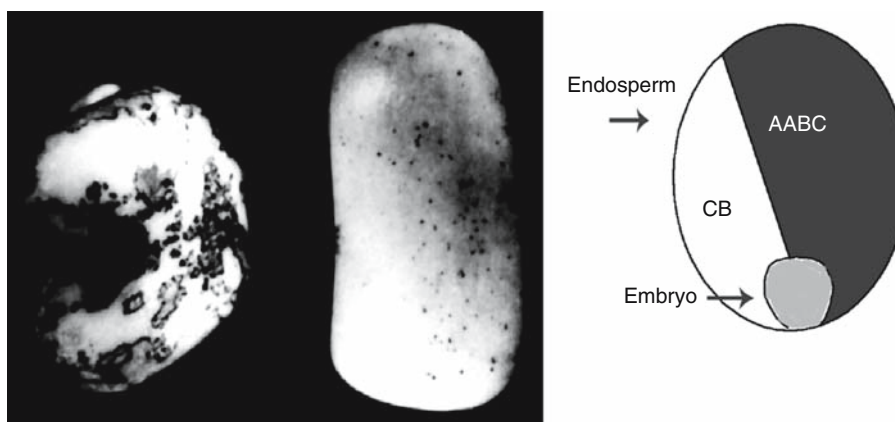


Figure B62. Left side is colorless. The right side is colored because of the AA gene

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(in human chromosome 17q21), is responsible for 25% of the cases diagnosed before age 30. BRCA1 along with CREB is part of the pol II holoenzyme. It activates transcription when it is associated by its C-terminus with RNA helicase A and pol II. In BRCA1 of the 12 RNA polymerase subunits the activation of hRPB2 and hRPB10 α are most critical. Predisposition to breast cancer is inherited as a dominant trait but the somatic expression (manifestation of cancer) requires that in these heterozygotes the normal allele would be lost or inactivated during the lifetime of the individual who inherited one BRCA susceptibility allele. The BRCA1 reading frame encodes 1,863 amino acids (22 exons) with a Zn finger domain at the NH₂ end. Amino acids 1,528 to 1,863, i.e., the C-terminal domain appear to be a transcriptional activator. The primary single transcript is 7.8 kb and is expressed primarily in the testis and the thymus but also in the breast and ovary. The transcript displays alternative splicing. Mice mutant in *Brcal* also develops increased risk for breast cancer because progesterone receptors are overexpressed in mammary epithelial cells. Treatment of *Brcal*/p53-deficient animals with the progesterone antagonist mifepristone can prevent tumorigenesis (Jovanovic PA et al 2006 Science 314:1467).

Gene Id4 is an important negative transcriptional regulator of BRC1 expression. BRCA1 is an important component of the 18-protein complex (SWI/SNF) involved in chromatin remodeling. BRCA1 strongly binds DNA and protects it from nucleolytic attack without sequence specificity and it is involved in double-strand DNA repair. BRCA1 binds to BRG1. As a transcription factor, it enhances the expression of several genes including p53. The BRCA1 sequences are well conserved in mammals but absent in chicken. The defects in the gene varies in the different kindreds from 11 bp deletion to frame shifts, nonsense, missense mutations or other alterations causing instability. The phenotype of the patients varies between the kindreds indicating that the specific mutations at the locus may affect its expression. It was noteworthy that there were female carriers of the mutation(s) who by age 80 failed to develop breast or ovarian cancer. Apparently, the expression is affected to some extent by extraneous genetic and environmental factors. Receptor-associated protein 80 (RAP80) is a BRCA1-interacting protein in humans. It contains a tandem ubiquitin-interacting motif domain, which is required for its binding with ubiquitin in vitro and its damage-induced foci formation in vivo. RAP80 specifically recruits BRCA1 to DNA damage sites and functions with BRCA1 in G2/M checkpoint control (Kim H et al 2007 Science 316:1202).

The BRCA1 protein may also be aberrantly localized in the cytoplasm and complicates the expression pattern. BRCA2 in human chromosome

13q12-q13 encodes 3,418 amino acids within a 6-cM region, is also a dominant early onset disease, responsible for about 45% of all *hereditary* breast cancers. Its highly conserved third exon is homologous to the c-Jun oncogene where the JNK protein binds. The 18–60 amino acid residues are potential activation sites. On both sides of exon-3 are inhibitory regions (IR1 & 2). It does not create a substantial risk for ovarian and other cancers but the chance for breast cancer in males may be slightly elevated, in contrast to BRCA1. Deletions 185delAG in BRCA1 and deletion 617delT in BRCA2 occur with carrier frequencies of 1.09% and 1.52%, respectively in Ashkenazy Jewish populations. The BRCA2 protein is cytoplasmically located. Its nuclear localization factor resides within the C-terminal 156 amino acids, and deletion in that region (e.g., 617delT) prevents the translocation of the protein to the nucleus and it consequently loses its ability to suppress tumorigenesis. The PALB2 protein normally binds BRCA2 and its mutation reduces its ability to bind and causes deficiency in homologous recombination and cross-link repair. Its mutation increases familial occurrence of breast cancer as well as prostate cancer (Erkko H et al 2007 Nature [Lond] 446:316). In 36% of the BRC families, chromosomal rearrangements (deficiencies, duplications) may be present (see Fig. B63).

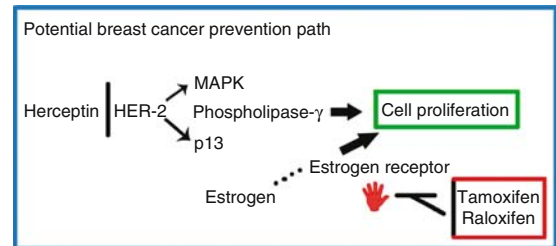


Figure B63. Breast cancer pathway. (Modified after Nass, S.J. et al. 1998 Nature Medicine 4:761)

The normal allele of BRCA1 transactivates the cyclin-dependent protein kinase inhibitor p21^{WAF1/CIP1} without the cooperation of p53 and thus the entry into the S-phase of the cell cycle is prevented. This process, however, depends on the normal allele of p21. BRCA1 appears to be involved in transcription-coupled repair of oxidative DNA damage and the defective BRCA1 conveys hypersensitivity to ionizing radiation and hydrogen peroxide. Human Cds1 phosphorylates the BRCA1 protein at serine 988 after DNA damage and assists cell survival. The BRCA2 appears to be a cofactor of the radiation hypersensitivity genes Rad51 mediating double-strand DNA repair by homologous recombination or transcription-coupled repair upon phosphorylation by ATM or ATR (an ataxia telangiectasia mutated and RAD3-related protein). The BRCA2 tumor

suppressor is essential for error-free repair of double-strand breaks of the DNA. The repair is mediated by RAD51, which is attracted to the break-point by BRCA2. BRCA2 has eight ~30-amino acid repeats, which bind RAD51 and the ~700-amino acid domain binds to single-strand DNA. RAD51 elongates by polymerization the BRCA2-nucleated repairing DNA filament, which then ties the single strand to the double-strand DNA at the new junction (Yang H et al 2005 Nature [Lond] 433:653). BRCA2 has been localized to the midbody during cytokinesis and its defect results in chromosomal instability and aneuploidy (Daniels MJ et al 2004 Science 306:876). BRCA1 and BRCA2 proteins apparently interact in the cell. The Brc3 and Brc4 peptides of Brca2 protein and several low-penetrance genes are of potential importance. Homozygosity of mutant (truncated) BRCA2 (unexpectedly) also blocks cell proliferation and causes chromosomal breakage but mutations in spindle assembly checkpoint genes (p53, Bub1, Mad3L) relieve this growth arrest and restart (neoplastic) proliferation (Lee H et al 1999 Mol Cell 4:1). BRC2 (384 kDa) also involves double-stranded DNA repair (Yang H et al 2002 Science 297:1837). Normally BRC2 binds RAD51 protein, which mediates homologous pairing and recombinational repair. CDK-dependent phosphorylation of Ser 3291 site of RAD51 increases as cell proceeds toward mitosis. C-terminal damage of BRC2, however, may limit phosphorylation and interaction of BRC2 and RAD51 and leads to predisposition to radiation sensitivity and cancer because of the lack of repair (Ezashi F et al 2005 Nature [Lond] 434:598; Galkin VE et al 2005 Proc Natl Acad Sci USA 102:8537).

One of the remaining types of breast cancer is supposed to be due to a mutation in the *KRAS2* (Kirsten sarcoma) gene in human chromosome 6 when at codon 13 a G → A transition takes place resulting in Gly → Asp substitution. Ductal breast cancer was attributed to the loss of genes in human chromosome 1q21ter but also chromosomes 2, 14 and 20 were implicated. In families with high incidence of breast cancer a small secreted protein gene, expressed only in human breast cancer, was mapped to chromosome 21q22.3. **BASE** (breast cancer and salivary gland expression) a secreted protein (20q11.21), is associated with many breast cancers but not with normal tissues (Egland KA et al 2003 Proc Natl Acad Sci USA 100:1099). A dominant gene product serologically reacts with murine monoclonal antibody DF3. In the region of chromosome 17p13.3, the *TP53* regulator of tumor protein p53 was found but it could not be ruled out that a regulator exists 20 megabases telomeric to *TP53*. AIB1 steroid receptor (20q, member of the SRC-1 family oncogenes) is either amplified or overexpressed in the tumors. AIB1 seems to be a co-activator. Some observations

suggest that loss of BRCA1 may lead to perturbation and destabilization of the inactive X chromosome and that explains why this disease occurs in females (Ganesan S et al 2002 Cell 111:393). Although BRCA1 and BRCA2 are the major suppressors of breast cancer, loss of heterozygosity at 1p, 1q, 3p, 6q, 7q, 8p, 11p, 13q, 16q, 17p, 17q, 18q, 19p, 21q and 22q may also affect the development of the cancer (Miller RJ et al 2003 Am J Hum Genet 73:748).

Some forms of breast cancer also affects males and the incidence of breast cancer in Klinefelter (XXY) men is almost as high as that in women. It appears the BRCA2 carrier males have increased risk for prostate and pancreatic cancer and possibly also bone and pharynx cancer (van Asperen CJ et al 2005 J Med Genet 42:711).

Some types of breast cancers are associated with cancers in other organs. *FOXC2* transcription factor, which is involved in specifying mesenchymal cell fate during embryogenesis, is associated also with the metastatic capabilities of cancer cells. *FOXC2* expression is required for the ability of murine mammary carcinoma cells to metastasize to the lung, and overexpression of *FOXC2* enhances the metastatic ability of mouse mammary carcinoma cells (Mani SA et al 2007 Proc Natl Acad Sci USA 104:10069). The risk of recurrence of breast cancer among first-degree relatives may be as high as 50%. In a transgenic mouse model, in the HER2-induced mammary tumors the increased level of the transcriptional repressor Snail, involved transition from epithelial-to-mesenchymal cells and higher relapse of cancer (Moody SE et al 2005 Cancer Cell 8:197). The risk of breast cancer is increasing with age, unmarried status, obesity, radiation exposure, etc. Several environmental chemicals (heterocyclic amines, o-toluidine, dibromoethane, glycidol, etc.) may cause breast cancer. In North America, the lifetime risk of breast cancer in females is about 10%. Of all breast cancer incidences about 5–10% is due to inherited causes. Genetic testing is now available for BRCA1 and BRCA2 for women who on the basis of family history have an increased risk for developing the disease. Unfortunately, individuals appearing negative in the standard test may be false negatives because rearrangements at these loci (~12%) remain undetected. Furthermore CHEK2, TP53 and PTEN mutations (~5%) also increase the risk, and members of the high-risk families should be tested for these mutations (Walsh T et al 2006 J Am Med Assoc 295:1379).

The incidence of breast cancer rises steeply between ages 25 to 50 and levels off after apparently because of the petering level of estrogens. Chromosomes 2q35 and 16q12 harbor estrogen receptor susceptibility (Hunter DJ et al 2007 Nature Genet 39:870). The development of breast cancer for BRCA1 and BRCA2 carrier females by age 70 is 28–87% and for ovarian cancer ~25–30%. The male

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carriers also have an increased risk for breast, prostate, colon, pancreas, gall bladder, bile duct, stomach cancers and melanoma (Liede A et al 2000 *Am J Hum Genet* 67:1494). The contralateral occurrence of breast cancer is much higher than the prevalence of breast cancer in the general population. BRCA1 gene is responsible partly also for ovarian and prostatic cancers. DNA repair defect seems to be involved. BRCA1 forms a complex with proteins hRAD50-hMRE11-p95. BIC (breast cancer information core) address: <http://www.breast-cancer-network.info/breast-cancer-information-core.html>, environmental risk factors: <http://envirocancer.cornell.edu/>. (See the genes responsible for ►Peutz-Jeger syndrome, ►Cowden syndrome, ►androgen receptor, ►p53, ►ataxia telangiectasia, ►Muir-Torre syndrome, ►Li-Fraumeni syndrome and the ►Nijmegen breakage syndrome may also increase breast cancer risk, ►p53, ►p21, ►BRG1, ►BACH, ►hormone ►receptors, ►estrogen receptor, ►mifepristone, ►estradiol, ►AIB, ►abraxane, ►tamoxifen, ►raloxifen, ►herceptin; ►phospholipases, ►p13, ►HER-2, ►oncogenes, ►genetic screening, ►cancer, ►PARP, ►Li-Fraumeni syndrome, ►Nijmegen breakage syndrome, ►Fanconi anemia, ►multiple hamartoma, ►granin, ►Klinefelter syndrome, ►tumor suppressor, ►Stat, ►multiple hamartomas, ►Jun, ►JNK, ►RAD50, ►p95, ►RNA helicase, ►RNA polymerase, ►mouse mammary tumor virus, ►ZAG, ►ataxia telangiectasia, ►ATM, ►ATR, ►PTIP, ►Cdc1, ►contralateral, ►ovarian cancer, ►cyclin D, ►homologous recombination, ►Replication Protein A, ►laser-capture microdissection, ►microarray hybridization, ►midbody, ►NHEJ, ►plantibody, ►Xist, ►MammaPrint; Welch PL et al 2000 *Trends Genet* 16:69; Cui J et al 2001 *Am J Hum Genet* 68:420; Risch HA et al 2001 *Am J Hum Genet* 68:700; Nathanson K et al 2001 *Nature Med* 7:552; Welch PL, King M-C 2001 *Hum Mol Genet* 10:705; Nathanson KL, Weber BL 2001 *Hum Mol Genet* 10:715; Narod SA 2002 *Nature Rev Cancer* 2:113; Bhatia S, Sklar C 2002 *Nature Rev Cancer* 2:124; Chlebowski RT 2002 *Annu Rev Med* 53:519; susceptibility markers: <http://cgems.cancer.gov/>.

Breathing Of DNA: A reversible, short-range strand-separation below the melting temperature. ►[melting temperature](#)

Breeding System: Mating within a population may be random (each individual has an equal chance to mate with any member of the opposite sex) or it may be self-fertilization (in monoecious species) or inbreeding (in dioecious species). Also random mating and inbreeding both take place within the group. The term breeding system denotes these alternatives.

The predominant breeding system of a few plant species is tabulated (A: apomictic, D: dioecious, I: self-incompatible, M: monoecious, O: outbreeding, S: selfing)

Table B6. Predominant breeding system in selected plant species

| | | | |
|------------------|------------------|-------------------|-----------------|
| Alfalfa O-S | Cherry O-I | Mulberry D | Rubus O |
| Almond O-I | Chestnut O | Mustard O-I | Rye O-I |
| Alder M | Citrus O-I | Oak M | Rye grass O-I |
| Antirrhinum O-S | Clover O-I | Oat S | Sorghum O-S |
| Apple O-I | Coffee O-I | Oenothera O-S | Soybean S |
| Apricot O | Collinsia S | Onion O | Squash M |
| Arabidopsis S | Cotton O-S | Orchard grass O-I | Spinach D |
| Ash M-D | Cucumber-M | Osage orange D | Spruce M |
| Asparagus D | Date palm D | Parsley O | Stock S |
| Barley S | Datura S | Pea S | Strawberry D-S |
| Basswood O | Eggplant O | Peach O | Sugar beet O |
| Beach M | Elm M | Peanut S | Sugarcane O-I |
| Bean S | Fescue O-S | Pear O | Sunflower O-I |
| Belladonna O | Flax S | Petunia O-S | Sweetclover O-S |
| Beet O-I | Grape O | Pine M | Sweetpea S |
| Birch M-I | Hemp D-M | Pineapple O-I | Sycamore M |
| Blue grass O-A-S | Hop D | Plum O-I | Tea O |
| Broad bean S | Lentil S | Poplar D | Teosinte M |
| Brome grass O | Lespedeza O | Potato O-S-I | Timothy O |
| Buckwheat O-I | Lettuce S | Radish O-I | Tobacco S |
| Cabbage O-I | Lupine O-S | Ramie O | Tomato S |
| Carnation S | Maize M | Rape seed O-I | Tripsacum M |
| Carrot O | Maple O | Rice S | Triticale S |
| Castorbean M | Meadow foxtail O | Rose O | Walnut M |
| Celery O | Millet O-S | Rubber O | Wheat S |

Breeding Value: The quantitative value a genotype, judged on the basis of the mean performance of the offspring. Actually, it is twice the mean deviation of the offspring from the mean of the parental population. The doubling is used here because each parent contributes a haploid gamete to the offspring and thus half of its genes. Breeders frequently call it the additive effect. The observed performance of individuals is called the *phenotypic value* (P) that is measured as the mean value of the population. The average value of two homozygotes is called the *midpoint*. It is equal to zero (only in case when the frequency of the two alleles is equal, 0.5) because the two parents deviate from it by a quantity of (+a) and (−a), by definition, and their sum cancel out each other. The *genotypic value* of the heterozygotes is designated by (d). In the absence of dominance $d = 0$, with complete dominance $d = a$, with overdominance $d > a$:

Table B7. Calculating breeding value

| | | | |
|------|-------|------|----|
| aa | 0 | Aa | AA |
| ← −a | → ← | +a → | |
| | ← d → | | |

The mean value (\bar{x}) is usually calculated as the weighted mean, i.e., multiplied by the genotypic frequencies in the population. If the population is in equilibrium, the mean is:

$$\bar{x} = p^2(a) + 2pq(d) + q^2(-a) + 2pq(d) = (a)(p + q)(p - q) + 2pq(d) \text{ and because } p + q = 1, \\ \bar{x} = (a)(p - q) + 2pq(d) \text{ and if several loci are involved, } \bar{x} = \sum [(a)(p - q) + 2pq(d)].$$

►gain; heritability, ►OMIA, ►Hardy-Weinberg equilibrium, ►merit; Falconer DS, Mackay TEC 1996 Introduction to quantitative genetics. Longman/Addison Wesley, White Plains, New York.

Brefeldin A (γ ,4-dihydroxy-2-[6-hydroxy-1-heptenyl]-4-cyclopentanecrotonic acid λ lactone): An inhibitor of passing peptides from the endoplasmic reticulum and Golgi complex. In the absence of brefeldin, yeast cells suffer chromosome instabilities. ►ARF, ►translocase, ►ARNO; Wigge PA et al 1998 J Cell Biol 141:967; Lang BD et al 2001 Nucleic Acids Res 29:2567.

Bremsstrahlung (brake radiation, [from German words]): Electromagnetic radiation resulting from retardation or acceleration of a high-energy particle.

BRENDA: A database of at least 40000 enzymes and 6900 organisms. Nomenclature, reaction and specificity, structure, isolation and stability information is presented. ►Recon; ►http://www.brenda.uni-koeln.de.

BRF: The binding factor in RNA synthesis initiation.

BRG1 (BRAHMA related gene-product): A 1613 amino acid, DNA-dependent human ATPase, active in SWI/SNF, RSC mediating chromatin remodeling. ►chromatin remodeling, ►SWI/SNF, ►BRAHMA; Strobeck MW et al 2001 J Biol Chem 276:9273; Barker N et al 2001 EMBO J 20:4935; ►breast cancer

Bric: ►Byler disease

Bridge: Anaphase tie between separating centromeres in dicentric chromosomes (see Fig. B64). ►breakage-fusion-bridge, ►inversion

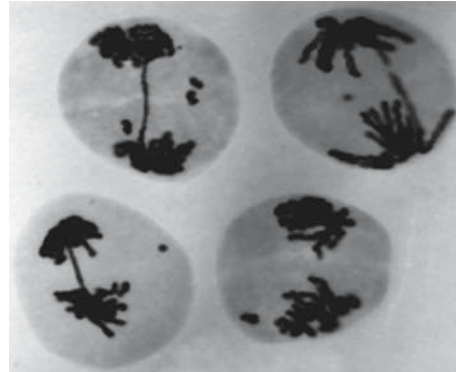


Figure B64. Bridge. Meiotic anaphase single and double bridges and 1 or 2 chromatid fragments resulting from 2 and 4 strand recombination in a paracentric inversion heterozygote (Courtesy of Dr. Arnold Sparrow)

BRIDGE: β -lactamase Reporter for Imaging Downstream gene expression. ► β -lactamase

Bridge Protein: Facilitates the interaction between viral particles and cell surface receptors.

Bridging Cross: If two genetically distant sexually incompatible species (A and B) are to be selected for gene transfer by sexual means. The problems can possibly be overcome by first mating one of the species with an intermediate compatible form (C) and then cross the hybrid (A \times C) to the other (B). C serves as the bridge.

Bright Paramecia: ►symbionts hereditary

Bright-Field Microscopy: Ordinary light microscopy. ►dark-field microscopy, ►fluorescent microscopy, ►phase contrast microscopy, ►Nomarski, ►stereomicroscopy

Brim: Break repair induced mutation. ►DNA repair, ►DNA repair

Bristle: ►chaetae

Britten & Davidson Model: This model was suggested as a working hypothesis in the 1960s for interpreting the processes involved in the regulation of eukaryotic

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gene functions. The external stimuli were supposed to be directed to *sensor* genes that activated *integrator* genes that in turn transmitted the signals to *receptor* genes, which affected then the *structural* genes, coding for protein. These systems might have operated then in series of interacting batteries. (Britten RJ, Davidson EH 1969 Science 165:349; Britten RJ 1998 Proc Natl Acad Sci USA 95:9372).

BRM: Animal chromatin remodeling ATPases of ~1,600 amino acids. ▶chromatin remodeling, ▶BRAHMA, ▶BRG1; Banine F et al 2005 Cancer Res 65:3542.

Brn: Eukaryotic transcription factors with POU domain controlling terminal differentiation of sensorineural cells. They are homologous to unc-86 in *Caenorhabditis*. ▶POU, ▶unc-86

Broad Bean (*Vicia faba*): $2n = 2x = 12$ and large chromosomes has been used extensively for cytological research (see Fig. B65). It is an important crop in cool climates. ▶favism, ▶*Vicia faba* for karyotype



Figure B65. Broad bean

Broad-Betalipoproteinemia: A hyperlipoproteinemia. ▶apolipoproteins, ▶hyperlipoproteinemia

Broad Sense Heritability: ▶heritability

Brody Disease (ATP2A1): A rare recessive disease encoded in human chromosome 16p12.1-p12.2, and it involves impairment of muscle relaxation, stiffness and cramps in the muscles. The basic defect is associated with the muscle sarcoplasmic reticulum calcium ATP-ase (SERCA1). ▶neuromuscular diseases, ▶sarcoplasmic reticulum, ▶Darier-White disease

Broken Tulips: Variegation (sectors) in the flowers is caused by viral infection (see Fig. B66). These sectorial tulips have commercial value in floriculture. In the seventeenth and eighteenth century the bulbs were so highly valued that they fetched gold of equal weight. ▶symbionts hereditary, ▶infectious heredity



Figure B66. Broken tulip

Bromodomain: A more or less cylindrical shape association of four helices of about 100 amino acids that form the docking sites in the chromatin for a large number of proteins (see Fig. B67). The lysine-acetylated H3 and H4 histones may be fitting into the bromodomains and are the conditions for gene transcription in eukaryotes. Bromodomains appear to anchor histone acetylase to the chromatin. ▶chromatin remodeling, ▶histones, ▶histone methyltransferases, ▶histone acetyltransferases, ▶p300, ▶SAGA, ▶PCAF, ▶SNF, ▶TAF, ▶TAF_{II}250; Ornaghi P et al 1999 J Mol Biol 287:1; Dhalluin C et al 1999 Nature [Lond] 399:491; Zeng L, Zhou M-M 2002 FEBS Lett 513:124.

Bromophenol Blue: ▶tracking dyes

Bromouracil (BU): A pyrimidine base analog that is mutagenic in prokaryotes because it may lead to base substitution after tautomeric shift. When incorporated into eukaryotic chromosomes it may cause breakage upon exposure to light. On this basis, it has been successfully used as a selective agent in animal cell cultures. The non-growing mutant cells failed to incorporate it and survived while the growing (wild type) cells were killed upon illumination. Eosinophil peroxidase may produce 5-bromodeoxycytidine and the latter is incorporated into DNA as 5-bromodeoxyuridine, which by mispairing with guanine may become mutagenic. ▶base substitution, ▶tautomeric shift, ▶hydrogen pairing, ▶chemical mutagens, ▶eosinophil; Benzer S, Freeze E 1958 Proc Natl Acad Sci USA 44:112.

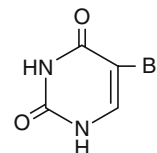


Figure B67. Bromouracil

Bronchitis: Inflammation of the air passages and lung.

Bronze Age: About 5000 years ago marked the development of crafts and urbanization.

Brood: The offspring of a single mating or the cluster of eggs (clutch) laid by a bird or reptile.

Brown Fat: Adipose tissue that mainly dissipates heat. Humans with pheochromocytoma have large deposits of brown fat. ▶adipocyte, ▶pheochromocytoma

Brownian Ratchet: A hypothesis explaining transport of molecules into the mitochondria by Brownian movement (thermal agitation of molecules). Mitochondrial Hsp70-bound ATP complex associates with Tim proteins and nuclear encoded pre-proteins destined to mitochondria slide into import channels. The Mge1 protein initiates the ADP exchange and thus prevents backward movement and the protein is imported into the organelle. ▶mitochondrial import, ▶Mge1, ▶ADP, ▶ATP; Brokaw CJ 2001 Biophys J 81:1333.

Brownian-Zsigmondy Movement: Colloidal particles in solution may be in a continuously-agitated motion due to collision with the medium. It can microscopically be observed also in the cytosol of living cells.

Browsers: They provide comprehensive views by Internet access on genes, annotations, genomic regions, chromosomes and other important aspects of genomes. (UCSC Genome browser: <http://genome.ucsc.edu>; Hsu F et al 2005 Nucleic Acids Res 33:D54; National Center for Biotechnology: <http://www.ncbi.nlm.nih.gov>; Wheeler DL et al 2005 Nucleic Acids Res 33:D39; ENSEMBLE browser: <http://www.ensembl.org>; Hubbard T et al 2005 Nucleic Acids Res 33:D447; Revised and updated list appears annually in the first issue of Nucleic Acids Research).

Bruce: A 528 kD peripheral membrane protein of the trans-Golgi network and functions as an inhibitor of apoptosis. ▶trans-Golgi network, ▶apoptosis; Bartke T et al 2004 Mol Cell 14:801.

Bruce Effect: The termination of pregnancy in mice by olfactory influence on a pregnant female of a male that is genetically different from the inseminator. ▶olfactogenetics, ▶pheromones; Rajendren G, Dominic CJ 1987 Exp Clin Endocrinol 89:188.

Brucella: Bacteria responsible (for brucellosis) abortion and infertility of animals and serious febrile infection of male and female humans. *Brucella suis* 3.31 Mb and *B. melitensis* 3.29 Mb DNA have been completely sequenced. (See DelVecchio VG et al 2002 Proc Natl Acad Sci USA 99:443; Paulsen IT et al 2002 Proc Natl Acad Sci USA 99:13148; genome: <http://bbrp.llnl.gov/bbrp/html/microbe.html>).

Brugada Syndrome (SCN5A, 3p21): A dominant LQT-type heart disease (idiopathic ventricular fibrillation) due to defect in exon 28 of a sodium channel (SCN5A) gene. SUNDS (sudden unexplained nocturnal death syndrome) relatively common in

Southeast Asia is controlled by an allelic gene. ▶LQT, ▶heart diseases, ▶ion channels; Vatta M et al 2002 Hum Mol Genet 11:337.

Brush Border: A dense lawn of microvilli on the intestinal and kidney epithelium that facilitates absorption by increasing the surface. ▶microvilli

Bruton's Tyrosine Kinase: ▶BTK, ▶agammaglobulinemia

Bryophytes: Mosses, liverworts and hornworts. They are green plants similar to algae but the organization of their body is more complex. Their gametangia is either unicellular or multicellular and show some cell differentiation. They usually have haploid and diploid life forms. The majority of them are terrestrial. ▶alga

BS: ▶Bloom syndrome

BSAP: ▶pax

BSE (bovine spongiform encephalopathy): ▶encephalopathies, ▶Creutzfeldt-Jakob disease

BSL (biological safety level): BSL is specified by governmental regulations, BSL-1 is the minimal and BSL-4 is the most stringent, depending on the hazards involved.

bT: as a prefix for *Bos taurus* (bovine) DNA or protein.

BTB: Protein domains named for the *Drosophila* transcription factors Bric-a-brac (bab), Tramtrack (ttk) and Broad-Complex (BR-C) that associate with cullins, ubiquitin ligase and are required for the degradation of the meiotic spindle and the assembly of the mitotic spindle. BTB is an adaptor for the SCF complex. ▶cullins, ▶ubiquitin, ▶SCF, ▶spindle; Pintard L et al 2003 Nature [Lond] 425:311; Xu L et al 2003 Nature [Lond] 425:316.

BT2: same as TFIIH. ▶transcription factors

BTG: Antiproliferative protein encoded in human chromosome 1q32. Its synthesis is regulated by p53. ▶p53

BTK (Bruton's tyrosine kinase): It belongs to a family of non-receptor tyrosine kinases. Its deficiency results in immunodeficiency by blocking differentiation of B lymphocytes. Syk and Lyn activate BTK with the mediation of BLNK. BTK phosphorylates transcription factor TFII-1 and loss of the TFII-1 gene results in Williams-Beuren mental defect. TFII-1 acts as a negative regulator outside the nucleus and interferes with calcium entry (Caraveo G et al 2006 Science 324:122). ▶agammaglobulinemia, ▶Sky, ▶Lyn, ▶B lymphocyte receptor, ▶Williams syndrome; Liu W et al 2001 Nature Immunol 2:897.

βTrCP: A ubiquitin ligase, frequently associated with SCF and regulates by degradation of diverse

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metabolic and developmental pathways. ►ubiquitin; Zhang J et al 2003 Proc Natl Acad Sci USA 100:14127.

BUB1, BUB2: These are checkpoint proteins arresting mitosis when the spindle attachment assembly is defective or there are problems with sister chromatid separation. ►cell cycle, ►meiosis I, ►MAD, ►p53; Krishnan R et al 2000 Genetics 156:489; Geymonat M et al 2002 J Biol Chem 277:29439; relation to p53: Gjoerup OJ et al 2007 Proc Natl Acad Sci USA 104:8334.

Bubble: A bubble is formed when at replication the two strands of the DNA separate or when transcription begins on DNA. Re-annealing the bubble at promoter clearance is called bubble collapse (Pal M et al 2005 Mol Cell 19:101). ►promoter clearance

Bubonic Plague: ►Yersinia

Buccal Smear: A sample of the epithelial cells from the inner surface of the cheek is spread onto microscope slides and used for rapid determination of the number of Barr bodies with 4–5% error rate. This procedure (mucosal swab) is non-invasive and the sampling is painless. The cells so sampled may also be used for DNA analysis by PCR after a rapid (ca. 1 hr) extraction. ►Barr body, ►PCR

Buckwheat (*Fagopyrum*): A feed and food plant ($2n = 2x = 16$). Eaten by animals or by humans, it may increase sensitivity to light and skin rash (see Fig. B68). ►favism



Figure B68. Buckwheat

Bud (budding protein of yeast): A cytoskeleton assembly-mediating protein family. Bud proteins associated with GTPase activating protein (GAP) are required for axial and bipolar budding patterns. ►Bni, ►cytoskeleton, ►profilin, ►polarity embryonic

Bud Scar: A chitin ring formed at the junction of the mother and daughter yeast cells that persists even after separation of the two cells. The number of bud scars may indicate the number of cell divisions (age) of the cell as well as polyploidy which is characterized by a different pattern of the bud scars.

Bud Sport: Genetically different sector (due to somatic mutation) in an individual plant (chimera).

Budding: Asexual reproduction by which the cell's cytoplasm does not divide into two equal halves, yet the bud after receiving a mitotically divided nucleus eventually reproduces all cytoplasmic elements and grows to normal size. Budding of enveloped viruses takes place by acquiring their membrane of lipid bilayer and proteins. They direct their surface glycoproteins into one or another type of cell membrane. They are pinching off either from the cell surface or into the cell lumen. The lipids of the bilayer come from the cell whereas the virus DNA specifies the proteins. ►Saccharomyces cerevisiae; retrovirus budding: Fisher RD et al 2007 Cell 128:841.

Budding Yeast: ►Saccharomyces cerevisiae (see Fig. B69).



Figure B69. Budding yeast

BUdR (5-bromodeoxyuridine): Animal cells deficient in thymidine kinase enzyme are resistant to this analog. It is a base analog mutagen, substituting for thymidine and may cause mutation. Its mutagenic efficiency is low, especially in eukaryotes although if cells with BUdR substituted chromosomes are exposed to visible light, chromosome breakage is induced. When chromosomes with BUdR substitutions, at least in one of the strands, are exposed to low LET ionizing radiation, double-strand breaks occur in proportion of the amount of substitutions. The presence of reducing agents (e.g., e^-_{aq}) favors breakage. ►bromouracil, ►base substitution mutation, ►sister chromatid exchange, ►hydrogen pairing

Buerger Disease: Autosomal recessive predisposition to thromboangiitis (inflammation of the blood vessels); its frequency is relatively high in some oriental ethnic groups.

Buffalo: Asiatic swamp buffalo (*Bubalus bubalis*) $2n = 48$, the Murrah buffalo (*Bubalus bubalis*) $2n = 50$, the African buffalos (*Syncerus caffer caffer*) $2n = 52$, and the *Syncerus caffer nanus* is $2n = 54$.

Buffer: A chemical solution capable of maintaining a level of pH within a particular range depending on the components of an acid-base system. Also a special storage area in the memory of a computer from where the information can be utilized at different rates by different programs; e.g., the printer can store information faster than it can print it.

Buffer Sequences: To avoid the loss of indispensable 5' and 3' tracts from linearized transforming DNA,

protective sequences may be added to the constructs. These buffers should not have cryptic splice or regulatory sites. Introns may be used.

Buffering, Genetic: A homeostatic mechanism that is supposed to maintain the function of genes at a certain level. ▶Redundancy (duplications), ▶feedback, ▶epistasis, ▶temperature-sensitivity, ▶modifier genes, ▶signal transduction, ▶chaperones, ▶apoptosis, etc. may mediate it. (Kitami T, Nadeau JH 2002 *Nature Genet* 32:191).

Bufo vulgaris (toad, $2n = 36$): A primarily terrestrial small frog species and it lives in water environment during the mating season. (▶*Rana*, ▶*Xenopus*, ▶frog, ▶toad)

Build: The sequence of the human genome. The most complete sequence in 2004 is denoted as Build 35. (See *Nature [Lond]* 431:931).

Bulge: Unpaired stretches in the DNA. They are involved in binding of regulatory protein domains, in enzymatic repairs, slipped mispairing in the replication of microsatellite DNA, intermediates in frame shift mutations and essential elements for naturally occurring antisense RNA ▶DNA repair, ▶binding proteins, ▶mismatching, ▶frame shift mutation, ▶microsatellite, ▶antisense RNA

Bulimia: A psychological disorder involving excessive eating and self-induced vomiting based on serotonergic abnormality. ▶anorexia, ▶obesity, ▶serotonin, ▶addiction; Bulik CM et al 2003 *Am J Hum Genet* 72:200.

Bulked Segregant Analysis: It is used in mapping recombinant inbred lines. The individuals in the population are identical at a particular locus but unlinked regions in the chromosomes are represented at random. ▶RAPD

Bulk-Flow Model: It postulates that targeting signals does not regulate export of molecules from the endoplasmic reticulum. Experimental evidence indicates, however, that even the constitutively excreted proteins carry some target specificities. ▶endoplasmic reticulum

Bulking: A plant breeding procedure when selection of segregants after a cross is delayed to later generations when the majority of individuals become homozygous by continued inbreeding. The number of heterozygotes by F_n is expected to be $0.5(n-1)$ for a particular locus where n stands for the number of generations selfed. Note: the F_1 is produced by crossing therefore we use $n - 1$. ▶inbreeding progress of, ▶inbreeding rate

Buller Phenomenon: When from dikaryotic mycelia nuclei may move into monokaryotic ones. ▶di-mon

Bullous Pemphigoid Autoimmune Disease: A human chromosome 6p12-p11 dominant autoimmune disease manifested as vesicles on the skin. It is based on a defect involving the ca. 230 kDa glycoprotein (antigen BPAG1e). This antigen affects also the nerve fibers. ▶filament, ▶autoimmune disease

Bundle: Protein α -helices running along the same axis. ▶protein structure

Bundle Sheath: Cells wrapped around the phloem bundles. Their chloroplasts do not show grana and synthesize carbohydrates through the C3 pathway although the other chloroplasts in the same plant operate by the C4 system. ▶chloroplasts, ▶C3 plants, ▶C4 plants

Bungarotoxin: ▶toxins

Buoyant Density: A molecule (e.g., DNA) suspended in a salt density gradient (such as a CsCl solution, spun for 24 hr at 40,000 rpm in an ultracentrifuge tube) comes to rest in the salt gradient at the position where the medium (CsCl) density is identical to its own. The buoyant density of, e.g., *Chlamydomonas* nuclear and chloroplast DNA is 1.724 and 1.695, respectively. Higher buoyant density reflects higher G + C content in the DNA. The refractive index determined by a refractometer, capable of 5-digit resolution, can be used to determine the density (ρ) of a cesium chloride solution in any sample withdrawn from the centrifuge tube. The relevant relationships at 25°C are the following:

Table B8. Determining Buoyant Density

| CsCl Weight% | Density g/mL | Refractive Index | Molarity |
|--------------|--------------|------------------|----------|
| 50 | 1.5825 | 1.3885 | 4.700 |
| 55 | 1.6778 | 1.3973 | 5.481 |
| 56 | 1.699 | 1.3992 | 5.651 |
| 57 | 1.7200 | 1.4012 | 5.823 |
| 58 | 1.7410 | 1.4032 | 5.998 |

The density of *E. coli* DNA is about 1.710 and that of *Mycobacterium phlei* is 1.732 and a deoxy A-T polymer has a (ρ) value of 1.679. Since none of these values are directly readable from the tabulation, interpolation is required that can be done by graphic representation. ▶density gradient centrifugation

Buphthalmos: ▶glaucoma

Burbank, Luther (1849–1926): American breeder credited with the production of over 800 new varieties and strains of plants, mainly in Santa Rosa, California. In addition, his success had a stimulating

B

effect on the development of plant breeding. Regrettably, his mystic, Lamarckian ideas also hindered scientific plant breeding. (See Crow J 2001 Genetics 158:1391).

Burden of Proof: The responsibility of proving the validity of an assertion, e.g., that a genetically modified organism or a drug is hazardous or harmful.

Burdo: A “graft hybrid” between tomato and nightshade (*Belladonna*), forming a periclinal chimera. The graft hybrids were assumed to be the result of fusion between the cells of different species combined at the site of the grafting. From this site then somatic hybrid cells regenerated into plants. ▶periclinal, ▶somatic cell hybrids; Winkler H 1907 Ber Dtsch Bot Ges 25:568.

Burkitt's Lymphoma: A human cancer caused frequently by the Epstein-Barr virus is most common in central Africa but occurs in other parts of the world, involved in nasopharyngeal (nose and throat) carcinoma and neoplasias of the jaws and the abdomen. It frequently involves a translocation between human chromosomes 8 (c-myc oncogene) to 14 (immunoglobulin promoter). The receptor of the Burkitt's lymphoma is activated by a chemokine that is targeted to B cells in the lymphoid follicles. The Epstein-Barr virus positive lymphomas display elevated amount of reactive oxygen species (ROS), a likely contributing factor to cancer (Cerimele F et al 2005 Proc Natl Acad Sci USA 102:175). ▶Epstein-Barr virus, ▶chemokine, ▶B cell, ▶lymphoma, ▶methylation of DNA, ▶immunoglobulins, ▶myc

Bursa: Generally a sac like pouch; the bursae Fabricius are located in the intestinal tract of birds and produce the B lymphocytes. ▶lymphocytes

Burst Size: The average number of phage particles released by the lysis of bacteria.

Bus: It is the circuit system in a computer that transmits information within the hardware or cables that link together various devices with the computer.

Bushmen: A designation for nomadic people who live in the wilderness (bush), such as the Australian aborigines or people in the Kalahari Desert. The anthropological characteristics are shared within the group but there is no known evolutionary relationship among the Bushmen inhabiting different geographical regions.

Busulfan (C₆H₁₄O₆S₂, most common trade name myleran): It is antineoplastic/carcinogenic chemical (see Fig. B70). It is a mitotic germ cell toxicant; eliminates primordial follicles. It is also a chemosterilant pesticide. ▶Myleran

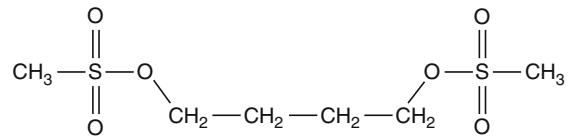


Figure B70. Busulfan

Buzzword Index (BWI): BWI indicates the varying trends of use of certain terms in the science literature.

$$BWI = Ln(n)X \frac{(n+1)/(N+1)}{(n^*+1)/(N^*+1)}$$

Where n is the number of times the term was mentioned in the past year and n^* is the number of times the word was mentioned during the past 10 years. N and N^* are similarly calculated on the basis of the occurrence of the word “biology” and this normalizes the score with respect to the general growth of biology papers. (Adopted from Jensen LJ et al 2006 Nature Rev Genet 7:119).

BvgS: *Bordetella pertussis* (bacterial) kinase affecting virulence regulatory protein BvgA. ▶pertussis toxin

Bypass Replication: It is capable of bypassing a DNA defect and continues the process beyond it. It does not lead to permanent repair. ▶DNA repair

Byr 2: A serine-threonine kinase of *Schizosaccharomyces pombe*. An analog of RAF. ▶raf, ▶signal transduction, ▶serine/threonine kinase

Byler Disease (PFIC1, 18q21): Progressive intrahepatic cholestasis. It is apparently allelic to the benign recurrent intrahepatic cholestasis (BRIC). Bile acid secretion is defective due to defect(s) in the ATP-binding cassette (ABC) transporter. ▶cholestasis, ▶Alagille syndrome, ▶ABC transporter

Bystander Activation: A hypothesis for the origin of autoimmune reaction. Viruses may induce inflammation resulting in cytokine production. The cytokines may reactivate dormant T cells with low activation threshold and these T cells may then attack self-antigens that normally escape their attention. Non-malignant immune cells infiltrating follicular lymphoma have profound effect on the development of this type of cancer (Dave SS et al 2004 New England J Med 356:2159). ▶self antigen, ▶immune response, ▶autoimmune disease, ▶immune tolerance, ▶bystander effect; Fournie GJ et al 2001 J Autoimmun 16:319.

Bystander Effect: Genetic vectors targeted to a particular cell type do not spread to neighboring cells, yet their synthesized transgene product (e.g., a toxin) may diffuse and also kill the surrounding cells. The bystander effect is a complex result of intercellular communication through gap junctions, apoptotic cell

death, release of cytokines, blocking of angiogenesis, etc. ►gene therapy, ►cancer gene therapy, ►Mo-MuLV, ►transgene, ►gap junctions, ►cytokines, ►apoptosis, ►angiogenesis, ►vectors, ►radiation response, ►radiation hazard; Zheng X et al 2001 Mol Pharmacol 60:262.

Byte: A computer unit of information consisting of a number of adjacent bits. Most frequently 1 byte is

8 bits that represent a letter or other characters that the computer uses. ►bit

B

bZIP: basic leucine zipper. ►leucine zipper, ►DNA-binding protein domains

B-Zip Protein: A DNA binding, protein contains a basic amino acid zipper domain. ►binding proteins

Historical vignette

William Bateson, the most ardent Mendelian, among many of his original contributions, discovered that the interactions among gene products modify the Mendelian ratios without compromising the validity of the basic principles. In 1926 TH Morgan eulogized Bateson with these words: "His intellectual rectitude was beyond all praise and recognized by friend and foe alike" (*Science* 63: 531).

Bateson enjoyed popularity in America and was personally familiar with most of his American colleagues. In 1922, at the University of Pennsylvania, he concluded a memorial lecture with the following warning:

"I think we shall do genetical science no disservice if we postpone acceptance of the chromosome theory in its many extensions and implications. Let us distinguish fact from hypothesis. It has been proved that, especially in animals, certain transferable characters have a direct association with particular chromosomes. Though made in a restricted field this is a very extraordinary and most encouraging advance. Nevertheless the hope that it may be safely extended into a comprehensive theory of heredity seems to me ill-founded, and I can scarcely suppose that on a wide survey of genetical facts, especially those so commonly witnessed among plants, such an expectation would be entertained. For phenomena to which the simple chromosome theory is inapplicable, save by the invocation of a train of subordinate hypotheses, have been there met with continually, as even our brief experience of some fifteen years has abundantly demonstrated" (*J. Genet.* 16: 201 [1926]).

W. Bateson
1922

C

C: An abbreviation of cytosine. ► [cytosine](#)

3C: ► [chromosome conformation capture](#)

4C (circular chromosome conformation capture):
► [chromosome conformation capture](#)

C6: Rat glioma cell line (tumor of tissues supporting the nerves). ► [glioma](#)

C6: Fungal zinc-binding protein cluster.

c25: A prolactin/cycloheximide responsive transcription factor similar to IRF-1 (interferon regulator factor); controls proliferation and anti-proliferation responses in cells. ► [transcription factors](#), ► [IRF](#), ► [interferon](#)

C α: The carbon atom(s) of amino acids to which an amino group, carboxyl group, hydrogen atom or a side chain is attached.

C Amount of DNA: Content of DNA in the gametes is 1C; it is 2C in the zygotic cells before S phase, 4C after S phase. The 1C amount actually means that the chromosomes have only one chromatid containing a single DNA double helix. After replication, each chromosome becomes double-stranded, i.e., composed of two chromatids held together at the centromere. The 4C stage usually is an indication of a diploid or zygotic cell. ► [cell cycle](#), ► [C value paradox](#)

C Banding: A type of banding pattern near the centromere (and some other limited areas, such as telomeres) obtained after staining chromosomes with the Giemsa stain (a mixture of basic dyes), particularly when, prior to staining, the chromosomes were exposed to the protease trypsin (see Fig. [C1](#)). ► [chromosome banding](#), ► [G banding](#), ► [R banding](#); Chen TR, Ruddle FH 1971 Chromosoma 34:51.



Figure C1. C banding

C.E.: Common Era; designation of historical time of, e.g., archeological sites.

C genes: Genes coding for the constant region of the antibody molecule (such as C μ , C δ , C γ , C ϵ , C α). ► [immunoglobulins](#); ► [antibody](#)

C1 Inhibitor: A proteinase inhibitor of the serpin family; it is a regulator of blood clotting. ► [serpin](#)

C Kinase: A Ca²⁺-dependent protein kinase attached to the plasma membrane. Diacylglycerols and/or phosphatidylserine may activate it. It may be indirectly involved in +/- regulation of genes. ► [RACK](#)

C Period: A full cycle of the replication of DNA measured in time units.

C₃ Plants: These plants produce three-carbon molecules (phosphoglycerate) as the first step in photosynthesis. By genetic engineering some of the C₄ enzymes can be expressed in C₃ plants. ► [Calvin cycle](#), ► [photosynthesis](#); Matsuoka M et al 2001 Annu Rev Plant Physiol Mol Biol 52:297.

C₄ Plants: The first products of their carbon fixation are four-carbon molecules (oxaloacetate, malate, aspartate); their photosynthetic efficiency is greater than that of C₃ plants. ► [C₃ plants](#)

C Terminus: The carboxyl end of a polypeptide chain. ► [collinearity](#), ► [amino end](#)

C Value: The amount of DNA in a single chromatid or chromosome before the DNA has replicated. Thus, the C value in the gametes is 1, in the diploid zygote it is 2, and after S phase before cell division takes place it may be 4 C. ► [genome](#); Plant DNA C Value Database: <http://www.rbgekew.org.uk/cval/database1.html>; Animal Genome Size Database: <http://www.genomesize.com/>.

C Value Paradox: The lack of relationship between evolutionary status (complexity of an organism) and its genome size, e.g., the size of the genome of the plant *Fritillaria* is $\sim 3 \times 10^8$ kbp whereas that of *Homo* is $\sim 3 \times 10^6$ kbp. ► [copy number paradox](#), ► [genome](#), ► [pseudogenes](#), ► [redundancy](#), ► [repetitious DNA](#), ► [junk DNA](#), ► [gene number paradox](#), ► [N value paradox](#), ► [H value paradox](#); Petrov DA 2001 Trends Genet 17:23; Gregory TR 2001 Biol Revs 76:65.

C₆ Zinc Cluster Protein: A group of transcriptional activators. Their DNA binding sites have the conserved CGG...CCG triplets and, in-between, a number of other bases in the different members of the family. Furthermore, there is a 19-amino acid carboxy-terminal region at the zinc cluster side, containing the linker and the beginning of the dimerization element that directs the protein to its preferred site. ► [transcription factors](#), ► [transcriptional activator](#), ► [zinc finger](#); Akache B et al 2001 Nucleic Acids Res 29:2181.

CAAT Box (CCAAT): A consensus sequence in the untranslated promoter region of eukaryotic genes, recognized by transcription factors. Housekeeping

genes may not have this box or a TATA box. ►C/EBP, ►AP, ►G box, ►asparagine synthetase, ►promoter, ►TATA box, ►housekeeping genes

C

CaaX Box: A membrane-binding protein motif.

CAB: ►chlorophyll-binding protein

Cabbage: ►*Brassica*

CaBP (calcium-binding protein): An endoplasmic reticulum chaperone protein (49 kDa) with two thioredoxin kind domains. ►PDI, ►chaperones

CAC (chromatin assembly complex): Includes histones H3 and H4 and the chromatin assembly factor. CAC subunits are p160, p60 and p48. ►histones, ►nucleosome, ►CAF, ►chromatin

Cacajo: ►Cebidae

Cacao (*Theobroma cacao*): A tropical plant; also a source of chocolate and cocoa derived from the dried oily cotyledons of the seed. The economically useful species are $2n = 2x = 20$. In the flavonol-rich content, epicatechin actively increases nitric oxide synthesis in the body causing vasodilation and this is beneficial for atherosclerosis. (Schroeter H et al 2006 Proc Natl Acad Sci USA 103:1024).

Cache: A memory in the computer that increases the speed and efficiency of the machine.

Cachectin: A hormone-like protein product of the macrophages which releases fat and lowers the concentration of fat synthetic and storage enzymes. It is encoded by a gene situated within the HLA cluster in human chromosome 6p21.3. ►HLA, ►macrophage; Jue DM et al 1990 Biochemistry 29:8371.

CACHET (condensation of amplification circles after hybridization of encoding tags): ►padlock probes

Cachexia: A condition of emaciation, of the wasting away of muscles. It may be caused by a 24 kDa proteoglycan as the consequence of cancer or other debilitating conditions. Tumor necrosis factor α may have an important role in it. The proteasome activity is aided by glucocorticoids, but NF- κ B aids the process by down-regulating MyoD, which replenishes muscle fibers. ►proteoglycan, ►TNF, ►NF- κ B, ►proteasome, ►MyoD, ►obesity; Rubin H 2003 Proc Natl Acad Sci USA 100:5384.

CACN1A4: α subunit of a brain-specific voltage-gated neuronal calcium ion channel, encoded at human chromosome 19p13.1. ►migraine, ►ion channels, ►spinocerebellar ataxia

Caco: Colon adenocarcinoma, a malignant adenoma. ►adenoma, ►carcinoma

Cactus: A protein product of the *cact* gene of *Drosophila* (2–52) which controls dorsoventral differentiation by maternal effect in the embryo. Its action is similar to Dorsal. The protein Toll dissociates Cactus from Dorsal and subsequently Dorsal moves into the nucleus. Pelle (serine/threonine kinase) and Tube mediate the signals from Toll to the Dorsal-Cactus complex (morphogenesis in *Drosophila*).

CAD (caspase-activated DNase): Degrades chromatin by cleavage between the histone-DNA complex of the nucleosomes during apoptosis. ►caspase, ►DNase, ►nucleosome, ►chromatin, ►ICAD, ►acinus, ►apoptosis, ►ICAD, ►endonuclease G; Enari M et al 1998 Nature [Lond] 391:43.

CAD (coronary artery disease): ►coronary heart disease

CAD: A three-enzyme complex trifunctional protein catalyzing the first three steps in the *de novo* pyrimidine pathways (carbamoyl phosphate synthetase II, aspartate transcarbamylase, and dihydroorotase). All the three identical polypeptide subunits (Mr 230,000, each) have active sites for the three reactions. In the Syrian hamster, the gene coding for it is 25 kbp; it has 37 introns and the mRNA transcript is 7.9 kb. When amplified, this complex is 500 kbp. The synthesis of carbamoyl phosphate synthetase II is stimulated by the epidermal growth factor (EGF) and ERK MAP kinase system. ►pyrimidine, ►EGF, ►signal transduction; Chen S et al 2001 Proc Natl Acad Sci USA 98:13802.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy): A complex syndrome encoded in an 800 kb region of human chromosome 19p13.2-13.1 (Notch3). It involves diffuse white matter in the brain, defects in the brain blood vessels, stroke, progressive mental illness, paralysis of the face, headaches, severe depression, etc. The basic defect is in a glycosylated transmembrane receptor protein, homologous to Notch of *Drosophila*. ►Notch, ►presenilins, ►morphogenesis in *Drosophila*, ►Alzheimer disease, ►transmembrane proteins, ►stroke, ►brain human, ►migraine, ►leukoencephalopathy

Cadastral: Within a topological boundary. Cadaster originally meant land maps for taxation generated in detail and at various scales, e.g., 1 inch on paper corresponding to yards or furlongs on the land.

Cadherins: Cell adhesion molecules (glycoproteins) dependent on the presence of Ca^{2+} . The quantity and quality of cadherins determines how cells of the same type stay together and how different types segregate during embryonic development, i.e., the nurse cells, follicle cells, and the embryo segregate to different

poles in the egg chamber of *Drosophila* (see diagram at maternal effect genes). Cadherins alone do not determine the specificity of cell sorting (Niessen CM, Gumbiner BM 2002 J Cell Biol 156:389). Cadherins are encoded in human chromosome 16q22.1. The human protocadherins genes PCDH α , β , γ are in chromosome 5q31, but PCDH7 is at 4p15 and PCDH22 is at Yp11.2. Protocadherin genes are found also at 13q21.1 and at 10q21-q22. The protocadherins are classified as nonclassic cadherins because—unlike the classic cadherins—they do not interact with catenins. They have a basic role in normal development and a reduction in their level increases the invasiveness of many types of cancerous growths. They have membrane-spanning and cytoplasmic domains. The former assures cell-to-cell contacts, the latter attaches to the cytoskeleton. Dominant negative cadherin mutants develop Crohn's disease-like symptoms, spina bifida and adenomas. Dysadherin, a 178 amino acid cell membrane glycoprotein, down-regulates E-cadherin and promotes metastasis. ▶Crohn's disease, ▶adenoma, ▶spina bifida; ▶integrin, ▶catenin, ▶gastric cancer, ▶deafness, ▶Usher syndrome, ▶snail, ▶pattern formation during development, ▶p38; Nollet F et al 1999 Mol Cell Biol Res Comm 2:77; Poser I et al 2001 J Biol Chem 276:24661; Alagramam KN et al 2001 Hum Mol Genet 10:1709; Ino Y et al 2002 Proc Natl Acad Sci USA 99:365; cadherins in development: Halbleib JM, Nelson WEJ 2006 Genes Dev 20:3199.

cADP-ribose: ▶cyclic ADP-ribose

***Caenorhabditis briggsae*:** A close relative of *Caenorhabditis elegans* and living in the same ecological

niche. It appears to have 19,500 protein-coding genes and 12,200 of them clearly orthologous to those of *C. elegans*. Only about 800 of its genes do not show matches in *elegans*. In 96% of the genes, collinearity is preserved. The repetitive sequence is 22.4% in *C.b.* but only 16.5% in *C.e.* (See Fig. C2; Stein LD et al 2003 PLOS Biol 1:166).

***Caenorhabditis elegans*:** A small nematode, which feeds on bacteria. It completes its life cycle in about $3\frac{1}{2}$ days. Approximately 99.8% of the animals have the following chromosomal constitution: 5 pairs of autosomes and two X chromosomes and are hermaphrodites; 0.2% of the populations are XO males generated by nondisjunction. Its genome is about ~97 million bp and has been sequenced. It includes a little more than 19,000 genes and 40% of them appears homologous to that of other organisms. The nervous system includes only about 302 cells. The neurons represent 118 structural classes and the number of positions of identifiable chemical synapses appears to be 7,600. More than 250 genes were identified by mutational analysis to be involved in behavior. All of its genes have been cloned and sequenced. It is one of the best organisms for molecular developmental studies. The simplest developmental pathway of animals is seen in this nematode, with approximately 958 somatic cells, including its nervous system, in a thin 1.2 mm long body of the adult. The egg usually develops hermaphroditically or by fertilization by the rare males, into a 550-cell embryo in the eggshell. Further divisions take place after hatching and passing, by moltings, through four larval stages. The entire

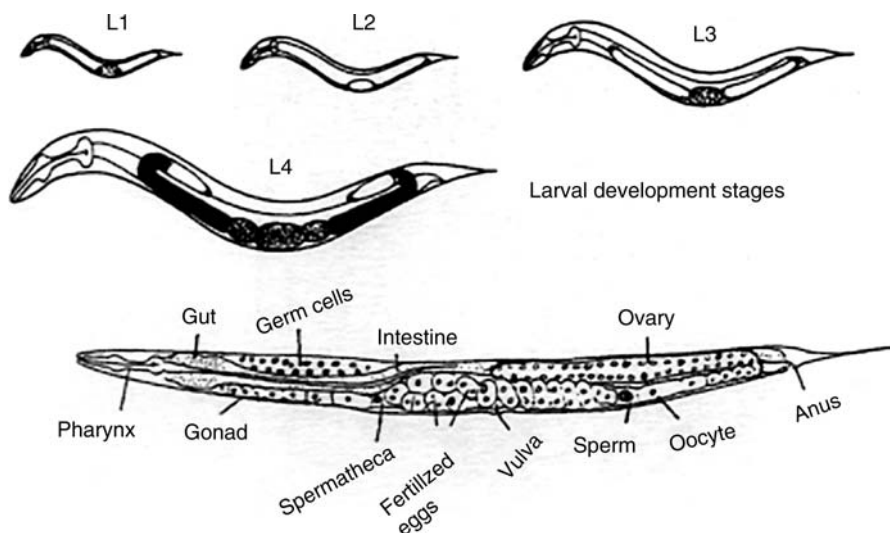


Figure C2. *Caenorhabditis elegans* adult hermaphrodites larval developmental stages

process may be completed in about three days. Through the transparent body, the migration of the embryonal cells and formation of organs can be traced under the microscope using Nomarski differential interference contrast optics. The pattern of differentiation and development displays very little variation. The somatic tissues generally have multicellular origin whereas the intestinal cells and the germline cells, each, are monoclonal. For differentiated functions, cytokinesis is not absolutely required. Differentiation is generally not controlled by the cellular milieu but by the identity of the particular cell (demonstrated by ablation experiments). Nevertheless, signal transduction among cells may also be required for the formation of the egg-discharging mechanisms. Through the involvement of a single anchor cell, the vulva is formed and the uterus passes the egg through the anchor and vulva on the culture medium contained in a Petri plate where development is completed. A somatic “distal tip cell” controls the mitotic activity of the “germ cells” which undergo meiosis and produce the gametes. The hermaphroditic XX females are self-fertilized, but by nondisjunction they also produce male gametes at a frequency of 0.1%. The XO males, when mated with an XX female, produce males and females in equal proportion (see Fig. C2). More than 40% of its estimated 19,000 genes have some homology to genes of other organisms. Of 44 human disease genes analyzed, 32 had significant similarities to its genes. ►unc-86, ►apoptosis, ►RNAi, ►Nomarski differential interference contrast microscopy, ►cell lineages, ►operons, ►dauer larva, ►*Photorhabdus*, ►*Xenorhabdus*, ►*Pristionchus*, egg laying controls: Schafer RS 2006 Annu Rev Genet 40:487; Hodgkin J, Herman RK 1998 Trends Genet 14:352; sequence biology; 1998 Science 282:2011; *Caenorhabditis* resources: Antoshechkin I, Sternberg PW 2007 Nature Rev Genet 8:518; www.wormatlas.org; <http://www.wormbase.org>, ►*elegans.swmed.edu*, <http://www.wormbook.org>; expressed sequence tags of 30 nematode species; <http://www.nematode.net/index.php>; Textpresso, *C. elegans* and *C. ramenei*: <http://wormbase.org>.

CAF (chromatin assembly factor): Facilitates the structural organization of the chromosomal elements in association with acetylated histones. Its three subunits are Cac1, Cac2, and Cac3. The small CAF-1 subunit p48 is identical to the retinoblastoma-associated protein 48 (RbAp48). The p48 homolog of *Arabidopsis* (AtMSI1) may regulate processes of tissue differentiation in a quantitative manner (Hennig L et al 2003 Development 130:2555). Deletion of any one single Cac increases UV sensitivity. CAF defect in *Arabidopsis* results in fasciation. ►chromatin,

►CAC, ►RCAF, ►retinoblastoma, ►ACF, ►chromatin remodeling, ►nucleosomes, ►fasciation, ►PCNA; Tyler JK et al 2001 Mol Cell Biol 21:6574.

CAF (CD8 antiviral factor): α -defensins or β -chemokines secreted by CD8 T cells appear to be the active elements. CAF1 and CCR4 are required for deadenylation. ►defensin, ►chemokine, ►T cells, ►acquired immunodeficiency; Zhang L et al 2002 Science 298:995.

Café-au-Lait Spot: A light brown skin macule. These spots can be diagnostic signs of neurofibromatosis (see Fig. C3). ►neurofibromatosis



Figure C3. Café-au-lait spot

Caffeic Acid (3,4-dihydroxycinnamic acid phenethyl ester, CAPE): Caffeic acid is related to flavonoids present in honeybees' glue. It has antiviral, antiinflammatory, immunomodulatory effects and it inhibits tumor growth, lipid peroxidation, lipoxygenase, ornithine decarboxylase, protein tyrosine kinase and the activation of NF- κ B. (See named entries separately, ►antimutagen)

Caffeine: A modified purine molecule, present in coffee, tea, cola nuts and other plants. It is biosynthesized from adenosine monophosphate and guanosine monophosphate through several steps first yielding xanthosine, which is methylated to 7-methylxanthosine that is converted into 7-methylxanthine then into 3,7-dimethylxanthine (theobromine) and then into 1,3,7-trimethylxanthine/caffeine (see Fig. C4) (Ogawa M et al 2001 J Biol Chem 276:8213).

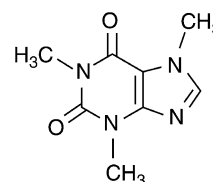


Figure C4. Caffeine

It is a stimulant and a diuretic. Caffeine itself is not a clastogen but it interferes with the repair of spontaneously or otherwise caused chromosomal damage, and thus may enhance the mutagenic potential of irradiation and chemicals by overriding

checkpoint controls in the cell cycle. A ubiquitin conjugating protein (encoded by fission yeast gene *rhp6*), required for entry into mitosis, may be affected by caffeine. Interference with Cdc25 phosphatase and Cdc2 opens the path to mitosis and does not leave enough time for DNA damage. Oral LDLo is 192 mg/kg for humans (see Fig. C5).



Figure C5. Chromosome breakage on caffeine. Human leukocyte culture in the presence of caffeine with multiple chromosome breakage. (From Ostertag W, Greif BJ 1967 Human Genet 3:282)

LD₅₀ orally for male mice is 127 mg/kg, for females 137 mg/kg. Caffeine action on the stimulation of the nervous system is controlled through DARPP32. Consumption of coffee with high diterpene content (kahweol, cafestol) may enhance detoxification of O⁶-alkylguanine and other mutagenic/carcinogenic compounds (Huber WW et al 2003 Fundamental Mol Mech Mutagen 522:57). By RNAi technology, theobromine synthase activity can be reduced in transgenic coffeea plants thereby reducing the caffeine content by genetic means (Ogita S et al 2003 Nature [Lond] 423:823). ▶**purine**, ▶**theobromine**, ▶**LDLo**, ▶**LD₅₀**, ▶**checkpoint**, ▶**Cdc25**, ▶**Cdc2**, ▶**alkaloids**, ▶**DARPP**, ▶**coffee**; Schlegel R, Pardee AB 1986 Science 232:1264; Linskog M et al 2002 Nature [Lond] 418:774.

CAGE (cap-analysis gene expression, CAGE tag): Used for the identification of transcription start sites and the associated promoters. The capped gene is subjected to reverse transcription. The biotin-labeled full-length cDNA is released and MmeI restriction endonuclease-recognition site (TCCRAC, 20-18 nt away) is introduced at the 5'-end. After PCR amplification the cloned fragments are sequenced (Kodzius R et al 2006 Nature Methods 3:211). ▶**cap**, ▶**biotin**, ▶**reverse transcription**, ▶**PCR**

Caged Compound: A caged compound is rendered inactive by combining it with a photosensitive molecule and then introducing it into the cell by microinjection, electroporesis or protoplast fusion

and subsequently irradiating it by UV light of a specific wavelength or by laser beam leading to liberation of the molecules (e.g., Ca⁺⁺, cAMP, GTP) from the sensitizer (e.g., nitrobenzyl side chain). This procedure permits the study of localized effects within the cytoplasm. Fluorochromes can also be caged for monitoring the behavior of subcellular structures, e.g., the function of tubulins. ▶**microinjection**, ▶**electroporation**, ▶**protoplast fusion**, ▶**fluorochromes**, ▶**UV**, ▶**laser**, ▶**tubulin**; Shigeri Y et al 2001 Pharmacol Ther 91:85.

CAHMR: A very rare autosomal recessive cataract, hypertrichosis and mental retardation syndrome. ▶**cataract**, ▶**hypertrichosis**, ▶**mental retardation**, ▶**cerebro-oculo-facio-skeletal syndrome**; Temtamy SA, Sinbawy AHH 1991 Am J Med Genet 41:432.

Cairns Structure: A DNA molecule undergoing bidirectional θ replication. ▶**θ replication**; ▶**bidirectional replication**; Cairns J 1963 Cold Spring Harb Symp Quant Biol 28:43.

Cajal Body (coiled body): Nuclear organelles, usually at the nucleolar periphery. They contain p80 coilin, fibrillarin, snRNP, etc., and are involved in processing mRNA, rRNA, snRNA; they interact with histones and neuronal functions, etc. A Cajal body-like (yet distinct from it) structure occurs in plants too and it is involved in processing miRNA (Song L et al 2007 Proc Natl Acad Sci USA 104:5437). ▶**coilin**, ▶**coiled body**, ▶**snurposome**, ▶**RNAi**, ▶**microRNA**; Gall JG 2000 Annu Rev Cell Dev Biol 16:273; sno and Cajal RNA: <http://gene.fudan.sh.cn/snoRNAbase.nsf>.

CAK (cyclin-dependent-activating kinase): CAK is, generally, a component of the TFIIF transcription factor, but in *Saccharomyces* it is not part of TFIIF. It activates CDC28. ▶**transcription factors**, ▶**Cdk**, ▶**MO15**, ▶**cyclin**, ▶**CDC28**; Chen J et al 2003 Nature [Lond] 424:228; Gall JG 2003 Nature Rev Mol Cell Biol 4:975.

CAK_β: ▶**CAM**

Calcineurin (serine/threonine protein phosphatase-IIB, PP2B): Its action is dependent on calcium and calmodulin. Calcineurin is the target of cyclosporin and FK506. Calcineurin, by binding to NF-AT, incites the immune system and activates neuronal and muscle development but not muscle growth. If this binding could be selectively blocked—without affecting other functions—immuno-suppression could be controlled to the great benefit of various therapeutic transplantations (Venkatesh N et al 2004 Proc Natl Acad Sci 101:8969). Calcineurin and Mpk1 (Map kinase) and Zds1 (regulator also of Cdc42) proteins regulate the action of gene *SWE1* (a member

of the *WEE1* family) at transcription and post-transcription and the calcium-induced delay in G2 phase of the cell cycle. The product of the DSCR1 (Down syndrome candidate region) gene is an inhibitor of calcineurin and increases senile Alzheimer plaques and neurofibrillary tangles two-three times (Chan B et al 2005 Proc Natl Acad Sci USA 102:13075). ▶calmodulin, ▶immunosuppressant, ▶cyclosporin, ▶FK506, ▶serine/threonine phosphoprotein phosphatases, ▶T cells, ▶NF-AT, ▶MAP, ▶Cdc42, ▶Wee, ▶cardiomyopathy hypertrophic familial, ▶BAD, ▶Bcl, ▶Alzheimer disease; Crabtree GR 2001 J Biol Chem 276:2313; Ermak G et al 2001 J Biol Chem 276:38787; Luan S et al 2002 Plant Cell 14:S389.

Calcinosis, Tumoral, Familial: The symptoms involve subcutaneous calcium deposits, mainly at the joints, caused by recessive mutation of the GALNT3 gene at 2q24-q34, encoding a glycosyltransferase-causing mucin type O-glycosylation. The patients also display hyperphosphatemia (increased blood phosphate level). GALNT2 and GALNT1 mutations are also known. Dominant form of the disease is due to mutation in the FGF23 (fibroblast growth factor) gene at 12p13.3 (Benet-Pagès A et al 2005 Hum Mol Genet 14:385). (See Topaz O et al 2004 Nature Genet 36:579).

Calcitonin (CT, 11p15.2-p15.1): An oligopeptide hormone of the thyroid gland, controlling calcium and phosphate levels, and an antagonist of parathyroid hormone. The calcitonin gene-related peptide and substance P induce inflammation by dilation of the blood vessels. Calcitonin receptors are encoded at 2q31-q32 and 7q21.3. ▶animal hormones, ▶immune privilege, ▶adrenomedullin

Calcium Ion Channels: These voltage-regulated channels are made up of several subunits, each encoded at different human chromosomal sites: CACNL1A2 (neuroendocrine/brain) at 3p14.3; the CACNL1A4 isoform is at 19p13; CACNA1S (skeletal muscle) at 1q32; CACNA1C (cardiac muscle) at 12p13.3; CACNA2D1 in several tissues modulate the activity of the channel at 7q21-q22; the β -subunit, CACB1, is at the same location; the γ -subunit, CACNG1, is encoded nearby at 17q24. Ca^{2+} -ATPase is one of the most important pumps for calcium uptake through cell membranes. ▶ion channels, ▶calmodulin, ▶second messengers, ▶dihydropyridine receptor, ▶ ω -agatoxin, ▶ ω -conotoxin, ▶neurotransmitters; Catterall WA 2000 Annu Rev Cell Dev Biol 16:521; Toyoshima C, Nomura H 2002 Nature [Lond] 418:605; muscle and nervous disorders: Rizzuto R, Pozzan T 2003 Nature Genet 34:135.

Calcium Signaling: Calcium plays the role of a second messenger and activates many enzymes in the cell. It regulates synaptic activity of the neurons, cell adhesions, motility, proliferation, etc. When phospholipase C (PLC) is activated, the cells release intracellular Ca^{2+} through the calcium-release activated calcium channels (CRACs), receptor-operated calcium channels (ROCs), and store-operated calcium channels (SOCs). The incoming calcium then replenishes the Ca^{2+} store in the cell; it is also called CCE (capacitative Ca^{2+} entry). Hormones may activate the CCE, by immune reactions or by neural receptors. Light signal transduction in *Drosophila* requires PLC activation, synthesis of IP3 and the release of Ca^{2+} . For normal vision the flies must be able to maintain Ca^{2+} homeostasis. Mutants are known (and cloned) that represent gene loci involved in calcium regulation. Nuclear gene expression may be regulated through the CRE element whereas the cytoplasmic signaling may be mediated by SRE. A large and transient rise of Ca^{2+} activates transcriptional regulators such as NF- κ B, JNK; NFAT is activated by low Ca^{2+} levels. Intracellular Ca^{2+} triggers the activation of T lymphocytes by antigen. ▶calmodulin, ▶calcium ion channels, ▶calcineurin, ▶calcitonin, ▶PLC, ▶IP3, ▶CRE, ▶SRE, ▶homeostasis, ▶NF- κ B, ▶JNK, ▶NFAT, ▶SKID, ▶Darier-White disease; Wallingford JB et al 2001 Curr Biol 11:652; Lewis RS 2001 Annu Rev Immunol 19:497; Carafoli E 2002 Proc Natl Acad Sci USA 99:1115; Sanders D et al 2002 Plant Cell 14:S401.

Calciumphosphate Precipitation: May significantly enhance the chances of DNA uptake by (*E. coli* or mammalian) cells to be transformed (transfected). ▶bacterial transformation, ▶cotransfection

Calcofluor White (Tinopal): A fluorescent brightener that can be used to monitor cell wall formation in protoplast suspensions. ▶fluorochromes

Caldesmon: An 83 kDa actin- and calmodulin-binding protein. During mitosis it dissociates from the microfilaments as a consequence of mitosis-specific phosphorylation of actomyosin ATPase. ▶calmodulin, ▶myosin, ▶ATPase; Krauze K et al 1998 Biochem Biophys Res Commun 247:576.

Calico Cat: Heterozygous *female* animals with black-yellow-white fur patches (see Fig. C6). The alternation of black and yellow fur is due to inactivation of the genes residing in one or the other of the two X chromosomes. In males, this pattern occurs only in connection with the Klinefelter (XXY) constitution. The white fur is an autosomal trait controlled by the S (spotted) gene. ▶X-chromosome inactivation, ▶tortoiseshell fur, ▶lyonization



Figure C6. Calico cat

Call: ►base-calling

Callicebus: ►Cebidae

Callithricidae: Callithricidae are new world monkeys (marmosets and tamarins). *Callithrix argentata* 2n = 44; *Callithrix humeralifer* 2n = 44; *Callithrix jaccus* 2n = 46; *Callimico goldi* 2n = 48, some males 47; *Cebuella pygmaea* 2n = 44; *Leontocebus rosalia* 2n = 46; *Sanguinis fuscicollis illigeri* 2n = 46; *Sanguinus oedipus* 2n = 46; *Tamarinus mystax* 2n = 46; *Tamarinus nigricollis* 2n = 46. ►primates

Callose: A carbohydrate (glucan) formed on injured plant tissue.

Callus: A solid mass of plant cells (generally) on synthetic media; thickening of animal skin; unorganized bone growth (see Fig. C7).

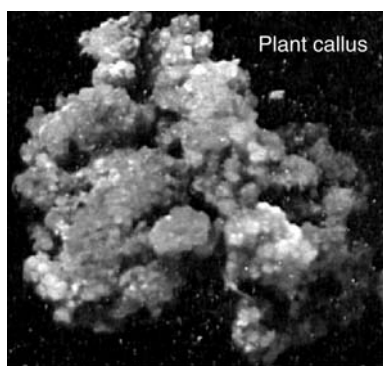


Figure C7. Plant callus

Calmette-Guérin: ►*Bacillus Calmette-Guérin*

Calmeglin: A Ca^{2+} protein with 54% homology to calnexin but its expression is limited to the stage of pachytene to spermatid development. It is a chaperone. ►calnexin, ►chaperone

Calmodulin (CaM): A 17,000 M_r acidic protein (of 108 amino acids) with 4 Ca^{2+} binding sites affecting (among others) membrane transport, chromosome

movement, and processes in fertilization; it functions as a regulatory unit of several enzymes although calmodulin itself is not an enzyme (see Fig. C8). The CaM superfamily includes ~600 proteins. Calmodulin binding results in conformational changes of the target proteins (~300). CaM binds calcium between the C and D helix and also at the E and F helices (loop) and CaM is also called a EF hand protein. The EF hand is rather well preserved in a variety of calcium-sensing proteins of diverse functions. The presence of Ca^{2+} /CaM is required for phosphorylation of several proteins (myosin light chain kinase, phosphorylase kinase). CaM-kinase II mediates the secretion of neurotransmitters. It activates tyrosine hydroxylase required in catecholamine biosynthesis. It is involved in the control of such brain functions as memory and learning. CaM-kinase II is capable of autophosphorylation even in the absence of Ca^{++} . CaM regulates adenylate cyclase (cAMP), and cAMP regulates CaM. A-kinase, regulated by CaM, phosphorylates the IP_3 receptor, and cAMP and CaM-kinases control CREB. The delta subunit of phosphorylase kinase is CaM. CaM activates cyclic nucleotide phosphodiesterase, an enzyme degrading cAMP. CaM is ubiquitous among eukaryotes and it is one of the most conserved proteins. In vitro proteome assay is available for calmodulin binding proteins (Shen X et al 2005 Proc Natl Acad Sci USA 102:5969). ►cAMP, ►phosphorylases, ►autophosphorylation, ►signal transduction, ►calcium signaling, ►cAMP, ► IP_3 , ►CREB, ►neurotransmitters, ►aequorin, ►CDC31; Fujisawa H 2001 J Biochem 129:193; Soderling TR et al 2001 J Biol Chem 276:3719; Corcoran EE, Means AR 2001 J Biol Chem 276:2975; Cyert MS 2001 Annu Rev Genet 35:647; Hoeflich KP, Ikura M 2002 Cell 108:739;

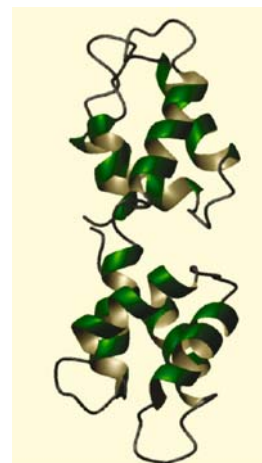


Figure C8. Calmodulin. © IUPAC.

Luan S et al 2002 *Plant Cell* 14:S389; polymorphism and multifunctionality: Ikura M, Ames JB 2006 *Proc Natl Acad Sci USA* 103:1159.

C

Calnexin: A membrane-bound chaperone with preference for glycoproteins (Molinari M et al 2003 *Science* 299:1397); it may also associate with an antigen before entering the endoplasmic reticulum. Its soluble homolog is calreticulin. ▶chaperones, ▶calreticulin, ▶endoplasmic reticulum, ▶Cne, ▶BiP; Danilczyk UG, Williams DB 2001 *J Biol Chem* 276:25532; Schrag JD et al 2001 *Mol Cell* 8:633.

Calorie: The amount of heat required to elevate the temperature of 1 gram of water from 14.5 °C to 15.5 °C (4.186 international joules). ▶joule

Calpains: Calcium-dependent neutral cysteine proteases of the papain family. Calpains may cleave neural growth activator protein 35 (p35) resulting in p25. Accumulation of p25 causes the mislocalization of CDK5 then CDK5 and p25 hyperphosphorylate tau, a microtubule-associated protein; consequently, the cytoskeleton disruption leads to death of neurons and to the apoptosis seen in Alzheimer's disease. CALPAIN10 (2q37.3) seems to be linked to diabetes (NIDDM1) and may be identical to it. Two other proteases, carboxypeptidase E/H in human chromosome 4 and pro-hormone convertase-1 (5q15-q21), also seem to be associated with diabetes. ▶protease, ▶papain, ▶tau, ▶Alzheimer's disease, ▶CDK, ▶cytoskeleton, ▶microtubule, ▶diabetes; McGrath ME 1999 *Annu Rev Biophys Biomol Struct* 28:181; Horikawa Y et al 2000 *Nature Genet* 26:163; Sorimachi H, Suzuki K 2001 *Biochem J* 129:653; Perrin BJ, Huttenlocher A 2002 *Int J Biochem & Cell Biol* 34:722.

Calphostin C: An inhibitor of diacylglycerol and Ca^{2+} -dependent phosphokinase CD (PKC). ▶T cells, ▶PKC, ▶diacylglycerol

Calreticulin: A calcium storage protein within the endoplasmic reticulum and also present in the nucleus. It may prevent the glucocorticoid receptor binding to its response element and it is thus a transcription factor and a chaperone. Calreticulin is also required for calcium signaling and cell adhesion by integrins. Calreticulin and heat-shock protein Hsp90 control expression of the human insulin receptor at its earliest maturation stages and modulate its movement within the endoplasmic reticulum before either degradation or cell surface expression (Ramos RR et al 2007 *Proc Natl Acad Sci USA* 104:10470). ▶hormone response element, ▶glucocorticoid, ▶tapasin, ▶integrin, ▶calnexin, ▶endoplasmic reticulum; Nakamura K et al 2001 *J Clin Invest* 107:1245; Fadel MP et al 2001 *J Biol*

Chem 276:27083; assay methods; Ireland BS et al 2006 *Methods Mol Biol* 347:331.

Calsenilin: A Ca^{2+} -binding protein which mediates apoptosis and Alzheimer's disease plaque protein, Aβ. ▶presenilin, ▶Alzheimer's disease, ▶apoptosis

Calvin Cycle: The pathway of fixation of CO_2 (1C) into 3-phosphoglycerate (3C), 1,3-bis-phosphoglycerate (3C) and glyceraldehyde-3-phosphate (3C). In this reaction, 3 molecules of ATP and 2 molecules of NADPH are used for each CO_2 converted into carbohydrate. ▶photosynthesis, ▶Krebs-Szentgyörgyi cycle

Calypso: *Drosophila* transposable element (7.2-kb) generally present in 10 to 20 copies per cell. ▶transposable elements, ▶hybrid dysgenesis

Calyx: The collective name of sepals, the basal whorl of the flowers. ▶flower, ▶differentiation

CaM: ▶calmodulin

CAM (cell adhesion molecule): Regulates monolayer formation in cultured mammalian cells and mediates neuronal connections with the aid of the fibroblast growth factor (FGF). Cell-to-cell adhesion is mediated by cadherins, immunoglobulins, selectins, and integrins (see Fig. C9). Integrins and transmembrane proteoglycan mediate cell-matrix adhesion. Focal cell adhesion, integrin-mediated contact between cells and the extracellular matrix is linked to the activation of pp125^{FAK} protein kinase. This enzyme is a member of the family of FakB, PYK2/CAKβ and RAFTK protein tyrosine kinases. PYK2 regulates calcium ion channels and the MAPK signaling pathway. The carboxy terminal of pp125^{FAK} is expressed as a nonkinase pp41/43^{FRNK}. This latter protein is an inhibitor of pp125^{FAK} and the phosphorylation of tensin and paxillin adhesion proteins. PYK2 activity is also coupled with the JNK signaling pathway. NCAM is the neural cell adhesion molecule. Cotranslational translocation of vascular cell adhesion molecule is inhibited by CAM741, a fungus-derived cyclopeptolide involving Sec61β, and subsequently degraded by proteases of the cell. Thus the peptide may have use in the control of some diseases (Besemer J et al 2005 *Nature [Lond]* 436:290). ▶cadherins, ▶ICAM, ▶immunoglobulins, ▶L1, ▶protein zero, ▶fibronectin, ▶selectins, ▶integrins, ▶RGD, ▶tenascin, ▶proteoglycan, ▶JNK, ▶ion channels, ▶extracellular matrix, ▶MAPK, ▶protein kinases, ▶Sec61 complex, ▶Usher syndrome, ▶ADAM, ▶MASA syndrome; Chen L et al 2001 *J Cell Biol* 154:841; Voura EB et al 2001 *Mol Biol Cell* 12:2699; Li R et al 2003 *Science* 300:795.

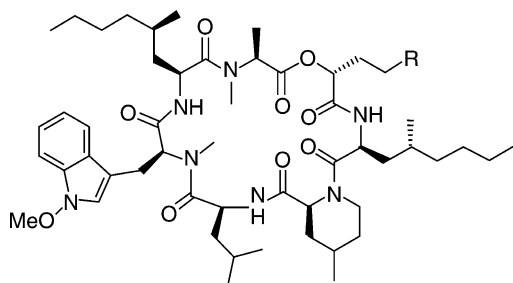


Figure C9. CAM 741

CAM: ► *Crassulacean acid metabolism*

cam (chloramphenicol transacetylase): Conveys resistance to chloramphenicol, which would block peptidyl transferase on the 70S ribosomes in prokaryotes and in eukaryotic organelles. ► *chloramphenicol*, ► *antibiotics*, ► *protein synthesis*

Camalexin: A phytoalexin that may be a player in the defense of plants against fungal diseases. ► *phytoalexins*, ► *host-pathogen relationships*; Pedras MS, Khan AQ 2000 *Phytochemistry* 53:59.

Cambium: A meristemic tissue layer around the stem of plants providing for growth in diameter. ► *meristem*

Cambrian: A geological era 500–600 million years ago. The fossil plant relics of this era are poorly preserved. All major animal groups, except the vertebrates, were already present. ► *evolution*, ► *geological time periods*

Camel: The two-humped camel (*Camelus bactrianus*): $2n = 74$ and its American relative, the vicuña (*Vicugna vicugna*), and all other camelids also have the same $2n = 74$. The large one-humped dromedary camel (*Camelus dromedarius*) is the “workhorse” of Arabia, North Africa, and India. Although the South American llamas were separated from camels about 3 million years ago, they can form hybrids. Their antibodies lack light chains and are highly soluble. A camelid heavy chain antibody fragment (VSA2) is specific for caffeine and provides a relatively simple and sensitive means for the detection of caffeine in cold or hot beverages even after exposure up to 90 °C (Ladenson RC et al 2006 *Anal Chem* 78:4501). (► *antibody*; Hamers-Casterman et al 1993 *Nature* 363:446; De Genst E et al 2006 *Proc Natl Acad Sci USA* 103:4586).

CAMFAK Syndrome: An apparently autosomal dominant cataract, microcephaly, failure to thrive, kyphoscoliosis (curved spinal column), arthrogryposis (flexure and/or contracture of the joints), and mental retardation. It has been termed also as CAMAK. It bears similarities to the Cockayne syndrome and to

cerebro-oculo-facio-skeletal syndrome and to other developmental anomalies. ► *scoliosis*, ► *cerebro-oculo-facio-skeletal syndrome*

CaMK (calcium-calmodulin-dependent protein kinase): CaMKII is necessary for several physiological processes including learning and memory. NMDA receptors control its translocation. Camk4 serine/threonine kinase is important for mice spermiogenesis. ► *calmodulin*, ► *kinases*, ► *titin*, ► *NMDA*; Yang Y et al 2001 *J Biol Chem* 276:41064.

CaM-KK: A CaMK kinase which activates PKB (protein kinase B), which phosphorylates the apoptotic protein BAD. BAD then interacts with protein 14-3-3 and cell survival is facilitated. ► *apoptosis*, ► *BAD*, ► *protein 14-3-3*, ► *protein kinases*; Tokomitsu H et al 2000 *J Biol Chem* 275:20090.

CaMO: ► *cauliflower mosaic virus*

cAMP: Adenosine 3':5' monophosphate (cyclic AMP, second messenger); has a crucial role in signal transduction and general gene regulation in bacteria and animals (see Fig. C10). For many years there was no convincing evidence for cAMP in plants. More recently though several facts have indicated the role of cAMP in plant development. In 1997, adenylyl cyclase was identified in tobacco tissues. Some molecules can increase the level of cAMP (adenylate cyclase) by binding to certain transmembrane receptors whereas other cellular signal molecules are inhibitory. The stimulatory G_s protein activates adenylyl cyclase. Actually the α_s subunit dissociates from the two other chains and binds to, and hydrolyzes, GTP; it then binds to adenylyl cyclase and boosts the production of cAMP. Upon binding to adenylyl cyclase GTPase activity will increase and an inactive G_s is formed again by recombining α_s with $\beta\gamma$.

Cholera toxin (produced upon infection by the bacterium *Vibrio cholera*) mediates the transfer of adenylyl to α_s and this fact prevents the hydrolysis of its GTP. Therefore, the adenylyl cyclase function stays on, resulting in increased levels of cAMP. This condition then opens a very active sodium and water efflux through the intestinal walls, causing debilitating diarrhea and dehydration of the entire body.

The inhibitory trimeric G_i has a special α_i subunit and it is activated by other types of cellular signals. In G_i the $\beta\gamma$ subunits are dissociated from the α_i subunit and these subunits then directly and indirectly interfere with adenylyl cyclase. More importantly, G_i opens K^+ ion channels in the plasma membrane. The pertussis toxin (due to *Bordetella* bacterial, whooping cough)—in contrast to the cholera toxin—mediates the adenylation of α_i subunit that interferes with responding to the receptors and GDP remains

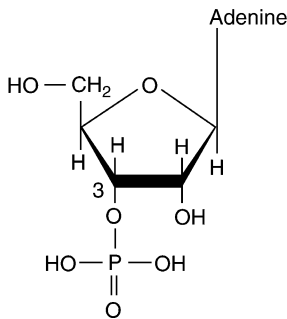
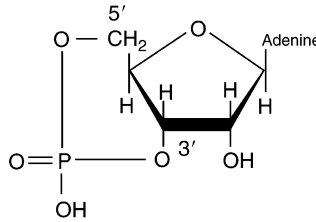
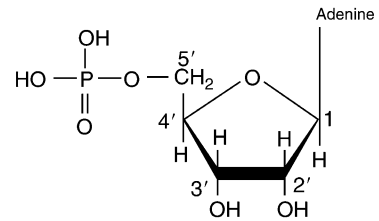
Adenosine 3'-phosphoric acid
(3'-adenylic acid)Adenosine 3',5'-phosphoric acid
(cyclic adenylic acid)Adenosine 5'-phosphoric acid
(adenylic acid; 5'-adenylic acid)

Figure C10. cAMP

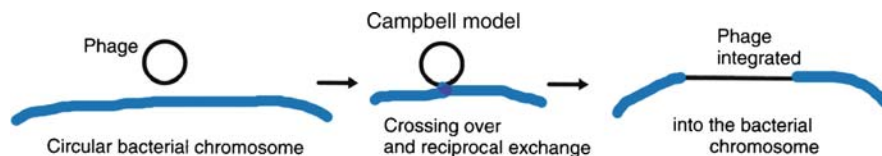


Figure C11. Campbell model

bound to the G-protein; the adenylate cyclase activity is not blocked and potassium channels are not opened.

One of the most important functions of cAMP is the activation of the four-subunit *protein kinase A*. This phosphorylase enzyme then adds phosphate groups from ATP to serine and threonine residues in certain proteins. Protein kinase A is activated by cAMP through forming a complex with two of its regulatory subunits while the two other separated catalytic subunits are turned on. The enzyme exists in two forms; one is cytosolic whereas the other is bound to membranes and microtubules.

cAMP controls the transcription, in a positive or negative manner, of several other genes. The CREB (cAMP response elements)—located in the upstream region of genes—promote transcription upon phosphorylation of a specific serine residue in the binding proteins whereas the CREM α and β are repressors. cAMP also controls the secretion of cortisol by the kidney cortex, the thyroid hormone, the secretion of the luteinizing hormone (progesterone), adrenaline and glucagon production and glycogen and triacylglyceride breakdown, heart muscle and other muscle functions, etc. ►adenosine-3', ►5' ►monophosphate, ►adenylate cyclase, ►G-protein, ►epinephrine, ►cAMP-dependent protein kinase, ►signal transduction, ►CREB, ►CBP, ►progesterone, ►forskolin, ►cyclic ADP-ribose; Montminy M 1997 Annu Rev Biochem 66:807.

cAMP Receptor Protein (CRP): Assists in the binding of *E. coli* RNA polymerase to the operator of carbohydrate operons (positive regulation), but it may also act as an activator of the negative regulator CytR and as such becomes a corepressor. The DNA binding site is 22 bp arranged in a rotational symmetry. The binding results in DNA bending. ►Lac operon, ►positive control, ►negative control, ►repressor, ►corepressor, ►promoter, ►RNA polymerase, ►DNA bending

Campbell Model: The Campbell model of recombination suggested, first, the mechanism of integration of the (pro)phage into bacteria by reciprocal recombination between the circular bacterial and temperate phage DNA molecules (see Fig. C11) (only a part of the circular bacterial chromosome is shown; in lighter color). ►bacteriophages, ►*E. coli*; Campbell AM 1962 Advances Genet 11:101.

cAMP-Dependent Protein Kinase: ►protein kinase A, ►phosphorylase B kinase

Campomelic Dysplasia (CD, CMD1): A most likely recessive/haploinsufficiency (rather than dominant) bone-formation and gonad-development defect due to mutation in the SOX9 gene in human chromosome 17q24.1-q25.1. The congenital bowing of the skeletal bones and malformation of the head bones usually causes death in early infancy; however, some

individuals survive to early adulthood. This defect is often associated with chromosomal rearrangements and sex reversal. ▶SRY, ▶SOX, ▶sex reversal, ▶gonad; Preiss S et al 2001 J Biol Chem 276:27864; Hill-Harfe KL et al 2005 Am J Hum Genet 76:663.

Camptodactyly: Autosomal dominant bent fingers (see Fig. C12).

CAMPTODACTYLY →



Figure C12. Camptodactyly

Camptothecin ($C_{20}H_{16}N_2O_4$): A plant alkaloid, which is an antibiotic and anticancer agent targeting DNA topoisomerase I-DNA complexes. It breaks single-stranded DNA. ▶topoisomerases, ▶etoposide, ▶Werner syndrome; Arimondo PB et al 2002 J Biol Chem 277:3132.

Campylobacter jejuni: A gram-negative, spiral, flagellate bacterium, pathogenic to the stomach and an inducer of the Guillain-Barré syndrome. Its circular DNA chromosome contains 1,641,481 bp encoding 1,654 proteins and 54 stable RNAs. Its genome is virtually free of insertion or phage-associated sequences and has rare repeats but contains short hypervariable sequences. ▶Guillain-Barré syndrome; Parkhill J et al 2000 Nature [Lond] 403:665.

Camurati-Engelmann Disease (CED, diaphyseal dysplasia, 19q13.1-q13.3): Progressive bone formation on the shaft of the long bones and the skull. Muscular weakness and pain, facial paralysis, hearing and vision problems, etc., may be caused by defect in the transforming growth factor-β1 subunit. ▶TGF

CaMV: | cauliflower mosaic virus

Canalization: A genetic buffering mechanism that reduces the visible variations beyond what is expected on the basis of genetic diversity. It is the developmental path modulated by environmental inputs, the epigenetic landscape. It permits the maintenance of hidden genetic variations and thus facilitates the conservation of a “normal” phenotype. Also, it eliminates from the populations those genotypes that cannot adjust to environmental fluctuations. Mutants generally have reduced buffering capacity compared to the wild type (which is best canalized for survival), and can be readily eliminated. ▶genetic homeostasis, ▶genetic assimilation, ▶homeostasis, ▶epigenesis, ▶reaction norm, ▶robustness; Waddington CH 1940 J Genet 41:75; Newman SA, Muller GB 2000 J Exp Zool 288:304.

Canale-Smith Syndrome (ALPS): An autoproliferative disease caused by deficiency of the Fas protein and

defect in apoptosis. ▶Fas, ▶lymphoproliferative diseases, ▶apoptosis

Canary: ▶pathogen identification

Canavan disease: ▶aspartoacylase deficiency

Canavanine: A competitive inhibitor of arginine (natural plant product). ▶competitive inhibitor

Cancer: Cells which continue to divide when cell divisions are not expected; it is an uncontrolled growth, a malignant growth. The cancer cells proliferate irrespective of the normal growth signals or growth regulatory mechanisms, tend to evade apoptosis or immunosurveillance commandeer angiogenesis and all means leading to replication, and invade other cells and tissues by metastasis. Some of the cancers may originate from a small fraction of the cells in a tissue, the *cancer stem cells* (Beachy PA et al 2004 Nature [Lond] 432:324). Some so-called transit-amplifying cells divide a few times than differentiate and lose their proliferating abilities. Loss of polarity during stem cell divisions may lead to cancer. Cells may spread through the blood stream to other locations in the body and initiate secondary foci of malignant growth (metastasis). Cancer may occur in a variety of forms such as leukemia, adenoma, lymphoma, sarcoma, but it is not exactly known how these different types are specified. It appears that there are more than 200 types of cancers. More than 1% of the human genes (291) are involved with cancer; 90% display somatic mutations and 20% show germline mutations, and 10% both (Futreal PA et al 2004 Nature Rev Cancer 4:177). In each cancer several (3–6) different mutations may be found (Hahn WC, Weinberg RA 2002 Nature Rev Cancer 2:331). Among 1,007 somatic mutations in cancer cells, 921 were single base substitutions, 78 were small chromosomal aberrations, and 8 were complex alterations. The number of somatic mutations varied substantially among different types of cancer and was dependent also on recurrent gliomas, which have been treated earlier by alkylating anticancer drugs (temozolomide) or in melanomas ([18.54/Mb] apparently caused by UV light) or in lung cancer ([4.21/Mb] in smokers). Deficiency of DNA repair [32.29/Mb] was also a significant factor although high numbers of mutations could be ascertained that were due to unknown factors. Generally, high frequency of somatic mutations was observed in tissues with rapid turnover and easy exposure to environmental effects (lung cancer [4.21/Mb], gastric cancer [2.10/Mb], colorectal cancer [1.21/Mb]) but some apparently protected tissues (e.g., ovary had also high rates [1.85/Mb]). Generally, nonsynonymous mutations had higher incidence yet it appeared that some synonymous mutations were more frequent than

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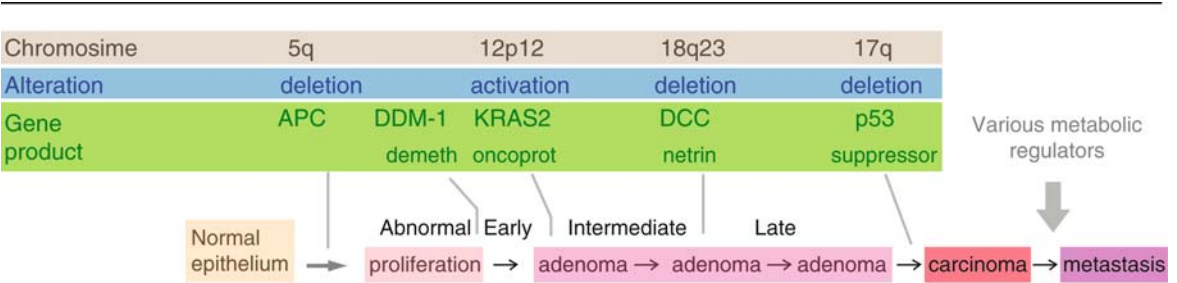
expected by chance indicating that some had conveyed selective advantage in proliferation (“driver mutations”). A somewhat smaller portion of the mutations did not appear selectively advantageous for proliferation (“passenger mutations”). Some, but not all, the *driver mutations* involved one or another protein kinase domains (Greenman C et al 2007 Nature [Lond]: 446:153). Cancer ESTs (expressed-sequence tags) have greater variations than normal ESTs for > 70% of the tested genes. Cancer EST variations were not random, but were determined by the composition of the substituted base (b) as well as that of the bases located upstream (up to base –4) and downstream (up to b + 3) of the substitution event. The replacement base was also not randomly selected but corresponded in most cases (73%) to a repetition of b – 1 or of b + 1. Base substitutions follow a specific pattern of affected bases: A and T substitutions were preferentially observed in cancer ESTs. In contrast, cancer somatic mutations and SNPs identified in the genes occurred preferentially with C and G. On the basis of these observations, a working hypothesis suggested that cancer EST heterogeneity results primarily from increased transcription infidelity (Brulliard M et al 2007 Proc Natl Acad Sci USA 104:7522).

The anomaly in malignant growth is that cells do not remain in a quiescent stage (G₀). They proceed either through terminal differentiation or death (apoptosis), but from G1 phase, and independently from normal cellular regulation, continuing indefinitely to S phase, mitosis and cell division. Normal cells pause at the G1 *restriction point* and respond to the instructions coming through the cyclins. The cyclins (CLNs) coupled with the labile cyclin dependent kinases (CDK4, CDK6) are receptive to mitogens but they are kept in check by several INK (inhibitors of kinase) proteins. When, normally, tumor suppressors such as the retinoblastoma (RB) and other proteins (E2F family) become phosphorylated, the cells exit from G1 and embark on DNA

synthesis. The phosphorylated tumor suppressors transactivate CDKs, and unless cell divisions are blocked at various checkpoints, divisions will continue and proceed in an accelerated and uncontrolled manner. The G1-phase-specific cyclin E-CDK2 complex stimulates more phosphorylation of the tumor suppressors RB and E2F and the dependence on mitogens is diminished. CLN-A–CLN-B dependent kinase (CDK2) reinforces the phosphorylation process and dephosphorylation does not set in until the completion of mitosis. CLN-E and CLN-A associated CDK2 assist the DNA replication machinery. CLN-dependent kinases are also suppressed by CDK inhibitors, p21^{CIP1}, p27^{KIP1}, and p57^{KIP2}, but if the latter ones are deleted or mutated both cell numbers and size increase. Methylation of the promoter of tumor suppressor genes may lead to their silencing and neoplasia. Hypomethylation of oncogenes or retroelements or latent viral sequences in the genome may increase cancerous transformation. The patterns of hyper- and hypomethylation may be quite variable at different restriction enzyme recognition sites. Hypomethylation of some DNA sites may facilitate chromosomal instability, a common cause of neoplasia. Comparative genomic data are summarized in Struski S et al 2002 Cancer Genet Cytogenet 135:63. Cytosine methylation, histone modification and chromatin remodeling are major factors in cancerous transformation (see Table C1) (Jones PA, Baylin SB 2007 Cell 128:683).

Germline mutations are responsible only for about 1% of all cancer cases, and about 10–15% of all cancer has substantial hereditary components. Many cancer genes (oncogenes) have now been cloned but several genes acting in the same biochemical pathway may be responsible for one type of cancer. Also, single genes may be involved in different types of cancer. It has been observed that the range of expression of germline mutations of the same cancer gene is different from those of somatic mutational events. Allelic differences within a gene may cause

Table C1. Some protooncogenes and their role is carcinogenesis



demeth: demethylation, oncoprot: oncoproteins, netrin: guidance protein (Modified after Fearon ER & Vogestein B 1990 Cell 61:757)

different cancers. The majority of cancer cases are the result of somatic mutations arising during the lifetime of the individuals and some are due to unknown environmental factors and thus represents phenocopies. Cancerous growths may be initiated by mutations in structural genes, suppressor genes, methylation of tumor suppressors, transmembrane receptors, transcription factors, regulator genes, cell cycle genes, aneuploidy (hypo- and hyperploidy) repair functions, chromosomal rearrangements (translocations, inversions, transpositions, duplications, deletions), and viral insertions in the chromosomes. Although a single mutation may suffice for uncontrolled cellular proliferation, several additional factors may be involved for full-scale development. The initial mutation may take place in proto-oncogenes. Mutations or loss of the CLN-D1 locus (human chromosome 11q13) and the CDK4 gene (human chromosome 12q13), INK4a (CDK^{INK4a}, chromosome 9p21), p16, p53 are common in many types of cancers. p53 also regulates p21, p27 and p57 proteins. The gene encoding p53 is in human chromosome 17p 13.15-p12 and it is altered in a large number of different cancers. The normal function of p53 is required for the development of the centrosome and proper segregation of the chromosomes (see Fig. C13).

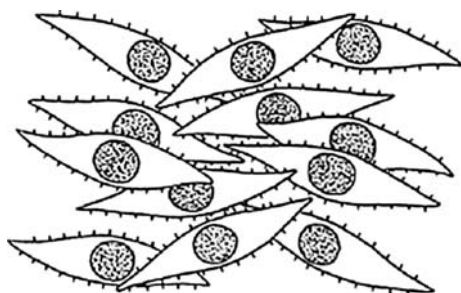


Figure C13. Culture cancer cells lose contact inhibition and grow in overlapping fashion. (After Dulbecco R 1967 Sci. Amer. 216[4]:28)

Hundreds of proto-oncogenes have now been discovered and their possible malfunction due to mutation, chromosomal rearrangement or loss is many fold (see diagram). Some estimates indicate that 1% of the genes may affect cancer (Futreal PA et al 2004 Nature Rev Cancer 4:177). These mutations, similar to other mutations, are generally (not always) recessive and not expressed in diploid cells. When, through another event(s), they become homozygous or hemizygous, a cancerous growth may follow.

This may be the reason why, for the development of cancer, a long period is required after the initial genetic lesion. These genes have normal cellular functions (some of the proto-oncogenes, e.g., *Ras*, encode

G-proteins and play an important role in healthy signal transduction) but mutation may alter their normal role and they may become (cellular) c-oncogenes. The v-oncogenes are viral counterparts of the c-oncogenes. When c-oncogenes are inserted into chromosomes of animals they may provide efficient promoters for cellular genes involved in growth.

In the development of cancer, the products of more than a dozen tumor suppressor genes (e.g., p53, p16) play a major role. Because of mutation, they no longer are capable of controlling genes of the cell cycle. Normal mammalian cells grow in the cultures in an anchorage-dependent fashion, in monolayer. Cancerous cells differ in their growth habit by growing in disarray, in layers (see Fig. C14). Gene expression profiles of tumor-derived cell lines may differ from that of in vivo cancer cells (Sandberg R, Ernberg I 2005 Proc Natl Acad Sci USA 102:2052). Since the human body contains about a billion cells per gram solid tissue, an average adult human body may have about 10^{14} to 10^{15} diploid cells according to the various estimates. Average mutation rates are within the range of 10^{-5} to 10^{-8} per genome, per generation, therefore all human individuals must have suffered numerous mutations with neoplastic potentials yet only a fraction of the human population is afflicted by this group of diseases. The causes of this discrepancy are diploidy, that masks recessive mutations, and the immunological surveillance system recognizes mutant surface antigens, developed on cancer cells, and destroys them before they get out of control. When the immune system weakens by advancing age, by certain diseases (e.g., AIDS) or by taking immunosuppressive drugs, the incidence of cancer increases. The cancerous growth itself is not necessarily lethal but it generally deprives the body from its normal metabolism and the patients succumb to secondary, opportunistic diseases.



Figure C14. Benzo(a) pyrene induced cancer in the laboratory by painting the carcinogen on the skin of a rodent. (Courtesy of Drs Nesnow S and Slaga T)

The general assumption is that cancer develops monoclonally, i.e., in the tumor each cell has a single common ancestor.

This assumption does not preclude, however, that in the same cell lineage additional mutations occurred during the process of multiplication although experimental evidence does not show appreciable frequency of mutation during the progression of cancer. In very rare cases, it has been shown, however, that a particular cancer in an individual may not be monoclonal but that more than a single founder cell contributed to its formation. Also, in some cancer cells, multiple and different genetic mutations, primarily chromosomal alterations, were observed. Some of these multiple alterations may be due to the rearrangement of mini- or microsatellite sequences, some of which are just the consequences of defects in the genetic repair system.

With the technique of inter-simple sequence repeat PCR (INTER-SS PCR), a very large number of chromosomal alterations (insertions, deletions, translocations) are detectable (see Fig. C15). The aberrant karyotypic state of cells is correlated with their response to anticancer drugs and this feature may be used to screen for potential drugs (Roschke AV et al 2005 Proc Natl Acad Sci USA 102:2964).

The PCR product is produced by using a single primer homologous to dinucleotide repeats and attached at 3' by two nonrepetitive sequences as diagrammed below (R = purine, Y = pyrimidine):

The numbers of alterations (genetic instability) are determined by the formula:

$$N = \frac{(\text{No. of altered bands/PCR}) \times (\text{Total genome size}) \times (\text{No. uniquely altered bands})}{[\Sigma \text{ size of PCR fragments}]}$$

(after Boland CR, Ricciardiello L 1999 Proc Natl Acad Sci USA 96:1465. In colorectal cancer cells and premalignant polyps (Stoler DL et al 1997 Proc Natl Acad Sci USA 96:15121) they found extremely high frequency, approximately 11,000 alterations, per cell. They concluded: "...genomic instability being a cause rather than an effect of malignancy....")

The point-mutational origin of cancer has been questioned because (i) there are carcinogens that do not induce gene mutation or are very ineffective mutagens, e.g., asbestos, nickel (Ni^{2+}), butter yellow, urethan, etc., [should be noted that authors list arsenic as a nonmutagenic carcinogen but in barley plants arsenates are strong mutagens]; (ii) the majority mutations in the various types of cancers are not present in all types of cancers; (iii) no genes isolated

from cancers induce mutations in animal or human cells and the loss of the oncogenes, e.g., RAS does not revert cancer cells to normal cells; (iv) the long period of latency does not seem to be consistent with the mutational origin; (v) the cancer cells are unstable whereas mutations are most commonly stable; and (vi) virtually all solid tumors are aneuploid. Wang et al (2002 Proc Natl Acad Sci USA 99:3076) do not find experimental evidence for the presence of mutator activity in colorectal cancer. Loeb et al (2003 Proc Natl Acad Sci USA 100:776) argue in favor of mutator mechanisms because of the extensive genetic heterogeneity in various tumors. Peter Duesberg and coworkers assume that aneuploidy is the basic cause of cancerous transformation (Li R et al 2000 Proc Natl Acad Sci USA 97:3236). The aneuploid cells grow slowly and are less competitive than normal cells and that would explain the delay of the onset of cancer. Furthermore, aneuploids are unstable and with time may affect the expression of many genes.

Genetic tests for cancer risk have serious technical limitations, as it is obvious from the discussions above. In a few instances such as intestinal polyposis, the detection of the presence of the cancer gene may warrant earlier and continued surveillance by colonoscopy. In the presence of defects (MEN2) in RET alleles, prophylactic thyroidectomy may be considered. Identification of individuals with the BRC1 or BRC2 breast cancer genes may warn of the increased possibilities of breast or ovarian cancer, however, preventive surgery may be too high of a price for the uncertain manifestation of the neoplasia. Metastatic conditions may be detected by blood DNA analysis for specific oncogenic markers. RT-PCR and PSA levels may indicate (not just prostate cancer) micro-metastatic conditions. For these types of analyses molecular methods are available. These may detect LOH, microsatellite heterogeneity, telomerase deficiency, or eventually, SAGE and DNA chip analyses may become practical. In cancer, many proteins are altered in expression to various extents. By high-throughput immunoblotting, 64 protein alterations were detected in prostate cancer and in the metastatic stage, an additional 156 alterations occurred (Varambally S et al 2005 Cancer Cell 8:393). When high-throughput genotyping by mass spectrometry queried 238 known oncogene mutations across 1,000 human tumor samples, of 17 oncogenes analyzed,

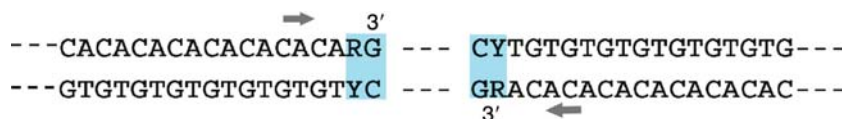


Figure C15. Cancer PCR product

it was found that 14 mutated at least once, and 298 (30%) samples carried at least one mutation. This type of analysis of mutations permits the study of multiple cancer genes simultaneously and in “real time” to guide cancer classification and rational therapeutic intervention (Thomas RK et al 2007 Nature Genet 39:347).

After two decades of epidemiological research no convincing evidence has been found for the putative leukemogenic effect of low-frequency electromagnetic fields for children. About 85% of human cancers involve solid tumors which are most commonly associated with loss of several genes regulating the cell cycle, growth hormones, cell surface receptors, cell adhesion molecules, etc. Mitotic crossing over may also generate homozygosity for oncogenes. Aneuploidy is common in solid tumors. In tumors of the hematopoietic or lymphatic system, chromosome translocations are frequent. Some of the multiple chromosomal rearrangements in cancer follow a preferred path. In human cells, chemical and physical agents (carcinogens) can induce cancerous growth in culture. The transformation of the coding sequence for the large catalytic subunit of the telomerase (hTERT), the T oncogene of Simian virus 40 and the RAS oncogene into epithelial and fibroblast cell cultures leads to cancerous proliferation and maintenance of this state. Cytokines regulate tumor development at several levels. *Drosophila* has many genes that are homologous to mammalian oncogenes, tumor suppressors, and other genes responsible for abnormal cellular proliferation. Cancer is initiated and maintained by many different mechanisms, yet all of them share the properties of independence of external growth signals, limitations to respond to growth inhibitory and apoptotic signals, and steady proliferative potentials supported by steady angiogenesis and metastasis. The incidence of cancer increases dramatically after age 40 in humans but a plateau is reached after 80. Epithelial carcinomas (breast, prostate, lung, colon, etc.) represent about 9% of cancer in children but by adulthood the share grows to above 80%. ▶genetic tumors, ▶oncogenes, ▶protein tyrosine kinases, ▶cellular transmission of tumor, ▶epigenesis, ▶EC, ▶leukemias, ▶melanoma, ▶carcinogens, ▶ROS, ▶immunological surveillance, ▶environmental mutagens, ▶chromosome breakage, ▶aneuploidy, ▶mosaic variegated aneuploidy, ▶imprinting, ▶Knudson's two mutation theory, ▶Wilms tumor, ▶retinoblastoma, ▶Bloom syndrome, ▶xeroderma pigmentosum, ▶neurofibromatosis, ▶tuberous sclerosis, ▶von Hippel-Lindau syndrome, ▶nevoid basal cell carcinoma, ▶multiple hamartomas, ▶MEN, ▶lentigin, ▶leiomyoma, ▶lipomatosis, ▶tumorigenesis, ▶Beckwith-Wiedemann syndrome, ▶Werner syndrome,

▶Rothmund-Thompson syndrome, ▶focal dermal hypoplasia, ▶Fanconi anemia, ▶adenomatosis endocrine, multiple, ▶agammaglobulinemia, ▶Wiskott-Aldrich syndrome, ▶ataxia telangiectasia, ▶Gardner syndrome, ▶polyposis, ▶colorectal cancer, ▶polyposis hamartomatous, ▶gonadal dysgenesis, ▶Down syndrome, ▶neuroblastoma, ▶Li-Fraumeni syndrome, ▶exostosis, ▶keratosis, ▶breast cancer, ▶Klinefelter syndrome, ▶leukemias, ▶prostate cancer, ▶liver cancer, ▶phorbol esters, ▶adenovirus, ▶Epstein-Barr virus, ▶*Helicobacter pylori*, ▶*Schistosoma*, ▶Hepatitis B virus, ▶Hepatitis C virus, ▶gatekeeper gene, ▶tumor suppressor, ▶inflammation, ▶tumor antigen, ▶LOH, ▶methylation of DNA, ▶DNA repair, ▶microsatellite, ▶SAGE, ▶DNA chips, ▶PSA, ▶RT-PCR, ▶cancer susceptibility, ▶Toll-like receptor, ▶cancer gene therapy, ▶cancer prevention, ▶E2F, ▶TNF, cell cycle and the named factors listed separately, ▶telomerase, ▶cytokines, ▶apoptosis, ▶angiogenesis, ▶metastasis, ▶stem cell, ▶tissue microarray, ▶proteomics, ▶PEG-3, ▶Tasmanian devil, ▶cancer classification, ▶mutator genes, for cancer characterization by microarray: Nature Medicine 4:844; microarrays in cancer studies: Tinker AV et al 2006 Cancer Cell 9:333; RLGS; Hoeijmakers JHJ 2001 Nature [Lond] 411:366; Sánchez-García I 1997 Annu Rev Genet 31:429; Knudson AG 2000 Annu Rev Genet 34:1; Bertram JJ 2000 Mol Aspects Med 21:167; Balmain A 2001 Nature Rev Cancer 1:77; Hahn WC, Weinberg RA 2002 Nature Rev Cancer 2:331; mouse models: Jonkers J, Berns A 2002 Nature Rev Cancer 2:251; molecular markers: Sidransky D 2002 Nature Rev Cancer 2:210; Mikkers H et al 2002 Nature Genet 32:153; Strausberg RL et al 2003 Nature Rev Genet 4:409; cancer cytology: Albertson DG et al 2003 Nature Genet 34:369; proliferation versus apoptosis: Lowe SW et al 2004 Nature [Lond] 432:307; checkpoints: Kastan MB, Bartek J 2004 Nature [Lond] 432:316; Oncomine; <http://www.cancergenetics.org>; Cancer Gene Anatomy Project [CGAP]: <http://www.ncbi.nlm.nih.gov/dbEST/index.html>; <http://www.ncbi.nlm.nih.gov/ncicgap>; cancer gene expression databases: <http://www.ncbi.nlm.nih.gov/SAGE>; <http://www.ncbi.nlm.nih.gov/geo/>; <http://cged.hgc.jp>; cancer statistics: <http://seer.cancer.gov/>; cytogenetics: <http://AtlasGeneticsOncology.org/>; <http://www.helsinki.fi/cm/g>; <http://www.infobiogen.fr/services/chromcancer>; cancer resources: <http://cis.nci.nih.gov/resources/resources.html>; <http://www.oncomine.org>; gene expression modules in cancer: <http://ai.stanford.edu/~erans/cancer/>; catalog of somatic mutations in

cosmic; cancer cell lines: <http://www.sanger.ac.uk/genetics/CGP/CellLines>; general information on cancer: www.cancerquest.org; cancer susceptibility markers: <http://caintegrator.nci.nih.gov/>

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cgems/; <http://cgems.cancer.gov>; cancer gene catalog: <http://www.sanger.ac.uk/genetics/CGP/Census/>; cancer gene mapping and expression: <http://cgap.nci.nih.gov/>; cancer genes: <http://cbio.mskcc.org/cancergenecatalog/>; mouse tumor biology database: <http://tumor.informatics.jax.org/mtbwi/index.do>; cancer sequencing:

<http://www.genome.gov/cancersequencing/>; cancer and related genes online [CARGO]: <http://cargo.bioinfo.cnio.es/>; normal and cancer gene expression: <http://www.gepis.org/>; cancer associated mutation predictor: <http://www.cgl.ucsf.edu/Research/genetech/canpredict/index.htm>.

Cancer Chromosomes: Includes information on spectral karyotyping, Multiplex-FISH, Comparative Genomic Hybridization, Mittelman database, etc. (See <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=CancerChromosomes>).

Cancer Classification: Many human genetic diseases involve syndromes, and the symptoms of different syndromes frequently overlap. Therefore, clear separation of a disease may not be straightforward. Similar and even worse is the situation in various types of cancers. Cancers with similar phenotypes may respond differently to therapies. Also, early

the chances of successful treatment. The expression of cancer may depend on a good number of genes. Thus, identifying the expression patterns of the genes may help classification of cancers of similar phenotypes. The cancer investigator faces two main problems: (i) discovery of the main type and possible subtypes of the neoplasia; (ii) predict which class(es) the cancer investigator/therapist deals with. Using microarray hybridization of thousands of genes expressed in the tumors, some smaller groups of genes can be selected for detailed analysis and can be specifically targeted for therapy (Bild AH et al 2006 *Nature [Lond]* 439:353). Recurrent amplification of a liver cancer DNA sequence in mouse chromosome 9qA1 and the corresponding to human chromosome 11q22 revealed the coamplification of the apoptosis inhibitor cIAP1 and the YAP transcription factor. Both of these genes contribute to carcinogenesis. Thus these experiments seem promising to the annotation of human cancer genes (Zender L 2006 *Cell* 125:1253). Comparative genomic hybridization revealed that Nedd9/Hef1 (6p25-p24) was highly expressed in vitro and in vivo in metastasis of melanoma in mice and humans (Kim M et al 2006 *Cell* 125:1269). In yeast, hairpin-capped double strand breaks occur near Alu-like palindromic sequences and can lead to the formation of intra-chromosomal amplicons with large inverted repeats or extra-chromosomal palindromes similar in function to mammalian double-minute chromosomes.

These amplicons can lead to tumor formation in mammals (Narayanan V et al 2006 *Cell* 125:1283). ▶microarray hybridization, ▶cluster analysis, ▶recursive partitioning, ▶cancer, ▶predictor gene, ▶RLGS, ▶cancer signature, ▶aptamer, ▶DiGE, ▶IAP, ▶YAP, ▶comparative genomic hybridization, ▶amplicon, ▶DM (double-minute) chromosome, ▶palindrome; Golub TR et al 1999 *Science* 286:531; Wooster R 2000 *Trends Genet* 16:327; Zhang H et al 2001 *Proc Natl Acad Sci USA* 98:6730.

Cancer Death Rate: Usually initiated by several somatic mutations and only about 5% of the cases are attributable to germline mutations. In the USA, annually, 1.6–2.5 million new cancer cases occur and the death rate is about 560,000/year. The worldwide cancer death rate is about 6.6 million/year. In men, the most common types of cancer is that of the prostate (43%), and lung and bronchus cancer (13%). In women, breast cancer is most common (30%), lung/bronchus (13%) and colon/rectum cancer (11%) follow. Lung cancer claims more deaths (32% and 25%) in both sexes than any other types. Although the rates of cancer deaths are somewhat declining, the incidence of cancer is not. About 70% of the cancer victims may show some remission, 50% of them relapse and become unresponsive to currently available treatments. ▶cancer, ▶cancer therapy, ▶cancer gene therapy

Cancer Drug Trials: See <http://www.cancer.gov/clinicaltrials>.

Cancer Family Syndrome: ▶Li-Fraumeni syndrome, ▶Lynch cancer family syndrome

Cancer Gene Therapy: Transforming by (1) cytokine genes; (2) introducing genes encoding foreign antigens; (3) using antisense RNA or DNA constructs; (4) functional tumor suppressor alleles; (5) introducing the wild type dominant oncogenes; (6) ribozyme technology; (7) transferring the *Herpes simplex* virus thymidine kinase (HSVTK) gene, making the tumor sensitive to ganciclovir (GCV); (8) using artificial transcription factors for remodeling gene expression may be exploited; (9) RNAi technology. Sensitive cancer targets (such as growth signals or apoptosis evasion) can be identified by the use of short, interfering RNAs (Ngo VN et al 2006 *Nature [Lond]* 441:106). Using the aptamer-siRNA chimeric RNA construct facilitated the targeting of siRNA to specific cancer cells. The aptamer part of the PSMA cell surface receptor, overexpressed in prostate cancer cells and in tumor vascular epithelium, recognized the target, the construct was taken up and the siRNA specifically inhibited tumor growth (McNamara JO II et al 2006 *Nature Biotechnol* 24:1005). Phosphorylation of GCV (GCV-TP)

inhibits DNA polymerase that stops cancer cell proliferation, (10) using the multiple drug resistance gene, MDR; (11) magic bullets have been attempted; (12) and some approaches of tumor vaccinations are now in clinical trials. Cancer vaccines are based on whole cells, cell extracts and specific antigens, including carbohydrate-protein conjugates, GM2, GD3, and fucosyl GM1 gangliosides, globo H, Lewis blood group antigens and mucin core structures. The difficulty facing immunological defense is that cancer cells are of self-origin and the immunological response to them is not good. Rejection of the malignant cells is very effective if tumor vaccines, e.g., after viral infection or transfection, elicit the expression of a foreign gene by a viral gene. Some individuals are immunosuppressed probably because some suppressor T cells down-regulate the effector T cells. In some cases, the signaling to the T cell receptors seem to be disabled or diminished. Some studies indicated an activation of the immune system by introduction of cytokine genes into the tumors. This might be the result either of better signaling or the recruitment of granulocyte-macrophage-colony-stimulating factor (GM-CSF). The tumor cells may display unusual epitopes (mutated β -catenin, caspase) on their MHC molecules and thus be recognized by the immune system, causing the rejection of the parent-type tumor cells. These epitopes may actually occur as differentiation antigens, present in reduced amounts in normal cells too, and the treatment must avoid hurting the normal cells. There may be substantial variations among the different tumors, thus the immunotherapy faces complications. Some of the human cancers are of viral origin, and in these cases proteins essential for the maintenance of the cancerous state can be targeted. The therapeutic strategy must also consider whether cell-mediated (T cell) or antibody-mediated defense (Th1 helper cells) may be the most effective route to go. In case the patients were exposed to radiation or chemotherapy, they may be immunosuppressed or tolerant and the immunotherapy reduces chances for success. Some instances of “generic”

immunotherapy may help, but “custom” therapies using the mutated self-antigens of the patients may have higher probability for success. Tumor cell-based vaccines, immunization with tumor peptides, DNA- or RNA-based vaccination, stimulation of the lymphocytes, or reintroduction into the patients of their own in vitro stimulated lymphocytes or antigens are within some of the therapeutic repertoires. When mice experimental tumors were rendered transgenic for TNF (tumor necrosis factor, IL-2, IL-12 IL-4 [interleukin]), IFN- γ (interferon), GM-CSF (granulocyte-macrophage colony stimulating factor), the tumors went into remission or rejection. Actually, IL-2 itself is not directly curbing the proliferation of cancer cells; rather it stimulates the expansion of lymphocytes, which have antitumor activity. CD8⁺ T lymphocytes recognize 8–10-amino acid peptides generated from, and selected for by, in vitro sensitization of T cells and then cytoplasmic proteins by proteasomes, and displayed on the cancer cell surface by class I HLA molecules. CD4⁺ T cells—in contrast—recognize extracellular proteins, engulfed and digested in the endosomes, and displayed on the cell surface by class II HLA molecules. Based on these properties, cancer antigens can be purified and characterized. Cancer antigens can be tested on intact cancer cells by this *reverse immunology*. Another newer technology is represented by SEREX. In cancer cells, thousands of genomic instabilities may occur generating a great variety of new types of cancer antigens.

Some success was achieved in the rejection of melanoma and lymphoproliferative cancers by immunization *via* the sensitized lymphocytes (adoptive therapy). Autologous T lymphocytes, transgenic for the T cell receptor, when introduced into melanoma caused regression of the cancer in some patients (Morgan RA et al 2006 Science 314:126). Administration of IL-2 cytokines substantially enhances the effectiveness of some immunotherapies (Rosenberg SA 2001 Nature [Lond] 411:380). The use of IL-12 in humans is avoided because of liver toxicity.

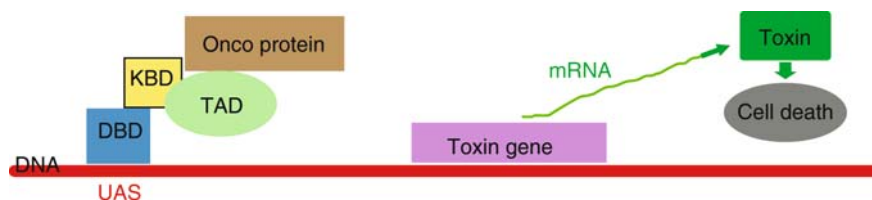


Figure C16. Cancer gene therapy. The toxin gene is transactivated and turned on, killing the cancer cell after it has been exposed to the transactivator by connecting the circuit through the oncoprotein to the upstream activator sequence (UAS). (Diagram modified after Da Costa, LT et al 1996 Proc Natl Acad Sci USA 93:4192).

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New technologies are continuously developed. One of such cancer therapy design would convert the cancer genes (oncoprotein) into cancer killer genes by activating a toxin gene according to a construct outlined (see Fig. C16). The oncoprotein has a DNA-binding domain (DBD), transactivator domain (TAD) and the killer-binding domain (KBD). Another possibility is to fuse the *Pseudomonas* exotoxin (PEA) to the extracellular domain of the HER2 transmembrane receptor protein. Transformed lymphocytes can then introduce, into the cancer cells, the toxin that inactivates elongation factor-2 (EF-2). Transfection of antisense RNA-producing constructs has been proven successful in animal models. Human tissue factor (TF), an important receptor of the blood coagulation cascade, can be targeted to endothelial blood vessels of the tumor by an appropriate antibody. TF complexed with antihemophilic factor VII activates the serine protease zymogen factors IX and X resulting in the formation of thrombin and blood clotting. Blocking specifically and locally the blood supply (antiangiogenesis) to the tumor may cause its substantial regression.

Small peptides—identified by the technique of phage display—that have a special affinity for the tumor blood vessels, can be linked to potent antibiotics (such as doxorubicin) and appear to be a promising alternative to chemotherapy. Unlike the dangers of drug resistance in chemotherapy, antiangiogenesis in endothelial cells does not lead to resistance. The cancer gene therapy vectors must be so designed that they would recognize and destroy the cancer cells without inflicting damage to the normal cells even if they are interspersed with tumor cells. By employing cancer cell-specific promoters (such as the melanocyte-specific tyrosinase promoter or the α -fetoprotein promoter specific for liver carcinomas or the c-erb-B2 specific for breast, ovarian cancer and neuroblastoma) the expression of the genes controlling cytotoxic substances can be localized. The *progression-elevated gene-3* (PEG-3) is an originally rodent gene, which is selectively expressed in a variety of cancer cells but not in normal cells. The transcription factors AP-1 and PEA-3 are the main factors in determining the cancer cell specificity of the promoter of PEG-3. Placing an apoptosis inducing gene (e.g., p53, mda-7/IL24) under the control of the PEG-promoter completely inhibited a prostate cancer xenograft in nude mice, indicating the potential and highly selective value of such a construct in cancer gene therapy (Su Z-Z et al 2005 Proc Natl Acad Sci USA 102:1059; Sarkar D et al 2005 Proc Natl Acad Sci USA 102:14034). Radiation responsive and hormonal receptor regulatory systems may permit the combination of radiation treatment and hormone therapy along with the cytotoxicity

transgene. Cancer cells may become resistant to treatment during the expansion of the tumor. The probability of resistance is proportional to the detectable cell number multiplied with the mutation rate ($M \times \mu$). If ($M \times \mu$) is much smaller than 1, then the expected number of resistant cells is independent of μ and increases with M (Iwasa Y et al 2006 Genetics 172:2557).

Cancer gene therapy is an innovative, new research area and more work is required before it could become a general clinical practice (Varmus H 2006 Science 312:1162).

Some anaerobic (*Clostridium beijerinckii*, *Bifidobacterium longum*) or facultative (*Salmonella typhimurium*) anaerobic bacteria preferentially accumulate in some tumor tissues. A *Salmonella* strain transgenic for cytosine deaminase converts the nontoxic 5-fluorocytosine to the active antitumor 5-fluorouracil. Administration of this bacterium, followed by treatment of fluorocytosine, effectively regressed tumors in mice (Paglia P et al 1998 Blood 92:3172). Unfortunately, the first attempts to apply this technique to human melanoma were not effective. *Salmonella typhimurium* A1 strain auxotrophic for Leu/Arg amino acids and labeled with green fluorescent protein (or other fluorochrome) grew continuously in prostate tumor tissue and caused regression of the tumor without obvious harm to the host nude mice (Zhao M et al 2005 Proc Natl Acad Sci USA 102:755). ►gene therapy, ►cytokines, ►antisense technologies, ►RNAi, ►nanoparticles, ►tumor suppressor genes, ►tumor vaccination, ►multidrug resistance, ►magic bullet, ►epitope, ►MHC, ►MDR, ►transfection, ►ERBB2, ►biomarkers, ►exotoxin, ►EF-2, ►ganciclovir, ►plasmovirus, ►antihemophilic factors, ►tissue factor, ►cancer prevention, ►phage display, ►topoisomerases, ►camptothecin, ►cell therapy, ►MoMuLV, ►retroviral vectors, ►tTA, ►oncolytic viruses, ►OL (1)p53, ►p21, ►p16^{INK}, ►mda-7, ►AP-1, ►retinoblastoma, ►immunotherapy, ►immunotherapy adoptive, ►gangliosides, ►Lewis blood group, ►globo H, ►T cell, ►immune system, ►lymphokines, ►ribozymes, ►angiostatin, ►endostatin, ►adenovirus, ►adeno-associated virus, ►vaccinia virus, ►HIV, ►SEREX, ►mini-organ therapy, ►suicide vectors, ►oncogene antagonism, ►tumor infiltrating lymphocytes, ►tumor vaccination, ►dendritic cell vaccine, ►liposome, ►bystander effect, ►cancer death, ►cytosine deaminase, ►transcriptional targeting, ►Philadelphia chromosome, ►cancer therapy, ►informed consent, ►anti-4-1BB monoclonal antibody, ►immune surveillance, ►immunostimulatory DNA, ►Onyx-015, ►GFP, ►fluorochromes, ►auxotroph, ►nude mouse; Nettelback DM et al 2000 Trends Genet 16:174; Kudryashov V et al 2001 Proc

Natl Acad Sci USA 98:3264; McCormick F 2001 Nature Rev Cancer 1:130; Wadhwa PD et al 2002 Annu Rev Med 53:437; Ye Z et al 2002 Nature Med 8:343; Blancafort P et al 2005 Proc Natl Acad Sci USA 102:11716; Verma IM, Weitzman MD 2005 Annu Rev Biochem.74:711; cancer gene interaction network; Rual J-F et al 2005 Nature [Lond] 437:1173; RNAi therapy; Chang H 2007 Cancer Gene Ther 14:677, CBER; <http://www.fda.gov/cber/>; tumor associated antigen: <http://www.hpta.org/>; tumor transcriptome: <http://bioinfo-out.curie.fr/ittaca/>.

Cancer Genetic Markers for Breast and Prostate

Cancer: See <http://cgems.cancer.gov/>.

Cancer Genome Anatomy Project (CGAP): A collaborative network of cancer researchers to study the origin, formation, and progression of cancer and for the dissemination of information. Riggins GJ, Strausberg RL 2001 Hum Mol Genet 10:663; <http://cgap.nci.nih.gov/>.

Cancer Genome Atlas: Provides information toward understanding the basis of the different types and stages of the over 200 kinds of cancers. <http://cancergenome.nih.gov>.

Cancer, Pathogen Induced: ►Epstein-Barr virus, ►*Helicobacterium pylori*, ►Hepatitis B, ►Hepatitis C virus, ►*Schistosoma*

Cancer Prevention: Prevention of cancer is different from cancer chemotherapy in as much as it is not expected to kill fully cancerous cells; rather, it is aimed at blocking either the primary or the secondary malignancy routes. The chemical treatment may reverse neoplastic development or block preneoplastic conditions without substantial toxicity. Chemicals that stop metabolic activation of procarcinogens were also sought. The cyclooxygenase (COX-2) enzyme appears to increase during the development of intestinal tumors. Blocking the activity of this enzyme by MF-tricyclic without side effects is one approach. Breast cancer may be blocked by tissue-specific estrogen inhibitors (raloxifen, LY353381). Prostate cancer prevention is feasible by interference with estrogen receptors (flutamide). Lung cancer development may be arrested by restoration of the expression of a retinoic acid receptor- β by 13-cis-retinoic acid. Approaches to vaccination against cancer are being worked on. Glycopeptides resembling cell surface tumor antigens may be produced by laboratory techniques. These may then trigger immune responses. Early detection of a cancerous condition may facilitate more effective medication. Various such tests are available, e.g., breast cancer mammography, Pap smear for cervical cancer, the PSA test for prostate

cancer, and fecal occult blood test or colonoscopy for colon polyps. It is highly desirable to find noninvasive and accurate markers for other neoplasias. One approach is to examine blood samples for mutant DNA molecules. In the plasma, 47,800 molecules of the adenomatous polyposis (APC) gene occurred/mL and in a test, 8% of them were found to be mutants in affected individuals. In comparable healthy samples a level of only 0.01 to 1.7% mutant molecules appeared (Diehl F et al 2005 Proc Natl Acad Sci USA 102:16368). ►cyclooxygenase, ►RAR, ►tamoxifen, ►raloxifen, ►retinoic acid, ►immunological surveillance, ►peptide vaccination, ►cancer, ►breast cancer, ►Gardner syndrome, ►Pap test, ►prostate cancer; Levi MS et al 2001 Curr Med Chem 8:1439.

Cancer Prognosis: ►cancer signature

Cancer Promoter: ►phorbol esters

Cancer Signature: Cancer is an abnormal development and it is important to know why and how normal cells embark on such a trajectory(s) of disease. On the basis of microarray hybridization data available in databases it appears that the E2F transcription factor regulates many types of cancers, whereas Myc-Max, Rel and ATF were disproportionately expressed in specific types of cancer cells. In breast cancer, coordinated amplification of MYC and CSN5 genes provides a prognosis for the progression (Adler AS et al 2006 Nature Genet 38:421). Unfortunately, most of the lists of predictor genes display small overlaps and do not permit the making of reliable trajectories for individual cases. Efforts are still underway to make prognosis and spare patients from hard radiation or chemotherapies unless there is a high probability for success (Ein-Dor L et al 2006 Proc Natl Acad Sci USA 103:5923). Dynamic imaging traits in noninvasive computed tomography (CT) systematically correlate with the global gene expression programs of primary human liver cancer. Combinations of twenty-eight imaging traits can reconstruct 78% of the global gene expression profiles, revealing cell proliferation, liver synthetic function, and patient prognosis. Thus, genomic activity of human liver cancers can be decoded by noninvasive imaging, thereby enabling noninvasive, serial and frequent molecular profiling for personalized medicine (Segal E et al 2007 Nature Biotechnol 25:675). ►E2F, ►Myc, ►ATF, ►Polycomb, ►Oncomine, ►tomography, ►cancer classification; Rhodes DR et al 2005 Nature Genet 37:579.

Cancer Stem Cell: Cancer stem cells can be found in small numbers in tumors. They can recapitulate the original type of tumor. They have been found in human leukemia and breast cancer. In the brain cells of a mouse, neoplastic activity is maintained only in

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the presence of CD133. Some of the stem cells are actually *transit amplifying cells*, which, after some self-renewal, produce differentiated rather than cancer cells. The stem cell niche, which provides the factors necessary for self-renewal, determines the capacity of the transit amplifying cell to be proliferative or assume terminal differentiation. Self-renewal is regulated by suppression of differentiation. Leukemia stem cells can maintain the identity of the progenitor from which they arose but a limited number of them can express genes of normal hematopoietic stem cells if initiated by MLL–AF9 fusion (Krivtsov AV et al 2006 Nature [Lond] 442:818). In a mouse gene, *Bmi1* suppresses differentiation of hematopoietic stem cells. *Bmi1* regulates oncoproteins and (Tp53, p16^{Ink4a}, p19^{Arf}) determines whether they promote proliferation or stay tumor suppressors (Kim WY et al 2006 Cell 127:265). The first step in cancer development is a mutation, which inactivates expansion of normal stem cells. The transit amplifying cell continues to proliferate without differentiation and subsequently additional mutations generate self-renewing cancer stem cells (Clarke MF, Fuller M 2006 Cell 124:1111). The relatively small number of stem cells in cancer can mutate and acquire resistance to drug therapy (Dean M et al 2005 Nature Rev Cancer 5:275). ▶**stem cells**, ▶**progenitor**, ▶**EC**, ▶**p16^{Ink4a}**, ▶**p53**, ▶**CD133**, ▶**MLL**; AF, Singh SK et al 2004 Nature [Lond] 432:396; Dalerba P et al 2007 Annu Rev Med 58:267.

Cancer Susceptibility: Susceptibility to cancer may be affected by environmental factors and genotypic differences. The most effective environmental carcinogens are polycyclic aromatic hydrocarbons and aromatic amines. The genetic predisposition depends on the individual differences in the activation and detoxification systems. The major risk factors are mutation(s) in tumor suppressor genes. Somewhat less important are the mutations in activating enzymes that may, however, become important under conditions of longer or repeated exposure to carcinogens. The detoxification process itself may also involve activation of the procarcinogens into carcinogens. The metabolic factors include the P450 cytochrome system, glutathione-S-transferase (GST), epoxide hydrolase and *N*-acetyltransferase (NAT), and defects in apoptosis, cell cycle, genetic repair, etc. Individuals with mutations in the enzymes' modulating responses to carcinogens may be at increased risk. Generally, the contributing factors include interactions among several of the modulatory enzymes. Therefore, the risk on the basis of analyzing a single enzyme may not be sufficient. Ethnic, sex, and age differences exist in susceptibility. Some of

the differences may be caused by cultural and environmental factors (diet, smoking, etc.). So far no general method is available for cancer screening. Binding antibodies isolated from whole serum can screen random peptide libraries generated by phage display. This procedure then identifies potential targets for drug therapy as well the metastatic stage of prostate cancer (Mintz PJ et al 2003 Nature Biotechnol 21:57). ▶**cancer**, ▶**carcinogens**, ▶**environmental mutagens**, ▶**activation of mutagens**, ▶**P450**, ▶**glutathione-S-transferase**, ▶**epoxide**, ▶**cancer signature**; Taningher M et al 1999 Mutation Res 436:227; QTL analysis; Demant P 2003 Nature Rev Genet 4:721.

Cancer-Testis Antigens: These antigens are coded in several human chromosomes and are expressed in different types of cancer, including the testis. ▶**MAGE**

Cancer Therapy: On the basis of progress in annotation of the sequenced genes, specific targets can now be identified. Among them the oncogenes-activating kinases can be neutralized. Small molecules may target oncogenic signals. Specific monoclonal antibodies can be joined with cytotoxic agents and delivered to selected cancer sites. One newer approach for finding anticancer molecules is to mix two isogenic cell lines; in one of them the cancer suppressor K-Ras allele has been deleted by homologous recombination. The two lines are marked differently by fluorescent tags (YFP and BFP, respectively). The cell mixture is exposed to a library of ~30,000 chemicals. The growth differential of the two cell lines (determined by the intensity of the label) can be assessed on a large scale and selectively, and it was revealed that a novel cytidine analog (sulfinyl cytidine, SC-D) is selectively toxic to the cancer but does not interfere with the healthy cells. In addition, the chemical inhibited xenografts of the mutant Ras (Torrence CJ et al 2001 Nature Biotechnol 19:940). Bacterial infection may reduce the proliferation of cancer cells. *Salmonella typhimurium* leu-arg auxotrophs grow in viable as well as necrotic areas of tumors; the nutritional auxotrophy severely restricts growth in normal tissue. The antitumor efficacy of the *S. typhimurium* auxotrophic leu-arg has increased antitumor virulence in prostate cancer (Zhao M et al 2007 Proc Natl Acad Sci USA 104:10170). The immune effector cell population of cytokine-induced killer cells along with oncolytic virus (thymidine kinase deleted Vaccinia) effectively targeted the tumors and synergistically attacked mouse mammary cancer cells without harming normal cells (Thorne SH et al 2006 Science 311:1780).

Liposomase (liposome-lysing enzyme) of *Clostridium novyi-NT* bacterium can enhance the release of cancer drugs with increased efficiency when delivered by liposomes. Mouse tumors treated with this bacterium and liposomal doxorubicin (an antineoplastic agent) eradicated tumors (Cheong I et al 2006 Science 314:1308). Boron Neutron Capture Therapy (BNCT), based on selective capture of thermal neutrons, is capable of neutralizing malignant melanoma—when successfully targeted to tumor cells—in case other treatments fail (Hawthorne MF 1993 Angewandte Chem Int Ed English 32:950). In the majority of cancer cells, reactive oxygen species (ROS) accumulate and aid further proliferation of and increase in genetic instability. The cancer cells try to cope with this problem with the production of antioxidants such as glutathione. β -phenylethyl isothiocyanate, a natural product in cruciferous vegetables, is known to disable antioxidants in the cells. Thus, when provided to cancer cells, it further boosts ROS effects and thus selectively kills cancer cells and improves the survival of nude mice. ROS molecules are particularly deleterious to mitochondrial membranes. Normal cells are not much affected, probably because their antioxidant level is usually low (Trachootham D et al 2006 Cancer Cell 10:241).
 ▶cancer gene therapy, ▶magic bullet, ▶cisplatin, ▶immunotoxin, ▶adenovirus [dl1520], ▶antimitotic agents, ▶cytostatic, ▶tamoxifen, ▶cytokines, ▶doxorubicin, ▶liposomes, ▶chemotherapy, ▶radiation effects, ▶cell cycle, ▶BCL, ▶antisense technologies, ▶multiple drug resistance, ▶NF- κ B, ▶biomarkers, ▶plasmovirus, ▶cancer prevention, ▶telomerase, ▶telomerase, ▶angiogenesis, ▶angiostatin, ▶endostatin, ▶bleomycin, ▶tumor infiltrating lymphocyte, ▶clonogenic test, ▶Yttrium, ▶imaging, ▶electroporation, ▶alkyltransferase, ▶immunological surveillance, ▶shark cartilage, ▶biomarkers, ▶plantibody; Hurley LH 2002 Nature Rev Cancer 2:188; Strausberg RL et al 2004 Nature [Lond] 429:469; targeted therapy; Sawyers C 2004 Nature [Lond] 432:295.

Cancer Vaccines: ▶cancer gene therapy, ▶vaccines

Candela: A unit of luminous intensity. A standard radiator produces 60 candela/cm² at the freezing temperature of platinum (−2,046K); 1/60 candela = 1 candle (new unit). 1 foot candle = 10.76 lux; 1 lux = 1 lumen/m²; 1 lumen = is the total visible energy emitted from one candle point luminous intensity.

Candida albicans: A human diploid (n = 8) fungal opportunistic pathogen in hospitals with ~200 species. The mating type is determined by a mechanism similar to that in *Saccharomyces cerevisiae*. There is a difference, however, in the regulation of the

system. In *C. albicans* the **a** mating type dependent genes require activation by a high mobility group of protein **a2**, encoded by the *MATa* locus, whereas in basically the same system in *S. cerevisiae*, the **a**-dependent genes are normally until repressed by the **α 2** protein encoded by the *MATa* locus (Tsong AE et al 2006 Nature [Lond] 443:415). The chromosomes frequently display polymorphism because of rearrangements. The largest chromosome is frequently designated as R because it contains the ribosomal DNA cluster. Conjugating laminarin (β -glucan) with diphtheria toxoid CRM197 (inactivated exotoxin) provided a highly effective vaccine against vaginal candidiasis and also *Aspergillus fumigatus* in rodents (Torosantucci A et al 2005 J Exp Med 202:597). Isochromosome of two left arms of chromosome 5 is associated with resistance to azole drugs (Selmecki A et al 2006 Science 313:367). Azole drugs are used as systemic antifungal agents; they block 14 α -lanosterol demethylase, essential for ergosterol biosynthesis.
 ▶candidiasis, ▶*Aspergillus*, ▶ergosterol, ▶mating type determination in yeast; Janbon G et al 1998 Genetics 95:5150; genome databases; <http://genolist.pasteur.fr/CandidaDB>; <http://www.candidagenome.org/>.

Candidate Gene: A candidate gene is already mapped in a chromosomal region and possibly included in the DNA fragment to be mapped, but it is not known (although hoped) that it is involved in a particular function or phenotype associated with a mutation. The functional identity of the isolated DNA requires rigorous biochemical proof. In case multiple alleles of the gene are available, the verification of the identity is greatly facilitated. In case the wild type allele of the isolated gene is returned by transformation in a mutant stock and the normal phenotype is restored, there can be no doubt about identity. ▶gene isolation, ▶transformation genetic; Ernst JF 2000 Microbiol 146:1763; candidate gene prediction for hereditary disease: <http://www-micrel.deis.unibo.it/~tom/>; in *Arabidopsis* and rice: <http://www.scbio.org/qtl2gene/new/>.

Candidiasis, Familial, Chronic Mucocutaneous (FCMC):

An apparently autosomal recessive (2p) immunodeficiency involving T lymphocytes, resulting in infections of the mucous membranes, skin and nails by *Candida* fungi. The diploid *C. albicans* (n = 7, 16 × 10⁶ bp) is the most prevalent pathogen in this type of disease and it is responsible for the very common and frequently lethal nosocomial infections. During infection of the murine urinary tract by *Candida glabrata* (a nicotinic acid auxotroph), nicotinic acid supply becomes limited and this results in silencing of NAD⁺-dependent histone deacetylase. As a consequence, the normally silent adhesin genes are

expressed and candidiasis ensues (Domergue R et al 2005 Science 308:866). ▶[immunodeficiency](#), ▶[nosocomial](#), ▶[rosacea](#); De Backer MD et al 2000 Annu Rev Microbiol 54:463; Chibana H et al 2000 Genome Res 10:1865.

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Candle: ▶[candela](#)

Canine Transmissible Venereal Tumor (CTVT, Sticker sarcoma): CTVT is transmitted as an allograft from existing tumors by sexual intercourse of dogs, biting and other contact of affected areas, but not by dead cells or cell filtrates. A LINE1 element is found in all transmissible venereal tumors near a c-myc oncogene. Current extensive evidence indicates that cancer cells can evolve into a transmissible parasite (Dingli D, Nowak MA 2006 Nature [Lond] 443:35). The CTVT of dogs seems to have originated from a wolf or East Asian breed of dog between 200 and 25,000 years ago, and it has been somatically propagated in diverse modern breeds. The dog leukocyte antigen gene of the tumors differed from that of normal dogs and seems to be clonally transmitted. The control region of the mtDNA also supported the clonal origin of the tumors despite some mutations. The original clone diverged into two subclades during early evolution and is maintained as such today. The tumor is highly aneuploid yet its current karyotype is remarkably constant (Murgia C et al 2006 Cell 126:477). ▶[aneuploidy](#), ▶[HLA](#), ▶[oncogene](#), ▶[LINE1](#), ▶[clade](#), ▶[Tasmanian devil](#)

Cannabinoids: About 60 related compounds synthesized by the hemp plants (*Cannabis*) and present in the psychoactive drug marijuana (see Fig. C17). Besides the psychoactive effects, they have various immunosuppressive properties and may control pain initiation and transmission through modulation of the rostral ventromedial medulla of the brain and tremor in multiple sclerosis. Some “endocannabinoids” are present in cocoa, milk and other human food, but do not appear to be responsible for cravings after chocolate or have other psychoactive effects. Δ^9 -Tetrahydrocannabinoid may reduce sexual activity and fertility by affecting steroid metabolism. THC (1 mg kg^{-1}) orally administered (thus below the psychotropic effect) reduces atherosclerosis in mice (Steffens S et al 2005 Nature [Lond] 434:782).

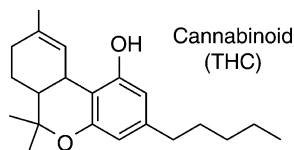


Figure C17. Cannabinoid (THC)

Endocannabinoids, in cooperation with leptin, also regulate food intake and body weight; leptin restricts food craving whereas endocannabinoids increase appetite. Anandamide also protect the central nervous system against inflammation (Eljaschewitsch E et al 2006 Neuron 49:67). The endocannabinoid anandamide, in low concentration, promotes receptivity of the mouse uterus to embryo transplantation, whereas at higher levels the receptivity is reduced. So far there is no evidence for the normal control of fertility although obese mice may be sterile until leptin is supplied. Endocannabinoids also activate the pleasure sensations, e.g., in eating tasty food, and this may explain addiction to cannabinoids. They may adversely affect/facilitate long-term potentiation of memory. An endocannabinoid transporter can increase cannabinoid level in the brain by 5-fold and points to the potential use of endocannabinoid transporter antagonists (Moore SA et al 2005 Proc Natl Acad Sci USA 102:17852). ▶[immunosuppressants](#), ▶[leptin](#), ▶[excitotoxicity](#), ▶[Cannabis sativa](#), ▶[horseradish](#), ▶[osteoporosis](#), ▶[analgesic](#); Iversen LL 2000 The Science of Marijuana Oxford Univ Press, New York; Di Marzo V et al 2001 Nature [Lond] 410:822; Carlson G et al 2002 Nature Neurosci 5:723; Mereu G et al 2003 Proc Natl Acad Sci USA 100:4915.

Cannabis sativa (hemp): A generally dioecious species (*Moraceae*) with a diploid chromosome number of 20, including either XX female or XY male flowers (see Fig. C18). The XXXY tetrasomics are also gynoeceous. Hermaphroditic forms are also known that produce more seed and only somewhat reduced amount of fiber. Low-cannabinoid genetic stocks are known. ▶[cannabinoids](#), ▶[hop](#); Onaivi ES (ed) 2002 Biology of Marijuana, Taylor & Francis, New York; de Meijer EPM et al 2003 Genetics 163:335.



Figure C18. *Cannabis*

Cannibalism: Animals eating members of their own species. In heterocannibalism the eaten individuals are not the offspring of the cannibal. Filial cannibals devour their own offspring. The latter class is generally less frequent because it is usually counterproductive

for fitness. Filial cannibals apparently lack the ability to identify their own offspring. Males are more likely to commit filial cannibalism than females because they have much less investment in the progeny. ►fitness; DeWoody JA et al 2001 Proc Natl Acad Sci USA 98:5090.

Canola: An erucic acid-free rapeseed oil crop, *Brassica napus* (2n = 38, AACC genomes). ►erucic acid

Canonical Sequence: A typical set of nucleotides in several genes (e.g., in a Pribnow box or Hogness box or other conserved elements).

Canyons: Deep structural sites on the viral surface where receptors bind.

CAP (catabolite activator protein): A homodimer with two subunits of M_r 22,000. It has a binding site for cAMP and DNA with a helix-turn-helix motif. As long as glucose is available in the nutrient medium the *Lac* operon of *E. coli* is inactive because glucose, a catabolite of lactose, represses the operon (catabolite repression). In order to turn on the operon the CAP protein must be attached to the CAP site, in a process mediated by cAMP. The adenyl cyclase enzyme forms the latter from ATP and this process is inhibited by glucose. When glucose is used up, cAMP is formed and the latter binds to CAP; the complex binds to its palindromic site in the DNA (GTGAGTTAGCTCAC) near the promoter of the operon and transcription by the RNA polymerase is activated. Without CAP the promoter is very weak. In order to pursue normal transcription the grip of the repressor protein must also be lifted and this is mediated by lactose (allolactose). The cAMP-CAP complex also regulates the arabinose and galactose operons. ►negative control, ►positive control, ►transcriptional activation, ►regulation of gene activity, ►lac operon, ►arabinose operon, ►galactose operon, ►cAMP, ►palindrome; Johnson CM, Schleif RF 2000 J Bacteriol 182:1995; Benoff B et al 2002 Science 297:1562.

CAP (ceramide-activated protein): CAP kinase mediates tumor necrosis factor and interleukin-1 β functions. It also phosphorylates Raf1 on Thr 269 and increases Raf affinity for ERK kinases. ►RAF, ►ceramides, ►ERK, ►TNF, ►interleukin; Chalfant CE et al 2000 Methods Enzymol 312:420.

Cap: A methylated guanylic residue linked at transcription to the 5' end of the eukaryotic mRNA (7MEG_{5'}ppp-mRNA) or 2,2,7-trimethyl guanosine in U RNA. The prokaryotic mRNA has only three phosphates at the 5' nucleotide end. The cap of the (long-life) eukaryotic mRNA stabilizes it (makes it less sensitive to nucleases), assures the transport of

the mRNA to the cytosol, and facilitates its binding to the ribosome and initiation of transcription by lending itself as an anchor to eIF4F eukaryotic initiation factors. The eIF factors and various binding proteins determine which mRNAs are transcribed at a certain stage of the development. The eI-4E binding protein 4E-BP may also act as a tumor suppressor. Upon phosphorylation, 4E-BP dissociates from the eIF4F complex resulting in increase of translation. This and other inhibitory proteins regulate nerve function and the consolidation of memory (Richter JD, Sonnenberg N 2005 Nature [Lond] 433:477). The cap also regulates splicing of the first intron. A capping complex (CBC), composed of cap-binding nuclear proteins, CBP80 and CBP20 mediates the effect of cap on pre-mRNA splicing. CBC then mediates the export of RNA. The U3 snRNA also has a trimethylated cap that is added in the nucleus and the RNA remains in the nucleus. Binding between the cap and the poly(A) tail promotes translation. Picornavirus mRNAs lack the 5' caps and thus translation initiation is cap-independent and it begins at an IRES site. ►capping enzymes, ►eIF4, ►regulation of gene activity, ►ribosome scanning, ►FLAG, ►poly[A], ►IRES; Rottman F et al 1974 Cell 3:197; Efimov VA et al 2001 Nucleic Acids Res 29:4751.

Cap3: The N-terminal domain of FLICE. ►FLICE

CAP'n'Collar Genes (CNC): CNC genes are basic leucine zipper transcription factor regulating homeotic genes. ►DNA binding protein domains, ►homeotic genes

Cap Snatching: Viral RNA replication secures primers for its initiation by cleaving off about a dozen nucleotide long pieces from the 5'-end of nuclear RNA polymerase II transcripts. The cleavage is mediated by a virus-encoded endonuclease. The priming does not involve hydrogen bonding between the primers and the 3'-end of the viral RNA template. ►primer; Duijsings D et al 2001 EMBO J 20:2545.

Capacitation of Sperm: ►fertilization

Cap-Binding Protein Complex (CBC): Binds to the 5'-end of the mature mRNA and facilitates U snRNA export. ►protein synthesis, ►U RNA, ►export adaptors, ►nuclear pore, ►eIF, ►translation initiation

Capillary: A structure resembling hair; usually bearing a small bore through which liquids can move, such as in the capillary veins or capillary tubes, or soil capillary spaces.

Capillary Electrophoresis: Capillary electrophoresis uses gel-filled glass/quartz tubes of 50–100 μ m

diameter and 20–50 cm length to facilitate fast separation of substances in the electric field by applying high voltage (10–30 kV) without excessive heating up of the system because of better dissipation of the heat. UV or fluorescence detects labeling.

►electrophoresis, ►ultrathin-layer chromatography, ►DNA sequencing; Guttman A, Ulfelder KJ 1998 *Adv Chromatogr* 38:301.

Capillary Transfer: Capillary transfer is used to draw a buffer by wicks from a reservoir to an electrophoretic gel containing separated DNA fragments. The gel is in contact with the absorbent papers. The moving stream elutes the DNA from the gel and deposits it onto a nitrocellulose or nylon filter in immediate contact with the gel, in between the gel and the stack of papers topped by a glass plate and weighted down. ►Southern blotting

Capping Enzymes: Generate the mRNA cap by using GTP and the diphosphate splits off from the first nucleotide triphosphate of the first residue in the pre-mRNA (see Fig. C19). The 5' terminal triphosphate is replaced by the guanyl group of GTP and it loses the γ and βPO_4 groups.

No capping takes place if, at the terminal position, there is a monophosphate. The capped G indicates the beginning of the transcript. The G is methylated by guanosine-7-methyl transferase at the 7 position. The 2'-OH is subsequently methylated by 2'-O-methyl transferase using SAM as a methyl donor. The capping reaction is associated with Pol II and the triphosphate termini of U6 RNA, 5S RNA and the pre-tRNAs, transcribed by Pol III, are not capped. The caps stabilize the mRNA and facilitate the ribosomal attachment. Initiation factor eIF-4E recognizes the cap and mediates its binding to the 40S ribosomal subunit. Picornaviruses do not need the cap and they inactivate the cap-binding proteins of the host and thus turn off the synthesis of host proteins. ►class II genes, ►cap, ►picornaviruses, ►Pol II eukaryotic, ►transcription factors, ►eIF, ►FLAG; Cho EJ et al

1997 *Genes Dev* 11:3319; Shuman S 2000 *Progr Nucleic Acid Res Mol Biol* 66:1; Changela A et al 2001 *EMBO J* 20:2575; Pei Y et al 2001 *J Biol Chem* 276:28075.

CAPS (cleaved amplified polymorphic sequences): CAPS are produced by digesting PCR products by restriction enzymes to find polymorphism in the DNA. ►PCR, ►restriction enzyme, ►AFLP

Capsaicin: The pungent substance of *Capsicum* peppers. It may be anticarcinogenic due to its antioxidant function. The capsaicin (vanilloid) receptor is a cation channel required for heat and pain perception. Bradykinin and nerve growth factors activate a G-protein-coupled and tyrosine kinase receptors and phospholipase C signals to the primary afferent neurons. The potentiation also requires the VR1 heat-sensitized ion channel on sensory neurons. PIP₂ controls its receptor's sensitivity (Prescott ED, Julius D 2003 *Science* 300:1284). The alkaloid galanthamine present in some *Amaryllidaceae* plants is also supposed to have beneficial effects on some nervous diseases, particularly on Alzheimer disease (see Fig. C20).

Capsaicin-containing fruits are generally avoided by wild mammals but not by birds (Jordt S-E, Julius D 2002 *Cell* 108:421). It is apparently a self-defense substance in the plants because birds are efficient dispensers of the seed but mammals are not because the seed passing through their alimentary channel loses germination in contrast to a bird's. Some spider toxins also invoke inflammatory pain by activating capsaicin receptors (Siemens J et al 2006 *Nature [Lond]* 444:208). ►phenolics, ►nociceptor, ►kininogen, ►nerve growth factor, ►signal transduction, ►phospholipase, ►alkaloids, ►horseradish, ►PIP₂; Chuang H-h et al 2001 *Nature [Lond]* 411:957; capsaicin synthase and biosynthetic pathway: Prasad BCN et al 2006 *Proc Natl Acad Sci USA* 103: 13315.

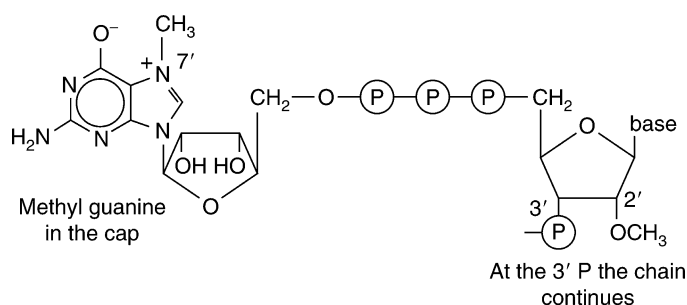


Figure C19. Cap of the eukaryotic mRNA

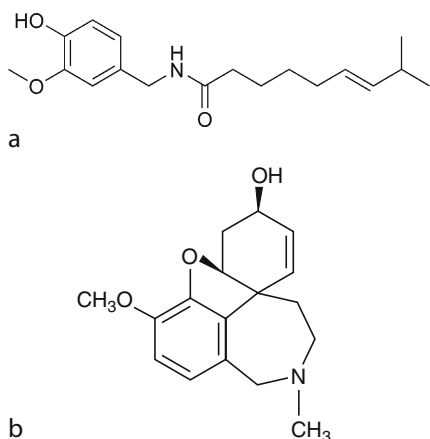


Figure C20. a. Capsaicin, b. Galanthamine

Capsid: The protein shell of the viral genetic material. In complex viruses, a lipid bilayer may be acquired from the host during budding (exit) of the virus. In some viruses, nucleic acids may also be found in the shell. For completion of the infection the capsid is shed and the genetic material is uncoated. ►virus, ►viral capsid; <http://viperdb.scripps.edu/>.

Cap-Snatching: Some RNA viruses (tomato spotted wilt, influenza virus) cleave by an endonuclease 10–20 nucleotides from the 5' end of a host messenger RNA and use the capped leader for priming their transcription or viral RNA synthesis (van Knippenberg I et al 2005 Virology 335:122; Rao P et al 2003 EMBO J 22:1188).

Capsomer: The protein subunits of the viral capsids.

Capsule: A polysaccharide coat of bacterial cells or in general structure with polysaccharide content or a fungal sporangium, or a seed capsule of plants formed by fusion of two or more carpels. In *E. coli* about 80 capsular serotypes have been recognized. The serotype-specific structures are lipopolysaccharides or capsular polysaccharides and have an important role in bacterial virulence (Whitfield C 2006 Annu Rev Biochem 75:39). ►LPS, ►serotype, ►carpel

Capture PCR: Facilitates the isolation of DNA sequences of next to known nucleotide segments. To restriction enzyme-digested DNA ends, linkers of two base-paired oligonucleotides are ligated. By using a biotinylated primer of known sequence the construct is extended. This permits the capture of the extended products on a streptavidin-coated medium. These products are further amplified by PCR with the aid of another specific oligonucleotide hybridized to the 3'-end of the biotinylated sequence. The simultaneous isolation of a large number of fragments, if greatly facilitated by the use of a manifold, connected

to each individual, well of a microtiter plate. ►PCR, ►restriction enzyme, ►biotinylation, ►streptavidin, ►microarray hybridization; Lagerstrom M et al 1991 PCR Methods Appl 1:111.

CAR: Cyclic AMP receptor. ►cAMP

CAR1 (coxsackie and adenovirus receptor): A 368 amino acid receptor that recognizes the avian leukosis-sarcoma virus envelope and induces apoptosis upon infection. It is homologous to the TNF/NGF mammalian family (TRAIL) receptors. CAR is also a cellular attachment receptor for adenovirus, a useful vector in gene therapy. CAR-transgenic mice are promising models for human gene therapy. ►TRAIL, ►TNF, ►NGF, ►apoptosis, ►coxackie viruses, ►adenovirus; Tallone T et al 2001 Proc Natl Acad Sci USA 98:7910.

CaR: An extracellular calcium receptor and thus regulator of diverse metabolic functions.

CAR-β (constitutive androstane receptor): CAR-β is negatively regulated by androstanes. ►androstane

C3a-R: Receptor of C3a complement component. Its mass varies (83–104 kDa). ►complement

C5a-R: Receptor of the C5a complement component. The size of this protein encoded in human chromosome 19q13.3 varies greatly (8–52 kDa) depending on the cells it is found on. ►complement

Carbachol (carbamylcholine chloride): A cholinergic agonist, resistant to cholinesterase; carbachol may increase phosphorylation of RAS. ►cholinesterase, ►RAS

Carbamoylphosphate Synthetase Deficiency (CPSI, 2q35): Hyperamonemia is caused by defects in several enzymes in the mitochondria; others are encoded by several autosomes and are cytosolic. Carbamoylphosphate synthetase/aspartate transcarbamoylase/dehydroorotase (2p21) is a three-enzyme locus involved in pyrimidine synthesis. Ornithine transcarbamylase deficiency (OTC) is encoded at Xp2.11. ►urea cycle, ►CAD, ►channeling

Carbenicillin: A semi-synthetic antibiotic of the penicillin family; effective against gram-negative and some gram-positive bacteria (see Fig. C21). ►antibiotics

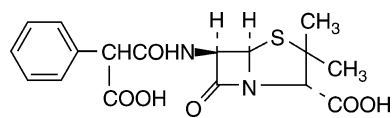


Figure C21. Carbenicillin

Carbocation: ►carbonium ion

Carbohydrate: Sugars and their polymers. See <http://www.dkfz.de/spec2/sweetdb>; carbohydrate-protein interactions; <http://www.functionalglycomics.org/static/consortium/>.

C

Carbohydrate Arrays: Detect the specific binding of various oligosaccharides to different proteins. Oligosaccharide decorated proteins have numerous functions in healthy and diseased cells. See <http://www.glycosciences.de/tools/>.

Carbon Dating: ►radiocarbon dating

Carbon Fixation: Photosynthetic organisms form sugars from atmospheric CO₂. ►C3, ►C4 plants

Carbonic Anhydrase (CA): Catalyzes the reactions $\text{H}_2\text{CO}_3 \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2$, i.e., it provides an equilibrium between carbonic acid and carbon dioxide, and the addition reaction of $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+$ plus, i.e., the formation of carbonium ion from carbon dioxide. This is a Zn enzyme of about M_r 30,000 and is common in various eukaryotic tissue (1–2 g per L of mammalian blood). It is an extremely active enzyme but a much lower rate also catalyzes the hydration of acetaldehyde. In humans, seven isozymic forms have been identified. CA 1, 2 and 3 were located to chromosome 8q13-q22. CA2 is about 20 kb apart from CA3 and it is transcribed in the same direction while CA1 and CA3 are separated by about 80 kb and their direction of transcription is opposite. CA1, 2, and 3 are common in the muscles. CA2 (8q22) deficiency is involved in osteopetrosis with renal tubular acidosis. CA4 (17q23) and CA9 (17q21.2) are closely linked. CA5 (16q24.3), an apparently mitochondrial protein, does not appear to be of specific significance; it may participate in gluconeogenesis. The CA6 gene is present in chromosome 1p37.33-p36.22 and the gene is expressed in saliva. The CA7 gene is in another chromosome (16q21-q23) and is specific for the kidney, lung and liver mitochondria. The CA10 (chromosome 7) codes for α -carbonic anhydrase. CA11 (19q13.2-q13.3) is primarily a brain enzyme but it is also expressed in the spinal cord and other tissues. CA12 (15q22) shows slightly elevated expression in some tumors. CA14 is expressed primarily in the adult brain and several visceral organs but only in the fetal heart (1q21). ►osteopetrosis, ►mitochondrial genetics, ►mtDNA, ►gluconeogenesis

Carbonium Ion: A group of atoms containing only 6 electrons (rather than the normal octet); it is considered highly reactive and is supposed to be involved in the reactions following alkylative processes in chemical mutagenesis and carcinogenesis (see Fig. C22). ►mutagen specificity, ►alkylating agents, ►carcinogen

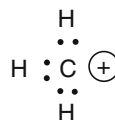


Figure C22. Methyl carbonium ion

Carbonyl group: Such as occurs in aldehydes and ketones (see Fig. C23).



Figure C23. Carbonyl group

Carboxyl group: (see Fig. C24).



Figure C24. Carboxyl group

Carboxyl Terminus: ►C-terminus

Carboxypeptidase: A zinc-containing proteolytic enzyme cleaving the polypeptide chain at the carboxyl end after substrate binding caused an “induced fit”, i. e., a conformational change in the enzyme protein. The “electronic strain” due to the presence of Zn accelerates catalysis. ►latexin, ►mast cells, ►aspar-toacylase deficiency

Carcinoembryonic Antigen (CEA): CEA may be expressed in the normal epithelium of the colon but it is frequently found in colorectal, gastric, pancreatic and in some breast and non-small-cell lung carcinomas. It may be targeted by genetic immunization. ►immunization genetic; Jacobsen GK et al 1981 Oncodev Biol Med 2:399.

Carcinogen: An agent that is capable of causing cancerous transformation of cells. Carcinogens include chemical, physical, and viral agents. *De novo* carcinogenicity may have several steps: initiation (DNA adduct formation, mutation), promotion (DNA methylation, clonal expansion of the altered cell(s), progression (increased methyltransferase activity, additional mutational events and/or other chemicals modulating the process), and invasive events (metastasis). Some of the carcinogens do not act by mutation though. The chemical compounds may be genotoxic; they act directly on the DNA (e.g., ethyleneimine, various epoxides, lactones, sulfate esters, mustard gas, 2-naphthylamine, nitroamides and nitrosoureas, etc.). They can be procarcinogens that require enzymatic activation (e.g., polycyclic or heterocyclic hydrocarbons such as benzo[a]pyrene, benzanthracene, etc.) or can be inorganic compounds or

elements that interfere with the fidelity of DNA replication. Some carcinogens act by some sort of physical means (e.g., various polymers, asbestos). Some hormones may also promote carcinogenesis in an indirect manner. Phorbol esters, n-dodecane, etc., may not be the primary cause of cancer but are considered to be promoters of cancerous growths. The latter group of chemicals, not acting directly on DNA, is frequently called *epigenetic carcinogens*. Carcinogens include most of the mutagens, many industrial and laboratory chemicals, pesticides, insecticides, fungicides, drugs, cigarette smoke, benzo(a)pyrene, medicines (cyclosporin, estrogens, tamoxifen, etc.), diethylstilboestrol, cadmium and nickel compounds, cosmetics, food preservatives, food additives, flame retardants, cross-linking agents, plastics, solvents, paints, adhesives, exhaust fumes, other products of combustion, tar, soot, benzenes, naphthalenes, carbamates, cyanates, metals, nitroso compounds, alkylating agents, terpenes, some fibers (asbestos), arsenics, etc. Several natural plant products are potential carcinogens, e.g., pyrrolizidine alkaloids, safrole, mycotoxins such as aflatoxins, antibiotics such as streptozotocin, viruses such as the Epstein-Barr virus, Simian virus 40, HIV, hepatitis B and C virus, some papilloma viruses, adenoviruses, etc. Many food products such as oxidized fats, overcooked meats, etc., are also potential carcinogens because of the carcinogens formed in them during their exposure to certain conditions. The direct assays of carcinogens involve testing the induction of skin or lung tumors in rodents, breast tumors in young female Wistar or Sprague-Dawley strains of rats, examination of rodent livers for carcinogenic response, etc. The determination of carcinogenicity at relatively low potency is extremely difficult by direct animal assays because tumorigenesis may occur only after a long delay (months or years) following exposure. Furthermore the required population size may be practically prohibitive. Also, all experiments must include an equal size concurrent control to obtain reliable information. The application of the carcinogen to the test animals may be by painting the skin, through subcutaneous or intravenous injection, through the diet or drinking water, through inhalation, etc. Since many of the carcinogens are also mutagens the preliminary tests are generally conducted by mutagenic assays that permit the evaluation in large populations, within a short time and at low cost. The mutagenic assays (Ames test) usually try to substitute for the animal activation system by human or animal liver (microsomal) fractions. In human and animal populations, the high caloric diet may be an important factor in tumor formation. The response of humans to carcinogens is not entirely identical to that of animals; e.g., the prostate, pancreas, colon, cervix/uterus cancers are low in lab rodents but high in humans.

In contrast, liver, kidney, forestomach, and thyroid gland cancers are frequent in animals but relatively rare in humans. Arsenics are human carcinogens but not for laboratory rodents. Humans cannot be subjected to direct cancer tests and most reliable cancer information could come from epidemiological studies. Humans defective in epoxide hydrolase and glutathione *S*-transferase M1 have increased susceptibility to carcinogens. Unfortunately, complex factors and low frequencies frequently bias data. The carcinogenesis process itself may be due to increased energy production by glycolysis and by the expression of oncogenes [defects in tumor suppressors] (Ramanathan A et al 2005 Proc Natl Acad Sci USA 102: 5992). ▶genetic tumors, ▶neoplasia, ▶cancer, ▶oncogenes, ▶hepatitis B virus, ▶hepatitis C virus, ▶Epstein-Barr virus, ▶SV40, ▶mutagen assays, ▶ionizing radiation, ▶radiation effects, ▶radiation hazard assessment, ▶adduct, ▶activation of mutagens, ▶cocarcinogens, ▶cigarette smoke, ▶bioassays in genetic toxicology, ▶MTD, ▶peroxisome, ▶ k_e test, ▶IARC Monographs; Kitchin KT ed 1999 Carcinogenicity, Marcel Dekker, New York; <http://www.iarc.fr/monoeval/allmonos.htm>; 1485 potential carcinogens: <http://potency.berkeley.edu/cpdb.html>.

Carcinogenesis: Carcinogenesis is the process of cancer induction and progression. Human cells require more genetic changes than mouse cells for neoplasia; there is also tissue specificity in carcinogenesis (Rangarajan A et al 2004 Cancer Cell 6:171). Mutator mutations decrease genome stability and accelerate the accumulation of random mutations, including those in oncogenes and tumor suppressor genes, especially when they occur early during development. However, if the mutator mutation is not in itself oncogenic, acquiring that mutation would add an extra, potentially time-consuming step in carcinogenesis (Beckmann RA, Loeb LA 2006 Proc Natl Acad Sci USA 103:14140) ▶cancer, ▶tumorigenesis, ▶carcinogen, ▶angiogenesis, ▶checkpoint, ▶Knudson's two-mutation theory; Ponder BAJ 2001 Nature [Lond] 411:336.

Carcinoma: A malignant cancer tissue of epithelial origin.

Carcinostasis: Tumor growth inhibition.

CARD (caspase recruitment domain, genes at several chromosomal locations): CARD is required for the recruitment and activation of caspase-9 by Apaf-1 in apoptosis. CARD15 also contains a nucleotide-binding domain and 10 COOH-terminal leucine-rich domain. Mutations in CARD 15 are involved in inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. CARD domains exist in double-strand RNA detecting helicases in response

to virals such as hepatitis C infection. Consequently, interferon regulatory factor (IRF3) and NF- κ B are activated as a protective measure (Meylan E et al 2005 Nature [Lond] 437:1197). ▶caspase, ▶Apaf, ▶apoptosis, ▶Crohn's disease, ▶colorectal cancer, ▶interferon, ▶NF- κ B; Bouchier-Hayes L et al 2001 J Biol Chem 276:44069; Lesage S et al 2002 Am J Hum Genet 70:845.

Cardiac Arrhythmia: ▶LQT, ▶cardiomyopathy arrhythmogenic ventricular. (See Glass L. 2005 Proc Natl Acad Sci USA 102:10409).

Cardiac Conduction Defect (PCCD, Lenegre disease, Lev disease): A common degenerative heart disease frequently requiring the application of a pacemaker. The defects are associated with sodium or potassium ion channels and are encoded in different chromosomes (19q13.3, 3p21).

Cardio-Auditory Syndrome: ▶Lange-Nielssen syndrome

Cardiochips: Microarray procedures using heart DNA or protein arrays for the in vitro study of the bases of heart diseases (Barrans JD, Liew CC 2006 Methods of Mol Med 126:157). (▶microarray hybridization; ▶protein chips)

Cardio-Facio-Cutaneous Syndrome (CFC, 7q34): Many of the symptoms are shared with the Noonan syndrome and the Costello syndrome: head and face defects, heart and lung anomalies, frequently keratotic skin, sparse friable hair and other malformations. 78% of the individuals displaying the clinical symptoms had mutations in the BRAF gene (7q34). Five individuals who did not have mutations in BRAF had missense mutations in the MEK1 (15q31) and Mek2 (19p13.3) effectors of B-Raf (Rodriguez-Viciano P et al Science 2006 311:1287). ▶Noonan syndrome, ▶Costello syndrome, ▶BRAF, ▶MEK, ▶RAF

Cardiolipin: A diphosphatidylglycerol most common in the mitochondria and bacterial membranes (see Fig. C25). Its deficiency is involved in Barth syndrome (endocardial fibroelastosis). HIV-1 gp41 envelope protein autoantibodies, mAbs 2F5 and 4E10 react with cardiolipin. Current HIV-1 vaccines may not induce these types of antibodies because autoantigen mimicry of the conserved membrane proximal epitopes of the virus (Haynes BF et al 2005 Science

3008:1906). ▶endocardial fibroelastosis, ▶acquired immunodeficiency, ▶autoantibody, ▶monoclonal antibody, ▶epitope, ▶mimicry macromolecular

Cardiomyopathies: A group of noninflammatory heart diseases affecting about 25,000 persons annually in USA. (see for details, ▶heart disease, ▶cardiomyopathy hypertrophic, ▶cardiomyopathy arrhythmogenic ventricular, ▶arrhythmogenic right ventricular cardiomyopathy, ▶Duchenne, muscular dystrophy, ▶Becker muscular dystrophy, ▶Barth syndrome [endocardial fibroelastosis], ▶Costello syndrome, ▶Acyl-CoA dehydrogenase deficiencies, ▶cardiomyopathy dilated, ▶superoxide dismutase, ▶cardiac arrhythmia, ▶cardiovascular diseases, ▶myopathy, ▶mitochondrial diseases in humans, ▶histiocytoid cardiomyopathy, ▶cathepsins; Seidman JG, Seidman C 2001 Cell 104:557).

Cardiomyopathy, Arrhythmogenic Ventricular (ARVD): The autosomal dominant (14q24.3, 14q12-q22, 1q32, 10p12-p14) and possibly recessive condition involves fibrous/fatty replacement of heart muscles particularly in the right ventricle. It causes unusual palpitation, faintings (syncope), heart failure and possibly sudden death. ▶cardiomyopathies, ▶arrhythmogenic right ventricular cardiomyopathy, ▶phospholamban

Cardiomyopathy, Dilated (CMD): CMD involves thinner than normal ventricular heart walls, reduced contractility, and heart failure. Prevalence in USA is about 4×10^{-4} and about 1/4 of them is hereditary and may benefit from heart transplantation. Defects may involve recessive β oxidation of fatty acids, including acyl-CoA dehydrogenase, carnitin palmitoyl transferase II, and impaired mitochondrial oxidative phosphorylation. Missense mutation in cardiac actin gene (ACTC, human chromosome 15q11-qter) seems to be involved. Also several genes for idiopathic dilated cardiac myopathy (IDC) have been located in human chromosomes Xp21, Xq28, 1p1-1q21, 1q32, 2q31, 2q14-q22, 3p22-25, 5q33-q34, 6p24, 6q12-q16, 9q13-q12, 10q21-q23, 14q11, 15q14, 15q22 and 17q21. Defects in dystrophin and myosin may also be involved. Cardiomyopathy CMD1A involves a defect in lamins (1q21.2-q21.3). Missense mutation in the transmembrane phosphoprotein, phospholamban (6q22.1), inhibits Ca^{2+} -adenosinetriphosphatase pump and causes myocell dysregulation (Schmitt JP et al 2003 Science 299:1410). Autoimmune dilated cardiomyopathy may be due to deficiency of the PD-1 receptor. Homoplasmic point mutations in mitochondrial tRNA^{His} may predispose for CMD. ▶cardiovascular diseases, ▶acetyl coenzyme A, ▶carnitin, ▶fatty acids, ▶mitochondrial diseases in humans, ▶actin, ▶dystrophin, ▶cardiomyopathies, ▶lamins, ▶PD-1; Chien KR 1999 Cell 98:555;

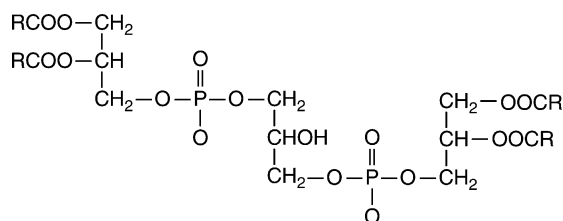


Figure C25. Cardiolipin

Schönberger J, Seidman CE 2001 *Am J Hum Genet* 69:249; Caforio AL et al 2007 *Circulation* 115:76.

Cardiomyopathy, Hypertrophic, Familial (FHC): FHC has heterogeneous autosomal dominant symptoms (thickening of the heart's ventricular walls, shortness of breath, arrhythmia and sudden death). Four genes are known to be involved controlling contractile heart proteins such as β myosin heavy chain (human chromosome 14q11-12), α tropomyosin (15q2), troponin T (1q3) and cardiac myosin binding protein C (11p11.2). Additional gene loci have been implicated in human chromosome 7q3, 18 and 16. Cardiac hypertrophy may be blocked by inhibitors of ADAM12 protein, which sheds heparin-binding epidermal growth factor (HB-EGF), responsible for hypertrophy. Calmodulin-binding transcription activators (CAMTA2) stimulate cardiac growth (hypertrophy) by opposing histone deacetylases (Song K et al 2006 *Cell* 125:453). [►cardiomyopathy dilated](#), [►cardiovascular diseases](#), [►myosin](#), [►troponin](#), [►cardiomyopathies](#), [►ADAM](#); Asakura M et al 2002 *Nature Med* 8:35.

Cardiomyopathy, Restrictive: Restrictive cardiomyopathy affects the expansion (diastole) of the heart without much effect on the contraction (systole). Only about 10% of the cases are clearly hereditary and X chromosomal or autosomal dominant. [►cardiomyopathies](#)

Cardiotrophin (CT-1, ~22 kDa, encoded at 16p11.1-p11.2): Cytokine regulating cardiac muscle cells. It shares a receptor with LIF and other cytokines. [►LIF](#), [►cytokine](#)

Cardiovascular Diseases: Affect the heart and the vein system. Generally premenopausal women show lower risk than men, but after menopause female susceptibility increases substantially (Mendelsohn ME, Karas RH 2005 *Science* 308:1583). [►coronary heart disease](#), [►mucopolysaccharidosis](#), [►lipidoses](#), [►lipoproteins](#), [►Tangier disease](#), [►lysosomal storage disease](#), [►hypertension](#), [►coarctation of the aorta](#), [►sickle cell disease](#), [►Ehlers-Danlos syndrome](#), [►Marfan syndrome](#), [►Norum disease](#), [►hyperthyroidism](#), [►LQT](#), [►cardiomyopathies](#), [►familial hypercholesterolemia](#), [►hypo-betalipoproteinemia](#), [►hypo- \$\alpha\$ -lipoproteinemia](#), [►homocystinuria](#), [►telangiectasia hereditary hemorrhagic](#), [►Williams syndrome](#), [►supravalvular stenosis](#), [►idiopathic ventricular fibrillation](#)

CaRE: A cis-acting element responsible for induction of the c-fos protooncogene by calcium. [►FOS](#), [►cis-acting element](#)

Caretaker Gene: The caretaker genes repair genetic defects that might lead to instability or cancer. [►gatekeeper](#), [►tumor suppressor genes](#); Kai M et al 2006 *Methods Enzymol* 409:183.

CaRG: A conserved promoter element [CC(A/T)₆GG] closely related to SRF. [►promoter](#), [►SRF](#)

CaRG Box: [►SRE](#)

Cargo Receptors: Special molecules in or on the plasma membrane that are recognized by adaptins associated with clathrin-coated vesicles and thus trap various molecules in the process of endocytosis. clathrin, endocytosis, receptors, adaptins; Moroianu J 1999 *J Cell Biochem Suppl* 32–33:76.

CARL: [►comparative anchor reference loci](#)

CARM1: Co-activator associated with arginine methyltransferase-1, related to AdoMet. It may mediate transcription when recruited to the steroid receptor co-activator (SRC-1) and cofactors p300 and PCAF. [►AdoMet](#), [►SRC-1](#), [►p300](#), [►PCAF](#), [►histones](#), [►pluripotency](#); Chen SL et al 2002 *J Biol Chem* 277:4324.

Carney Complex: Multiple and usually pigmented neoplasias of soft tissues and the heart (myxoma). One form is CNC2, located at 2p16, the other CNC1 is at 17q23-q24. The latter is presumably a dominant mutation in a tumor suppressor regulatory alpha unit of a cAMP dependent protein kinase (PRKAR1A). (Groussin L et al 2002 *Am J Hum Genet* 71:1433).

Carnitine (γ -trimethylamino- β -hydroxybutyrate): Facilitates the entry of fatty acids into mitochondria. It occurs in all organisms and it is most abundant in the muscles (0.1% of dry matter). Systemic carnitine deficiency involves progressive cardiomyopathy, skeletal myopathy, hypoglycemia, hyperammonemia and Sudden Infant Death Syndrome. The basic defect is in a gene encoding sodium-dependent carnitine transporter. Carnitine defects may be coded in human chromosomes 5q33.1, 3p21, 1p32, 11q13, 9q34. [►TAP](#)

Carnitine Palmitoyl Transferase Deficiency (CPT I, 11q13): CPT I regulates the carnitine transfer through mitochondrial membranes and its deficiency may be lethal, but it can be effectively treated by medium-chain triglycerides.

Carnosinemia: Carnosine is a neurotransmitter dipeptide of β -alanine and histidine. Enzymatically it may be split by carnosinase into two components, or by the action of a methyltransferase it may be converted into anserine. An autosomal recessive defect in carnosinase may lead to the excretion of carnosine, anserine and homocarnosine, and neurological disorders. [►neuromuscular diseases](#), [►anserine](#)

Caroli Disease: A recessive polycystic kidney disease (6p21.1-p12) due to fibrocystin defect. [►polycystic kidney disease](#)

C

Carotene, β : Widely considered as an anticarcinogen but recent studies indicate that it enhances the activity of several cytochrome (CYP) activating enzymes. Large-scale epidemiological studies indicate increase in cancer caused by a variety of carcinogens. (See Paolini M et al 1999 *Nature* 398:760; ►carotenoids, ►cytochromes, ►activation of mutagens).

Carotenoids: Accessory light absorbing pigments of yellow, red or purple color, including carotene, lutein and xanthophylls. (See Park H et al 2002 *Plant Cell* 14:321; Isaacson T et al 2002 *Plant Cell* 14:333; Grossman AR et al 2004 *Annu Rev Genet* 38:119; Kim J DellaPenna D 2006 *Proc Natl Acad Sci USA* 103:3474).

Carp (*Cyprinus carpio*): $2n = 98$, genome size bp/n = 1.7×10^9 .

Carpel: The floral leaf forming the (enclosure) site for the ovules (see Fig. C26). ►ovule, ►flower differentiation, ►gynoecium



Figure C26. Carpel

Carrier: A human heterozygote for a recessive gene that is not expressed in that individual but may be transmitted to the progeny. *Obligate carrier* is identified on the basis of family history; the natural parents of a homozygous recessive individual must be carriers unless a rare mutational event happened in the heterozygous embryo after fertilization or the natural father is not identical with the legal one.

$$R = \frac{P(Ma|A = D)}{P(Ma|A \neq D)} \times \frac{P(Mb|B = D)}{P(Mb|B \neq D)}$$

The posterior probability that chromosome A is the carrier of the mutation in question is $R/(R + 1)$ (see R at left); and Ma and Mb represent the marker information for chromosomes A and B, respectively. D stands for the mutation-bearing chromosome so $P(Ma|A = D)$ would indicate the probability that chromosome A would be carrying the mutation and $P(Mb|B = D)$ would be the same for chromosome B. Identification of carriers of human diseases using molecular, enzymological, cytological or other

techniques may be highly desirable for early treatment of various human diseases. Genetic counseling may take advantage of the information of the carrier status of the prospective parent(s). The knowledge of carrier frequencies may allow predictions about the occurrence of genetic diseases and may affect governmental health care as well as insurance policies. ►heterozygote, ►Bayes theorem, ►counseling genetic; microarray analysis: Watts JA et al 2002 *Am J Hum Genet* 71:791.

Carrier DNA: A nonspecific DNA that may be mixed with the specific DNA to facilitate transformation or other manipulations. ►transformation

Carrier Protein: Transports solutes through membranes while its conformation is altered. Some transport a single type of molecule (uniporter); others carry more in the same (symporter) or opposite directions (antiporter).

Carrot (*Daucus carota*): All cultivated forms are $2n = 2x = 18$.

Carrying Capacity: A term of ecological genetics. It means that in a particular environment only a certain number of species or individuals of a species can survive and their survival depends on their genetic adaptation. The carrying capacity of a vector is the size of the DNA that it can accommodate. ►ecogenetics, ►vectors

CART (cocaine- and amphetamine-regulated transcript): A leptin-dependent molecule that suppresses craving for food and antagonizes the feeding stimulatory neuropeptide Y. ►leptin, ►neuropeptide Y

Carter-Falconer Mapping Function: The Carter-Falconer mapping function is based on the assumption that there is substantial positive interference along the length of the chromosome: map distance = $0.25 \{0.5[\ln(1 + 2r) - \ln(1 - 2r)] + \tan^{-1}(2r)\}$ where r = the observed recombination fraction, \ln = natural logarithm, \tan = tangent. ►Haldane's mapping function, ►Kosambi's mapping function, ►mapping function; Carter TC, Falconer DS 1950 *J Genet* 50:307.

Cartilage: A fibrous connective tissue; it may also be converted into bone tissues during postembryonic development. It is rich in collagen and chondroitin sulfate. The Ror2 receptor-like tyrosine kinase deficiency leads to skeletal abnormalities and brachydactyly. ►collagen, ►chondrocyte, ►brachydactyly, ►arthritis, ►aggrecanase, ►shark cartilage; Mariani FV, Martin GR 2003 *Nature [Lond]* 423:319.

Cartilage-Hair Dysplasia: ►chondrodysplasia McKusick type

Cartilage-Hair Hypoplasia (CHH): Dwarfism, short fingernails, cartilage deficiency, and weak immune system due to a chromosome 9 defect. The condition is common among the Lancaster county Amish and some Finnish populations. ► [Amish](#)

Caruncle: A small outgrowth on animal and plant tissues.

Caryonide: A clonal derivative of a cell, which, after conjugation, retains the original macronucleus in ciliates and all macronuclei in the subclones are derived from a single macronucleus. ► [Paramecium](#)

Caryopsis: The “seed” (kernel) of some monocots containing the single embryo and endosperm and also tissues derived from the fruit (pericarp) (see Fig. C27).



Figure C27. Caryopsis

CAS: Chemical Abstract Service Registry that identifies chemicals by specific numbers.

It is a most comprehensive database of chemistry, including information related to life sciences: <http://www.cas.org/>.

CAS (Crcas): A ≈ 130 kDA human microtubule-associated protein involved in the control of chromosome segregation, cell adhesion, cell migration, growth factor stimulation, cytokine receptor engagement, bacterial infection, actin stress fiber formation and Src oncogene-induced transformation. ► [microtubule](#), ► [spindle fibers](#)

CAS (Cse 1p): A transport factor, a nuclear export receptor of α importin. ► [nuclear pore](#), ► [importin](#), ► [karyopherin](#)

Casamino Acids: Hydrochloric acid hydrolysate of casein, containing amino acids (except tryptophan that is destroyed by the process). Total nitrogen content 8 to 10%, NaCl 14 to 38%.

Cascade: (In genetics) is a sequence of events depending on specific consecutive steps such as feedback control, signal transduction and differentiation. Cascades direct temporal programs of successive gene expression during development. Feed-forward, feedback and checkpoints can be elementary motifs of a larger cascade of events of a network and noise may affect the output. Longer cascades require larger number of motifs (Hooshangi S et al 2005 Proc Natl Acad Sci USA 102:3581). ► [network](#), ► [genetic network](#), ► [feed-forward](#), ► [feedback](#), ► [checkpoint](#)

Cascade Hybridization: The procedure for enriching a certain fraction of the DNA transcribed at a particular developmental stage (see Fig. C28). Total cDNA is hybridized in a cascade of events with 20, 50 and 100 in excess amounts of mRNAs synthesized at stage 2. The hybrid is then adsorbed into a hydroxyapatite column. Unbound molecules are passed through. The unbound emanate is then hybridized

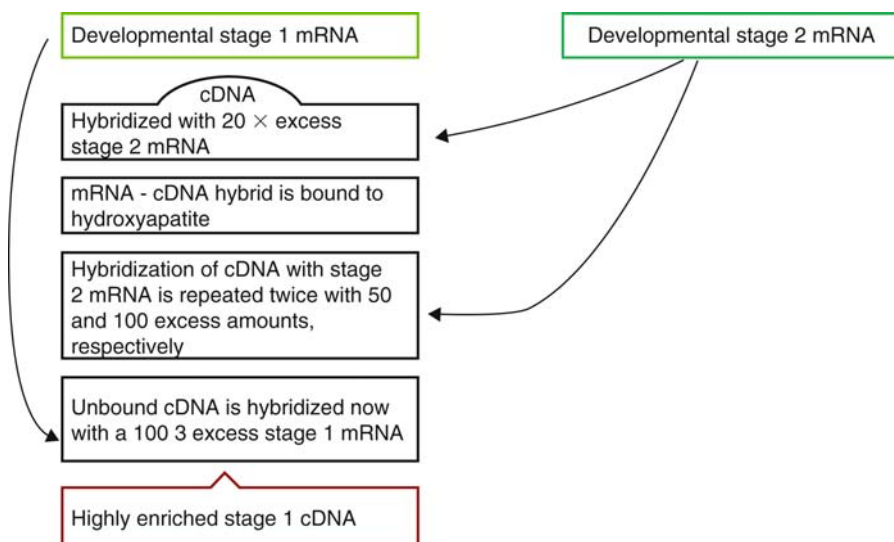


Figure C28. Cascade hybridization

with 100 excess of stage 1 mRNAs. Thus, the cDNA transcribed only in stage 1 is much enriched. (See diagram, ►mRNA, ►cDNA, ►hydroxyapatite, ►subtractive cloning; Timberlake WE 1980 Dev Biol 78:497).

C

Cascade Testing: Cascade testing is basically a genetic screen for carriers in a population beginning with the natural parents of a proband and then extended to relatives. Such a test has a much higher chance to locate carriers than a random one and it is more economical. ►proband, ►carrier, ►genetic screening; Krawczak M et al 2001 Am J Hum Genet 69:361.

CASE (computer automated structure evaluation): CASE relates the correlation between chemical structure and biological activity of chemicals. ►SAR, ►MULTICASE, ►biophore

Casse-Case Design: The deviation from the theoretical expectation that a certain disease phenotype, independent from environmental exposure, can be used to assess the environmental component of prevalence. Also, some health liabilities increase the sensitivity to another, e.g., the APOE E allele increase the chances and the degree of expression of Alzheimer disease and hypertension aggravates the disease (Kang JH et al 2005 Neurobiol Aging 26:475). Reduced efficiency alleles of melanocortin-1 receptor gene reduces skin pigmentation and increases the susceptibility to UV light-induced skin cancer (Rees JL 2004 Am J Hum Genet 75:739). ►prevalence, ►phenylketonuria, ►melanocortin, ►xeroderma pigmentosum, ►environmental effects, ►epidemiology

Case Control Design: Case control design is often used in human genetics when the genetic determination of a polygenic disease condition is compared to unaffected "controls." Such studies on gene frequencies are frequently loaded by errors because of differences in ethnicity. Inferences based on sibs provide better information. The prospective cohort studies employ the presence of risk markers for the potential expression of the disease. ►sib, ►genomic control, ►incidence; Wilson JF, Goldstein DB 2000 Am J Hum Genet 67:926; Manolio TA et al 2006 Nature Rev Genet.7:812.

Cash: ►apoptosis

Cask: A nuclear-binding protein indirectly facilitating nucleosome assembly. ►nucleosome; Wang GS et al 2004 Neuron 42:113.

Caspase: A class of 14 cysteine-dependent aspartate-directed heterotetramer proteases that regulate apoptosis and oogenesis. Caspases are activated by

different mechanisms (Shi Y 2004 Cell 117:855). When a virus infects an organism the natural killer cells (NK) secrete to the surface of the infected cell perforin that allows (among other proteins) the entrance of granzymes into the infected cells. Granzyme B then processes pro-caspases into active caspases and these mediate the suicidal process of apoptosis. The binding of the Fas ligand (FASL) to FAS receptors and the recruitment of pro-caspases can activate caspases and subsequently lead to apoptotic suicide. Caspase-8/Mach (2q33) initiates apoptotic death signals downstream of the death receptors located on the plasma membrane through effector caspases 6 (4q25), 3 (11q22) and 7 (10q25). Caspase-8 is required for the activation of NF- κ B, which is a factor of lymphocyte activation. Thus, caspase-8 deficiency involves defective apoptosis and immunodeficiency because of impairment of T, B and killer lymphocyte functions (Su H et al 2005 Science 3007:1465). Caspase-8 expression suppresses metastasis in neuroblastoma (Stupack DG et al 2006 Nature [Lond] 439:95). Six-nucleotide insertions and deletions in the promoter of CASP-8 increase cancer susceptibility (Sun T et al 2007 Nature Genet 39:605). Caspase 3 and 7 are essential for apoptotic function (Lakhani SA et al 2006 Science 311:847). Caspase activity is required also for nonapoptotic functions such as sperm development, neural stem cell differentiation, erythrocyte, keratinocyte and lens differentiation and lymphocyte proliferation. In *Drosophila*, IKK-related kinase regulates NF- κ B activation or interferon regulatory factor in mammals and determines inhibitor of apoptosis, IAP1 (Kuranaga E et al 2006 Cell 126:583).

Cellular/mitochondrial damage may also lead to the release of cytochrome c into the cytosol resulting in the activation of the pro-caspase-9 (1p34) and thereby eventually apoptosis. The effector caspases then target the CAD-Inhibitor-CAD (I^{CAD}) complex and release CAD (a DNase) from the cytoplasm into the nucleus. Mutation in caspase-10/Flice (2q33) may lead to the autoimmune lymphoproliferative syndrome, ALPS. Caspase-12 is activated by stress of the endoplasmic reticulum and may contribute to neurotoxicity by amyloid- β . Caspase-2 (12q21.33-q23.1) has homology to ICH1. Caspase-2 is a pro-inflammatory molecule and Bcl-2 and Bcl-X_L antiapoptotic molecules regulate it. The Bcl family proteins interact with the NLR family of proteins (such as NALP1), which involve caspase and NF- κ B activation in vertebrates, but are absent from *Caenorhabditis* and *Drosophila* (Bruey J-M et al 2007 Cell 129:45).

Activation of caspase may have a therapeutic effect by slowing down or preventing the accumulation of the huntingtin protein, and it is conceivable that the

production of A β in Alzheimer's disease is proportional to the cleavage activity of caspase(s). There is no agreement among research workers on whether the mitochondria would have the leading role in the initiation of apoptosis or if the mitochondrial events are only part of the apoptosis process already underway. Caspase-mediated cleavage of inhibitor proteins may lead to gain in function. Cysteine proteases may be required for infection of plants by potyviruses and their inhibitors may confer resistance to tobacco etch virus and potato virus Y. ►apoptosis, ►oogenesis, ►lymphocytes, ►NF- κ B, ►killer cells, ►granzyme, ►perforin, ►FAS, ►Apaf, ►CAD, ►ICAD, ►CARD, ►Smac, ►cytochromes, ►IAP, ►DIABLO, ►BIR, ►AKT, ►RGD, ►ALPS, ►NALP, ►Huntington's chorea, ►Alzheimer disease, ►Egl, ►Bcl/apopain, ►ICE, ►ICH, ►scaffold-mediated activation; Earnshaw WC et al 1999 Annu Rev Biochem 68:383; Goodsell DS 2000 Stem Cells 18:457; Goyal L 2001 Cell 104:805; Tinel A, Tschopp J 2004 Science 304:843, caspase regulation review: Riedl SJ, Shi Y 2004 Nature Rev Mol Cell Biol 5:897.

Casper (Flip): ►apoptosis, ►FLIP

Cassava (*Manihot esculenta*): Belongs to the Euphorbiaceae; originally an American perennial shrub and an important source of carbohydrate. The 98 species all have $2n = 36$ chromosomes.

Cassette: ►vector cassette

Cassette Mutagenesis: A synthetic DNA fragment is used to replace a short sequence of DNA and thus alters the genetic information at a site. ►mutation induction, ►localized mutagenesis, ►TAB mutagenesis, ►targeting genes; Cho SW et al 2001 Eur J Biochem 268:3205.

Cassettes Model of Sex Expression: The cassette model explains switches of the mating type in homothallic (*HO*) yeast by the transposition of either one or the other (*a* or α) silent, distant elements (cassettes) to the sex locus *MAT* where they can be expressed as shown in the diagram (see Fig. C29). ►mating type determination in yeast

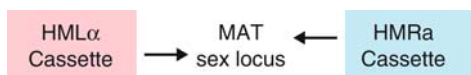


Figure C29. Cassette model of sex expression

Caste: A specialized group within an insect society, e.g., workers among bees. The social and ethnic complexities of the castes of the Indian subcontinent are very difficult to define. Although intermarriage among the

castes was limited, some ethnic mixing diluted the cultural isolation. During the 1500–1200 BC period, several Aryan groups have invaded the subcontinent and some of the descendants of the invaders, the Brahmins, retained their elite, priestly status. The Brahmins were less bound by the strict rules of marriage than the rest of the castes, i.e., they could take wives from outside their caste. Their existence is mainly legal and legendary evidence of their origin and evolution. Recent DNA studies based on mitochondrial and Y chromosomal evidence indicate that the only egg-transmitted DNA displays the same variations as the average of the populations. The Y chromosome DNA is apparently more similar to the European human races. These data confirm the earlier anthropological views about their origin and also prove that women had chances for upward mobility while the male lineages were more strictly controlled. ►Eve foremother of mitochondrial DNA, ►Y chromosome; Majumder PP 2001 Genome Res 11:931; Bamshad M et al 2001 Genome Res 11:994.

Castor Bean (*Ricinus communis*): An oil crop and ornamental plant adapted to a wide range of climates (see Fig. C30). The viscosity of its oil is rather constant at various temperatures and it is thus a good lubricant for high-speed engines. Also, it is a very potent irritant and laxative and used for medical purposes. The plant also contains the lectin ricin that is one of the most toxic compounds known; 2–5 mg/kg is lethal for humans and in mice the intraperitoneal minimal lethal dose is 0.001 μ g ricin nitrogen/g body weight. All species are $2n = 20$.



Figure C30. Castor bean

Castration: The surgical removal of the gonads or the chemical prevention of testosterone production to prevent reproduction and reduce sex drive. A male deprived of testes is also called a eunuch. The surgical removal of the female gonads is spaying (oophorectomy). ►eunuch, ►ovariectomy, ►estrogen, ►androgen; Kolvenbag GJ et al 2001 Urology 58 (2 Suppl.): 16; Muss HB 2001 Semin Oncol 28:313.

CAT (chloramphenicol acetyltransferase): Conveys resistance to the antibiotic chloramphenicol.

Cat (*Felis catus*): The domesticated cat, $2n = 38$; the majority of wild cats have also $2n = 38$ or 36. The first cat-like carnivores appeared ~35 million years ago and modern species diverged ~11 million years ago (Johnson WE et al 2006 Science 311:73). Cats have been domesticated for about 10,000 years ago. Among the over 30 distinct breeds about 200 genetic diseases are known and many of them are homologous to the hereditary diseases of humans. See Gold L 1996 Cats are not Peas: a Calico History of Genetics Copernicus O'Brien SJ et al 2002 Annu Rev Genet 36:657; ►conservation, ►genetics

Cat Cry Syndrome: ►cri du chat

Cat Eye Syndrome: Autosomal dominant; it involves vertical pupil, nonperforated anus, heart, kidney malformations, etc. The patients display tissue mosaicism and generally there are one or more copies of a modified human chromosome 22q11.2 site (microduplications or microdeletions in a low copy-number repeat). ►coloboma, ►eye diseases, ►DiGeorge syndrome; Ensenuer RE et al 2003 Am J Hum Genet 73:1027.

Cat Scan: ►tomography

CAT Transporters: Transport through membranes the cationic amino acids (arginine, lysine, ornithine, histidine). ►transporters, ►ABC transporters, ►translocon; Vékony N et al 2001 Biochemistry 40:12387.

Catabolic: (An adjective) ►catabolism

Catabolism: Degradative metabolism of chemical substances in the cells, mediated by enzymes, most commonly for energy utilization.

Catabolite Activator Protein (CAP): ►CAP

Catabolite Repression: Carbohydrates (glucose) repress the synthesis of enzymes involved in carbohydrate metabolism or other metabolic steps by decreasing the level of cyclic AMP. In some instances, the glucose repression does not depend on cAMP because cAMP does not relieve its repression (e.g., pyrroline dehydrogenase, putrescine aminotransferase). Some bacteria fail to synthesize sufficient amounts of cAMP (*Bacillus megaterium*), and yet they display an intense glucose effect. Catabolite repression may be strongly modulated by the catabolite modulation protein factor (CMF). The catabolite repressor-cAMP system may also function as an activator of genes. Catabolite repression may switch to activation in case the gene carries overlapping promoters or when divergent dual promoters

exist. Some organisms (e.g., yeast) can discriminate among different nitrogen sources (and turn off the utilization of the less desirable ones) by a mechanism called nitrogen catabolite repression. ►glucose effect, ►feedback controls, ►Lac operon, ►cAMP, ►DNA bending, ►cytosine repressor [CytR], ►FNR, ►promoter; Gancedo JM 1998 Microbiol Mol Biol Rev 62:1092; Stülke J, Hillen W 2000 Annu Rev Microbiol 54:849.

Catalase (CAT): Enzymes that mediate the reaction $2\text{H}_2\text{O}_2$ (hydrogen peroxide) $\rightarrow 2\text{H}_2\text{O} + \text{O}_2$. CAT is encoded in human chromosome 11p13. In plants, the catalase enzymes are essential under conditions of photorespiration and for lipid metabolism. ►peroxide

Catalysis: Mediates chemical reactions without being used up in the process. Enzymes are biocatalysts. ►enzymes

Catalytic Antibody: Catalytic antibodies contain catalytic and selective binding sites in one molecule and perform enzymatic reactions as enzyme mimics. Their catalytic efficiency is generally suboptimal, however, the range of the specificity may be broader than that of the regular enzymes. ►abzyme; Hilvert D 2000 Annu Rev Biochem 69:751; Wentworth P Jr 2002 Science 296:2247.

Catalytic RNA: ►ribozymes

Catalytic Site: ►active site

Catalytic Triad: Three amino acids (Ser-His-Asp or Cys-His-Asp) frequently found in the catalytic domain of enzymes, although they are not necessarily juxtaposed. (See Chen SC, Bahar I 2004 Bioinformatics 20(1):177).

Cataplexy: A muscular defect evoked by emotional effects; it is usually associated with narcolepsy. ►narcolepsy

Cataracts: Diseases of the eyes causing opacity of the lens. Cataracts are under X-chromosomal (Xp), autosomal dominant (connexin, 1q21-q25; crystallin, 2q33-q35; developmental regulator *PITX3*, 10q25, 16q22.1, 17q24, 13q11-q12) and autosomal recessive (galactosemia [17q24], chondrodysplasia punctata, Zellweger syndrome [7q11, 12q11-q13]) control (see Fig. C31). The normal eye displays no opacity whereas the cataract appears in various shapes and

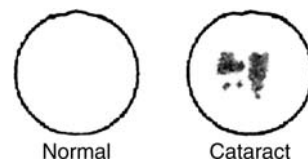


Figure C31. Cataracts

distribution of opacity on the lens. In a juvenile-onset hereditary cataract, a single amino acid substitution (Arg-14→Cys) in the γ -crystallin protein was responsible for progressive opacity. The dominant disorder MIP at 12q14 represents a membrane-bound aquaporin protein. An autosomal dominant cataract has been assigned to 15q21-q22. A recessive locus at 9q13-q22 is responsible for a progressive adult cataract. Recessive homozygosity for chromosome 7p21.3-p15.3 encoding a 521-amino acid protein (hyccin) involves demyelination of the white matter in the brain and the peripheral nervous system is responsible for bilateral cataracts (Zara F et al 2006 Nature Genet 38:1111). A chromosome 20q locus (CHMP4B) has a different subcellular distribution than wild type and an increased capacity to inhibit release of virus-like particles from the cell surface, consistent with deleterious gain-of-function effects. These data provide the first evidence that CHMP4B, which encodes a key component of the endosome sorting complex required for the transport-III (ESCRT-III) system of mammalian cells, plays a vital role in the maintenance of lens transparency (Shiels A et al 2007 Am J Hum Genet 81:596). ▶ Wilms' tumor, ▶ Lowe's disease, ▶ chondrodysplasia, ▶ eye diseases, ▶ microbody, ▶ ASMD, ▶ aquaporin, ▶ connexin; Héon E et al 2001 Amer J Hum Genet 68:772.

Catastroph, Mitotic: Disruption of nuclear division by chemical, physical, or other agents. ▶ error catastrophe

Catatonía, Periodic: A form of schizophrenia with psychomotor disturbances controlled by a major factor at 15q15. ▶ schizophrenia; Stöber G et al 2000 Am J Hum Genet 67:1201.

CATCH: Cardiac defect, abnormal face, thymic hypoplasia, cleft palate, hypocalcemia are symptoms associated with a deletion in human chromosome 22q11.2. ▶ DiGeorge syndrome, ▶ velocardiofacial syndrome, ▶ cleft palate, ▶ hypocalcemia

Catecholamines: Catecholamines are neurotransmitters. ▶ neurotransmitters

Categorical Study: A study conducted by categories, such as all deafness.

Catenanes: Interlocked DNA circles (see Fig. C32).

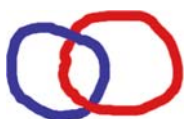


Figure C32. Catenanes

Catenated: Attached like two links of a chain.

Catenins: Intracellular attachment proteins, connecting the inward-reaching carboxyl end of cadherins to actin filaments within the cell; β -catenin is involved in axial polarity of development, in cell proliferation pathways and the development of adenomatous polyposis of the colon, breast cancer and other tumors; its degradation predisposes it to Alzheimer's disease. β -Catenin activates the transcription of cyclin D1 and the promoters, which display TCF/LEF binding sites. p21^{ras} also activates cyclin D1 at promoters with Ets and CREB sites. In adenomatous polyposis cells, the degradation of β -catenin is reduced. A dominant negative TCF is inhibitory to the expression of cyclin D1. Overproduction of β -catenin increases hair growth in mice. ▶ cadherin, ▶ actin polyposis adenomatous intestinal, ▶ LEF; ▶ Tcf, ▶ p21^{ras}, ▶ CREB, ▶ cyclins, ▶ ETS, ▶ Gardner syndrome, ▶ conductin, ▶ presenilin, ▶ Armadillo, ▶ cyclin D, ▶ wingless; Huber AH, Weis WI 2001 Cell 105:391; cell lineage determination: Olson LE et al 2006 Cell 125:593.

Cat-Eye Syndrome: The pupil appears vertical because of a deformity of the iris; heart anomaly, imperforate anus, and various degrees of mental retardation occur. The anomaly is apparently caused by the presence of an extra copy of a very short metacentric chromosome 22q (partial trisomy or tetrasomy). The symptoms vary depending on the structure of this extra chromosome. ▶ mental retardation, ▶ trisomy, ▶ tetrasomy, ▶ duplication

Catfish (*Ictalurus punctatus*): One of the economically most important freshwater fish species. (See Waldbieser GC et al 2001 Genetics 158:727).

CATH: A hierarchical classification of protein domain structures. ▶ protein structure, ▶ protein domains, ▶ SCOP; http://www.biochem.ucl.ac.uk/bsm/cath_new/index.html; <http://www.cathdb.info>.

Cathecolamine: ▶ neurotransmitter

Cathepsins (CTS): Intracellular cysteine proteases generally relegated to the lysosomes. In humans, CTSK and CTSO are encoded at 1q21; in a mouse, four cathepsins are in as many different chromosomes. In mice, deficiency in cathepsin C may not affect their health, but their cytotoxic lymphocytes (CTL) are inactive because granzymes A and B are not processed. Cathepsins may be involved in processing of keratins. Secreted cathepsin L may generate endostatin from collagen XVIII. Mutation in cathepsin K may underlay osteopetrosis or osteosclerosis. Cathepsins are upregulated in different tumors and may be considered as targets for therapy (Joyce JA et al 2004 Cancer Cell 5:443). CTS is substantially expressed in some breast cancers and suspected to favor metastasis. It can cleave a 16 kDa

part off of prolactin, which seems to be responsible for postpartum cardiomyopathy (Hilfiker-Kleiner D et al 2007 Cell 128:589). ▶antimicrobial peptides, ▶lysosomes, ▶pseudosyndactylism, ▶Toulouse-Lautrec, ▶periodontitis, ▶keratin, ▶endostatin, ▶collagen, ▶granzyme, ▶Ebola Virus, ▶prolactin, ▶cardiomyopathies; McGrawth ME 1999 Annu Rev Biophys Biomol Struct 28:181.

C

Cathode Rays: Electromagnetic radiation emitted by the cathode toward an anode in a vacuum tube. After exposure of a metal target to this radiation, X-rays are generated (see Fig. C33). ▶electromagnetic radiation, ▶X-rays

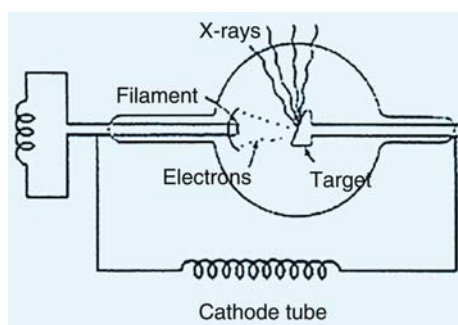


Figure C33. Cathode tube

Cation: A positively charged atom or radical. ▶ion, ▶electrolyte

Cation Exchange: Replacement of one positive ion by another on a negatively charged surface.

Cationic Amino Acids: ▶CAT transporters

Cationic Lipid: ▶liposome, ▶cytofectin GS2888, ▶lipid cationic, ▶lipofection

Cationic Liposome: ▶liposome

Cation- π Interaction: Plays a role in determining protein structure. It is more likely that a cationic side chain of lysine or arginine, when close to an aromatic amino acid (phenylalanine, tyrosine or tryptophan), would result in an interaction than with a neutral amine. Arg and Trp are most likely to be involved. ▶protein structure

Catkin: Male inflorescence of some plants, e.g., oak (see Fig. C34).



Figure C34. Catkin

CATR1: A genetic element encoding 79 amino acids and a long untranslated region, expressed in malignant tumors. This element does not have homology with other oncogenes or tumor suppressor genes. It has been localized to human chromosome 7q31-q32. ▶cancer, ▶tumor oncogenes, ▶tumor suppressor, ▶AIG; Li D et al 1995 Proc Natl Acad Sci USA 92:6409.

CATS (comparative anchor tagged sequences): ▶comparative maps, ▶anchoring

Cattalo: The hybrid of buffalo ($2n = 60$) and cattle ($2n = 60$) with reduced male fertility.

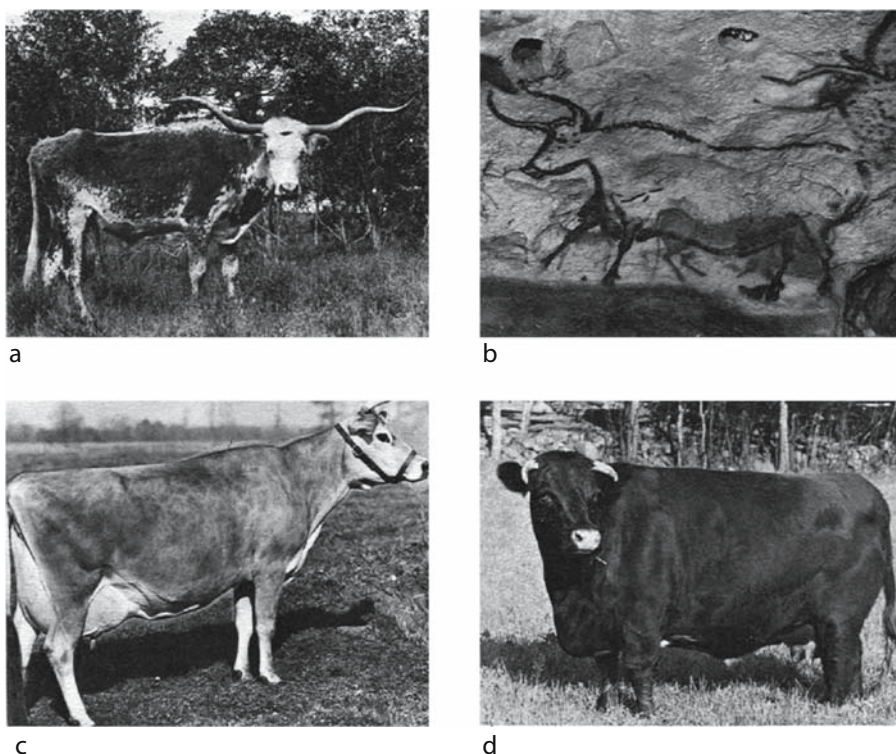
Cattanach Translocation: Involves the X-chromosome and autosome 7 of mouse. It includes several X-chromosomal fur color genes that may be subject to lyonization. ▶lyonization, ▶translocation; Cattanach BM 1975 Annu Rev Genet 9:1.

Cattell's Paradox: An apparent negative correlation between family size and average IQ of children that would lead to a gradual decline of IQ in the progenies. The observation was due to improper ascertainment, ignoring the childless descendants. ▶IQ, ▶ascertainment test; Higgins JV et al 1962 Eugenics Quart 9:84.

Cattle (*Bos taurus*): $2n = 60$. Genetic evidence indicates that the European breeds originated from Near East herds, rather than the now extinct European wild ox (*Bos primigenius*). The Indian cattle, the zebu (*Bos taurus indicus*) (see Fig. C35), were domesticated independently in the Indus Valley, the present day Pakistan (Beja-Pereira A et al 2006 Proc Natl Acad Sci USA 103:8113). The domesticated African cattle seem different from other domesticated breeds on



Figure C35. Zebu



C

Figure C36. (a) Old Texas longhorn bull; (b) Neolithic cave bull; (c) Modern Jersey dairy cow; (d) Modern shorthorn beef cattle

the basis of mitochondrial DNA (see Fig. C36). (Troy CS et al 2001 Nature [Lond] 410:1088; Hanotte O et al 2002 Science 296:336; microsatellite map: Ihara N et al 2004 Genome Res 14:1987; <http://www.tigr.org/tdb/tgi>; bovine genome database: <http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/intro2.pl?Base=goat>).

Caucasoid (Caucasian): A commonly used misnomer for ethnic groups of European, North African, Near-East and Indian descent. The term has been coined erroneously when anthropologists believed their origin was in the Caucasus area. It is sometimes used as collective term for white-skinned people. In fact, the group includes many brown-skinned populations too.

Caudal: Tail oriented.

Caudates Structure: A tail-like appendage.

Cauliscent: Leaves that are born separated by visible internodes on a stem (see Fig. C37). ▶ [rosette](#)



Figure C37. Caulescent

Cauliflower Mosaic Virus: (CaMV) is a (~8 kbp) double-stranded DNA virus with limited potential use for genetic engineering. It infects cruciferous

plants like turnip, broccoli, *Arabidopsis*, etc. The DNA of the virus shows three discontinuities (“gaps”), 1 in one of the strands and 2 in the other. The promoter of the 35S transcript of the virus drives high-level constitutive expression of genes spliced to it and it is widely used; the promoter of the 19S peptide gene has not been proven nearly as good for biotechnology. ▶ [agroinfection](#), ▶ [retroid virus](#), ▶ [activation tagging](#); Balázs E et al 1985 Gene 40:343; Hirth L 1986 Microbiol Sci 3:260; Hohn T, Fütterer J 1992 Curr Opin Genet Dev 2:90, al-Kaff N, Covey SN 1994 J Gen Virol 75 [Pt 11]:3137.

Caulobacter: A dimorphic Gram-negative group of prokaryotes. The cells may have either a long flagellum or a thicker stalk of about 2/3 of the 2 μm length of the cell. The formation of these appendages has been extensively studied and the hierarchy of genes regulates them. *Caulobacter crescentus* genome of 4,016,942 bp encodes ~3,767 genes. ▶ [Gram-negative/Gram-positive](#); Niernan WC et al 2001 Proc Natl Acad Sci USA 98:4136.

Caulonema: In the gametophyte of some mosses a special type of cells are formed subapically and separated by oblique walls.

Cave Art: ▶ [Lascaux cave](#)

C

Caveolae (plasmalemmal vesicles): Caveolae are ~70 nm diameter flask- or Ω -shape, detergent-insoluble glycolipid vehicles/rafts moved by actin motors on the surface of T cells and other endothelial cells. The caveolae are loaded with kinases, protectin/CD59, decay accelerating factor (DAF), alkaline phosphatase, Thy-1 glycoprotein, and signaling adapter molecules. After DC28 engages the T cell receptor, the rafts are attracted to the area where the antibody contacts the TCR. The caveolae concentrate lipids, proteins, prenylated proteins, glycosylphosphatidyl inositols, various membrane receptors, actin, myosin, ezerin, NSF, signal transducing proteins, etc. Caveolae have a role in the transmission of the Pr^{Sc} prions, transfer into the cells pathogens (SV40, *Campylobacter*) and protein toxins of pathogens (cholera, *Plasmodium*, *Trypanosoma*, *Leishmania* toxins). Caveolae may play a role in cardiovascular diseases because they transport cholesterol, lipoproteins and affect blood clotting. ▶raft, ▶DC28, ▶CD48, ▶TCR, ▶DAF, ▶protectin, ▶flotillin, ▶Thy-1, ▶endocytosis, ▶antigen-presenting cell, ▶signal transduction, ▶potocytosis, and other terms at their alphabetical locations; Shin J-S, Abraham SN 2001 Science 293:1447; Galbiati F et al 2001 Cell 106:403.

Caveolin (CAV): CAV-3 (300–350 kDa), encoded at human chromosome 3p25 as homo-oligomers consisting of 12–14 monomers and are associated with the sarcolemma and co-localized with dystrophin. The same RNA encodes CAV-1 (21–24 kDa) and CAV-2 but processed differently. They are integral membrane proteins and bind G proteins. Caveolin-1 is a negative regulator of caveolae-mediated endocytosis to the endoplasmic reticulum. CAV-1 is essential for regeneration of the liver in mice by coordinating lipid metabolism. In *cav-1*^{-/-} animal glucose also facilitated survival (Fernández MA et al 2006 Science 313:1628). ▶sarcolemma, ▶dystrophin, ▶muscular dystrophy, ▶prostate cancer; Engelman JA et al 1998 Am J Hum Genet 63:1578; Anderson RGW 1998 Annu Rev Biochem 67:199; Pol A et al 2001 J Cell Biol 152:1057; Le PU et al 2002 J Biol Chem 277:3371.

Cavitation: After the formation of the 32-cell stage of the mammalian embryo a fluid secretion occurs during the blastocyte stage, which initially accumulates between the cells, and then it is collected in the blastocoele. ▶blastocyte, ▶blastocoele

CBAVD: ▶congenital bilateral aplasia of the vas deferens

CBC: ▶cap-binding protein complex

CBER: Center for Biological Evaluation and Research: A branch of the United States Food and Drug Administration involved in blood, vaccines, cellular/

gene therapy, tissue and devices relevant to human health. (See <http://www.fda.gov/cber/>).

CBF/NF-Y: A trimeric CCAAT binding (factor) protein, which, with other proteins, facilitates transcription. ▶CAAT; Maity SN, de Crombrughe B 1998 Trends Biochem Sci 23:174.

C57BL: Strains (B6 and B10) of black inbred mouse commonly used for genetic studies (mutation).

CBL2 (oncogene): Three cellular homologs of this viral oncogene are expressed in mammalian hematopoietic (blood cell forming) systems. In humans it was located to chromosome 11q23.3. Its translocations to chromosome 4 are associated with acute leukemia and B cell lymphoma. The oncogene is present in the ecotropic Cas-Br-M virus and the form present in lymphomas is a recombinant between the virus and the cellular oncogene. The 100 kDa transforming fusion protein has sequence homology to the yeast transcription factor GCN4 and to *sli-1* regulator of vulval development in *Caenorhabditis*. Apparently, this family of genes modifies receptor tyrosine-kinase mediated signal transduction. Cbl-b controls the dependence of T cell activation by CD28. ▶oncogenes, ▶signal transduction, ▶Jacobsen syndrome, ▶Src, ▶Syk, ▶CD28, ▶SLAP; Thien CBF, Langdon WY 2001 Nature Rev Mol Cell Biol 2:294.

CBP (CREB binding protein, p300): CBP is associated with CREB and mediates the induction of some promoters by cAMP (see Fig. C38). It interacts with p300 (or may be the same), the nuclear hormone-receptors and the basic transcription machinery. In addition, it interacts with a range of transcriptional activators and coprecipitates with RNA polymerase holoenzyme. CBP has a signal-regulated transcriptional activation domain, regulated by Ca²⁺ and calmodulin-dependent protein kinase and cAMP. CBP with histone acetyltransferase activity may function also as a coactivator of p53. The loss of CBP may be the basis of the Rubinstein-Taybi syndrome. ▶cAMP, ▶CREB, ▶p300, ▶E1A, ▶APC, ▶transcriptional activators, ▶Rubinstein syndrome, ▶p53, ▶cap, ▶histone acetyltransferase, ▶transcription factors, ▶calmodulin; Mayr BM et al 2001 Proc Natl Acad Sci USA 98:10936; Tunell AS et al 2005 Nature [Lond] 438:690.

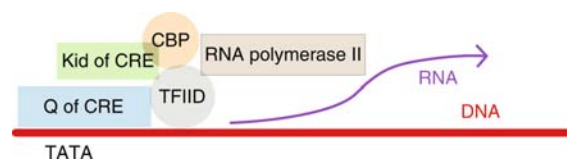


Figure C38. cAMP regulation of transcription. (Modified after Montminy, M. 1997 Annu. Rev. Biochem. 66:897)

CBP2: A cellular-binding protein required for splicing class I mitochondrial introns. The catalytic RNA domains must be in a folded form before CBP2 binds to them. Subsequently, other proteins are attached to the 5' domain. In this ribozyme, the catalytic component remains the RNA but the protein associated with it increases the splicing rate by three orders of magnitude. ▶intron, ▶ribozyme, ▶spliceosome, ▶mtDNA; Shaw LC, Lewin AS 1997 Nucleic Acids Res 25:1597.

CBP-II: Similar to eIF-4F translation factor. ▶eIF-4F

CbpA: A protein of *E. coli* that is similar in function and structure to the DnaJ co-chaperone, but its transcription is initiated with stationary phase σ^{38} subunit of the RNA polymerase. ▶DnaJ, ▶Hsp70, ▶co-chaperone; Ueguchi C et al 1995 J Bacteriol 177:3894.

CBS (conserved sequence elements): Three short sequences in the mtDNA where the transition from DNA to RNA synthesis takes place. ▶DNA replication mitochondria, ▶mtDNA

CBS (chromosome breakage sequence): A 15 bp nucleotide sequence at 50 to 200 sites in the micronuclear DNA of ciliates near the breakage sites where the genome rearrangement occurs in the macronuclear chromosomes. ▶Tetrahymena; Fan Q, Yao MC 2000 Nucleic Acids Res 28:895.

CC57: A very popular black inbred mouse line. Has low spontaneous mammary tumors but highly prone to lung tumors. A large number of variants exist.

CC CKR5: A chemokine receptor. ▶chemokines, ▶RANTES, ▶CXCR, ▶CCR; Combadiere C et al 1996 J Leukoc Biol 60:147.

CCAAT: ▶CAAT box

CCCH Zinc Finger Proteins: mRNA inhibitors and antiviral agents. They contain CCCH amino acids (3 cysteine, 1 histidine) in the tandem zinc-finger domain. ▶DNA binding protein domains; Lai WS et al 2002 J Biol Chem 277:9606.

CCDS: The Consensus CDS (CCDS) project is a collaborative effort to identify a core set of human and mouse protein coding regions that are consistently annotated and of high quality. The long-term goal is to support convergence toward a standard set of gene annotations. ▶consensus; www.ncbi.nlm.nih.gov/CCDS.

CCE (cell cycle element): CCE has 11 bp that bind the histone nuclear factor (HiNF-M), required for the activation of Histone 4. ▶HiNF, ▶IFN, ▶IRF-2, ▶immune surveillance

CCG-1: CCG-1 is the hamster gene responsible for G1 phase cell cycle arrest.

CCL5: ▶RANTES

CCL39: A hamster lung fibroblast cell line.

CCR: Chemokine receptors; same as CKR. CCR2 is the receptor for MCP-1 and related chemokines MCP-3, MCP-4, MCP-5. CCR7⁺ cells express lymphnode-homing receptors without having immediate effector function. CCR7⁺ possesses effector function and they differentiate from CCR7⁺ cells upon activation by cytokines and antigens. ▶chemokine, ▶CKR5, ▶CXCR, ▶MCP-1, ▶acquired immunodeficiency syndrome, ▶effector, ▶metastasis; Luther SA, Cyster JG 2001 Nature Immunol 2:102.

CCR4-NOT: A deadenylation complex.

CCSB-HI: Center for Cancer Systems Biology Human Interactome. (Rual J-F et al 2005 Nature [Lond] 437:1173).

CCT: Cytosolic chaperonins. ▶chaperonins, ▶Bin3p, ▶Bin2p, ▶TRiC, ▶TCP20

CCW: Counterclockwise (see Fig. C39).



Figure C39. CCW

CD1: Antigen-presenting molecules—distantly related or unrelated to MHC proteins—for the T lymphocytes. CD1 can deliver to T cells endosomal lipoglycan antigens and other non-peptide ligands to the T cells, which are then stimulated to produce γ interferon and interleukin-4. CD1 is encoded in human chromosome 1q22-q23. ▶T cell, ▶killer cell, ▶cytokines, ▶interferon, ▶HLA, ▶antigen presenting cell, ▶major histocompatibility antigen, ▶lipid antigen, ▶saposin, ▶lipid antigen; Park S-H, Bendelac A 2000 Nature [Lond] 407:788; Zhou D et al 2004 Science 303:523, Mattner J et al. 2005 Nature [Lond] 434:525.

CD2: A T cell surface glycoprotein, mediating cell adhesion (to antigen-presenting cells) and the transduction of signals; it is encoded in human chromosome 1q22-q23. Haploinsufficiency for CD2-associated protein increases the susceptibility to kidney glomerular lesions (Kim JM et al 2003 Science 300:1298). Anti-CD2 protein is used for in vivo lymphocyte depletion to prevent immune

intolerance to the foreign antigen in therapeutic application of stem cells. ▶CD48, ▶haploinsufficient, ▶kidney diseases

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CD3: Immunoglobulins of γ (25 K), δ (20 K), ϵ (20 K) and ζ (16 K) molecular (weight) chains expressed on all T cells; assist in transducing signals when the major histocompatibility-antigen complex binds to the surface. CD3 δ -negative lymphocytes fail to induce the ERK kinase and are unable to undergo positive selection. They are encoded in human chromosome 11q23. ▶immunoglobulin, ▶HLA, ▶signal transduction, ▶T cell receptor, ▶tumor vaccination, ▶ERK, ▶LAT

CD4: Cell surface protein (55 kDa) with domain binding major histocompatibility (MHC II) molecules on helper T cells. CD4⁺ T cells induce clonal proliferation of B cells along two paths. CD4⁺ B cells prime CD8⁺ T cells for clonal proliferation when they repeatedly encounter foreign antigens. Foreign antigens switch on through the B cell antigen receptors. When CD8⁺ T cells are not primed this way, they undergo apoptosis through the TRAIL ligand (Janssen EM et al 2005 Nature [Lond] 434:88). The CD40L (CD40 ligand) and interleukin-4 (IL-4) promote the proliferation of B cells. CD95 (Fas) and Fas ligand (FasL) limit the access of mitogenic signals and mediate apoptosis in response to auto-antigens. T cells are co-stimulated by CD80 (B7.1) or CD86 (B7.2) by binding to CD28 on the antigen-presenting cells (APC). For normal function both CD40 and Fas functions must be maintained. CD4 is encoded in human chromosome 11q13. ▶HLA, ▶MHC, ▶T cells, ▶B cells, ▶CD8, ▶CD40, ▶LCK oncogen, ▶autoantigen, ▶apoptosis, ▶TRAIL, ▶interleukins, ▶FAS, ▶APC, ▶CD80, ▶CD86, ▶CD28; Groux 2001 Microbes Infect 3:883.

CD5: A transmembrane protein on the surface of T cells and some B cells. It may be a negative regulator of the T cell receptor (TCR) mediated signal transduction. Encoded at human chromosome 11q13. ▶T cell receptor; Weston KM et al 2001 J Mol Recognit 14:245.

CD8: Homo- or heterodimer proteins (M_r 70 K) on cytotoxic T cells (CTL), binding class I major histocompatibility molecules. CD8 lymphocytes recognize the endogenously generated antigens, associated with MHC class I molecules, and such as those formed in cancer cells. CD8A and CD8B are encoded in human chromosome 2p12. CD8 is an active player in the T cell recognition complex. Regular activated T lymphocytes are associated with heterodimeric CD8 $\alpha\beta$ ligands, whereas the memory T cells differentiate from the homodimeric CD8 $\alpha\alpha$ (Madakamutil LT et al 2004 Science 304:590).

▶T cell, ▶HLA, ▶MHC, ▶CD4, ▶LCK oncogen, ▶memory immunological; Fujii S et al 2001 Blood 98:2143.

CD9: A transmembrane protein of the tetraspanin family. It is a "molecular facilitator." The eight exons of the murine CD9 extends to 20 kb. Homozygous knockouts are physically normal in both males and females, however, only 50–60% the females produced offspring. Some reduction in fertility was observed also in the homozygous males. The pup mortality was also higher. CD9 associated integrin $\alpha 6\beta 1$ is apparently required for egg-sperm fusion. ▶tetraspanin, ▶CD81, ▶CD 82, ▶integrin, ▶fertilin, ▶fertilization, ▶knock-out; Charrin S et al 2001 J Biol Chem 276:14329.

CD11a/18: Binds CD54 (ICAM) and mediates cell adhesion. CD11 is α integrin (human chromosome 16p12-p11); CD18 is β integrin (human chromosome 21q22.3). CD11b/CD18 are the CR3 complement receptors binding the C3b complement component. Salmonella infection is spread from the gastrointestinal tract to the bloodstream by CD18-expressing phagocytes. ▶integrin, ▶ICAM, ▶complement

CD14: Glycosylphosphatidylinositol-anchored membrane protein sensing lipopolysaccharides of invading microbes as part of the defense mechanism. It enhances B lymphocyte and monocyte differentiation and it is encoded at the human chromosome 5q23-q31 region. ▶innate immunity, ▶Toll; Glück T et al 2001 Eur J Med Res 6:351.

CD15 (α -fucosyltransferase, 11q21): Important for the function of leukocyte adhesion molecule, LAD2. ▶leukocyte adhesion; Nakayama F et al 2001 J Biol Chem 276:16100.

CD16 (Fc γ RIII, immunoglobulin G [IgG] Fc receptor III): A neutrophil-specific antigen encoded at 1q23. It may be involved in cytokine signaling to lymphocytes. ▶antibody; Paolini R et al 2001 Proc Natl Acad USA 98:9611.

CD18: ▶CD11a/CD18

CD19 (16p11.2): Important for the differentiation of B cells; it is a tyrosine kinase receptor. On mature B cells it is associated with CD81 and CD21. CD19 immunotherapy can be used during pre-B lymphocyte malignancies as well as in autoimmune diseases and humoral transplant rejection (Yazawa N et al 2005 Proc Natl Acad Sci USA 102:15178). ▶leukemia, ▶BCP, ▶B cell, ▶genistein; Uckun FM et al 1993 J Biol Chem 268:21172; Otero DC et al 2001 J Biol Chem 276:1474.

CD21: C3dg/C3d complement receptor 2 (CR2), 150 kDa. CD21 provides signals for B lymphocyte survival in the germinal center. ▶complement, ▶TAPA-1, ▶germinal

center, ▶TCL; Cherekuri A et al 2001 J Immunol 167:163.

CD22: Associated with immunoglobulin of B cell membranes. Tyrosine phosphorylated CD22 activates SHP protein tyrosine phosphatase and this down-regulates signaling through the immunoglobulin (Igμ). If CD22 is prevented from binding to μIg, the B cell may become 100-fold more receptive. CD22 is encoded at human chromosome 19q13.1. ▶lymphocytes, ▶B cell, ▶signal transduction; van Rosenberg SM et al 2001 J Biol Chem 276:12967.

CD23: A low-affinity receptor of immunoglobulin E (IgE) playing a role in allergy. ▶allergy; Kilmon MA et al 2001 J Immunol 167:3139.

CD25: The interleukin-2 receptor α chain encoded at human chromosome 10p15-p14. ▶interleukins; Suttmuller RP et al 2001 J Exp Med 194:823.

CD26 (dipeptidyl-peptidase IV, DPP IV): A pluripotent exopeptidase, expressed on the membrane of memory T cells, endothelial and epithelial cells. It interferes with immune reactions. It processes chemokines. ▶chemokines, ▶CXCR; Collebaut C et al 1993 Science 262:2045; Herrera C et al 2001 J Biol Chem 276:19532.

CD27: A TNF receptor glycoprotein encoded at 12p13. It regulates immune reactions; the CD27-ligand, CD70 is encoded at 19p13. ▶TNF, ▶TRAF; Jacquot S et al 2001 Int Immunol 13:871.

CD28: A homodimeric immunoglobulin (M_r 80 K), encoded in human chromosome 2q33-q34, present on the surface of helper T cells. The CD28/B7 and LFA-1 provide co-stimulation to T cell activation. CD28 is also a specific activator of JNK or the NF-κB in the presence of the T cell receptor (TCR). Co-stimulation initiates the active transport of protein and lipid domains to the area of the cell-to-cell contact, depending on myosin. ▶T cell, ▶B cell, ▶TCR, ▶CTLA, ▶ICOS, ▶CD80, ▶CD86, ▶anergy, ▶JNK, ▶NF-κB, ▶caveolae, ▶motor proteins, ▶Cbl; Salomon B, Bluestone JA 2001 Annu Rev Immunol 19:225.

CD30: A member of the tumor necrosis factor/nerve growth factor receptor family, including also TNF-R1, TNF-R2, CD40, CD27, Fas, etc. Their extracellular domain has cysteine-rich repeats. It interacts with TRAFs and indirectly with NF-κB. Deficiency for CD30 disarms CD8 positive T cells very aggressively and destroys pancreatic islets and contributes to the autoimmune reaction leading to diabetes in cooperation with other genes. CD30 is encoded at human chromosome 1p36. (See items

separately, ▶allergy; Hombach A et al 2001 Gene Ther 8:891).

CD31: Inhibitory receptor of myeloid, platelet endothelial and some T cells, encoded at 17q23. (See Balduini CL et al 2001 Br J Haematol 114:951).

CD33 (human chromosome 19q13.3): Inhibitory receptor of myeloid cells with sialic acid ligand. (See Mingari MC et al 2001 Immunol Rev 181:260).

CD34: A sialomucin-like adhesion protein expressed on 1–3% of the (CD34⁺) bone marrow cells and is associated with hematopoietic function; it is encoded in human chromosome 1q32. ▶hematopoiesis, ▶selectin, ▶SDF; Pratt G et al 2001 Br J Haematol 114:937.

CD35: Receptor CR1 (190 kDa) of the C3b complement component encoded at human chromosome 1q32. ▶complement; Klein MA et al 2001 Nature Med 7:488.

CD36 (Fat): The CD36 gene is in rat chromosome 4 and is responsible for the quantitative effects of diabetes type2, obesity, hyperlipidemia, essential hypertension and platelet formation. The human gene was mapped to 7q11.2. The gene encodes fatty acid translocase. CD36 deficiency (common in some African and Asian human populations) may increase susceptibility to malaria. CD36 and CD51 regulate dendritic cells and thereby the immune response. CD36 is also a sensor of microbial diacylglycerides and is a factor in susceptibility (Hoebe K et al 2005 Nature [Lond] 433:523). ▶diabetes, ▶hypertension, ▶hyperlipidemia, ▶malaria, ▶immune response, ▶diacylglycerol; Urban BC et al 2001 Proc Natl Acad Sci USA 98:8750.

CD38 (Okt10/p45): A 45 kDa antigen, encoded in human chromosome 4p15, of acute lymphoblastic leukemia cells with an activity similar to adenylyl-ribosyl cyclase. It is a multifunctional protein regulating cell adhesion, differentiation and proliferation, and it is a marker of the progression of HIV-1 infection. In CD38-deficient mice, oxytocin level of the plasma decreased and the social behavior was affected. Replacement of oxytocin rescued social memory and maternal care in the animals (Jin D et al 2007 Nature [Lond] 446:41). ▶leukemia, ▶cyclic ADP-ribose; Cakir-Kiefer C et al 2001 Biochem J 358 [pt2]:399, crystal structure: Liu Q et al 2005 Structure 13:1331.

CD40 (TNFR/SF5): A 48–50 kDa transmembrane glycoprotein (encoded at 20q12-q13.2) expressed on the surface of B cells; their interaction with CD40 ligands is a requisite for the activation of B cells by helper T cells. This system appears critical for the

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development of humoral immunity. CD40 signaling may prevent Fas-induced apoptosis of B cells by cross-linking the immunoglobulin M complex. It induces B cell differentiation and Ig isotype switching and the expression of CD80. CD40 cytoplasmic tail interacts with CRAF1, a tumor necrosis receptor associated protein. CD40 is expressed also in dendritic cells, activated macrophages, epithelial cells, and several tumors. In the absence of CD40, immunodeficiency arises and initiation of germinal centers suffers. CD40 is upregulated by IFN, IL-1, TNF and possibly by IL-6. CD40 signaling to lymphocytes is mediated by NF- κ B through upregulation of the antiapoptotic proteins Bcl-x and Bfl-1. ▶immunodeficiency, ▶B lymphocyte, ▶T cells, ▶CD40 ligand, ▶germinal center, ▶apoptosis, ▶Fas, ▶Ig α , ▶CRAF, ▶CD80, ▶B7, ▶immunoglobulins, ▶CRAF, ▶dendritic cell, ▶macrophage, ▶hyper-IgM syndrome, ▶adjuvant immunological, ▶CD154, ▶IFN, ▶IL-1, ▶IL-6, ▶TNF, ▶germinal center, ▶Alzheimer's disease; Tone M et al 2001 Proc Natl Acad Sci USA 98:1751.

CD40 Ligand (gp39/CD40L/TBAM; Xq26-q27.2): A membrane-bound signaling molecule associated with CD40 transmembrane protein found on the lymphoid follicles of CD4⁺ T lymphocytes. It may regulate adhesion and movement. Its defect is responsible for X-linked hyper-IgM immunodeficiency. ▶CD40, ▶T cell, ▶immunodeficiency, ▶hyper-IgM syndrome; Vidalain PO et al 2001 J Immunol 167:3765.

CD43: Cell-surface sialoglycoprotein of blood cells and encoded in human chromosome 16p11.2; it is deficient in the Wiskott-Aldrich immunodeficiency. ▶Wiskott-Aldrich syndrome; Bagriacik EU et al 2001 Immunol Cell Biol 79:303.

CD44: A family of cell surface receptors involved in adhesion and movement. The cytokine osteopontin (Eta-1) is one of its ligands, activating chemotaxis but not cell aggregation. Hyaluronate (a carbohydrate ligand) on the other hand affects growth. Thus, metastasis of cancer cells may be controlled by the state of CD44, encoded in human chromosome 11pter-p13. Sulfated CD44 stimulated by TNF- α results in binding of B leukocytes to inflammatory sites. Cells within the CD44⁺ population of human head and neck squamous cell carcinoma possess the unique properties of cancer stem cells in functional assays for cancer stem cell self-renewal and differentiation, and form unique histological microdomains that may aid in cancer diagnosis (Prince ME et al 2007 Proc Natl Acad Sci USA 104:973). ▶osteopontin, ▶TNF, ▶lymphocytes, ▶diabetes mellitus; Ponta H et al 1998 Int J Biochem Cell Biol 30:299;

Teder P et al 2002 Science 296:155; Ponta H et al 2003 Nature Rev Mol Cell Biol 4:33.

CD45 (leukocyte common antigen): A protein tyrosine phosphatase (JAK phosphatase), a transmembrane glycoprotein, activated by antigens on the surface of red blood cells and regulates T and B lymphocytes. Antibodies that react with this leukocyte antigen may prevent rejection of allografts. It is encoded in human chromosome 1q31. In some families with multiple sclerosis, CD45 is altered. ▶lymphocytes, ▶allograft, ▶antibody, ▶multiple sclerosis, ▶lupus erythematosus, ▶lymphoid protein tyrosine phosphatase receptor-type; Virts EL, Raschke WC 2001 J Biol Chem 276:19913.

CD46: A complement-regulatory protein encoded at human chromosome 1q32. ▶antibody, ▶complement, ▶MCP; Evlashev A et al 2001 J Gen Virol 82 [pt9]:2125; Marie JC et al 2002 Nature Immunol 3:659.

CD47: An integrin-associated protein serving as a marker of self-identity on red blood cells. ▶integrin; Blazar BR et al 2001 J Exp Med 194:541.

CD48: A membrane (glycosylphosphatidylinositol associated) protein (1q21.3-q22) cooperating with CD2 in the interaction of the antigen-presenting cell with the T cell receptor. Uptake of bacteria by mast cells may depend on CD48 caveolae. ▶CD2, ▶antigen presenting cell, ▶T cell receptor, ▶caveolae; Veréb G et al 2000 Proc Natl Acad Sci USA 97:6013.

CD52 (CAMPATH-1 antigen): A very small glycosylphosphatidylinositol protein molecule with special recognition for lysing human lymphocytes. It has been effectively used before in therapeutic stem cell transplantation to prevent antigenic reaction to the foreign cells. ▶stem cells

CD54 (19p13.3-p13.2): ▶ICAM

CD55: ▶decay accelerating factor

CD59: ▶protectin

CD62: Its ligand is not expressed in defective B lymphocyte receptors to guard against autoimmunity. (Hartley SB et al 1993 Cell 72:325).

CD63: A transmembrane protein of the tetraspanin family involved in suppression of metastasis. ▶tetraspanin; Ryu F et al 2000 Cell Struct Func 25:317.

CD64 (Fc γ RI, 1q21.2-q21.3): A receptor 1 of the antibody G Fc domain. ▶antibody; Shen L et al 1987 J Immunol.139:534.

CD66 (19q13.2): Inhibitory receptors on granulocytes and some lymphocytes (T, B, NK, Nair KS, Zingde SM, 2001 *Cell Immunol* 208:96).

CD70: ▶ **CD27**

CD80: A member of the interleukin family of proteins encoded at 3q21, same as B7.1, and BB-1. ▶ **antigen presenting cells**, ▶ **CD4**, ▶ **CD28**, ▶ **CD40**, ▶ **B7**, ▶ **interleukins**, ▶ **anergy**, ▶ **co-stimulator**; Hattori H et al 2001 *Clin Exp Allergy* 31:1242.

CD81 (target of antiproliferative antibody/TAPA): A tetraspanin cooperating with CD9. ▶ **CD9**, ▶ **tetraspanin**, ▶ **TAPA**; Charrin S et al 2001 *J Biol Chem* 276:14329.

CD82: A transmembrane protein of the tetraspanin family involved in suppression of metastasis and viral infection. ▶ **tetraspanin**, ▶ **CD9**; Pique C et al 2000 *Virology* 276:455.

CD85: ▶ **ILT**

CD86 (B7.2): T lymphocyte co-stimulatory molecule (encoded at 3q21), binding to the CD28 receptor of antigen presenting cells. ▶ **antigen presenting cell**, ▶ **CD28**, ▶ **anergy**; Flo J et al 2001 *Cell Immunol* 24:156.

CD89: An immunoglobulin A (IgA) receptor (FcαRI) expressed on monocytes, eosinophils and macrophages. ▶ **antibody**; Herr AB et al 2003 *Nature [Lond]* 423:614.

CD95: ▶ **Fas**, ▶ **FADD**

CD98: A regulator protein of integrin-mediated cell adhesion and transport (encoded at 11q13); it indicates T cell activation. CD98 heavy chain mediates integrin-dependent signals and promotes tumorigenesis (Feral CC et al 2005 *Proc Natl Acad Sci USA* 102:355). ▶ **integrin**, ▶ **lymphocytes**; Suga K et al 2001 *FEBS Lett* 489:249.

CD117: The receptor for stem cell factors in thymic lymphocyte precursors. ▶ **T cells**, ▶ **stem cell factor**, ▶ **steel factor**; Shimizu M et al 2001 *Exp Cell Res* 266:311.

CD120 (12p3): A TNF family ligand recognizing the TWEAK receptors. ▶ **TNF**, ▶ **TWEAK**

CD122: A mediator of immunological memory.

CD133 (prominin): Antigens occurring primarily in stem cells; their formation is apparently deregulated upon differentiation. CD133⁺ colon cancer cells—unlike CD133[−] cells—grew exponentially for more than 1 year in vitro as undifferentiated tumor spheres in a serum-free medium, maintaining the ability to engraft and reproduce the same morphological and antigenic pattern of the original tumor (O'Brien CA

et al 2007 *Nature [Lond]* 445:106; Ricci-Vitani L 2007 *Nature [Lond]* 445:111). For glioma stem cells CD133 conveys protection against therapeutic radiation by activating the DNA repair pathway (Bao S et al 2006 *Nature [Lond]* 444:756). ▶ **stem cell**, ▶ **cancer stem cell**, ▶ **colorectal cancer**, ▶ **glioma**

CD134: A receptor or co-receptor of lymphocytes, frequently with the costimulatory OX40.

CD137: Stimulates the response of CD8⁺ T cells to viruses. ▶ **T cell**; Halstead ES et al 2002 *Nature Immunol* 3:536.

CD146 (S-Endo 1 Ag, Mel-Cam, MUC18): A primarily endothelial integral membrane protein, but also occurring in nonmalignant and malignant (melanoma) cells. (See Anfosso F et al 2001 *J Biol Chem* 276:1564).

CD147: A transmembrane glycoprotein with two immunoglobulin-like domains; it is a regulatory part of the γ-secretase complex. ▶ **secretase**; Zhou S 2005 *Proc Natl Acad Sci USA* 102:7499.

CD150: CD150 is important in the activation of interferon-γ and it thus builds immunity to viruses. Some viruses direct the synthesis of homologous proteins to elude the host defense. ▶ **interferon**; Sidorenko SP, Clark EA 2003 *Nature Immunol* 4:19.

CD151: A tetraspanin-forming stable complex with α3β-integrin, a laminin receptor on the cell surface. ▶ **integrin**, ▶ **laminin**, ▶ **tetraspanin**

CD152: ▶ **CTLA**

CD154 (M_r ~ 39K): A CD40 ligand and an immunological adjuvant. A member of the TNF receptors encoded at 20q12-q13.2. Antibodies blocking CD154 interfere with the rejection of tissue transplants in monkeys. ▶ **CD40**, ▶ **adjuvant immunological**; Pierson RN et al 2001 *Immunol Res* 23:253; McGregor CM et al 2004 *Proc Natl Acad Sci USA* 101:9345.

CD200 (OX2): A membrane glycoprotein negatively regulating macrophages. ▶ **macrophage**; Clark DA et al 2001 *Semin Immunol* 13:255.

CD Antigens (cluster of differentiation antigens): A large number of antigens of the leukocytes that can be classified and identified by monoclonal antibodies. ▶ **CD proteins**; Mason D et al 2001 *J Leukoc Biol* 70:685.

C/D Box: ▶ **snoRNA**

CD Fraction (constant dosage): of the DNA in a chromosome including the functionally known genes. They are expected to be balanced with each other within a chromosome. These genes may, however, be amplified without serious detriment,

but changing the dosage of the syntenic genes (aneuploidy) may have very undesirable consequence. ► [aneuploidy](#)

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CD proteins (clusters of differentiation): Accessory proteins on the surface of the T cells. ► [T cells](#), ► [integrins](#), ► [LFA](#), ► [ICAM](#)

CDC (cell division cycle): The CDC genes encode cyclin-dependent kinase. More than 100 CDC genes have been discovered, and in 2001, Leland Hartwell, Paul Nurse and Tim Hunt were awarded the Nobel Prize for the original discoveries. ► [cell cycle](#), ► [CDK](#)

CDC1: A regulatory subunit of DNA polymerase δ . CDC1 seems to regulate the cellular Mn^{2+} level. ► [pol \$\delta\$](#) , ► [CDC27](#); Reynolds N, MacNeill SA 1999 Gene 230:15.

CDC2: A protein, which, when associated with mitotic cyclin proteins, becomes the MPF (maturation promoting factor) of the oocytes, a serine/threonine protein kinase. Cdc2 controls the transition from the G_1 to the S phase and prevents the reinitiation of the cell cycle at G_2 . Cdc2 also interacts with ORC. Phosphorylation of Cdc2 on threonine-14 (by *Xenopus* protein Myt1) and tyrosine-15 (by fission yeast protein Wee1) inhibits the activity of the Cdc2. For the activity of Cdc2, CAK (cyclin-dependent kinase) phosphorylates threonine-161. At the $G_2 \rightarrow M$ transition Cdc25 protein dephosphorylates Thr¹⁴ and Tyr¹⁵ and consequently Cdc2 suppresses MPF during interphase. High CDC2 activity inhibits anaphase but not the degradation of securin. ► [MPF](#), ► [cell cycle](#), ► [Cdc5](#), ► [securin](#), ► [separin](#), ► [mitosis](#), ► [ORC](#), ► [Plx1](#), ► [CDK](#), ► [Wee1](#), ► [Mik1](#), ► [Cdc25](#), ► [LATS](#); Vas A et al 2001 Mol Cell Biol 21:5767; Karaïskou A et al 2001 J Biol Chem 276:36028; Stemmann O et al 2001 Cell 107:715.

CDC4 (Fbw7/Ago): A protease required for the transition from the G_1 to the S phase during the cell cycle in cooperation with CDC34, CDC53 (cullin), and SKP1. CDC4 contains an F box, which interacts with SKP1 and 8 WD-40 repeats common for proteins involved in protein-protein interactions. Inactivation of human CDC4 results in chromosomal instability that may precede carcinogenesis (Rajagopalan H et al 2004 Nature [Lond] 428:77). ► [cell cycle](#), ► [CDC34](#), ► [WD-40](#), ► [SKP1](#), ► [APC](#); Desautels M et al 2001 J Biol Chem 276:5943.

CDC5: A fission yeast meiotic checkpoint control gene homologous to polo kinase. The CDC5 proteins are related to Myb and conserved through evolution. CDC5 is required for splicing pre-mRNA. ► [checkpoint](#), ► [Myb oncogene](#), ► [polo kinase](#), ► [splicing](#); Lee SE et al 2001 Curr Biol 11:784; Lee BH, Amon A 2003 Science 300:482.

CDC6: A protein DNA polymerase δ that appears in G_1 and early S phase and late mitosis. Apparently it takes part in the formation of the pre-replicative complexes and ORC. It is encoded at 17q21.3. ► [cell cycle](#), ► [ORC](#), ► [MCM](#), ► [cdt1](#), ► [cdc18](#), ► [DNA polymerases](#), ► [geminin](#); Yanow SK et al 2001 EMBO J 20:4648; Gowen Cook J et al 2002 Proc Natl Acad Sci USA 99:1347.

CDC7: A cell division cycle serine/threonine kinase with histone (H1) specificity. ► [cycle](#), ► [histones](#), ► [DBF4](#); Guo B, Lee H 1999 Somat Cell Mol Genet 25:159.

CDC10: A transcription factor for ribonucleotide reductase (CDC22). CDC10 mediates also budding in yeast. ► [ribonucleotide reductase](#); Jeong JW et al 2001 Mol Cells 12:77.

CDC13: A protein which is a regulator of gene *cdc2* in cooperation with genes *wee1* and *cdc25*; it is required also for the maintenance of telomeres in yeast. To accomplish meiosis in fission yeast the Mes1 protein suppresses the degradation of CDC13. Mes1 protein is specific for meiosis II but it is not required for regular mitosis (Izawa D et al 2005 Nature [Lond] 434:529). ► [wee1](#), ► [cdc25](#), ► [Stn1](#), ► [cell cycle](#), ► [telomere](#); Pennock E et al 2001 Cell 104:387; Chandra A et al 2001 Genes & Dev 15:404.

CDC14: A monocyte differentiation factor (5q31.1); a phosphatase, which inactivates cyclinB/Cdk1 and activates Swi5, which facilitates the transcription of Sic1. Sic1 is normally phosphorylated by cyclinB/Cdk1. CDC14 dephosphorylates also Cdh1 resulting in the activation of APC. CDC14 is initially detectable in the nucleolus where it is sequestered by another protein Cfi1 (CDC14 factor inhibitor) but eventually spreads into the nucleus and even to the cytoplasm. CDC14 regulates mitotic exit in cooperation with other proteins. ► [cyclinB](#), ► [Sic](#), ► [Cdk1](#), ► [Swi](#), ► [Cdh1](#), ► [APC](#), ► [cell cycle](#), ► [E2F](#), ► [mitotic exit](#), ► [FEAR](#), ► [Net1](#), ► [separin](#), ► [microtubules](#); Guertin DA, McCollum D 2001 J Biol Chem 276:28185; Azzam R et al 2004 Science 305:516.

CDC15: An inhibitor in MEN, controlling exit from mitosis along with TEM1. ► [MEN](#), ► [TEM1](#); Mah AS et al 2001 Proc Natl Acad Sci USA 98:7325.

CDC16 (APC6): ► [CDC27](#), ► [APC](#)

CDC17: *Saccharomyces cerevisiae* gene for DNA polymerase α and CDC17⁺ is a DNA ligase I gene of *Schizosaccharomyces pombe*. ► [DNA polymerases](#), ► [DNA replication](#); Adams MA et al 2000 Mol Cell Biol 20:786.

CDC18: A rate-limiting activator (initiator) of replication. It interacts with ORC2. In the human chromosome it is encoded at 17q21.3. In budding yeast it is

- CDC6. ▶ORC2, ▶cell cycle, ▶CDC6, ▶cdt1, ▶geminin; Yanow SK et al 2001 EMBO J 20:4648.
- CDC19** (Nda1): A component of the minichromosome maintenance complex (MCM). The human homolog is encoded at 3q21. ▶MCM; Liang DT et al 1999 J Cell Sci 112 [pt4]:559.
- CDC20**: DNA polymerase ϵ and anaphase spindle checkpoint (repair) protein. It is encoded at human chromosome 9q12-q22. It plays a role in the activation of the anaphase-promoting complex (APC). ▶checkpoint, ▶cell cycle, ▶spindle, ▶anaphase, ▶APC, ▶CDH1; Pflieger CM et al 2001 Genes Dev 15:2396.
- CDC20-50**: Potentiate passing beyond metaphase to anaphase in the absence of spindle formation. ▶cell cycle, ▶CDC20, ▶CDC50; Schott EJ, Hoyt MA 1998 Genetics 148:599.
- CDC21**: A component of the minichromosome maintenance complex (MCM), encoded at human chromosome 8q11.2 ▶MCM; Satoh T et al 1997 Genomics 46:525.
- CDC22**: A ribonucleotide reductase acting on purine and pyrimidine nucleoside di- and triphosphates and catalyzes the formation of DNA precursors. ▶ribonucleotide reductase, ▶cdt1; Fernandez Sarabia MJ et al 1993 Mol Gen Genet 238:241.
- CDC23** (APC8): A member of the APC protein complex, encoded at human chromosome 5q31.1. ▶APC; Goh PY et al 2000 Eur J Biochem 267:434.
- CDC24**: A guanine nucleotide exchange factor (GEF) in signal transduction and a DNA replication factor responsible for chromosome integrity. ▶CDC42, ▶GEF; Bose I et al 2001 J Biol Chem 276:7176.
- CDC25**: The cyclin-dependent CDC25 (A, B and C at 5q31) phosphatases remove inhibitory phosphates from tyrosines and threonines to facilitate the transition from G² to mitosis during the cell cycle. In human and mouse cells they represent a multigene family. In about a third of the breast cancers, CDC25B is overexpressed. In *Saccharomyces cerevisiae*, CDC25 genes regulate RAS/cAMP pathway and their mutation causes defects in G₁ phase of the cell cycle. CDC25 is thus a proto-oncogene and when growth factors are exhausted it can induce apoptosis. CDC25 may be downregulated by p53 binding to the DNA and cell cycle arrest (St Clair S et al 2004 Mol Cell 16:725). The *Drosophila* homolog is *stg* (*string*). ▶cell cycle, ▶cdk, ▶ras, ▶budding yeast, ▶MYC, ▶Plx1, ▶Chk1, ▶protein 14-3-3, ▶parvulins, ▶CDC2, ▶GEF, ▶CDF, ▶checkpoint, ▶p53, ▶SOS recruiting system; Forrest A, Gabrielli B 2001 Oncogene 20:4393; Busino L et al 2003 Nature [Lond] 426:87.
- CDC27** (APC3): A member of the tumor necrosis factor receptor family and restricts DNA replication to one round per cell cycle in cooperation with CDC16. It is also a component of the anaphase-promoting complex encoded at 17q12-q13.2. CDC27/p66 is a component of DNA polymerase δ ; its N-terminal 1–166 amino acids binds to CDC1 and its C-terminal 362–369 amino acids interact with PCNA and thus the processivity is supported. ▶TNF, ▶anaphase promoting complex, ▶PCNA, ▶processivity; Shikata K et al 2001 J Biochem [Tokyo] 129:699; Bermudez VP et al 2002 J Biol Chem 277:36853.
- CDC28**: CDC28 in *Saccharomyces cerevisiae* and CDC2 (in *Schizosaccharomyces pombe*) genes are responsible for the start of mitosis in the cell divisional cycle. CDC28p/Cdk1p protein is a cyclin-dependent kinase (CDK). Binding cyclin-3 activates CDC28. The human homolog encoded at 2q33 is a Ser/Arg-rich protein required for splicing of pre-mRNA. ▶cell cycle, ▶CDC2, ▶CDK, ▶CDC34, ▶CDC45, ▶Sic, ▶mRNA; Russo GL et al 2000 Biochem J 351:[pt 1]: 143; CDC28 regulates initiation of meiotic double breaks; Henderson KA et al 2006 Cell 125:1321.
- CDC30**: A member of the tumor necrosis factor receptor family. It is also involved in the control of sporulation of yeast. ▶TNF; Dickinson JR et al 1988 J Gen Microbiol 134 [pt 9]:2475.
- CDC31** (centrin): A Ca²⁺-binding protein in the microtubule-organizing center. ▶MTOC, ▶centrin, ▶calmodulin; Ivanovska I, Rose MD 2001 Genetics 157:503.
- CDC33**: Encodes the eIF-4E translation initiation protein. ▶eIF-4E; Brenner C et al 1988 Mol Cell Biol 8:3556.
- CDC34**: An ubiquitin-activating enzyme. It is required for the G₁→S transition in the cell cycle. The human homolog is encoded at 19p13.3. It facilitates the destruction of Cyclin 2 (CLN2) and Cyclin 3 (CLN3) and degrades the CDK inhibitor, SIC1. CLN2 and CLN3 are phosphorylated by CDC28 before CDC34-dependent ubiquitination. ▶cyclins, ▶SIC1, ▶ubiquitin, ▶cell cycle, ▶Wee1, ▶glucose induction; Ptak C et al 2001 Mol Cell Biol 21:6537.
- CDC39**: A gene with a glutamine-rich repressor product affecting G₁/S phase transition. ▶cell cycle; Collart MA, Struhl K 1994 Genes Dev 8:525.
- CDC40**: A member of the tumor necrosis factor receptor family. It is a pre-mRNA splicing factor. ▶TNF, ▶splicing; Russel CS et al 2000 RNA 6:1565.
- CDC42**: A RHO (Rac) family GTPase protein (encoded at human chromosome 1p36.1). It is involved in signal transduction pathways (see Fig. C40). In yeast, it affects the mating pheromone, signaling and binding several proteins; CDC42 is an activator of the JNK and

C



Figure C40. Structure of CDC42. (Courtesy of Laue, E.D.; from Moreale, A. et al. 2000 Nature Struct. Biol. 7:384)

ERK pathways, including the one responsible for the Wiskott–Aldrich syndrome. CDC42 activation is sufficient to promote a premature cellular senescence that depends on p53 (Wang L et al 2007 Proc Natl Acad Sci USA 104:1248). It causes depolarization of actin and regulates the exit of proteins from the trans-Golgi network. Its GDP-GTP exchange factor is CDC24. It is a substrate for caspases and cooperates with the Fas apoptotic pathway. Integrin-mediated activation of CDC42 is involved in controlling astrocyte polarity with the cooperation of PKC and dynein. CDC42 regulates, also, the attachment of the spindle fibers to the kinetochore. Activation of CDC42 can be monitored by the application of the S-SO dye, which detects conformational changes in proteins (see Fig. C41) (Nalbant P et al 2004 Science 305:1615). The S-SO family of dyes are described by Touthkine A et al (203 J Am Chem Soc 125:4132). ▶actin, ▶integrin, ▶PKC, ▶dynein, ▶astrocyte, ▶Wiskott–Aldrich syndrome, ▶RHO, ▶Rac, ▶Fas, ▶apoptosis, ▶kinetochore, ▶mating type determination in yeast, ▶GTPase, ▶PAK, ▶Bin, ▶JNK, ▶ERK, ▶signal transduction, ▶cell migration, ▶CDC24, ▶Golgi, ▶faciogenital dysplasia; Tu S, Cerione RA 2001 J Biol Chem 276:19656; Etienne-Manneville S, Hall A 2001 Cell 106:489.

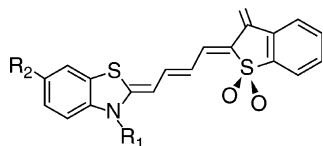


Figure C41. S-SO(benzothiophene-3-one-1,1-dioxide)

CDC44: A *Saccharomyces cerevisiae* gene, encoding the large subunit of RFC. ▶RFC, ▶Okazaki fragment; McAlear MA et al 1996 Genetics 142:65.

CDC45/CDC46-MCM5: Proteins (receptor-like transmembrane protein tyrosine phosphatases) are required for the initiation of chromosomal replication in association with CDC28 and other cyclin kinases. This complex, in association with GINS (Sld5, Psf1, Psf2, Psf3) proteins that are found at the yeast replication fork, are probably involved in eukaryotic helicase machinery (Moyer SE et al 2006 Proc Natl Acad Sci USA 103:10236). The human homolog of CDC45 is encoded at 22q11.2, the CDC46MCM at 22q13.1. Inactivation of CDC45 leads to lymphoproliferation and autoimmunity. ▶MCM, ▶CDC28, ▶cell cycle, ▶helicase, ▶DiGeorge syndrome, ▶autoimmune disease; Ehrenhofe-Murray AE et al 1999 Genetics 153:1171.

CDC48 (p97): An AAA family protein with roles in: the cell cycle, membrane fusion, endoplasmic reticulum assembly, nuclear fusion, Golgi reassembly, degradation of ubiquitin fusion proteins, transcription factor processing, degradation of endoplasmic reticulum associated proteins, apoptosis and chaperone-like activity. ▶terms at separate entries, ▶endoplasmic reticulum-associated degradation, ▶p97; Thoms S 2002 FEBS Lett 520:107.

CDC50: Controls START in the G1 phase of the cell cycle. ▶CDC20, ▶START; Radji M et al 2001 Yeast 18:195.

CDC53 (cullin, CUL): CUL2 was mapped to human chromosome 10p11.2-p11.1; CUL3 is in human chromosome 2. ▶CDC4, ▶glucose induction, ▶cullin; Botuyan MV et al 2001 J Mol Biol 312:177.

CDC55: Mammalian homolog of the yeast CDC20, a mitotic protein. ▶CDC20, ▶spindle; Wang Y, Burke DJ 1997 Mol Cell Biol 17:620.

CDC68 (Spt16): A transcription elongation factor on active chromatin. ▶FACT, ▶transcription factors, ▶chromatin remodeling; Formosa T et al 2001 EMBO J 20:3506.

CDCV: ▶PAF

CDE Elements: ▶centromere, ▶CDF

CDF: A facultative repressor of the cell division cycle. It regulates the expression of CDC25, cyclin A and

MYB. CDF-1 acts on repressor sites CDE (GGCGG) and CHR (ATTTGAA). In the late S phase, CDF binding to promoters leads to derepression of transcription. Binding E2F1 to the promoter upregulates transcription in late G1 phase. Binding both E2F and CDF results in intermediate kinetics. ►cell cycle, ►CDC25, ►E2F1, ►CDE, ►cyclins, ►MYB, ►CHR; Nettlebeck DM et al 1999 Gene Ther 6:1276.

CDH1 (Hct1): An APC-regulatory WD protein with functions similar to CDC20. During anaphase CDC20 is replaced by CDH1. ►Apc, ►CDC20, ►CDC14, ►WD-40, ►mitotic exit, ►mitotic catastrophe, ►Id proteins; Pfleger CM et al 2001 Genes Dev 15:1759.

CDK: Cyclin-dependent kinases involved in cell division (replication) or apoptosis. These kinases do not operate without cyclin. CyclinD-CDK4, CDK6 are involved in G1 of the cell cycle; cyclinE-CDK2 drive G1-S phase and DNA replication; cyclinA-CDK is active in S phase and cell division requires cyclinA-CDK1 and cyclinB in G2 and M phases. CDK2 is essential for the completion of prophase I of meiosis but its deletion does not affect much mitotic cell proliferation or survival in mice (Ortega S et al 2003 Nature Genet 35:25). Full activity is achieved by phosphorylation by CAK. Some cells (myocytes) may be protected from apoptosis by p21^{CIP1} and p16^{INK4a} inhibitors of CDK. p16^{INK4a} prevents the binding of cyclin D to CDK4/CDK6. Among the CDK inhibitors, p15, p16, and p18 specifically inhibit CDK4 and CDK6, whereas p21, p27, p28 and p57 are inhibitors of a wide range of CDK cyclin complexes. CDK4 is a tyrosine phosphorylated in G1 and dephosphorylation is required for the progression into S phase. UV irradiation may prevent dephosphorylation and cells are arrested in G1. If the CDK4 is not phosphorylated in G1, chromosomal breakage increases and a cell death may result. CDK-activating kinase is a component of the CAK-complex and part of the carboxy-terminal of transcription factor TFIIF. The CDK proteins are similar in size (35–40K) and display >40% identity in the different organisms where the somewhat different enzymes are denoted differently. CDC2 is the typical enzyme for fission yeast; and in budding yeast, the cyclin box comparable protein is CDC28, whereas in human cells it is CDK1/CDK. The 300 amino residue catalytic subunit is inactive as a monomer or in the unphosphorylated form. In the inactive state, the substrate-binding site is blocked and the ATP-binding sites are not readily available for the phosphorylation required for activity. The binding of CDK to the ≈100 amino acid cyclin box is indispensable for function. CDK5/p35 are involved in neural development. When p35 is cleaved

into a p25 fragment, CDK5 excessively phosphorylates tau and Alzheimer neurofibrillar tangles appear in the brain. Human CDK7 is homologous to the yeast Kin28 and has subunits of the general transcription factor TFIIF; it phosphorylates the carboxyterminal domain of RNA polymerase II after the formation of the preinitiation complex. CDK7/K in 28 promote transcription. CDK8 is homologous to the yeast Srb10 and it is a subunit of the Pol II enzyme; it is also capable of phosphorylation of the C-terminal domain of Pol II before the formation of the preinitiation complex. CDK8/Srb10 actually inhibit transcription. The difference between Kin28 and Srb10/11 is in the temporal sequence of action. The effect of Srb10 does not apply generally to all genes, but it affects genes which determine cells types, meiosis and sugar utilization. Srb2, 4, 5, and 6 all are positive regulators of transcription. CDK9 (encoded in human chromosome 12) is a cofactor of lentiviral transcription. CDC2 may associate with a few different cyclins whereas CDC28 may be attached to nine different cyclins during the course of the cell cycle. The level and form of cyclins may vary during the cell cycle and their destruction is mediated by ubiquitins. In yeast, activation of CDC28 by the G1 cyclins stimulates the cyclins CLN1 and CLN2 to degrade mitotic cyclins (CLB), after which the G1 phase CLB levels may be elevated leading to the repression of G1 cyclins. When CDC28 is activated CLB decay begins. The CDK-cyclin complex may be inhibited by phosphorylation near the amino end of CDC2 and CDK2 (at Thr 14 and Tyr 15). Phosphorylation at these two residues is followed by a rise of mitotic cyclins (CLB). At the end of the G2 phase Thr 14 and Tyr 15 are dephosphorylated by CDC25 phosphatase and CDC2 is activated. CDK may also be inactivated by protein CKI (a family of inhibitory proteins to the cyclin CDK complex by attaching to the complex). The inhibitory subunits include p21 and p27 and other proteins. Eventually, the CKIs also decay and the cyclic events continue. Selective inhibitors of these kinases may be potential therapeutics. CDK1 is also called CDC28. Human CDK8 and cyclin C carry out the same function as Srb10 and Srb11, the negative regulators of transcription in yeast. ►cyclin, ►kinase, ►tau, ►Alzheimer's disease, ►CAK, ►KIN28, ►PHO85, ►Srb, ►CDC28, ►cell cycle, ►p16^{INK}, ►p53, ►KIP, ►CIP, ►apoptosis, ►UV, ►ubiquitin, ►CLB, ►p21, ►p27, ►p16, ►p57, ►CKI, ►preinitiation complex, ►lentiviruses, ►cyclin T, ►centrosome, ►PITALRE, ►polycystic kidney disease, see also Andrews B, Measday V 1998 Trends Genet 14 (2):68, for CDK inhibitors: Knockaert M et al 2002 J Biol Chem 277:25493; cell cycle: Pagano M, Jackson PK 2004 Cell 118:535.

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CDKN2A (CDKN2/TP16/p16^{INK4}, 9p21): A cyclin-dependent kinase inhibitor and general tumor suppressor. The gene encodes two proteins p16^{INK4A} regulating retinoblastoma gene (RB) and p19^{ARF}, which regulates p53. ▶**CDK**, ▶**p16**, ▶**ecclampsia**; Palmieri G et al 2000 Br J Cancer 83:1707.

cDNA: DNA complementary to mRNA (made through reverse transcription) and which does not normally contain introns. ▶**reverse transcriptases**, ▶**transcription**, ▶**mRNA**, ▶**Okayama & Berg procedure** (see Fig. C42), <http://www.kazusa.or.jp/huge>, mammalian: <http://mgc.nci.nih.gov>; human database free clones: <http://fldb.hri.co.jp/cgi-bin/cDNA3/public/publication/index.cgi>, Ota T et al 2004 Nature Genet 36:40; Gustincich S et al 2006 J Physiol 575(2):321.

cDNA Library: A collection of DNA sequences complementary to mRNA. ▶**mRNA**, ▶**processed genes**

cDNA Library Screening: Can be carried out by probing the DNA sequences, either with special binding proteins for the purpose of high degree purification or with any DNA or RNA in order to identify genes or gene products isolated from different organisms. ▶**gel retardation assay**, ▶**cloning**, ▶**probe**

CCDP: A mammalian displacement protein at the CCAAT sequence of DNA and competes for binding of CP1, a CCAAT box-binding protein. It is a transcriptional repressor. ▶**CP1**, ▶**CAAT box**; Ellis T et al 2001 Genes Dev 15:2307.

CDP (cytidine diphosphate): A nucleotide involved in the biosynthesis of phospholipid synthesis.

CDPK: Ca²⁺-dependent protein kinases regulate signaling pathways. ▶**signal transduction**; Allwood EG et al 2001 FEBS Lett 499:97; Zhang XS, Choi JH 2001 J Mol Evol 53:214.

CDR: CDR is the complementarity determining region of the antibody's hypervariable region that binds the antigen; it is the antigen-binding site (idiotype). ▶**antibody**, ▶**paratope**, ▶**idiotype**, ▶**look-through mutagenesis**; Furukawa K et al 2001 J Biol Chem 276:27622.

CDR (cerebellar degeneration-related autoantigen, Xq27.1-q27.2): Autoantigens directed against the cerebellar degeneration protein that occurs in neoplasms of the lung, breast, ovary and Hodgkin's disease (Chen YT et al 1990 Proc Natl Acad Sci USA 87:3077). CDR3 is apparently at 17q25 (Fletcher CF et al 1997 Genomics 45:313).

CDS: Protein-coding sequences in the genome. Raddatz G et al 2001 Bioinformatics 17:98.

CDS1: A fission yeast kinase, an inhibitor of CDC2. Human CDS1 phosphorylates the breast cancer protein (BRCA1) at serine 988 after DNA damage and assists thus cell survival. ▶**CDC2**, ▶**breast cancer**; Boddy MN et al 2000 Mol Cell Biol 20:8758.

CDT1: A fission yeast protein (with similarities to deoxyribonuclease I) required for assembly of the DNA pre-replication complex in concert with CDC22, CDC18/CDC6 and MCM. Its homologs are present in vertebrates. CDTs (cytolethal distending toxins) have the special feature of affecting DNA rather than cellular proteins. The cul-4 ubiquitin ligase restrains replication, which is mediated CDT1. In the cells lacking CUL-4, CDT becomes uncontrolled and additional S phase replications may increase DNA content up to 100 C. Geminin can inhibit the CDT1 component of the replication-licensing factor (Lee C et al 2004 Nature [Lond] 430:913). ▶**C value**, ▶**CDC6**, ▶**CDC18**, ▶**CDC22**, ▶**DNA replication**, ▶**replication fork**, ▶**replication licensing factor**, ▶**ubiquitin**, ▶**MCM**, ▶**geminin**, ▶**chloroplast**; Yanow SK et al 2001 EMBO J 20:4648; Zhong W et al 2003 Nature [Lond] 423:885.

CD-Tagging Methods: Uses, for insertion mutagenesis, a DNA cassette that when inserted into an intron and transcribed and spliced, the mRNA will contain a special tag (guest tag). Upon translation, the polypeptide will also carry a tag (guest peptide). The latter can be identified by a monoclonal antibody, specially prepared for this epitope. The mRNA and the DNA sequences can be identified by PCR. Thus this method simultaneously labels DNA, RNA and the peptide; hence its name, central dogma tagging. ▶**insertional mutagenesis**, ▶**monoclonal antibody**, ▶**epitope**, ▶**PCR**; Jarvik JW et al 1996 Biotechniques 20:896.

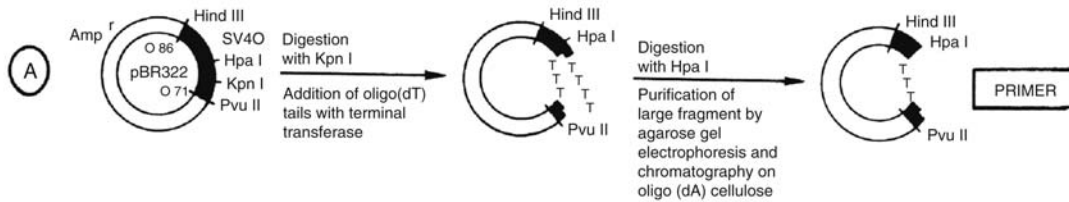
CDw32 (FcγRII): An antibody Fc domain receptor. ▶**antibody**; McKenzie SE, Schreiber AD 1994 Curr Opin Hematol 1:45.

CDX1: A homeobox protein regulating intestinal epithelium and it is apparently a suppressor of oncogenesis. ▶**colorectal cancer**, ▶**Barrett metaplasia**; Wong NACS et al 2004 Proc Natl Acad Sci USA 101:574.

Cdx2: A cell fate-determining transcription factor required during the differentiation of the mouse trophectoderm; forming the fetal-maternal interface during blastocysts development. It interacts with Oct3/4 transcription factor (Niwa H et al 2005 Cell 123:917).

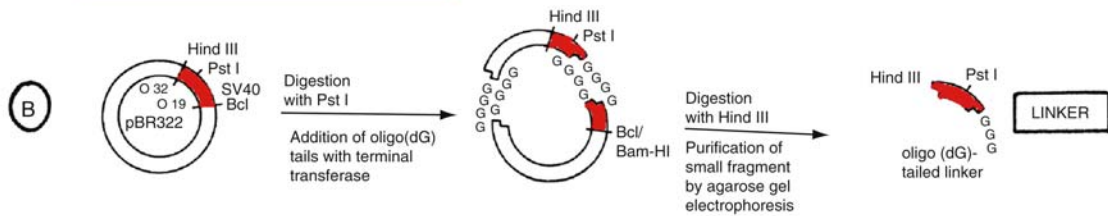
ce: Prefix for *Caenorhabditis elegans* DNA, RNA or protein.

► Construction of Plasmid Primer:



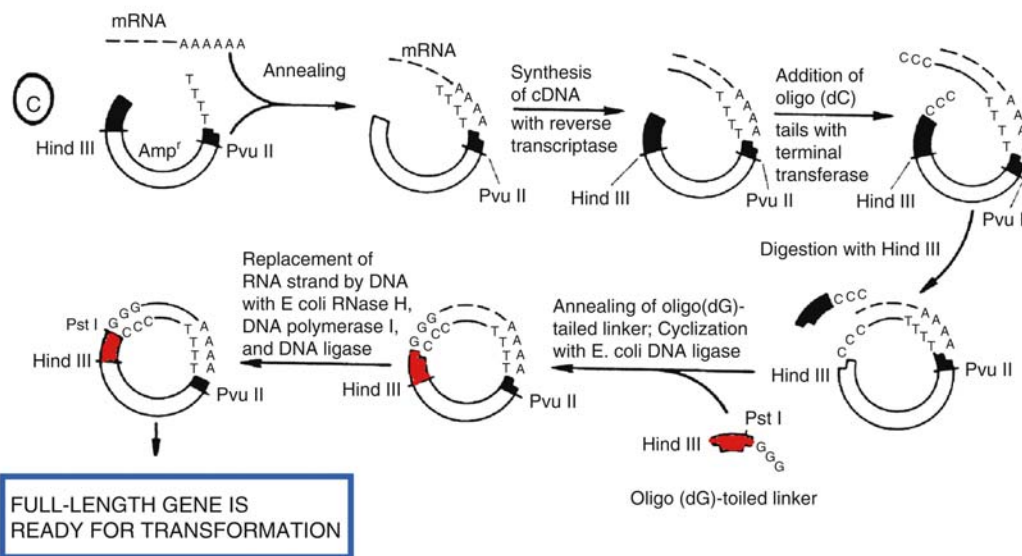
The hybrid plasmid consists of pBR322 + a piece of SV40 (black), the decimals are map coordinates of the virus.

► Construction of Oligo dG Tailed Linkers:



The unshaded part is pBR322, the stippled comes from SV40

► Cloning of the mRNA:



mRNA is extracted from post-lysosomal supernatant of reticulocyte lysate of rabbits made anemic by phenylhydrazine injections. The globin mRNA is recovered in the alcohol precipitate of phenol extract or prepared with the aid of the guanidium thiocyanate methods. The poly(A)-tailed mRNA is annealed to the dT-tailed vector-primer and the first strand of the cDNA is made by reverse transcription. Oligo dC tails are added to both 3'-OH ends. The oligo C ends must be removed by Hind III and the linker (B) is substituted for it. The RNA is removed by 3' to 5' exonuclease activity (RNase H) of the reverse transcriptase and it is replaced by DNA polymerase I-made DNA strand and ligation follows. Propagation by transformation.

Figure C42. (A) Construction of plasmid primer; (B) Construction of oligo dG tailed linkers; (C) Cloning of the mRNA. Okayama M & Berg P Method of isolation full-length cDNA. (Modified after Mol. Cell Biol. 2: 161)

C.E.: An abbreviation for Common Era of historical time.

Cebidae: Families of New World monkeys. *Aotus trivirgatus* 2n = 54; *Aotus trivirgatus griseimembra* 2n = 52, 53, 54; *Ateles geoffroyi* 2n = 34; *Callicebus moloch* 2n = 46; *Callicebus torquatus* 2n = 20; *Cacajao* 2n = 46; *Cebus albifrons* 2n = 54; *Lagothrix ubericolor* 2n = 62; *Pithecia p. pithecia* 2n = 48; *Scaimii sciureus* 2n = 44 ► **primates**

C/EBP (CEBP): CAAT/Enhancer Binding Protein is transcription factor AP1, product of JUN and FOS oncogenes. The protein is essential for the differentiation of granulocytes. Its mutation is common in acute myelogenous leukemia (Pabst T et al 2001 Nature Genet 27:263). These proteins regulate different cellular functions, including adipogenesis. The C/EBP family of proteins affects the storage and suppression of memory (Chen A et al 2003 Neuron 39:655). ► **AP**, ► **JUN**, ► **FOS**, ► **enhancer**, ► **granulocyte**, ► **leukemia**, ► **memory**, ► **aging**; Lekstrom-Himes J, Hanthopolus KG 1998 J Biol Chem 273:28545; McKnight SL 2001 Cell 107:259.

Cebus (capuchin monkey): ► **Cebidae**

Cecropin: ► **antimicrobial peptides**

CED: ► **apoptosis**

Cefotaxime (Claforan): A cephalosporin type general medical antibiotic with relatively mild toxicity to plant cells (see Fig. C43). It is thus widely used to free plant tissue from *Agrobacterium*, infected for the purpose of genetic transformation. ► **genetic transformation**, ► **Agrobacterium**; Husson MO et al 2000 Pathol Biol [Paris] 48:933.

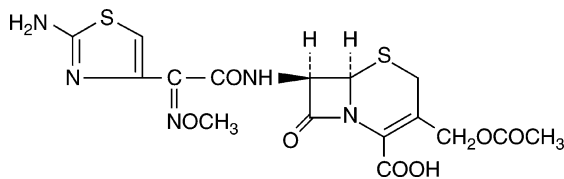


Figure C43. Cefotaxime

Ceiling Principle: A statistical procedure for the conservative estimation of the odds for the likelihood that DNA fingerprints would match. The odds against a chance match is usually determined on the basis of the frequency of a particular genetic marker in a certain population (such as Caucasians, Blacks, Hispanics, Orientals, etc.). The markers used for DNA fingerprint analysis are supposed to be of low frequency, below 10 or 5%, but for the majority of subpopulations such information is not available yet. In such cases they take into account, say, 0.1 as a maximal frequency (a ceiling). The chance that a

particular person would have the same DNA marker as another individual in its group would be $0.1 \times 0.1 = 0.01$. The probability that 8 markers would be identical by chance would be $(0.1)^8 = 1/100,000,000$, and if 0.05 is chosen as a ceiling it would be approximately 2.6×10^{-10} . The world's population of 6 billion is about 23% of 2.6×10^{10} . Some population geneticists disagree with the use of the rather arbitrary "ceilings" and advocate the theoretically more valid use of mean frequencies with the pertinent confidence intervals. Today, more information is being made available on gene frequencies and therefore direct frequencies can be used for the majority of the genes involved. Abandoning the ceiling principle increases the accuracy of establishing individual liabilities and does not allow unwarranted advantage for the criminals. The recommended genetic markers for forensic comparison (in lieu of the ceiling principle) are variable number tandem repeats, VNTR (D2S44, 75 alleles and D1S80, 30 alleles), short tandem repeats, STRs (HUMTHO1, 8 alleles) simple sequence variations, SSV (DQA, 8 alleles, poly-marker [5 loci, 972 combinations]), and mtDNA D-loop with >95% diversity. ► **DNA fingerprinting**, ► **confidence intervals**, ► **allelic frequency**, ► **Frye test**; Slimoewitz JR, Cohen JE 1993 Am J Hum Genet 53:314.

Ceinsulin: An insulin-like growth hormone in *Caenorhabditis elegans*. ► **insulin**, ► **Caenorhabditis**

Celera: A genomics and diagnostics laboratory. <http://www.celera.com/>.

Celery (*Apium graveolens*): The stalks are used as food or the celeriac is a root vegetable; 2n = 2x = 22.

Celiac Disease (coeliac disease, sprue, 6p21.3): In certain individuals the intestinal enzymes do not digest some water-insoluble proteins like the gliadin (glycoprotein in gluten) in wheat (also in other cereals). Intolerance to oats is less common but does exist. This protein then causes inflammation of the intestinal lining and bloating of the abdomen. Its incidence in the general population is about 4/1000 and the genetic recurrence risk in the brothers and sisters of afflicted sibs is about 2 to 3%. The genes responsible for A2-gliadin synthesis were located to the long arm of chromosomes 6A, 6B and 6D of hexaploid wheat. Some gliadin genes are also in chromosome 1. There are substantial quantitative differences among the different chromosomes concerning the production of this protein. In the intestinal endomysium (reticular sheath of muscle fibers), a tissue-specific transglutaminase exists. Deamidation of gliadin opens up epitopes, which bind then HLA-DQ2 on antigen presenting cells and facilitate the recognition by intestinal T lymphocytes. It appears particularly important for the inflammation response

when glutamine 148 is converted into acidic glutamate. The CD4⁺ T cells then stimulate helper T cells (T_H) to secrete cytokines such as TNF- α , which in turn induces the release of metalloproteinases which degrade fibrillar collagen, proteoglycans and matrix glycoproteins. The T_H cells facilitate immunoglobulin-A (IgA) production by B lymphocytes. IgA then turns against gliadin and gliadin complexes.

Some anthropologists suggested that the ancient Egyptians consumed high gliadin wheat varieties or some of the pharaohs were more susceptible to the disease (these families practiced high degree of inbreeding) because of the extended bellies observed on several royal mummies and on the statues of Tutankhamen. About 40% of disease cases are under the control of the HLA-DQ2 genes in humans but one 6p locus, 30 cM from the telomere (thus outside HLA), has been identified for the predisposition. At 19p13.1 in intron 28 of the myosin 9B gene there is an important variant controlling actin remodeling in epithelial enterocytes. As a consequence the intestinal barrier to the uptake of gliadin is diminished and individuals heterozygous for the gene have 2.3 times increased chance for the disease (Monsuur AJ et al 2005 Nature Genet 37:1341). Low-*lod* score putative linkage was observed with several chromosomal sites. Besides the HLA region (6q21.3), significantly increased risk factors were found at 4q27

(van Heel DA et al 2007 Nature Genet 39:827). ▶HLA, ▶immuno-globulins, ▶T cells, ▶T_H, ▶immune system, ▶metalloproteinases, ▶Triticum, ▶glutenin, ▶gynecomastia; King AL et al 2000 Ann Hum Genet 64:479 Sollid LM 2000 Annu Rev Immunol 18:53; Kumar R et al 2002 J Mol Biol 319:593; Fleckenstein B et al 2002 J Biol Chem 277:34109; Schuppan D, Hahn EG 2002 Science 297:2218.

Cell: ▶cell structure, ▶cell comparisons, ▶single cell analytical methods

Cell Adhesion Molecule: ▶CAM

Cell Autonomous: The product of the gene is limited to the cell expressing it; it does not diffuse to other cells.

Cell Body: The main part of the nerve cell containing the nucleus and excluding the axons and dendrites.
▶neurogenesis

Cell Comparisons: Cells of various organisms have common features, yet differences exist that can be compared by the tabulation shown in the table (see Table C2). Prokaryotes in general lack organelles; certain bacteria have something similar, the carboxysome, which processes carbon (Kerfeld CA et al 2005 Science 308:936). There are nomenclature problems when various cell types (phenotypes) need description. It is especially difficult to make

Table C2. Cell comparisons

| CRITERIA | PROKARYOTES | PLANTS | ANIMALS |
|----------------------------------|---------------------------|------------------------|------------------|
| Cell wall | Present | Present | Absent |
| Nucleus | Nonenveloped nucleoid | Enveloped | Enveloped |
| Plastids | Absent | Present | Absent |
| Mitochondria | Absent | Present | Present |
| Ribosomes | 70S | 80S | 80S |
| (organellar) | Not applicable | 70S | 70S |
| Endoplasmic reticulum | Absent | Present | Present |
| Centrioles | Absent | Absent | Present |
| Spindle fibers | Absent | Present | Present |
| Microtubules | Absent | Present | Present |
| DNA location | Nucleoid | Nucleus | Nucleus |
| | Plasmids | Mitochondria, plastids | Mitochondria |
| Chromosomal composition | DNA | DNA | DNA |
| | Minimal protein | Protein | Protein |
| | or RNA | RNA | RNA |
| Division of the genetic material | Replication and partition | Replication | Replication |
| | | Mitosis, meiosis | Mitosis, meiosis |

C

comparisons among various eukaryotic cell phenotypes (including mutants) and their developmental, evolutionary origin among the different taxonomic groups. Bard J et al (2005 Genome Biol 6:R21) proposed ontology for cell types for the major model organisms and it is available free at <http://search.msn.com/results.aspx?q=obo+sourceforge+nbt&FORM=USNO/>, wide-ranging information on cells and tissues: <http://ccdb.ucsd.edu/CCDBWebSite/index.html>.

Cell Cortex: On the inner surface of the animal plasma membrane there is an actin-rich layer of the cytoplasm, mediating movement of the cell surface.

Cell Culture: Generally, the culture of isolated cells of higher eukaryotes, although growing bacteria or yeast is also cell culturing. ▶tissue culture

Cell Cycle: The phases of cell reproduction and growth are G1→S→G2→M and cytokinesis, the generation of two daughter cells from one. The duration of the cell cycle varies among different organisms, and it is influenced by several factors (temperature, nutrition, age, stage, etc.). In *Drosophila* embryos it may be completed within 8 min and in other early embryos the cycle may be completed within half an hour. In other cells the approximate numbers of hours required are shown in the table (see Table C3).

The S and M phases are present in all dividing tissues, the G phases can be clearly distinguished only in cells where the divisions are less fast because of differentiation.

Before the cell enters the cell cycle the pre-replication complex (pre-CR) is assembled. This complex consists of the Origin Recognition Complex (ORC), the cell division cycle 6 protein (Cdc6p), and MCM (mini-chromosome maintenance proteins).

The cell cycle has been studied most frequently in vitro by the dividing egg of mammals manipulated by microinjection of various cellular components or by fusion of cells of different developmental stages. In plants, it is analyzed in somatic cells where division is triggered by the application of hormones

and, in yeast, by accumulating conditional (temperature-sensitive) mutations and then by the introduction of the wild-type allele through transformation. Throughout the cell cycle (except mitosis) RNA and protein synthesis takes place. The G1 phase (Gap 1, named not very felicitously) is actually a phase of cell growth when a commitment is made for DNA replication. This point of commitment is called START by yeast cell biologists, and by animal cell biologists, RESTRICTION POINT.

For START, the cell requires the activity of a cyclin-dependent protein kinase composed of the catalytic subunit of protein CDC28 and one of the three cyclins (C/n1, -2 or -3). After START, cyclin 5 B and cyclin 6 kinases are required. The latter two kinases are inhibited by protein SIC1 and the latter must be inactivated by proteolysis, carried out by the ubiquitin-conjugated CDC34. Some cells may stay very long at this preparatory stage and this is when it is called the G₀ stage. In the S phase, DNA synthesis is completed. The cells cannot enter G2 (Gap 2, another cell growth phase) before the completion of S phase. Several genes were found to cooperate in *checkpoints* that provide clearance before the next phase could be entered. CLB-Cdc28 prevents reinitiation of the S phase by phosphorylating CDC6 and removal of MCM2-7. Thus the cell avoids polyteny or polyploidy. G2 is committed to the preparations of mitosis, a task that follows, if, during interphase, all the nutritional requisites for carrying out mitosis build up. The two G phases and S phase combined are frequently named *interphase*, i.e., the phase between nuclear divisions (mitosis). In very rapidly dividing embryonic tissue, G1 and G2, involved in cell growth, may be extremely brief or even absent and therefore the daughter cells become only half the size of the mother cells by each division. This is possible because the egg cell is generally very large at the time of fertilization. Some mature animal eggs may be thousands or tens of thousands of times larger than an average body cell and it is loaded with nutritious material. In such cases the cell cycle may

Table C3. Approximate number of hours of duration of stages of the cell cycle

| CELL TYPES | G1 | S | G2 | M | TOTAL | SOURCE |
|-------------------------------|------|------|------|------|-------|------------|
| Onion roots | 1.5 | 6.5 | 2.4 | 2.3 | 12.7 | Van't Hoff |
| Mouse fibroblasts | 9.1 | 9.9 | 2.2 | 0.7 | 22.0 | John Lewis |
| <i>Xenopus</i> early gastrula | 3.5 | 4.5 | 8.0 | 0.5 | 16.5 | John Lewis |
| <i>Xenopus</i> late gastrula | 2.0 | 2.0 | 3.5 | 0.5 | 8.0 | John Lewis |
| <i>Saccharomyces</i> | 0.45 | 0.45 | 0.45 | 0.15 | 1.5 | Fante |
| <i>Schizosaccharomyces</i> | 0.26 | 0.24 | 1.85 | 0.16 | 2.5 | Fante |

include only S (DNA synthetic) and M (mitosis, nuclear division) phases. Feeding labeled nucleotides, which are then incorporated into the DNA, can identify the S phase. The fraction of the cells doing so, the *labeling index*, can be determined. From the fraction of cells undergoing mitosis in a tissue, the *mitotic index* is derived. The cell division is an extremely complex process, involving the cooperation of a very large fraction of all the genes and affecting the expression of many others. Cell division requires the presence of several *protein kinases* (phosphorylases), *phosphatases*, and other activating proteins such as *cyclins*. The cyclins were named so because they are synthesized during the cycles of mitoses but not much is made during the intervening (interphase) periods. In fission yeast, gene CDC2 (cell division cycle) is involved in the control through its 34 kDa phosphoprotein product (p34^{cdc2}) that is a serine/threonine kinase, activated by cyclins, and the complex becomes a cyclin-dependent protein kinase (CDK). The cyclin-dependent protein kinase associated with cyclin B is also called MPF (*maturation protein factor*). In the phosphorylation, a cyclic-AMP-dependent protein kinase (cAPK) also has a role. MPF-dependent activation of cAMP-protein kinase A (PKA) and degradation of cyclin are required for the passage from mitosis into interphase. There are a large number (over 70) of CD genes. The CDC2 homolog in budding yeast is CDC28. Most of these genes have been well preserved during eukaryotic evolution and homologs are present in yeasts, in animals, and higher plants. There are several different cyclins. The G1 cyclins are cyclin C and a number of different cyclin Ds and cyclin A which when bound to the CDK protein(s) control the onset of the S phase. The mitotic cyclin (cyclin B, encoded by CDC13 in fission yeast) binds to CDK before the onset of mitosis. MYC in cooperation with RAS mediates, also, the progression of the cell cycle from G1 to the S phase through induction of the accumulation of active cyclin-dependent kinase and transcription factor E2F. Actually, similar genes and functions occur in all eukaryotes but they are named differently. CLN and numbers denote the cyclin homolog genes in budding yeast. Remember that in fission yeast usually the genes are symbolized with lower case letters, and + or – superscripts depending on whether wild type (+) or mutant genes (–) are represented. In budding yeast, the wild type allele is capitalized and the mutant is in lower case. In both yeasts the genes are italicized whereas the protein symbols are not. Upon the binding of CDC and cyclin, the conformation of the former is altered allowing the phosphorylation of the threonine at position 161 of CDC2 and the complex becomes a fully active promoter of mitosis. The Thr 161

phosphorylation is mediated by a CDK (cyclin-dependent kinase), called also CAK (CDK-activating kinase). cAPK is autophosphorylated at a Thr197 residue. Cyclin binding is also followed by dephosphorylation of the tyrosine 15 residue by phosphatases. Before the cell can enter the M phase in the majority of organisms, phosphorylation of this protein decreases. In fission yeast other proteins (encoded by genes *wee1*, *nim1*, *mik1*) exert negative control over the passage into the M phase. Eventually, CDC2 protein is dephosphorylated (gene CDC25 regulates a phosphatase activity) and cyclin is degraded making the CDC2 monomers available for another round of association with newly synthesized cyclins. If the DNA is damaged, the CHK1 kinase is activated and that prevents the exit from the G2 phase into the M phase. The MAPKK mitogen-activated serine/threonine kinase is also required for the G2→M transition. The degradation of the cyclins is mediated by ubiquitin-dependent proteolytic cleavage pathways also controlled by MPF. Genes that block entry into the M phase regulate exit from the M phase. The product of gene *suc1*, p13^{Suc1} may be required (among other proteins) for the termination of mitosis (see Fig. C44).

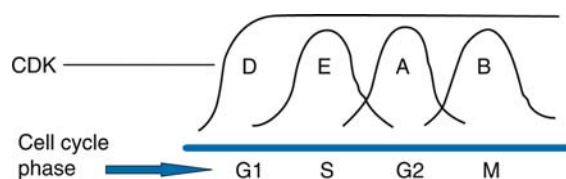


Figure C44. Tumour growth factors checkpoints, genes *wee1* in yeast, *ATM* in animals. In the various phases of the cell, cyclin-dependent kinases (CDKD, CDKE, CDKA, and CDKB) reach their peak activity and at the same time other proteins (promoters and inhibitors) are also changing and balancing each other's effect on the progression of the cell cycle. The diagram shows only the cyclin activities in relation to the mitotic phases and tumor formation checkpoint.

If S phase takes place but mitosis is not completed, endopolyploidy may result, i.e., the chromosome number is multiplied (polyploidy). By this time the organellar material (plastids, mitochondria) are also readied for fission. There are some differences in the cell cycles of yeasts and other fungi from higher eukaryotes. In the former group, the nuclear envelope is present throughout the cell cycle, whereas in the latter it disappears from view from metaphase through telophase and is reformed after late telophase (see Fig. C45). In fission yeast, the cell division resembles that of higher eukaryotes by forming a cell plate in between the two daughter nuclei. In budding

yeast, one of the daughter nuclei moves into an extrusion of the cell, a bud, and eventually grows into a normal size cell. In fungi, the spindle apparatus is located inside the nucleus rather than in the cytoplasm as in higher eukaryotes. These processes require, in addition, other regulatory mechanisms. It must be assured that DNA replication (S phase) produces complete sets of all essential genes and preferably *not* in multiple copies unless such amplification is required. In the regulation of the cells' cycle ubiquitin appears to have an important role. Three yeast proteins CD16, CD23 and CD27 (or their homologs in other organisms) mediate the attachment of ubiquitin to cyclin, resulting in its degradation at the end of mitosis.

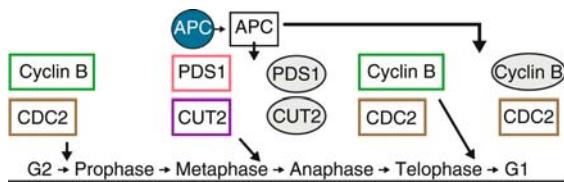


Figure C45. Proteolytic controls during the progression of mitosis. The heavy lines indicate activation, the gray lines stand for blocking the transition. The symbols in gray indicate lack of activity and the gray circle stand for degradation. CDC2 = cell division cycle protein 2, PDS and CUT are non-cyclin proteins, APC = anaphase promoting complex.

The initiation of a new cycle is hampered until an inhibitor (p27) is removed from the cyclin-CDK complex. This inhibitor is degraded by ubiquitin, placed on the proteins of the spindle by CD16, before a new S cycle is entered.

As the anaphase initiates the cell cycle becomes irreversible and as the cohesion between sister-chromatids breaks down the spindle fibers pull the new chromosomes (they were until now called chromatids) toward the poles. This process is mediated by the anaphase-promoting protein complex (APC/NR/TSG24), also called *cyclosome*. APC

is an ubiquitin-protein ligase that apparently manages that the chromosome would be properly arraigned in the metaphase plane and other proteins also would be functional. After entering mitosis, CDKs activate the APC complex and it remains active as long G1 phase substrates are available. After degradation of the ubiquitin-conjugating protein E2 (UbcH10), cyclin A stabilizes again and a new cell cycle can restart (Rape M, Kirschner MW 2004 Nature [Lond] 432:588) as CDH1/HCT1 activate APC. Anaphase entry and Mitosis exit are promoted by APC-dependent proteolysis of cell cycle proteins. Thus an oscillatory mechanism alternates between the start and stop of the cycle. CDC20 promotes the degradation of the early-acting proteins and HCT1 assists the degradation of Clb2 type cyclins (see Fig. C46).

The M phase cyclins are now lysed by the 26S proteasome after the telophase is completed. Other protein factors, which are no longer needed, are also ubiquitinated. APC operates through the proteolytic pathway (shown in the diagram). Another proteolytic pathway during the cell cycle is mediated through protein CDC34 ▶ CDC34

The p34^{cdc2} and homologous proteins in cooperation with other factors (MPF) mediate the condensation of chromosomes through activation of H1 histone and control lamins to mediate the breakdown of the nuclear envelope (except in yeast). MPF controls tubulins and actins for the function of the mitotic spindle, etc. The cell cycle is intimately associated with signal transduction pathways, DNA topoisomerases, DNA polymerase, DNA ligase, RNA polymerases, transcription factors, etc. After all these events are successfully passed, the cell divides into two daughter cells and the cycle may be resumed depending also on environmental conditions. Aphidicolin blocks DNA synthesis, hydroxyurea interferes with the formation of DNA nucleotides and therefore DNA synthesis is halted. In case, along with hydroxyurea, caffeine is added an abortive DNA replication and mitosis results in cell death. Some of the mutations involving defective DNA repair inhibit

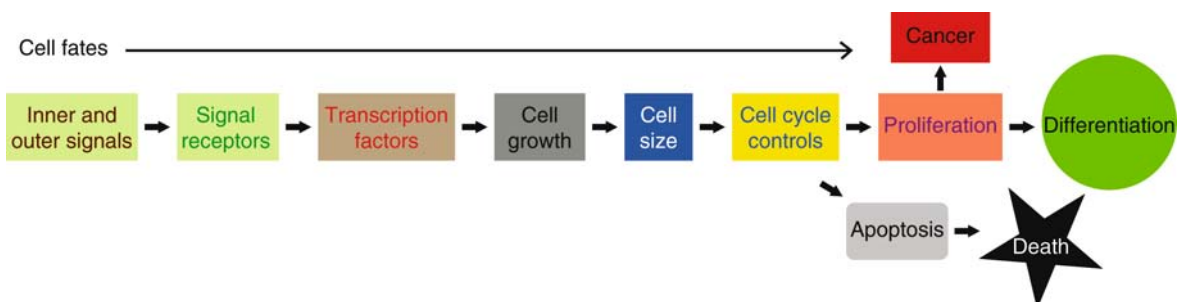


Figure C46. Cell fates

cell cycle and cell divisions. The various growth factors are all directly or indirectly involved with the cell cycle. The p53, p16, p21 proteins are regulators of the cell cycle and some of their mutations no longer control the pace of orderly cell divisions and are thus instrumental in tumorigenesis. Breakdown of some cell cycle signals causes failures in attachment of the spindle fibers to the kinetochore resulting in nondisjunction and aneuploidy. An overview of events leading to the overall fate of cells through the cell cycle can be represented below. A genome-wide analysis of the human cell cycle, cell size, and proliferation by targeting >95% of the protein-coding genes in the human genome using small interfering RNAs (siRNAs) showed that depletion of 1,152 genes strongly affected cell-cycle progression (Mukherji M et al 2006 Proc Natl Acad Sci USA 103:14819).

Meiosis has similar controls but the modulations are different. The primary oocyte is at an arrested G2 stage until a hormonal stimulation pushes the process to the first meiotic phase (reduction division) resulting in the formation of the first polar body in animals. In plants, this is the stage of the megaspore dyad. In mammalian oocytes, the diplotene stage (called dictyotene) may then last from early embryonic development (about 3rd month in humans) to puberty. This is followed by the formation of the second polar body and the egg. In plants, from the four products of the “female” meiosis only one megaspore (most commonly the basal one) remains functional, and unlike in animals, undergoes 3 more divisions to eventually form the egg.

Upon fertilization of the interphase egg, diploidy is restored, and cleavage divisions follow. The cell cycle has central importance for various processes of differentiation (Lee LA, Orr-Weaver TL 2003 Annu Rev Genet 37:545). The p21 protein regulates CDKs and combined with PCNA controls DNA replication. p21 also blocks keratinocyte differentiation. The CAK subunit of TFIIH transcription factor is involved with RNA polymerase II preinitiation complex. Cyclins regulate also tumor suppressor gene RB (retinoblastoma) and MyoD muscle differentiation factor. RB binds to the E2F family of cell cycle transcription factors and the RB-E2F complex blocks transcriptional activation by recruiting histone deacetylase (HDAC). The HDAC-SWI/SNF nucleosome-remodeling complex inhibits the cyclin E and A genes and arrests the cell cycle at the G1 phase and prevents the exit from the G1 phase. The RB-SWI/SNF complex regulates the exit from the S phase. BRG and BRM may assist RB in incapacitating E2F. In the human cell cycle, oligonucleotide array analysis detected the involvement of about 700 genes. More than 1,000 genes appear to control

the cell cycle in plants. The cell cycle in prokaryotes is also a highly organized process although they lack mitosis. In the enteric bacterium *Caulobacter*, about 19% of the 553 genes display cell cycle regulated expression. The participating proteins show fixed topology (Ryan KR, Shapiro L 2003 Annu Rev Biochem 72:367). The *Caulobacter* cell cycle proceeds through an elaborate circuitry of genes/proteins (Biondi EG et al 2006 Nature [Lond] 444:899).
 ▶mitosis, ▶meiosis, ▶cell division, ▶SCF, ▶CDC, ▶Chk, ▶PIN1, ▶CDK, ▶Cds, ▶CKI, ▶endomitosis, ▶cdc 14, ▶CDC25, ▶CDC27 cyclin, ▶CDC28, ▶CDK, ▶MCM, ▶CAK, ▶p21, ▶p15^{INK4B}, ▶p16^{INK4B}, ▶PCNA, ▶ubiquitin, ▶IFR, ▶HiNF, ▶licensing factor, ▶MCH, ▶SKP1, ▶MBF, ▶SBF, ▶apoptosis, ▶gametogenesis, ▶amplification, ▶polyteny, ▶polyploidy growth factors, ▶tumor suppressor gene, ▶senescence, ▶regulation of gene activity, ▶asparagine synthetase, ▶ataxia telangiectasia, ▶proteasomes, ▶apoptosis, ▶substrate ordering, ▶cancer, ▶differentiation, ▶replication, ▶Pds, ▶Ase1, ▶MYC, ▶RAS, ▶cullin, ▶APC, ▶SCF, ▶ORC, ▶transcription factors, ▶MyoD, ▶keratin, ▶retinoblastoma, ▶PCNA, ▶PIK, ▶CDF, ▶mitogen-activated protein kinase, ▶signal transduction, ▶RB, ▶histone deacetylase, ▶SWI/SNF, ▶E2F1, ▶BRG; Cho RJ et al 2001 Nature Genet 27:48; Israels ED Israels LG 2001 Stem Cells 19:88; Simon I et al 2001 Cell 106:697; Groisman I et al 2002 Cell 109:473; Vandepoele K et al 2002 Plant Cell 14:903; APC and SCF controls: Vodermaier HC 2004 Current Biol 14:R787; cell cycle controls in budding and fission yeast: Bähler J 2005 Annu Rev Genet 39:69; cell cycle and cell size control by RNAi: Björklund M et al 2006 Nature [Lond] 439:1009; <http://www.nature.com/celldivision>; <http://genome-www.stanford.edu/cellcycle/>; <http://cellcycle-www.stanford.edu/>; cell cycle regulation – cancer: <http://cyclonet.biouml.org>.

Cell Division: In eukaryotes involving two steps, nuclear division (karyokinesis) is followed by division of the rest of the cell (cytokinesis) (see Fig. C47). The cell cycle is a process of cycling as shown in the diagram, rather than as frequently depicted as a circle. A summary of the end results of the cell cycle is doubling of the chromatids as a consequence of the DNA replication during the S phase and changes in the C values of the nuclei. The estimated number of cell divisions in the germline of human males before puberty is ~30, whereas in the females it is ~22.
 ▶cell cycle, ▶mitosis, ▶cytokinesis, ▶partitioning, ▶for bacterial cell division; Rothfield L et al 1999 Annu Rev Genet 33:423; Nanninga N 2001 Microbiol Mol Biol Rev 65:319; Scholey JM et al 2003 Nature [Lond] 422:746 microarray data relevant to mitosis

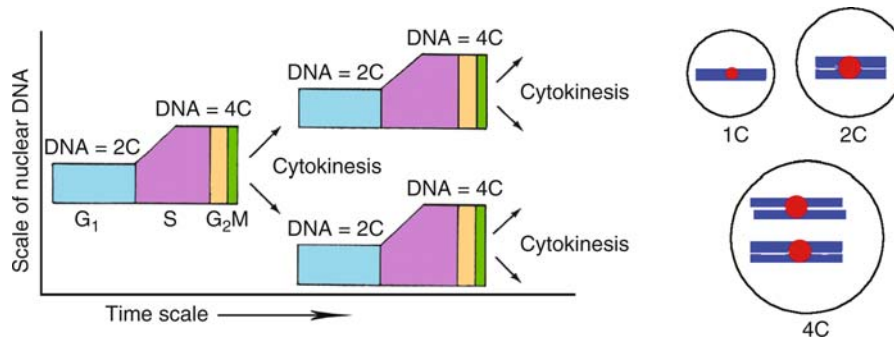


Figure C47. The relation between the nuclear cycles and cell divisions. During S phase the amount of DNA doubles and each 1 C chromosome will have 2 C amounts (2 chromatids), and a diploid cell will have a total of 4 C amounts of DNA before mitosis takes place and then cell division (cytokinesis) ensues.

meiosis and gametogenesis: <http://www.germonline.org/>.

Cell Fate: The program that determines the morphology and function of the undifferentiated cells in the embryo. ► [morphogenesis](#), ► [cue](#), ► [fate map](#)

Cell Fractionation: Separation of the different subcellular organelles, generally by differential centrifugation, in variable density media. ► [density gradient centrifugation](#), ► [centrifuge](#)

Cell Fusion: Cell fusion is involved in many cellular processes such as phagocytosis, cell migration, axon growth, and synaptogenesis (see Fig. C48). Influenza virus hemagglutinin and HIV1 envelope protein (both class I viral fusion proteins) contain an inner hydrophobic fusion-peptide that requires proteolytic cleavage before insertion into the target membrane. Intracellular vesicles fuse with the aid of α -helical structures upon recognition by Rab GTPases and SNARE effectors. For the formation of muscle fibers, mononucleated myoblasts fuse with the aid of several proteins. During mammalian fertilization a sperm penetrates the outer layer, the zona pellucida of the egg. That is followed by secretion of lysosome-like

enzymes of the acrosome. Then the sperm enters the previtelline layer and the sperm and egg plasma membranes fuse. Although several proteins participate in this process only a tetraspanin, CD9, has played a critical role in the fusion. In the mammalian placenta, fused trophoblasts separate the maternal and fetal tissues. Macrophage fusing generates multinucleated osteoclasts and giant cells. The former ones have a role in bone resorption and the latter, in immune response. Hematopoietic stem cells can fuse with cardiac myocytes, hepatocytes, Purkinje cells and can differentiate in different ways. The formation of hybridomas is based on cell fusion. Somatic gene therapy requires cell fusion. Several different proteins have been implicated in these fusions (Chen EH, Olson EN 2005 Science 308:369).

Somatic cell fusion is also a means to generate somatic cell hybrids. In contrast to hybridization by gametic fusion when the two nuclei fuse but usually only the maternal cytoplasm is preserved, in the fusion of somatic cells the entire content of the cells is combined in the somatic hybrid. For the fusion to take place, polyethylene glycol, a high concentration of calcium or higher pH medium has been used.

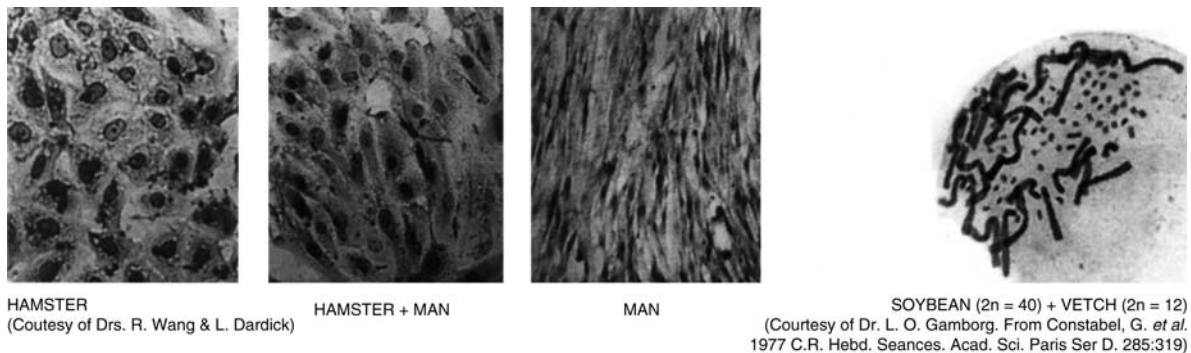


Figure C48. Cell fusion

(Inactivated Sendai virus addition also promotes the fusion of animal cells.) Carbon-fiber ultra-microelectrodes may make possible the fusion of selected cells or cells and liposomes. For the selective isolation of somatic cell hybrids both of the two types of cells generally carry recessive mutations that interfere with the survival of the cells on basic media. For example, thymidine kinase-deficient animal cells die because they cannot synthesize thymidylic acid (DNA); hypoxanthine–guanine phosphoribosyl transferase deficient cells cannot make purine nucleotides (DNA). The fused cells being heterozygous are functional at non-allelic loci, and can selectively be isolated in large cell populations. Somatic cell fusion made important contributions to genetics involving human and other animals because it made possible to carry out allelism tests, facilitated the assignment of genes to chromosomes, identified the functional significance of chromosomal regions (in case of deletions). Somatic cells of very distantly related or entirely unrelated organisms, e.g., chicken and yeast, tobacco and humans, human and rodent cells all can be fused although their further division may not usually be possible. Cell fusion has an important role in fertilization and many developmental events under normal conditions (Shemer G et al 2004 *Current Biol* 14:1587). ▶phagocytosis, ▶synaptic vessels, ▶somatic cell hybrids, ▶fusion of somatic cell [photo], ▶protoplast fusion, ▶microfusion, ▶liposomes, ▶radiation hybrids; see terms used under separate entries; Cocking EC 1972 *Annu Rev Plant Physiol* 23:29; Ephrussi B 1972 *Hybridization of Somatic Cells*, Princeton Univ. Press, Princeton, NJ; Hotchkiss RD, Gabor MH 1980 *Proc Natl Acad Sci USA* 77:3553; McKay R 2002 *Nature Biotechnol* 20:426.

Cell Genetics: Nearly all genetics is cell genetics because geneticists generally think at the cellular level; in the narrow sense this term is applied to the genetic manipulations with isolated cells of multicellular organisms. ▶cell fusion, ▶somatic cell hybrids, ▶fusion of somatic cells, ▶mitotic crossing over, ▶transformation, ▶nuclear transplantation; FL-REX; Ruddle FH, Creagan RP 1975 *Annu Rev Genet* 9:407; Puck, 1974 *Stadler Symp* 6:47; Dudits D et al eds. 1976 *Cell Genetics of Higher Plants*. Akad Kiadó, Budapest.

Cell Growth: In any particular time $N = 2^g N_0$ where N is the final cell number, N_0 = the initial number of cells, and g = the time required for a complete cell cycle. This equation is valid as long there is no limitation on multiplication by nutrients, air, differentiation pattern, etc. In the absence of any limitation, cell growth indicates the cell-doubling process. In fact, as in the above statement, growth is frequently used in place of

cell proliferation. Growth really is an increase in volume or size and not in cell number. ▶proliferation, ▶turbidity, ▶plating efficiency, ▶growth retardation

Cell Hybridization: Fusion of somatic cells. ▶cell fusion, ▶cell genetics

Cell Interaction: The influence of cells on each other during differentiation and development. ▶contact inhibition, ▶nurse cells, ▶morphogenesis, ▶maternal effect genes

Cell Junction: The area involved in the connection and communication between and among cells and extracellular matrices. ▶extracellular matrix, ▶morphogenesis, ▶contact inhibition, ▶transmembrane proteins; Tepass U et al 2001 *Annu Rev Genet* 35:747.

Cell Lethal: Mutations may not be isolated or ascertained because of the cells involved cannot live.

Cell Line: A (homogeneous) population of cells (of eukaryotes) that can be maintained in live (growing) conditions. ▶clone, ▶clonal analysis

Cell Lineages: The traces of the path of growth (multiplication) of the cells through several cell divisions (see Fig. C49). The descent of the germline cells or the signs of visible mutations in the somatic tissues is shown by the pattern of the sectors formed in chimeric organisms. In *Caenorhabditis*, the cell lineage development can be detected by automated time-lapse confocal microscopy in 31 planes at 1 μm apart at a resolution of every minute. The SRARRY-NIGHT computer software aids in identification of the lineage from 4 to a 350-cell stage. This is a relatively simple organism where the embryo development from 1–558 cells is completed in 13 h (Bao Z et al 2006 *Proc Natl Acad Sci USA* 103:2707). ▶clonal analysis, ▶fate maps, ▶nondisjunction, ▶phyllotaxis, ▶founder cells, ▶*Caenorhabditis*; Stern CD, Fraser SE 2001 *Nature Cell Biol* 3:E216; Liu YJ 2001 *Cell* 106:259.

Cell Membranes: Membranes surround all cells and inside the cells there are membrane-enclosed bodies (nucleus, mitochondria, plastids, vacuoles, Golgi bodies, dictyosomes, lysosomes, peroxisome). The endoplasmic reticulum, the mitochondrial crests, and thylakoids are all membranous structures. Cellular imports and exports pass through the membranes by active and passive mechanisms (see Fig. C50). The bulk of the plasma membranes consist of proteins and lipids (phospholipids, cholesterol, other sterols and glycolipids, triacylglycerols, steryl esters, etc.). The composition varies in the different organisms and according to the particular membranes. The

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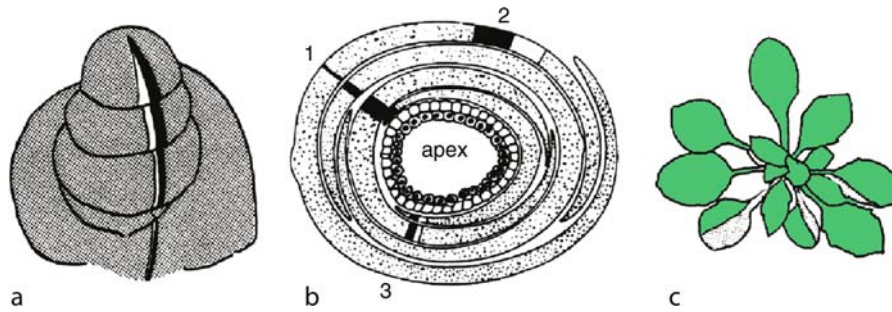


Figure C49. Cell lineages. Mutation, deletion, nondisjunction during embryogenesis may potentially be identified during and after embryogenesis if the organism is heterozygous for a distinguishable somatic marker(s). (a) Organization of the apical dome of a wheat plant showing diagrammatically the consequence of nondisjunction. (b) In the monocot apex the leaf initials wrap around the central axis and overlap each other; the humps at the leaves indicate the midribs. The oldest leaf initials are outside. Note that the outmost leaf and the one next below it have their midrib at opposite sides. Sector 1 is very narrow at the surface (old) leaf and it becomes wider in the (younger) ones below. Also, the oldest sector is left from the midrib of the first leaf but it is at the right side of the one just below and again at the left side in the third. Sector (2) representing nondisjunction and twin sectors (black and white) occurred only in one leaf because of a tangential event in a region of the embryonal apex. Sector (3) is a late occurring nondisjunction indicated by the narrow twin sectors. (c) Somatic mutation in a single cell of the mature embryo of the dicot *Arabidopsis*. Three leaves displayed white sectors because they differentiated from the same cell line of the apex. Nonsectorial leaves appeared in-between the mutant sectors because of phyllotaxis

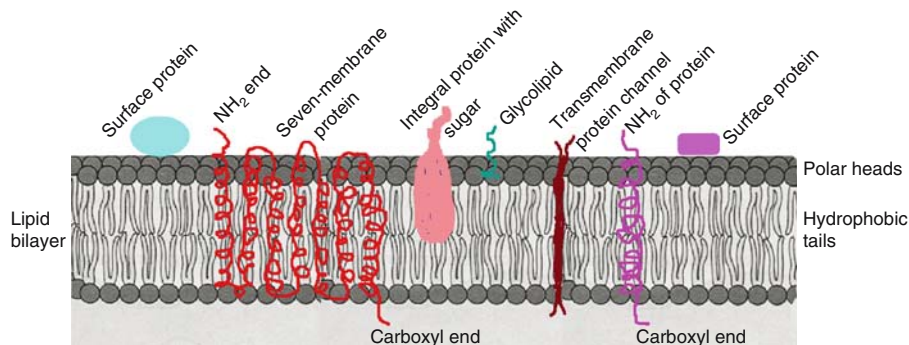


Figure C50. Cell membrane

ultra-structure of the various membranes has common features and specificities. The basic structural element is the lipid bilayer of about 5 to 8 nm in thickness. In the double structure the polar head of the lipid face the aqueous environment and the tails inward are hydrophobic.

Unsaturated lipids are concentrated in the inner layer of the structure. The outer surface of the membrane is also different from the inner surface that envelops organelles or vesicles.

The inner side carries on the surface-charged groups, the outward surface may have a variety of peripheral proteins (glycoproteins) that determine the surface antigenicity of the cells. Some other proteins are integral parts of the membrane sunken in the fluid lipid bilayer. The fluidity is somewhat stabilized

by the presence of sterols. The so-called “seven membrane proteins” traverse the lipid bilayer and form within it a cluster of seven folds, the amino end at the outside and the carboxyl end inward. Other transbilayer polypeptides have hydrophilic domains both outside and inside, and outward are ports for communication (ion channels) with special proteins and lipids (transporters, permeases). Some of the peripheral proteins are attached to the membrane by electrostatic forces and H bonds. The proteins are regulators of membrane bound enzymes (e.g., phospholipase C) and mediate signal transduction. Membranes have a flexible structure to curl up into vesicles that ferry within the cell lipids and proteins in a protected manner. The membranes have the ability to fuse with another membrane at the delivery target.

Exocytosis and endocytosis are the means of traffic. Fusion of the egg with the sperm, fusion between protoplasts of plant cells, somatic cell hybridization, protein synthesis within the endoplasmic reticulum, etc., are mediated by membrane functions. Membranes can be targeted through labeled myristoylated and palmitoylated proteins. Such modifications of the membranes may affect the membrane attached G proteins, involved in signal transduction. Ca^{2+} -regulated exocytosis repairs damaged plasma membranes. (See diagram, ►cell structure, ►fatty acids, ►myristic acids, ►lipids, ►prenylation, ►raft; Reddy A et al 2001 Cell 106:157; Maxfield FR 2002 Current Opin Cell Biol 14:483; Veréb G et al 2003 Proc Natl Acad Sci USA 100:8053; Chernomordik LV, Kozlov MM 2003 Annu Rev Biochem 72:175; newer concepts of membrane structure and function in 2005: Nature [Lond] 438:577–621).

Cell Memory: The properties of differentiated cells that they reproduce through numerous cell divisions are similar specialized cells to what they have been committed. ►differentiation, ►morphogenesis, ►memory immunological; Anfossi N et al 2001 Immunol Rev 181:269.

Cell Migration: Common during animal development. Precursors of the blood cells, the germ cells, neurons, cells of the somites, metastasis, immune surveillance, etc., move through the embryo and are guided by cell surface receptor proteins and aided by the extracellular matrix of fibronectin whereas chondroitin sulfate proteoglycan interferes with the movement. The Kit protein in the membrane of the migrating cells and the ligand Steel factor produced by the cells, which are contacted by the migrant also control the movement. During oogenesis in *Drosophila*, EGF receptor signals passed through a TGF- α -like ligand as a guidance cue. Gastrulation requires cell movement of mesodermal cells through the fibronectin-rich matrix in the blastocoele. Contraction of actin and myosin is aided by changes in focal adhesion (Gupton SL, Waterman-Storer CM 2006 Cell 125:1361). CDC42 stimulates actin polymerization in the forward direction of filopodia and Rac aids the formation of lamellipodia. For cell migration in vertebrates, lysophospholipids are important. The Dock2 proteins regulate lymphocyte migration. ►proteoglycan, ►chondroitin sulfate, ►Steel factor, ►EGF, ►TGF, ►KIT oncogene, ►fibronectin, ►tenascin, ►integrin, ►FAK, ►CDC42, ►Rac, ►filopodium, ►lamellipodium, ►microtubules, ►metastasis, ►actin, ►sphingolipids, ►extracellular matrix; Lauffenburger D et al 1996 Cell 84:359; Fukui Y et al 2001 Nature [Lond] 412:826; Ridley AJ et al 2003 Science 302:1704.

Cell Model: Within large groups of the prokaryotic, animal and plant kingdom the cells have some common essential features. Nevertheless, each cell type of the body has special signaling systems and receptors. Special regulatory networks process the signals. The common functional networks determine cell-specific combinations of cellular machines and are responsible for the observed phenotypes and behavior. The complex animal cells contain an estimated $\sim 100,000$ components (protein, lipid, sugar ion, nucleotide) and each interacts with several others creating an almost incomprehensible complexity. To overcome these difficulties a silico system may be employed to study binary interactions and graph theory applied for the analysis. The final goal is to generate predictive models by relying on all the biological, molecular, mathematical tools. ►networks, ►genetic networks, ►signal transduction, ►graph theory; Ma'ayan A et al 2005 Annu Rev Biophys Biomol Struct 34:319.

Cell Numbers: Cell numbers in: a small *Arabidopsis* plant, about 5×10^6 ; in an *Arabidopsis* seed, about 6,000–7,000; in a wheat embryo, 10 days after fertilization, about 40,000, and 150,000 at maturity (including the scutellum); at the surface of a maize endosperm, about 1,400; in the human body, about 6×10^{15} per 60 kg weight (ca. 1 billion per gram tissue) are found (Robert DeMars, personal comm.) The number of cells in a tissue depends on cell division, cell death, and possibly on migration (in animals). The number of cells per particular structure is affected also by cell size. The local number of cells may be controlled by the tissue environment or extrinsic factors. The number of cells depends primarily on the cell divisional cycles, controlled by a large number of hormones and other proteins. Protein p27 in mouse appears to be a potent inhibitor of the growth of the cell number and cell size by controlling cyclin and cyclin-dependent protein kinases. In diploids the body size apparently depends on cell number rather than size (Trump A et al 2001 Nature [Lond] 414:768) but in polyploids the size of the cells is larger. ►cell cycle

Cell Plate: The precursor of a new cell wall in dividing plant cells. ►cytokinesis; Verma DPS 2001 Annu Rev Plant Physiol Plant Mol Biol 52:751.

Cell Receptors: ►receptors, ►transmembrane proteins, ►signal transduction

Cell Sap: The fluid, non-particulate cell content.

Cell Selection: Each cell of a multicellular organism is expected to have the same array of genes. Polyploidy, deletion, aneuploidy and epigenetic alterations, and

other extrinsic factors may bring about differences in the same cell lineage and can generate competition. (See Khare A, Shauly G 2006 Nature Rev Genet 7:577).

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Cell Sizes: Cell sizes vary a great deal depending on organisms and function. An *E. coli* cell is about $800 \times 2,000 \text{ nm}^2$. Plant and animal cells generally have a diameter of 20 to 60 μm and their length is much more variable. Some fibrous cells may be 20 cm long. Important regulators of cell size are the S6 kinase, PI3-kinase, and the Akt proteins. The upstream binding factor (UBF1) controls the activity of rRNA synthesis. In yeast cells, several regulatory proteins control ribosome biosynthesis and cell size in response to nutritional cues (Jorgensen P et al 2004 Genes Dev 18:2491). In animal cells, the insulin-like growth factor I/insulin receptor substrate I control about 50% of the growth of cell size in culture (Drakas R et al 2004 Proc Natl Acad Sci USA 101:9272). In budding yeast the gene *WHI3* increases the cell size whereas increasing the number of copies of *CLN3* decreases the cell volume. ▶ [S6 kinase](#), ▶ [cell number](#); Conlon IJ et al 2001 Nature Cell Biol 3:918.

Cell Sorter: Cells can be labeled by cognate antibodies coupled with a fluorochrome or by other incorporated material. In a mixture where only one in a few thousands of cells carries this distinctive label, the latter ones can be separated using an electronic device. When a file of cells passes in front of a laser beam the fluorescent cells receive a different electric charge from the unstained ones. The high intensity electric field in the path then separates the positively charged fluorescing cells from the negatively charged (unstained) ones. ▶ [labeling index](#), ▶ [dielectrophoresis](#), ▶ [cell cycle](#), ▶ [fluorochromes](#), ▶ [antibody](#), ▶ [laser](#), ▶ [segregation distorter](#), ▶ [sex](#), ▶ [selection](#); Asai J et al 1999 Clin Neurol Neurosurg 101:229.

Cell, Stem: The stem cells of animals are capable of differentiation into various types of cells. ▶ [stem cells](#)

Cell Strain: Animal cell culture obtained directly or recently from an organism. It usually has a limited, usually less than 50, generation lifespan. These cultures are not immortalized. ▶ [immortalization](#)

Cell Structure: Living cells are very complex and are crowded by a variety of small molecules and large macromolecules, cytoskeletal filaments, and organelles. Membranes separate some of the structures, e.g., as seen in organelles, but other complexes also display microcompartmentation without separating by membranes. The function of molecules differs under crowded conditions as compared to sparse distribution that is encountered when the contents of

cells are extracted. Artificial, synthetic cell models are being generated for better study of the ongoing processes within cells, which are too complex (Long MS et al 2005 Proc Natl Acad Sci USA 102:5920). (See Fig. C51).

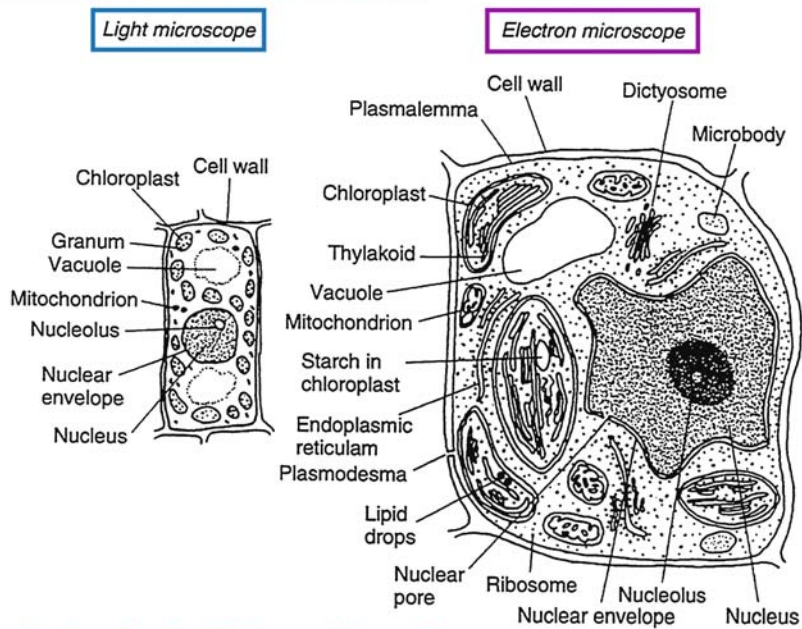
Cell Theory: Cell theory was proposed in the nineteenth century. It states that the cells are the elementary units of life, and they can be produced only from preexisting cells by mitosis (or meiosis). Abiogenetic reproduction of cells, assumed to exist in the seventeenth century, has not been shown yet to exist in the present geological period of the earth. ▶ [origin of life](#), ▶ [spontaneous generation](#)

Cell Therapy: Cell therapy refers to the transfer of specific cells to an organ in the body with the purpose of letting them propagate there and restore a defective function. The transplanted cells may cure diseases such as Duchenne muscular dystrophy, or replace degenerated retinal macula or dopaminergic neurons in Parkinson's disease or bone marrow cells to restore the hematopoietic system or Langerhans islets to fight diabetes, etc. Cell therapy may be part of a cancer treatment. Before radiation or chemotherapy, hematopoietic stem cells may be withdrawn, multiplied, and after the anticancer therapy, reintroduced into the body to restore the immune system. ▶ [gene therapy](#), ▶ [cancer gene therapy](#), ▶ [adoptive cellular therapy](#), ▶ [transplantation of organelles](#), ▶ [xeno-transplantation](#), ▶ [stem cells](#), ▶ [muscular dystrophy](#), ▶ [retinal dystrophy](#), ▶ [Parkinson's disease](#), ▶ [hematopoiesis](#), ▶ [diabetes](#); Strom T et al 2002 Curr Opin Immunol 14:601.

Cell Transformation Assays in Genetic Toxicology: Generally, hamster embryo cells or mouse prostate cells are exposed to chemicals and tumorigenicity is tested after introducing the cells into live animals (rodents). In vitro the transformed cell does not grow in monolayer as do normal cells, but rather forms a dense mass or colony on top of the monolayer. Also, the activation of c-oncogenes (AKR, adenovirus) by chemicals is investigated. ▶ [bioassays in genetic toxicology](#)

Cell Wall: Exists in bacteria, fungi, and plants; animal cells are surrounded only by a membrane. The wall is made of polysaccharides, proteins, and lipids in bacteria. In plants the wall is mainly cellulose (polysaccharide), but lignin, (a hard phenylalanine and tyrosine polymer), suberin (a corky wax), and cutin (a fatty acid polymer) also occur. In fungi the wall may also contain chitin, a linear polysaccharide differing from cellulose by a replacement at the C-2 OH group by an acetylated amino group. More than 1,000 gene products are involved in the synthesis of the plant cell wall and its components (Somerville C

Idealized plant cell viewed through



Idealized animal cell viewed through

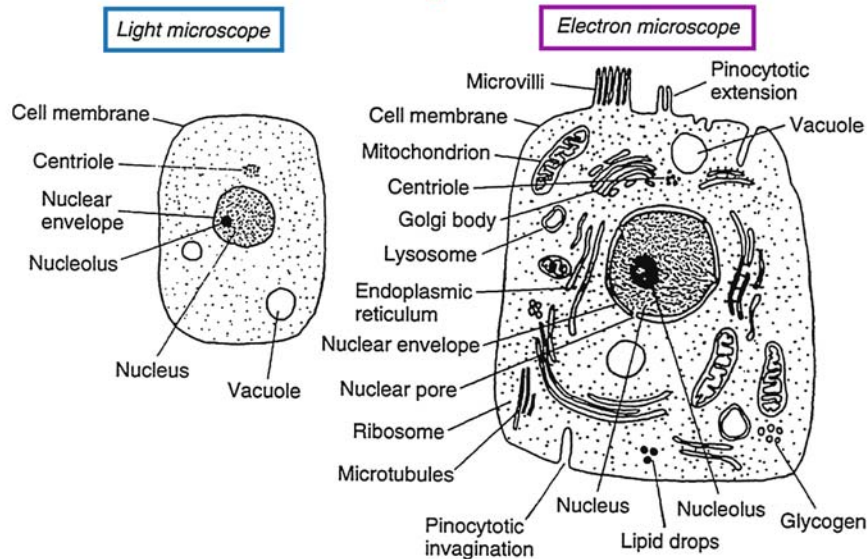


Figure C51. Cell structure. Generalized structure of plant and animal cells by light and electron microscopy. The diagrams do not show the cytoskeleton and various microtubules, filaments or transport vesicles

et al 2004 Science 306:2206). In the cell wall of grasses (1,3;1,4)- β -glucan occurs and it is synthesized by a cellulose synthase-like *CsIF* genes (Burton RA et al 2006 Science 311:1940). ►cell wall

Cell-Free Extract: Cell-free extract is prepared by grinding cells (tissues) in a buffer or other solutions and removal of insoluble particulate material by filtration or centrifugation. Such extracts may be used

for enzyme assays or for the purification of soluble cellular constituents.

Cell-Free Protein Synthesis: Refers to in vitro protein synthesis in the presence of ribosomes, mRNA, tRNA, aminoacylating enzymes, amino acids, and all the complex of translation factors and energy donor nucleotides. ►rabbit reticulocyte assay, ►wheat germ assay

Cell-Free Translation: ►cell-free protein synthesis

Cell-Mediated Immunity: ►immune system, ►T lymphocytes

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Cell-Mediated Mutagenesis: Chemical mutagen activation is provided by the addition of suitable activated (liver) cells as feeders to the culture. These feeder cells may be genetically modified to express high levels of the activating enzymes. ►activation of mutagens, ►host-mediated assay; Rudo K et al 1987 Cancer Res 47:5861; Langenbach R, Nesnow S 1983 Basic Life Sci 24:377.

Cell-Penetrating Peptides (CPPs): CPPs are 11–34 amino acid residues long and are extremely effective in entering cells. This ability includes, also, transport of various cargoes into the cell, and in some instances traversing even the blood-brain barrier. They are (transportan, penetratin, TAT, and MAP) of different length, cargo delivery, and different penetrating abilities (Hallbrink M et al 2001 Biochim Biophys Acta 1515:101). ►BBB, ►nuclear pore, ►CRM1; Zenklusen D, Stutz F 2001 FEBS Lett 498:150; Galouzi I-E, Steitz JA 2001 Science 294:1895.

Cellular Immunity: Cellular immunity is mediated by the T cells and macrophages. ►T cells, ►macrophage

Cellular Transmission of Tumors: Mediated by allografts, lesions, and biting. Thus, the transmissible agent is the tumor cell itself. ►Tasmanian devil, ►canine transmissible venereal tumor, ►cancer

Cellulase: An enzyme digesting cellulose. Generally, a collection of enzymes is used for removal of the cell wall and gaining plant protoplasts, such as the *Onozuka R-10*. ►protoplast, ►macerozyme, ►cellulose

Cellulose: A polysaccharide consisting of glucose subunits. It strengthens the plant cell wall and forms the plant vascular system. Cellulose is synthesized by cellulose synthase. By spinning disk confocal microscopy, its rate and path of deposition in functional association with microtubules could be revealed (Paredes AR et al 2006 Science 312:1491). ►cellulase, ►cell wall; Delmer DP 1999 Annu Rev Plant Physiol Plant Mol Biol 50:245.

Cellulosome: The macromolecular complex that degrades cellulose and associated polysaccharides (Shoma Y et al 1999 Trends Microbiol 7:275).

CEM15: ►APOBEC3G

CEN: the symbol of centromere DNA sequences. ►centromere

Cenancestor: The most recent common ancestor of two taxa. ►taxon

Cenozoic: A geological period dating back to 75 million years ago when mammals and humans appeared. ►geological time periods

CENP: A protein that is diffusely located in the cytoplasm during G2 and prophase. During prometaphase it associates with the kinetochore until metaphase. At anaphase, it is located in the midzone of the spindle and degraded after cytokinesis. ►cell cycle, ►mitosis, ►spindle, ►kinetochore; ►centromere proteins CENP-A, ►CENP-B, ►CENP-C; Fukagawa T et al 2001 Nucleic Acids Res 29L3796.

Censoring: A statistical concept. Censoring may be due to several different events, the trait cannot be classified because of time factors (too early or too late), use of medication conceals the phenotype, etc. In such cases the mean or the variance may be biased.

Centaurea cyanus: Called blue cornflower; its color is due to a complex of six molecules of anthocyanin and flavone complexed with one ferric, one magnesium and two calcium ions in a supermolecular complex (see Fig. C52) (Shino M et al 2005 Nature [Lond] 436:791). ►pyrrolizidine alkaloids



Figure C52. Centaurea

centiMcClintock: Used by some maize geneticist to indicate the length of a chromosome arm; 1 cMC = 1% of the length of a chromosome arm where a particular gene is situated.

Centimorgan: The unit of eukaryotic recombination; 1% meiotic recombination is one map unit (m.u.) = 1 centimorgan (cM) \approx 10 kb DNA in humans. ►recombination frequency, ►mapping genetic, ►mapping function, ►CentiRay

CentiRay (cR): A chromosomal span within which a break can be induced with 1% probability by a specified dose of X-radiation. 1 cR \approx 3×10^4 bp of DNA. ►radiation hybrid

Centisome: A quantitative unit of genomic sites.

Central Body (centrosome): ►centrosome

Central Core Disease (19q13.1): A nonprogressive muscle weakness; the core of the muscle fibers is generally absent. It is a complex disorder with usually ryanodine receptor defects. ►ryanodine

Central Dogma: The concept that the flow of genetic information follows the path DNA→RNA→Protein; it had to be slightly modified by the discovery of reverse transcriptases and ribozymes (see Fig. C53). ▶[ribozyme](#), ▶[reverse transcriptases](#); Crick FHC 1958 Symp Soc Exp Biol 12:138.

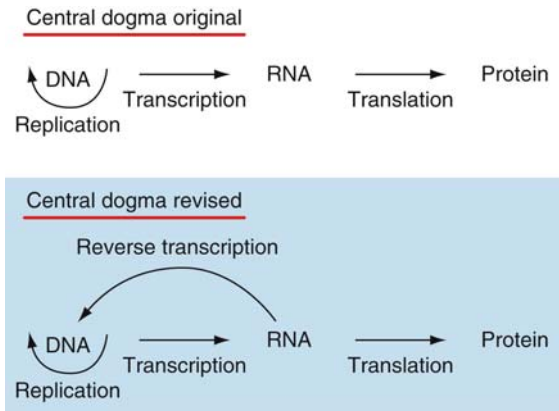


Figure C53. Central dogma

Central Limit Theorem: A variable large sample representing the sum of many components is expected to approach the normal distribution. This basic statistical principle has important implications also for genetics, when population samples and segregation data are evaluated. ▶[normal distribution](#); Klein EK et al 1999 Theor Popul Biol 55 [3]:235.

Central Nervous System: The brain and the spinal cord. ▶[brain human](#)

Central Tendency: A statistical index—such as the median, mean, and mode—of the typical or average distribution of some characteristics of a population. ▶[median](#), ▶[mean](#), ▶[mode](#)

Centric Fusion: The fusion of two telocentric chromosomes into a biarmed single chromosome. ▶[Robertsonian translocation](#), ▶[telocentric chromosome](#), ▶[acrocentric](#), ▶[misdivision](#)

Centric Shift: Changing the position of the centromere and thus the relative arm length of a chromosome by pericentric inversion or transposition. ▶[inversion](#), ▶[transposition](#), ▶[shift](#)

Centrifuge: An instrument for sedimenting or separation of material by centrifugal force according to density. Low-speed centrifuges generally spin the suspended material at less than 5,000–6,000 rpm (revolution per minute), table-top centrifuges usually reach a maximum speed of 10,000–12,000 rpm, high-speed

centrifuges may reach about 20,000 rpm and are usually refrigerated so biological material suffers minimal degradation. Ultracentrifuges, using refrigerated vacuum chambers, may reach much higher speeds and may exceed $300,000 \times g$ force and can separate even molecules. The conversion of revolution per minute into g force is generally done on the basis of tables provided by the manufacturers. The actual centrifugal force $F = \pi^2 S^2 M R / 900$ where $\pi = 3.14159$, S = revolutions per minute, M = the mass in grams and R is the radius in centimeters. It is more convenient to express it as $\times g$ force where $g = 980.665 \text{ cm/s}^2$. Thus, e.g., when the maximal rpm is 20,000, the relative centrifugal force (RCF) may be $41,320 \times g$, but this actually varies from the maximum at the bottom of the centrifuge tube to a lower value at the top, etc. ▶[ultracentrifuge](#), ▶[buoyant density centrifugation](#), ▶[density gradient centrifugation](#)

Centrin: Cellular motor of polar bodies, centrioles. ▶[spindle pole body](#), ▶[mitosis in unicellular protists](#), ▶[spasmoneme](#), ▶[CDC31](#); Middendorp S et al 1997 Proc Natl Acad Sci USA 94:9141; Salisbury JL et al 2002 Current Biol 12:1297.

Centriole: Hollow cylinders formed by nine microtubule triplets surrounded by a dense area in the centrosome. The two centrioles in each centrosome serve as the attachment point for the spindle fibers during nuclear divisions and along with the radial array of microtubules form the two *asters* in animal cells. Centrioles are essential for the formation of centrosomes, cilia and flagella, but are not essential for several aspects of *Drosophila* development (Basto R et al 2006 Cell 125:1375). RanGTP mediates this organization in association with the nucleotide exchange factor RCC1 and other proteins such as γ TurRC (γ -tubulin ring complex) and microtubule-associated protein. The nuclear mitotic apparatus protein (NuMA) is involved in the organization of asters and NuMA also interacts with importin- β , making a link between spindle assembly and nuclear import. ▶[centrosome](#), ▶[centromere](#), ▶[spindle fibers](#), ▶[Ran](#), ▶[RCC1](#); Wiese C et al 2001 Science 291:653; Marshall WF 2001 Curr Biol 11:487; Dammermann A et al 2004 Developmental Cell 7:815; centriole assembly path: Pelletier L et al 2006 Nature [Lond] 444:619.

Centromere: Region of the attachment of chromatids after chromosome replication and of spindle-fiber attachment at the kinetochore (localized within the centromere) during nuclear divisions. The centromere used to be called the primary constriction of the chromosomes because by the light microscopic techniques it frequently appears as a short slender

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region. (Secondary constrictions mark the juncture of the chromosomal satellites). In some organisms (*Juncaceae*, *Parascaris*, *Spirogyra*, *Scenedesmus*, etc.) the centromeres are “diffuse”, i.e., their position spreads over the length of the chromosome (holocentric, polycentric chromosome). Under some conditions “neo-centromeres” are visible, i.e., the spindle fibers may associate at more than one location within the chromosomes. The cloned centromeric region of yeast extends to a minimum of 150 bp. Although the base sequences in various centromeres of budding yeast are not identical, there is substantial homology. All contain a core (element II) of 83–84 bp that are 93–95% A = T. In addition, there are TCAC and TG identical stretches in flanking element I (11 bp) and on the other flank (element III, ~25 bp) there are GT and TG and T and CCGAA and TAAAA identical sequences that are separated by one to four different bases. The general structure of the yeast centromeres can be represented as shown below.

The regions of the centromere elements (CDEI [8 bp], II [78–86 bp] and III [25 bp]) are less susceptible to nuclease attack than the rest of the chromosomes and this seems to indicate that they are associated with different types of proteins. CDEIII is the site of the centromere-binding factor 3 (CBF3), essential for segregation of the chromosomes.

CDEI contains a nucleotide octamer, similar to the *octa* sequences present in the promoters of several genes where it binds a 39-kDa transcriptional activator protein (Cpflp/CP1/CBF1). The arrangement of these 3 elements is shown (see Fig. C54). Centromere-specific DNAs are not preserved among evolutionarily distant species. The centromeric structure is different in the various eukaryotes and the centromeric activity is epigenetically controlled (Morris CA, Moazed D 2007 Cell 128:647).

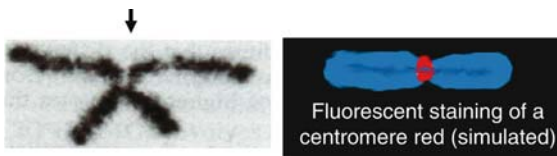


Figure C54. Centromere

A number of known proteins, with not entirely known functions, assure the formation of the centromere-kinetochore complex and the attachment of the spindle fiber. The localized centromeres—in contrast to the holocentric ones—may be either *point*

or *regional centromeres*. The point centromere contains about 250 bp, tightly packaged into a nuclease resistant structure and binds only a single microtubule. The point centromere may be arranged around a special nucleosome. Mammalian centromere function depends upon a specialized chromatin organization where distinct domains of CENP-A (centromere-binding protein) and dimethyl K4 histone H3, forming centric chromatin, are uniquely positioned on or near the surface of the chromosome. These distinct domains are embedded in pericentric heterochromatin (characterized by H3 methylated at K9). The mechanisms that underpin this complex spatial organization are unknown. An essential histone variant H2A.Z is a structural component of the centromere. Along linear chromatin fibers H2A.Z is distributed nonuniformly throughout heterochromatin, and centric chromatin where regions of nucleosomes containing H2A.Z and dimethylated K4 H3 are interspersed between subdomains of CENP-A (Greaves IK et al 2007 Proc Natl Acad Sci USA 104:525). The H2B and H4 histones may be altered and another highly variable protein, related to H-3 (Cse4), is present. Cse4 protein apparently interacts with centromere elements I and II, but not III. (Cse4 is an exclusively centromeric protein in *Saccharomyces* like the Cid [centromere identifier] in *Drosophila* or HCP-3 in *Caenorhabditis*). At the centromere a specific histone CenH3 replaces the regular H3 histone (see Fig. C55). The H3.3 histone replaces histones displaced by replication and it serves as a marker for transcribed regions (Henikoff S et al 2004 Trends Genet 20:320).

H-3-like histones are also present in the nucleosomes at the holocentric chromosomes of *Caenorhabditis*. The latter assists chromosome segregation. Point centromeres are found in yeasts (*Saccharomyces cerevisiae*, *Schizosaccharomyces uvarum*, *Kluyveromyces lactii*).

The regional centromeres may consist of several kilobases and may be quite polymorphic. Actually, the *Schizosaccharomyces pombe* centromere is more similar to the mammalian centromeres than to that of the budding yeast. The *S. pombe* centromeres vary between 40 and 100 kb and the core of 4–7 kb may be surrounded by direct and inverted repeats. There is a larger array of proteins associated with the regional centromeres. In the majority of higher organisms the centromere is surrounded by heterochromatin and apparently not transcribed. The budding yeast centromeric DNA (CEN) in chromosome 3 (CEN3) appears to contain an open reading frame capable of coding for a peptide of 52 amino acids. There is no

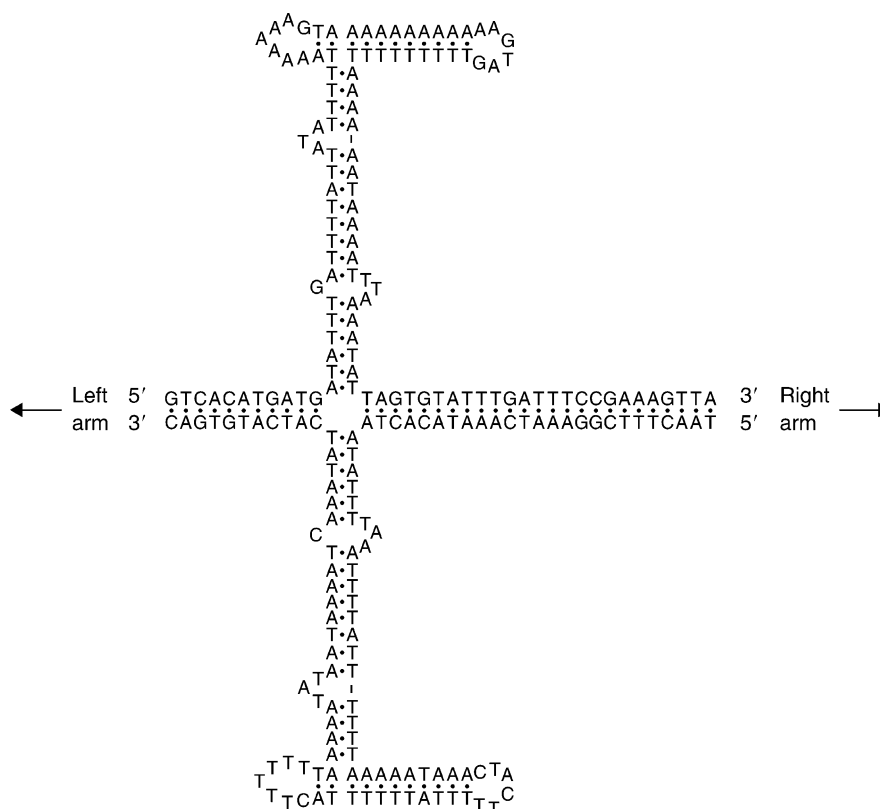


Figure C55. Centromere, structure. Nucleotide sequences of chromosome 3 centromeric region (627 bp) of yeast. (From Clark L et al 1981 Stadler Genet Symp 13:9)

evidence for transcription to take place, however, in the centromere. Actually, this heterochromatic region suppresses the expression of open reading frames even if they are transposed or inserted in this region, indicating that “silencing” may be essential for the proper function of the centromere in chromosome disjunction. This earlier view may require revision now because in the five centromeric regions of *Arabidopsis*, especially of centromeres 2 and 3, not just transcription but transcriptional hot spots were detected in both strands of the DNA. The transcribed tracts were transposons, retrotransposon-like sequences, but also unique DNA (Yamada K et al 2003 Science 302:842).

The centromeric Swi6p (yeast), HP1 (mammalian) proteins are repressors and *Drosophila* protein *Pc* (*Polycomb*) is a negative regulator of the *Bithorax* (*BXC*) and the *Antennapedia* (*ANTX*) complexes. In the *Drosophila* centromeric region, the 220 bp Bora Bora complex sequences, flanked either 5' or 3' by about a 200 bp “simple” sequence, have been identified. The former is believed to contribute to the kinetochore formation, the latter may control sister chromatid association. The centromeres of mammals display considerable variations and larger

number of proteins including centromere-binding proteins (CENP-A, -B, -C, -D, the kinesin-related MCAK and CENP-E, dynein, INCENPs [move to the microtubules in mitosis], etc). In the centromeric region of a wide range of organisms, a special histone-3-like protein (CENP-A) is present in the nucleosomes and it replaces histone-3 (H3). This protein is presumed to mark the centromere in higher organisms because this appears to be a common feature in yeast to mammals (Lee H-R et al 2005 Proc Natl Acad Sci USA 102:11793). In higher organisms there is no DNA consensus for the centromeric region, unlike budding yeast where a unique, about 125-bp sequence, specifies the centromere. Heterochromatin—usually surrounding the centromere—does not appear to convey determination because the neocentromeres are not heterochromatic.

The centromeres may also have functions during interphase. In the human centromere, the common H3 histone is replaced by a variant CENP-A. In the centromeric chromatin, H3 and CENP-A are interspersed. In human and *Drosophila* centromeric chromatin (CEN), both CENP-A and H3 are dimethylated at lysine 4 sites. This chromatin is continuous across the whole centromeric site and it is different

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from the common chromatin. CEN chromatin is flanked by heterochromatin with H3 lysine sites di- or tri-methylated. The human centromeric region contains a higher order of 171-bp monomeric tandem repeats, the so-called α -satellite and noncentromeric DNA. The antifungal protein, blasticidin, gene was expressed at sites binding CENP-A but not at H3 methylated at lysine 9, indicating that the formation of CEN chromatin within a repetitive DNA does not prevent gene expression (Lam AL et al 2006 Proc Natl Acad Sci USA 103:4186).

In human cells the centromeres seem to be associated with the nucleolus during interphase. The fact that the centromeres are different yet functional when interchanged seems to indicate that the differences are not all functional specificities. The centromeric DNA in fission yeast is quite different from those of budding yeasts and shows more similarity to the centromeres of higher eukaryotes that are many times larger. The centromeres of higher eukaryotes are composed of repeated sequences and some losses may not necessarily affect the transmission of the chromosomes. Sequencing of the human centromeric regions was difficult because of the extensive duplications. The primate centromeric region repeatedly expanded in central active region during evolution (Schueler MG et al 2005 Proc Natl Acad Sci USA 103:10563). The telocentric chromosomes generated by misdivision usually have impaired transmission and the same is true for the B chromosomes that are prone to nondisjunction.

Recombination is usually much reduced in the centromeric regions. The centromeres contain relatively few genes and pseudogenes, although in *Arabidopsis*, 5 and 12 genes per 100 kb were suggested in two centromeric regions in contrast to 25/100 kb in the normal arms. These genes seem to encode functions of mobile elements, tRNA, regulatory activity and also metabolic steps. Although genes within heterochromatic regions are suppressed, there is evidence for the transcription of some of the genes. The CEN regions include 180-kb repeats.

Although prokaryotes do not have structures exactly homologous to the eukaryotic centromere, the partitioning site of the plasmid DNA (involved in the distribution of the replicated DNA ring) has been called centromere. This partitioning site, *parS*, forms a module including protein ParA (an adenosine triphosphatase) and ParB (a *ParS*-binding protein). Similar to the eukaryotic centromere, prokaryotic genes on the flanks of *ParS* may be silenced.

The availability of cloned centromeric DNAs permitted the construction of yeast artificial chromosomes (YACs). These YACs, when properly constructed (see YACs and yeast centromeric vector), can

be subjected to tetrad analysis. YACs are very useful tools for the physical mapping of larger DNAs. Centromeric proteins determine chromosome segregation and regulate the difference between anaphase I and anaphase II disjunction of chromosomes and chromatids, respectively. ▶mitosis, ▶meiosis, ▶tetrad analysis, ▶centromere mapping, ▶YAC, ▶kinetochore, ▶aster, ▶spindle fibers, ▶microtubule, ▶Roberts syndrome, ▶octa, ▶kinesin, ▶dynein, ▶ α satellite, ▶yeast centromeric vector [for nucleotide sequences], ▶neocentromere, ▶holocentric chromosome, ▶telochromosome, ▶misdivision, ▶centromere A protein, ▶passenger proteins, ▶B chromosome, ▶sister chromatid cohesion, ▶heterochromatin, ▶histones; Copenhaver GP et al 1999 Science 286:2468; Dobie KW et al 1999 Curr Opin Genet Dev 9:206; Gindullis F et al 2001 Genome Res 11:253; Sullivan BA et al 2001 Nature Rev Genet 2:584; Choo AKH 2001 Developmental Cell 1:165; Hennikoff S et al 2001 Science 293:1098; Schueler MG et al 2001 Science 294:109; Hudakova S et al 2001 Nucleic Acids Res 29:5029; Smirnova JB, McFarlane RJ 2002 J Biol Chem 277:19817; Smith MM 2002 Current Opin Cell Biol 14:279; Blower MD et al 2002 Developmental Cell 2:319; Hall IM et al 2003 Proc Natl Acad Sci USA 100:193; human pericentromeric regions: She X et al 2004 Nature 431:857; centromeric proteins: Shueler MG, Sullivan BA 2006 Annu Rev Genomics Hum Genet 7:301.

Centromere A Protein (CENP-A): A 17-kDa histone 3-like protein and part of the centromeric nucleosomes. Its disruption or loss severely affects mitosis and causes fragmentation of the chromatin. Its normal role is to mark centromere organization in the chromosome. ▶centromere, ▶centromere B protein, ▶centromere C protein, ▶CENP, ▶histones; Murakami Y et al 1996 Proc Natl Acad Sci USA 93:502; Sugimoto K et al 2000 Cell Struct Funct 25:253.

Centromere Activation: Transposition of the centromere to a new position within the chromosome. ▶neocentromere, ▶centromere, ▶holocentric

Centromere B Protein (CENP-B): 80 kDa and it binds to the 17-bp CEN-B box that is present in human α -satellite and the mouse minor satellite DNA. CENP-B is not life-essential for mouse yet it leads to lower body weight and testis size. ▶centromere, ▶CENP-A, ▶CENP-C, ▶CENP, ▶ α -satellite DNA; Chen C et al 1999 Mamm Genome 10:13.

Centromere C Protein (CENP-C): 140 kDa; it apparently binds DNA and is essential for embryo survival in mouse beyond 3.5 days after conception. ▶centromere, ▶CENP-A, ▶CENP-B, ▶CENP; Pluta AF et al 1998 J Cell Sci 111 [pt14]:292; Fukagawa T et al 2001 Nucleic Acids Res 29:3796.

Centromere Index: The length of the short arm divided by the length of the entire chromosome $\times 100$.
 ▶ chromosome arm

Centromere Mapping in Fungal Tetrads: ▶ tetrad analysis

Centromere Mapping in Higher Eukaryotes: In heterozygous autotetraploid (triplex: AAAa) or trisomic (duplex AAa) progenies, the greater the proportion of recessive individuals for a particular marker the further is that locus from the centromere because only crossing over between gene and centromere (maximal equational segregation) can produce double recessive gametes. Thus, in very large populations the relative distances can be estimated (see Fig. C56). More precise estimates of gene centromere distance can be obtained in allopolyploids by using telochromosomes that are usually not transmitted through the pollen. The experimental design may be as follows (only one pair of chromosomes is shown in the diagram).

The centromeres of the chromosomes of rice were mapped using RFLP markers in telo- and isotrisomics. The distance was calculated on the basis of linkage intensities of markers on the opposite sides of the centromere, inferred by gene dosage. In mouse, Robertsonian translocations can be exploited for centromere mapping. In most eukaryotes the centromeric region has repeated sequences and these can also be used for centromere mapping of RFLPs. ▶ allopolyploid, ▶ telochromosome, ▶ tetrad analysis, ▶ half-tetrad analysis, ▶ trisomic analysis, ▶ Robertsonian translocation, ▶ maximal equational segregation, ▶ RFLP; Sears ER 1966 Hereditas, 2:370.

Centromeric Fission: ▶ misdivision of the centromere, ▶ telochromosome

Centromeric Fusion: The joining of two telocentric chromosomes into a single bi-armed one.

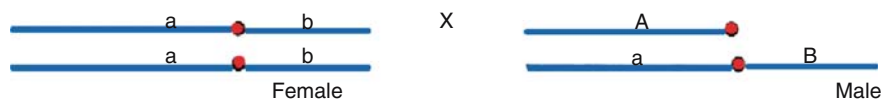
Centromere Silencing: Through breakage-fusion-bridge or neocentromere formation a single chromosome may acquire more than one centromere. In a maize study, 6/23 chromosome derivatives of breakage-fusion-bridge cycle (between a B chromosome and chromosome 9) contained two centromere-specific

regions (detected by immunolabeling) and were mitotically stable despite expectation according to the notion that dicentric chromosomes so derived would show bridge and breakage. This observation indicates that centromere inactivation may be common in plants (Han F et al 2006 Proc Natl Acad Sci USA 103:3238). ▶ B chromosomes, ▶ breakage-bridge-fusion cycles

Centromeric Vector: ▶ YAC

Centrosome: The center ($\sim 1 \mu\text{m}$) where spindle fibers (microtubules) originate (a microtubule organizing center, MTOC) and develop from a pair of centrioles toward the centromeres during nuclear divisions in animals (and few lower plants). In normal mammalian cells there are two centrosomes at the opposite poles (see Fig. C57). The mother centrosome normally remains anchored to the hub of the *Drosophila* germ stem cell interface and is inherited by the stem cell, whereas the daughter centrosome moves away from the hub and is inherited by the cell that commits to differentiation (Yamashita YM et al 2007 Science 315:518). In the human mammary epithelial cells there may be split centrosomes as an anomaly. Loss of p16^{INK4a} causes splitting of the centriole that can lead to the formation of aneuploidy and genomic instability because multipolar mitoses may take place. Normally, p16^{INK4a} in cooperation with p21 regulate cyclin-dependent kinases and prevent the splitting of the centriole. Such a condition may lead to tumorigenesis. In the mammalian female, meiosis centrosomes are lacking and the chromosomes nucleate and stabilize the bipolar spindle. This task is performed by the *chromosomal passenger complex* containing the Dasra A and B proteins, INCENP (inner centromere protein), Survivin, and the Aurora kinase (Sampath SC et al 2004 Cell 118:187). Ubiquitination and deubiquitination enzymes are required for the association and dissociation of Survivin to the centromeres for chromosome alignment and segregation (Vong QP et al 2005 Science 310:1499). In case the spindle emanates from the centrioles, Ran GTPase releases factors from a pool sequestered by β -importin required for activation of spindle assembly. A pericentriolar material made of γ -tubulin and Asp (asymmetric spindle) protein of 220 kDa surrounds

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The frequency of chromosomes of constitution indicates the frequency of recombination between locus A and the centromere (●) in the male

Figure C56. Centromere mapping in wheat

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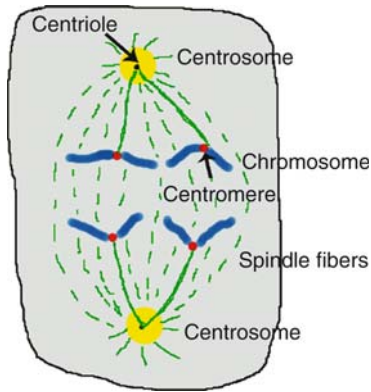


Figure C57. Centrosome

the centrioles. The γ -globulin ring complex (γ -Turc) can fulfill its function even when it is outside the centrosome (Müller H et al 2006 Science 314:654). Asp has phosphorylation sites for p34 and other mitogen-activated kinases as well as binding domains for actin and calmodulin. The fast growing (plus) ends of the microtubules project into the cytoplasm whereas the slow-growing (minus) ends are embedded into the γ -globulin ring. MAPs (microtubule-associated proteins) are also required for the nucleation at the centrosomes. The division of the centrosome (also called centrosome cycle) is essential for the completion of the cell cycle in animals and it may be blocked by mutation in gene *cdc31*. For the initiation of the division of the centrosome in *Xenopus*, egg calcium, calmodulin and calcium/calmodulin-dependent protein kinase II are required (Matsumoto Y, Maller JL 2002 Science 295:499). The aurora-2/STK15 serine/threonine kinase (encoded in human chromosome 20q13.2) is associated with the centrosome and its amplification interferes with the normal function of the centromere resulting in aneuploidy in common cancer cells. The PML protein also regulates centrosome duplication by suppression of the Aurora protein (Xu Z-X et al 2005 Mol Cell 17:721). CDK2-cyclin E may cause abnormally high proliferation of the centrosomes as it phosphorylates nucleophosmin, a centrosomal protein. Hsp90 is also a component of the centrosomal core, along with several other proteins. The deficiency of the p53 tumor suppressor protein results in multiple centrosomes and unequal distribution of chromosomes. Similar are the consequences of defects in PLK1 and an ataxia telangiectasia (*rad3*)-related (ATR) mutation. Plants do not have such distinct structures. Recently, mutations affecting the centrosomes have been isolated. The centrosome is paternally derived during fertilization in the majority of the animal species. Depending on the sperm donor, the size of the

aster may vary. The centrosome is required also for DNA synthesis during the cell cycle. Defect of centrosomes may lead to aneuploidy and cancer and centrosome anomalies contribute to several human diseases (Badano JL et al 2005 Nature Rev Genet 6:194). ▶mitosis, ▶centrioles, ▶p16^{INK4}, ▶p21, ▶centromere, ▶spindle, ▶microtubule, ▶nucleation, ▶kinesis, ▶dynein, ▶importin, ▶RAN, ▶spindle pole body, ▶aster, ▶centrosomin, ▶multipolar spindle, ▶Cdk; ▶p34, ▶actin, ▶calmodulin, ▶p53, ▶Hsp90, ▶aneuploidy, ▶survivin; ▶aurora, ▶promyelocytic leukemia; Brinkley BR 2001 Trends Cell Biol 11:18; Stearns T 2001 Cell 105:417; Bornens M, Piel M 2001 Curr Biol 12:R71; Bornens M 2002 Current Opin Cell Biol 14:25; Meraldi P, Nigg EA 2002 FEBS Lett 521:9; Andersen JS et al 2003 Nature [Lond] 425:570; centrosome-centriole duplication: Leidel S, Gönczy P 2005 Developmental Cell 9:317.

Centrosomin: One of the essential protein components of the centrosome. ▶centrosome; Vaizel-Ohayon D, Schejter ED 1999 Curr Biol 9:889.

CEPH (Centre d'Étude du Polymorphisme Humain): A France-based research institute located in Paris, where human cell lines are collected and maintained from four grandparents, two parents and their multiple children in order to map their genes and study their transmission. The institute is involved in the study of the human genome. (See <http://www.cephb.fr>).

Cephalic: Involves the head or indicates the direction toward the head.

Cephalohepatorenal Syndrome: ▶Zellweger syndrome

Cephalosporin Type Antibiotics: These antibiotics derived their name from *Cephalosporium acremonium* and include a number of natural and semi-synthetic antibiotics. The latter may be resistant to the enzyme penicillinase. Their action involves interference with the cross-linking of the peptidoglycans of the bacterial cell wall. ▶ β -lactamase, ▶lactam, ▶antibiotics, ▶penicillin; Clin Microbiol Infect 2000 Suppl. 3:1.

Ceramides: Ceramides are structural units of sphingolipids, a fatty acid attached by $-NH_2$ linkage to a sphingosine molecule. Ceramides mediate stress responses, apoptosis, cell cycle arrest, and senescence. ▶sphingolipids, ▶Farber's disease, ▶CAP [ceramide activating protein]; Hannun YA, Luberto C 2000 Trends Cell Biol 10:73.

Cerberus: A factor expressed in the organizer of *Xenopus* embryos, causing the development of

ectopic heads, duplicated hearts and livers. (It was named after the mythological three-headed monster guarding the gate of the underworld). ►organizer, ►ectopic expression

Cercopithecidae (Old World monkeys): *Allenopithecus nigroviridis* 2n = 48; *Cercocebus torquatus* 2n = 42; *Cercopithecus aethiops sabaeus* 2n = 60; *Cercopithecus ascanius* 2n = 66; *Cercopithecus cephus* 2n = 66; *Erythrocebus patas* 2n = 54; *Macaca fascicularis* 2n = 42; *Macaca mulatta* 2n = 42; *Miopithecus talapoin* 2n = 54; *Papio* spp. 2n = 42; *Presbytis melalophos* 2n = 44; *Presbytis senex* 2n = 44. ►primates

Cerebellum: A hind part of the brain supposed to be involved in the coordination of movements. Recent information indicates that the cerebellum acquires and discriminates among sensory informations rather than directly controlling movements. The Purkinje cells in the cortex are involved in the information output. Each Purkinje cell is innervated by the *mossy fiber system* (up to 200,000 parallel fibers originating from the deeper layers of the cerebellum) and by a single *climbing fiber* originating from the oliva (a mass of cells) below the surface of the cerebellar cortex. ►Purkinje cells, ►cerebrum, ►brain human

Cerebral Cholesterinosis (CTX): Human chromosome 2q33-qter, recessive deficiency of sterol-27 hydroxylase, mitochondrial P-450 and other mitochondrial proteins as well as adrenodoxin reductase cause lipid (cholesterol) accumulation in the tendons, brain, lung, and other tissues. ►mitochondria, ►cholesterol, ►adrenodoxin; Rosen H et al 1998 J Biol Chem 273:14805.

Cerebral Gigantism (Sotos syndrome): A rare autosomal dominant (5q35, 3p21 or 6p21) condition involving excessive bone growth, dysmorphism, and usually mental retardation. Male-to-male transmission is predominant because of paternal microdeletions or chromosome rearrangements. ►mental, ►retardation; Douglas J et al 2003 Am J Hum Genet 72:132; Miyake N et al 2003 Am J Hum Genet 72:1331.

Cerebral Palsy: ►palsy

Cerebro-Costo-Mandibular Syndrome (CCMS): A mental retardation accompanied by defects of the palate, small jaws (micrognathia), misplaced tongue (glossoptosis), rib-vertebral malformation (costovertebral abnormality), and other anomalies. Autosomal dominant or recessive inheritance may be involved. (See Plotz FB et al 1996 Am J Med Genet 62:286).

Cerebro-Oculo-Facio-Skeletal Syndrome (COFS, 10q11): A recessive, progressive brain (microcephaly, atrophy), eye and joint anomaly with resemblance to the Cockayne syndrome and to the CAMFAK syndrome. Defective nucleotide exchange repair may be involved. ►Cockayne syndrome, ►Martsolf syndrome, ►CAMFAK, ►CAHMR; Graham JM et al 2001 Am J Hum Genet 69:291.

Cerebrosides: Cerebrosides are sphingolipids; sugars linked to a ceramide. In the membranes of neural cells the sugar is generally galactose and in other cell membranes it is generally glucose. ►sphingolipids

Cerebrotendinous Xanthomatosis: Same as cerebral cholesterinosis.

Cerebrum: The major part of the brain in two lobes, filling the upper part of the cranium. ►brain, ►human, ►cerebellum

Cerenkov Radiation: Cerenkov radiation occurs when charged particles pass through an optically transparent material at speed exceeding that of light causing emission of visible light. Cerenkov radiation is used in high-energy nuclear physics, and also in molecular biology, for the detection of charged particles and to measure their velocity.

Cernunnos: ►XRCC

Ceroid Lipofuscinosis (NCL): Ceroid Lipofuscinosis is, apparently, autosomal recessive (assigned to several chromosomes). Brown ceroid (wax-like) deposits in several internal organs, including the nervous system, causes spasms and mental retardation. The infantile subtype (CNL1) was located to chromosome 1p32 and it involves rapidly progressing mental deterioration due to a deficiency of palmitoyl protein thioesterase. Its prevalence is about 1/12,500. CNL3 (16q12.1) or Batten disease/Vogt-Spielmeyer disease involves neuronal degeneration, loss of brain material, and retinal atrophy. The affects are either a lysosome-associated membrane protein or neuronal synaptophysin. Its prevalence at live birth is $\sim 4-5 \times 10^{-6}$ to 5×10^{-5} . CLN2 (11p15.5, Jansky-Bielschowsky disease) is a late juvenile type. The late-infantile neuronal ceroid lipofuscinosis (CLN5, 13q22) was attributed to a pepstatin-insensitive lysosomal peptidase or lysosomal transmembrane protein. CLN6 (15q21-q23) is another late infantile form. Some other variants with granular osmiophilic deposits and others have also been described. ►epilepsy, ►mental retardation, ►prevalence, ►pepstatin, ►Batten disease, ►synaptophysin, lipofuscin; Lehtovirta M et al 2001 Hum Mol Genet 10:69; Gao H et al 2002 Am J

Hum Genet 70:324; Batten disease: <http://www.ucl.ac.uk/ncl/>.

C

Certation: Competition among elongating pollen tubes for fertilization of the egg. Genetically-impaired pollen tubes are at a disadvantage and this may cause a distortion of the phenotypic ratios because certain phenotypic classes may not appear, or may appear at a reduced frequency. ▶[gametophyte](#), ▶[gametophyte factor](#), ▶[male sterility](#), ▶[cytoplasmic male sterility](#), ▶[segregation distortion](#), ▶[selection conditions](#), ▶[meiotic drive](#), ▶[last-male sperm precedence](#); Nilsson H 1915 Lunds Univ. Aarskr. N.F. Adf.2 (12):1; Konishi T et al 1990 Jap J Genet 65:411.

Ceruloplasmin: A blue copper-transporting glycoprotein in the vertebrate's blood. It is located in human chromosome 3q. ▶[aceruloplasminemia](#), ▶[Wilson's disease](#)

Cervical Cancer: Cervical cancer appears to be associated with infection by the human papilloma virus, however, there seems to be a genetic predisposition to susceptibility. Vaccine has been approved for protection. ▶[papilloma virus](#), ▶[Pap test](#), ▶[uterus](#)

Cervix: ▶[uterus](#)

Cesium: An alkali-metal element; its salts CsCl (MW 168.4) and Cs₂SO₄ (MW 361.9) are used as density gradient solutions for preparative and analytical ultracentrifugation, respectively. ▶[ultracentrifugation](#), ▶[buoyant density](#)

CETP (cholesterylester transfer protein): Mediates the catabolism of HDL and the transfer of cholesterol to the liver, and may be thus antiatherogenic. ▶[HDL](#), ▶[atherosclerosis](#)

Cetyl Trimethylammonium Bromide (CTAB): A detergent suitable for the precipitation of DNA. Generally used in a stock solution in 0.7 M NaCl. (See formula at CTAB).

Cetylpyridinium Bromide (CPB): A cationic detergent used for the precipitation of (radiolabeled) oligonucleotides.

CFP (cyan fluorescent protein): CFP can be used for in vivo staining and detected by FRET microscopy. ▶[FRET](#); Galperin E, Sorkin A 2003 J Cell Sci 116:4799.

CFTR (cystic fibrosis transmembrane conductance regulator): ▶[cystic fibrosis](#)

CFU (colony-forming unit): Number of cells/mL capable of propagation in in vitro culture. ▶[pfu](#)

CG: Dinucleotide is where the cytosine is most commonly methylated in vertebrates. The so-called

maintenance methylase enzyme acts on it when paired in a complementary manner in the DNA. The methylation may be transmitted through DNA replication. ▶[methylation of DNA](#)

CGAP (cancer gene anatomy project): The cancer gene anatomy project attempts to identify the function(s) of all human genes, one time estimated to be 60,000 to 150,000. The number now appears to be ~30,000—or less. (See <http://www.ncbi.nlm.nih.gov/ncicgap/>).

CGH: ▶[comparative genomic hybridization](#)

CGIAR: An international food and agricultural policy institute.

cGMP: A cyclic guanosylmonophosphate, a second messenger. Cyclic-di-GMP is a ubiquitous second messenger in bacteria. It is synthesized by a soluble guanylyl cyclase enzyme (sGC). ATP inhibits this enzyme through binding to an allosteric purinergic site of the protein. sGC is an intracellular sensor of ATP that couples nitrogen oxide-dependent cell functions with metabolic and energetic signaling. ▶[cAMP](#), ▶[second messenger](#), ▶[nitric oxide](#); Ruiz-Stewart I et al 2004 Proc Natl Acad Sci USA 101:37; Jena U, Malone J 2006 Annu Rev Genet 40:385.

C2H2: A ubiquitous zinc-finger regulatory protein domain.

CH₅₀: An *in vitro* assay for the activity of the complement. ▶[complement](#)

Chaetae: The bristles of insects and sensory organs of the peripheral nervous system (see Fig. C58). The large ones called macrochaetae are mechanical sensory organs and the smaller ones of different types are microchaetae (a fraction of them are chemoreceptors). ▶[tormogen](#), ▶[trichome](#), ▶[microchaetae](#)

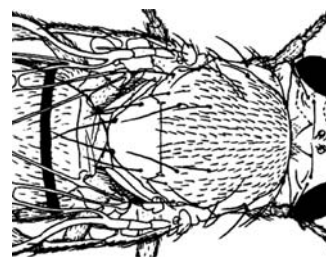


Figure C58. Chaetae

Chagas Disease: A nonhereditary potentially fatal disease caused by infection by *Trypanosoma cruzi*. ▶[Trypanosoma](#), ▶[paratransgenic](#), ▶[kinetoplast](#); Cohen JE, Gürtler CE 2001 Science 293:694.

Chain-Sense Paradox: Expresses the problem of conformational switch from B to Z DNA. ►DNA types

Chain Shuffling of antibodies: ►phage display

Chain Termination: ►transcription termination and nonsense codons, ►initiator codon, ►DNA sequencing (Sanger method)

Chalaza: The site on the plant seed where the funiculus unites with the ovule. Points in the bird eggs where the yolk is connected to the eggshell. ►hilum

Chalcones: Phenylalanine is converted to *trans*-cinnamic acid and cinnamoyl-CoA that, through a condensation reaction, yields chalcone (see Fig. C59). A series of other plant pigments (flavonones, flavones, flavonols, anthocyanidins, etc.) are derived through single gene-controlled biochemical steps. The Rs in the formulas (see diagram) stand for, H, OH, CH or OCH₃ residues, respectively, in the different pigments. ►*trans*-cinnamic acid, ►anthocyan

Chalones: Chalones are water-soluble glycoproteins which can inhibit mitosis.

Chambon's Rule: Splice points at the ends of intervening sequences are generally GT.....AG (except in tRNA genes and other minor classes of genes). ►introns, ►splicing

Chameleon Proteins: Chameleon proteins contain a short amino-acid sequence that may fold either as an α -helix or a β -sheet depending on its position. ►protein, ►structure

Chanarin-Dorfman Disease (ichthyotic neutral lipid storage disease, CDC, human chromosome 3p21):

A triglyceride storage disease with defective long-chain fatty acid oxidation. The basic defect involves an esterase/lipase/thioesterase protein. Within the cells, triacylglycerol droplets are found and liver, muscle, eye anomalies may accompany ichthyosis. ►ichthyosis; Lefèvre C et al 2001 Am J Hum Genet 69:1002.

Chance: Statistical probability or uncertainty. ►probability, ►likelihood

Change of State: Different levels of methylation of a genetic sequence. ►Spm

Channel: A path through which signals (molecules) can be transmitted. ►hemichannel

Channeling (tunneling): The transfer of a common metabolite between two enzymes in a sequential and parallel function (see Fig. C60). For e.g., a mutation may shut down (✋) the carbamyl phosphate pool leading to arginine synthesis but an overflow through a "tunnel" from the carbamyl phosphate precursor in the pyrimidine pathway may substitute for the defect and eliminate the dependence on exogenous arginine because of the channeling (\Rightarrow) of the accumulated carbamyl-P_{pyr} into the arginine pathway when another mutation blocks (✋) the pyrimidine path. Tryptophan synthase, glutamine phosphoribosylphosphate amido-transferase and asparagine synthetase, and other multi-functional enzymes also display this phenomenon. Channeling may go both ways between two metabolite pools. ►regulation of gene activity; Ovádi J, Srere PA 2000 Int Rev Cytol 192:255; Huang X et al 2001 Annu Rev Biochem 70:149.

Channeling: Channeling is the topologically constrained intramolecular recombination of transposons. Such

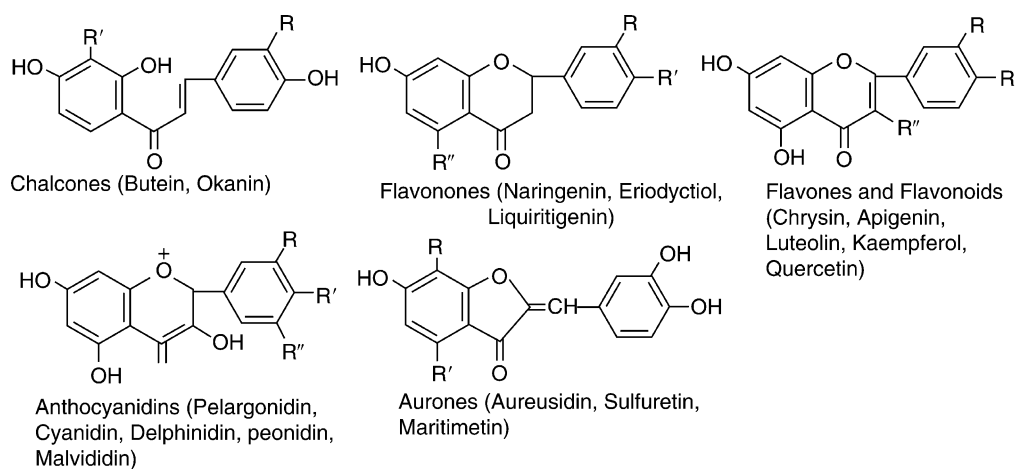


Figure C59. Chalcones and related pigments

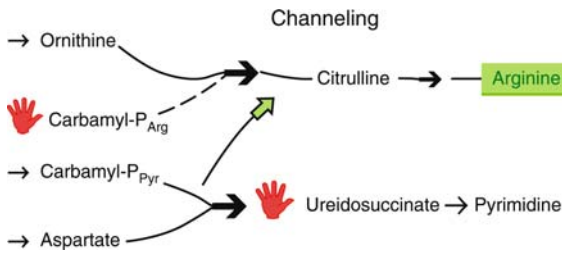


Figure C60. Channeling

an event may lead to the formation of a new element rather than to its destruction.

Channelopathy: ►ion channels

Chaos: A system extremely sensitive to minute perturbations, that are also called the “butterfly effect.” Although in common usage of the word chaotic conditions are meant to be uncontrollable and unpredictable because many degrees of freedom should be dealt with simultaneously. There are, however, high dimensional systems where the “attractor” (the dynamics) is low dimensional. Among the infinite varieties in the system, one can be selected and stabilized by minute changes in one parameter. The task is to locate the critical points in a multitude of “noise.” Various mathematical algorithms have been worked out to deal with the problems. Systems of chaos are characterized by nonlinear dynamics. The control of chaotic systems have great relevance to biology and genetics where a large number of genetic (epistatic), epigenetic and environmental factors interact, such as the chaos in the heart, the neuronal information processing, epileptic seizures, development, differentiation, etc. Chaos control (anticontrol) may then be applicable to harness the system and manipulate controls over it even when all the details are not understood. ►fractals, ►algorithm; Williams GP 1997 *Chaos theory tamed*. Taylor & Francis, Bristol, Philadelphia; Bar-Yam Y 1987 *Dynamics of complex systems*. Addison-Wesley, Reading, Massachusetts.

Chaotrope: The interaction between ion-protein complexes is more attractive than uncomplexed proteins. This is also called salting-out. When the interaction between protein-ion complexes is more repulsive (kosmotrope) than in uncomplexed proteins, salting-in is observed. (See Curtis CA et al 2002 *Biotechnol Bioeng* 79:367)

Chaperone: A protein mediating the conformational change or assembly of polypeptides (usually) without becoming a permanent part of the final product (e.g., the heat-shock protein families Hsp70 and Hsp 60,

rubisco, etc.). Their major function is prevention of inappropriate conformation, aggregation, and interaction with incorrect ligands. Chaperones may restore to native conformation some aggregates in case the denaturation is not irreversible. In eukaryotes, a class of chaperones (CLIPS) is engaged in folding the nascent proteins or the newly misfolded ones and another group of chaperones assist in the restoration or disposal of environmentally damaged proteins (Albanèse V et al 2006 *Cell* 124:75). The chaperones come in greatly different molecular sizes that are shown in their designation (in kDa). snRNAs may mediate the folding of rRNAs (Weeks KM 1997 *Curr Opin Struct Biol* 7:336). An RNA-dependent ATPase may chaperone RNAs (Mohr S et al 2002 *Cell* 109:769). The heat-shock proteins may also play a role in signal transduction by modifying the folding of steroid hormone receptors. The chaperones may be classified into the Hsp70 (heat-shock protein 70) and into the chaperonin families such as the Hsp60s. Hsp60 also mediates regeneration from blastema. The chaperones recognize short extended polypeptides rich in hydrophobic residues that are released upon ATP hydrolysis. Chaperones may facilitate protein degradation within the cells. The chaperonins are large oligomeric ring complexes. The mitochondrial proteases (Lon, Apg3p, Rca1p) can carry out chaperone functions and assemble mitochondrial proteins. The small *intramolecular chaperones* (IMC) are different from the *molecular chaperones* inasmuch as they do not require ATP for folding, are very highly specific and not reusable, and can change the structure of mature proteins. Misfolding of proteins may lead to the development of Alzheimer’s disease, prions, etc. ►heat-shock proteins, ►HSE, ►chaperonins, ►Hsp70, ►HSP, ►DnaJ, ►GroEL, ►flexer, ►PDI, ►PPI, ►CLIPS, ►antichaperone ►protein folding, ►prion, ►cue, ►trigger factor, ►Alzheimer’s, disease, ►prion, ►blastema; Ellis RJ, van der Vies SM 1991 *Annu Rev Biochem* 60:321; Frydman J 2001 *Annu Rev Biochem* 70:603; Dobson CM 1999 *Trends Biochem Sci* 24:329; Rutherford SL 2003 *Nature Rev Genet* 4:263.

Chaperonins (cpn): Ring proteins (chaperonin 60 and 10) mediate the assembly of 12 identical phage (λ, T4, T5)-encoded polypeptides and these serve as the template for lining up the phage head precursors. Chaperonin 10 releases the phage proteins from chaperonin 60 (see Fig. C61). Homologous proteins occur in bacteria and mitochondria and chloroplasts of eukaryotes. Their most essential function is (generally ATP- and K⁺-dependent) folding of proteins. The best known chaperonin proteins belong to two families: the GroEL/GroES (include Hsp60 and rubisco binding proteins) and the TRiC. These

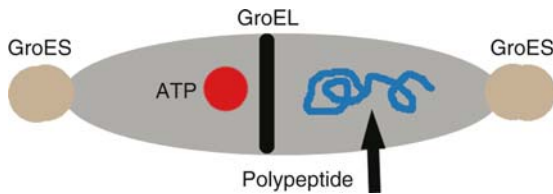


Figure C61. Chaperonin

form a porous cylinder of 14 subunits. The folding of proteins has numerous implications for normal function of proteins as well as for pathological conditions. The thermosome (TF55/TCP1) chaperonins occur in the thermophilic Archaea bacteria. The latter are related to other cytosolic chaperonins of eukaryotes (animals and plants). The *cytosolic chaperonins* (CCT, ca. $2-3 \times 10^5$ complexes per mammalian cell) function similarly to the organellar chaperonins (ATPase activity, folding nonnative proteins) although structurally they are different. All chaperonins have the molecular mass of 800–1,000 kDa, built of ca. 60 kDa subunits, ($\alpha, \beta, \gamma, \epsilon, \zeta, \eta, \delta, \theta$) encoded by *Cct* genes. The GroES heptamer has 10 kDa subunits. The folding takes place within a GroEL chamber after it has entered through the small GroES capping proteins. ▶[chaperones](#), ▶[heat-shock](#), ▶[proteins](#), ▶[GroEL](#), ▶[TRiC](#), ▶[TCP-1](#) rubisco, ▶[Cpn60](#), ▶[Cpn21](#), ▶[Cpn60](#), ▶[Cpn10](#), ▶[7B2](#); Ang D et al 2000 Annu Rev Genet 34:439; Gottesman ME, Hendrickson WA 2000 Curr Opin Microbiol 3:197; Thirumalai D, Lorimer GH 2001 Annu Rev Biophys Biomol Struct 30:245; Hartl FU 2001 Cell 107:223; Levy-Rimler G et al 2002 FEBS Lett 529:1.

Char Syndrome: ▶[patent ductus](#), ▶[arteriosus](#)

Character: Character, in genetics, is a trait that may or may not be expressed through inheritance. It also includes any symbol used for conveying information, e.g., letters, numerals, punctuation marks, etc.

Character Displacement: Character displacement occurs when two species occupying similar but not identical habitat share a common area and in this shared zone each differ more from the other regarding a particular trait(s) than in the nonshared area.

Character Matrix: A device for classifying different groups regarding a trait as “have it (1)” or “not (0).” On this basis, then, a *similarity index* can be obtained and the distinguished groups are called operational taxonomic units (OTU). If the differences are counted or measured a *distance matrix* is obtained (see Fig. C62). On the basis of the similarities/differences branching

phenograms or *dendrograms* can be constructed. ▶[species](#); Ward BB 2002 Proc Natl Acad Sci USA 99:10234.

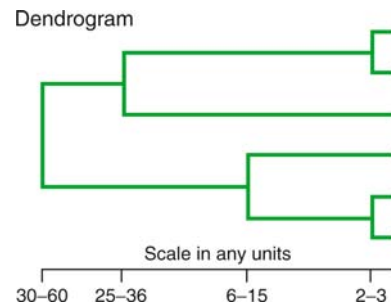


Figure C62. Character matrix

Character Process Model: The character process model analyzes the changes in a trait during a process and the correlation of stages of the process according to the expanded formula: $G(s,t) = v_g(s)v_g(t) \rho_g(|s - t|)$ where v_g = genetic variance, s and t are stage/time variations and $\rho_g(|s - t|)$ = genetic correlation between stages/time.

Charcot-Marie-Tooth Disease (CMT, hereditary motor and sensory neuropathy): CMT is known in multiple forms with autosomal recessive, dominant, or even Xq13-linked types. Its frequency is about 0.0004. The disease affects the nervous system and hearing; it is debilitating but not lethal. The average age of onset is early teens but it manifests more clearly by the late 20s. The defect Type 1B involves human chromosomes 1p21-23 or HNPP at 17p12-p11.2 encoding myelin 22. Dominant intermediate DI-CMT genes were assigned to 10q24-q25.1 (Verhoeven K et al 2001 Am J Hum Genet 69:889) and 1p34-p35 (Jordanova A et al 2003 Am J Hum Genet 73:1423). The latter locus was shown to involve tyrosyl-tRNA synthetase (Jordanova A et al 2006 Nature Genet 38:197). The chromosome 1p36.2 mutation of MFN2 GTPase involves a defect in mitochondrial fusion (Zuchner S et al 2004 Nature Genet 36:449). Its presence can be detected by genetic screening in the affected families. In the basic defect, connexin 32 encoded at Xq13.1 has also been implicated. The type 2 disease was found to be associated with human chromosome 1q21.2-q21.3, 3q13-q22, and 7p15. The latter location encodes at least 10 mutations in the glycyl-tRNA synthetase (GlyRS, GARS) gene responsible for CMT. The crystal structure of human GlyRS affects the sides of the protein dimer interface. The CMT phenotype, however, does not correlate with aminoacylation activity (Nangle LA et al 2007 Proc Natl Acad Sci

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USA 104:11239). The chromosome 3 muscle weakness, foot ulcers are due to mutations in RAB7, an endosomal protein (Verhoeven K et al 2003 Am J Hum Genet 72:722). The recessive demyelinating dual-specificity phosphatase (myotubularin-related protein-2) is encoded at 11q22. Another recessive demyelinating form encodes (11p15) a “pseudophosphatase,” an inactive phosphatase (Azzedine H et al 2003 Am J Hum Genet 72:1141). This disease may also be caused by a duplication due to unequal crossing over in the peripheral myelin gene (chromosome 17) induced by a transposable element resembling *mariner* in *Drosophila*. The defective human chromosome 17p11.2 gene expressed in mice can be successfully corrected phenotypically by ascorbic acid (Passage E et al 2004 Nature Med 10:396). An autosomal recessive form is determined by chromosome 8q21.1 (GDAP1) and in 1p36 another locus has been implicated. An axonal form of the disease maps to 19q13.3 encoding the two PDZ domain proteins, periaxins. In the mouse the *trembler* mutation and some others are involved in hypomyelination. ▶neuropathy, ▶connexins, ▶myelin, ▶genetic, ▶screening, ▶MLE, ▶MITE, ▶mariner, ▶hypomyelinopathies, ▶RAB, ▶Pelizaeus-Merzbacher disease, ▶HNPP, ▶PDZ, ▶domain; Leal A et al 2001 Am J Hum Genet 68:269; Sherman DL et al 2001 Neuron 30:677; Zhao C et al 2001 Cell 105:587; Cuesta A et al 2002 Nature Genet 30:22.

Chargaff's Rules: In double-stranded DNA, nucleotides are paired as A = T and G = C. ▶hydrogen, ▶pairing, ▶DNA. Therefore, the amount of adenine equals that of thymine, and the quantity of guanine is about the same as that of cytosine in double-stranded DNA. In the majority of organisms AT is not equal in amount to GC. The recognition of this fact contributed significantly to the construction of the Watson-Crick model of DNA. Chargaff's second rule states that if a sufficiently long (>100 kb) strand of genomic DNA that contains *N* copies of a mono- or oligonucleotide, it also contains *N* copies of its reverse complementary mono- or oligonucleotide on the same strand. This rule has rather general validity for coding and noncoding sequences, except in some mitochondrial DNAs. Inversions and inverted transposition could be a major contributing if not dominant factor in the almost universal validity of this rule (Albrecht-Buehler G 2006 Proc Natl Acad Sci USA 103:17828). ▶Watson and Crick model; Forsdyke DR, Mortimer JR 2000 Gene 261:127.

CHARGE (coloboma, heart anomalies, choanal atresia, [obstruction of the nasal passageway by bony malformation], retardation, genital and ear anomalies): A complex human disease association syndrome,

which is about 8% familial (incidence at birth $\sim 8 \times 10^{-5}$). Chromosomes 14q22-q24.3 and 22q11 have been implicated but unequivocally not demonstrated. A 2.3 Mb microdeletion at chromosome 8q12 was found in many CHARGE-affected individuals (Vissers LE et al 2004 Nature Genet 36:955). A CHARGE-like X-chromosomal syndrome has also been reported. The majority of affected individuals have mutations in the chromodomain helicase DNA-binding domain (8q12.1) or in the semaphorin-3E gene ▶coloboma, ▶familial, ▶chromodomain, ▶semaphorin

Charge-Coupled Devices (CCDs): CCDs are used for highly sensitive imaging of fluorescence, bioluminescence, and tomography. The devices are based on semiconductors arranged in a manner that the output of one serves as input for the next.

Charge Clusters: Charged residues (amino acids) in proteins are distributed nonrandom and these proteins are frequently involved in transcription activation, developmental control, and membrane receptor activities. Charged clusters may contribute to protein folding, protein-protein and protein-nucleic acid interactions. Charge cluster are much more common in eukaryotes than in prokaryotes (Karlin S 1995 Curr Opin Struct Biol 5:360). ▶amino acids, ▶protein folding, ▶protein interactions, ▶regulation of gene activity

Charges tRNA: The transfer RNA carries an amino acid. ▶tRNA, ▶protein synthesis, ▶aminoacyl tRNA synthetase

Charge-to-Alanine Scanning Mutagenesis: ▶homolog-scanning mutagenesis

Charomids: Charomids are specially constructed phage lambda-derived vectors. The constructs must be of a minimum of 38 kb otherwise they cannot be packaged into infectious particles. A conventional cosmid vector is 5 kb, therefore, the minimal size of an insert would be 33 kb. When the fragment to be cloned is much smaller, charomids are used that carry repeating units of about 2 kb fragments of plasmid pBR322 in head-to-tail arrangement as space fillers. Thus, depending on the nature of charomids, they can be used for cloning DNAs from 2 to 45-kb length. In *recA⁻* bacteria (ED8767) these vectors are quite stable and can be used just like cosmids. ▶cosmids, ▶vectors, ▶Rec; Saito I, Stark GR 1986 Proc Natl Acad Sci USA 83:8664.

Charon Vector(s): Charon vectors are modified phage λ plasmids (pronounce kharon; named after the mythical ferryman who carried dead souls through the

infernal Styx river). The Charon vectors are primarily replacement vectors, i.e., they can place DNA into deleted parts of the stuffer region (between λ genes J and N, see diagram at lambda phage). There are a large number of Charon vectors with somewhat different features. Charon 4 was used mainly to generate eukaryotic genomic libraries. In the replacement (stuffer) region there are E.coRI of 6.9 kb and 7.8 kb containing the β -galactosidase (*Lac Z*) and the biotin (*bio*) genes, respectively. Successful replacement is recognized by the inability of *lac*- bacteria carrying this vector to develop blue color on Xgal medium because the vector cannot provide the galactosidase function any more. Replacement of the *bio* gene results in biotin dependence in a similar way. The vector is also *Spi*⁻ (wild type lambda phages are unable to grow in bacteria containing prophage P2 and have the designation *Spi*⁺ [sensitive to P2 interference]). The *Spi* selection is inoperable with Charon 4. Charon vectors that have lost the *red* and *gam* functions [required for recombination] can grow in P2 lysogens and are called *Spi*⁻. The bacteria have the *rec*⁺ gene (mediating recombination) and the phage has its own *chi* element (a substrate for the *recBC* system of recombination) or the inserted foreign gene contains one (mammalian DNA has numerous *chi* elements). Also, *supE* and *SupF* (amber suppressors) must be present in the host to allow for selection of recombinant libraries by in vivo recombination because the vectors *A* and *B* genes carry amber mutations (chain termination codon UAG). Besides the EcoRI sites there is an XbaI site in the stuffer region that accepts an up to 6-kb insertion. Charon 32 vector permits cloning DNA fragments at EcoRI (substitution up to 19 kb), HindIII (substitution up to 18 kb) and SacI sites (insertion up to 10 kb). In these cases *recA*⁻ hosts suffice because the vector is *gam*⁻. When Charon 32 is used as a substitution vector for EcoRI-SalI, SalI-XhoI, or EcoRI-BamHI fragments the host must be *recA*⁺ because *gam* is lost. Charon 34 and Charon 35 are suitable for cloning fragments up to 21 kb at polycloning sites, using BamHI, EcoRI, HindIII, SacI, XbaI, and SalI, as well as their combinations. These vectors retain *gam* functions. Charon 40 is useful for cloning fragments from 9.2 to 24.2 kb. In the stuffer region there are 16 restriction sites in opposite orientation near the ends. The poly-stuffer can be broken down into small fragments by the use of restriction enzyme NaeI (GCC↓GGC) and can be collected by precipitation with polyethylene glycol. The vector retains *gam*. ▶**vectors**, ▶**lambda phage**, ▶*Spi*⁺, ▶*supC*, ▶*supD*, ▶*SupE*, ▶*supF*, ▶*supG*, ▶*supU*, ▶**restriction enzyme**, ▶**Xgal**, ▶**Lac operon**; Chauthaiwale VM et al 1992 Microbiol Rev 56:577.

Chase method: ▶**haploids**

Chasmogamy: Pollination takes place after the flower opened. ▶**cleistogamy**

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CheA, CheB, CheR, CheC, CheD, CheW, CheY, CheZ:

Bacterial cytoplasmic proteins mediating the transduction signals of chemoeffector through transducers to switch molecules. CheA is an autophosphorylating (histidine) kinase that phosphorylates also CheY and CheB. CheY also autophosphorylates spontaneously in a few seconds and the process is accelerated by CheZ. CheA is central to information processing by the four transducers in cooperation with CheW. CheR, CheB: cytoplasmic bacterial proteins mediating the return of the chemotaxis excited cells to the normal state (adaptation). CheR is a methyltransferase; CheB is a methylesterase. CheC is phosphatase. CheD is a receptor-modifying deamidase. CheC inhibits CheD and CheD stimulates CheC. ▶**effector**, ▶**transducer**, ▶**proteins**, ▶**autophosphorylation**, ▶**esterases**, ▶**transferases**, ▶**enzymes**, ▶**chemotaxis**, ▶**excitation**, ▶**switch genetic**, ▶**chemotaxis**; Sourjik V, Berg HC 2000 Mol Microbiol 37:740; Bray D 2002 Proc Natl Acad Sci USA 99:7; Charon NW, Goldstein SF 2002 Annu Rev Genet 36:47; Chao X et al 2006 Cell 124:561.



Figure C63. Crystal structure of CheY. Courtesy of Alm E & Baker D 1999 Proc. Natl. Acad. Sci. USA 96: 1305

CheBI (chemical entities of biological interest data based): Catalogs small molecules, atoms, ions, ion pairs, radicals, and other chemicals of biological interest. (See <http://www.ebi.ac.uk/chebi>).

Checkerboard: A representation of the genotypic array of snapdragon flowers in the style of a checkerboard where the top line and the left-most column of symbols display the gametic combinations (see Fig. C64). Note

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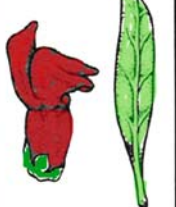
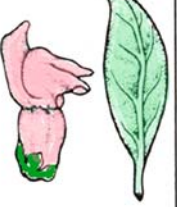
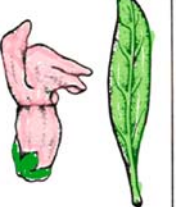
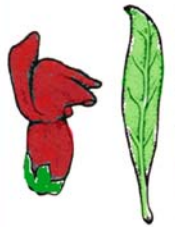
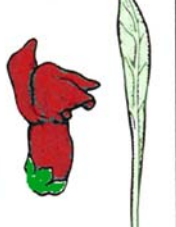
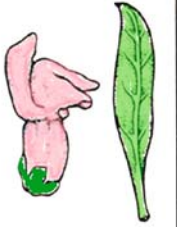
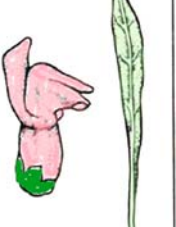
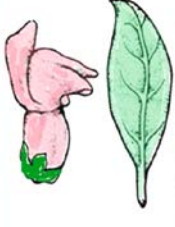

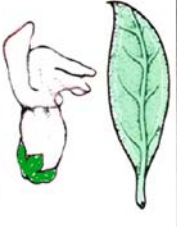
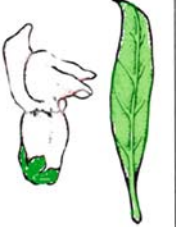
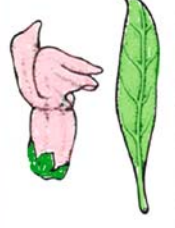
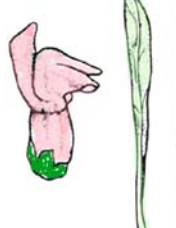
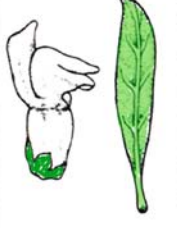
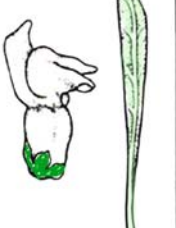
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Figure C64. Checkerboard

the 1:2:1 segregation in each of the four boxes. The left-top individual is homozygous for both dominant alleles; the right bottom is homozygous for both recessives. At the diagonal from bottom left to top right all genotypes are heterozygous for the two genes.

The diagonal from top left to bottom right represents homozygotes at both genes. Also along the other left to right diagonals within the four boxes the immediate neighbors are of identical constitution. This representation is called also Punnett square.

►modified, ►checkerboard, ►Punnett square, ►Mendelian segregation, ►Mendelian laws

Checkpoint: Critical phases in the progress of cell division where the cycle can be stopped and kept, and yet, when conditions become appropriate, progress may be resumed (see Fig. C65). The main role of the check point is to prevent progression to G₂ phase until the S phase is completed. There may also be a check point at the G₂ phase preventing the completion of the cell cycle. The checkpoint indicates a step initiating a new direction in the progression; before the cell embarks on a new path, the preceding steps must be completed. The purpose of the checkpoints is to prevent mitosis of defective cells. Several proteins have now been identified in different organisms to mediate checkpoints. The checking is generally mediated by different cyclin-dependent kinases, CDKs.

In yeasts there are fewer checkpoints whereas in animal cells different ones specialize for each checkpoint. The CDKs may be activated/deactivated by phosphatase/kinase action and, in addition, binding proteins, cyclin kinase inhibitors (CKI) and other modifiers may participate. These proteins are also subject to proteolytic destruction. In multicellular higher organisms apoptosis is also involved, and that does not stop the cell cycle at a stage but eliminates the cell with a defect.

In yeasts, a network of checkpoints have been identified including *RAD9*, *RAD17*, *RAD24*, *RAD53*, *DDC1*, *PDS1*, *POL2*, *PRI1*, *RFC5*, *MEC3*, *MEC1* genes. Protein 14-3-3 σ is also a component of the G₂ checkpoint; in the absence of its function the cell cycle fails to stop and proceeds to death. Protein 14-3-3 normally binds Cdc25 phosphorylated at Ser²¹⁶ and the cell cycle proceeds but phosphorylated CDC25 is ferried out of the nucleus after DNA damage and the G₂ checkpoint is abrogated. Chk1 phosphorylates CDC25 at 216. Protein 14-3-3 σ is transcribed upon the action of p53 and it sequesters cyclin B1 and CDC2 in the cytoplasm and prevents their entry into the nucleus and thus the cell cycle is not completed when the DNA is damaged. ►cell cycle, ►SCF, ►replication at the S phase in eukaryotes, ►p56^{chk1}, ►PIK, ►FK506, ►PIK, ►FK506, ►RAD, ►APC, ►ATM, ►ATR, ►protein 14-3-3, ►p21, ►p53,

►CDC2, ►CDC25, ►chk1, ►cyclin, ►B, ►CDC28, ►CDC5, ►PDS, ►sister chromatid, ►cohesion, ►wee, ►FKH, ►restriction point, ►ATR; Skibbogens RV, Hieter P 1998 Annu Rev Genet 32:307; Nigg EA 2001 Nature Rev Mol Cell Biol 2:21; Melo J, Toczyski D 2002 Current Opin Cell Biol 14:237; Nyberg KA et al 2002 Annu Rev Genet 36:617, DNA repair – checkpoint: Lisby M et al 2004 Cell 118:699, checkpoints in carcinogenesis: Kastan MB, Bartek J 2004 Nature [Lond]: 432:316, checkpoint and DNA damage repair: Harrison JC, Haber JE 2006 Annu Rev Genet 40:209.

Chediak-Higashi Syndrome (CHS): An autosomal recessive defect of the cytotoxic T cells in human chromosome 1q42.1-q42.2. The afflicted individual displays reduced pigmentation of the hair and eyes, avoidance of light, reduction in the number of neutrophilic lymphocytes (neutropenia), high susceptibility to infections, and lymphoma. In the heterozygotes the lymphocytes appear abnormally granular. Similar diseases occur in many mammals. Molecular investigations reveal a defect in a protein with carboxy-terminal prenylation and multiple potential phosphorylation sites (LYST). It may be involved as a relay integrating cellular signal response coupling, mediated through the lysosomes. Its mouse homolog is the *beige* locus. ►albinism, ►lymphocytes, ►neutrophil, ►lymphoma, ►Hermansky-Pudlak syndrome; Stinchcombe J et al 2004 Science 305:55.

CHEF: CHEF stands for contour-clamped homogeneous electric field that alternates between two orientations. Multiple electrodes along a polygonal contour generate the electric field. The method applies the principles of electrostatics (statical electricity) to gel electrophoresis of very large molecules such as the entire DNA of small chromosomes. ►pulsed gel electrophoresis

Cheirology (dactylogy): The study of hands, fingerprints. ►fingerprinting

Chelation: The holding of a hydrogen or metal atom between two atoms of a single molecule. Hemin and chlorophyll are chelated. Chelation may improve solubility of metals. It is also used for relieving metal poisoning.

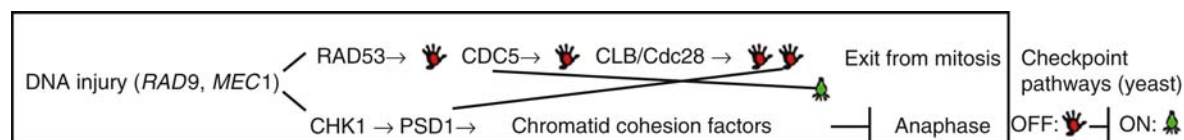


Figure C65. Checkpoint. (Diagram modified after Sanchez, Y. et al 1999 Science 286: 1166)

ChemBank: A free database of more than 2,000 small molecules of potential applications for perturbing biological systems. ►[chemical genetics](http://chembank.med.harvard.edu/); <http://chembank.med.harvard.edu/>.

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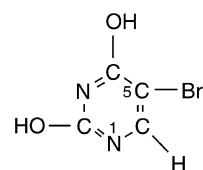
Chemical Biology: Uses interdisciplinary approaches for the translation of basic science into the needs of societal problems such as control of disease, providing insights into the proteome of pathogenesis, drug development, engineering new diagnostic systems, etc. ►[synthetic biology](#)

Chemical-Genetic Profiling: Identifies the effects of chemicals/groups of chemicals on physiology and on particular genes. The information obtained can reveal the action of drugs on proteins. Two-dimensional clustering analysis and probabilistic sparse matrix fertilization analyses are tools employed. (Parsons AB et al 2006 Cell 126:611).

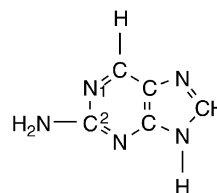
Chemical Genetics: Develops small molecules that can modify proteins or nucleic acids and thus alter gene function. In parallel synthesis, small molecules and peptides are synthesized in separate containers in a combinatorial manner. In the split-pool procedure a mixture of beads is initially split in several containers and the first amino acid is attached to the beads. Then all the beads are pooled and re-split into separate containers/wells, where the second amino acid is hooked to the first one. This process allows the synthesis of millions of chemicals by only a few hundreds of reactions (Smukste I, Stockwell BR 2005 Annu Rev Genomics Hum Genet 6:261). The results may be applicable to the development of drugs and reveal developmental mechanisms. ►[ChemBank](#), ►[combinatorial chemistry](#); Bishop AC et al 2000 Nature [Lond] 407:395; Tan DS 2002 Nature Biotechnol 20:561.

Chemical Mutagens: These include an extremely large number and wide variety of different chemical groups (see Fig. C66). Their effectiveness varies within a great range. About 80% of the chemical mutagens are also carcinogens. Some of these agents pose health hazards as industrial, agricultural, and medical chemicals. A much smaller fraction is used for the experimental induction of mutation for research purposes. A not-comprehensive classification includes (i) DNA base and nucleoside analogs 5-bromouracil or 5-bromodeoxyuridine (BuDR), 2-aminopurine (2-AP).

These compounds are of relatively very low efficiency and can be utilized only under highly selective conditions in microbial populations. They act, primarily, either through incorporation at the wrong place in the DNA or by replacing their normal counterparts followed by mispairing (tautomeric



5-Bromouracil



2-Aminopurine

Figure C66. Chemical mutagens

shift) and in both cases causing base substitution. (ii) Chemical modifiers of nucleic acid bases such as nitrous acid (HNO_2) that oxidatively deaminates cytosine into uracil, adenine into hypoxanthine (resulting actually in A→G transitions) and guanine into xanthine (causing lethal effects because of interference with replication). Nitrous acid is not an effective mutagen for higher eukaryotic cells because of the high protein content of the chromosomes and nitrous acid also has a destructive effect on proteins, but it was used very advantageously for tobacco mosaic virus and other viruses. Nitrous acid may nitrosate, however, several plant products (black pepper, beer [if the barley is improperly dried], soybean and faba bean products and cruciferous vegetables [cabbage, etc.]). Hydroxylamine targets primarily cytosine and thus changes a G≡C pair into A = T. (iii) Alkylating agents of a diverse group such as sulfur- and nitrogen mustards, epoxides, ethyleneimins, unsaturated lactones (aflatoxin), alkyl and alkene sulfonates are powerful mutagens for different organisms. The nitrogen mustards induce, primarily, chromosome breakage like X-rays and are frequently referred to as radiomimetic agents.

The mustards are no longer used as laboratory mutagens because of the relatively low efficiency compared to their lethal effects and because the risks involved in routine handling. Among these, the most commonly used alkylating mutagens are methyl and ethyl methanesulfonate ($\text{CH}_3\text{SO}_2\text{OCH}_2\text{CH}_3$) that are highly effective in practically all organisms. They alkylate the guanine at the 7 position but the major mutagenic action results from the alkylation of the O^6 of guanine. To a lesser extent, they alkylate mutagenically other bases too. Alkylation may also break the linkage between the ribose and the N9 of the purines resulting in depurination and breakage of the DNA strand. (iv) N-nitroso compounds such as

nitrosamines, nitrosoureas, methyl-nitro-nitrosoguanidine (MNNG, $C_2H_5N_5O_3$), etc., are very potent mutagens. The latter one predominantly induces point mutations at pH 6 but it must be handled in the dark as it rapidly decays in the light. (v) A variety of compounds that produce free radicals such as hydrazines and hydrazides, hydrogen peroxide or organic peroxides, aldehydes and phenols are mutagenic but usually not employed for the induction of mutation, except perhaps maleic hydrazide that induces high frequency chromosomal breakage. (vi) Acridine dyes (proflavin, acriflavin, acridine orange, etc.) are intercalating agents and induce frameshift mutations at neutral pH. ►physical mutagens, ►radiomimetic, ►alkylation, ►biological mutagenic agents, ►environmental mutagens, ►depurination, ►chromosome breakage, ►frameshift, ►tautomeric shift, ►laboratory safety, ►chemicals hazardous; Ames test; Hollaender A (ed) 1971–80 Chemical mutagens. Principles and methods for their detection. Plenum, New York.

Chemical Mutation: Chemical mutation alters the active site of an enzyme by modifying the (tertiary) structure of the protein. The biologically relevant chemical space represents only a small fraction of the estimated 10^{60} types of molecules. ►protein structure

Chemical Products: Natural compounds have been classified into structural categories with the aim of developing greater utilization on the basis of properties (Koch MA et al 2005 Proc Natl Acad Sci USA 102:17272). ►chemical space

Chemical Space: Chemical space includes all possible organic molecules, including, and beyond, all C-containing molecules in the biological systems. The majority of the potential drugs used in medicine are smaller than 500 D. ►chemical products; Dobson CM 2004 Nature [Lond] 432:824.

Chemicals, Hazardous: The total number of chemicals identified exceeds 6 million. The various industries use over 60,000 chemical compounds and an estimated 700 new chemicals are introduced annually for various uses. Since the biological effects (mutagenicity, carcinogenicity) of only a relatively small fraction are known with certainty, the majority of chemicals should be regarded with appropriate caution. ►environmental mutagens, ►chemical mutagens, ►carcinogens, ►laboratory safety; <http://toxnet.nlm.nih.gov/>.

Chemiluminescence (chemoluminescence): Chemiluminescence is the production of light without heat by chemical reaction.

Chemiosmotic Coupling: Chemiosmotic coupling uses a pH gradient through a membrane to drive energy requiring processes. ►chemosmosis

Chemoattractant: ►chemotaxis

Chemoautotroph: An organism that obtains energy from inorganic chemical reactions.

Chemoeffectors: Refers to elicit bacterial response by bacterial signal transducers in chemotaxis.

Chemogenomics: Chemogenomics seeks out potential new drug targets by proteomic technology. Genes identified by genomic analysis are expressed as proteins. Potential drug-like libraries are tested to see whether the compounds bind the protein targets. The outcome of these tests facilitates either the selection or synthesis of additional, improved, structurally similar compounds. Selected molecules are then tested in biological systems for therapeutic effectiveness. ►combinatorial chemistry; Agrafiotis DK et al 2002 Nature Rev Drug Discovery 1:337.

Chemoheterotroph: An organism that obtains energy from the breakdown of organic molecules.

Chemokines (chemotactic cytokines): Chemicals (moving proteins) involved in defense systems or much activation by chemical agents. Chemokines are classified according to their cysteine motifs into CXC, CC, C, and CX3C groups. Chemokines are participants in specific inflammatory responses and some of them are identical to specific lymphokines. Chemokines also lure the lymphocytes to the sites of infection and inflammation. These small proteins have four conserved cysteines of which two are either adjacent or one other amino acid is in between the two. Chemokine α is represented by IL-8 and others encoded in close vicinity to each other in human chromosome 4q12-q21. On the surface of human neutrophils, 20,000 high affinity receptors have been found. They are encoded in human chromosome 2q34-q35. The β chemokine family includes MIP and the others are homologous to 28–73%, and are encoded in close linkage in human chromosome 17q11-q21. The MIP/RANTES receptor is encoded in 3q21. Chemokines cause a rise of free calcium, release of microbicidal oxygen radicals and bioactive lipids, storage granules containing proteases from neutrophils and monocytes, histamine from basophils and cytotoxic proteins from eosinophils. Chemokines interact with seven-transmembrane G protein-coupled receptors, CCR, CXCR and CX3CR. The CXC or α chemokines act on neutrophils and T cells; the CC or β chemokines such as the monocyte chemoattractant protein (MCP-1) act on monocytes, basophils, eosinophils, T cells (NK) and dendritic cells but usually not on neutrophils. Chemokines

trigger the activation of phosphoinositide kinase (PIK). Chemokines mediate cell polarization in differentiation, movement HIV-1 infection, and immune response. Homo- or heterodimerization of the chemokine receptors activate specific signaling pathways.

Eotaxins select only eosinophilic and basophilic granulocytes. Lymphotactin and fractalkine select monocytes and neutrophils. Chemokines interact with seven-transmembrane, G protein-coupled receptors of about 40 kDa size. ▶**lymphokines**, ▶**RANTES**, ▶**MIP**, ▶**fusin**, ▶**cytokines**, ▶**CCR**, ▶**CXR**, ▶**blood**, ▶**histamine**, ▶**antimicrobial**, ▶**peptides**, ▶**radical**, ▶**SDF**, ▶**acquired immunodeficiency syndrome**, ▶**lymphoid organs**, ▶**G proteins**, ▶**signal transduction**, ▶**PIK**; Cyster JG 1999 *Science* 286:2098; Mellado M et al 2001 *Annu Rev Immunol* 19:397; Mellado M et al 2001 *EMBO J* 20:2497; Schwarz MK et al 2002 *Nature Rev Drug Discovery* 1:347; Allen SJ et al 2007 *Annu Rev Immunol* 25:787.

Chemolithoautotroph: An organism that, for biosynthesis, relies on inorganic material and inorganic chemical energy. ▶**chemoheterotroph**

Chemoprevention of Cancer: Chemoprevention of cancer is generally based on regulation of cell division, ligands of nuclear receptors, selective modulation of the estrogen receptors, vitamin D analogs, inhibitors of cyclooxygenase, NF-κB, anti-inflammatory agents (curcumin [anti-cancer phenolic], resveratrol [antioxidant], caffeic acid [phenolic antioxidant]), chromatin modifiers (histone deacetylase inhibitors, methyl transferases), agents that control signal transduction (herceptin), and enhancers of the SMAD complex pathway which boost TGF-β signaling that is usually down-regulated in some cancers. ▶**cancer therapy**, ▶**nuclear receptors**, ▶**cyclooxygenase**, ▶**SMAD**, ▶**TGF**, ▶**herceptin**, ▶**NF-κB**; Sporn MB, Suh N 2002 *Nature Rev Cancer* 2:537.

Chemoreceptor: A gene product activated by chemical signal(s). In *Caenorhabditis* ~1,000 seven-transmembrane receptors genes have been identified which may be chemoreceptors although only half of them seems to be functional. Yet this is the largest gene family in this nematode. ▶**olfactogenetics**, ▶**taste**; Gestwiczki JE, Kiessling LL 2002 *Nature [Lond]* 415:81.

Chemosensitivity: The administered drugs affect many genes at the same time and the response of individual genes in different patients may vary. By exposing cells to various compounds at different concentrations, the 50% growth inhibition (GI₅₀) can be scored. The most sensitive and the most resistant cell lines can then be evaluated with the aid of microarray

hybridization. The information so derived may be of help for predictions of drug response, e.g., by cancer patients. ▶**multidrug resistance**, ▶**microarray hybridization**; Staunton JE et al 2001 *Proc Natl Acad Sci USA* 98:10787.

Chemosmosis: A chemical reaction across membranes.

Chemosterilant: A chemosterilant prevents or controls reproduction by natural or synthetic chemicals. ▶**sex hormones**, ▶**contraceptive**, ▶**busulfan**; Magdum S et al 2001 *J Appl Entomol* 125:589.

Chemostat: An apparatus for culturing bacteria at a steady level of nutrients, aeration, temperature, etc., so cell divisions are continuously maintained. ▶**bioreactor**; microchemostat: Balagaddé FK et al 2005 *Science* 309:137.

Chemotaxis: The movement toward chemical attractants and away from chemical repellents. Bacteria have very high sensitivity receptors for chemical signals. The receptors upon binding the chemical ligand propagate in clusters on the bacterial surface but single receptors also exist and thus they can adapt (respond) to a very wide concentration range (five orders of magnitude) of the chemicals. The receptor then transmits the signal through PLC and PIK to the cellular interior for further processing. In response to chemoattractant signals, the PI3K enzyme and its product PIP₃ accumulate on the plasma membrane on the side of the chemoattractant and the PIP₃-degrading PTEN and its product PIP₂ localize in a complementary pattern. Effector proteins dock to PIP₃ and induce polarization and regulate cytoskeleton function (Gamba A et al 2005 *Proc Natl Acad Sci USA* 102:16927). The cytoskeleton is highly polarized in migrating *Dictyostelium discoideum*. F-actin is in the anterior part of the cell and myosin II in the lateral and posterior regions. Extracellular 3',5' cyclic monophosphate activates its surface receptors, which transmit the signals when associated with trimeric G proteins. A number of additional proteins (phospholipase C, phosphoinositides, etc.) regulate the chemotactic pathway (Kimmel AR, Parent CA 2003 *Science* 300:1525). Macrophages, neutrophils, eosinophils, and lymphocytes are attracted to a wide variety of substances causing inflammation and the chemotactic mechanisms are basically similar to that of *Dictyostelium*. ▶**actin**, ▶**myosin**, ▶**G protein**, ▶**phosphoinositides**, ▶**phospholipases**, ▶**CheA**, ▶**blood cells**, ▶**PLC**, ▶**PIK**, ▶**PTEN**; Mori I 1999 *Annu Rev Genet* 33:399.

Chemotaxonomy: The study of evolutionary relatedness on the basis of chemical compounds.

Chemotherapy: The curing of a disease by chemical medication or fighting cancerous proliferation by antimitotic (cytostatic) chemicals. ▶**cancer**, ▶**cancer**

therapy, ►cytostatic, ►multiple drug resistance, ►genetic medicine, ►biomarkers; Huang Y 2007 Cancer Metastasis Rev 26:183.

Chemport: Provides links to important databases and scientific publications (electronic journals), patent offices, etc.: <http://chemport.org/html/english/about.html>.

Cheney Syndrome (acroosteolysis): An autosomal dominant bone disease with similarities to pycnodysostosis, but here, rather than hardening of some of the bones (osteosclerosis), bone loss (osteoporosis) was accompanied with early loss of teeth, laxity of the joints, etc. In this syndrome the stature of the patients was not necessarily short. ►pycnodysostosis

Chernobyl: ►atomic radiation

Cherry (*Prunus cerasus*): $x = 7$, but a wide variety of diploid and polyploid forms are known.

Cherubism: The dominant (4p16.3) proliferation of the lower (mandibula) or upper (maxilla) jawbone usually beginning at age 2–5 years and receding after puberty. The distortion of the face pulls down the lower eyelids and the eyes seem to be gazing upward. The distorted teeth and visual anomalies may remain (see Fig. C67). Fibroblast growth factor (FGF3) mapping to the same general area may be involved. Recent evidence indicates mutations in the SH3-binding protein SH3BP2. SH3BP2 is a regulator of M-CSF (macrophage colony stimulating factor) and rank ligand RANKL (Ueki Y et al 2007 Cell 128:71). ►FGF; ►macrophage colony stimulating factor, ►TRANCE; Mangion J et al. 1998 Am J Hum Genet 65:151; Tiziani V et al ibid. p.158; Ueki Y et al 2001 Nature Genet 28:125.



Figure C67. Cherubism

Chestnut (*Castanea* spp): A monoecious tree, $2n = 2x = 24$.

Chestnut Color: In horses it is due to homozygosity for the d allele; actually this color is expressed when the genetic constitution of the animals is $AAbbCCdd$.

Chetah: *Acionyx jubatus*, $2n = 38$.

Chi Elements (χ , crossing-over hotspot instigator): Chi elements are crossing-over hot spots-inciting DNA sequences in both prokaryotes and eukaryotes. The prokaryotic chi elements have the consensus

5'-GCTGGTGG-3' and nicking by the RecBCD complex takes place 4 to 6 bases downstream during recombination. In phage DNA chi sequences are required for the function of the bacterial genes *RecBC* coding for exonuclease V. The product of phage gene *gam* inhibits this enzyme. In *E. coli* there are about 500 to 600 chi elements. Chi promotes recombination in a region within 10 kb from its location. It may be activated by double-strand breaks within a range several kb downstream. Chi probably facilitates the production and availability of free 3' end for recombination. The hepatitis B virus encapsidation signal carries a 61-bp sequence (called 15AB) and is a hotspot for recombination; a cellular protein binding to this sequence appears to be a recombinogenic protein. The same nucleotide sequence (5'-CCAAGCTGTGCCTTGGGTGGC-3') has been identified with approximately 80% homologies also in the rat, mouse, and human genomes. Note the pentanucleotides in bold, they are present also in the prokaryotic chi elements as shown above. It appears that this element is responsible for some of the chromosome rearrangements observed in hepatocarcinomas. ►crossing over, ►recombination, ►rec, ►hepatoma, ►molecular mechanisms of recombination; Anderson DG et al 1999 J Biol Chem 274:27139; Lao PJ, Forsdyke DR 2000 Gene 243:47.

Chi forms: Recombinational intermediates representing consummated chiasmata. ►chiasma

Chi square (χ^2): A statistical device for testing the goodness of fit to a particular (null) hypothesis.

$$\chi^2 = \sum \frac{[\text{observed number} - \text{expected number}]^2}{\text{expected number}}$$

where Σ stands for sum. When the degree of freedom is 1, the use of the Yates correction may be justified and the formula becomes:

$$\chi^2 = \sum \frac{[|\text{observed} - \text{expected}| - 0.5]^2}{\text{expected}}$$

The Yates correction may be applied for other degrees of freedom in case the size of any particular class is 5 or less. It may be a better practice, however, to avoid using this correction factor and keeping in mind that our chi square figure is conservative. Although the χ^2 is very useful it must be remembered that it has a general weakness because it was derived from the principles of normal distribution but it is actually applied for discrete classes. An alternative to the above χ^2 statistics is the likelihood ratio criterion χ^2_L which is easier to compute in some cases and may give a more realistic estimate: $\chi^2 = 2 \sum \text{observed} \times \ln \left(\frac{\text{observed}}{\text{expected}} \right)$; the degree of freedom is calculated the same way as in other cases.

A slightly different type of formula is used in tetrad analysis to determine whether the frequency of

$\chi^2 = \frac{(PD-NPD)2}{PD+NPD}$ parental ditype (PD) tetrads really exceeds that of the nonparental ditypes (NPD). In linkage PD should exceed that of NPD. When the population size exceeds 30, use $\sqrt{2\chi^2 - \sqrt{2n - 1}}$ as a normal deviate. ▶chi square table, ▶homogeneity test, ▶association test, ▶degrees of freedom, ▶tetrad analysis, ▶lod score

Chi Square Table: The chi square table displays the probability of a greater χ^2 . Determine the value of the χ^2 by using the chi square formulas. Locate the nearest higher value in the body of the table (see Table C4) on the appropriate line of degrees of freedom (df). On the top line at the intersecting column you find the corresponding level of probability (P).

For a particular degree of freedom, the smaller χ^2 value indicates a better fit to the theoretical expectation (null hypothesis). By statistical convention when $P > 0.05$, the fit is not questionable, when P is between 0.05 and 0.01 the fit is more or less in doubt. When P is below 0.01 the null hypothesis is no longer tenable. (In the majority of statistical books more extensive χ^2 tables can be found)

Chiari Malformation: A variable cranial and neurological anomaly and syringomyelia with autosomal dominant inheritance. ▶syringomyelia

Chiasma (plural chiasmata): A chromatid overlap in prophase (appearing through the light microscope like the Greek letter chi [χ]), resulting in genetic exchange between bivalents. If the number of chiasmata truly represents the points of genetic exchange of chromosomes, from the cytological observation of chiasma frequency the length of the genetic map could be inferred because each crossing over corresponds to 50% recombination (see Fig. C68). Thus the number of chiasmata multiplied by 50 should be equal

to the sum of map distances. For example, C.D. Darlington observed 3 chiasmata in chromosome 3 of maize, thus $3 \times 50 = 150$. In fact, according to the modern map, the length of this chromosome is about ~ 167 m.u. According to B. Lewin the number of chiasmata per meiocyte in *Drosophila melanogaster* was 6.6 and $6.6 \times 50 = 300$ and the new cytogenetic map appears to be of ~ 297 m.u.

Recent analyses of plant recombination and chiasma data find that the frequency of recombination is higher than the chiasma frequency.



Figure C68. Multiple chiasmata in a male grasshopper chromosome. (Courtesy of Dr. B. John). Schematic representation of one chiasma in each arm

This revelation may or may not affect the general validity of the correspondence suggested earlier because of the cytological difficulties obtaining very precise estimates on chiasmata. Also, the recombination data may have some inherent errors even if mapping functions are used. It is well known that interference varies along the length of the chromosome and according to species, etc., and no general mapping function can fully appreciate that fact. Chiasmata take place as the bivalents represent 4 strands (chromatids).

In about 6–10% of the X chromosomes there are no chiasmata, whereas 60–65% of the bivalents display one, and 30–35% show two, but a higher number of chiasmata is very rare. The frequency of chiasmata usually varies between male and female meiosis and it is usually higher in the latter. The occurrence of

Table C4. Chi square table

| P→ | 0.99 | 0.90 | 0.75 | 0.50 | 0.25 | 0.10 | 0.05 | 0.01 | 0.005 |
|-----|------|------|------|------|-------|-------|-------|-------|-------|
| df↓ | | | | | | | | | |
| 1 | 0.00 | 0.02 | 0.10 | 0.45 | 1.32 | 2.71 | 3.84 | 6.64 | 7.90 |
| 2 | 0.02 | 0.21 | 0.58 | 1.39 | 2.77 | 4.60 | 5.99 | 9.92 | 10.59 |
| 3 | 0.11 | 0.58 | 1.21 | 2.37 | 4.11 | 6.25 | 7.82 | 11.32 | 12.82 |
| 4 | 0.30 | 1.06 | 1.92 | 3.36 | 5.39 | 7.78 | 9.49 | 13.28 | 14.82 |
| 5 | 0.55 | 1.61 | 2.67 | 4.35 | 6.63 | 9.24 | 11.07 | 15.09 | 16.76 |
| 6 | 0.87 | 2.20 | 3.45 | 5.35 | 7.84 | 10.65 | 12.60 | 16.81 | 18.55 |
| 7 | 1.24 | 2.83 | 4.25 | 6.35 | 9.04 | 12.02 | 14.07 | 18.47 | 20.27 |
| 8 | 1.64 | 3.49 | 5.07 | 7.34 | 10.22 | 13.36 | 15.51 | 20.08 | 21.97 |

chiasmata may display substantial variations even within a bivalent. There is evidence that the occurrence of chiasma facilitates orderly segregation of the chromosomes and reduces nondisjunction. In the majority of organisms chiasmata are rare at the tip and at the centromeric regions. Special genes regulate chiasmata. In *Saccharomyces* the Rad50 protein (an ATP-dependent DNA-binding protein, localized at interstitial sites) seems to be involved in the development of the axial structure of chromosomes, pairing, and recombination. ▶meiosis, ▶crossing over, ▶recombination frequency, ▶mapping genetic, ▶interference, ▶chromatid interference, ▶isochores, ▶achiasmate, ▶desynapsis, ▶sister chromatid cohesion, ▶separin, ▶mapping function, ▶association point, ▶recombination nodule, ▶nondisjunction, ▶count-location models, ▶stationary renewal; Tease C 1998 Chromosoma 107:549; Meneely PM et al 2002 Genetics 162:1169.

Chiasma Interference: ▶chromatid interference, ▶interference

Chiasma Terminalization: ▶terminalization of chromosomes

Chiasmata (plural of chiasma): ▶chiasma

Chicago Classification: The Chicago classification of human chromosomes was based on banding and morphology and it has been refined since 1966. ▶human chromosomes, ▶Denver classification, ▶Paris classification

Chick Pea (*Cicer arietinum*): The grain legumes representing the pulses. The chromosome number is generally $2n = 2x = 16$.

Chicken: *Gallus domesticus* $2n = \text{ca. } 78$. There are two sex chromosomes, ZW in the heterogametic females and ZZ in homogametic males. There are also 38 pairs of autosomes of widely different sizes. The microchromosomes have only 5 million to 20 million base pairs, and their G-C level is relatively high and repetitions are relatively low. The macrochromosomes are about two orders of magnitude larger. Genome size in $\text{bp/n} \cong 1.2 \times 10^9$. Estimated gene number 20,000–23,000. About 2,200 loci have been mapped with a total length of $\sim 4,000 \text{ cM}$. A physical map of the genome is available (Wallis JW 2004 Nature [Lond] 432:761). Segmental duplications in the chromosomes are relatively short ($>10 \text{ kb}$) and generally limited to within the chromosome rather than among chromosomes. Recombination rates vary and the rates are much higher in the short minichromosomes ($\sim 2.8 \text{ cM/Mb}$) versus macrochromosomes ($\sim 6.4 \text{ cM/Mb}$). Their average rate in human chromosomes is 1–2 cM/Mb.

A draft sequence of the Asian chicken (red jungle fowl, *Gallus gallus*, female shown at left) genome is available (see Fig. C69). When aligned with the human sequences, long blocks of synteny are conserved (Int. Chicken Genome Consortium. 2004 Nature [Lond] 432:695). About 60% of the protein-coding genes have a single human homolog, and the identity of the homologs is 75.3%, in contrast the human-mouse homologs with $\sim 88\%$ consensus. The chicken genome lacks genes for vomeronasal receptors, casein milk proteins, salivary-associated proteins, enamel proteins, α -interferon, etc. The OR5U1/OR5BF-1-like (olfactory receptor) genes contribute to the majority of the 283 olfactory genes, a number comparable to that in humans, although olfaction in chickens is somewhat debated. Some other protein families are either under- or over-represented in the chicken relative to other vertebrates. Among red jungle chicken, in Broiler and Silkie breeds the average single nucleotide polymorphism is 2.8 million (Int. Chicken Polymorphism Map Consortium. 2004 Nature [Lond] 432:717). The chicken genome exhibits only 51 retroposed duplicates in contrast to humans that show more than 15,000.



Figure C69. Jungle fowl

The number of retrotransposons (CR1)—resembling the L1 elements of mammals—is about 200,000 in the chicken genome. Most of the CR1 elements are probably inactive currently. Processed pseudogenes are relatively rare in chickens. Copia and gypsy elements are absent. Retroposons with Long Terminal Repeats (LTR) are of the mammalian type. Only two types of DNA transposons were detected.

Transgenic chickens can be produced at relatively low cost. Their speed of development and the production of a flock and potentially appropriate glycosylation of target proteins have led to the use of

C

chickens as a bioreactor for therapeutically needed proteins (Lillico SG et al 2005 Drug Discovery Today 10(3):191). Lentiviral vectors derived from equine infectious anemia virus were designed to minimize the potential for homologous recombination. Humanized ScFv-Fc mini-antibody (miR24), derived from a mouse monoclonal antibody—shown to have potential for the treatment of malignant melanoma—or human interferon 1a carrying vectors were injected in the oviduct and produced functional proteins as a component of the abundant egg white. The high-titer vector was introduced into packing cell lines or injected beneath the blastoderm of the un-incubated egg. Injected embryos were cultured for 21 days through hatching. The chicks were then raised to sexual maturity; the roosters with semen positive for the transgene were mated with wild-type hens, and the offspring were screened for the presence of the transgene (Lillico SG et al 2007 Proc Natl Acad Sci USA 104:1771). ▶DT40, ▶antibody, ▶interferon, ▶melanoma; consensus genetic map: Groenen M et al 2000 Genome Res 10:137; genes; inbred lines; functions; Brown WRA et al 2003 Nature Rev Genet 4:87; historical significance of poultry genetics; Pettitt JN, Mozdziaik PE 2007 Proc Natl Acad Sci USA 104:1739; <http://poultry.mph.msu.edu/>; <http://www.tigr.org/tdb/tgi.shtml>; <http://www.chicken-genome.org>; <http://www.genome.iastate.edu/chickmap/dbase.html>; variations in the chicken genome; <http://chicken.genomics.org.cn>; chicken genome; http://www.ensembl.org/Gallus_gallus/index.html.

Chickenpox: A highly contagious skin disease of children and young adults with possible serious complications, caused by the Varicella zoster virus. Vaccination is very effective (Nguyen HQ et al 2005 New Engl J Med 352:450). ▶shingles, ▶Varicella zoster virus

CHILD syndrome (congenital hemidysplasia [asymmetric symptoms] with ichthyosiform erythroderma and limb defects): CHILD syndrome is caused by deficiency of 3- β -hydroxysteroid- δ -8, δ -7 isomerase at Xp11.23-p11.22 (EBP) or by the NAD(P)H steroid dehydrogenase-like protein at Xq28 (NSDHL, ichthyosis, Conradi-Hünemann syndrome).

Chimaerin (chimerin): A family of Rac-GTPase-activating proteins. ▶Rac, ▶epiboly

Chimera: A mythological monster that had a serpent's tail, goat's body and lion's head, and vomited flames through her mouth. (See also chimera below).

Chimera: A mixture of genetically different tissues within an individual or other structures of two or more different fused elements; frequently it displays visible sectoring. The term is used also for embryos that

contain both animal and human genetic material although fertilization of human eggs with animal sperms or animal eggs with human sperm is prohibited in all countries. Within a hybrid plant seed the embryo is diploid, the endosperm is usually triploid and the seed coat is maternal, making it essentially a triple chimera. In the armored scale insects the chimerism is complex. The three polar bodies, products of the female meiosis, are not eliminated as in the majority of the animals, but the three cells fuse. Subsequently, they may fuse with one cell of the diploid embryo and give rise to the pentaploid *bacteriome*, which accommodates the symbiotic bacteria of the mother. This pentaploid cell lineage then coexists with the diploid tissues during development. In most scale insects the paternal genome is eliminated as the common fate of sex determination. Such elimination does not take place, however, in the bacteriome. Thus, the bacteriome has a two haploid maternal chromosome set plus one male haploid set (Normark BB 2004 PLoS Biol 2:298). The word is adopted from the mythological monster of lion head-goat body-serpent tail (see Figs. C70 & C71). ▶periclinal chimera; ▶mericlinal chimera; ▶multiparental hybrids; ▶sex determination; ▶marmoset



Figure C70. Chimera, ancient Greek bronze statue



Figure C71. Chimeric plant

Chimeraplasty: Chimeraplasty was designed to repair (with the aid of Rec A, MutS) single nucleotide defects in mammalian (human) cells and also in

plants. The perfected procedure is expected to also create specific mutations. The complementary DNA is hybridized with 2'-O-methyl-RNA to protect the construct from nuclease attacks. The delivery is by injection in liposomes and it is supposed to be taken up by a sialoglycoprotein receptor. The targeting in this system is supposedly excellent. The initial experiments involved mismatch repair in the Crigler-Najjar cells and hepatocytes. During the years following the first reports the reproducibility was quite disappointing in several laboratories and the applicability of the procedure is now questionable at best. ▶[RecA](#), ▶[MutS](#), ▶[mismatch repair](#), ▶[liposome](#), ▶[sialic acid](#), ▶[Crigler-Najjar disease](#); Stephenson JJ 1999 Am Med Assoc 281:119; Taubes G 2002 Science 298:2116.

Chimeric Clones: Chimeric clones result when two segments of DNA derived from noncontiguous regions of the chromosomes are joined together. A high level of homologous recombination may cause this. These joined areas are cloned together (co-cloning). Co-cloning is disadvantageous for the construction of physical maps. ▶[chimeric DNA](#), ▶[physical map](#)

Chimeric DNA: ▶[recombinant DNA](#)

Chimeric Plasmids: Chimeric plasmids contain genetic sequences from other genomes along with their own DNA. ▶[plasmid](#), ▶[vector](#)

Chimeric Proteins: May be used to gain additional function(s) by the same molecule. That can be constructed by adding new domains. The desired domain may be provided with “sticky ends” through PCR procedures. The sticky ends are supposed to pair with homologous portions of a target in a single-strand vector and after replication one of the new strands of the double-stranded DNA will contain the sequences coding for a polypeptide corresponding to the donor molecule. Chimeric proteins may also be obtained by the use of translational fusion vectors. ▶[primer extension](#), ▶[translational gene fusion](#), ▶[vector](#); Louis JM et al 2001 Biochemistry 40:11184.

Chimeric YAC: Produced when more than one piece of DNA is ligated to the same vector arm. It is generally undesirable for chromosome walking toward a particular locus because it may direct toward different direction(s) than the region of interest. ▶[YAC](#), ▶[chromosome walking](#)

Chimpanzee (*Pan troglodytes*, $2n = 48$): The chromosome number of the great apes higher than that in humans (46) because in humans chromosome 2 is fused from two chromosomes. The ape chromosomes have been renumbered recently according to the human system (McConkey EH 2004 Cytogenet



Figure C72. Chimpanzee

Genome Res 105:157). Chimpanzee is the closest to humans among the great apes by DNA sequences (see Fig. C72). Human diverged from the chimpanzee line about 6 million years ago. A newer estimate, based on 167 nuclear protein-coding genes, suggests the divergence was 4.98–7.2 millions years ago (Kumar S et al 2005 Proc Natl Acad Sci USA 102:18842). The divergence between the human and chimpanzee X chromosomes appears more recent than the rest of the genome. This is interpreted that after the initial divergence of the two species genetic exchanges occurred again before the final separation (Patterson N et al 2006 Nature [Lond] 441:1103). The mean pair-wise sequence difference (MPSD) among chimpanzees is about four times higher (0.13%) than among humans (0.037%). Similarly, the mtDNA is more variable among different chimpanzee subspecies. This information indicates also the longer evolutionary history of this ape. The average divergence from the human nucleotide sequence is ~1.23%. One of the most important genes separating human from apes is FOXP2, responsible for the development of speech. The nonsynonymous/synonymous nucleotide substitution rate in 13,454 human-chimpanzee genes is low, 0.23, higher however than that in mouse-rat comparisons, 0.13. The same index is about the same as that among humans, ~0.23–0.20. About 33% of the longer deletions in humans are human-specific but in chimpanzee only 17% are chimpanzee-specific. There are ~7,000 Alu elements in humans but only 2300 in the chimpanzee genome. L1 element number is about the same in the two genomes. There are about 35 million nucleotide, 5-million indel difference and many chromosomal rearrangement changes between the two species. Many human disease genes have counterparts—some with different variants—in the chimpanzee genome (Li W-H, Saunders MA 2005 Nature [Lond] 437:50; The Chimpanzee Sequencing and Analysis Consortium 2005 Nature [Lond] 437:69).

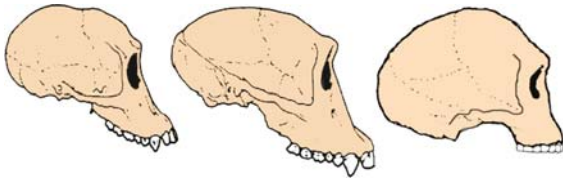


Figure C73. Bonobo, chimpanzee, and hominid

One third of the human chromosomal duplications are not represented in chimpanzee. Chimpanzee-specific hyper-expansion (more than 100 copies) represents major quantitative differences between the two species. Segmental duplications had more impact on the differences than base substitutions (Cheng Z et al 2005 *Nature [Lond]* 437:88). Preliminary data indicate that 83% of the coding sequences of chimpanzee and humans differ at the amino acid level (Tateno Y et al 2005 *Nucleic Acids Res* 33: D25–28), complicating the evolutionary views. A detailed comparative map is available between the corresponding human chromosome 21 and the chimpanzee chromosome 22 indicating nearly 68,000 indels in addition to SNPs and a rather complicated evolution of these chromosomes (Watanabe H et al 2004 *Nature [Lond]* 429:382). A draft of the entire genome sequence became available in 2005 (*Nature [Lond]* 437, 1 Sept.). A report on the finished sequences of the chimpanzee Y chromosome (Kuroki Y et al 2006 *Nature Genet* 38:158) has been criticized (Hughes JF et al 2006 *Nature Genet* 38:853) and defended (Kuroki Y et al 2006 *Nature Genet* 38:854). Gene expression pattern in five different tissues of chimpanzee and humans displayed modest differences only. The transcriptome of the brain differs less between the two species than in other tissues although genes expressed in the brain accumulated more changes in humans. In the human lineage an unknown gene (MGC 8902), containing a functionally unknown domain (DUF1220), is repeated 212 times. This domain is highly expressed in the brain and the increase in humans, chimpanzees and macaques was found in the proportion of 49, 10 and 4, respectively, suggesting it to be an important factor in human evolution (Popesco MC et al 2006 *Science* 313:1304). In the intergenic sequences of protein-coding genes of the human cerebellum a noncoding RNA gene (HAR1F) is critically expressed with reelin in the cortical region during the period of 7 to 19 weeks of gestation. Several other evolutionarily, highly accelerated (HAR) areas occur in humans and they regulate neurodevelopment and therefore they are considered critical for the separation of humans from chimpanzee and other apes and for the continued evolution of humans (Pollard KS et al

2006 *Nature [Lond]* 443:167). The transcriptome of the testis shows more differences than brain, heart, liver, and kidney tissues. In general, genes expressed in more tissues show fewer differences in expression than those expressed in a single tissue (Khaitovich P et al 2005 *Science* 309:1850). Results based on 14,000 genes indicate that the number of positively selected genes is substantially smaller in humans than in chimps, despite a generally higher nonsynonymous substitution rate in humans. These observations are explainable by the reduced efficacy of natural selection in humans because of their smaller long-term effective population size, but refute the anthropocentric view that a grand enhancement in Darwinian selection underlies human origins (Bakewell MA et al 2007 *Proc Natl Acad Sci USA* 104:7489).

Chimpanzee populations in the wilds of Cameroon, Africa, may contain antibodies in 29–35% of the individuals to the SIVcpz immunodeficiency virus, a close relative of HIV-1. This indicates chimpanzees to be a source of human infection by HIV-1, the causative agent of acquired immunodeficiency. The reclusive populations were tested for nucleic acids and antibodies from fecal samples found in the forests (Keele BF et al 2006 *Science* 313:523).
 ▶transcriptome, ▶Pongidae, ▶primates, ▶malaria, ▶sialic acid, ▶indel, ▶SNP, ▶bonobo, ▶endorphin, ▶acquired immunodeficiency, ▶noncoding RNA, ▶reelin, ▶language; Wildman DE 2002 *BioEssays* 24:490; Muchmore EA 2001 *Immunol Rev* 183:86; Gagneux P 2002 *Trends Genet* 18:327; Olson MV, Varki A 2003 *Nature Rev Genet.* 4:20; medical relevance; http://www.chimpanzoo.org/medical_database.html.

Chinese Restaurant Syndrome: An adverse reaction (headache, stiffness of the neck and back, nausea, etc.) to the flavor enhancer monosodium glutamate in certain foods such as soy sauce, hot dog, etc. It may be controlled by a recessive gene. ▶monosodium glutamate; Walker R, Lupien JR 2000 *J Nutr* 130 (4):1049S.

ChIP (chromatin immunoprecipitation): ChIP assay can be used to identify definite regulatory sequences in the DNA by the use of antibodies against specific transcription factors. Chip-on-Chip (Chip-chip) uses immunoprecipitation of a DNA–protein complex and this then is followed by a microarray hybridization for mapping and quantifying the enriched short sequence (Bullwinkel J et al 2005 *J Cell Physiol* 206:624; Kondo Y et al 2004 *Proc Natl Acad Sci USA* 101:7398). ▶immunoprecipitation, ▶ChIP-chip; Zeller KI et al 2001 *J Biol Chem* 276:48285.

CHIP (channel-forming integral protein): A member of water transporters to various types of cells and tissues in cellular organisms. Chip interacts with several homeodomain proteins involved with differentiation and development of eukaryotes. In humans, the aquaporin-1 gene in chromosome 7p14 encodes it.

Chip: An electronic circuit within a single piece of semiconducting material, e.g., silicon. ▶semiconductor

Chip: ▶microarray hybridization, ▶protein chip

ChIP-chip: Chromatin immunoprecipitation followed by detection of the products using a genomic tiling array. ▶ChIP, ▶tiling; Buck MJ, Lieb JD 2004 Genomics 83:349.

Chipmunk: *Eutamias amoenus* 2n = 38; *Eutamias minimus* 2n = 38; *Funambulus palmarum* 2n = 46; *Funambulus pennanti* 2n = 54; *Glaucmys volans* 2n = 48.

CHIP-PET: DNA is immunoprecipitated and cloned into a library and then converted into paired-end (PET) ditags. Concatenated CHIP-PET library is sequenced. ▶immunoprecipitation, ▶paired-end diTAG

Chiral compound: ▶enantiomorph

Chirality: The dissymmetry of a molecule, i. e., its plane mirror image cannot be brought to coincide with itself. ▶enantiomorph (see Fig. C74).



Figure C74. Chiral isomers

Chironomus Species (2n = 8): Chironomus species are favorable organisms (dipteran flies) for cytology because of the very conspicuous differences in the banding of the salivary gland chromosome among species and within species, reflecting the activity of genes by the pattern of puff formation. ▶giant chromosomes, ▶puff, ▶Rhynchosciara, ▶Sciara; Phillips AM et al 2000 Methods Mol Biol 123:83.

Chitin: Poly-N-acetylglucosamine is part of the exoskeleton of insects, of other lower animals, and of the cell wall of fungi (see Fig. C75). Chitin is apparently absent from mammalian cells yet chitinase exists and may play a role in IL-13 pathway of Th2 induced asthma (Zhu Z et al 2004 Science 304:1678). The chitinase enzyme plays a role in the protection of plants against fungal and insect damage. In chitinases the nonsynonymous mutations in the DNA exceed the synonymous ones, indicating the tendency of adaptive

evolution in the plant defenses. ▶host-pathogen relations, ▶insect resistance, ▶exoskeleton; Bishop JG et al 2000 Proc Natl Acad Sci USA 97:5322; Zhang B et al 2002 Mol Plant Microbe Interact 15:963.

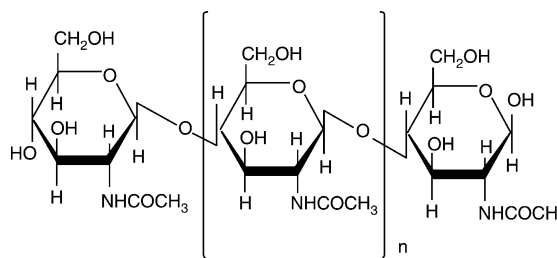


Figure C75. Chitin

Chk1: A 476 amino acid G2 cell cycle phase checkpoint serine/threonine kinase, which prevents the cell to enter the M phase in case the DNA is damaged. CDC25 protein phosphatase in yeasts and human cells dephosphorylate CDC2 at tyrosine 15 and thus activate it and turn on the cell cycle. CDC25 phosphorylated at serine-216 by Chk1 binds to proteins 14-3-3, such as RAD24, and the complex brings about the cell cycle arrest while the DNA damage is corrected. CDC25 is basically a cytoplasmic protein but it enters also the nucleus to activate CDC2 under normal conditions. After the cell is damaged, e.g., by irradiation, RAD24 facilitates the nuclear export of CDC25 and the checkpoint arrest is created. Chk1 heterozygosity by haploinsufficiency can contribute to tumorigenesis by inappropriate entry into the S phase of the cell cycle, accumulation of DNA damage during replication and failure to restrain entry into mitosis (Lam MH et al 2004 Cancer Cell 6:45). ▶cell cycle, ▶protein 14-3-3, ▶Cdc25, ▶checkpoint, ▶p53, ▶Cdc2, ▶Cdc25, ▶haploinsufficient; Chen P et al 2000 Cell 100:681.

CHK2: A checkpoint kinase, a mammalian homolog of RAD53 in *Saccharomyces cerevisiae* and Cds1 of *Schizosaccharomyces pombe*. This protein is phosphorylated in response to replication arrest or DNA injury. In vitro CHK2, like CHK1, phosphorylates CDC25C and thus prevents entry into mitosis and seems to be involved with ATM. ▶CDC25, ▶ATM, ▶RAD53, ▶p53, ▶ataxia, ▶FHA; Ward IM et al 2001 J Biol Chem 276:47755.

Chlamydia: A pathogenic bacteria. *C. pneumoniae* (1.23 Mb) causes respiratory injuries, atherosclerosis and is a sexually transmitted pathogen; *C. trachomatis* (1.05/1.07 Mb) causes blindness. Several other chronic diseases may be affected by *Chlamydia* and by other microbes. (See Zimmer Z 2001 Science 293:1977).

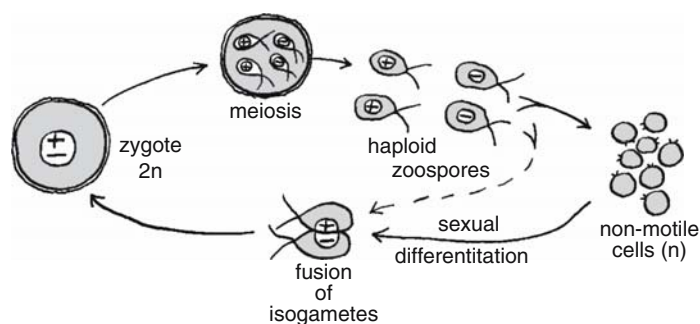


Figure C76. The life cycle of *Chlamydomonas*

Chlamydomonas eugametos ($n = 7$): A unicellular green alga.

Chlamydomonas reinhardtii: A unicellular green alga showing both haploid and diploid stages. (see Fig. C76). The fusion of (+) and (−) mating type gametes (that are not identifiable by morphology) gives rise to diploid cells that immediately undergo meiosis and release haploid zoospores. This progeny can be subjected to unordered tetrad analysis. On solid media they produce only rudimentary flagellae but in liquid culture they are flagellated. The zoospores may readily divide by mitosis but they sexually differentiate under nitrogen starvation and gametic fusion follows. Their basic chromosome number $n = 8$ (1.2×10^6 bp). This sequenced genome contains 17 linkage groups including 15,143 genes (Merchant SS et al 2007 Science 318:245). They contain one large chloroplast (with about 196-kbp DNA). Chloroplast genes normally show uniparental inheritance in 99% of the progeny. When the male (*mt*−) cells are irradiated with UV before mating, biparental plastids are formed. The heterozygotes for plastid genes (cytohets) display recombinations of plastid genes in their single-plastid progeny. Recombination is either reciprocal or nonreciprocal among the plastid genes. On this basis, strictly genetic maps could be constructed for the circular plastid DNA. Physical maps are also available and are used mainly for determining gene positions. Molecular analysis revealed that one plastid gene *psa* (a photosystem protein) contain three exons; exon 1 is 50 kb away from exon 2 and from this exon 3 is 90 bp apart. In between, there are several other transcribed genes. Further complication is that exon 1 is in opposite orientation to the other two. It is supposed that for the expression of this gene transsplicing is used, i.e., (in contrast to the regular, common mechanism of splicing neighboring exons), here distant transcripts are brought together in the mRNA. The mitochondrial DNA is about 15.8 kb. Some alga mutants (*minutes*) are apparently mitochondrial and resemble

petites in yeast. Since insertional mutagenesis became feasible, genetic and molecular analysis of the photosynthetic apparatus is greatly facilitated. Gene targeting, transformation, homologous recombination, site-directed mutagenesis, etc. techniques are available. [The name of this alga is often spelled as *Chlamydomonas reinhardi*.] ▶petite colony mutants, ▶chloroplast DNA, ▶chloroplast genetics, ▶eyespot, ▶mitochondria, ▶biolistic transformation; Rochaix J-D 1995 Annu Rev Genet 29:209; Rochaix J-D et al (eds) 1998 The molecular biology of chloroplasts and mitochondria in chlamydomonas. Kluwer, Dordrecht, Holland; Harris EH 2001 Annu Rev Plant Physiol Mol Biol 52:363; Grossman AR et al 2004 Annu Rev Genet 38:119; <http://www.chlamy.org>.

Chlamydospore: A thick-walled persistent asexual spore.

Chloracne: An eruption on the skin caused by exposure to chlorine and related compounds.

Chlorambucil: [p-(di-2-chloroethylamino)phenyl]butyric acid]: A radiomimetic nitrogen-mustard derivative causing primarily deletions and translocations. It had been used as an antineoplastic drug and it is also a carcinogen. ▶radiomimetic, ▶carcinogen

Chloramphenicol: An antibiotic affecting peptidyl transferase in bacterial and mitochondrial protein synthesis (see Fig. C77). In human populations about 5×10^{-5} of the individuals may be very sensitive to the drug and develop anemia. ▶cycloheximide, ▶mitochondrial human disease

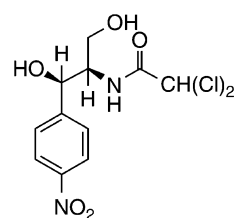


Figure C77. Chloramphenicol

Chloramphenicol Acetyltransferase (CAT): The CAT gene has been extensively used as a reporter for transformation in cell culture by becoming resistant to the antibiotic chloramphenicol and thus selectable.

►antibiotics, ►transformation

Chlorate: Chlorate has been used for the isolation of nitrate reductase deficient mutations that are not poisoned by chlorate. Some mutations, however, are hypersensitive to chlorate. Chlorate-sensitivity is apparently based also on uptake problems. ►nitrate reductase

Chlorenchyma: A tissue with green plastids (chloroplasts).

Chloride Diarrhea, Congenital: A recessive defect involving ion transport, encoded in human chromosome 7q31. ►chlorate

Chlorodeoxyuridine: ►bromodeoxyuridine

Chloronema: A gametophytic cell row in mosses. ►gametophyte

Chlorophyll: Magnesium-porphyrin complexes (chlorophyll-a, -b, protochlorophyll, bacteriochlorophyll) in green plants and bacteria, receptors of light energy for carbon fixation and photosynthetic phosphorylation. The synthetic pathway: α -ketoglutaric acid \rightarrow δ -aminolevulinic acid \rightarrow porphobilinogen \rightarrow protoporphyrin IX \rightarrow Mg-protoporphyrin \rightarrow protochlorophyllide a \rightarrow chlorophyllide a \rightarrow chlorophyll a [and chlorophyll b]. When Mg is removed from porphyrin pheophorbide results and the grayish color appears. Genetically-determined failure to open the pheophorbide ring is responsible for the retention of greenness during senescing (Asrmstead I et al 2007 Science 315:73). ►Calvin cycle, ►chlorophyll-binding proteins; Suzuki JY et al 1997 Annu Rev Genet 31:61; Grossman AR et al 2004 Annu Rev Genet 38:119; degradation pathway: Hörtensteiner S 2006 Annu Rev Plant Biol 57:55.

Chlorophyll-Binding Proteins (CAB, chlorophyll A and B binding proteins, light-harvesting chlorophyll protein complex, LHCP): Chlorophyll-binding proteins are situated in the membrane of the thylakoids. They modify the plane of orientation of chlorophylls. Due to this modification the chlorophyll does not fluoresce when excited by visible light (as it would do without CAB). The light energy absorbed by (an antenna) chlorophyll is rather transferred to a neighboring chlorophyll molecule and then excites this second chlorophyll while the first one returns to the ground state. This *resonance energy transfer* is continued to further neighbors until the *photochemical reaction center* is reached. In this molecule an electron is raised to a higher energy orbital, and this

electron is transferred to the *electron transfer chain* of the chloroplast resulting in an electron hole (empty orbital). The electron acceptor thus gains a negative charge and the lost electron by the reaction center is replaced by another electron coming from a neighbor molecule, which therefore becomes positively charged. As a consequence, the light sets into motion an oxidation-reduction chain and the generation of ATP and NADPH. About 16 genes encode the CAB complex, and a LHCP system has also been identified. The red algae and cyanobacteria, which have only chlorophyll a, use phycobilisomes for light harvesting. Several types of accessory pigments (carotenoids, pteridins, phycoerythrobilin, etc.) may be associated with the light-harvesting complex. ►photosynthesis, ►photosystems, ►photophosphorylation, ►Calvin cycle, ►phycobilins, ►Z scheme; Grosman AR et al 1995 Annu Rev Genet 29:231; LHC structure; Liu Z et al 2004 Nature [Lond] 428:287.

Chloroplast: The green, chlorophyll-containing organelle of plant (algal) cells where photosynthesis takes place. It contains several rings of DNA that are transcribed and translated. The chloroplast genome of higher plants encodes about 60 to 80 proteins. Other plastid proteins (about 3,500) are imported from the cytosol and some of the proteins are under the control of the nucleus and the chloroplast genome. The division of the chloroplast DNA follows a mechanism similar to that of the prokaryotic nucleoid. Although plastid and nuclear divisions can be uncoupled, the cell cycle and plastid divisions are coordinated for normal development (Reynaud C et al 2005 Proc Natl Acad Sci USA 102:8216). ►chloroplasts, ►chloroplast genetics, ►evolution of organelles, ►Cdt1; Osteryoung KW, McAndrew RS 2001 Annu Rev Plant Physiol Plant Mol Biol 52:315.

Chloroplast Endoplasmic Reticulum: ►nucleomorph; ►endoplasmic reticulum

Chloroplast Envelope: A double membrane, which surrounds this organelle and controls the uptake of metabolites and the transport of proteins encoded by nuclear genes. Furthermore, it participates in the biosynthesis of many plastid molecules. A few of the plastid envelope components are coded, however, by ctDNA. ►chloroplasts

Chloroplast Genetics: The most successfully studied in the *Chlamydomonas* alga. *C. reinhardtii* has only one chloroplast with about 80 cpDNA molecules of 196 kbp each. The transmission of the cpDNA genome is largely uniparental, i.e., inherited most commonly through the mt^+ (comparable to egg) cytoplasm although in 1–10% of the cases biparental transmission may take place (alfalfa, *Oenothera*). The chloroplast nucleoid (DNA) transmitted by the

mt^- mate is usually completely digested in *Chlamydomonas* within 10 minutes after zygote formation, whereas the mitochondrial nucleoid still remained intact. Specially, e.g., in conifers, uniparental male transmission may also exist. The uniparental mt^+ transfer may sometimes be spurious in cases when the coding of the subunits of a particular protein is under the control of nuclear and organelle genes, respectively. In diploid vegetative zygotes of *Chlamydomonas* the biparental transmission of the extranuclear genes is most likely. Incubation in dark or postponing the meiosis by nitrogen starvation, however, favors uniparental transmission (see Fig. C78).

In higher plants, the transmission of the plastid is usually through the female but biparental or only

male transmission also occurs. The plastid nucleoids may be eliminated from, or degraded in, the sperms during the first or second nuclear division in the pollen, or they are left behind when the generative nucleus enters the egg.

In tobacco the frequency of transmission of transgenes through the pollen into the cotyledons of F1 seedlings was 1.58×10^{-5} (at 100% cross-fertilization); transmission into the shoot apical meristem was significantly lower, 2.86×10^{-6} (Ruf S et al 2007 Proc Natl Acad Sci USA 104:6998). In another experiment, plastids from the transgenic plastids of the male tobacco were transmitted (10^{-4} – 10^{-5}) frequencies indicating again that the transgene can be reasonably well contained if it is carried by the plastids

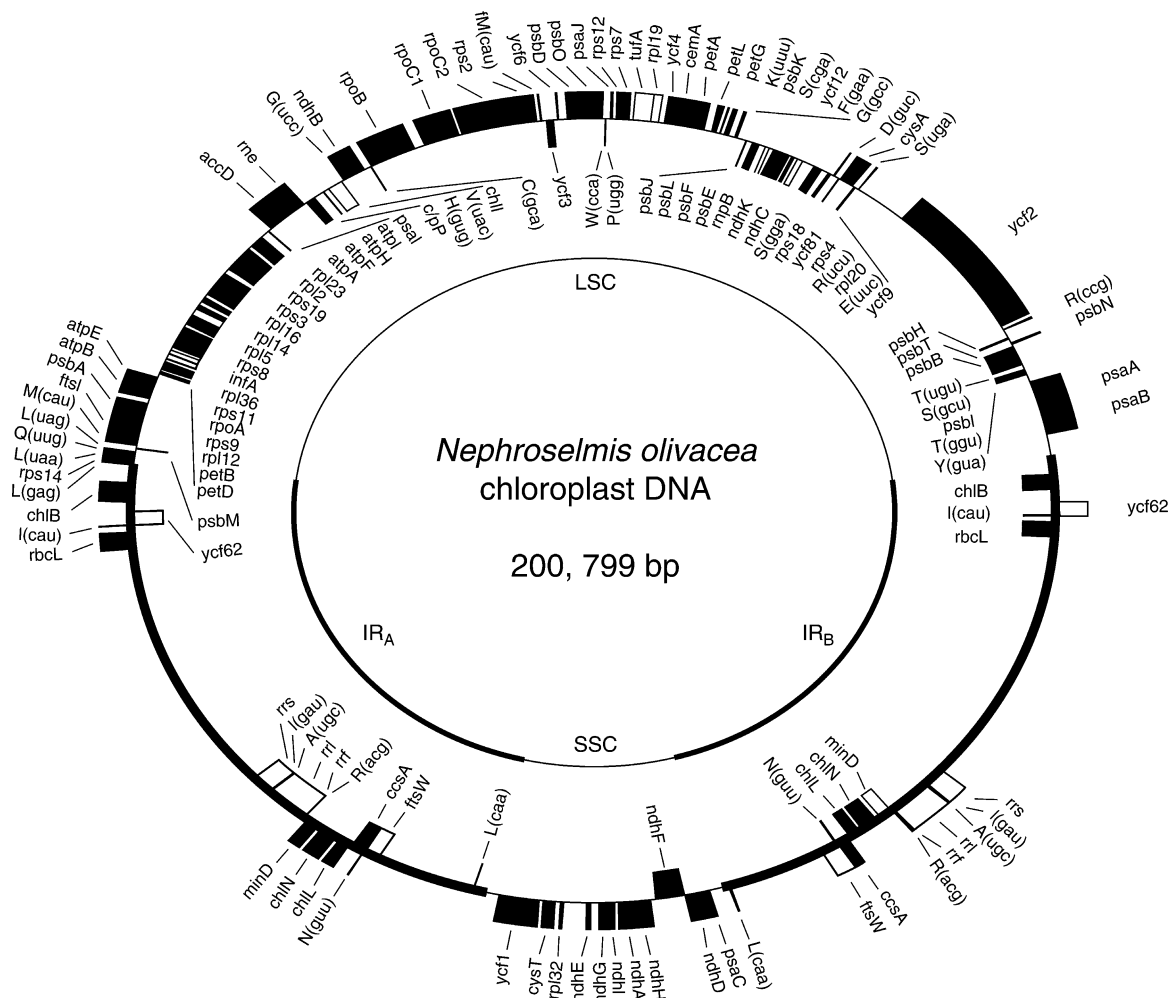


Figure C78. Chloroplast genetics. The chloroplast DNA map of the alga *Nephroselmis*. Lsc: large single-copy sequences, ssc: small single copy sequences. genes outside the large circle are transcribed clockwise and the inner set is transcribed counterclockwise. The thicker lines on the inner circle represent the two copies of the rRNA genes (IR). The gene sequences differ from some other algae and land plants. (From Turmel M et al 1999 Proc Natl Acad Sci USA 96:10248)

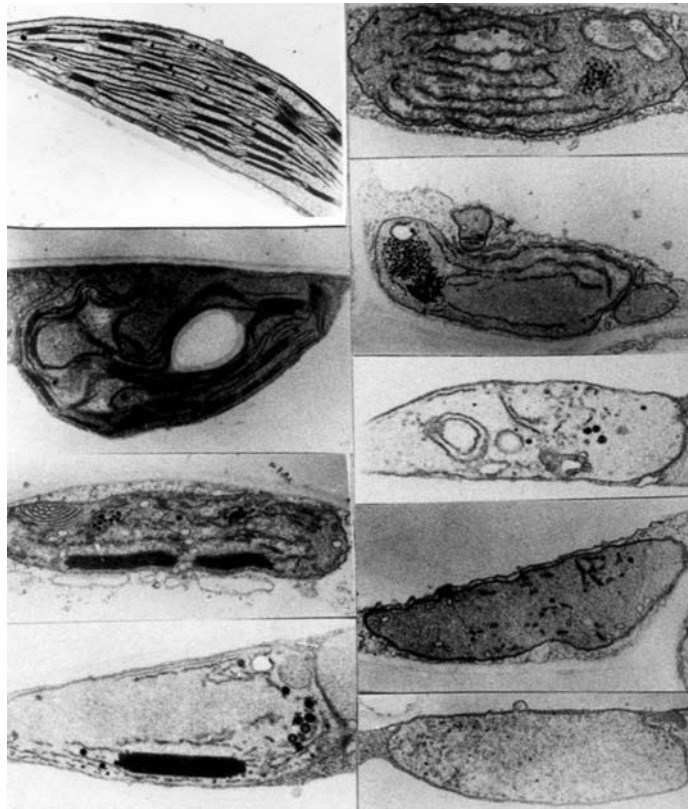


Figure C79. Mutant plastids in *Arabidopsis* induced by a nuclear mutator gene. At left in the top bloc, a normal chloroplast is shown. Because of the presence of the mutator, within single cells, morphologically different plastids are visible. The mutator shows biparental recessive inheritance. The plastid mutations are transmitted only through the egg. The mutator effect in *Arabidopsis* has been attributed to defects in the mitochondrial DNA. A similar mutator gene in *Oenothera* appears to be responsible for template slippage during DNA replication, however the mutations are transmitted through the chloroplast DNA. (From Rédei GP 1982 Genetics. Macmillan, New York)

rather than by the nucleus (see Fig. C79). It was an interesting observation that the entire plastome (not only a fragment of it) and also the mitochondria were simultaneously transmitted at this rate (Svab Z, Maliga P 2007 Proc Natl Acad Sci USA 104:7003).

The most common algal mutations (at different loci) require acetate as the carbon source because they cannot fix CO₂. Antibiotic resistance (or antibiotic dependent) mutations involve the rRNA or ribosomal proteins. Fluorodeoxyuridine is a specific mutagen for cpDNA. Arsenate and metronidazole are selective for nonphotosynthetic mutations. Photosynthesis defective mutations (nuclear or cpDNA) can also be screened under long-wave-length UV. Also, in higher plants, streptomycin, spectinomycin (16S rRNA) lincomycin (23S rRNA), etc., resistance mutations could be induced and isolated.

The partial inactivation of the mt⁺ cells by UV permits the transmission of cpDNA genes by the mt⁻ cells and this makes possible recombinational studies. However, some progeny cells are heteroplasmic even

after 3 divisions of the zygote. In the cpDNA, only closely situated genes display linkage with about 1 kb/map unit. Mapping is practical by physical methods: either by deletional analysis or by positional cloning, or in interspecific crosses when RFLP exists by co-segregation with restriction endonuclease fragments (*C. eugametos* x *C. moewusii*). The nature of the recombination map was hotly debated until it turned out that genes within the inverted repeats map as if the area would be linear, whereas a recombination of genes outside this region reflects the circular nature of the cpDNA. A single recombination between two circular molecules may result in a cointegrate. Recombination of cpDNA genes in higher plants also occurs albeit apparently quite rarely. The chloroplasts usually do not “synapse.” Within cells of interspecific (intergeneric) somatic fusion in the *Solanaceae* recombination of antibiotic resistance markers has been demonstrated.

Co-segregation of mitochondrial traits (cytoplasmic male sterility and chloroplast antibiotic markers)

C

was also shown. Transforming of appropriate genes (Atrazine resistance) into the cell nucleus, using T-DNA vectors, may alter chloroplast functions. Transformation—using biolistic procedures—of cpDNA can be accomplished at high frequencies (up to 1×10^{-4}) in *Chlamydomonas* and higher plants. The insertion takes place around the passenger and vector junctions and the insert replaces the resident copy in the nucleoid.

The insertion takes place by site-specific recombination and thus it is nonrandom. In tobacco the integration may be the outcome of multiple recombination events. Co-transformation of antibiotic resistance genes situated in the inverted repeats and photosynthetic genes (situated in the unique regions) can be accomplished by the simultaneous use of two vectors. Alternatively, the bacterial *aadA* gene (that detoxifies antibiotics) is used. The gene is equipped by cpDNA transcription and translation elements and surrounded by the appropriate target sequences. Whether or not the transformation involves correction of a resident gene or insertion of a foreign gene (e.g., *uidA* [glucuronidase]), the integration requires homologous recombination within the flanking sequences. Transformation has also been achieved by direct transfer and integration of the cloned gene into protoplasts in the presence of polyethylene glycol or by the biolistic methods. Under selective conditions sorting out of the transgene takes place rapidly.

The segregation and sorting out of chloroplast genes were subjected to analysis by the methods of population genetics and computer simulation. The biological observations do not seem to support the stochastic models of sorting out.

Mobile genetic elements as Group I introns, encoding the I-CreI (or I-CeuI) endonuclease and locating in the large ribosomal subunit gene or in the cytochrome b gene (I-CsmI endonuclease) in *mt*⁺ (mating type) plastid nucleoids, have been found in different *Chlamydomonas* chloroplasts. The I-CreI endonuclease has a recognition site of 24 bp. These mobile elements resemble those of I-Sce in the mitochondria of yeast.

The promoter regions of the cpDNA genome are similar to that of prokaryotes. There are generally 10 nucleotides between the TATA box (TATAAT or longer) and the first translated codon and again 17–19 bases separate the TATA box from the 5'-TTGACA promoter consensus at about -35. Internal and further upstream promoters have also been identified. Many genes are transcribed into polycistronic RNAs. In spinach, 18 major RNAs were made from a single polycistronic transcript. The 3' termini of the transcripts generally contain inverted repeats that have probably only some processing and/or stabilizing functions along with some 5'-untranslated sequences. Higher

plants appear to have a second DNA-dependent RNA polymerase, which is encoded by the nucleus (Liere K et al 2004 Nucleic Acids Res 32:1159). This polymerase transcribes a different set of chloroplast genes. Binding proteins (3') seem to be involved in the processing of the RNA. Despite common ancestry with bacterial translation, chloroplast translation is more complex and involves positive regulatory mRNA elements and a host of requisite protein translation factors that do not have counterparts in bacteria. Previous proteomic analyses of the chloroplast ribosome identified a significant number of chloroplast-unique ribosomal proteins that expand upon a basic bacterial 70S-like composition (Manuell L et al 2007 PloS Biol 5[8]:e209). Some observations indicate that polycistronic transcripts may bind to the ribosomes and translated without processing, perhaps with reduced efficiency. Translation of the chloroplast mRNA appears to be light-regulated. Apparently, an activator protein binds to the upstream untranslated region of the mRNA and the regulation is mediated through the redox state of this protein. Endonucleolytic processing of the transcripts may provide alternative leader sequences and binding sites for transcription factors. Ribosomal proteins may exert activation also by induction and modulation of translation. The chloroplast mRNAs are not capped and the initiation of transcription is regulated in a manner similar to that in prokaryotes. In the untranslated upstream regions (UTR) there are binding sites for nuclear encoded proteins that regulate transcription. Other proteins may bind to the 3' downstream sequences. Nuclear proteins mediate translational control (Choquet Y, Wollman F-A 2002 FEBS Lett 529:39). The chloroplast DNA most commonly encodes ~30 tRNAs. In the plastids of nongreen plants, the tRNA gene number is reduced to about half. ▶chloroplasts, ▶chloroplast mapping, ▶physical mapping, ▶ctDNA, ▶RFLP, ▶cointegration, ▶deletion mapping, ▶biolistic transformation, ▶transformation of organelles, ▶β-glucuronidase, ▶mutation in cellular organelles, ▶heteroplastidic, ▶sorting out, ▶introns, ▶twintrons, ▶maturase, ▶mitochondrial genetics, ▶transcription, ▶ribosomes, ▶σ, ▶translation, ▶mating type, ▶polycistronic, ▶promoter, ▶nucleoid, ▶binding protein, ▶processing, ▶redox reaction, ▶RNA editing, ▶endosymbiont theory, ▶nucleomorph, ▶metronidazole; Sugiura M et al 1998 Annu Rev Genet 32:437; Jarvis P 2001 Curr Biol 11:R307; Hagemann R 2000 J Hered 91:435; Rodermel S 2001 Trends Plant Sci 6:471; Ogihara Y et al 2002 Mol Genet Genomics 266:740; genome database: <http://chloroplast.cbio.psu.edu/>.

Chloroplast Import: The chloroplasts do not have structures for through-membrane traffic comparable

to the nuclear pores. Four proteins are involved in import through the outer membrane of the chloroplast envelope and two with import through the inner membrane (IAP = import intermediate associated proteins). Proteins enter the chloroplasts through the Toc (transport outer chloroplast membrane) complex (M_r 159K). The 159K complex may contain Toc132 or Toc120. Toc86 has proteolytic function, Toc34 appears to be a GTP-regulated import receptor, and Toc75 forms a transport channel within the membrane. Toc75 is immunologically related to heat-shock protein 70. Two others (also called IAP34 and IAP85) are guanosine triphosphate-binding proteins. Protein transport within the chloroplast and into the thylakoid lumen requires proteins SecA and SecY, homologous to translocation proteins present in bacteria. In addition, plastocyanin and the 23-kDa and the 17-kDa subunits of the oxygen-evolving complex (OEC) are involved in thylakoid transport. The Clp chaperone may also be involved in folding the imported proteins in the chloroplast stroma. [▶mitochondrial import](#), [▶Clp](#), [▶Sec](#), [▶plastocyanin](#); Bauer J et al 2001 Cell Mol Life Sci 58:420.

Chloroplast Mapping: In some algae the chloroplasts can be mapped by genetic means, a not completely natural process in most lower or higher plants. In addition, in higher plants, the number of chloroplasts per cell may be quite high and recombination is a process involving, simultaneously, multiple events. Physical maps, based on molecular techniques, are much more practical and provide more detailed information on the organization of the plastid genome. In the majority of higher plants (about 150 kbp) and *Chlamydomonas* algae (about 195 kbp) the 16, 23, 4.5 and 5 S ribosomal RNA genes occur in two repeats, separated by a long and a shorter sequence, coding for about 35 tRNAs and about 100 proteins. There are also different organizations. In *Euglena* alga, with about 145-kbp genome, the repeated rRNA clusters are adjacent. In *Pisum* (pea) the genome is only about 120 kbp and the 16S and 23S rRNA genes are located in a single cluster. In the first completely sequenced higher plant chloroplast genome of tobacco (155844 bp) the inverted rRNA repeats include 25,339 bp and the two single copy sequences contain 86,684 and 18,482 bps. (For more details see Sager R 1972 Cytoplasmic genes and organelles, Academic Press, New York; Shinozaki K et al 1986 EMBO J 5:2043–2049; Palmer JD 1991 In: Bogorad L, Vasil IK (eds), Molecular biology of plastids. Academic Press, San Diego, California, pp. 5–53A; [▶chloroplasts](#), [▶chloroplast genetics](#)).

Chloroplast stroma: The fluid phase of the chloroplast content is the site of CO₂ fixation, RUBISCO,

the Calvin cycle, chlorophyll synthesis, metabolism of amino acids, fatty acid synthesis, etc. Proteins can be exchanged among plastids. [▶RUBISCO](#), [▶Calvin cycle](#)

C

Chloroplasts: Chloroplasts are chlorophyll-containing organelles (2–20 μ m) in green plants with double-stranded circular DNA (cpDNA of 120–180 kbp in 10–100 copies/plastid) genetic material and a capacity of transcription and translation. Chloroplasts of higher plants contain about 3,000 proteins but only about 5% are encoded within this organelle. Some of the proteins are under dual (nuclear and plastid) genes. The cpDNA codes for 16S, 23S, 5S and 4.5S ribosomal RNAs and has ribosomes of about 70S size, resembling those of prokaryotes. This genome codes for about 100 polypeptides and 35 different RNAs (rRNA, tRNA). The genes are frequently transcribed into polycistronic RNA, resembling bacterial gene clusters. Their rRNA genes (10–30 kbp) are generally inversely repeated in land plants. Eighteen genera of the legumes *Fabaceae* do not have such inverted repeats. The unique sequences have a small (15–25 kbp) and a large (80–100 kbp) tract. *Pelargonium hortorum* (geranium) displays a 76-kbp repeat and this includes also some usually “unique” sequences (genes) here, though duplicated. The cpDNA usually contains other inverted repeats. The cpDNA of *Chlamydomonas* algae is larger (195–294 kbp) but has similar inverted repeats, and the unique sequences consist of two, about equal tracts with gene order differing from land plants. They have a recombination system acting among the different repeats. The *Euglena* cpDNA is similar in size (130–152 kbp) to that of land plants yet it lacks the two inverted repeats of rRNA, but it has triple tandem repeats and two-fold tandem 16S rRNA genes. The tRNAs are clustered 2–5, each. Variations are found in several miscellaneous genes too. Other algae show additional variations. The colorless algae and plants (*Epifagus*) have smaller genomes (about 70 kbp) and lacks about 95% of the genes encoding the photosynthetic apparatus, yet they have genes required for protein synthesis (rRNA, 17 tRNAs, 80% of the ribosomal proteins, etc.).

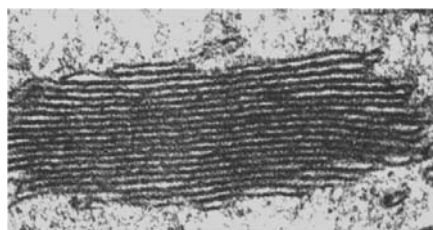


Figure C80. Stacked thylakoids form granum

C

The major function of chloroplasts is photosynthesis. Actually, the chloroplasts reduce CO₂ and split water and release O₂. Enzymes of the chloroplast stroma convert CO₂ into carbohydrate. Some of the chloroplast genes have introns and some sequences in the cpDNA have homologies with both nuclear and mitochondrial and *E. coli* DNA. In bleached mutants or in antibiotic-sensitive plants callus growth can be maintained on carbohydrate-supplied culture media. The genetic code in the plastid DNA is the universal one, unlike in mitochondria. Nuclear genes encode several plastid functions and the proteins or RNAs may be imported into the plastids from the cytosol with the assistance of transit peptides. An assembly of nuclear and plastid genes encode some of the plastid protein subunits. The chloroplast genome has apparently evolved through endosymbiosis from an ancestral prokaryote(s). The size of the chloroplasts varies from 1 to 3 µm in diameter and about 2 to 3 times as much in length. The double membrane enclosing its content has no pores.

The internal flattened membrane vesicles called *thylakoids* are stacked into *grana* and they harbor the photosynthetic apparatus. The grana are connected by the *stroma lamellae*. The stroma is the fluid phase of the chloroplasts. The photosynthetic apparatus of green bacteria and some lower algae is structurally simpler. ▶chloroplast genetics, ▶plastid male transmission, ▶cpDNA, ▶ribosomal RNA, ▶plastid number, ▶compatibility of organelles and the nuclear genome, ▶introns, ▶spacers, ▶chlorosome, ▶chromatophore, ▶chloroplast envelope, ▶chloroplast endoplasmic reticulum, ▶FtsZ, ▶photorespiration, ▶photosystems, ▶evolution by base substitutions, ▶organelle sequence transfer, ▶differentiation of plastid nucleoids, ▶endosymbiont theory, ▶nucleomorph, ▶nucleoid, ▶transformation of organelles, ▶retrograde regulation, ▶Dinoflagellates, ▶*Plasmodium*; Osteryoung KW, McAndrew RS 2001 *Annu Rev Plant Physiol Plant Mol Biol* 52:315.

Chloroquine: An antimalaria drug and an immunosuppressant compound that may be used for post-treatment of animal cells transfected by the calcium phosphate precipitation method. It may increase the expression of the introduced DNA. ▶transformation-calcium phosphate precipitation, ▶malaria

Chlororespiration: The interaction between photosynthetic and respiratory electron transports. ▶photosystems, ▶photorespiration; Nixon PJ 2000 *Philos Trans R Soc London B Biol Sci* 355:1541; Bennoun P 2001 *Biochim Biophys Acta* 1506:133.

Chlorosis: A condition of plants when the chlorophyll content is reduced either by a nutritional deficiency

(iron) or infection by viruses or other parasites. ▶chlorophylls

Chlorosomes: Chlorosomes are non-membraneous, light-harvesting structures in green bacteria.

Chlorosulfuron (2-chloro-*N*-[(4-methoxy-6-methyl-1-3,5-triazin-2-yl-amino carbonyl]): A herbicide to which resistant mutations have been isolated at the rate of about 1.2×10^{-7} . ▶herbicides; Haughn GSW, Somerville CR 1990 *Plant Physiol* 92:1081.

Ch-No38: A chicken protein involved in shuttle functions between nucleus and cytoplasm and in the assembly of ribosomes. ▶ribosomes

CHO (Chinese hamster ovary cells): CHO are frequently used for mutation studies in cell culture because hemizyosity permits the identification of recessive mutations in these diploid cells ($2n = \pm 44$). ▶radiation hybrid; Puck TT 1974 *Stadler Symp* 6:47.

Cholecystokinin: A peptide (neuropeptide) hormone controlling appetite and several other physiological processes related to steroid hormones. ▶obesity; Malendowicz LK et al 2001 *Endocrinology* 142:4251.

Cholelithiasis (gallstone, human chromosome 1p): The genome-wide association indicates a role for hepatic cholesterol transporter (ABCG8) (Buch S et al 2007 *Nature Genet* 39:995).

Cholera Toxin: The cholera toxin causes the severely debilitating intestinal efflux of water and Na⁺ as a consequence of infection by the *Vibrio cholerae* bacterium. This enterotoxin enzyme mediates the transfer of adenylate from NAD⁺ to the Gs subunit of G_{sα}-protein. ADP-ribosylation factors also play an important role (O'Neal CJ et al 2005 *Science* 309:1093). As a consequence, G_{sα} stops acting as a GTPase. Therefore, adenylate cyclase continuously synthesizes cAMP resulting in the disturbance of the water and salt balance. Until recently, the etiology of the disease posed some tough questions because very often the *Vibrio* appeared entirely harmless. It has been shown that toxin production depends on the acquisition of the *ctx* gene complex from the filamentous phage CTX. The *ctx* complex can then be transferred from one bacterium to others. The information transfer requires that the bacterium have active pili. These toxin-coregulated pili (TCP) are encoded within the pathogenicity islands (VPI) of the *Vibrio*. The pathogenicity-island itself is also a single stranded DNA phage. The new information explains the difficulties of immunization against this infection affecting hundreds of thousands in certain years, particularly in South-East Asia. ▶G-proteins, ▶G_s, ARF, ▶pilus, ▶pathogenicity island, ▶*Vibrio*

cholerae; Tsai B et al 2001 Cell 104:937; restricting *Vibrio* propagation by phage; Jensen MA et al 2006 Proc Natl Acad Sci USA 103:4652.

Cholestasis: Cholestasis includes recessive benign recurrent intrahepatic (liver) cholestasis (BRIC or Summerskill syndrome) and recessive familial intrahepatic cholestasis (PFIC1 or Byler disease), a more serious form of impaired bile flow. Both are located at human chromosome 18q21-q22 and should be named FIC1 (familial intrahepatic cholestasis). The normal alleles encode a P-type ATPase most likely involved in the transport of amino phospholipids. The similar PFIC2 is at 2q24 and controls a bile salt export pump. PFIC3 is a mutation of the multidrug resistance glycoprotein gene at 7q21. Cholestasis-lymphedema is a severe childhood disease of the bile. Farnesoid X hormone receptor antagonists may have potential for clinical treatment of cholestasis (Stedman C et al 2006 Proc Natl Acad Sci USA 103:11323). ▶[bile salts](#), ▶[farnesoid receptor](#), ▶[ATPase](#), ▶[phospholipid](#), ▶[ABC transporters](#), ▶[cirrhosis of the liver](#), ▶[steroid 5-beta reductase](#); Bull LN 2002 Current Op Genet Dev 12:336.

Cholesterols: Cholesterols are amphipathic (lipid) molecules with a polar head and a non-polar hydrocarbon tail, and are found in membranes (▶[cell membranes](#)). Cholesterols are the principal sterols in animals; they occur also in plants (stigmasterols, sitosterol) and in fungi (ergosterol). Bacteria generally lack sterols (see Fig. C81). Cholesterols are synthesized from acetate through mevalonate, isoprenes, and squalenes to a four-ring steroid nucleus. The principal regulatory enzyme is 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Most of the cholesterol synthetic activity takes place in the liver and used as bile acids (cholesteryl esters). The excess cholesterol is generally degraded into bile acids and is catalyzed by the cytochrome P450 cholesterol 7 α -hydroxylase (CYP7A1). The farnesoid X receptor (FXR), and 4 other orphan nuclear receptors are involved in the transcriptional control. The level of bile acids also regulates the activity of CYP7A1. A small heterodimer partner (SHP) and the liver receptor homolog 1 (LRH-1) modulate the process. Cholesterols are parts of membranes and steroid hormones, and are precursors of vitamin D. Cholesterols are indispensable for numerous functions and are generally synthesized in sufficient amounts by the human body, although dietary cholesterol may increase its level. Accumulation of excessive amounts of cholesterol bound to low-density lipoproteins (LDL) may lead to occlusion of the blood vessels (atherosclerotic plaques) leading to coronary heart disease. Familial combined hyperlipidemia (low density lipoproteins) seem to be

controlled at 2p25.1, and loci 9p23 and 16q24.1 seem to be responsible (lod score > 2.0) for the low level of high-density lipoprotein cholesterol. Several other loci are involved in the control of the lipoproteins at variable levels of significance and differently by ethnicity (Pajukanta P et al 2003 Am J Hum Genet 72:903). HMG-CoA and Δ^7 -reductase deficiency result in embryonic malformation in rodents. The Δ^7 -reductase deficiency in humans results in the Smith-Lemli-Opitz syndrome. Δ^7 -reductase and Δ^{24} -reductase control the step preceding cholesterol from 7-dehydrocholesterol and desmosterol, respectively. Recessive desmosterolosis (1p31.1-p33) is due to a defect of 3 β -hydroxysterol Δ^{24} -reductase (Waterham HR et al 2001 Am J Hum Genet 69:885). Defects in cholesterol transport and uptake are also deleterious to embryonal (brain) development in mice. The receptors of the LDL and VLDL lipoproteins are apparently of minor importance for the embryo but deficiency of the scavenger receptor (SR-BI) expressed on the surface of the mouse yolk endodermal cells and within the placenta may cause embryo lethality. Similarly deficiency of LDL receptor-related protein (LRP) involves lethality. Defects in another lipoprotein receptor, megalin, cause death after birth by holoprosencephaly (a neural tube defect) and other anomalies. Cholesterols modify the hedgehog protein involved in developmental signaling. Cholesterol biosynthesis is regulated through the LXR receptors. LXR α forms a dimer with receptor RXR and they bind to a DNA response element after being activated by two oxysterols. LXR α -deficient mice are unable to convert efficiently cholesterols to bile acids. The N-terminal basic helix-loop-helix leucine zipper domain of SREBP-2 (sterol regulatory element-binding protein 2) is a nuclear transcription factor of cholesterol and unsaturated fatty acid metabolism (Lee SJ et al 2003 Science 302:1571). Scap protein binds SREBP and moves it and the binding proteins from the endoplasmic reticulum to the Golgi apparatus where SREBs are processed by Site-1 and Site-2 proteases to active fragments, which enter the nucleus and facilitate the expression of genes in cholesterol synthesis and uptake. When cholesterol accumulates in the endoplasmic reticulum, Scap/SREB are not transported by COP coated vesicles, the processing stops and the target gene activity declines. Insig (insulin-introduced gene) binding retains Scap in the endoplasmic reticulum and SREBP is degraded by proteasomes (Goldstein JL et al 2006 Cell 124:35). ▶[lipids](#), ▶[sphingolipids](#), ▶[lanosterol](#), ▶[Scap](#), ▶[Insig](#), ▶[prenylation](#), ▶[familial hypercholesterolemia](#), ▶[raft](#), ▶[high-density lipoprotein](#), ▶[hypertension](#), ▶[myocardial infarction](#), ▶[CETP](#), ▶[Wolman disease](#), ▶[Niemann-Pick disease](#), ▶[Smith-Lemli-Opitz syndrome](#), ▶[Tangier disease](#), ▶[CHILD syndrome](#),

►cerebral cholinesterosis, ►holoprosencephaly, ►apolipoprotein, ►hedgehog, ►farnesoid X receptor, ►statins, ►lovastatin, ►SR-BI; Krieger M 1999 Annu Rev Biochem 68:523; Repa JJ, Mangelsdorf DJ 2000 Annu Rev Cell Dev Biol 16:459; Goldstein JL, Brown MS 2001 Science 292:1310; Nwokoro NA et al 2001 Mol Genet Metabol 74:105; Haas D et al 2001 Neuropediatrics 32:113.

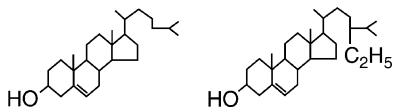


Figure C81. Left: animal cholesterol, Right: plant sitosterol

Cholesterol-Efflux Regulatory Protein (CERP): ►Tangier disease, ►ABC transporters

Cholesteryl Ester Storage Disease: ►Wolman disease

Cholic Acid ($C_{24}H_{40}O_5$): Bile acid produced from cholesterol by 7α -hydroxylase and 12α -hydroxylase enzymes. Defects in the genes CYP7A1 (8q21.13) and CYPB1 (8q21.3) that encode these enzymes may result in cholestasis (blockage of bile) and cirrhosis of the liver (fibrous alteration of the parenchymal tissue). ►cholesterol, ►cirrhosis of the liver, ►farnesoid receptors

Choline: In the form of acetylcholine, choline is a neurotransmitter and affects the development of the brain. Choline is also a methyl donor for methionine and contributes to the biosynthesis of membranes and in signaling phospholipids, sphingomyelin, phosphatidylcholine, etc. It is recommended that pregnant and lactating mothers include 450–550 mg/day, respectively, in their diet. Lysophosphatidylcholine is a ligand of the immunoregulatory G2A receptor; a defect in this mechanism may lead to autoimmune disease and atherosclerosis. ►acetylcholine, ►sphingolipids, ►autoimmune disease, ►atherosclerosis; Kabarowski JHS et al 2001 Science 293:702.

Cholinesterase: Hydrolase that splits acyl groups from choline, and is required for the normal functioning of the nervous system. Organophosphorus insecticides (parathion, chlorpyrifos, [Dursban], diazinon, and the nerve gas, sarin, can poison cholinesterase. Paraoxonase (PON1), an enzyme associated with high-density lipoproteins, may detoxify organophosphate compounds but substantial human polymorphism exists in PON1. About 1/2,500 people lack cholinesterase activity and may suffer life-threatening paralysis if succinylcholine anesthetic is used before/during surgery. ►pseudocholinesterase; Stewart R

2001 Lancet 358:73; Walker AW, Keasling JD 2002 Biotechnol Bioeng 78:715.

Chondriolite: The nucleoid of the mitochondrion. ►nucleoid, ►mitochondria

Chondriome: The genome in the mitochondria.

Chondriosome: An old name for the mitochondrion. ►mitochondria

Chondrocyte: A cartilage cell of mesenchymal origin that can secrete collagen and glucosaminoglycans (polysaccharides with alternating sequences of more than one type of sugar). Bone morphogenetic protein function is essential for chondrogenesis (Yoon BS et al 2005 Proc Natl Acad Sci USA 102:5062). ►cartilage, ►SOX, ►nitric oxide

Chondrodysplasia (CD): In the autosomal *dominant* form (Conradi-Hünemann disease) excessive bone formation occurs at the epiphysis (bone ends). The additional characteristics of this disease are other abnormal bone formations and relatively rare (in less than 30% of afflicted cases) cataracts and skin anomalies. The dominant CPDX2 Conradi-Hünemann syndrome gene at Xp11.22-p11.23 encodes a 3β -hydroxysteroid- Δ^8, Δ^7 -isomerase involved in cholesterol biosynthesis, converting cholest-8(9)-en- 3β -ol into cholest-7-en- 3β -ol (lathosterol). Excessive calcium deposits accompany the autosomal recessive forms and hence the name chondrodysplasia punctata, as the name punctata refers to the spotted calcification of the cartilage. The stippled appearance of the cartilage in this condition is similar to that in the Zellweger syndrome. Cataracts develop in about two-thirds of the cases. The symptoms may be phenocopied by maternal exposure to the warfarin pesticide that depletes vitamin K-dependent blood coagulation. However, a form of autosomal CD punctata accompanied by a deficiency in the hereditary blood coagulation factor may be cured by vitamin K. Another *dominant X-chromosomal* dwarfism gene (supposedly at Xq28) also manifests bald or scar-like spots (“punctata”) apparently caused by lower peroxisomal functions. The rare autosomal dominant Murk Jansen type CD is characterized by short legs, extreme disorganization of the limb (metaphysis) and foot bones, and defects of the spine, pelvis, and fingers. This type of CD, like most other forms, involves the accumulation of calcium, but also shows reduced phosphate levels in the blood. The basic defect is in the gene encoding the parathyroid hormone-related peptide involving replacement of histidine²²³ by arginine. The autosomal recessive Hunter-Thompson acromesomelic chondrodysplasia (the shortening of the limbs is most pronounced in the distal bones) is caused by defects in the

cartilage-derived morphogenetic protein (CDMP1), a member of the TGF- β superfamily of growth factors. The *metaphyseal chondrodysplasia* (McKusick type) is a recessive 9p1 short-limb dwarfism accompanied by sparse blonde hair; it is caused by mutation RNase MRP. *Rhizomelic chondrodysplasia punctata* (RCDP1, 6q22-q24) is caused by mutation of the peroxin 7 gene (DAPAT) but similar symptoms occur in other diseases involving peroxisomes. The Schmid type metaphyseal chondrodysplasia (6q21q22.3) is a defect in the α chain of collagen X. Mutations in the diastrophic dysplasia sulfate transporter (DTDST/SLC26A2, 5q32-q33.1) are responsible for several diseases (multiple epiphyseal dysplasia, neonatal osseous dysplasia, diastrophic dysplasia, achondrogenesis Type 1B) due to the deficiency of inorganic sulfate uptake required for the normal formation of glycosaminoglycan-containing extracellular matrix. The reduced sulfate uptake affects several tissues but primarily the cartilage (Forlino A et al 2005 Hum Mol Genet 14:859). *Jeunal asphyxiating thoracic dysplasia* (JATD) is genetically heterogeneous, with one locus at chromosome 15q13. A screen of 12 consanguineous JATD pedigrees was found to identify three families showing patterns consistent with linkage to a locus in chromosome 3q24-3q26. This autosomal recessive chondrodysplasia often leads to death in infancy because of a severely constricted thoracic cage and respiratory insufficiency. It frequently involves also retinal degeneration, cystic renal disease, and polydactyly. The basic defect is the mutation of an intraflagellar transport protein, IFT80 (Beales PL et al 2007 Nature Genet. 39:727). ▶dwarfism; ▶vitamin K; ▶vitamin K-dependent blood clotting factors; ▶antihemophilic factors; ▶peroxisome; ▶collagen; ▶Zellweger syndrome; ▶Smith-Lemli-Opitz syndrome; ▶Schwartz-Jampel syndrome; ▶asphyxiating thoracic dystrophy; ▶TGF; ▶GDF; ▶microbodies; ▶warfarin; ▶RNase MRP; ▶peroxins; ▶collagen; ▶CHILD syndrome

Chondroitin Sulfate: A heteropolysaccharide composed of alternating units of glucuronic acid and acetylglucosamine; related compounds form the ground substance, an intracellular cement, of the connective tissue. ▶mucopolysaccharidosis, ▶spondyloepiphyseal dysplasia

Chondrome: The complete set of the mitochondrial genes. ▶mtDNA

CHOP (Children's Hospital of Philadelphia): The future home of the Center for Applied Genomics, a database for human diseases and drug development.

CHOP: ▶GADD153

Chopase: Chopase is a term used for a recombination enzyme breaking DNA double strands versus the "nickase" which cuts only the single DNA strand. ▶recombination molecular mechanisms

Chordin: ▶organizer, ▶bone morphogenetic protein

Chordoma (7q33): An apparently dominant, rare, and malignant tumor of the notochordal remnants that may metastasize. ▶notochord, ▶metastasis; Kelley MJ et al 2001 Am J Hum Genet 69:454.

Chorea: Chorea refer to complex, involuntary, jerky movements. ▶Huntington's chorea, ▶benign hereditary chorea

Chorea-Acanthocytosis (CHAC, 9q21): Chorea-acanthocytosis is a neurodegenerative and erythrocyte-related malformation with an onset generally between ages 25 to 45. The basic defect is due to the 3,174-amino acid protein, chorein. ▶acanthocytosis; Ueno S-i et al 2001 Nature Genet 28:121.

Choreoathetosis, Kinesigenic Paroxysmal (PKC): PKC refers to recurrent involuntary movements caused by a neurological dominant defect at 16p11.2-q12.1. Males are three to four times more frequently affected than females.

Chorion: The chorion is the outermost envelope of the mammalian embryo (fetus); in arthropods, fishes etc., it is the non-cellular membrane surrounding the egg. ▶amnion, ▶allantois, ▶chorionic villi, ▶trophoblast

Chorionic Villi: The thread-like protrusions or tufts on the surface of the chorion. They are used in amniocentesis. ▶amniocentesis

Chorismate: A precursor of the biosynthesizers tryptophan, phenylalanine, tyrosine, and various derivatives. In the following pathway, the enzymes involved are shown in parenthesis. Phosphoenolpyruvate + Erythrose-4-phosphate → (2-keto-3-deoxy-D-arabino-heptulosonate-7-phosphate synthase) → 2-Keto-3-deoxy-D-arabino-heptulosonate-7-phosphate → (dehydroquinase synthase) → 3-Dehydroquinase → (3-dehydroquinase dehydratase) → 3-Dehydroshikimate → (shikimate dehydrogenase) → Shikimate → (shikimate kinase) → Shikimate-5-phosphate → (enolpyruvylshikimate-5-phosphate synthase) → 3-Enolpyruvylshikimate-5-phosphate → (chorismate synthase) → Chorismate. ▶tryptophan, ▶tyrosine, ▶phenylalanine, ▶phenylketonuria, ▶alkaptonuria; Dosselaere F, Vanderleyden J 2001 Crit Rev Microbiol 27:75.

Choroid: An inner layer of the eyeball supplying blood to the optical nerves. ▶retinal dystrophy

Choroidal Osteoma: An autosomal dominant eye neoplasia with bony-like cells. Choroidal sclerosis and choroid plexus calcification are autosomal recessive conditions. ▶choroid

C

Choroid Plexus: Choroid plexus forms in the blood-brain barrier and produces cerebrospinal fluid. ▶BBB

Choroideremia: A X-linked recessive atrophy of the choroid and the retina. ▶choroid, ▶retina, ▶eye diseases

Choroidoretinal Degeneration: Choroidoretinal degeneration is a type of X-linked retinitis pigmentosa, distinguished by a brilliant patch at the macula of the eye. ▶retinitis pigmentosa, ▶macula, ▶macular degeneration, ▶macular dystrophy, ▶foveal dystrophy

Chotzen Syndrome (Saethre–Chotzen syndrome, acrocephalosyndactyly, ACS): ACS is the dominant inheritance of syndactyly of fingers and toes, asymmetric and narrow head, etc., encoded in human chromosome 7p21–p22 by a gene appearing homologous to *Twist* of *Drosophila*, coding for a 490 amino acid protein containing a basic helix-loop-helix motif. *Twist1* and the related *Hand2* dimerization and phosphorylation seem to be responsible for limb-related defects (Firulli BA et al 2005 Nature Genet 37:373). ACS may involve haplo-insufficiency. ▶syndactyly, ▶Apert syndrome, ▶Robinow syndrome, ▶limb defects, ▶craniosynostosis syndromes, ▶helix-loop-helix, ▶*Twist*; Yousfi M et al 2002 Hum Mol Genet 11:359.

CHR: ▶cluster homology region, ▶CDF, ▶corticotropin releasing factor

CHRC (chromatin-accessibility complex): ▶nucleosome

Christmas Disease: ▶antihemophilic factors

Chromaffin Cell: Chromaffin cells are specifically receptive to staining by chromium salts.

Chromalveolate Hypothesis: The chromalveolate hypothesis suggests that a monophyletic super assemblage (*chromalveolata*) and a single secondary endosymbiosis of a red alga formed the four major lineages of protists—cryptophytes, haptophytes, heterokonts, and alveolates. Plastids have subsequently been eliminated. This evolutionary hypothesis did not gain general acceptance.

Chromatid: A chromosomal strand containing one DNA double helix (see Fig. C82). After replication, each chromosome usually contains two chromatids, held together at the left and right sides of the centromere. ▶chromosome, ▶centromere

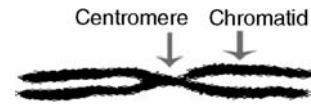


Figure C82. Chromatid

Chromatid Bridge: Whenever dicentric chromosomes are formed (paracentric inversion heterozygotes, breakage-bridge-fusion cycles, ring chromosomes) the spindle fibers pull the chromosomes to the opposite poles; at one region the chromosomal material is stretched (not unlike a stretched rubber band) and this thin connecting tie is called the chromosome bridge (see Fig. C83). The bridge eventually breaks and this leads to an unequal distribution of genes to the poles, resulting in duplications and deficiencies in the daughter cells. ▶breakage-bridge-fusion cycles, ▶bridge, ▶inversion, ▶ring chromosome, ▶bridge



Figure C83. Chromatid bridge

Chromatid Conversion: ▶tetrad analysis

Chromatid Interference: Crossing over within a chromatid reduces the chance for another to occur. Chromatid interference can genetically be determined by a tetrad analysis, where in the absence of chromatid interference, 2-strand, 3-strand, and 4-strand double crossing over should occur in the proportion 1:2:1. Any deviation from this proportion is chromatid interference. The evidence for positive chromatid interference is rare. ▶double crossing overs, ▶interference, ▶coincidence; Zhao H et al 1995 Genetics 139:1057; Copenhaver GP et al 2002 Genetics 160:1631.

Chromatid Segregation: Chromatid segregation takes place after recombination and in case of polysomy exerts a detectable effect on the segregation ratios. In the mouse, the left-right dynein motor gene mutation may alter the laterality of visceral organs and also selectively affect chromatid segregation (Armakolas A, Klar AJS 2007 Science 315:100). ▶autopolyploidy, ▶trisomy, ▶situs inversus viscerum, ▶dynein

Chromatin: The material forming the eukaryotic chromosome (DNA, RNA, histones, and non-histone proteins) is known as chromatin. The DNA in the chromatin of a chromosome stretches from telomere to telomere and attracts the various acidic proteins and RNA present in the matrix. The DNA has short bp (80–100). An “average” eukaryotic chromosome

at metaphase may be 10 to 15 μm long but the DNA in it may be 100,000 times longer when fully extended. The problem of accommodation is comparable to fitting a 2.5 km long thread into a 2.5 cm long skein 3 mm across the diameter. The folding must be extremely orderly and stable to assure perfect synapsis preceding recombination and still flexible enough to make possible error-free replication within a few hours. The elementary DNA double helices form nucleosomal structures with supercoiled stretches of histone proteins. When the majority of the protein is digested away from the DNA, the remaining structure appears in the form of a protein scaffold with DNA loops attached. The regions where the DNA is attached to the nuclear matrix is called MAR (matrix attachment region). The MAR sequences are generally rich in AT. They seem to contain transcriptional activators and recognition sites for topoisomerase II. Chromosomes condensed by various nuclear stains (Giemsa stain, a mixture of basic dyes) display characteristic C (centromeric region) and G bands that helps to identify several regions along the chromosomes. The nature of the specificity of the G staining is not known. That *rotational positioning* of the nucleosome in which the histone octamer is facing away from the minor groove of the DNA permits DNase I to cleave the chromatin into 10 bp sequences. *Translational positioning* of the nucleosomes in the chromatin defines the position of the nucleosomes relative to the site of transcription initiation of a gene about 300 to 150 bp away. In yeast, the MFa2 repressor regulates positioning. When a histone octamer is at the TATA box, transcription is hindered. Histone 1 is a repressor of all three eukaryotic RNA polymerases. During active transcription the nucleosomes are apparently not removed but only reconfigured. Genes in the chromatin may be attached to the nuclear scaffold at areas of their separation and thus are insulated from each other by these 'boundary elements'. The locus control element (LCR) in the chromatin seems to regulate the activity of groups of genes. Genes that are co-expressed are frequently clustered in the chromatin. These *open chromatin* regions are thus distinguished from the *closed chromatin* regions lacking active genes (Roy PJ et al 2002 Nature [Lond] 418:975). ▶stains, ▶FISH, ▶chromosome painting, ▶chromosome banding, ▶nucleosome, ▶chromosomal proteins, ▶heterochromatin, ▶euchromatin, ▶high mobility group of proteins, ▶histones, ▶histone variants, ▶on-histone proteins, ▶nucleosome, ▶nuclease hypersensitive sites, ▶LCR, ▶nuclease-sensitive sites, ▶prochromatin, ▶antichromatin, ▶chromatin code; Widom J 1998 Annu Rev Biophys Biomol Struct 27:285; Cremer T, Cremer C 2001 Nature Rev Genet 2:292; Gasser SM

2002 Science 296:1412; Ishii K et al 2002 Cell 109:551; Kadam S, Emerson BM 2002 Current Opin Cell Biol 14:262; Cavalli G 2002 Current Opin Cell Biol 14:269; Hansen JC 2002 Ann Rev Biophys Biomol Struct 31:361; functional organization: Spector DL 2003 Annu Rev Biochem 72:573; review of structures and methods of analysis: Rando OJ 2007 Trends Genet 23:67; effects on gene expression: Higgs DR et al 2007 Annu Rev Genomics Hum Genet 8:299; <http://sgi.bls.umkc.edu/waterborg/chromat/chromatn.html>.

Chromatin Assembly Factor (CAF): During genetic repair, the chromatin and the nucleosomal organization of the cell have to be destabilized and after repair reorganized. The nucleosomal structure, replication complex, the various transcription factors, etc., must be restored after excision of the DNA defects. This process requires a series of sequentially interacting proteins, commonly known as CAFs. ▶chromatin, ▶Rad53, ▶histone variants; Emili A et al 2001 Molecular Cell 7:13.

Chromatin Code: The chromatin code is the hypothesized system regulating the folding of chromatin fibers of eukaryotes. ▶chromatin

Chromatin Diminution: Chromatin diminution occurs when pieces of chromosomes are excised or entire genomes are fragmented to generate minichromosomes. Such a phenomenon is normal during the 2nd to 8th cleavage divisions of *Ascaris* and related nematodes and during the formation of the macronuclei of ciliated protozoa. The fragments may be reintegrated again into much larger chromosome(s) in the generative cell nuclei or the germline may develop from a single cell that has not undergone chromosome diminution. The fragmentation is followed by the addition of 2–4-kb telomeric repeats (TTAGGC). Such repeats may be added also at other chromosomal breakage region (CBR) sites. AT-rich sequences near the CBR (approximately 1/4 of the germ-line DNA, including the two types of Tas retrotransposons) are eliminated during diminution. ▶*Ascaris megalocephala*, ▶*Paramecium*, ▶telomere; Müller F, Tobler H 2000 Int J Parasitol 30:391; Redi CA et al 2001 Chromosoma 110:136; Goday C, Esteban MR 2001 Bioessays 23:242.

Chromatin Filament: Chromatin filament is a nucleosomal DNA fiber 30 nm across the diameter that appears as a beads-on-string structure during electron microscopy; the beads being the nucleosomes. The folding of the fiber may be the consequence of H1 histone-induced contraction of the internucleosomal angle as the salt concentration approaches the physiological level. Decondensation required for transcription may be the consequence of depletion

of the linker histone or acetylation of the core histone tail domain. ►nucleosome, ►histones, ►chromatin, ►lamins; Moir RD et al 2000 J Struct Biol 129:324.

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Chromatin Modification: ►chromatin remodeling

Chromatin Remodeling: Chromatin remodeling is a change effected in the nucleosomal structure by establishing nuclease hypersensitive sites in front of active genes. In recent years several protein factors have been identified with this type of function. The first was the ATP-dependent yeast SWI/SNF (switch/*Saccharomyces* nuclear factor, 11 subunits in yeast, 8 subunits in humans) recognized by transcriptional activation. The Snf2-like subunits display helicase-like function. The NURF (nucleosome remodeling factor) and an ATP-dependent 4-subunit protein were found in *Drosophila*. Its critical subunit ISWI (imitation switch, 140-kDa; human homolog of hSNF2h) is shared by yeast. Isw2 complex represses some genes upon its recruitment by Ume6p to specific loci. Ume6 is a sequence-specific binding protein. ACF has an ISWI subunit of ATP, and also topoisomerase II activity. The RSC (remodeling *Saccharomyces* chromatin, 15 subunits) protein works on the chromatin around the centromere and is specialized probably for the regulation of the kinetochore function. The bromodomain of Gcn5/p300 co-ordinates the remodeling of nucleosomes. RSF (remodeling and spacing factor) and FACT (facilitator of chromatin transcription) mediate the initiation of transcription on chromatin template depending on ATP and other protein factors. They also facilitate elongation of the transcript through the nucleosomes. RSC can recognize acetylated nucleosomes and facilitate passage of Pol II through them supporting the view that histone modifications regulate accessibility of the coding region to Pol II (Carey M, Workman JL 2006 Mol Cell 24:481). CHD1, together with the chaperone NAP-1, assembles nucleosome arrays from DNA and histones in vitro and in vivo (Konev AY et al 2007 Science 317:1087).

A mutant form of the p53 protein was found to assume a gain-of-function switch regulating the cell cycle and causing polyploidy in the Li-Fraumeni syndrome. SWI/SNF and RSF can facilitate the expression of transcriptional repressors too. The NUR protein also has both chromatin remodeling and histone acetylation capabilities. Some of these factors participate both in the assembly of nucleosomes and in remodeling. The Swr1 chromatin remodeling protein complex facilitates the replacement of the H2A/H2B histone complex by H2AZ/H2B. The replacement recruits the Sir2, Sir3 and Sir3 silencers to the so-modified nucleosomes. As a consequence the telomeric heterochromatin is

distinguished from the adjacent euchromatin by localized silence (Mizuguchi G et al 2004 Science 303:343). Besides histone acetyltransferases and phosphorylases, methylation of lysine residue 9 near the N-end of histone 3 regulates the activity of chromatin. Methylation of Lys⁹ interferes with phosphorylation of Serine¹⁰, and may involve aberrant mitotic divisions. Phosphorylation of histone 3 (by ERK, RSK, MSK, p38) at serine 10 is linked to transcriptional activation of the DNA. Ubiquitylation, sumoylation, ADP ribosylation, deamination and proline isomerization can also affect histones (Kouzarides T 2007 Cell 128:693). Pontin (Tip49) and Reptin (tip48) are components of chromatin remodeling complexes and transcription. They interact with several proteins (TBP, β -catenin, Myc, Wnt) and are thus involved in several regulatory/developmental pathways (Etard C et al 2005 Mech Dev 122:545).

►DNase hypersensitive site, ►nucleosome, ►chromatin, ►PIC, ►histones, ►histone deacetylase, ►histone variants, ►silencer, ►heterochromatin, ►nuclear receptors, ►promoter, ►histone acetyltransferase, ►bromodomain, ►RAG1, ►CHRAC, ►BRG, ►BRM, ►SSRP, ►MSK, ►SANT, ►SNF, ►SWI, ►SAGA, ►ERK, ►RSK, ►MSK, ►p38, ►PBAF, ►PCAF, ►TAF_{II}, ►TAF_{II}230-250, ►topoisomerase, ►transcription map, ►Li-Fraumeni syndrome, ►DiGeorge syndrome, ►Williams syndrome, ►Coffin-Lowry syndrome, ►p53, ►kinetochore, ►transcription factors, ►Polycomb, ►methylation of DNA, ►ACF, ►CAF, ►Sin3, ►p300, ►GCN5; Tyler JK et al 1999 Cell 99:443; Knoepfler PS, Eisenman RN 1999 Cell 99:447; Gebuhr TC et al 2000 Genesis 26:189; Cheung P et al 2000 Cell 103:263; Cosma MP et al 2000 Cell 97:299; Nakayama T, Takami Y 2001 J Biochem 129:491; Fry CJ, Peterson CL 2001 Curr Biol 11:R185; Sassone-Corsi P 2002 Science 296:2176; Tsukiyama T 2002 Nature Rev Mol Cell Biol 3:422; Olave IA et al 2002 Annu Rev Biochem 71:755; Horn PJ, Peterson CL 2002 Science 297:1824; Pandey R et al 2002 Nucleic Acids Res 30:5063; chromatin remodeling in plants: Hsieh T-F, Fischer RL 2005 Annu Rev Plant Biol 56:327; mammalian differentiation and chromatin remodeling: de la Serna IL et al 2006 Nature Rev Genet 7:461.

Chromatin State Fixation: A hypothetical mechanism that stabilizes the function of certain genes and keeps others dormant (by heterochromatinization). ►heterochromatin

Chromatin-Negative: Cells that do not display heterochromatic Barr bodies. ►sex chromatin, ►Barr body

Chromatography: Chromatography, in various forms, partitions molecular mixtures between a stationary

(sugar, cellulose, silica gel, sepharose, hydroxyapatite) and a water base or organic liquid phase. ▶ [thin layer chromatography](#), ▶ [Rf value](#), ▶ [column chromatography](#), ▶ [high performance liquid chromatography](#), ▶ [affinity chromatography](#), ▶ [ion exchange chromatography](#)

Chromatoid Body: A perinuclear mRNA-containing cytoplasmic organelle during germ cell development; it is the processing center of RNAs. It also includes microRNA, siRNA, and proteins involved in their processing. It is very similar to nuage. ▶ [microRNA](#), ▶ [RNAi](#), ▶ [nuage](#), ▶ [piRNA](#); Kotaja N et al 2006 Proc Natl Acad Sci USA 103:2647.

Chromatophores: The pigmented cells or the pigment-rich invaginations of the cell membrane.

Chromatosome: A part of the nucleosome, obtained as an intermediate during digestion with micrococcal nuclease. It contains a core particle of a histone octamer wrapped around by about 1 and 3/4 turn of about 146 bp plus 20 on each side, held together at the entry and exit points by H1 histone. ▶ [nucleosome](#); Zlatanova J et al 1999 Crit Rev Eukaryot Gene Expr 9:245.

Chromocenter: Heterochromatin aggregates such as the common attachment point of the polytenic chromosomes in the salivary gland nuclei. ▶ [salivary gland chromosomes](#); Clark DV et al 1998 Chromosoma 107:96.

Chromodomain: A conserved domain in the family of *Polycomb* genes, and also in heterochromatin protein HP1. Chromodomains are supposed to be involved in the maintenance of chromatin structure by interacting between proteins and RNA, and repress transcription. Chromodomains may be regulators of dosage compensation in males. ▶ [chromatin](#), ▶ [dosage compensation](#), ▶ [SET](#), ▶ [heterochromatin](#), ▶ [Swi6](#), ▶ [Polycomb](#), ▶ [histones](#), ▶ [CHARGE](#); Jones DO et al 2000 BioEssays 22:124; Grewal SI, Jia S 2007 Nature Rev Genet 8:35.

Chromogranins (CGA, CGB): Inositol 1,4,5-trisphosphate-sensitive Ca^{2+} storage proteins of the secretory granules of neuroendocrine cells. They occur in the cytoplasm and in the nucleus. CGB appears to control (+ or -) the transcription of several genes, including those encoding transcription factors. ▶ [InsP³](#), ▶ [transcription factors](#); Yoo SH et al 2002 J Biol Chem 277:16011.

Chromokinesins: The proteins that hold the chromosomes on the mitotic/meiotic spindle. ▶ [NOD](#), ▶ [Xklp1](#), ▶ [spindle](#); Levesque AA, Compton DA 2001 J Cell Biol 154:1135.

Chromomere: The densely stained bead-like structures along the chromosomes at early prophase. Chromomeres represent increased coiling of the chromatin fibers (see Fig. C84). In the lampbrush chromosomes the loops seem to emanate from the chromomeres. In the salivary chromosome bands there are appositioned chromomeres of a large number of chromatids. Chromomeric structures were recognized and their constant number observed by Balbiani in 1876. In the 1920s, John Belling counted their number in the genome and assumed that chromomeres are physically identical to genes and that the 2,193 chromomeres in the lily, *Lilium pardalinum*, indicated 2,193 genes as well. The chromomeric structure of the chromosomes is useful in identifying chromosomal aberrations by light microscopy. In the human autosomes the chromomere number varies from 499 to 386. ▶ [chromosome morphology](#), ▶ [salivary gland chromosomes](#), ▶ [lampbrush chromosomes](#), ▶ [pachytene analysis](#), ▶ [gene number](#); Judd BH 1998 Genetics 150:1; Jagiello GM, Fang JS 1982 Am J Hum Genet 34:112.

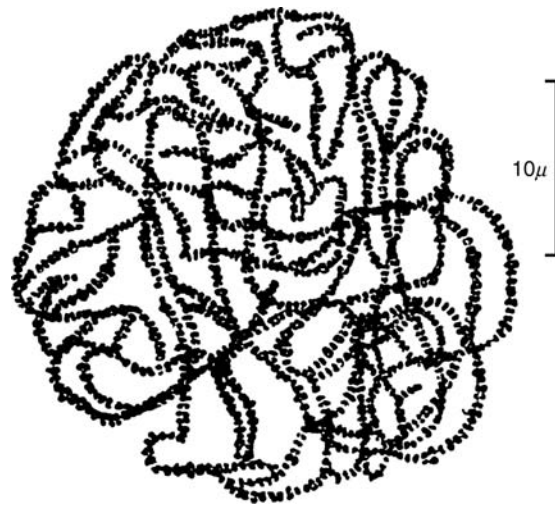


Figure C84. Chromomeres as illustrated by J. Belling [1928] (University of California Publ. Bot 14:307)

Chromomethylase: Chromomethylases are enzymes of plants that methylate CpXpG chromosomal sites, especially within transposons. Histone protein (HP1) directly binds to the telomeric DNA and histone methylases methylate H3K9 and are both required for silencing telomeric sequences but telomere elongation is under the rule of H3K9 methylation. (Perrini B et al 2004 Mol Cell 15:467). Histone-3 lysine 9 (H3K9) methylase (controlled by the *Kryptonite* gene in *Arabidopsis*) and Chromomethylase-3 (CMT3) controls H3K27 positions. DNA methylation requires the simultaneous action of both of these enzymes

(Lindroth AM et al 2004 EMBO J 23:4146). ▶methylation of DNA, ▶transposon; Tompa R et al 2002 Curr Biol 12:65.

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Chromomycin A3: Chromomycin A3 is used as a stain, specifically for GC nucleotides in the DNA.

Chromonema: Chromonema is a term that is used for the chromosomes of prokaryotes and for the smallest light-microscopically visible chromosome thread, chromatin filament, or genophore. ▶genophore, ▶Mosolov model, ▶chromosome structure, ▶chromatin filament; Nicolini C et al 1997 Mol Biol Rep 24 [4]:235.

Chromophore (dye): A chemical substance that gives color to a structure upon binding to other compounds. ▶stains, ▶fluorochromes

Chromoplasts: Plastids in which red and yellow pigments (rather than chlorophylls) predominate, as in the fruits of mature tomatoes and other plants, e.g., *Capsicum*. ▶plastids

Chromoshadow Domain: ▶heterochromatin; Lechner MS et al 2000 Mol Cell Biol 20:6449; Lomberg G et al 2006 Genome Biol 7:228; Verschure PJ et al 2005 Mol Cell Biol 25:4552.

Chromosomal Aberrations: ▶chromosomal rearrangements, ▶chromosome breakage, ▶X-ray breakage of chromosomes; Mutation Res 504, issues 1–2 (2002).

Chromosomal DNA: ▶chromatin

Chromosomal Inheritance: Chromosomal inheritance is a somewhat outdated term for inheritance of nuclear genes since frequently organellar DNA molecules are also called chromosomes.

Chromosomal Instability (CIN): CIN may occur spontaneously in cultured cells of animals and plants and its frequency depends on the age and composition of the nutrient media. Generally the frequency of the anomalies is lower in liquid media. Mitotic anomalies (nondisjunction) as well as polyploidy, aneuploidy, and rearrangements occur. One of the major contributing factors may be the lack of coordination between nuclear divisions and cell divisions. Chromosomal instabilities may be found in intact organisms as well, and are caused primarily by natural insertion and transposable elements, and also by insertions introduced by transformation. In yeast, the inactivation of Mad2 anaphase promoting protein and p53-dependent checkpoint pathway also controls chromosome instability (Burds AA et al 2005 Proc Natl Acad Sci USA 102:11296). The chromosomal complement of a cancer cell is generally unstable. The signature of chromosomal instability of particular genes is predictive of metastasis and prognosis for cancer

(Carter SL et al 2006 Nature Genet 38:1043). ▶hybrid dysgenesis, ▶RIP, ▶Roberts syndrome, ▶isochores, ▶transposable elements, ▶RIZ, ▶chromosomal rearrangements, ▶chromosomal aberrations, ▶MAD, ▶p53, ▶checkpoint, ▶cancer, ▶metastasis, ▶Nijmegen breakage syndrome, ▶Bloom syndrome, ▶Werner syndrome, ▶Fanconi anemia, ▶caffeine, Kolodner RD et al 2002 Science 297:552.

Chromosomal Interchange, Reciprocal: ▶translocation breakage syndrome, ▶Bloom syndrome

Chromosomal Mosaic: Not all the cells in the body have the same chromosomal constitution, i.e., patches of different chromosomal morphology or number co-exist. Hence the term chromosomal mosaic. ▶chimera

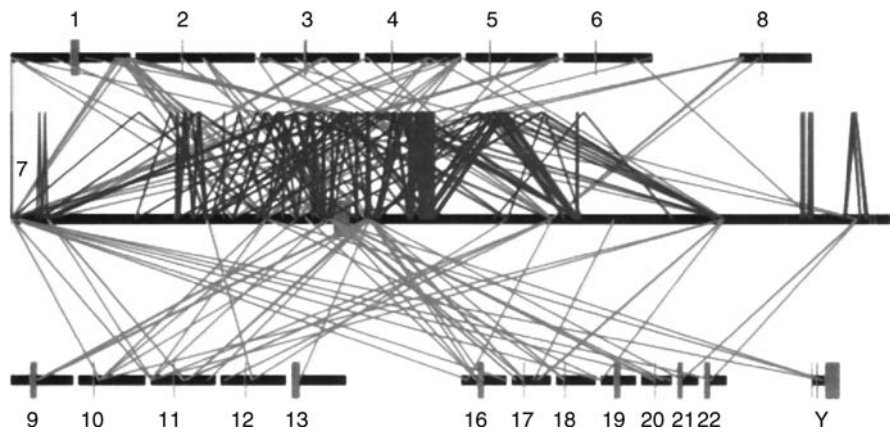
Chromosomal Mutation: Chromosomal mutations include mutations that involve defects detectable by the light microscope, and generally, mutations involving structural and numerical alterations of the chromosomes and mutations other than base substitutions. ▶chromosomal rearrangements, ▶chromosome breakage, ▶deficiency, ▶duplication, ▶inversion, ▶translocation

Chromosomal Passenger Complex: ▶centrosome

Chromosomal Polymorphism: Chromosomal polymorphism means that more than one type of chromosomal morphology or arrangement is present in a population.

Chromosomal Proteins: Chromosomal proteins include histones and a variety of non-histone proteins involved in the determination of the structure, replication, and transcription, as well as the regulation of these processes in eukaryotes. Protamines, instead of histones, are found in sperms. Histones are absent in a majority of fungi but eukaryotic viruses such as SV40 chromosomes have nucleosomal structure. Compared with eukaryotic chromosomes, prokaryotic chromosomes contain a lesser variety and quantity of proteins. ▶chromatin, ▶histones, ▶non-histone proteins

Chromosomal Rearrangements: Chromosomal rearrangements include (internal) deletions, (terminal) deficiencies, duplications, transpositions, inversions, and translocations (see Fig. C85). The majority of the chromosomal rearrangements are deleterious because they involve loss or altered regulations of functions (chromosomal aberrations are concomitant with several types of cancers), yet duplications and inversions play a role in evolution (see diagram). Besides neoplasias, several hereditary human diseases involve chromosomal alterations. Chromosomal rearrangements play an important role in the etiology of



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Figure C85. Chromosomal rearrangements. Major rearrangements involving human chromosome 7. The chromosomes represented by lines above and below, chromosome 7 shown in the center. Vertical bars mark centromeres. The darker lines indicate rearrangements within chromosome 7, the lighter lines show the translocations between the chromosomes numbered and chromosome 7. (After Hillier LW et al 2003 Nature [Lond] 424:157 by permission of Dr. Richard K. Wilson)

cancer. Deletions may eliminate genes controlling important checkpoints in the cell cycle (tumor-suppressants). Inversions and translocations may result in gene fusions, and proliferative processes may be activated (oncogenes, transcription factors, transcriptional activators, etc.). If the c-MYC oncogene is inserted in the immunoglobulin heavy chain or in an immunoglobulin κ or λ gene or T cell receptor gene, the oncogene may be activated. When the ABL oncogene (9q34.1) is translocated to the breakpoint cluster (BCR) in the Philadelphia chromosome (22q), myelogenous and acute leukemia may develop as a consequence of elevated protein tyrosine kinase activity. Inversion of human chromosome 14q(11; q32) involving the T cell receptor (14q11) and the immunoglobulin heavy chain (14q32.33) results in the fusion of the variable region of the immunoglobulin and the T cell receptor (TCR α) may cause lymphoma. Translocations may facilitate protein dimerization and changes in transcription. Site-directed chromosome rearrangements can be induced by the techniques of molecular biology. The *loxP* prokaryote gene can be inserted site-specifically by recombination into two selected chromosomal positions. Then the *Cre* prokaryotic recombinase is introduced into the same embryonic mouse stem cells by a transient expression transformation procedure. Thus, translocation involving the MYC oncogene (chromosome 15) and an immunoglobulin (IgH) gene (chromosome 12) were reciprocally translocated. The selectable markers neomycin phosphotransferase (*neo*) and hypo-xanthinephosphoribosyl transferase (*Hprt*) facilitated the selective isolation of the translocations. The frequency of this type of exchange is in the 10^{-6} to 10^{-8} range. In budding yeast cells, mutations in genes RFA1, RAD27, MRE11,

XRS2, and RAD50 may increase gross chromosomal aberrations 600–5000 fold. In yeast genome-wide selection detected 10 genes that are suppressor of gross chromosomal aberrations (Smith S et al 2004 Proc Natl Acad Sci USA 101:9039). During the evolution of humans and mice, apparently one chromosomal rearrangement was fixed per Myr of evolution. Among cats, cows, sheep and pigs a far fewer (0.2/Myr) number of rearrangements took place during evolution. Among plants the rearrangement rates varied substantially from 0.15 to 0.41 per Myr to 1.1 to 1.3 per Myr. Chromosomal aberrations of larger size can be detected by light microscopic analysis of meiotic cells or sometimes the analysis of mitotic cells using old-fashioned stains (carmine or orcein) or the various banding procedures. The use of variations of the FISH technology greatly facilitates microscopic identifications. Very small chromosomes or chromosomal fragments can be studied by pulsed field gel electrophoresis. Human chromosome 2 appears to be the fusion product of two ancestral chromosome at a 2.6-Mb region of 2q21.1–2q22.2 (Hillier LW et al 2005 Nature [Lond] 434:724). Chromosomal rearrangements are restricted by the presence of Ku70-Ku80 heterodimers and by DNA replication checkpoints (Banerjee S et al 2006 Proc Natl Acad Sci USA 103:1816). ▶ chromosomal mutations, ▶ cryptic chromosomal aberration, ▶ ataxia, ▶ Bloom's syndrome, ▶ Cockayne syndrome, ▶ Fanconi anemia, ▶ Lynch syndromes, ▶ Werner syndrome, ▶ Wiskott-Aldrich syndrome, ▶ Cri du chat, ▶ Wolf-Hirschhorn, ▶ Williams syndrome, ▶ Langer-Gideon, ▶ WAGR, ▶ Prader-Willi syndrome, ▶ Smith-Magenis, ▶ Alagille syndrome, ▶ DiGeorge syndrome, ▶ Rubinstein-Taybi syndrome, ▶ Miller-Dieker syndrome, ▶ Charcot-Marie-Tooth disease, ▶ Pelizaeus-Merzbacher disease,

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►xeroderma pigmentosum, ►Robertsonian translocations, ►RecQ, ►helicase, ►sterility, ►position effect, ►gene fusion, ►cancer, ►chromosome breakage, ►Ku, ►targeting genes, ►neo, ►HPRT, ►MYC, ►immunoglobulins, ►Cre/loxP, ►homing endonuclease, ►Myr, ►aceto-carmine, ►aceto-orcein, ►FISH, ►pulsed field gel electrophoresis, ►chromosome banding, ►salivary gland chromosomes, ►genomic variation; Shaffer LG, Lupski JR 2000 Annu Rev Genet 34:297; Yu Y, Bradley A 2001 Nature Rev Genet 2:780; Stankiewicz P, Lupski JR 2002 Trend Genet 18:74; Inoue K, Lupski JR 2002 Annu Rev Genomics Hum Genet 3:199; Feuk L et al 2006 Nature Rev Genet 7:85; chromosomal variations in the human genome and phenotypic consequences; Sharp AJ et al 2006 Annu Rev Genomics Hum Genet 7:407; DNA rearrangement detection tool: <http://algorithm.cs.nthu.edu.tw/tools/SPRING/>.

Chromosomal Sex Determination: In most eukaryotes, female have two X-chromosomes (XX) and males have one X and one Y chromosome (XY); birds and butterflies have heterogametic females (WZ) and homogametic males (ZZ). In some species (frogs, platyfish, housefly) both types of sex determination is known (Ogata M et al 2003 Genetics 164:613). In the monotreme platypus, an unusual mammal displaying some phenotypic characteristics similar to those of ducks and water rats, five X and five Y chromosomes form a multivalent chain in meiosis. In the male the chain includes 5 X and 5 Y, which segregate into XXXXX and YYYYY-bearing sperm. In the monotreme platypus ten chromosomes form a multivalent chain at male meiosis, adopting an alternating pattern to segregate into XXXXX-bearing and YYYYY-bearing sperm. Which, if any, of these sex chromosomes bears one or more sex-determining genes remains unknown, and the largest X chromosome (at one end of the chain) bears homology to the human X chromosome, whereas the other end of the chain the X has homology to the Z chromosome of birds, indicating an evolutionary link between mammals and birds (Grützner F et al 2004 Nature [Lond] 432:913). Multiple sex chromosomes occur as sex determination anomalies in the plant *Melandrium*. Two Y chromosomes occur in some ecotypes of *Rumex*. In the nematode *Caenorhabditis* the males have only one X-chromosome (XO) and the hermaphrodites have two (XX); similar mechanism exists also in several fishes. In wasps and bees the females and workers hatch from fertilized eggs whereas the males are the products of unfertilized eggs or hatch from eggs which lost the paternal set of chromosomes after fertilization, although in the body cells the males may double their DNA content during development. In mammals the chromosomal

constitution determines the gonads/sex but the phenotype is controlled by hormones. ►sex determination, ►sex chromosomal anomalies in humans, ►hormonal effect on sex expression, ►X-chromosome counting, ►arrhenotoky, ►thelytoky, ►deuterotoky, ►mealy bug, ►mountjack, ►monotreme, ►*Rumex hastatulus*, ►*Melandrium*; Charlesworth B 1996 Curr Biol 6:149.

Chromosomal Virulence Loci (*chv*): The majority of the virulence loci (*vir*; controlling transfer of the T-DNA of the Ti plasmid) of *Agrobacterium* are situated in the plasmid but the *chv* genes are in the main DNA (chromosome) of the bacteria. ►*Agrobacterium*, ►Ti plasmid, ►virulence genes of *Agrobacterium*; Suzuki K et al 2001 DNA Res 8:141.

Chromosome: The DNA containing nuclear structure, embedded in a protein and RNA matrix of eukaryotes. Chromosomes also refer to the DNA strings of prokaryotic nucleoids, mitochondria, and chloroplasts (sometimes also called genophores because the latter are associated with only small amounts of proteins in comparison to the eukaryotic nuclear chromosomes). The morphology (length, arm ratio, appendages [satellites], and banding pattern [natural or upon staining by special dyes]) and chromosome number are characteristic for the species in eukaryotes. The nuclear chromosomes of eukaryotes are generally linear but the organellar DNAs are circular chromosomes. Bacterial and viral chromosomes are generally circular. ►chromosome morphology, ►chromosome structure, ►satellite, ►and additional items beginning with ►chromosomal or ►chromosome

Chromosome Aberrations: Changes in chromosome numbers (polyploidy, aneuploidy, hypoploid, hyperploid) and changes in chromosomal structure (deficiency, deletion, inversion, translocation, transposition). Many chromosomal aberrations involve human disease. (See terms under separate entries, correlation of breakpoints with disease: <http://www.pdg.cnb.uam.es/UniPub/HCAD/>).

Chromosome Abnormality Database: e-mail address <mailto:simon@bioch.ox.ac.uk>.

Chromosome Addition: ►alien addition

Chromosome Arm: The portion of a chromosome on either side of the centromere (see Fig. C86). ►chromosome morphology, ►isobrachial, ►heterobrachial, ►arm ratio

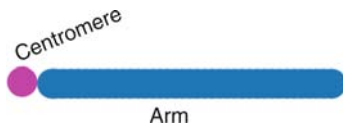


Figure C86. Chromosome arm

Chromosome Assignment Test: ►somatic cell hybridization

Chromosome 5B: A gene (*Ph*) in the B genome of wheat suppresses homoeologous pairing in this allohexaploid species. In case of loss of this chromosome or its pairing controlling region, synapsis may take place among all homoeologous chromosomes and multivalents are formed. Similar regulator genes occur in other chromosomes of wheat and other allopolyploid species. ►chromosome pairing, ►synapsis, ►multivalent, ►*Triticum*, ►allopolyploid; Dworak J, Lukaszewski AJ 2000 *Chromosoma* 109:410.

Chromosome Banding: Chromosome banding visualized by various staining techniques seems to have functional significance. Broadly expressed genes generally cluster in GC isochores and in R bands and their number is low in G bands (Lercher MJ et al 2003 *Hum Mol Genet* 12:2411). ►C-banding, ►G-banding, ►Q-banding, ►R bands, ►T bands, ►isochores, ►SR motif, ►comparative chromosome painting, ►comparative genomic hybridization, ►evolution of the karyotype

Chromosome Breakage: Chromosomes may break “spontaneously” or by the effects of chemical and physical agents (ionizing radiation). The breakage may involve only one of the chromatids or both (isochromatid breaks) (see Fig. C87).

Single breaks may lead to terminal losses of chromosomes (chromosome deficiency) whereas double and multiple breaks may cause internal deletions and various rearrangements such as transposition, inversion, and translocation. Deletions require only single breaks to occur at first order kinetics, chromosomal rearrangements generally follow second or multiple order kinetics. At first order kinetics the breakage occurs in a linear proportion to the dose of the agent causing it, at second order kinetics the number of breaks are proportional to the square of the dose (exponential response), i.e., at low doses the rise of the number of breaks is slow and at higher doses the rise in the number is steeper ►kinetics

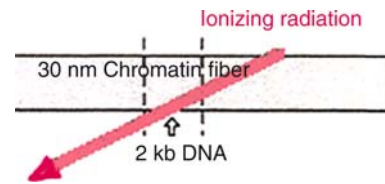


Figure C87. Chromosome breakage. The ionizing radiation traversing an elementary chromosome fiber may simultaneously inflict damage at multiple sites within 2000 basepairs hit. (After Rydberg B et al 1995 in *Radiation Damage to DNA*, p.56; Fuciarelli AF, Zimbrick JD eds., Batelle, Columbus, OH)

The electrons may directly hit the DNA or may generate reactive OH[•] radicals.

In response to DNA damage on consensus sites recognized by ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia Rad3-related), more than 900 regulated phosphorylation sites encompassing over 700 proteins were detected. Functional analysis of a subset of this data set indicated that this list is highly enriched for proteins involved in the DNA damage response. This set of proteins is highly interconnected and consists of a large number of protein modules and networks (Matsuoka S et al 2007 *Science* 316:1160).

Chromosomal double breaks may also be caused by the localized hits of two or more OH[•] radicals. The radical may affect only one strand at a site and a second hit may take place 10 bp away (*hybrid attack*) on the other strand of the double helix. A very low energy electron transfer may be sufficient to break the second strand; thus resulting in a double-strand break that may follow single electron absorption. When several hits are delivered at close proximity, clusters of complex damage may occur (see Boudaïffa B et al 2000 *Science* 287:1658). The final outcome is modified also by the efficiency of repair mechanisms. Cancerous growth is frequently associated with chromosome breakage although it is unknown how many cases were caused by chromosome breakage and how often this occurred only during the process of abnormal cell proliferation. Infection by adenovirus, cytomegalovirus, herpes, Epstein-Barr virus, etc., may cause human chromosomal breakage. An increased frequency of chromosome breakage and/ or deficiency of genetic repair accompanies several human diseases and or deficiency of genetic repair Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, xeroderma pigmentosum, Cockayne syndrome, and leukemia. Leukemias and solid tumors often involve chromosome breakage and concomitant gene fusion. Tumorigenesis is commonly initiated by a recombination-like event of the immunoglobulin genes or of the sequences in the T cell receptor (TCR) genes.

C

Chromosomal translocations may bring transcriptional activators, enhancers, DNA binding proteins, protein ligands, or transcription factors in the vicinity of genes resulting in the production of growth and cell cycle factors. ▶Roberts syndrome, ▶deletion, ▶inversion, ▶translocation, ▶transposition, ▶cancer, ▶chromosomal rearrangements, ▶chromosome breakage programmed, ▶environmental mutagens, ▶mutator genes, ▶DNA repair, ▶position effect, ▶cancer, ▶isochores, ▶X-ray caused chromosome breakage, ▶immunoglobulins, ▶T cell receptor, ▶transcription factors, ▶binding proteins, ▶enhancer, ▶transcriptional activators, ▶ataxia; Sánchez-García I 1997 Annu Rev Genet 31:429; Anderson RM et al 2002 Proc Natl Acad Sci USA 99:12167.

Chromosome Breakage as a Bioassay: Many mutagenic and carcinogenic agents cause chromosome breakage that is cytologically (by light microscope) detectable. Such breakage involves single chromatid lesions, double (isochromatid) breaks, deletions, transpositions, translocations, inversions, chromosome fusions, dicentric and acentric fragment formation, etc. The frequency of these alterations can be quantitated during mitotic and meiotic nuclear divisions of suitable plant (root tips, flower buds) and animal systems (cultured lymphocytes, fibroblasts, cells withdrawn from amniotic fluids during gestation, bone marrow cells, and spermatocytes). The cytological assays can also reveal aneuploidy and polyploidy, which do not involve chromosome breakage but non-disjunction may be the result of damage either to the centromere or to the spindle fibers. ▶bioassays in genetic toxicology, ▶heritable translocation assays; Chu EHY, Generoso WM (eds) 1984 Mutation, Cancer and Malformation, Plenum, New York.

Chromosome Breakage, Programmed: Programmed chromosome breakage occurs during the development of ciliated protozoa (*Tetrahymena*) and ascarid nematodes (*Ascaris megalocephala*) and converts the larger chromosomes of the germline into many smaller chromosomes of the macronucleus. In *Tetrahymena* the 5 basic chromosomes contain 50 to 200 specific breakage sites and generate fragments of about 800 kb that persist during the vegetative life. The different breakage sites in *Tetrahymena thermophila* share a 15 bp conserved tract (5'-TAAAC-CAACCTCTTT-3'). After the breakage the broken ends, 5–25 bp away, form new telomeres and lose about 25–65 bp around the breakage point. ▶*Tetrahymena*, ▶*Ascaris megalocephala*; Fan Q, Yao M-C 2000 Nucleic Acid Res 28:895.

Chromosome Breakage Syndromes: ▶fragile X syndrome, ▶Bloom syndrome, ▶Fanconi anemia, ▶ataxia, ▶trinucleotide repeats

Chromosome Bridge: ▶bridge, ▶chromatid bridge

Chromosome Coiling: The status of condensation of chromosomes (see Fig. C88). During interphase the chromosomes are almost entirely stretched out but as the cell cycle proceeds the coiling increases reaching a maximum at metaphase. The two chromatids may be twisted around each other during prophase (relational coiling). This type of coiling does not permit the coiled strands to separate entirely unless the separation begins at one end and is completed to the other end (plectonemic coiling). In case the coiling resembles pushing two spirals together, they can be separated in a single movement because they are not entangled (paranemic coiling). The coiling is not usually detectable in all cytological preparations unless specially treated (e.g., with ammonia vapor). ▶concatenate, ▶supercoiling, ▶SMC, ▶Mosolov model; Dietzel S, Belmont AS 2001 Nature Cell Biol 3:767.

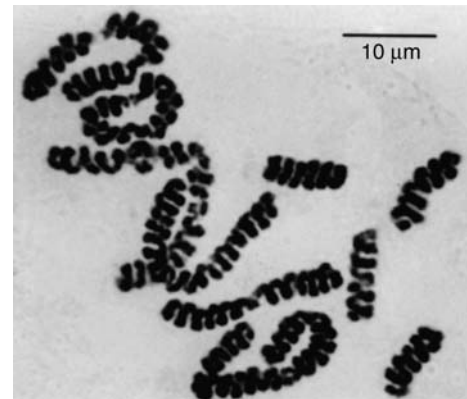


Figure C88. Chromosome coiling. The *Tradescantia virginiana* photo is the courtesy of Vosa CG; from Clowes FA, Juniper BE 1968. Plant Cells. Blackwell, Oxford, UK

Chromosome Compaction: The folding and packaging of the elementary chromosome fibers into the chromosomes, visible through light microscopy. ▶chromatin

Chromosome Complement: A haploid chromosome set. ▶haploid

Chromosome Condensation: The increasingly-tight winding of chromosomal coils from interphase to metaphase. ▶chromosome coiling, ▶mitosis, ▶meiosis, ▶condensin, ▶DNA packaging, ▶packing ratio, ▶Mosolov model; Uhlmann F 2001 Curr Biol 11:R384; Pflumm MF 2002 BioEssays 24:411.

Chromosome Configuration (meiotic configuration): The manner of pairing or assembly of chromosomes during meiosis. ▶meiosis, ▶translocation, ▶inversion

Chromosome Conformation: The relative spatial disposition of the chromatin fiber. The conformation affects gene expression, interaction and genetic repair processes (Dekker J et al 2002 Science 295:1306).

Chromosome Conformation Capture (3C method): The 3C method can detect interaction between two chromosomal loci (see Fig. C89). The chromosomes can occupy a dynamic state within the nucleus and an appropriate technique can fix the conformation of two chromosomes relative to each other. At the interaction site formaldehyde can fix the pairs, endonucleases digestion can cut the area, and PCR determine the interacting nucleotide sequence. Functionally distinct AT- and GC-rich domains can display different conformations (Dekker J et al 2002 Science 295:1306). Circular chromosome conformation capture (4C) involves a circularization step that enables high-throughput screening of physical interactions between chromosomes without a preconceived idea of the interacting partners. Several of the 114 unique sequences from all autosomes were found to interact primarily with the maternally inherited *H19* imprinting control region (Zhao Z et al 2006 Nature Genet 38:1341). 4C technology (chromosome conformation capture (3C)-on-chip) allows for an unbiased genome-wide search for DNA loci that contact a given locus in the nuclear space. Active and inactive genes are engaged in many long-range intrachromosomal interactions and can also form interchromosomal contacts (Simonis M et al 2006 Nature Genet 38:1348). ▶PCR, ▶imprinting, ▶chromosome territories; review: Krueger C, Osborne CS 2006 Trends Genet 22:637.

Chromosome Contamination: ▶hybrid dysgenesis

Chromosome Core: The central axial part of the chromosome; it is well visible in lampbrush chromosomes. ▶lampbrush chromosome, ▶synaptonemal complex

Chromosome Crawling: The same as inverse PCR. ▶inverse PCR

Chromosome Crisis: Chromosome crisis occur when abnormalities in the cell lead to telomere dysfunction and to other chromosome anomalies that eventually lead to malignant transformation and cancer. ▶telomere, ▶cancer; Maser RS, DePinho RA 2002 Science 397:565.

Chromosome Dimer: A chromosome dimer is formed by recombination between two DNA rings or two ring chromosomes (see Fig. C90).

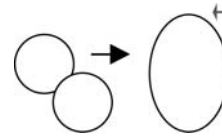


Figure C90. Chromosome dimer

Chromosome Diminution: Chromosome diminution refers to the fragmentation of the large (polycentric) meiotic chromosomes in the soma line of *Ascaris megalocephala univalens* with one pair of meiotic chromosomes and *A. bivalens* with two meiotic pairs into 52 to 72 and 62 to 144 small chromosomes in the soma, respectively. ▶macronucleus, ▶Paramecia, ▶internally eliminated sequences; Niedermaier J, Moritz KB 2000 Chromosoma 109:439.

Chromosome Doubling: Chromosome doubling can be brought about by chemical or physical agents, which block the function of the spindle fibers during meiosis or mitosis. Commonly the alkaloid colchicine is used but other agents such as acenaphthene (a petroleum product used in pesticides, industry, and plastic manufacturing), have also been employed. The purpose of chromosome doubling is the induction of polyploidy and in species hybrids to restore fertility of those hybrids which would be sterile without doubling the chromosome number because the distantly related chromosomes would not have homologs to pair with. ▶colchicine, ▶polyploid, ▶amphidiploid; Otto SP Whitton J 2000 Annu Rev Genet 34:401.

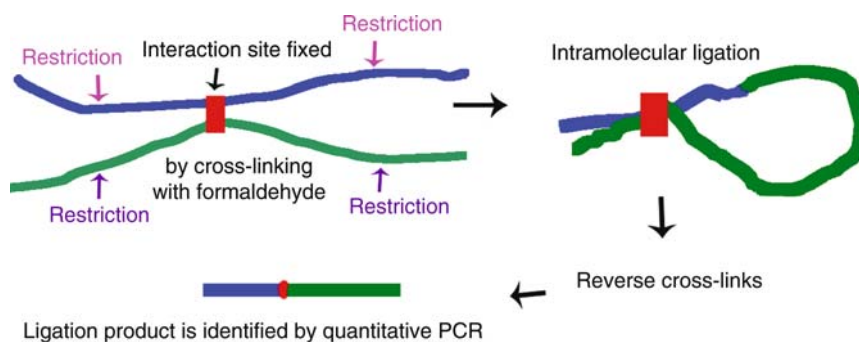


Figure C89. Chromosome conformation capture

Chromosome Drive: ► [meiotic drive](#)

Chromosome Elimination: Somatic chromosomes may be lost as a natural process during cleavage divisions in dipteran and hemipteran insects but the germline cells retain the entire and intact genome. In *Ascaridea* and some other species certain chromosomal segments may be lost as part of chromosomal differentiation during mitosis. In *Ascaris megalocephala univalens* only one pair of chromosomes is involved during meiosis and that is fragmented into several smaller chromosomes during somatic cell divisions. The macronuclei in *Paramecia* have only metabolic functions and they disintegrate after the exconjugants are formed following fertilization; only the micronuclei are retained. The macronuclei are reformed after mitoses of the diploid zygotes. Nondisjunction may also result in elimination because both the non-disjoined chromosomes pass to one pole. The gene *polymitotic* (*pol*, map location 6S-4) of maize may eliminate several or even all the chromosomes after meiosis during successive divisions because nuclear divisions do not keep up with the rapid succession of cell divisions. In the pentaploid *Rosa canina* ($2n = 35$) 7 bivalents are formed both at male and female meiosis but in the male generally all the univalents are lost whereas in the female one set of the 7 chromosomes derived from the bivalents and the univalents are retained in the basal megaspore and in the egg. Thus upon fertilization the 35 chromosome number is restored in the zygotes. Chromosome elimination occurs regularly in species with supernumerary chromosomes that have unknown function and a defective centromere. Because of the nature of the centromere, the supernumerary chromosomes commonly display nondisjunction and additional losses after fragmentation. Chromosome elimination occurs when *Hordeum bulbosum* is crossed either with *H. vulgare* or hexaploid wheat. In somatic cell hybrids of human and mouse cells, the human chromosomes are gradually eliminated unless they carry genes essential for the survival of the hybrids. ► [Hordeum bulbosum](#), ► [haploids](#), ► [cybrid](#), ► [chromosome diminution](#), ► [Ascaris megalocephala](#), ► [Paramecium](#), ► [Rosa canina](#), ► [bivalent](#), ► [univalent](#), ► [B chromosomes](#), ► [cybrid](#), ► [assignment test](#); Ruddle FH, Kucherlapati RS 1974 *Sci Am* 231[1]:36; Goday C, Esteban MR 2001 *Bioessays* 23:242.

Chromosome Engineering: Chromosome engineering generates rearrangements in the genomes, making alien additions and translocations, and facilitates homoeologous pairing and recombination, alien transfers, alien substitutions, monosomics, chromosomal rearrangement, targeting genes, etc., with the primary goal to improve the species for agronomic purposes. About 20% human pregnancies are afflicted with different kinds of major or minor

chromosomal rearrangements and genetic engineering in mice permits reconstruction of these defects (van der Weyden L, Bradley A 2006 *Annu Rev Genomics Hum Genet* 7:247). ► [individual entries for these terms](#), ► [Cre/loxP](#); Sears ER 1972 *Stadler Symp* 4:23; Higgins AW et al 1999 *Chromosoma* 108:256; Choo KH 2001 *Trends Mol Med* 7:235; Mills AA, Bradley A 2001 *Trends Genet* 17:331.

Chromosome Hopping: ► [chromosome jumping](#)

Chromosome Inheritance: Chromosome inheritance is determined by the mitotic and meiotic apparatuses. Disturbance in the normal transmission of chromosomes may cause genetic anomalies, disease, and cancer. Several proteins control the complex process. (See Dobie KW et al 2001 *Genetics* 157:1623).

Chromosome Interference: ► [interference](#)

Chromosome Jumping: Chromosome jumping is a special type of chromosome walking that takes advantage of the breakpoints of chromosomal rearrangements as guide posts and permits the cloning of the two ends of a DNA sequence without the middle section. The procedure may take advantage of existing chromosomal rearrangements or the genomic DNA may be partially digested with any restriction endonuclease or with enzymes that cut very rarely. The DNA fragments are circularized with the aid of DNA ligase and cloned in such a way that the cloning vector contains a known *E. coli* sequence between the ligation sites. The cloned product is then digested by a restriction enzyme that does not cut within the special *E. coli* sequence. Thus the fragments generated contain the *E. coli* sequence flanked by the cloned target DNA sequence that was originally far away (100–150 kb) in the chromosome. The *E. coli* sequence containing fragments are then recloned in a phage vector and the DNA is probed to a DNA library to identify the clones that contain sequences far away in the eukaryotic genome. This procedure thus facilitates the rapid movement toward the genetic cloning target. It may also be combined with chromosome walking to approach the desired gene. ► [chromosome walking](#), ► [jumping library](#); Bender W et al 1983 *J Mol Biol* 168:18.

Chromosome Knobs: The dark-stained structures in the chromosomes best recognized during pachytene stage, representing local condensation of the chromatin (see Fig. C91). Dark knobs are a characteristic feature of certain genomes within a species. The presence of knobs may affect recombination frequencies in their vicinity and knobs may be involved in preferential segregation. ► [chromosome morphology](#), ► [knob](#), ► [karyotype](#), ► [pachytene analysis](#), ► [preferential segregation](#); Ananiev EV et al 1998 *Genetics* 149:2025.

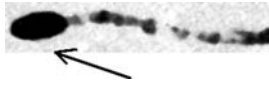


Figure C91. Chromosome knob. Pachynema of maize chromosome 9 tip, homozygous for large knob K^L . (Courtesy of Dr. Gary Kikudome)

Chromosome Landing: An approach for gene isolation from large eukaryotic genomes by first identifying linkage to close physical markers. It is a substitute for chromosome walking which is frequently impractical in these organisms. ▶chromosome walking; Tanksley SD et al 1995 Trends Genet 11:63.

Chromosome Library: A collection of individual chromosomes isolated by flow cytometric separation or pulsed field gel electrophoresis. Such a library may facilitate the manipulation of large eukaryotic genomes. ▶flow cytometry, ▶pulsed field electrophoresis; Zeng C et al 2001 Genomics 77:27.

Chromosome Maintenance Region 1 (CRM1, also called exportin 1): A karyopherin-like protein involved in nuclear import along with NES (nuclear export signal), a leucine-rich protein. CRM1 may also affect chromosome segregation. ▶karyopherin, ▶exportin, ▶importin, ▶RNA export, ▶nuclear pore; Lindsay ME et al 2001 J Cell Biol 153:1391.

Chromosome Map: ▶mapping genetic, ▶physical mapping, ▶radiation mapping

Chromosome Marker: A morphological (e.g., knob, satellite, band) or molecular (restriction enzyme recognition site) signpost on a chromosome. ▶chromosome knob, ▶satellite, ▶banding

Chromosome Mobilization: *mob*, conjugation.

Chromosome Morphology: Chromosome morphology is generally identified at metaphase and accordingly meta-, submetacentric, acro-, and telocentric chromosomes are distinguished (see Fig. C92). Furthermore, secondary constrictions and appendages (satellites)

are distinguished. The various banding techniques permit the analysis of individual chromosomes on the basis of differential staining. By the application of probes with fluorochromes chromosomes paint in different details (translocations, transpositions) and can be identified. In interphase and prophase (pachytene) some chromosomes display chromomeres, cross bands (salivary gland chromosomes, giant chromosomes), or natural knobs. The non-nuclear, prokaryotic and viral chromosomes are usually circular. ▶karyotype, ▶chromosome banding, ▶chromosome painting, ▶fluorochromes, ▶FISH, ▶PRINS, ▶pachytene analysis, ▶chromosome knobs, ▶nucleolar organizer, ▶centromere, ▶secondary constriction, ▶organelles

Chromosome Mutation: Any change (beyond the size of a nucleotide or codon) involving the structure or number of the chromosomes. ▶chromosomal aberration, ▶chromosomal rearrangement, ▶chromosome doubling, ▶point mutation, ▶codon

Chromosome Numbers: Chromosome numbers are variable among the different species and although the numbers may vary, they are important and stable taxonomic features (see Table C5). The basic number is represented by x , the gametic number by n , and the somatic number by $2n$. Thus in a diploid species like *Arabidopsis* $x = 5 = n$. In hexaploid wheat $6x = 2n$. The chromosome number may vary between males and females as a mechanism of sex determination. Also, centromeric fusion may generate one bi-armed chromosome from two telocentrics (acrocentric) or the opposite may take place. In cultured cells of mice the chromosomes may become acrocentric and double in number. The majority of bacteria have a single circular chromosome. Some other species, e.g., *Rhodobacter sphaeroides*, *Agrobacterium tumefaciens*, *Brucella melitensis*, *Vibrio cholerae* also have multiple chromosomes. Chromosome numbers of organisms often studied in genetics are shown here and additional numbers are found under the English (or scientific) name of different organisms.

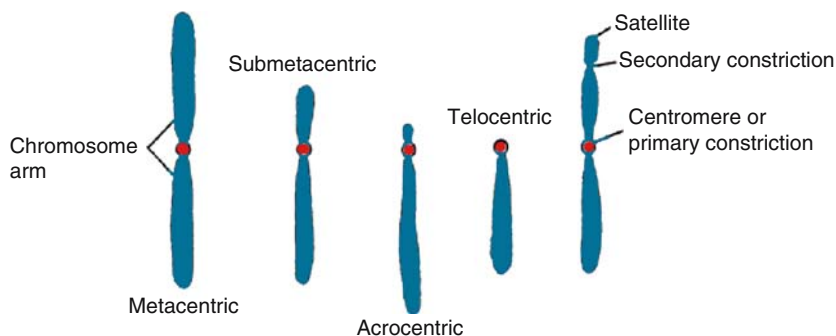


Figure C92. Chromosome morphology

Table C5. Chromosome numbers

| MICROORGANISMS | x |
|---|-----------|
| <i>Aspergillus nidulans</i> | 8 |
| <i>Chlamydomonas reinhardi</i> | 8 |
| <i>Dictyostelium discoides</i> | 7 |
| <i>Neurospora crassa</i> | 7 |
| <i>Saccharomyces cerevisiae</i> | 16 |
| <i>Saccharomyces pombe</i> | 3 |
| PLANTS | |
| <i>Arabidopsis thaliana</i> | 5 |
| Barley (<i>Hordeum vulgare</i>) | 7 |
| Broad bean (<i>Vicia faba</i>) | 6 |
| <i>Datura</i> sp. | 12 |
| <i>Epilobium</i> sp. | 18 |
| <i>Haplopappus gracilis</i> | 2 |
| Lily (<i>Lilium</i> sp.) | 12 |
| Maize (<i>Zea mays</i>) | 10 |
| <i>Oenothera lamarckiana</i> | 7 |
| <i>Petunia hybrida</i> | 7 |
| Potato (<i>Solanum tuberosum</i> , 2n = 48 = 4x) | 12 + 12 |
| Tobacco (<i>Nicotiana tabacum</i> , 2n = 48 = 4x) | 12 + 12 |
| | 12 |
| (<i>Nicotiana plumbaginifolia</i> , 2n = 24) | |
| Tomato (<i>Lycopersicum</i> sp.) | 12 |
| Wheat (<i>Triticum aestivum</i> , 2n = 42 = 6x) | 7 + 7 + 7 |
| | 7 + 7 |
| (<i>Triticum turgidum</i> , 2n = 24 = 4x) | |
| | 7 |
| (<i>Triticum monococcum</i> , 2n = 14) | |
| ANIMALS | |
| Cattle (<i>Bos taurus</i>) | 30 |
| <i>Caenorhabditis elegans</i> (female 2n = 12, male 2n = 11) | 6 |
| Chimpanzee (<i>Pan troglodytes</i>) | 24 |
| Cricket (<i>Gryllus campestris</i> , female 2n = 30, male 2n = 29) | 15 |
| <i>Drosophila melanogaster</i> | 4 |
| Hamster (<i>Mesocricetus auratus</i>) | 22 |
| Honeybee (<i>Apis mellifera</i> , female 2n = 32, male 1n = 16) | 16 |

Table C5. Chromosome numbers (Continued)

| | |
|--|----|
| Housefly (<i>Musca domestica</i>) | 6 |
| <i>Homo sapiens</i> | 23 |
| Mouse (<i>Mus musculus</i>) | 20 |
| Rat (<i>Rattus norvegicus</i>) | 21 |
| Sea urchin (<i>Strongylocentrotus purpuratus</i>) | 18 |
| Silkworm (<i>Bombyx mori</i>) | 28 |
| Swine (<i>Sus scrofa</i>) | 19 |
| <i>Tetrahymena pyriformis</i> | 5 |
| Toad (<i>Xenopus laevis</i>) | 18 |
| Wasp (<i>Habrobracon</i> sp., female 2n = 20, male 1n = 10) | 10 |

►genome, ►polyploid, ►haploid, ►acrocentric, ►telocentric, ►chromosome arm, ►sex chromosomes, ►Robertsonian translocation

Chromosome Painting: Chromosome painting is the identification of chromosomes by in situ hybridization using fluorochrome-labeled probes (see Fig. C93). With recent refinements in these techniques each human chromosome can be distinctly identified by color and various rearrangements can be detected in an unprecedented manner. ►fluorochromes, ►fluorescence microscopy, ►chromosome morphology, ►in situ hybridization, ►FISH, ►WCPP, ►USP, ►spectral karyotyping, ►telomeric probes; Fauth C, Speicher MR 2001 Cytogenet Cell Genet 93:1.



Figure C93. Chromosome painting. (Courtesy of M. Speicher)

Chromosome Pairing (synapsis): The ability of homologous (or under some circumstances, homoeologous)

eukaryotic chromosomes to associate intimately during the prophase of meiosis and form bivalents (see Fig. C94). The bivalents represent the essentially identical, homologous paternal and maternal chromosomes. In some organisms chromosomes may pair during mitoses also but this association is generally not considered as intimate as during meiosis, although in the salivary glands of *Drosophila* (and other dipterans) homologous chromosomes are tightly associated (somatic pairing). Synapsis, most commonly, begins at the termini of chromosomes at the zygotene stage and proceeds toward the centromere. By pachytene the pairing is complete and if not it is unlikely to get completed at all and some areas will remain unpaired. The pairing is genetically determined and single, specific genes may prevent pairing such as *as1* (*asynaptic*, chromosomal location 1–56 in maize). Curiously, in *as1* maize crossing over may increase. In the *phs1* mutation of maize (38 kDa protein) pairing between homologous chromosomes is replaced by synapsis between non-homologs and because of the uncoupling of Rad51 recombination is reduced. Similar genes are present in other plants too (Pawlowski WP et al 2004 Science 303:89). In hexaploid wheat the *Ph* gene suppresses homoeologous association of chromosomes but when it mutates or deletes (monosomics and nullisomics for chromosome 5B), high degree of homoeologous pairing occurs even in hybrids of related species. Some *desynaptic* genes terminate pairing precociously. In polyploids (polysomics) the homologous chromosomes may display multivalent association but at any particular point the synapsis is only between two chromosomes. In the salivary glands of trisomic flies the three chromosomes may be paired all along their length. In diptera where the X and Y chromosomes share homologous euchromatic termini, a short-duration, delayed pairing occurs (touch-and-go pairing). Synapsis is facilitated by the formation, beginning in leptotene, of the synaptonemal complex, a tripartite protein structure formed between the paired chromosomes. Synapsis provides the opportunity for the homologous chromosomes to experience crossing over and recombination. When chiasma and recombination takes place the distribution of the chromosomes at anaphase is orderly (*exchange pairing*), whereas in the absence of chiasmata (*distributive pairing*) the chance for nondisjunction increases. There are various types of pairings quite distinct from synapsis and these non-specific associations at the chromocenter of salivary gland chromosomes, association of telomeric heterochromatin in monosomes, or self-pairing in certain univalents may be observed if they possess more or less homologous sequences. ▶meiosis, ▶distributive pairing, ▶illegitimate pairing, ▶crossing over, ▶recombination, ▶somatic

pairing, ▶parasexual mechanisms, ▶pachytene analysis; Sybenga J 1999 Chromosoma 108:209.

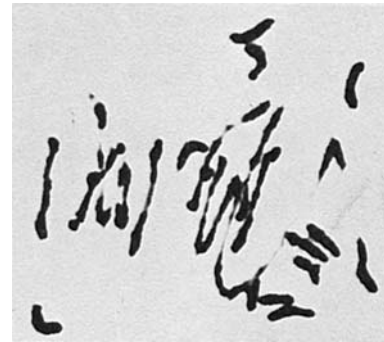


Figure C94. Chromosome pairing. Multivalent pairing in F1 hybrid of *Triticum aestivum* (AABBDD) x *Aegilops variabilis* (C^uC^uS¹S¹) in the absence of chromosome 5B (pairing inhibitor). (Courtesy of Dr. Gordon Kimber)

C

Chromosome Partitioning: Chromosome partitioning in prokaryotes occurs after replication, when one of the two chromosomes, each, is delivered to the daughter cells. ▶mitosis, ▶DNA replication prokaryotes; Lemon KP et al 2001 Proc Natl Acad Sci USA 98:212.

Chromosome Passenger: Chromosome passengers are proteins associated with chromosomes (centromeres) during early mitosis and which, after anaphase, move to the mid-zone of the spindle. ▶centromere, ▶spindle, ▶mitosis

Chromosome Positioning: Chromosome positioning occurs in prokaryotes when the old and new (replicated) chromosomes tend to move to opposite poles of the cell. A defect in positioning may involve a condition analogous to nondisjunction in eukaryotes, i.e., the 0–2 distribution. Chromosome positions in the interphase eukaryotic nucleus are not random. In primates the gene-rich chromosomes such as human chromosome 19 tends toward the center of the nucleus, whereas the gene-poor chromosome 18 is situated at the periphery (Tanabe H et al 2002 Proc Natl Acad Sci USA 99:4424). The centromeres tend to interact with nuclear lamina at the pores. ▶anaphase; McEwen BF et al 2001 Mol Biol Cell 12:2776; Marshall WF 2002 Current Biol 12[5]: R186.

Chromosome Puffing: Chromosome puffing takes place in the polytenic chromosomes (of animals and plants) when genes are activated and begin synthesizing large amounts of RNA. When transcription is

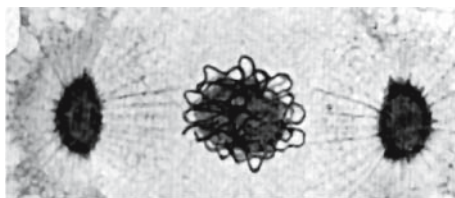
terminated the puffs recede. Puffing may be stimulated by the administration of hormones (e.g., ecdysone in insects). See illustration at puff, ►**ecdysone**; Thummel CS 1990 Bioessays 12:561.

C

Chromosome Region Maintenance: ►CRM

Chromosome Replication: Chromosome replication numbers in human sperm prior to that produced at age A can be determined by the formula $N_A = 30 + 23(A - 15) + 5$; thus, in males aged 20, 30, 40, and 50, N_A is 150, 380, 610, and 840, respectively. Therefore it is not unexpected that the offspring of older fathers may be loaded with more new mutations. In human females the number of replications is much smaller as a function of age. Indeed the mutation of paternal genes is significantly higher in many hereditary diseases. There is an almost complete absence of mutant males in 13 X-linked traits that are lethal or sterilizing in females. This is due to the generally high male mutation rate. Affected males would have heterozygous mothers. These observations make sense if the rate of mutation in females is low. In the diseases Duchenne muscular dystrophy and neurofibromatosis, based on very large genes, the mutations are generally not of paternal origin. In these latter cases the mutations are not caused by replicational errors but by deletions and duplications. In hemophilia there is a higher male rate for point mutations and a higher female rate for deletions. ►**replication**, ►**dictyotene stage**, ►**mutation rate**, ►**muscular dystrophy**, ►**neurofibromatosis**, ►**hemophilias**; Crow JF 1999 Genetics 152:821.

Chromosome Rosette: At the prometaphase stage (lasting about 5–10 min in human cells) the chromosomes are arranged like a wheel, centromeres oriented toward the hub and the arms assuming an arrangement like spokes in a wheel (see Fig. C95). The homologs appear at opposite positions of the rosette. If the chromosomes are painted by fluorochrome labels. ►**mitosis**, ►**metaphase**, ►**FISH**; Munkel C et al 1999 J Mol Biol 285:1053.



Monocystis magna rosette

Figure C95. Chromosome rosette

Chromosome Scaffold: The structurally preserved form of the chromosome freed from histone proteins.

►**chromatin**, ►**chromosome structure**; Stack SM, Anderson LK 2001 Chromosome Res 9:175.

Chromosome Segregation: Chromosome segregation is the basis of Mendelian inheritance (mitosis and meiosis). In autopolyploids the chromosomes may segregate reductionally, e.g., at anaphase I in an autotetraploid chromosomes with A, A, A, A may move toward one pole and chromosomes with a, a, a, a toward the other. This is called reductional segregation (R). Alternatively, the distribution may be Aa, aA , and aA, Aa , or aA, Aa and Aa, Aa , (respectively) i.e., equational segregation (E) occurs. These two types of separations follow the proportion of 1R:2E. The term *chromosome segregation* is also used for cases in polyploids when genes are closely linked to the centromere and crossing over does not take place between them, in contrast to *maximal equational segregation* when one crossing over takes place between gene and centromere in each meiocyte.

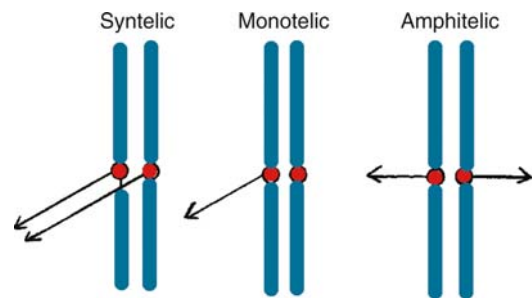


Figure C96. Chromosome segregation

The segregation of the chromatids (vertical lines) is controlled by anaphase promoting complex (APC) regulated by the Aurora B kinase. If conditions are normal, the centromeres segregate equationally in mitosis (amphitelic segregation) and the two centromeres (circles) are pulled to opposite poles by the spindle fibers (arrows). This is facilitated by destroying cyclin B and securin proteins. When syntelic or monotelic movements are sensed Aurora inhibits APC at a checkpoint. Such a control assures that the daughter cells will be normal. ►**meiosis**, ►**autotetraploid**, ►**Aurora**, ►**centromere**, ►**spindle fibers**, ►**cyclin B**, ►**securin**, ►**APC**; Nasmyth K 2002 Science 297:559; chromosome and plasmid segregation: Ghosh SK et al 2006 Annu Rev Biochem 75:211.

Chromosome Set: A group of chromosomes representing once all the chromosomes of the haploid set, the genome. It is represented by x. ►**genome**, ►**haploid**

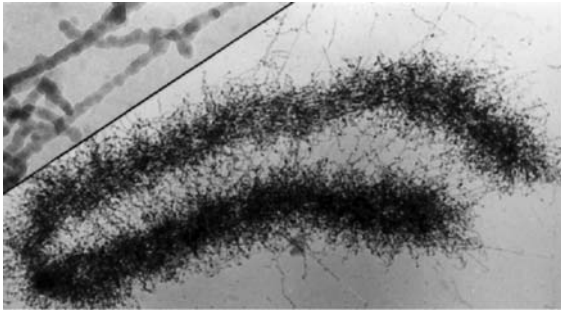


Figure C97. The image above represents a loosely packaged acrocentric human chromosome isolated from a Burkitt's lymphoma cell. The individual fibers are shown on the inset at approximately 85,000x magnification. (Photomicrograph from Lampert F, Bahr GF, and DuPraw EJ 1969 Cancer 24:367)

Chromosome Sorting: ► [flow cytometry](#)

Chromosome Stickiness: The apparent adhesion of chromosomes that tend to stay together.

Chromosome Structure: The electron-microscopic image of a chromosome reveals many more details than a light-microscopic image. The light microscope, however, shows great advantage in the study of chromosomal behavior such as chiasmata, non-disjunction, misdivision, etc., occurring during mitosis and meiosis. ► [chromatin](#), ► [nucleosomes](#), ► [Mosolov model](#); Woodcock CL, Dimitrov S 2001 Curr Opin Genet Dev 11:130.

Chromosome Substitution: Chromosome substitution can be alien substitution (see there) or inter-varietal substitution when the corresponding chromosome of another variety in polyploids replaces one chromosome of a variety where monosomic or nullisomic lines can be propagated (see Fig. C98). Thus some desirable genes can be transferred without altering the genetic background. Although E.R. Sears developed chromosome substitution primarily for hexaploid wheat plants since the 1930s, it is applicable to any other system for the localization of QTLs or other

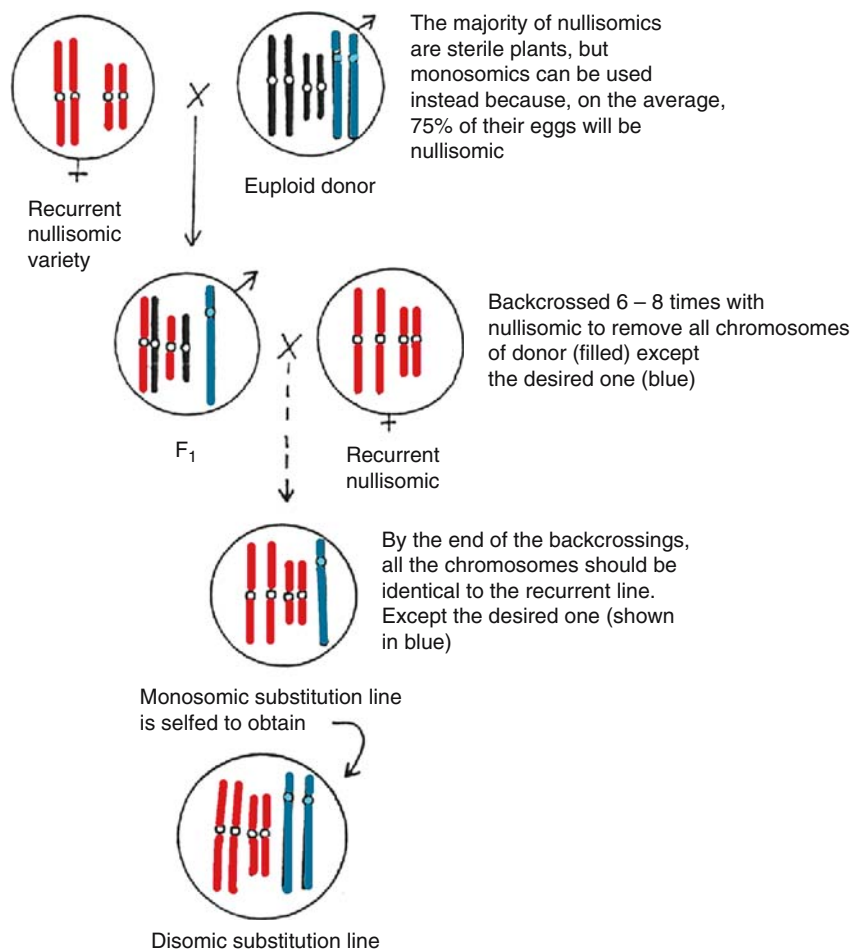


Figure C98. Chromosome substitution

genes. Complex traits can be analyzed also in mice by the use of chromosome substitution (Singer JB et al 2004 Science 304:445). ►flowchart, ►linkage in breeding, ►genetic engineering, ►QTL, ►alien substitution, ►consomic

C

Chromosome, Supernumerary: ►B chromosome, ►cat-eye syndrome

Chromosome Symbols: ►*Drosophila*, ►gene symbol

Chromosome Telocentric: ►telocentric chromosome

Chromosome Ten Tumor Suppressors: ►PTEN

Chromosome Territories: The domains occupied by the chromosomes in the nucleus. The majority of genes prefer to occupy the surface of the territory, others loop apart and associate with nuclear bodies involved in transcription (activation or repression) (see Fig. C99). Gene-rich, early replicating chromosomal regions are generally clustered in the internal areas.

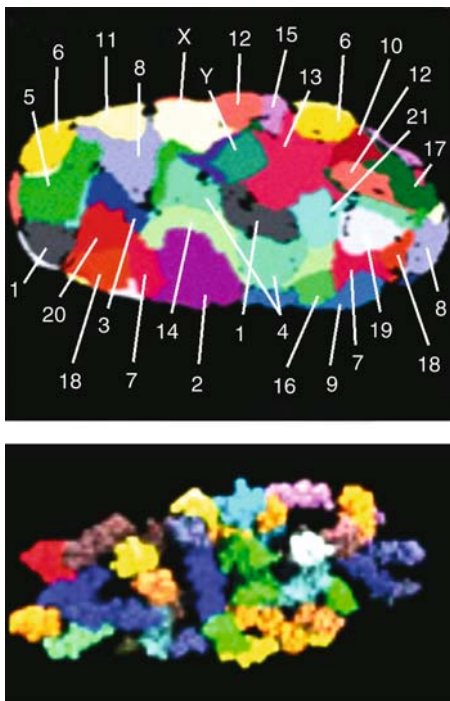


Figure C99. Chromosome territories. Human chromosome territories in false color. Each chromosome is numbered. Below: three dimensional simulation of the chromosome arrangement; prepared as specified in the Methods of the paper cited below. (From Bolzer A, Kreth G, Solovei I, Koehler D, Saracollu K et al (2005) Three-dimensional maps of all human male fibroblast nuclei and prometaphase rosettes. PLoS Biology 3(5):e157. Courtesy of Dr. Michael R. Speicher)

Whereas gene-poor, late-replicating regions seem to be located at the periphery (Tanabe H et al 2002 Mutation Res 504:37). A newer study using multiplex FISH technology applied to human fibroblast nuclei permitted three-dimensional positioning of each human chromosome (see Fig. C100). The prometaphase chromosomes provided a probabilistic, non-deterministic model of the positions as well as an assessment of the chromosomal territories in quiescent, G₀ and in cycling, S-phase cells. Small chromosomes, independently of gene density, were found closer to the center, whereas larger chromosome preferred the nuclear periphery. This arrangement was not the result of geometric constraints and it was observed in other cell types too. Gene-poor regions tended to be situated in a layer beneath the nuclear envelope whereas the gene-dense regions of the chromatin were enriched in the nuclear interior (Bolzer A et al 2005 PLoS 3[5] e157). In yeast cells, upon the mating pheromone alpha factor stimulation the myosin-like protein Mlp1 (involved in mRNA export) and the genes dependent on it tended toward the nuclear pores. This observation indicated that the chromosomal conformation and spatial arrangement were altered by developmental cues (Casolari JM et al 2005 Genes Dev 19:1188). In ultrathin cryosections of phytohemagglutinin-activated human lymphocytes painted by an improved FISH showed some intermingling of chromosomal territories. These intermingling areas contained DNA. The volume of 41% of chromosome 3 intermingled with the rest of the genome and the extent of intermingling of other chromosomes was similar. The intermingling correlated with translocation potential of the non-homologous chromosomes. Furthermore, inter-mingling facilitates interactions with transcription factories.

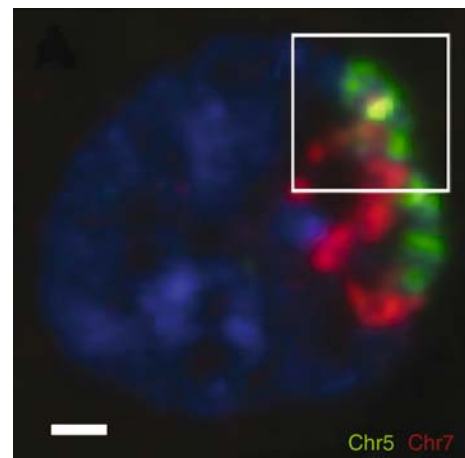


Figure C100. Intermingling of human chromosomes 5 and 7. (Courtesy of Branco MR & Pombo A 2006 PLoS Biol. 4(5): e138.)

Decondensed stage of the chromosomes such as in interphase and the presence active genes are favorable for intermingling. The new information provides a more meaningful view on chromosome organization and its relation to chromosome functions (Branco MR, Pombo A 2006 PLoS Biol. 4(5):e138). E.J. DuPraw published already in 1970 that the completed mount electronmicroscopic picture of human leukocytes revealed islands of chromosome fibers with numerous interconnections. ▶perichromatin fiber, ▶chromosome positioning, ▶transcriptome map, ▶nucleus, ▶FISH, ▶interchromosome domain compartment, ▶interchromosomal interactions, ▶transcription factories, ▶chromosome conformation capture; Cremer T, Cremer C 2001 Nature Rev Genet 2:292; Kosak ST, Groudine M 2004 Science 306:644; brief review: Meaburn KJ, Misteli T 2007 Nature [Lond] 445:381; regulation of transcription by territories review: Yang PK, Kuroda MI 2007 Cell 128:777; review: Fraser P, Bickmore W 2007 Nature [Lond] 447:413.

Chromosome Texture: ▶oligostickiness

Chromosome Theory: The chromosome theory was developed at the beginning of the twentieth century and stated that genetic material is contained in the

chromosomes, and the Mendelian laws are based on the mechanisms of meiosis. ▶Mendelian laws, ▶Mendelian segregation; Sutton WS 1903 Bull Biol 4:231.

Chromosome Transfer (chromosome-mediated gene transfer): ▶chromosome uptake, ▶chromosome substitution

Chromosome Uptake: (see Fig. C101)

Chromosome Walking: The mapping of the position of a DNA site or a gene by using overlapping restriction fragments(see Fig. C102). The principle involved is somewhat similar to that in classical cytogenetic mapping with overlapping deletions. It is used also for map-based isolation and then cloning of specific genes. The success of isolation of genes by this method is greatly affected by the size of the genome and even more importantly on the distance that must be “walked” from a known genomic position toward the desired gene.

Some means must also be found for determining the function of the gene so its identity can be verified. In large eukaryotic genomes, the procedure is facilitated if physical maps are already available. ▶cosmid vectors, ▶YAC vectors, ▶chromosome

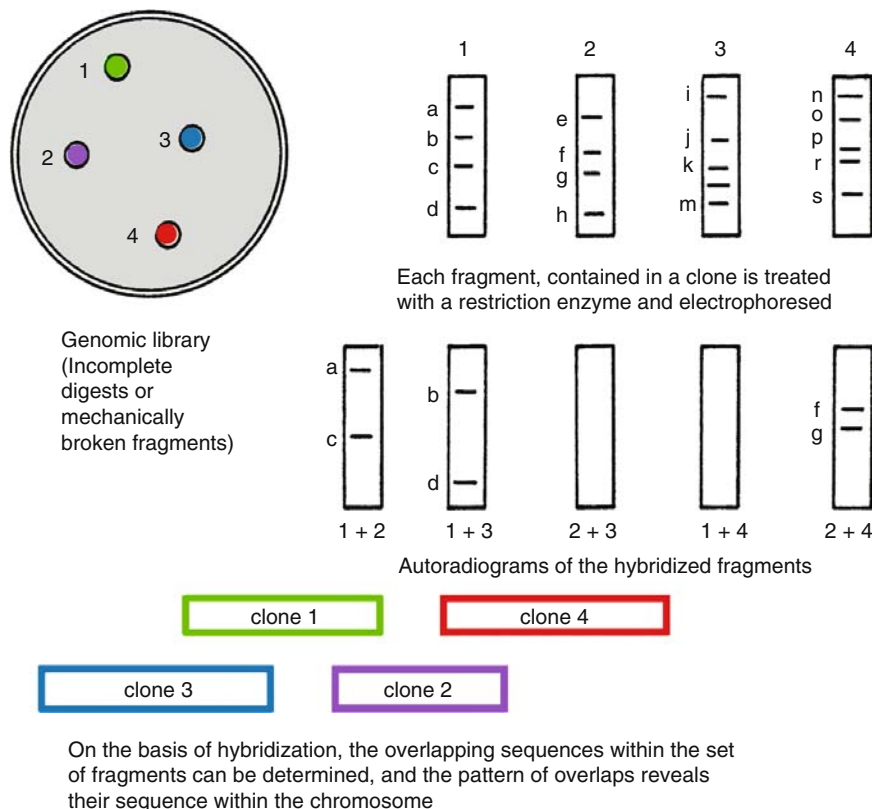


Figure C101. Chromosome walking

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Chromosome uptake

- The transferred segment may be 17 to 1000 kbp and microscopically invisible (microtransgenome)
- Microscopically visible segments (macrotransgenomes) constitute about 15% of the transformants
- Integration is generally not by homology, rather by random events like translocations
- Transferred genes are expressed, frequently at higher intensity because of larger copy number
- Both partially degraded and more or less intact fragments become stable after integration

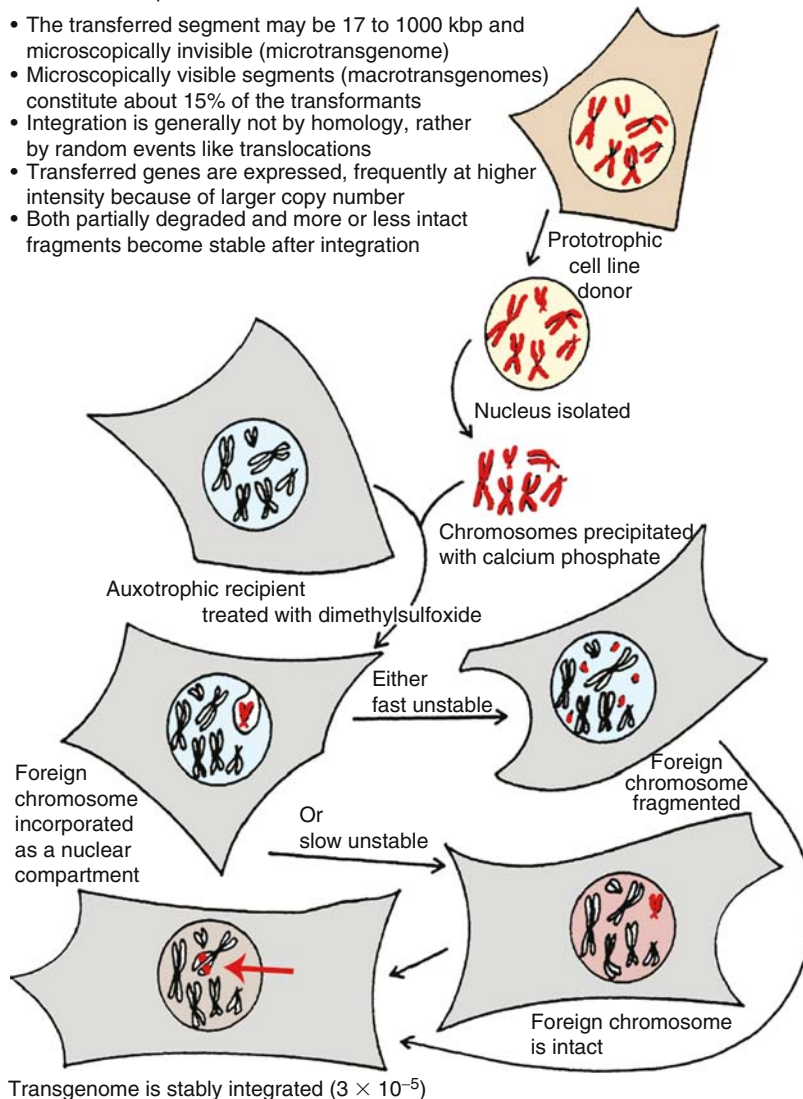


Figure C102. Chromosome uptake

jumping, ►map based cloning, ►chromosome landing, ►position effect; Bender W et al 1983 J Mol Biol 168:17; Kneidinger B et al 2001 Bio-techniques 30:248; diagram.

Chromosome-Specific Cell Line: The cells of species (A) are heavily irradiated and are fused with normal (unirradiated) cultured cells (B). Cells are then selected that contain only one chromosome of the A line and allowed to hybridize genes (DNA sequences) to this cell so that on the basis of binding to the critical chromosome, physical mapping can be achieved like in the use of radiation hybrids. Also, flow cytometer-sorted chromosomes or chromosome fragments can be mapped by the use of polymerase chain reaction

(PCR) and fluorescent staining. ►radiation hybrid, ►polymerase chain reaction, ►flow cytometer, ►addition line, ►alien addition, ►chromosome substitution; VanDevanter DR et al 1994 Proc Natl Acad Sci USA 91:5858.

Chromosomin: A non-histone protein of the chromatin. ►chromatin

Chronic Granulomatous Disease (CGD): A complex disease based on the inability of the phagocytizing neutrophils to destroy infectious microbes due to defects in delivering sufficient levels of oxygen to the neutrophil membranes. Laboratory diagnosis is generally based on the failure of the phagocytes to reduce nitroblue tetrazolium. Prenatal diagnosis

exists for males and carriers. The afflicted persons are liable to infections. The human gene was localized to Xp21, and it has apparently a defect in the cytochrome b system, probably most commonly in the β subunit (CYBB), whereas the autosomal form (human chromosome 16q24) is defective in the α subunit (CYBA). In some variants other functions may also be involved. (►immunodeficiency, ►cytochromes, ►neutrophil, ►phagocytosis). (See McBride OW, Peterson JL 1980 Annu Rev Genet 14:321).

Chronic Lymphocytic Leukemia (CLL): ►leukemia

Chronic Radiation: Radiation dose(s) delivered continuously without interruptions. ►fractionated dose

Chronic Wasting Disease (CWD): A prion disease-like encephalopathy of (~4%) wild deer and (~1%) of elk in the American North-West. Its transmission and symptoms are similar to other encephalopathies although the epidemiological information is still limited. It may pose a danger to cattle, eaters of venison, and to taxidermists. Infectious prions present in the saliva, blood, urine, and feces of the sick animals are a source of transmission (Mathiason CK et al 2006 Science 314:133). ►encephalopathies, ►prion; Angers RC et al 2006 Science 311:1117.

Chronological Aging: The length in time of the lifespan. ►aging, ►replicative aging, ►lifespan, ►longevity

Chronology of Genetics: ►genetics chronology of

CHUK: A synonym of I κ B- α kinase. ►I κ B

Chrysanthemum (*C. indicum*): Herbaceous perennial ornamental; 2n = 20, 45–30.

Churg-Strauss Vasciculitis: A deficiency of the C1-INH complement component resulting in allergic inflammation of the vessels system. ►complement

chv: Chromosomal virulence loci in *Agrobacterium*. ►virulence genes of *Agrobacterium*

Chylomicron: The transporters of lipoproteins ingested or synthesized in the small intestines. ►hyperlipoproteinemia, ►Anderson disease, ►Marinesco-Sjögren syndrome

Chymases: Chymases are similar to chymotrypsin and hydrolyze peptide bonds near the carboxyl end of hydrophobic amino acids. They are regulated by IL-15 (Orinska Z et al 2007 Nature Med13:927). ►chymotrypsin, ►IL-15

Chymotrypsins: Proteases (M_r 25 K) cleaving near aromatic amino acids, non-polar groups, ester bonds. They are targeted by nerve gas (DFP).

Ci (Curie): A measure of radioactivity; 1 Ci = 3.7×10^{10} disintegrations/sec. ►radioactivity, ►isotopes, ►radioactive label

cl: A phage λ repressor. ►lambda phage

CIA: ASF1.

CIBD (chronic inflammatory bowel disease): The prevalence of CIBD in the western world is 2×10^{-3} . ►Crohn disease

CIBEX (Center for Information Biology Gene Expression Database) <http://cibex.nig.ac.jp/>.

CIC (chloride ion channel): The CIC controls the excitability of skeletal muscles and blood pressure, acidifies endosomal compartments, and regulates GABA responses. ►endosome, ►GABA, ►ion channels

CID (collision-induced dissociation): CID is a fragmentation of molecules, e.g., peptides at particular bonds and sheds information on the peptide sequence analyzed by mass spectrometry in proteomics. ►mass spectrometer, ►MALDI/TOF/MS, ►neutral-loss scan; Wells JM, McLuckey SA 2005 Methods Enzymol 402:148.

CID (centromere identifier): A nucleosome assembly complex that localizes the CenH3, centromere-specific histone, a variant of the H3 histone, into the centromere. ►histones, ►histone variants

CIGAR: The CGGAAR (R = purine) enhancer motif of Herpes simplex virus. ►TAT-GARAT, ►Herpes

Cigarette Smoke: Cigarette smoke contains dozens of various combustion products including the most potent carcinogens and mutagens, e.g., benzo(a) pyrene (about 20–40 ng/cigarette) responsible for the majority of lung cancer cells, which carry mutations in the p53 tumor suppressor gene, mainly G→T transversions, at codons 157, 248, and 273. The codon 157 hot spot is absent from other types of cancers. These hot spots are the sites of adduct formation by benzo(a) pyrene diol epoxide and guanine-N². Gene expression arrays are suitable for the determination of the genes permanently or transiently affected by the expression of bronchial cells (Spira A et al 2004 Proc Natl Acad Sci USA 101:10143). ►p53, ►cancer, ►hot spot, ►benzo(a) pyrene, ►transversion; Izzotti A et al 2001 Mutation Res 494:97.

CIITA (class II transactivator): An apparently non-DNA-binding modulator of the synthesis of class II MHC molecules. When it binds GTP it moves to the cell nucleus where it interacts with the complex RFX. RFX is bound to MHC II gene promoters. CIITA transcription uses four promoters. Promoter 1 specifically

controls its expression in dendritic cells, Promoter 3 is essential in B and T lymphocytes, and Promoter 4 is activated by interferon- γ . CIITA is also a global co-activator of the human leukocyte antigen-D (HLA-D) genes and it also regulates import through the nuclear pore. ▶MHC, ▶HLA, ▶RFX, ▶dendritic cell, ▶interferon, ▶nuclear pores, ▶transactivator; Wiszniewski W et al 2001 J Immunol 167:1787.

Cilia (singular cilium): Cilia, the hair-like structures formed from microtubules, are extensions of the basal bodies. They are used for locomotion (swimming) in watery media or on viscous films by a vibratory or lashing movement (see Fig. C103). Cilia are involved also in sensory reception and signaling through intra-flagellar transport. The Joubert syndrome, Meckel syndrome, Alström syndrome, Bardet-Biedl syndrome, Kartagener Syndrome, Polycystic Kidney Disease, and Nephronophthisis may show defects in cilia and in the anchoring basal bodies. ▶axoneme, ▶microtubule, ▶flagellum, ▶dynein, ▶kinesin, ▶basal body, ▶named syndromes; Scholey JM, Anderson KV 2006 Cell 125:439; < 1,200 non-redundant human proteins: <http://www.ciliaproteome.org/>.

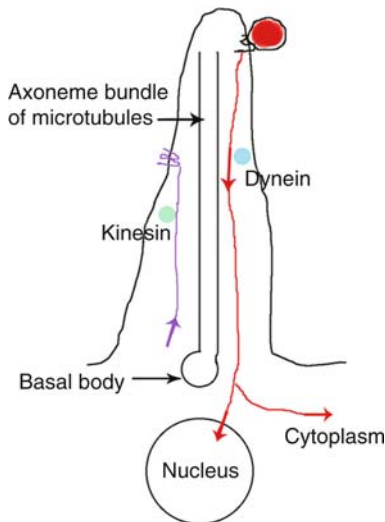


Figure C103. Ciliary function

Ciliary Dyskinesia, Primary: In primary ciliary dyskinesia, the basic defect is in the axonemal heavy chain dynein at 7p21. Half of those afflicted by Kartagener's syndrome show the same mutation. ▶Kartagener syndrome

Ciliary Neurotrophic Factor (CNTF, human chromosome 11q12.2): Glial cells release CNTF to repair damaged neurons. CNTF is also involved in the general differentiation of nerve cells (gliogenesis)

from multipotential precursor cells. Its 41-kDa receptor, CNTFR, is encoded at 9p13. CNTF specifically stimulates also the JAK-STAT signal transduction pathway leading to cell fate determination. CNTF deficiency is not involved in any known human disease although CNTF may show beneficial effects in amyotrophic lateral sclerosis. It has some effects like leptin. ▶neuron, ▶neurogenesis, ▶signal transduction, ▶APRF, ▶nerve growth factor, ▶amyotrophic lateral sclerosis, ▶leptin, ▶obesity; Linker RA et al 2002 Nature Med 8:620.

Ciliates: ▶Oxytricha

CIMP (CpG island methylator phenotype): CIMP activates neoplasias by interfering with the expression of tumor suppressor genes. ▶CpG island, ▶methylation of DNA, ▶tumor suppressor genes

CIN: chromosome instability factors. ▶chromosomal instability

Cin: An invertase. ▶invertases, ▶Cin4

Cin4: non-viral retroposons, hybrid dysgenesis I – R.

Ciona intestinalis (Ascidian): A chordate evolutionarily ancestral to vertebrates. It has ~16,000 protein-coding genes in its genome (2n = 16) draft. (See Dehal P et al 2002 Science 298:2157; Satoh N 2003 Nature Rev Genet. 4:285; tunicate database: <http://dbtgr.hgc.jp/>).

CIP (calf intestinal alkaline phosphatase): CIP is used for the removal of 5' phosphate from nucleic acids and nucleotides, and is a general inhibitor of CDKs. ▶CDK, ▶KIP

CIP: ▶p21, ▶p/CIP

Ciprofloxacin: Ciprofloxacin is a fluoroquinolone antibiotic that inhibits bacterial DNA gyrase and topoisomerase IV cleavage and resealing, and thus, DNA replication. It is used effectively against anthrax. The same family of drugs (under different trade names) is used against other bacteria too. ▶antibiotics, ▶gyrase, ▶topoisomerase, ▶antibiotic resistance, ▶anthrax

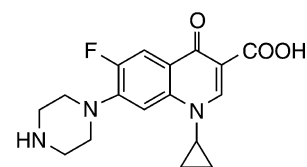


Figure C104. Ciprofloxacin

CIR: The cardiac inwardly rectifying ion channel. ▶ion channels, ▶I_{KAch}

Circadian Rhythm (circadian clock): The circadian rhythm has a daily (24 h) periodicity; the term is derived from the Latin *circa diem* [around the day]. Such periodicity (rhythm) may occur in plants in opening and closing flowers and in translocation of metabolites, or may affect in various ways in animals daily behavioral and metabolic patterns such as, sleep, social activities, etc. The transcriptional coactivator PGC-1 α integrates the mammalian circadian clock with energy metabolism (Liu C et al 2007 Nature [Lond] 447:477). The circadian rhythm usually independent of temperature. In *Arabidopsis*, nearly 500 genes are affected by the daily rhythm. A clock-controlled promoter sequence (AAAATATCT) repeats many times in most cycling genes. In *Arabidopsis* mutants, when the clock periods matched the environmental light cycles, plants produced more chlorophyll, fixed more carbon, grew faster, and survived more successfully, indicating the biological advantage of the circadian rhythm (Dodd AN et al 2005 Science 309:630).

In *Drosophila*, the *per* (period) mutation shows, however, a dimerization domain PAS that is subject to temperature effects. The *per* genes encode Thr-Gly repeats in 14, 17, 20, and 23 dipeptide lengths in the various ecological races of different *Drosophila* species. The 17 and 20 alleles are predominant in Mediterranean regions and the northern regions of Europe, respectively. In animals the control spot for the circadian periodicity resides in the suprachiasmatic nucleus of the hypothalamus in the brain. Injecting glutamate, methyl-D-aspartate, or nitric oxide into the brain produces the same effect as light does in controlling periodicity. Intracellular Ca²⁺-ryanodine channels play a regulatory role. Circadian rhythm is involved in olfactory responses too. Some prokaryotes also display this rhythm but *Saccharomyces* and *Schizosaccharomyces* eukaryotes apparently lack it. The molecular mechanism of the circadian oscillations seems complex but it appears that it is dependent on activation of the E-box and transcription of genes *Per* and *Time* by the genes *Clock-MOP3* complex. Clock is a histone acetyltransferase (Doi M et al 2006 Cell 125:497). After the mRNAs are translated, the protein may eventually feedback inhibits *Clock* and the daily oscillations come to a full circle. The expression of *vrille* is a requisite for *Clock*. In *Drosophila*, the gene *Doubletime* product (DBT) that destabilizes *Per* in the evening has been identified. DBT plays this role until sufficient quantity of *Tim* (Timeless) accumulates and protects *Per* from DBT. The *Neurospora* clock gene (frequency, *FRQ*) regulates rhythmically its own expression by the transcriptional activator, White collar Complex (*WCC*), through cyclically modulating phosphorylation. Dephosphorylation and

activation of *WCC* require protein phosphatase 2A (PP2A). Hypophosphorylated *WCC* binds to the clock box of *FRQ* promoter. Hyperphosphorylated *WCC* binding is compromised even when *FRQ* is depleted (Schafmeier T et al 2005 Cell 122:235). The *Doubletime* homolog of Syrian hamster (*TAU*) encodes a casein kinase1 epsilon (CK1 ϵ) protein. Then *Per* and *Tim* pass to the nucleus and cause their feedback inhibition. By the morning, these two gene-products fade away and *Clock* and other proteins will turn on again *Per* and *Tim*. *Drosophila* controls the circadian functions by five major genes. Similar systems based on homologous genes and proteins operate in other animals. Under the conditions of 24-h nights or 24-h daylight in the arctic regions, the diurnal rhythm of polar animals is temporarily suspended (van Oort BEH et al 2005 Nature [Lond] 438:1095). The circadian light receptor in mammals resides in the eyes and the pineal gland and the signals are chemically transmitted to the organs (deep in the body) that are not accessible to light. In plants, the control is slightly different. In the transparent body of *Drosophila* or zebrafish, internal organs also have light oscillators. A common circadian rhythm disorder is the *jet lag*, based on maladjustment to longer-than-5 h time zone differences, especially while traveling from the west to the east. Jet lag is an F-box protein with leucine-rich repeats and promotes the degradation of Timeless (Koh K et al 2006 Science 312:1809). Evidence is accumulating for the role of PDF (pigment-dispersing factor, a neuropeptide) in the control of genetic clock genes. An analog of the *Clock* gene (*NPA2*) expressed in the forebrain of mammals is regulated by the redox state of NAD cofactors. The human gene (Advanced sleep-phase syndrome, FASPS) homologous to *Per2/CKI* of *Drosophila* has been mapped 2q37.3. It involves a serine→glycine substitution at site 662 in the casein kinase-I- ϵ gene ((Tooh KL et al 2001 Science 291:1040). Its mutation controls early sleeping and early awakening. A human threonine → alanine substitution at site 44 in the CKI δ protein in transgenic *Drosophila* was seen to cause increased circadian period, whereas in mice (similarly to humans) it showed a shorter circadian period, indicating different regulation in insects and mammals (Xu Y et al 2005 Nature [Lond] 434:640). Clock mutants of mice have diminished diurnal feeding rhythm and become hyperphagic and obese (Turek FW et al 2005 Science 308:1043). Knocked-out *CLOCK* in mouse indicates that this gene is not necessary for full circadian function (DeBruyne JP et al 2006 Neuron 50:465). ▶*per* mutation in *Drosophila*, ▶endogenous rhythm, ▶hypothalamus, ▶nitric oxide, ▶clock genes, ▶brain human, ▶E box, ▶F-box, ▶ryanodine, ▶rhodopsin, ▶cryptochrome,

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►entrainment, ►oscillator, ►zeitgeber, ►zeitnehmer, ►melatonin, ►pineal gland, ►NAD, ►oxidation-reduction, ►lithium, ►photoperiodism, ►Cyanobacteria; Young MW 1998 Annu Rev Biochem 67:135; Dunlap JC 1999 Cell 96:271; Scully AL, Kay SA 2000 Cell 100:297; Lowrey PL, Takahashi JS 2000 Annu Rev Genet 34:533; Shearman LP et al 2000 Science 288:1013; Clayton JD et al 2001 Nature [Lond] 409:829; McClung CR 2001 Annu Rev Plant Physiol Mol Biol 52:29; Rutter J et al 2001 Science 293:510; Ueda HR et al 2002 J Biol Chem 277:14048; crystal structure of *Per*: Yildiz Ö et al 2005 Mol Cell 17:69; Lowrey PL, Takahashi JS 2004 Annu Rev Genomics Hum Genet 5:407; multiple oscillators in various organisms: Bell-Pedersen D et al 2005 Nature Rev Genet 6:544; Per-Tim interactions: Mayer P et al 2006 Science 311:226; circadian oscillations in gene expression and circadian oscillations in metabolic activity: Wijnen H, Young MW 2006 Annu Rev Genet 40: 409; common features with the cell cycle: Hunt T et al 2007 Cell 129:461.

Circle: A geometric figure with circumference = $2\pi r$; area = $r^2\pi$, where r = radius and $\pi \cong 3.14159$.
►geometric solids

Circular Dichroism: The difference between the molar absorptivities for left-handed and right-handed polarized light as observed in chiral molecules (enantiomorphs). Circular dichroism detects Z DNA structures and the interaction of drugs and carcinogens/mutagens with the DNA. ►enantiomorph, ►chirality, ►Z DNA

Circular DNA: Covalently closed ring-shaped DNA such as the genetic material of bacteria, eukaryotic organelles, and the majority of the plasmids (see Fig. C105).



Figure C105. Circular DNA

Circularization: Circularization is the phenomenon of forming a circle, like in plasmids; unwanted circularization of DNA can be prevented by directional cloning or treatment with bacterial phosphatase to remove terminal phosphates needed for joining DNA ends. ►directional cloning

Circumcision: Circumcision in the *male* involves the removal of the foreskin (prepuce) from the distal end of the penis of infants. It is thought to reduce the

chance of sexually transmitted disease. Recent results from studies in Africa indicate substantial reduction (50–60%) of AIDS infection in circumcised males (Newell ML, Bärnighausen T 2007 Lancet 369:617). However, this procedure should not be considered a preventive measure against AIDS, at the risk of not observing other safety rules. In the *female*, circumcision is a barbaric procedure practiced in some underdeveloped regions of the world and is considered ethically unacceptable (see Fig. C106). At the least, it involves the surgical removal of the clitoris but in more drastic forms the labia minora are also removed. ►clitoris, ►vagina

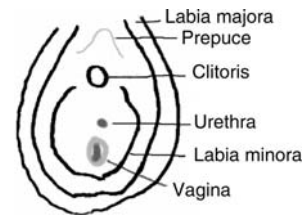


Figure C106. Female external genitalia

Circumnutation: A movement of plants around their axis, as in the case of tendrils (see Fig. C107).
►tendrils



Figure C107. Circumnutation

Cirrhosis of the Liver: Liver cirrhosis includes mainly autosomal recessive diseases characterized by fibrous structure of the liver. It may be precipitated by various environmental factors such as copper toxicity, alcoholism, and antitrypsin deficiency. Hepatitis C virus infection is a causal agent and may affect as many as 170 million persons in a year causing 3000.000 annual deaths. It may occur as a component of other syndromes. The quantitative gene locus HC, encoding complement factor 5, has a causal role in fibrogenesis in mouse and humans (Hillebrandt S et al 2005 Nature Genet 37:835). Cirrhotic liver loses its ability to regenerate normal cells, apparently because of diminished telomerase activity. Childhood cirrhosis characterized by cholestasis, was localized to 16q22 (Chagnon P et al 2002 Am J Hum Genet 71:1443). The telomerase gene, carried by adenoviral

vector, was found to improve cirrhosis in telomerase deficient mice. ►Wilson's disease, ►galactosemia, ►transaldolase deficiency, ►antitrypsin, ►alcoholism, ►autoimmune diseases, ►complement, ►cholestasis, ►cholic acid, ►adenovirus, ►gene therapy; Friedman SL 2000 J Biol Chem 275:2247; Iredale JP 2007 J Clin Invest 117:539.

CIS (CISH, cytokin-inducible-SH2-containing protein, 3p21.3): CISH contains 222 amino acids and binds to tyrosine-phosphorylated IL-3 and erythropoietin receptors. It may be a part of the system turning off cytokine signaling. Its deletions are frequent in lung and kidney tumors. ►cytokines; ►IL-3; ►erythropoietin; ►SH2 domain; ►SOCS-box; ►JAB; ►SSI-1; Uchida K et al 1997 Cytogenet Cell Genet 78:209.

Cis Arrangement: CIS arrangement occurs when two genes (or two different mutant sites) of a locus are within the same chromosome strand, e.g., *a b*. ►trans arrangement, ►cis-trans test

Cis Preference: The protein products of the L1 retrotransposons usually (not necessarily) bind to the encoding RNA. ►LINE

Cis-Acting Element: The Cis-acting element must be located in the same DNA strand as its target to act upon it during transcription. Genes that are conserved across species will also display conservation at the level of their transcriptional regulation and this will be reflected in the organization of cis-elements mediating this regulation. Using a computational approach, clusters of transcription factor binding sites that are absolutely conserved in order and in spacing across human, rat, and mouse genomes were identified. These regions are called (PRIs), pattern-defined regulatory islands (Cheung TH et al 2007 Proc Natl Acad Sci USA 104:10116). ►trans-acting element, ►cis-regulatory modules, ►LCR, predictor of cis-regulatory elements: <http://bibiserv.techfak.uni-bielefeld.de/jpredictor/>; transcription factor annotation tool on chromatin immunoprecipitation arrays: <http://ceas.cbi.pku.edu.cn/>; binding site detection tool for longer regulatory modules: <http://stubb.rockefeller.edu/>; cis-regulatory elements in *Arabidopsis*: <http://www.athamap.de/>; coregulated by cis elements in *Arabidopsis*: <http://www.atted.bio.titech.ac.jp>.

Cis-Dominant: Dominance affecting only alleles in *cis* position but not those in *trans*. ►cis arrangement

Cis-Golgi: The side of the Golgi apparatus where molecules enter the complex. ►Golgi apparatus, ►trans-Golgi network

Cis-Immunity: The property of transposons to prevent integration of another element within the boundary of the insertion element. ►self-immunity, ►transposon

Cis-Morphism: The variation in low-copy repeats within the same chromosome strand. ►transmorphism

Cisplatin (cis-diamminedichloroplatinum, $\text{PtCl}_2(\text{NH}_3)_2$, cis-DDP): Cisplatin is a DNA cross-linking agent and an (90%) effective anticancer drug with some specificity for testicular tumors. It inhibits DNA and RNA polymerases and avoids nucleotide excision repair. High-mobility group proteins are attracted to the DNA distorted by cis-DDP and may mediate anti-tumor activity. The clinical response to cisplatin is influenced by cell-to-cell communications via gap junctions. The signal is produced by the kinase function of Ku70, Ku80 and the DNA-dependent protein kinase complex (Jensen R, Glazer PM 2004 Proc Natl Acad Sci USA 101:6134). It may cause kidney, neural and hearing damage. Cisplatin resistance may eventually develop by several different mechanisms. The rapamycin derivative RAD001 (everolimus) increases the likelihood of apoptosis in the presence of the wild type p53 protein by inhibition of the translation of p21 mediated through TOR (Beuwink I et al 2005 Cell 120:747). A GeneChip array was found to identify variations in human cell populations of different ethnicity ranging from 27% to 29%, to 45% due to 8, 2, and 16 quantitative trait loci, respectively (Huang RS et al 2007 Amer. J. Hum. Genet. 81:427). ►cancer therapy, ►high-mobility group of proteins, ►rapamycin, ►p53, ►p21, ►TOR, ►Ku70, ►DNA-PK, ►melanoma, ►GeneChip; Lippert B (ed) 1999 Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug. Helvetica Chimica Acta Vlg; Zürich Ch; Jung Y et al 2001 J Biol Chem 276:43589; Wei M et al 2003 J Biol Chem 278:1769; Reedijk J 2003 Proc Natl Acad Sci USA 100:3611.

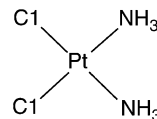


Figure C108. Cisplatin

Cis-Regulatory Modules (CRMs): CRMs are modular units of a few hundred base pairs in the DNA and mediate the multiple binding of transcription factors. They play important roles in the development and tissue-specific expression of genes. ►tissue specificity; Berman BP et al 2002 Proc Natl Acad Sci USA 99:757.

CISS Hybridization (chromosome in situ suppression): Before DNA probes are applied to chromosomes for in situ hybridization, the chromosomes are treated with DNA to block the non-target sequences so that these do not interfere with annealing of the specific labeled probes. ▶ *in situ hybridization*, ▶ *probe*; Sadler MT et al 2000 Genome 43:1081.

CIS-SYN Dimer: CIS-SYN dimer is a mutagenic cyclobutane UV photoproduct (see Fig. C109). DNA polymerase η apparently can replicate through such dimers and insert new nucleotides despite the distorted structure (Washington MT et al 2003 Proc Natl Acad Sci USA 100:12093) but the fidelity of the replication is diminished (McCulloch SD et al 2004 Nature [Lond] 428:97). ▶ *cyclobutane*, ▶ *UV photoproducts*, ▶ *DNA polymerases* [Pol η], ▶ *translesion*; McCullough AK et al 1998 J Biol Chem 273:13136; Park H et al 2002 Proc Natl Acad Sci USA 99:15965; Johnson RE et al 2005 Proc Natl Acad Sci USA 102:12359.

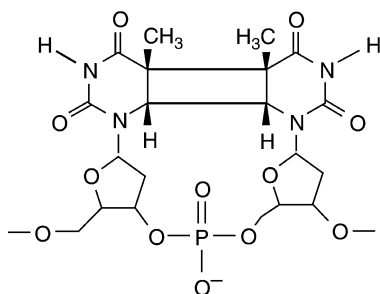


Figure C109. Cis-Syn dimer

Cis-Trans Test: A procedure for determining allelism. If two independent *recessive* mutations are made heterozygous in a diploid (or by using an F' plasmid in bacteria), are located in the opposite strands (in trans position), $\frac{m_1}{+} \frac{+}{m_2}$ and fail to complement each other (i.e., the phenotype is mutant), then the two mutations are allelic (occupy the same cistron). When, however, the two recessive mutations are both in the same DNA strand (in cis $\frac{+}{m_1} \frac{+}{m_2}$ position) and are made heterozygous (or merozygous in prokaryotes) they are expected to be complementary, i.e., non-mutant in phenotype, because the strand containing the two non-mutant sites permits the transcription of a wild type (un-interrupted) mRNA in the heterozygote. Molecular geneticists involved in physical DNA mapping use the term allele for any physical variation that is inherited by a Mendelian fashion and occupies the same chromosomal locus. ▶ *allele*, ▶ *allelism test*, ▶ *cistron*, ▶ *SSNC*, ▶ *pseudalleles*; Lewis EB 1951 Cold Spring Harbor Symp Quant Biol 16:159.

Cisterna: A membrane-enclosed space that frequently contains fluid.

Cistron: A segment of the DNA coding for one polypeptide chain or determining the base sequence in one tRNA or one rRNA subunit. Mutant sites within a cistron generally do not fully complement, i.e., the heterozygotes are not wild type, although, in rare cases weak allelic complementation may be observed. ▶ *allelic complementation*, ▶ *cis-trans test*; Benzer S 1957 p. 70. In: McElroy WD, Glass B (eds) The Chemical Basis of Heredity. Johns Hopkins University Press, Baltimore.

Cis-Vection: Cis-vection is a position effect, operational only when the genetic elements are syntenic, e.g., the promoter, some DNA binding protein elements (UAS) and structural gene. (▶ *position effect*; ▶ *syteny*; ▶ *operon*; ▶ *pseudoalleles*; ▶ *cis-acting element*; UAS; Lewis EB 1950 Advances Genet 3:73).

Citation Index: A publication of the Institute of Scientific Information (ISI, <http://www.isinet.com/isi/>) listing the number of times a particular journal paper has been cited in the scientific literature by first author. ▶ *impact factor*

Citric Acid Cycle: ▶ *Krebs-Szentgyörgyi cycle*

Citron: A RHO-regulated protein kinase mediating myosin-based contractility of the spindle fibers during cytokinesis. Its overproduction may lead to multinucleate cells. ▶ *spindle fibers*, ▶ *cytokinesis*, ▶ *myosin*, ▶ *RHO*, ▶ *PDZ*; Madaule P et al 2000 Microsc Res Tech 49:123.

Citrullinemia (ASS): ASS is a family of chromosome 9q34 (CTLN1) and 7q21.3 (CTLN2) recessive defects in the enzyme argininosuccinase. Normally citrulline is converted, via aspartate, into argininosuccinate. If the latter cannot be cleaved, citrulline and ammonia accumulate and as a consequence there may occur incontinence, insomnia, sweating, vomiting, diarrhea, convulsions, psychotic anomalies, and even periods of coma. The disease has an early onset and may proceed progressively into adulthood; rarely is the onset during adult life. Craving for high arginine food (legumes) and avoidance of low arginine food and sweets are noticeable symptoms. According to hybridization by a DNA probe, the ASS genes may be present in 10 copies per human genome scattered over several chromosomes. The multiple copies are presumably pseudogenes. ▶ *arginine*, ▶ *urea cycle*, ▶ *argininemia*, ▶ *amino acid metabolism*, ▶ *pseudogene*, ▶ *urea cycle*

Citrullinuria: Same as citrullinemia.

Citrus (*Citrus* spp): The taxonomy is unclear but several species are known, $x = 9$ and diploid as well as

tetraploid forms exist among lemons, oranges, mandarin, lime, grapefruit, etc.

Civilization: ►humanized antibody

CJD: ►Creutzfeldt-Jakob disease

CJM: A cell junction molecule. ►gap junction

CKB (casein kinase genes): The product of CKB genes is required for the completion of anaphase. (►cell cycle; McKay RM et al 2001 Dev Biol 235:378).

CKI: An inhibitor of the CDK-cyclin complex. ►CDK, ►FAR

C-Kinase: A protein phosphorylase activated by Ca^{2+} and diacylglycerol. (See Hartness ME et al 2001 Eur J Neurosci 13:925).

CKR: A chemokine receptor. ►chemokines, ►acquired immunodeficiency, ►CCR

CKS1: Cks1 is a subunit of cyclin-dependent kinases (CDKs) and is an essential cofactor in the ubiquitination of p27 CDK inhibitor by SCF. Cks2 controls the transition from metaphase I to anaphase during mammalian meiosis. ►meiosis, ►CDK, ►SCF, ►ubiquitination; Harper JW 2001 Curr Biol 11: R431; Spruck CH et al 2003 Science 300:647.

Clade: A group of distinct families/subfamilies descended from a common ancestral taxonomic entity by an evolutionary split.

Cladistic: Cladistic links and nodes show representation of descent in the manner of a dendrogram, i.e., in the divergence of taxonomic groups. ►dendrogram, ►evolutionary tree, ►parsimony, ►character index, ►homoplasy, ►stratocladistics

Cladogenesis: An evolutionary change involving branching of lineage of descent. ►anagenesis

Cladogram: ►evolutionary tree, ►character index

Claforan: ►cefotaxim antibiotic

Clam (bivalve): There are about 7,000 species of bivalves, including clams, oysters, mussels, and scallops (see Fig. C110). Most clams inhabit seas and oceans but some occur in lakes. Not all clams have byssus (an anchoring organ) but the majority can float and move. Some bivalves feed on dinoflagellates, which can produce a very powerful neurotoxin (saxitoxin, paralytic shellfish poison, PST) (see Fig. C111). The softshell clam (*Mya arenaria*) can acquire resistance to PST by mutation from glutamic acid to glutamine or to aspartic acid in the α subunit of the voltage-gated ion channel. Alteration at a single amino acid site may reduce by 1000-fold the binding of saxitoxin and selectively assure the survival of the clam but it also greatly

increases the toxicity of clams for human consumption. ►ion channels; Bricelj VM et al 2005 Nature [Lond] 434:763.

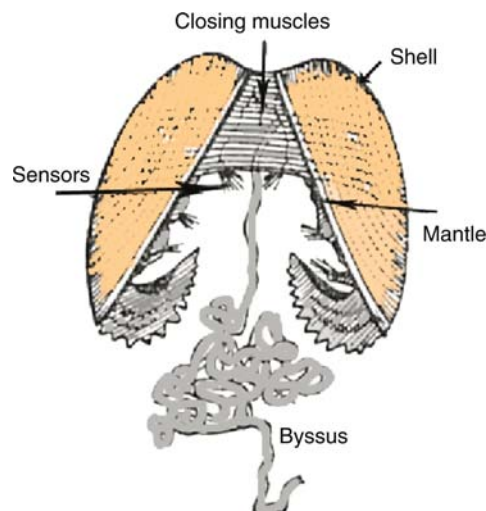


Figure C110. Clam

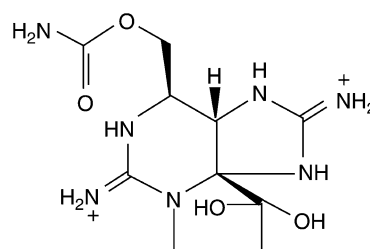


Figure C111. Saxitoxin

Clamp-Loader: A conformation of some proteins capable of assisting ring-shaped DNA polymerase processivity factors to be placed in the DNA. It is generally a component of the eukaryotic DNA polymerase holoenzyme. It is essential for DNA replication, repair, and recombination in prokaryotes and eukaryotes. In its absence mutation rate may increase probably by an impaired mismatch repair system. ►processivity, ►DNA polymerase, ►DNA repair, ►replication, ►replication machine, ►sliding clamp; for structure: Bowman GD et al 2004 Nature [Lond] 429:724; Ellison V, Stillman B 2001 Cell 106:655; Jeruzalmi D et al 2002 Curr Opin Struct Biol 12:217; Johnson AS, O'Donnell M 2005 Annu Rev Biochem 74:283.

Claspin: A protein required for strong ATR activation of Chk1 phosphorylation during the cell cycle. Claspin is an adaptor protein required for Chk1 activation and it becomes degraded at the onset of mitosis. The degradation is triggered by its interaction with, and

ubiquitylation by, the SCF·TrCP ubiquitin ligase. This interaction required the activity of the Plk1 kinase and the integrity of a β TrCP recognition motif (phosphodegron) in the N terminus of Claspin (Mailand N et al 2006 Mol Cell 23:307). ▶ATR, ▶ATRIP, ▶Chk1, ▶cell cycle, ▶SCF, ▶phosphodegron; Kumagai A et al 2004 J Biol Chem 279:49599.

Class I Genes (eukaryotic): Class I genes are transcribed by RNA polymerase I; these include 5.8S, 18S and the 28S ribosomal RNAs. ▶pol I eukaryotic

Class II Genes: Class II genes are transcribed by eukaryotic RNA polymerase II; these include mRNA and snRNA (except U6 RNA). They carry in the mRNA transcript a 7-methyl guanine cap (with the exception of the picornaviruses), and a 2,2,7-trimethyl guanine in the U RNAs. In lower eukaryotes, a 75 to 125-residues-long- and in vertebrates, a 200 to 300 residues-long poly-A tail is added posttranscriptionally. Histone mRNAs and U RNAs have no poly A tails. Some mRNAs include N6-methylated adenine, while U RNAs have modified uracils. They are regulated by cis- and trans-acting elements. The cap is associated with a cap-binding protein, the capping enzyme. ▶pol II, ▶eukaryotic, ▶transcription, ▶transcription factors, ▶transcription termination in eukaryotes, ▶transcription unit, ▶capping enzyme, ▶polyA mRNA, ▶U RNA, ▶cis-acting, ▶trans-acting

Class III Genes: The class III genes of eukaryotes are transcribed by RNA polymerase III; they include 5S ribosomal RNA and some small cytoplasmic RNAs. ▶pol III eukaryotic

Class Switching: Class switching is the change in expression of immunoglobulin (antibody) heavy chain genes during cellular differentiation of an antibody-producing lymphocyte by changing the production from one immunoglobulin heavy chain to another, e.g., the IgM constant region in one gene is replaced by the constant region of another class of immunoglobulin such as IgG, IgA or IgE. The efficiency of class switching is correlated with the length of the switch region, which is several kb long (Zarrin AA et al 2005 Proc Natl Acad Sci USA 102:2466). ▶immunoglobulins, ▶AID, ▶antibody gene switching, ▶hyper-IgM syndrome; Stavnezer J 2000 Curr Top Microbiol Immunol 245:127; Kinoshita K, Honjo T 2001 Nature Rev Mol Cell Biol 2:493; Petersen S et al 2001 Nature [Lond] 414:660.

Classical Genetics: Studies functions based on phenotype and genotype of the genetic material serve the primary guidance to the understanding of the mechanisms involved, in contrast to reversed genetics where the analysis begins with molecules. ▶reversed genetics

Classical Hemophilia: ▶hemophilia

Classification: The sorting out of phenotypes (or genotypes) by groups. It may be difficult in case of continuous variation or when the penetrance or expressivity is low. (▶expressivity, ▶penetrance).

Classification and Regression Tree (CART): A multivariate analysis for future classification.

Clastogen: Any agent that can cause chromosomal breakage directly, or indirectly by affecting DNA replication. Clastogenic agents may be ionizing radiation, bleomycin, hydroxyurea, maleic hydrazide, etc. ▶chromosome breakage

Clathrin: Clathrins are 192-kDa triskelion proteins that in cooperation with smaller (~35 kDa) polypeptides form the polyhedral coat on the surface of the coated vesicles involved in intracellular transport between cellular organelles. Before fusing with the target, the vesicle coats are stripped with the assistance of chaperones (hsp70) and another cofactor, auxilin. Clathrin is also required during the mitotic spindle function. (Royle SJ et al 2005 Nature [Lond] 434:1152). ▶adaptin, ▶triskelion, ▶auxilin, ▶cargo receptors, ▶endocytosis, ▶coatamer, ▶chaperone, ▶lysosomes; Kirchhausen T 2000 Annu Rev Biochem 69:699; Ford MGJ et al 2002 Nature [Lond] 419:361.

Claudin-11 (3q26.2-q26.3): An oligodendrocyte transmembrane protein controlling a paracellular barrier of tight junctions required for normal spermatogenesis and nerve conduction. Mutation in Claudin-16 (3q27) may involve hypercalciuria, hypomagnesemia, and chronic renal failure (Müller D et al 2003 Am J Hum Genet 73:1293). Claudin-5 (22q11.2) deletions lead to a transmembrane defect and velocardiofacial syndrome. Claudin-1 is implicated in a late step of the Hepatitis C virus entry procedure (Evans MJ et al 2007 Nature [Lond] 446:801). ▶tight junction, ▶velocardiofacial syndrome, ▶hepatitis; Gow A et al 1999 Cell 99:649.

Claw-Foot (Roussy-Levy hereditary areflexic [no reflexes] dysplasia): An autosomal dominant anomaly usually involving paternal transmission. It bears resemblance to the Charcot-Marie-Tooth disease but is accompanied by hand tremors. ▶Charcot-Marie-Tooth disease

Clavulanate: A product of streptomycetes is suicide substrate for β -lactamase; it enhances the effect of amoxicillin and is an effective weapon for circumventing some antibiotic resistance (see Fig. C112). ▶amoxicillin, ▶ β -lactamase, ▶antibiotics

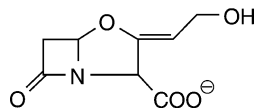


Figure C112. Clavulanate

Claw-like Fingers and Toes (curved nail of fourth toe): A rare, apparently autosomal recessive nail deformity of the fourth (and fifth) toes and fingers.

CLB: A mitotic cyclin protein. CLB6 activates only the early origins of replication of the chromosome whereas CLB 5 activates both early and late replicational origins. To prevent polyteny or polyploidy a complex of CLB–Cdc28 prevents an additional cycle of replication when one is completed. ▶cyclin, ▶CDK, ▶DNA replication during the cell cycle, ▶DNA replication eukaryotes

CIB Method: The *CIB* method detects new sex-linked lethal mutations among the grandsons of *Drosophila* males on the basis of altered male: female ratios (*C* is an inversion, eliminating cross-over chromosomes, *l* is a lethal gene, and *B* stands for *Bar eye* [narrow]). If a new recessive lethal mutation (*m*) occurred in the X-chromosome of the grandfather, either the grandson receiving this, or the *CIB* chromosome will die (see Fig. C113). In F₂ the males carrying either the *CIB* or the mutant X-chromosome will die; without the new mutation (*m*) the female: male ratio is

2:1. In case of a new lethal mutation no grandsons may survive; in case the expressivity of the new lethal gene is reduced, some males may survive. ▶*Basc*, ▶autosomal dominant, ▶autosomal recessive mutation; Muller HJ 1928 Genetics 13:279.

C

CLC: The chloride/proton antiporter family of proteins of the chloride ion channels. ▶CIC, ▶antiporter; Picollo A, Pusch M 2005 Nature [Lond] 436:420.

Cleanroom: A laboratory or manufacturing facility where the biological or chemical material is relatively safe from contamination and aseptic conditions can be maintained during use and in between use. Generally 4 grade levels are distinguished by government regulations on the basis of the maximum floating particle size (0.5 μm to 5 μm) and number per m³, flowhood circulation, etc. The institutional safety officer should be able to provide up-to-date information.

Cleavage Furrow: The cleavage furrow is an early embryonal division (that gives rise to the blastomeres) by which the larger fertilized egg breaks up into several smaller cells without growth. In general, the furrow splits cells, organelles, and macromolecules into two. The cleavage furrow is formed by an actomyosin structure of the *contractile ring*. ▶actomyosin; Glotzer M 2001 Annu Rev Cell Dev Biol 17:351.

Cleavage Nucleus: The nucleus of the dividing egg.

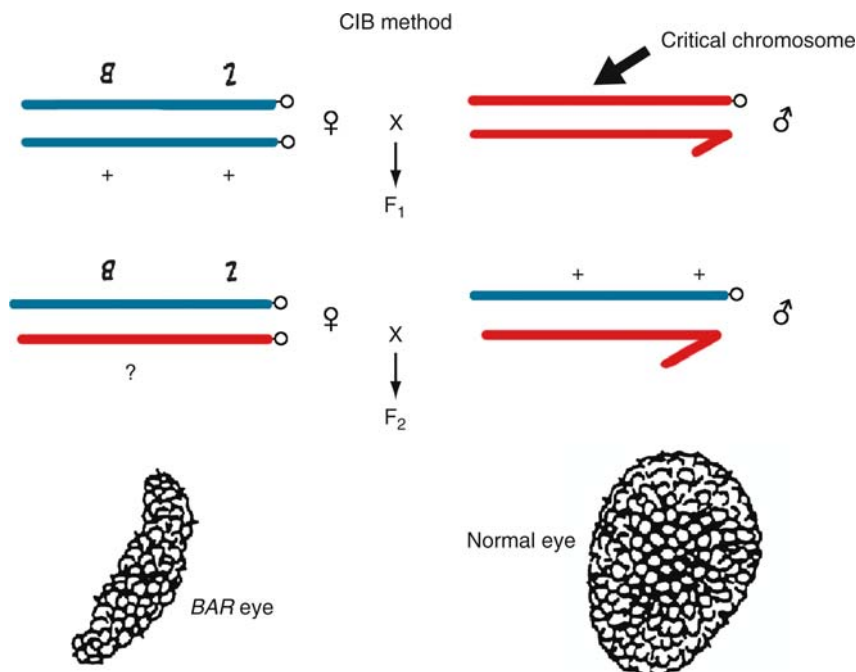


Figure C113. CIB method

C

Cleavage Stimulation Factors: Cleavage stimulation factors mediate the polyadenylation of the majority of mRNAs. CstF is a heterotrimeric protein of 77, 64 and 50-kDa subunits and recognizes the G + U-rich element downstream of the RNA transcript. CstF-64 binds to the RNA. CstF-77 (a homolog of suppressor of forked in *Drosophila*) bridges the 64 and 50 subunits and interacts with the AAUAAA polyadenylation signal-binding factor CPSF (cleavage-polyadenylation specificity factor). CstF-50 contains WD-40 repeats and interacts with the largest subunit carboxy-terminal domain of RNA polymerase II. ▶polyadenylation signal, ▶WD-40, ▶BARD-1, ▶forked, ▶polyadenylation signal; Gross S, Moore C 2001 Proc Natl Acad Sci USA 98:6080.

Cleft Lip: ▶harelip

Cleft Palate: An oral fissure frequently associated with harelip (lip fissure). Its incidence in the general population is about 4 to 20/10,000. Its recurrence risk in sibs of an affected individual are about 2% or more, in monozygotic twins the risk is 50%. Actually, these developmental anomalies may be parts of autosomal or X-linked dominant or autosomal recessive syndromes and some trisomies. Human chromosomal regions 2q32, 4p16-p13, and 4q31-q35 may be associated with the disorder. In mouse, deficiency of the $\beta 3$ subunit of the A type γ -aminobutyric acid receptor results in a cleft palate. In mouse, mutation in the LIM domain of a homeobox gene *Lhx8* appears to be critical for the determination of the cleft palate. Glycogen synthase kinase 3 β deficiency can result in midline defects (cleft palate, incomplete fusion of the ribs) in mice and its replacement at critical stages of development during gestation may rescue the condition (Liu KJ et al 2007 Nature [Lond] 446:79). In humans the condition is associated with variation in the epidermal growth factor level. The CLPEDI (cleft lip/ectodermal dysplasia) gene encoding nectin-1 (PRR1) was assigned to 11q23. Nectin is a cell adhesion protein and the principal receptor for α -herpesvirus; its mutation may convey resistance to these viruses. Cleft palate with ankyloglossia (adherent tongue) has been located to human chromosome Xq21 and occurs due to mutation in the T-box transcription factor TBX22. ▶recurrence risk, ▶sib, ▶trisomy, ▶neural crest, ▶Van der Woude syndrome, ▶GABA, ▶CATCH, ▶harelip, ▶GSK3, ▶EGF, ▶homeobox, ▶LIM, ▶herpes; Braybrook C et al 2001 Nature Genet. 29:179.

Cleidocranial Dysostosis (syn. cleidocranial dysplasia, 6p21, CCD): Autosomal dominant and recessive mutations may lead to deficiency of closure of the skull sutures, supernumerary teeth, chest, shoulder, hip and finger anomalies, short stature, etc. Autosomal

dominant forms may also show reduced jaw size, absence of thumbs or toes, and loss of distal digital bones. A mutation in mouse chromosome 6 may involve the CBFA-1 (core binding factor) gene (apparently homologous with CCD) encoding or regulating osteocalcin, a protein that controls osteoblast formation. This molecule may function as a transcription factor for bone forming genes. The term CCD is now used for the human central core disease of the muscles in humans due to mutation in the ryanodine receptor (RYR1, 19q13.1). ▶stature in humans, ▶osteogenesis imperfecta, ▶dysostosis, ▶pseudospondylosis, ▶central core disease

Cleistogamy: The shedding of pollen before the flowers open, thus resulting in self-fertilization in plants. ▶autogamy, ▶protandry, ▶protogyny

Cleistothecium: A closed, spherical fruiting body of ascomycetes such as in *Aspergillus* and powdery mildew fungus (see Fig. C114). The asci containing the spores are released after the rupture of the wall of the fruiting body. ▶perithecium, ▶gymnothecium, ▶ascogonium

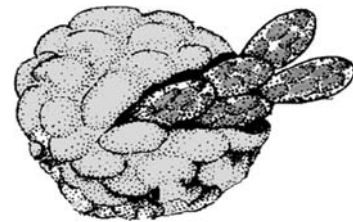


Figure C114. Cleistothecium

CLIA (Clinical Laboratory Improvement Amendments): A US government organization that oversees the laboratory procedures for clinical testing of genetically determined diseases.

Cline: A gradual change in the distribution of genotypes or phenotypes within a large population caused by the environment, population density, or other factors. ▶aclinal

Clinical Genetics: clinical genetics deals with practical genetic problems encountered during patient care. ▶empirical risk, ▶medical genetics, ▶human genetics, ▶genetic counseling, ▶counseling genetic, ▶informed consent, ▶bioethics; <http://bioinfo.weizmann.ac.il/cards/index.html>.

Clinical Laboratory Tests: see <http://www.genetests.org>.

Clinical Tests for Heterozygosity: Many genes fail to reveal their anomalous alleles by simple visual observation. Some of these are detectable by enzyme

or serological assays in biopsies, by amniocentesis, and cell cultures. These tests may not be able to identify with certainty the genetic constitution of all samples because the same function may be affected by different gene loci. Some mutant alleles can be identified by RFLP or PCR analysis. ▶ [carrier](#), ▶ [PCR](#)

Clinical Trial Phases: Clinical trial phases, applicable also to gene therapy, are conducted in three steps. (I) the first trial with a few humans, expected to provide information on safety/maximal dose, timing, and body reaction. (II) More individuals are tested for safety as well as efficacy. (III) large-scale experimental treatment is expected to reveal efficacy compared with alternative methods of treatments and side effects. Rarely, the phase I clinical trials may result in injury to some volunteers (Wood AJJ et al 2006 New England J Med 354:1869). ▶ [informed consent](#), ▶ [experiments](#)

Clinodactyly, Congenital: Crooked finger(s); may be observed in several syndromes of genetic malformations involving bones.

CLIP (class II-associated invariant-chain complex protein): ▶ [major histocompatibility complex](#)

CLIPS (chaperone-linked protein synthesis): In eukaryotes, some chaperones assist in folding of the nascent proteins while others are destined either to restore distressed proteins, or assist in their disposal. ▶ [chaperone](#)

ClIP: ▶ [sister chromatid cohesion](#)

Clipboard: The clipboard of a computer is a storage area of the memory system from where information can be transferred to different documents created in the computer.

Clitoris: An oval body 7 to 13 cm long (homologous to the male penis) in the inner side of the cleft between the opening of the urethra and the vagina of female mammals. Its expansion results in relaxation following sexual excitement (climax, orgasm) without ejaculation. ▶ [circumcision](#), ▶ [penis](#)

CLN: Cyclin genes regulating cell division. ▶ [cyclin](#), ▶ [CDK](#)

Cloaca: Cloaca, in lower vertebrates, is the joint passageway of urinary and fecal discharge. In mammals it is the terminus of the hindgut before its differentiation into rectum, bladder, and genital primordia. ▶ [bladder exstrophy](#)

Clock Genes: Clock genes affect the biological clock such as the diurnal rhythm and endogenous rhythm or aging. ▶ [circadian rhythm](#), ▶ [endogenous rhythm](#), ▶ [aging](#); Lakin-Thomas PL 2000 Trends Genet 16:135.

Clonal Analysis: The study of pattern formation (genetic mosaics) as a consequence of mutation, deletion, recombination, and nondisjunction. Such an analysis permits tracing the event to its origin, estimation of the number of cell divisions that have taken place since the event, the number of cells in the primordium involved, etc. Usually, the availability of appropriate genetic markers is a requisite for such an analysis. Cell autonomous genes are particularly useful for clonal analysis because genes of neighboring cells do not affect their expression. Heterozygotes for recessive color markers are frequently used because the loss or mutation of the dominant allele will result in the formation of recessive sector(s) and pseudodominance. An unstable (ring) X-chromosome in *Drosophila* may lead to the formation of gynandromorphs. Nondisjunction or somatic recombination may lead to the formation of twin spots (sectors). In *Drosophila*, developmental compartments of polyclonal origin may be revealed on the basis of the structures and organs affected simultaneously or consequently. Mutations formed in the last three divisions of the wing imaginal disk involve changes in cuticular elements e.g., hairs and wing veins. The presence of sectors also reveals that a gene is cell autonomous and also whether its expression is modified by the product of other genes. Extracts of wild type lymph, mRNA, or protein injected into mutants may correct genetic defects in a localized form according to a gradient or in a particular pattern, depending on the nature of the function of the corresponding mutant allele being a specific transcription factor, a transmembrane protein, or a signal receptor, among others. DNA labeled by fluorochromes and hybridized in the tissues may identify the regions of mRNA distribution of a particular gene. The function of particular genes in regulation of others can be detected by immunostaining of particular loci with specific antibodies. ▶ [morphogenesis](#), ▶ [cell lineage](#), ▶ [fate map](#), ▶ [fluorochromes](#), ▶ [probe](#), ▶ [immunostaining](#), ▶ [luciferase](#); GUS; Steffensen DM 1968 Am J Bot 55:354; Hotta Y, Benzer S 1972 Nature [Lond] 240:527; Duchmann R et al 2001 Clin Exp Immunol 123:315.

Clonal Interference: The competition between beneficial mutations in asexual lineages within populations.

Clonal Restriction: In clonal restriction, proliferating cells are propagated only within the pre-ordained pattern of differentiation. ▶ [clonal analysis](#), ▶ [cell lineages](#)

Clonal Selection: Clonal selection involves selection and propagation of certain types of cells in a tissue. Specificity for certain antigens exists in the lymphocytes before exposure to antigens. A few antibody

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producing lymphocytes, which are committed to the production of a specific antibody, are selected for clonal proliferation and stimulated for the synthesis of that specific antibody when infected by the pertinent antigen. Immunity may thus build up. The B-lymphocytes with lesser selective value are eliminated by apoptosis. Clonal selection may also favor certain cell types and lineages during carcinogenesis. New evidence indicates that some B-lymphocytes can produce two functional immunoglobulins Gerdes T, Wabl M 2004 *Nature Immunol.* 5:1282). ►immune system, ►lymphocyte, ►antibody, ►immunoglobulins, ►B cell, ►apoptosis, ►memory immunological, ►receptor editing; Meffre E et al 2000 *Nature Immunol.* 1:379; Silverstein AM 2002 *Nature Immunol* 3:793.

Clone: The progeny of asexual reproduction or molecular cloning yielding identical products. ►asexual reproduction, ►cloning, ►molecular cloning, ►cloning vectors, ►nuclear transplantation; McLaren A 2000 *Science* 288:1775.

Clone Validation: Clone validation in large-scale genome sequencing terminology indicates that the clones accurately represent the genome. ►DNA sequencing, ►genome projects

CloneConvert: A computer program that converts a file into the "miniset.dat" format for individual Map-Search Probes. (See Rudd KE et al 1991 *Nucleic Acids Res* 19:637).

Clone-based Map: The genomic DNA is incompletely digested by restriction endonuclease to about 150 kbp pieces and propagated by BAC vectors. Subsequently, the clones are completely digested by restriction enzymes to generate a collection of smaller fragments. The fragments are then aligned by chromosome walking and finally sequenced repeatedly to obtain an accurate order of the nucleotides. This is one of the basic principles used for sequencing larger genomes. ►BAC, ►restriction enzyme, ►chromosome walking

Clonidine: An α -2-adrenoreceptor agonist. At low concentrations it decreases presynaptic firing of noradrenergic cells. Its antagonist is idazoxan. ►synapse, ►adrenergic receptor, ►agonist

Cloning: Asexual reproduction in eukaryotes or replication of DNA (genes) with aid of plasmid vectors in appropriate host cells (*molecular cloning*). *Reproductive cloning*, i.e., generating embryo from human stem cells is prohibited in most countries for ethical reasons. *Therapeutic cloning*, i.e., generating human tissues for medical purposes seems to be favored by biologists and medical researchers. ►clone, ►cloning vectors, ►DNA library, ►plasmids, ►DNA,

►expression cloning, ►nuclear transplantation, ►transplantation of organelles, ►therapeutic cloning, ►stem cells

Cloning Animals and Humans: Cloning is technically feasible by the use of the procedures of nuclear transplantation. However, because of technical problems the cloning of higher animals cannot be used as a routine procedure for propagation. Currently 15% or more of the cloned mammalian embryos suffer from chromosomal or metabolic defects. In cloning embryos, trophoctoderm and placental defect may frequently cause developmental failures.

Based on less-than-well informed ethical considerations, there is a rather widespread opposition to this type of research (reproductive cloning). Naturally, almost any technology can potentially be abused, but most of the condemning arguments against cloning are weak on biological grounds. Before the application of cloning or any other medical technology, sensible guidelines need to be formulated. Politically motivated banning of research may deprive society of expanding its repertory for remedying human disease. In 1997 (*Science* 278:2130) the gene for antihemophilic factor IX was introduced into sheep by nuclear transplantation, opening a new avenue to cure hemophilia B (Christmas disease). Many dread the ethical consequences of cloning humans. Others fear of the biological consequences. Unfortunately the ethical criteria are rather subjectively and ill defined. The biological consequences of poor technologies are real. It must be also considered that using somatic donor nuclei the risks of undesirable combination of homozygous deleterious genes can be avoided if the nuclei are taken from adults who have already withstood the test of being disease- or malformation-free. The potential risk of inbreeding should be and can be managed. In human cloning, distinction must be made between cloning cells for therapeutic purposes and cloning as a means of reproducing intact organisms. Consumption of animal products obtained through cloning (nuclear transfer) thus far (2007) has not revealed any difference from consumption of animal products obtained from conventionally bred herds (Yang X et al 2007 *Nature Biotechnol* 25:77). ►nuclear transplantation, ►hemophilia, ►bioethics, ►therapeutic cloning, ►embryo research, ►stem cells, ►trophoctoderm; Solter D 2000 *Nature Revs Genet* 1:199; Jaenisch R, Wilmut J 2001 *Science* 291:2552; Lanza RP et al 2002 *Science* 294:1893; O'Mathúana DP 2002 *EMBO Rep* 3:502; commercial and regulatory issues with animal cloning: Suk J et al 2007 *Nature Biotechnol* 25:47.

Cloning Bias: The deviation from randomness in the representation of fragments in a DNA library. The

bias may be caused by rearrangement of direct repeats in *Rec⁺* bacterial strains, (but can be avoided by *recA* hosts). Palindromic sequences may become unstable in some λ phage and plasmid vectors (can be avoided by the use of *recB* and/or *recC* and *shcB* strains of *E. coli*, base modification of the DNA, host restriction enzymes, etc.). ▶DNA library, ▶restriction enzyme, ▶cloning vectors

Cloning Sites: Recognition sequences for restriction enzymes within genetic vectors or other recipients where passenger DNA can be inserted. ▶restriction enzymes, ▶vectors, ▶passenger DNA

Cloning Strategy: The plan that permits the identification of the cloned copy either by a suitable probe (DNA, RNA or antibody) or one through a positional cloning or PCR based procedure. ▶probe, ▶PCR, ▶positional cloning, ▶gene isolation

Cloning Vectors: Cloning vectors are generally plasmid, phage, or eukaryotic virus-derived linear or circular DNA capable of reproduction (most commonly in bacteria or yeast) and producing (in large numbers) molecular clones of the DNA inserted into them. Cloning vectors must have replicator mechanisms (replication drive unit) for self-propagation, multiple cloning sites (single or few recognition sites for several restriction enzymes), selectable markers (for verifying the success of molecular recombination and uncontaminated maintenance), regulatory elements for their copy number in the host (generally smaller plasmids can be present in larger number of copies), mechanisms for equal partition among the daughter cells, and genetic stability to prevent rearrangement by host enzymes. Often, it is desirable to propagate in more than one host cell (shuttle vectors). Some cloning vectors are used only for propagation of DNA, others permit expression of the genes carried, and yet others may be useful in isolating functional elements of the hosts (promoters, enhancers) by virtue of in vivo gene fusion. ▶lambda vectors, ▶cosmids, ▶phagemids, ▶YAC, ▶BAC, ▶PAC, ▶SV40, ▶retroviral vectors, ▶agrobacterial vectors, ▶plasmids, ▶ColEI, ▶shuttle vector

Cloning Vehicles: Cells suitable to propagate the cloning vectors, e.g., *E. coli*, yeast, *Agrobacterium*, etc. ▶cloning vectors

Clonogenic Test: In a clonogenic test, isolated cancer cells seeded onto culture plates are exposed to radiation or other anti-cancer treatments, and incubated for about two weeks. Solid tumor cells in this assay die only when they divide, e.g., due to chromosome breakage. This fact indicates that mechanical injury to the chromosomes rather than apoptosis caused the demise of the cells as an evidence

of failure forming clones. Such an assay may reveal some information about the prospects of treatment of a particular cancer by different agents. Microvascular damage and apoptosis caused by radiation may be critical for the reduction of tumor growth because of the disruption of angiogenesis (Garcia-Barros M et al 2003 Science 300:1155). ▶cancer, ▶cancer therapy, ▶angiogenesis, ▶apoptosis

Clonote: The product of nuclear transplantation when an enucleated egg is combined with an isolated nucleus from a somatic cell. The term is coined from the analogy of a zygote that is the product of the natural fertilization of an egg by a sperm. Production of a clonote would be, in all essential ways, reproductive cloning. A clonote could also be exploited for stem cell research but it appears inadvisable to use it for human reproduction on both ethical and biological grounds. ▶in vitro fertilization, ▶nuclear transplantation, ▶stem cells; McHugh PR 2004 New England J Med 351:209.

Closed Promoter Complex: In a closed promoter complex, the transcriptase attached to the target promoter cannot start transcription because the DNA strands are not separated. ▶open promoter complex, ▶pol prokaryotic RNA polymerase

Closed Reading Frame: Chain termination (nonsense) codons block the translation of a closed reading frame.

Closed-Loop Model of Translation: In a closed-loop model of translation, the mRNA supposed to be translated is visualized as a molecule circularized by the 5'—3' ends. Support comes from the observation that the poly(A) tail promotes translation; electron microscopy has also been known to reveal RNA circles. The circularization is mediated by trans-acting protein factors such as eIF4G, eIF4F, polyA-binding proteins. ▶polyA tail, ▶eIF4G, ▶eIF4F; Jacobson A 1996 p. 85. In: Hershey JWB et al (eds) Translational Control. Cold Spring Harbor Lab. Press, Cold Spring Harbor, New York; Sachs A 2000 p. 447. In: Sonnenberg N et al (eds) Translational control of gene expression. Cold Spring Harbor Lab. Press, Cold Spring Harbor, New York.

Clostridium botulinum: An anaerobic bacterium, which produces botulinum toxin ($LD_{50} \cong 0.2$ ng/kg body weight). ▶biological weapons

Clostridium difficile: A bacterium that produces cytotoxins A and B responsible for antibiotic-induced diarrhea and pseudomembranous colitis in hospital settings. (See Reineke J et al 2007 Nature [Lond] 446:415).

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Clostridium perfringens: Flesh-eating Gram-positive bacterium that encodes several toxins, particularly serious is the one, which destroys muscles. Its genome of 3,031,430 bp comprises 2,660 protein-coding and 10 rRNA genes. ▶tetany, ▶host-resistance genes; Shimizu T et al 2002 Proc Natl Acad Sci USA 99:996.

Closure of Mapping: Approaching completion, when two-genome-size DNAs had been mapped, the use of random clones is very inefficient; therefore, non-random clones are used. ▶physical map

Clotting Factor: ▶antihemophilic factor

Cloverleaf: The cloverleaf is a representation of the tRNA in which, the single strand stem (amino acid arm) loop is akin to the stem, and the D (dihydrouracil), AC (anticodon), and T (thymine) loops like the three leaflets of a leaf of a clover plant (see Fig. C115). ▶tRNA

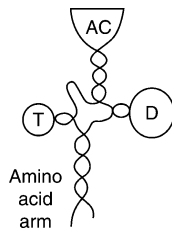


Figure C115. tRNA cloverleaf

Clovers (*Trifolium* spp): Clovers include about 250 species. The most prominent representatives are: white clover (*T. repens*, $2n = 32$), the fragrant alsike (*T. hybridum*, $2n = 16$), strawberry (*T. fragiferum*, $2n = 16$), red clover (*T. pratense*, $2n = 14$), crimson clover (*T. incarnatum*, $2n = 14$), and the subterranean clover (*T. subterraneum*, $2n = 16$).

Clp (*ClpX*): *ClpX* includes different prokaryotic proteins from the Hsp100 family, and are involved in chaperone or protease activities (see Fig. C116). The size of the different molecules may vary substantially. They include inducible and non-inducible forms and are distributed widely among eukaryotes and prokaryotes. *Clp* proteins also occur in chloroplasts and in the “plastids” of *Plasmodia*. The budding yeast Hsp104 *Clp* protein and the *E. coli* *ClpB* are intramolecular chaperones, and as such do not depend on ATP, but *ClpA* and *ClpX* are chaperones and ATP-dependent proteases. *Clp*-dependent proteolysis may protect against degradation of unmodified bacterial DNA by type I restriction endonucleases. ▶protease, ▶proteasome, ▶chaperone, ▶Hsp, ▶Plasmodium, ▶chloroplasts, ▶protein repair, ▶AAA proteins; Neuwald AF et al 1999 Genome Res 9:27; Kenniston JA et al 2005 Proc Natl Acad Sci USA 102:1390.

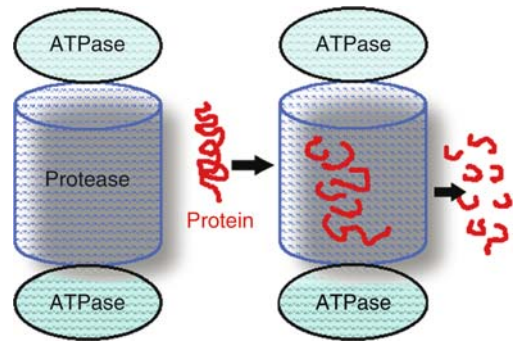


Figure C116. ClpA degradation

CLR4: ▶Suv39

Clubfoot (talipes): A hereditary malformation of the foot with a prevalence of below 0.1% and with a recurrence risk among the sibs of an afflicted child at about 4% (see Fig. C117). Thus, it appears to be under the control of more than one gene and depends on substantial environmental influences because even monozygotic twins may not be both afflicted. In New Zealand based and Polynesian populations, the occurrence of clubfoot appears to be controlled by a single dominant gene with 0.33 penetrance, and the gene frequency is predicted to be 0.009 (Chapman C et al 2000 J Med Genet 37:680). Various forms have been classified and only one is shown on the photo. ▶limb defects, ▶arthrogryposis



Figure C117. Clubfoot of an infant. (Courtesy of the CDC Public Health Image Library)

CLUSTAL W (improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice): A freely available computer program published in one of the ten most cited papers during 2000. The multiple sequence alignment program (MAFFT-5) has been improved over CLUSTAL

(Katoh K et al 2005 Nucleic Acids Res. 33:511). (See Thompson JD et al 1994 Nucleic Acids Res 22:4673, ITERALIGN, <http://www.ebi.ac.uk/clustalw>).

Cluster Analysis: The cluster analysis monitors simultaneously the expression patterns, based on DNA arrays, of thousands of genes at various stages of development or in response to any particular environmental influence. The method utilizes mathematical cluster analysis suitable for classification of multidimensional complex data. The GENECLUSTER computer program can perform calculations and assists in the interpretation of the biological meaning of the information collected. Alternatively, the differential expression of particular genes involved in similar functions can also be tested statistically. ▶microarray hybridization, ▶DNA chips, ▶support vector machine, ▶maps self-organizing, ▶GSEA, ▶regression; Tamayo P et al 1999 Proc Natl Acad Sci USA 96:2907; Eisen MB et al 1998 Proc Natl Acad Sci USA 95:14863; Miki R et al 2001 Proc Natl Acad Sci USA 98: 2199; Thomas JG et al 2001 Genome Res 11:1227; Harris RA et al 2002 Proteomics 2:212; Ramoni MF et al 2002 Proc Natl Acad Sci USA 99:9121; hierarchical clustering of proteins: <http://www.protonet.cs.huji.ac.il>; cross-species clustering analysis of microarray data: <http://biocomp.bioen.uiuc.edu/oscar>.

Cluster Homology Regions (CHR): CHR are homologous DNA sequences located in different chromosomes and probably are the results of gene duplication. In some cases, the coded protein is specialized to tissue- or organelle-specific functions or its function has changed, i.e., it has assumed a new function. ▶clustering of genes, ▶duplication, ▶evolution and duplication; Nagai K 2001 Gene 270:161.

Cluster of Differentiation (CD): CD are a very large number of specific surface glycoprotein antigens that identify particular differentiated cells (leukocytes), microbes, cancer cells, etc. and can be used for diagnosis, prognosis, and in therapeutic intervention. (See Woolfson A et al 2006 Pharmacogenomics 7:759).

Clusterin (complement lysis inhibitor, CLI): CLI is an evolutionarily highly conserved 75–80 kDA heterodimeric glycoprotein, encoded in human chromosome 8p21. Isoform 1 is repressed by androgens, whereas isoform 2 is upregulated by androgens through direct interaction with the first intron (Cochrane DR et al 2007 J Biol Chem 282:2278). Along with vitronectin, it prevents the attack of the C5b-9 complex upon the cell membrane. It also regulates lipoprotein metabolism, neuroendocrine

functions, and germ cell differentiation and is involved as well, in the development of inflammatory diseases such as Alzheimer's disease and Niemann-Pick disease. Its level may be elevated in some neurological disorders. ▶complement, ▶vitronectin, ▶Alzheimer's disease, ▶Niemann-Pick disease; Bailey RW et al 2001 Biochemistry 40:11828; Jones SE, Jomary C 2002 Int J Biochem & Cell Biol 34:427.

Clustering, Hierarchical: ▶cluster analysis

Clustering of Genes: Bacteriophage genes exist in a linear order of morphogenesis; several bacterial genes are clustered in the exact order of the biosynthetic pathway (tryptophan operon), others are located only within a group but not in strict biosynthetic order (histidine operon) and are under coordinated regulation. In the lower eukaryotes (fungi), some histidine genes and chorismic acid genes are in groups, although, they are not transcribed into a polycistronic RNA. The vertebrate homeotic genes of the HOX families are in functional groups and may be regulated by shared global enhancers. The ribosomal and tRNA genes are in a linear array in prokaryotes and eukaryotes and are processed after transcription into individual molecules. The histone genes in *Drosophila* and sea urchin are located in the same region but separated by spacers. Some of the antibody genes in mammals are clustered in gene families and are repeated many times. Some highly expressed mammalian housekeeping genes are clustered (Lercher MJ et al 2002 Nature Genet 31:180). The clusters are generally preceded by motifs, which facilitate the recruiting of transcription factors required by regulated expression of gene clusters (Conlon EM et al 2003 Proc Natl Acad Sci USA 100:3339). Essential genes may be clustered and recombination within the clusters seems to show low incidence (Pál C, Hurst LD 2003 Nature Genet 33:392). Some genes of the nematode *Caenorhabditis* are even polycistronic. Some (e.g., ribosomal) chloroplast genes are clustered according to the pattern of their prokaryotic ancestors. Some chromosomal clustering of chloroplast and mitochondrial genes in plants might have been favored by the advantage of proximity in expression (Alexeyenko A et al 2006 Trends Genet. 22:589). In mice, genes involved in spermatogenesis are not distributed at random in the genome, e.g., 10/25 spermatogonia-specific genes are located in the X chromosome and three in the Y chromosome. Of the 36 genes found to be involved in sperm production, only 23 are scattered among the 18 autosomes. In five eukaryotes (yeast, humans, *Caenorhabditis*, *Arabidopsis*, and *Drosophila*) 98 to 30% of the analyzed metabolic

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pathways are controlled by clustered genes. Only seven of the 69 pathways studied in these organisms were clustered in all five (Lee JM, Sonnhammer EL 2003 Genome Res 13:875). The clustered paralogous genes of higher eukaryotes are the consequences of duplications in the chromosomes that occurred during evolution. ▶operon, ▶coordinate regulation, ▶polycistronic mRNA, ▶His operon, ▶chorismate, ▶histones, ▶spacer DNA, ▶tRNA, ▶rRNA, ▶homeotic genes, ▶synexpression, ▶attenuator region; [for the tryptophan operon diagram]; ▶HLA, ▶RIDGE; Wicker N et al 2002 Nucleic Acids Res 30:3992; Boutanaev AM et al 2002 Nature [Lond] 420:666; Sproul D et al 2005 Nature Rev Genet 6:775.

Clustering of Phenotypes: Clustering of phenotypes may be caused by exposure to similar environmental effects. Epidemiological factors such as carcinogens in the environment and viral infections may precipitate the expression of phenotypes in an unusual distribution.

Clustering of Recombinants: Clustering of recombinants may be found in the progeny or in the gametes if recombination in the germline (mitotic recombination) preceded meiosis. The reality of clustering may need statistical verification by using the formula, (Tanaka MM et al 1997 Genetics 147:1769) where u_i = numbers in category u of brood i , k = total number of broods, $U = \sum u_i$ = total counts in category u , n_i = total number of progeny in brood i , and $N = \sum n_i$ = the total number of progeny in the set of data. ▶mitotic crossing over, ▶brood

$$V_W = \frac{1}{N} \sum_i^k \left[\frac{u_i^2}{n_i} - \frac{U^2}{N} \right]$$

Clusters of Differentiation: Antigens associated with distinct processes of differentiation are immunologically detectable. ▶CD proteins

Clutch: A cluster of eggs laid by a bird.

c.m. or c.M.: centi Morgan = 1% recombination; 1 map unit. ▶mapping genetic, ▶recombination

C-Meiosis: C-meiosis is meiosis arrested because colchicine is poisoning the spindle fibers. ▶meiosis, ▶colchicine

cMG1: A protein related to TIS11 (a 67 amino acid region is 72% identical), which responds to epidermal growth factor and cycloheximide.

CFI (cell-mediated immunity): ▶immunity

C-Mitosis: C-mitosis is mitosis in which, the poisonous effects of colchicine block mitotic anaphase, and consequently the cell and its progeny may become

polyploid (see Fig. C118). Endo-replication may take place and the two-chromatid chromosomes may sometimes be detected in juxtaposition. ▶C-meiosis, ▶colchicine, ▶partial karyotype at left

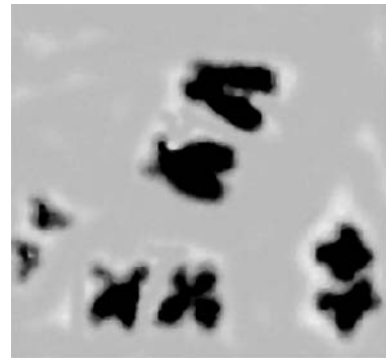


Figure C118. C-mitosis. (after W.V. Brown, 1972 Textbook of Cytogenetics, Mosby, St. Louis)

CMR (comprehensive microbial resource): Annotation of the sequenced microbial genomes; total of 250 bacteria, archaea and viruses. (See <http://cmr.tigr.org/tigr-scripts/CMR/CMrHomePage.cgi>).

CMRF35H (17q24): An inhibitory immune receptor on leukocytes.

cms: Cytoplasmically determined male sterility. ▶cytoplasmic male sterility

CMT: CMT refers to the monkey cell line expressing SV40 T antigen. ▶SV40

CMV: Cytomegalovirus, hCMV: human cytomegalovirus. ▶cytomegalovirus

Cne1, CneX: The yeast homologs of calnexin. ▶calnexin

CNE: Conserved non-coding element. ▶non-coding DNA

CNF (cytotoxic necrotizing factor): CNF inhibits GTPase activity and thus contributes to the activation of RHO (p21). CNF is a virulence factor of *E. coli* bacteria. ▶RHO, ▶p21, Thomas W et al 2001 Infect Immun 69:6839.

CNK (connector enhancer of KSR): CNK is a multi-domain protein involved in RAS signaling.

CNK^{N-term} enhances RAS signals, whereas CNK^{C-term} interferes with signaling when overexpressed. ▶KSR, ▶RAS; Anselmo AN et al 2002 J Biol Chem 277:5940.

cNMP Cyclase (cyclic nucleotide monophosphate cyclase): cNMP cyclase is involved in the biosynthesis of cAMP and cGMP. ▶cAMP, ▶cGMP; McCue LA et al 2000 Genome Res 10:204.

CNS: The central nervous system. ► [brain human](#)

CNS (conserved non-coding sequences): ► [non-coding sequences](#)

CNTF (ciliary neurotrophic factor): ► [APRF](#), ► [neurotrophins](#), ► [ciliary neurotrophic factor](#)

C-Oncogenes: Cellular oncogenes. ► [v-oncogenes](#)

Co⁶⁰: ► [isotopes](#)

CO₂ Sensitivity: CO₂ sensitivity in some strains of *Drosophila* is manifested as paralysis and death after being anesthetized with the gas. The condition is caused by infection with rhabdovirus sigma. This RNA virus resembles the vesicular stomatitis virus (VSV) of horses (an acute febrile [fever causing] infection of the tongues, mouth membranes, and lips) and some fish viruses (PFR, SVC) that can also elicit carbon dioxide sensitivity in *Drosophila*. The fly virus, however, cannot infect vertebrates. In the non-stabilized state, only the *Drosophila* females transmit the virus. In the stabilized state the transmission by eggs is 100%; the virus is also transmitted by the sperm, although, in the latter stabilized infection does not ensue. The *ref* mutants (in chromosomes X, 2, 3) are refractory to this type of infection. The ability to detect CO₂ helps blood-feeding insects (e.g., *Anopheles* mosquitos) to locate hosts by olfactory sensory neurons situated in their maxillary appendages (mouth palps). In *Drosophila*, two homologous chemosensory receptors are present in the sensory organs of the antennae (Jones WD et al 2007 Nature [Lond]: 445:86). ► [Rhabdoviridae](#), ► [Drosophila](#); L'Héritier P 1948 Heredity 2:325.

CoA: ► [acetyl coenzyme A](#)

Coacervate: The term coacervate refers to the colloidal aggregate of organic compounds. These compounds have probably played a role in organic evolution. ► [prebiotic evolution](#); Jensen SA et al 2000 J Biol Chem 275:29449.

Co-activator (AF, activator function): In addition to TBP, TAF, and general transcription factors, co-activator molecules are required for activation of gene transcription. Co-activators seem to acetylate histones, whereas histone deacetylases appear to be transcriptional co-repressors. ► [TBP](#), ► [TAF](#), ► [transcription factors](#), ► [TATA box](#), ► [high mobility group of proteins \[HMG\]](#), ► [transactivator](#), ► [nuclear receptor](#), ► [chromatin remodeling](#); Näär AM et al 2001 Annu Rev Biochem 70:475; Spiegelman BM 2004 Cell 119:157.

Co-adapted Genes: Co-adapted genes represent genotypes capable of expression of a satisfactory (fit) phenotype. (► [fitness](#), ► [outbreeding depression](#);

Dobzhansky T, Pavlovsky O 1958 Proc Natl Acad Sci USA 44:622).

Coagulation Factors: ► [antihemophilic factors](#)

Coalescence: The point or node of an evolutionary tree where two lineages merge (diverge) at a time or at any other scale. ► [evolutionary tree](#), ► [MRCA](#), estimation of coalescence times: Meligkotsiodou L, Fearnhead P 2005 Genetics 171:2073.

Coalescent: Coalescent is a statistical parameter of the genealogical information of genetic data. It is an approximation from a random sample of genes in a population with “constant size” over many generations without selection and recombination within the chromosomal sequences considered. The analysis should reveal the number of generations that the chosen entities have undergone since they were separated from the common ancestor. The analysis thus reveals the *most recent common ancestor* (MRCA) on what the genetic samples coalescing. The coalescent represents the dynamic (demographic) history of the populations. Genetic drift may be a confounding factor. ► [F_{ST}](#), ► [\[δμ\]²](#), ► [mutation age of](#), ► [drift genetic](#); Donnelly P, Tavaré S 1995 Annu Rev Genet 29:401; Rosenberg NA, Nordborg M 2002 Nature Rev Genet 3:380.

Coancestral: Coancestral gene(s) are identical by descent in two individuals, e.g., uncle and niece, first cousins, etc. ► [coefficient of coancestry](#), ► [consanguinity](#), ► [inbreeding coefficient](#)

Coarctation of the Aorta: The coarctation of the aorta is an apparently autosomal polygenic narrowing of the blood vessels leading to congenital heart failures. ► [cardiovascular disease](#), ► [heart disease](#), ► [supravalvular aortic stenosis](#)

Coassortment: ► [macronucleus](#)

Coat Color: ► [pigmentation of animals](#), ► [fur color](#). (see Fig. C119)

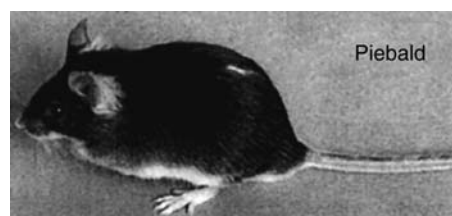


Figure C119. Coat color. (Courtesy of Dr. Paul Szauter, <http://www.informatics.jax.org/mgihome/other/citation.shtml>)

Coat Protein: The protein(s) of the viral capsid and some membrane surfaces. ▶capsid, ▶capsomer, ▶uncoating

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Coated Pits: Coated pits are generated on the surface of coated vesicles by invagination and pinching off. Thereby, they facilitate transport by losing the coat and fusing with other intracellular vesicles (lysosomes). ▶lysosomes, ▶dynamitin

Coated Vesicles: Clathrin-coated vesicles. ▶clathrin

Coatomer (coat-protomer): A coatomer is the large protein complex on the surface of vesicles (Golgi), mediating non-selective transport within cells. Its assembly requires ATP. After the transfer of the cargo, the coatomer is still retained and docks with another membrane. ▶clathrin, ▶COP transport vesicles; Sullivan BM et al 2000 Mol Biol Cell 11:3155.

cob: *apocytochrome b* gene in the mitochondrion (yeast) may exist both without introns and with introns (called boxes). Its exons code for the apocytochrome 1 protein, whereas the box 3 introns code for a “maturase” protein that excises the introns from the long form gene. A box 7-coded protein splices the exons of the adjacent cytochrome oxidase (*oxi3*) gene. For the stability of the cob Mrna, the nuclear gene product Cbp1 must interact with a CCG sequence in the 5' untranslated region. ▶cytochromes, ▶mtDNA

Cobalamin (cyanocobalamin): The vitamin B12, a coenzyme for methylmalonyl CoA mutase; it has therapeutic use in anemia and acidosis. Cobalamin is a cofactor also of homocysteine metabolism and branched-chain amino acid and odd-chain fatty acid catabolism. Hyperhomocysteinemia is observed in some cardiovascular and psychiatric diseases and cancer (Lerner-Ellis JP et al 2006 Nature Genet 38:93). Plants do not contain cobalamin, and a strictly vegetarian diet as well as the autoimmune diseases of the elderly may show deficiencies (Croft MT et al 2005 Nature [Lond] 438:90). ▶transcobalamin, ▶transcobalamin deficiency, ▶vitamin B12 defects

cob-box Genes: encode mitochondrial cytochrome oxydase with introns. The intron boxes may have independent functions in processing the apocytochrome transcripts. ▶mtDNA

Cobra-Fish (combined binary ratio-FISH): In the Cobra-Fish process, human chromosomes are painted in 24 colors by using four fluorophores. Three fluorophores (fluorescein, lissamine, and cy5) are used pair-wise for ratio labeling of a set of 12 chromosome-painting probes. The second set of 12 probes is labeled the same way but exposed also to a fourth

fluorophore (diethylaminocoumarin). See Tanke HJ et al 1999 Eur J Hum Genet 7:2; ▶combinatorial labeling, ▶FISH, ▶fluorescein, ▶coumarine, ▶Cy, ▶fluorophore

Cobratoxin: The major protein toxin in cobra venom. It blocks irreversibly, nicotinic receptors and cholinergic transmission at the neuromuscular junctions. ▶toxins

Coca (*Erythroxylon coca*): A source of cocaine; 2n = 2x = 24. ▶cocaine

Co-Carcinogens: Co-carcinogens, such as phorbol esters, may not be carcinogenic alone but may act as tumor promoters. ▶phorbol esters, ▶carcinogens

Cocaine (3-benzoyloxy)-8methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester): Cocaine is a topical anesthetic and a euphoriant. It is an addictive drug obtained either from *Erythroxylon* plants or produced by chemical synthesis. Cocaine-dependence and intense craving may return even after prolonged abstinence. The priming of the relapse seems to be mediated by the D₂-like receptor agonists of the dopamine system, whereas the D₁-like receptor agonists prevent cocaine-seeking behavior. The effect of cocaine seems to be the blocking of the dopamine transporter protein. In cocaine addiction, a specific serotonin receptor may be involved. Continued use of cocaine increase cAMP activity and PKA in the brain. Escalating cocaine use in rats causes structural reorganization of the lower hypothalamus and the changes are supposed to drive an increased craving for the drug (Ahmed SH et al 2005 Proc Natl Acad Sci USA 102:11533). Excessive expression of CREB in the rat brain nucleus accumbens (site in the brain that responds through rewarding actions to opiates) decreases the craving for cocaine and actually promotes aversion to it. Excessive expression of a dominant negative CREB mutation intensifies the cocaine reward. Blocking the opioid receptors by dynorphin may antagonize the CREB effect. Cocaine immunoconjugates may block substantially the effects of the drug. A computationally redesigned butyrylcholinesterase mutation may substantially accelerate the hydrolysis of cocaine and thus may have medical use (Pan Y et al 2005 Proc Natl Acad Sci USA 102:16656). ▶dopamine, ▶agonist, ▶serotonin, ▶dynorphin, ▶CREB, ▶PKA, ▶opiate, ▶cAMP, ▶alkaloids; Yarmolaieva O et al 2001 J Neurosci 21:7474.

Coccus: A small (~1 > μm) spherical bacterium.

Co-Chaperone: A co-chaperone assists in the function of a major chaperone, e.g., DnaJ for Hsp70 in *E. coli*. ▶chaperone, ▶Hsp70, ▶DnaJ, ▶CbpA, ▶heat-shock proteins

Co-Chaperonin: GroES in bacteria assists protein folding by GroEL chaperonin. Similar is the function of the bacteriophage encoded Gp31 protein, which can assist GroES or can substitute for it. ►[chaperonin](#)

Cochlea: A snail shell-like structure in the inner ear essential for normal hearing.

Cochliomya hominivorax (screwworm): A tropical and subtropical fly, an obligatory parasite of warm-blooded animals (see Fig. [C120](#)). Its infestation causes myiasis (weight loss and sometimes death). It punctures the skin (hide) of animals and thus leads to a multimillion-dollar annual loss to animal breeders. It is also a pest for humans. For its biological control, the mass release of genetically sterile (irradiated) males has been proven effective. ►[genetic sterilization](#), ►[myiasis](#), image from Insects; USDA Yearbook 1952 Stefferud A (ed), by permission.

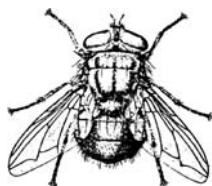


Figure C120. *Cochliomya hominivorax*

Cockayne Syndrome (CS): CS is characterized by very short stature, precocious aging, deafness, eye degeneration, mental retardation, and sensitivity to sunlight. The condition seems to be associated with a DNA repair defect but unlike other DNA repair problems (ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, Fanconi anemia) it does not involve increased proclivity to cancer. Some of the mutations (TAM) seem to be associated with the transcription-coupled nucleotide exchange repair of oxidative damage. It may be controlled by non-allelic autosomal recessive loci. CSA was assigned to human chromosome 5, CSB has been located to human chromosome 10q11 (and it functions as transcript elongation protein). CSB protein is a member of the SWI2/SNF2 family with roles in DNA repair and transcription. The purified recombinant CSB and the major human apurinic/apyrimidinic (AP) endonuclease, APE1, physically and functionally interact and under normal conditions protect against base excision repair (Wong H-K et al 2007 Nucleic Acids Res 35:4103). CSD is located in chromosome 19 and CSG in chromosome 13. Yeast has homologous genes *RAD2* and *RAD26*. All CS loci are involved in nucleotide exchange repair, base-excision repair, or in transcription-coupled repair. Complete inactivation of nucleotide exchange repair

in *Csbn/m/Xpa*^{-/-} (Cockayne syndrome/xeroderma pigmentosum) mutants of mice causes a phenotype that reliably mimics the human progeroid CS syndrome. Newborn *Csbn/m/Xpa*^{-/-} mice display attenuated growth, progressive neurological dysfunction, retinal degeneration, cachexia, and kyphosis and die before weaning. Mouse liver transcriptome analysis and several physiological endpoints reveal systemic suppression of the growth hormone/insulin-like growth factor 1 (GH/IGF1) somatotroph axis and oxidative metabolism, increased antioxidant responses, and hypoglycemia along with hepatic glycogen and fat accumulation (van der Pluijm P et al 2007 PloS Biol 5[1]e2). ►[DNA repair](#), ►[chromosome breakage](#), ►[light-sensitivity diseases](#), ►[ultraviolet-sensitivity syndrome](#), ►[DNA repair](#), ►[xeroderma pigmentosum](#), ►[trichothiodystrophy](#), ►[transcription factors \[TFIIH\]](#), ►[transcript elongation](#), ►[cerebro-oculo-facio-skeletal syndrome](#), ►[cachexia](#), ►[kyphosis](#), ►[somatotroph](#); Le Page F et al 2000 Cell 101:159; Lee S-K et al 2002 Cell 109:823; Licht CL et al 2003 Am J Hum Genet 73:1217; the paper by Le Page F et al on oxoguanine repair and transcription has been retracted; Le Page F et al 2005 Cell 123:711.

Cockroach: *Blattella germanica*, 2n = 23 male, 24 female 2n = 24.

This common pest of warehouses and homes is a source of allergic diseases and is a vector of pathogens (see Fig. [C121](#)). Its sex pheromone (blattellaquinone) is gentisyl quinone isovalerate, and its discovery may facilitate the control of cockroaches by luring the insects to improved traps (Nojima S et al 2005 Science 307:1104) (see Fig. [C122](#)).



Figure C121. Female cockroach

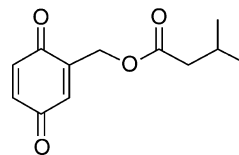


Figure C122. Blattellaquinone

Co-cloning: ►[chimeric clones](#)

Cocoa: ►[cacao](#)

C

Coconut (*Cocos nucifera*): The coconut ($2n = 2x = 32$) is a source of copra (endosperm), is used as food, and its oils are processed for margarine, etc. Before synthetic plant hormones became available commercially, coconut milk would be used in plant tissue cultures.

Co-Conversion: In co-conversion, two neighboring sites are simultaneously involved in gene conversion. (► [gene conversion](#))

Co-Cultivation: Co-cultivation refers to permitting plant cell proliferation on agar plates in the presence of *Agrobacterial* suspension (equipped with a vector plasmid) for a period of about one and a half to two days. During this period the T-DNA is transferred to the plant cells. Then the bacteria are stopped or killed by an appropriate antibiotic (e.g., cefotaxim or carbenicillin) and the transformed cells are selectively grown further on a medium to which, they are expected to be resistant. ► [transformation genetic](#), ► [vectors](#), ► [carbenicillin](#), ► [cefotaxim](#), ► [antibiotics](#)

Co-Deletion Analysis: Genes situated very closely to each other are jointly lost more frequently than those separated by a larger distance and this fact permits the construction of deletion maps. ► [deletion mapping](#)

Code, Comma-Free: In the 1950s, before the genetic code was experimentally identified, various speculations suggested that the code needs some marks to avoid ambiguity. Eventually, it was agreed that punctuation marks were unnecessary because the triplet codons could otherwise be read flawlessly. Actually, frame-shift mutations may alter the meaning of the text yet there are no signals between triplets. The nucleotide sequence needs only initiator codons and stop codons and some larger genes have additional demarcations by exons and introns. All nucleotide sequences are commaless ► [frame shift](#), ► [intron](#), ► [exon](#), ► [insulator](#); Crick FHC et al 1957 Proc Natl Acad Sci USA 43:416.

Code, Genetic: The genetic code specifies in adjacent nucleotide triplets (commaless code) each amino acid in the polypeptide chain. The triplets are generally called *codons* and are represented in mRNA nucleotides. The sequence of amino acids is determined by those codon sequences in the mRNA that are recognized by the anticodons in the tRNAs. The genetic code is redundant because some amino acids have up to 6 codons. The redundancy is also called *degeneracy* because several codons are degenerated (reduced) to the meaning of one amino acid. The code is *almost universal* from prokaryotes to eukaryotes, i.e., identical codons are used for the same amino acids across taxonomic boundaries. Exceptions to these rules exist in some mycobacteria, ciliates, and

mitochondrial DNAs. The 4 regular nucleotides in all possible combinations of 4 (4^3) generate 64 triplets from which 61 are *sense codons*, i.e., specify amino acids and 3 are *nonsense codons* (stop codons) because at their position in the mRNA the translation into protein stops and the polypeptide chain is terminated. In the customary codon table, the triplets are arranged into 16 families (► [see table of genetic code](#)) where the first two nucleotides may be sufficient for specifications although all 3 must be present. In higher organisms usually only one of the DNA strands is transcribed into mRNA codons; in prokaryotes both strands may be coding but in opposite orientation (always 5' to 3'). Although individual codons are *not overlapping*, the genes may be read, however, in overlapping registers ► [overlapping genes](#). This facilitates a better use of the relatively miniscule amount of DNA for a greater variety of functions in some bacteriophages. The *usage* of the redundant codons may vary from gene to gene ► [codon usage](#). Some suppressor mutations in DNA may alter the anticodons of the tRNAs, and the meaning of the stop or other codons may be altered, although, the mRNA codons remain the same. Changes in the codons require mutation in the DNA. Synthetic non-triplet codons may also be translated. ► [genetic code](#), ► [codon](#), ► [amino acid symbols in proteins sequences](#), ► [RNA editing](#)

Coden: Abbreviation of literature references as given by the Periodical Tables of the Chemical Abstracts Service.

Coding Capacity: The coding capacity of an organism or organelle is determined by the number and length of its open reading frames. ► [open reading frame](#)

Coding Dictionary: ► [code genetic](#), ► [genetic code](#)

Coding Joints: The junctures of the VDJ segments of the immunoglobulin and T cell receptor genes. ► [immunoglobulins](#), ► [TCR](#)

Coding Sequence (coding region): The coding sequence is transcribed into a functional RNA. The term coding has been used in two different ways. Some authors consider coding sequence only that part of the DNA that has the potential to be transcribed into RNA, which in turn may be translated into protein. In a somewhat broader sense, the transcription itself may be described as coding for RNA. The semantic problem is aggravated by the fact that some RNAs alone or in association with protein perform enzyme activity as ribozymes. ► [transcript](#); ► [RNA polymerase](#), ► [non-coding sequence](#), ► [ribozyme](#), ► [RNA editing](#), ► [open reading frame](#)

Coding Strand: The coding strand is the DNA strand, which has the same base sequence as the functional

RNA within the cell, except that in DNA thymine occurs at the place of uracil. The terminology has some ambiguity because in certain cases both strands of the DNA may be transcribed into RNA. Also, in some older papers coding strand is defined as the DNA strand, which is transcribed. Larger scale sequencing of *Drosophila* genome does not indicate much difference in the transcription of the two strands of the DNA (121:108) and in the areas crowded by genes the direction of transcription seems to alternate although in general it appears to be random. There is a possibility that transcripts of both strands of a DNA tract are combined for the translation of a particular protein. ▶anticoding strand, ▶antisense RNA, ▶sense strand, ▶template; Labrador M et al 2001 Nature [Lond] 409:1000.

CODIS (Combined DNA Index System): CODIS is a forensic database of biological evidence collected at crime scenes by the Federal Bureau of Investigation for the purpose of comparing DNA profiles local, state, and national, by participating organizations. It includes the Offender Index of individuals committing rape and other violent crime and felonies. As of October 2007 NDIS (National DNA Index) included a total of 5,265,258 profiles, forensic profiles of 194,785 and Convicted Offender profile of 5,070,473. The FBI also provides free information for procedures and standards over the Internet. ▶forensic genetics, <http://www.fbi.gov/hq/lab/codis/>.

Codominance: In codominance, both alleles at a locus are simultaneously expressed in the heterozygote (see Fig. C123). At the phenotypic level, observed without in depth analysis, codominance is not very common. At the protein level (using electrophoresis or serological tests) the majority of the heterozygotes (H) display the products of both alleles (that of P₁ and P₂) at a locus. ▶dominance

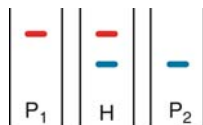


Figure C123. Codominance

Codon (a nucleotide triplet): 61 triplets specify the 20 natural amino acids, with 1 to 6 codons for each; and 3 codons (nonsense codons) signal the termination of the polypeptide chain. tRNAs can recognize synthetic 4-base codon with 4-base anticodons and unnatural amino acids can be incorporated into proteins. Similarly, 5-base codon can also be translated with tRNA with synthetic 5-base anticodons. Actually, in an *E. coli* mutant a GUGUG codon was translated

into valine by a 3-base-anticodon tRNA^{Val}. These unusual constructs are useful for studying the mechanisms of frame shift mutations and the effect of non-natural amino acids on protein function. ▶code genetic, ▶genetic code, ▶protein synthesis, ▶anticodon; Jukes TH 1978 Adv Enzymol 47:375; Hohsaka T et al 2001 Nucleic Acids Res 29:3646.

Codon Adaptation Index (CAI): The CAI measures the relative usage of each codon by particular genes and the codon usage by organisms. ▶codon usage; Sharp PM, Li WH 1987 Nucleic Acids Res 15:1281.

Codon Bias: ▶codon usage

Codon Choice: ▶codon usage

Codon Family (synonymous codons): A group of codons encoding the same amino acid. E.g., CGU, CGC, CGA, CGG, AGA, and AGG all code for arginine. ▶genetic code

Codon Preference: ▶codon usage

Codon Recognition: ▶protein synthesis, ▶aminoacyl tRNA, ▶anticodon

Codon Usage: Synonymous codons may not be selected at random but their usage varies from gene to gene, e.g., in the MS2 RNA phage the UAC codon for tyrosine is used 3 times as frequently as the UAU codon. In the δ -chain of human hemoglobin (146 amino acid residues), the CUU codon for leucine and the GUA codon for valine were not used at all but the CUG and GUG codons were relied on 12 and 13 times, respectively. In plants, the CUG codon for leucine was used on the average in 9%, whereas the CUU codons were employed in 27–28%, and the AAG lysine codon was used almost twice as frequently as the AAA codon. Similar variations occur in the use of other codons in the majority of organisms and genes. Nucleotides following the codons (N₁ context) generally affect codon usage in the sequenced eukaryotes (Fedorov A et al 2002 Nucleic Acids Res 30:1192). Codon usage may vary in different tissues of the same organism (Plotkin JB et al 2004 Proc Natl Acad Sci USA 101:12588). The most highly expressed genes tend to use codons corresponding to the major tRNAs, whereas the less frequently expressed genes rely mainly on rarer tRNAs. The highly expressed genes containing A and T chose for 3rd position C and if the first two bases are G and C, the third is preferentially T. TAA stops the translation of highly expressed genes and TAG and TGA nonsense signals block those of lower expression. The rate and accuracy of the translation is lowered by substitution of rare codons into the Mrna, and this may result also in frameshifts, skipping, or termination. The codon usage in eukaryotes may also vary in the different isochores. Gene

C

length and higher recombination frequency may also increase codon bias. Highly expressed genes may show higher codon bias and lower synonymous substitutions than genes with low level of expression. The optimally chosen codons are recognized by the most common tRNAs. There is, however, a bias also in tRNA usage. In humans, the highly used CUG^{Leu} codon has only 6 cognate tRNAs genes, whereas for the relatively rare UGU and UGC cysteine codons 30 tRNA genes are available. The nature of the second codon in the open reading frame may affect the efficiency of translation. ▶code genetic, ▶genetic code, ▶amino acids, ▶Grantham's rule, ▶antisense DNA, ▶sense DNA, ▶isochore, ▶amelioration of genes, ▶coding strand, ▶codon adaptation indexes, ▶translational selection; codon usage in bacteria: Sharp; PM et al 2005 Nucleic Acids Res 33:1141; McVean GAT, Vieira J 2001 Genetics 157:245; Dunn KA et al 2001 Genetics 157:295; Sato T et al 2001 J Biochem 129:851; <http://www.kazusa.or.jp/codon/>; <http://pbil.univ-lyon1.fr/pbil.html>; codon usage bias across genomes: <http://www.sysbiology.org/CodonO/>.

Co-eIF-2A: Similar to eIF-2C.

Coefficient of Coancestry (kinship, consanguinity): The coefficient of coancestry indicates the probability that one allele, derived from the same common ancestor, is identical by descent in two individuals (see Fig. C124). All diploid individuals have two alleles (paternal and maternal) at a locus and each parent has 50% chance for transmitting one or the other of these alleles to the offspring. Thus an allele of a grandmother has 0.5 chance to be transmitted to her daughter or son and that individual again has 0.5 chance for being transmitting to the grandchildren. Thus the probability that two first cousins would have the same allele of the grandmother is 0.5^4 . The degree of consanguinity varies a great deal in different cultures and within ethnic groups.

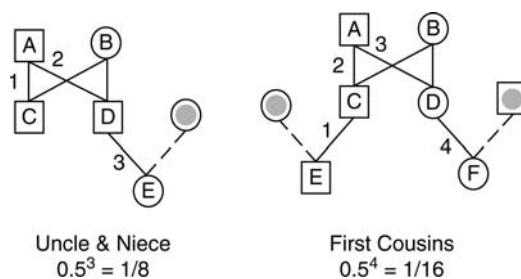


Figure C124. The coefficient of consanguinity can be derived from the pedigrees. The solid line paths through which a particular allele is transmitted are numbered

Overall in Europe, by the middle of this century, consanguinity remained below 1% (with rare exceptions).

In North, Central, and South America the frequency of consanguineous marriages was generally higher. In Asia it was significantly higher, especially in Southern India and Pakistan where in some areas the majority of the marriages were consanguineous. Similar situation existed in many African regions. Increased urbanization and expanding education result in reduction of inbreeding in human populations. ▶inbreeding, ▶inbreeding coefficient, ▶relatedness degree, ▶genetic load, ▶lethal equivalent, ▶incest

Coefficient of Coincidence: The coefficient of coincidence was designed by H.J. Muller in 1916 for estimating interference on the basis of dividing the number of double crossovers *observed* by the number of double crossovers *expected* by the probability of single crossover frequencies. In case the two crossing over events are independent, the coefficient of coincidence is 1 and there is no interference. Genes far apart generally have higher coincidence than those closely linked. An example for computation is the size of the testcross progeny is 3,000 individuals. Frequencies of single-recombinant individuals are 0.0687 and 0.2973. Thus expected frequency of double recombinants is $0.0687 \times 0.2973 \approx 0.0204$. Hence the expected number of double recombinants is $0.0204 \times 3,000 = 61.2$. The number of double recombinants observed was 50. Hence the coefficient of coincidence is $50/61.2 \approx 0.817$. (Note that coincidence must be computed from integers and not from fractions). The *positive interference* in the example shown here is $1 - 0.817 = +0.183$. In case of *negative interference* the actually observed double recombinants exceed the expectations based on single events. Thus, e.g., if the observed number of double recombinants would be 300 and the expected number 50, then the coincidence is 6, and hence the interference would be $1 - 6 = -5$. In some cases *high negative interference* has been observed which may be as high as -100 or more. Recent investigations indicate that coincidence is not related to the physical distance of genes (base pair or micrometers) but rather to the genetic distance expressed in map units. Accordingly, the coefficient of coincidence as a function of map distances for separated intervals can be calculated by the Foss equation (Genetics 133:681):

$$S_4 = (m + 1)e^{-y} \sum_{i=0}^{\infty} \frac{y^{m(m+1)i}}{[m + (m + 1)i]!}$$

where m = fixed number recombinational events resolved without crossing over between neighboring crossover events resolved with crossover, y = mean number of events ($y = 2[m + 1]x$) per tetrad that can result in gene conversion disregarding accompanying crossovers in a test intervals, and S_4 = coefficient of coincidence for separated intervals,

x = map distance in Morgan units (mean number of events resolved per tetrad in a given interval).

►interference, ►gene conversion, ►tetrad analysis, ►map unit; Zhao H et al 1995 Genetics 139:1045; Chase M, Doermann AH 1958 Genetics 43:332.

Coefficient of Consanguinity: ►coefficient of coancestry

Coefficient of Crossing Over: A term coined by Calvin Bridges (1937), stating the relation of the physical length relative to map distance. Bridges found in *Drosophila* that 1 map unit corresponded to 4.2 μ m length of the salivary gland chromosomes (see Fig. C125).

Today, the genetic length of chromosomes can be expressed in nucleotide numbers. Estimates among organisms may vary greatly depending on the amount of the DNA and the resolution of the genetic markers. In *Arabidopsis*, 1 map unit is about 140 kb, whereas in maize it is about 240,000 kb. These ratios become important in map-based isolation and cloning of genes. Until a genome is completely sequenced, the stated estimates may not be accurate. Another problem with the estimation of the coefficient of crossing over is the variation in genetic recombination frequencies among different lines of the same organisms. ►mapping genetic, ►mapping function, ►physical mapping, ►map based cloning, ►gene number, ►recombination hot spots, ►bands of polytenic chromosomes, illustration.

Coefficient of Inbreeding: ►F, ►inbreeding

Coefficient of Kinship: ►coefficient of coancestry

Coefficient of Selection: ►selection coefficient and fitness

Coefficient of Variation: C = standard deviation/arithmetic mean. ►standard deviation, ►mean

Coelocanth: (*Latimeria chalumnae*): The “living fossil” fish, survivor of the ancient fish appearing during

evolution about 350 million years ago. It has a large tail fin and side fins resembling limbs. Its body contains only cartilage, except in its head and at the base of the fins (see Fig. C126).

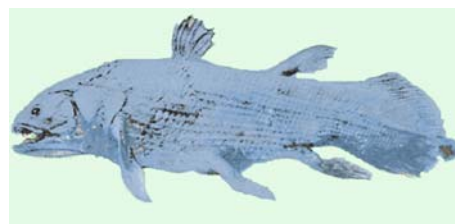


Figure C126. *Latimeria chalumnae*

Coelom: The inner cavity of the embryo. In mammals, there are two such cavities: the chest and the abdomen. (see Fig. C127)

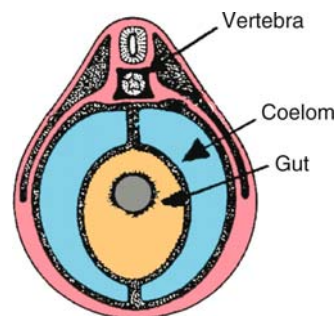


Figure C127. Coelom

Coelomocytes: Scavenger cells, which continuously and nonspecifically endocytose fluids of the body cavity of *Caenorhabditis*. ►endocytosis; Fares H, Greenwald I 2001 Genetics 159:123.

Coenobium: A colony of unicellular organisms enclosed by a single membrane.

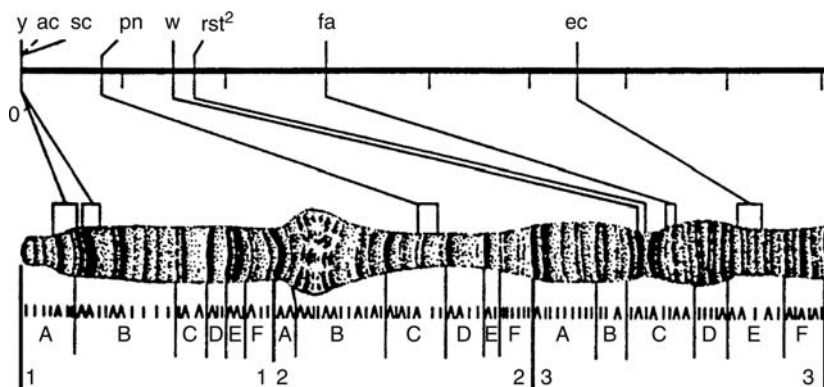


Figure C125. The distal end of the X-chromosome of *Drosophila*. (After Bridges CB 1935 J Heredity 26:69)

C

Coenocyte: A multinucleate protoplast or cell aggregate without separation by walls.

Coenospecies: Coenospecies have common phylogenetic origin yet they differentiated (in the overlapping area) into different forms (ecological species), which may have among them only a limited exchange of genes (See Turesson G 1922 *Hereditas* 3:211).

Coenzyme: A cofactor required for normal activity of enzymes; many coenzymes are vitamins. Coenzyme A (acetyl coenzyme A) transfers acyl groups within cells.

Co-Evolution: The evolution of two populations is concomitant because they have some mutual relationship, e.g., host and parasites, predators and preys, or two gene loci evolve as a unit. Interacting proteins may also display co-evolution (Fraser HB et al 2004 *Proc Natl Acad Sci USA* 101:9033). ▶ [selection types](#), ▶ [frequency-dependent selection](#), ▶ [high-dose/refuge strategy](#), ▶ [networks](#), ▶ [quorum sensing](#), ▶ [Red Queen hypothesis](#), ▶ [gene-for-gene](#), ▶ [introgression](#), ▶ [trophophoresis](#); Bergelson J et al 2001 *Annu Rev Genet* 35:469; Wade MJ 2007 *Nature Rev Genet* 8:185.

Cofactor: An inorganic or organic substance required for enzyme activity. ▶ [enzymes](#)

Coffee (*Coffea* spp): Coffee has about 90 species with $x = 11$ and the plants are either diploid or tetraploid. Mutants of *Coffea arabica* have been found with defect in caffeine synthase and accumulation of theobromine. These mutants are promising for the development of high quality flavor without significant caffeine content (Silvarolla MB et al 2004 *Nature [Lond]* 429:826). Surprisingly, coffee and tomato share a common gene repertoire (Lin C et al 2005 *Theor Appl Genet* 112:114). ▶ [caffeine](#), ▶ [tomato](#)

Coffin-Lowry Syndrome (CLS): CLS is a Xp22.3-p22.1 dominant condition that shows mental retardation, face anomalies, tapered fingers, and lysosomal storage defects. The MAPK/RSK signaling pathway is responsible for the expression of the Rsk-2 ribosomal S6 kinase that is affected in this anomaly by aberrant splicing. Rsk-2 is required for histone H3 phosphorylation activated by the epidermal growth factor (EGF). Deficiency of the ATF4 transcription factor leads to osteoblast defects involved in bone anomalies of CLS. ▶ [mental retardation](#), ▶ [head/face/brain defects](#), ▶ [lysosomal storage diseases](#), ▶ [MAPK](#), ▶ [RSK](#), ▶ [EGF](#), ▶ [osteoblast](#), ▶ [ATF2](#), ▶ [chromatin remodeling](#), ▶ [bromodomain](#); Zeniut M et al 2004 *Nucleic Acids Res* 32:1214.

Coffin-Siris Syndrome (fifth digit syndrome): The Coffin-Siris syndrome does not have clear criteria but generally its symptoms include mental retardation, broad nose, tapered fingers, sometimes the distal digits missing, poor nail development, and hypertrichosis on the body but hypotrichosis on the scalp. It is probably autosomal dominant with low penetrance although autosomal recessivity has also been claimed. ▶ [hypertrichosis](#), ▶ [Coffin-Lowry syndrome](#), ▶ [patella aplasia-hypoplasia](#)

Cofilin (actin depolymerizing factor, ADF): Cofilin is a small (M_r 15–20K) actin- and phosphatidylinositol-binding protein mediating the rapid turnover of actin in the cytoskeleton. Its phosphorylation by LIM kinase is activated by ROCK. Cofilin and Arp2/3 mediate barbed end formation involved in cell motility. ▶ [actin](#), ▶ [phosphoinositides](#), ▶ [cytoskeleton](#), ▶ [LIM kinase](#), ▶ [ROCK](#), ▶ [Williams syndrome](#); Bamburg JR et al 1999 *Trends Cell Biol* 9:364; Pfannstiel J et al 2001 *J Biol Chem* 276:49476; Ichetovkin I et al 2002 *Curr Biol* 12:79.

COG (cluster of orthologous groups): Genes that have common ancestry and related function. They may also be members of paralogous groups of genes. ▶ [orthologous](#), ▶ [paralogous](#); Tatusov RL et al 2001 *Nucleic acids Res* 29:22; includes also eukaryotes: Tatusov RL et al 2003 *BMC Bioinformatics* 4:41; <http://www.ncbi.nlm.nih.gov/COG/>.

COGENT (complete genome tracking): Database of fully sequenced genomes. It links genome sequences to other resources (Janssen P et al 2003 *Bioinformatics* 19:1451).

Cognate: Cognate molecules have the ability to recognize a particular molecule, like ligand and receptor, enzyme and substrate. ▶ [ligand](#), ▶ [receptor](#), ▶ [substrate](#)

Cognate tRNAs: Cognate tRNAs are recognized by an aminoacyl synthetase. ▶ [aminoacylation](#)

Cognitive Abilities: The major components of cognitive abilities include verbal and spatial abilities, memory, speed of perception, and reasoning. These components may have subcategories such as verbal comprehension, verbal fluency, vocabulary, etc. ▶ [behavior genetics](#), ▶ [human intelligence](#)

Cohen & Boyer Patents: US # 4.237.224 and 4.468.464 were obtained by Stanford University on the construction of cloning plasmid chimeras (pSC101), and for the products commercially produced with their aid. Users must thus pay reasonable royalties for these key procedures. The fact of patenting became the subject of a controversy because of its unusual nature, but it called to the attention of academic

institutions the benefits to be derived from the commercial exploitation of the results of scientific discoveries. ►patent

Cohen Syndrome: A highly complex autosomal recessive anomaly (psychomotor retardation, prominent incisors, high nasal bridge, eye defects, mental retardation, hypothyroidism, etc.) with suggested chromosomal locations 15q11, 5q33, 7p, 8q22. The 8q22 locus (COH1) encodes a protein of 4,022 amino acids with a presumed role in intracellular protein transport (Kolehmainen J et al 2003 Am J Hum Genet 72:1359). ►eye diseases, ►mental retardation

Cohesin: Cohesin is an at least four-protein (Smc1, Smc3, Scc1, Scc3) complex regulating in combination with other four proteins, including APC, the cohesion of sister chromatids primarily during interphase after the replication of DNA. The complex of Scc2 and Scc4 mediates the association of cohesin with chromosomes (Gillespie PJ, Hirano T 2004 Current Biol 14:1598). Cohesin (Scc1/Rad21) is removed by separase before the onset of anaphase and cytokinesis. Rad21-cohesin requires a special heterochromatin protein, Swi6, for the association at centromeres but not for that along the chromosome arms. Cohesin is required for double-break repair of DNA (Ström L et al 2004 Mol Cell 16:1003). Another cohesin function is mediated at the telomeres by tankyrase 1 (Dyrek JN, Smith S 2004 Science 304:97). *REC8* cohesin null mice display germ cell failure and sterility and meiotic recombination is aborted but recombination between sister-chromatids is promoted (Xu H et al 2005 Developmental Cell 8:949). Phosphorylation of Rec8 and recombination promote step-wise loss of cohesins against shugoshin and facilitate in meiosis II segregation (Brar GA et al 2006 Nature [Lond] 441:532). In *Schizosaccharomyces pombe*, cohesin proteins also mediate double-strand breaks during meiotic recombination (Ellermeier C, Smith GR 2005 Proc Natl Acad Sci USA 102:10952). Single-strand DNA breaks induce post-replicative repair (Ström L et al 2007 Science 317:242). DNA double-strand breaks can trigger genome-wide cohesion and acetyltransferase activity through factor Eco1/Ctf7 for preserving integrity of the genome (Ünal E et al 2007 Science 317:245). ►sister chromatid cohesion, ►ORC, ►meiosis I, ►condensin, ►CTF, ►adherin, ►securin, ►heterochromatin, ►cytokinesis, ►mitosis, ►shugoshin, ►tankyrase, ►monopolin, ►Scc1, ►APC, ►double-strand break, ►Rec8, ►De Lange syndrome; Tanaka T et al 1999 Cell 98:847; Nasmyth K et al 2000 Science 288:1379; Bernard P et al 2001 Science 294:2539; Kirsten A et al 2003 Nature Rev Genet 4:520; Marston AL et al 2004 Science 3003:1367.

Cohesion-Tension Theory: The cohesion-tension theory interprets the movements of sap through vessel system of plants. ►transpiration, ►guttation; Steudle E 2001 Annu Rev Plant Physiol Plant Mol Biol 52:847.

Cohesive Ends: Two DNA molecules have base complementarity ends that can anneal. (see Fig. C128)

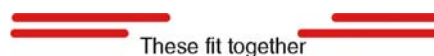


Figure C128. Cohesive ends

Cohort: In population studies, the term cohort is used to designate a particular group of individuals with common characteristics (age, treatment, ethnicity, education, taxonomic group, disease, etc.).

Coil: The tract of the unstructured backbone of the protein.

Coiled Body (CB, Cajal body): The coiled bodies are intranuclear elements (1–10 per nucleus) attached to the surface of the nucleolus. CB are formed from 0.15 to 1.5 μm tangled threads of snRNA and proteins. They are formed during G₁ phase of the cell cycle but disassemble during mitosis. ►nucleus, ►nucleolus, ►gemini of coiled bodies, ►coilin, ►snRNA, ►Cajal body; Gall JG 2000 Annu Rev Cell Dev Biol 16:273.

Coiled Coil: Two α helices of polypeptides wound around each other. Dodecanucleotide d (ATATATA-TATAT) coiled coil structure of DNA with single stranded two-base overhangs has also been determined by single-crystal X-ray crystallography (see Fig. C129). ► α -helix; mechanism of coiled coil formation: Steinmetz MO et al 2007 Proc Natl Acad Sci USA 104:7062, DNA model is by Campos JL et al 2005 Proc Natl Acad Sci USA 102:3663; courtesy of J.A. Subirana.

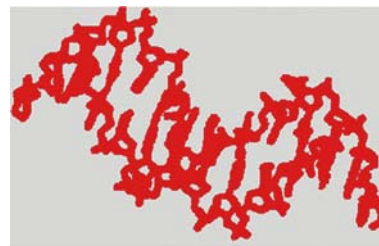


Figure C129. Coiled coil of DNA

Coilin: A 80 kDa protein in the nuclear coiled body (Cajal body), involved in processing of nucleolar and extranucleolar RNA. (Cajal body; Raska I et al 1991 Exp Cell Res 195:27).

Coincidence: ►coefficient of coincidence

C

Co-Inducer: A co-inducer is a chemical substance required, in addition to the inducer substrate, to activate the gene, e.g., in the arabinose operon besides the P protein, cAMP is also required for turning on the genes. ▶ *Arabinose operon*, ▶ *Lac operon*, ▶ *co-activator*

Cointegrate Vector: The cointegrate vector of *Agrobacterium* is a plant transformation vector containing both the T-DNA and the virulence genes in a single circular molecule. These vectors are usually free of oncogenes and carry both bacterially and plant-selected markers besides some engineered genes. ▶ *Ti plasmid*, ▶ *binary vector*, ▶ *selectable marker*

Cointegration: In cointegration, two circular plasmids combine, without loss, into a double size plasmid (see Fig. C130). Also, a circular donor plasmid carrying a transposable element fuses with a recipient circular plasmid and at each point of juncture there will be a copy of the transposable element.

This process requires the breakage of the phosphodiester bond and the duplication of the target site and the insertion element. This is replicative transposition.

The cointegrate includes the two plasmids and the two transposable elements. Upon resolution of the cointegrate, two plasmids are produced, each carrying a transposable element. ▶ *plasmid*, ▶ *transposable element*, diagram; Clewell DB 1975 Proc Natl Acad Sci USA 72:1720.

Coisogenic: A coisogenic organism has identical genes with another strain, except at a single locus. ▶ *isogenic*, ▶ *congenic*, ▶ *inbred*, ▶ *substrain*, ▶ *subline*

Coitus: Sexual intercourse.

Col: ▶ *colicin*

Colcemid (demecolcine, *N*-deacetyl-*N*-methylcolchicine): A synthetic colchicine. ▶ *colchicines*, ▶ *demecolcine*

Colchicine: An alkaloid produced by (*Colchicum autumnale* and other liliaceous plants) (see Fig. C131). Its tropolone ring specifically and strongly binds and disassembles microtubules of the mitotic spindle. Thus, the nuclear divisions are arrested in mitosis and cells skip at least one division resulting in doubling (or multiplying) of the chromosome number (polyploidization). It is particularly useful for doubling the chromosome number of interspecific and intergeneric hybrids, thereby making the otherwise sterile individuals fertile by securing a pair for all chromosomes. Colchicine alleviates some of the symptoms of gout, a mammalian disease caused by uric acid overproduction. Colchicine is synthesized from phenylalanine and tyrosine. The LDLo oral dose for humans is 5 mg/kg and therefore it is a dangerous substance, absorbed also through the skin (see Fig. C132). ▶ *chromosome doubling*, ▶ *autotetraploid*, ▶ *allotetraploid*, ▶ *colcemid*, ▶ *demecolcine*, ▶ *gout*, ▶ *c mitosis*, ▶ *microtubule*, ▶ *alkaloids*; Eigsti OJ, Dustin P Jr 1955 Colchicine. Iowa State College Press, Ames, Iowa; Ravelli RBG et al 2004 Nature [Lond] 428:198.

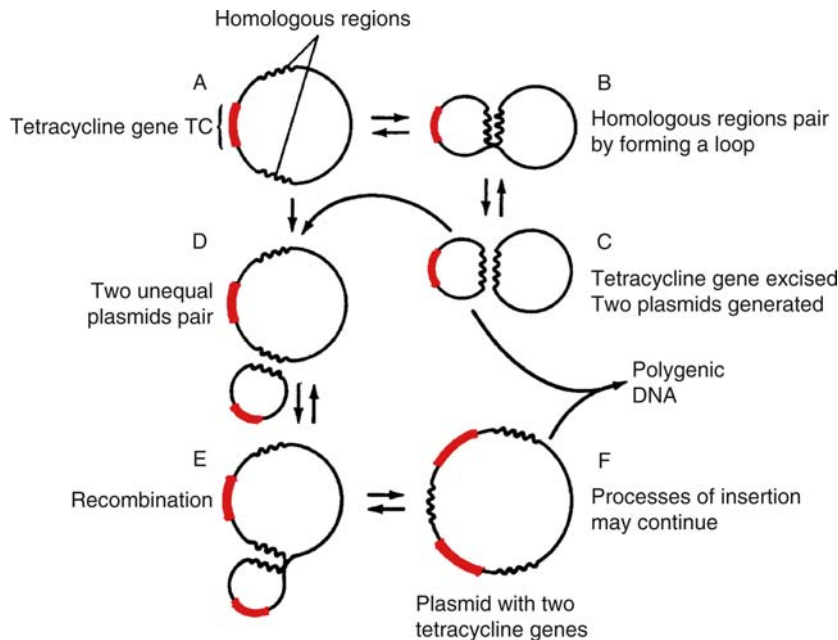


Figure C130. Cointegration

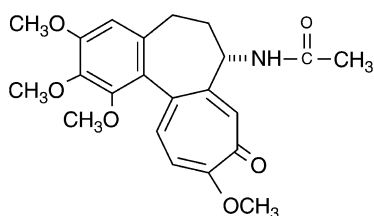


Figure C131. Colchicine



Figure C132. *Colchicum autumnale*.

Cold Hypersensitivity: Autosomal dominant genes may be responsible for the development of urticaria (allergy-like rash), joint discomfort, and fever after exposure to cold. It may be associated with amyloidosis (accumulation of fibrillar proteins) in various tissues. Amyloid nephropathy may be fatal. Familial cold urticaria (FCU) and the Muckle-Wells syndrome encode a protein with a pyrin domain and leucine-rich repeat at human chromosome 1q44. The Muckle-Wells syndrome has similar symptoms (rash, conjunctivitis, pain in the joints, and fever) but the symptoms are not elicited by cold. ▶[amyloidosis](#), ▶[hyperthermia](#), ▶[temperature-sensitive mutation](#), ▶[cold-regulated genes](#), ▶[urticaria familial cold](#), ▶[asthma](#), ▶[Muckle-Wells syndrome](#); Hoffman HM et al 2001 *Nature Genet* 29:301.

Cold-Induced Sweating (19p12): Cold-induced sweating includes a rare autosomal recessive disorder and several associated anomalies. The afflicted suffer from profuse sweating in some parts of the body at temperature of 7 to 18 °C. A two-base deletion was observed in the cytokine receptor-like factor 1. ▶[cytokine](#); Knappskog PM et al 2003 *Am J Hum Genet* 72:375.

Cold-Regulated Genes (COR): COR are required for acclimation to low temperature. Some plant mutants may become very sensitive to cool conditions. An *Arabidopsis* mutant was killed after a few days of exposure to 18 °C. The chilling may cause electrolyte leakage and changes in the synthesis of sterol esters. Cold acclimation is frequently based on microsomal

stearoyl coenzyme A desaturase activity. The unsaturated phosphoglycerides restore fluidity of cold-rigidified cell membranes. The COR genes are regulated by the binding of the CBF transcriptional activator to the CRT/DRE (C-repeat/drought responsive) element. Excessive expression of HOS1 (osmotically responsive gene) in transgenic *Arabidopsis* reduces the expression of CBF (C repeat binding factor) genes and decreases tolerance to freezing. HOS1 is a ubiquitin E3 ligase that mediates the degradation of ICE1 transcription factor (Dong C-H et al 2006 *Proc Natl Acad Sci USA* 103:8281). ▶[cold hypersensitivity](#), ▶[thermotolerance](#), ▶[anti-freeze proteins](#), ▶[glycerophospholipid](#), ▶[ubiquitin](#), ▶[fatty acids](#); CBF; Lee H et al 2001 *Genes Dev* 15:912; Karlson D et al 2002 *J Biol Chem* 277:35248; cold-adapted enzymes: Siddiqui KS, Cavicchioli R 2006 *Annu Rev Biochem* 75:403.

Cold-Shock Proteins: Cold-shock proteins are produced in response to an abrupt change to a lower temperature. At low temperatures, *E. coli* cold-shock proteins are anti-terminators of transcription and enhancers of translation. It appears that a wheat nucleic acid binding protein, similar to that in bacteria, is an RNA chaperone (Nakaminami K et al 2006 *Proc Natl Acad Sci USA* 103:10122). In mammals uncoupling proteins (UCP1, UCP2) transmit a proton electrochemical gradient across the inner membrane of the mitochondria resulting in generation of heat rather than ATP. A plant protein homolog (StUCP) appears to have a similar function. ▶[heat-shock proteins](#), ▶[uncoupling agent](#), ▶[Hsc66](#); Phadtare S et al 1999 *Curr Opin Microbiol* 2:175; Somerville J 1999 *Bioessays* 21:319; Manival X et al 2001 *Nucleic Acids Res* 29:2223, <http://www.chemie.uni-marburg.de/~csdbase/>.

Cold Resistance: In plants, a member (CBF3) of the centromere binding protein family transcription factor mediates cold tolerance. ICE1 inducer of CBF regulates this protein. ICE1 is a MYC-like basic helix-loop-helix (bHLH) transcriptional activator. In plants, the mitogen activated protein kinase (MKK2) regulates cold and salt stress (Teige M et al 2004 *Mol Cell* 15:141). ▶[antifreeze proteins](#), ▶[DNA binding proteins](#), ▶[MKK](#); Chinnusamy V et al 2003 *Genes Dev* 17:1043.

Cold Sensitive: A cold-sensitive mutant fails to grow normally at a lower temperature although it may behave entirely normally at a higher temperature. The TRP (transient receptor potential) family ion channels mediate thermosensation. ▶[temperature-sensitive mutants](#), ▶[cold hypersensitivity](#); McKemy DD et al 2002 *Nature [Lond]* 416:52.

Cold Spots: Chromosomal areas in which, mutation, recombination, or insertion are rare. ▶ [hot spot](#)

ColE1 Replicon: The colE1 replicon is similar in nature to pMB1. The replicon produces 15–20 copies per cell and does not require a plasmid-encoded function for replication for which, it uses DNA polymerase I and III, DNA-dependent RNA polymerase, and the long-living products of the bacterial genes *dnaB*, *dnaC*, *dnaD*, and *dnaZ*. When cell replication ceases in the presence of protein synthesis inhibitors (chloramphenicol, spectinomycin), this replicon can produce 2,000 to 3,000 plasmid copies per cell. The majority of modern bacterial vectors utilize this replicon. The name is derived from natural plasmids coding for colicine production. The 4.2 megadalton plasmid is non-conjugative. ▶ [colicins](#), ▶ [plasmids](#) [several entries], ▶ [cloning vectors](#), ▶ [phagemids](#), ▶ [replicon](#); Mruk I et al 2001 Plasmid 46:128.

Coleoptile: The membrane-like first leaf in monocotyledones enclosing succeeding leaves at the stage of germination (see Fig. C133). ▶ [embryogenesis in plants](#)

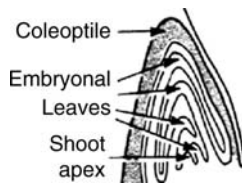


Figure C133. Coleoptile

Coleorhiza: An envelope of the root-tip of germinating grasses.

Coleus blumei: A leafy, shade-tolerant ornamental plant; $2n = 24$.

Colicinogenic Bacteria: Killer strains producing colicins (bacterial toxins)

Colicins: Produced by killer *E. coli* and *Shigella sonnei* bacteria, colicins are genetically (plasmid) controlled bacterial toxins that kill sensitive bacteria even at very low concentrations. Colicins require binding to the extracellular receptor (BtuB, vitamin B₁₂ receptor) of the target cells. Then Ton or Tol proteins mediate the translocation to the periplasm, followed either by voltage-gated depolarization of the inner cell membrane and/or nuclease action on ribosomes or the DNA. Colicin E1 and colicin K inhibit active transport, colicin E2 may contribute to the degradation of DNA, and colicin E3, E4, and E6 interfere with protein synthesis of the sensitive bacteria by attacking the 16S rRNAs at the 49th base from the 3' end and removing a small fragment from their

3' terminus. E5 colicin splits tRNAs of Tyr, His, Asp, and Asn, which contain the Q (queuine [a deazapurine]) at the wobble site of the anticodon. Colicin E5 bacteria harboring Col plasmids are immune to the lethal effects of colicins and this property is used to select Col-transformed bacterial cells. Each cell may normally carry about 20 copies of these plasmids. Colicin resistance mutations occur at appreciable frequencies in bacterial populations. The ColE1 plasmid has a molecular size of about 4.2 MDa and is non-conjugative. The ColE1 plasmid replicon has been used for the construction of genetic vectors and has been engineered into cosmids and other plasmids. ▶ [ColE1](#), ▶ [killer strains](#), ▶ [queuine](#), ▶ [deazanucleotides](#), ▶ [ion channels](#), ▶ [rock-paper-scissors model](#); Riley MA 1998 Annu Rev Genet 32:255; Stroud RM et al 1998 Curr Opin Struct Biol 8:525; Lazdunski CJ et al 1998 J Bacteriol 180:4993; Smajs D, Weinstock GM 2001 J Bacteriol 183:3949; colicin import mechanisms: Housden NG et al 2005 Proc Natl Acad Sci USA 102:13849.

Coliform: Enteric, gram-negative bacteria, related to *E. coli* (see Fig. C134). ▶ [E. coli](#)

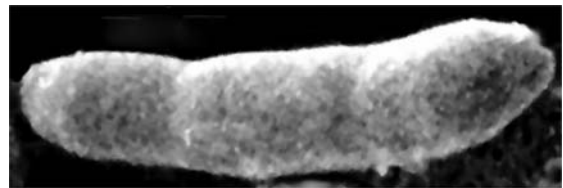


Figure C134. Coliform

Collinear: ▶ [collinear](#)

Coliphage: A bacteriophage, infectious for *E. coli* bacterium.

Collaborative Tagging: Web users are exposed to a resource and freely associate tags with it. Their interaction with the system also exposes them to tags previously entered by themselves and by other users. The aggregated activity of users leads to an emergent categorization of resources in terms of tags shared by a community. Tagging is designed to organize and share diverse online resources such as bookmarks, digital photographs, academic papers, music, and more (Cattuto C et al 2007 Proc Natl Acad Sci USA 104:1461).

Collagen: A fibrous protein built mainly from hydrophobic amino acids (35% Gly, 11% Ala, 21% Pro and hydroxyproline). It forms a left handed helix with three residues per turn, made up of repeated units with glycine at every third position. The collagens form triple helices from three polypeptide chains and play

structural roles in the cell (see Fig. C135). The 38-kbp chicken collagen gene (similar to the gene in humans and in mice) has 52 introns and short exons (54 to 108 bp) built of tandem repeats of nine bases. There are roughly nine types of collagens, encoded by about 17 gene loci in humans. This protein is the major component of the cuticle, tendons, and the cartilage. Synthetic collagen triple helices, longer than the natural ones, can be produced and have applicational potential (Kotch FW, Raines RT et al 2006 Proc Natl Acad Sci USA 103:3028). Some collagen diseases can be detected by prenatal analysis. In *Caenorhabditis*, about 150 collagen genes determine cuticle organization. Several mammalian diseases are based on defects in the collagen. ▶osteogenesis imperfecta, ▶osteoarthritis, ▶Ehlers-Danlos syndrome, ▶Alport syndrome, ▶Marfan syndrome, ▶Stickler disease, ▶Kniest dysplasia, ▶spondyloepiphyseal dysplasia, ▶achondrogenesis, ▶hypochondrogenesis, ▶epiphyseal dysplasia multiple, ▶chondrodysplasia, ▶muscular dystrophy, ▶Weissenbacher-Zweymüller syndrome, ▶aneurism aortic, ▶epidermolysis, ▶spondyloepiphyseal dysplasia, ▶dermatoparaxis of cattle, ▶metastasis, ▶porencephaly; Nimni ME (ed) 1988 Collagen. CRC Press, Boca Raton, Florida.



Figure C135. Collagen

Collagenases: Collagenases are cell surface metalloproteinases involved in remodeling the cellular matrix, and thus shape cells and facilitate cell migration. ▶collagen, ▶metalloproteinases; Saffarian S et al 2004 Science 306:108.

Collapsin: A member of the protein family of semaphorin; it seems to be inhibitory to axon outgrowth. ▶semaphorin, ▶CRMP-62, ▶axon, ▶neurogenesis; Liu BP, Strittmatter SM 2001 Curr Opin Cell Biol 13:619.

Collapsing Data: Collapsing data is used in some instances to reduce information into certain categories in order to facilitate statistical handling (See Hahn LW et al 2003 Bioinformatics 19:376).

Collateral: An accessory.

Collateral Relatives: Animals in a breeding program that have one or more common ancestors but are not direct descendants of these ancestors.

Collectins: Broad-spectrum, complement-like antimicrobial glycoproteins in mammals. They may assist in the removal of apoptotic bodies and may control inflammation. ▶complement, ▶apoptosis, ▶inflammation; Ohtani K et al 2001 J Biol Chem 276: 44222.

Collenchyma: Found in the stems of plants, collenchyma are parenchymal cells that fit together closely; they have thickened walls especially at the corners (see Fig. C136).

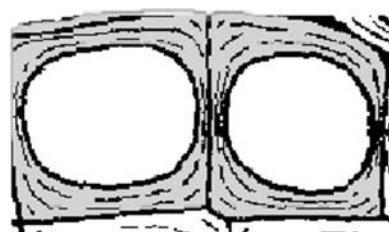


Figure C136. Collenchyma

Colletotrichum circinans: A fungal parasite producing “smudge” on sensitive onions. Generally white onions are susceptible because they lack the gene for the synthesis of parahydroxy acid that inhibits the parasite. Red onions have the *W* allele, which conveys resistance. Some varieties of onions have an *I* (inhibitor) allele that prevents the expression of *W*; thus in the F_2 of the double heterozygote there are 13 white susceptible and three red and resistant segregants.

Collie Eye: An eye anomaly occurring very frequently among collie dogs. It is detectable only by ophthalmoscope, yet often impairs the dog’s vision.

Collinearity (colinearity): Collinearity occurs when amino acid sequences in the polypeptide correspond to the codon sequences in nucleic acids, the 5' end of the mRNA matching with the NH₂ end of the polypeptide chain. Some *Drosophila* genes, e.g., within the *ANTC* (*Antennapedia* complex, chromosome 3-47.5) appear the same sequence in the map as the morphogenetic function they control (*lab*, *Pb*, *Dfd*, *Scr*, *Antp*). Similar collinearity has been shown in the *BXC* (*Bithorax* complex) *Ultrabithorax* segment. (Collinearity is spelled with two *ls* because derived from the Latin *cum* + *linearis* [*collineo*]). In the homeotic complexes generally there is another “position effect”; the products of the relatively posterior acting genes appear to be more abundant than that of the anterior ones. Recent information indicates that collinearity is not completely valid for some/most parts of the genome because the same genetic elements are used differently in different contexts of genes and form an interleaved or modular genomic architecture (Kapranov P et al 2007 Nature Rev Genet: 413). ▶*Lac* operon, ▶lambda phage, ▶morphogenesis in *Drosophila*, ▶homeotic genes; Yanofsky C, Horn V 1972 Biol Chem 247:4494.

Collinsia (Scrophulariaceae): ca. 20 plant species $2n = 2x = 14$; used in cytogenetic studies.

Collision between Replication and Transcription in Prokaryotes: ►leading strand, ►gene distribution

Collochores: Short heterochromatic sequences in the chromosomes supposed to be involved in chromosome association, especially in the absence of chiasmata, e.g., in the X–Y bivalents. In these cases, 240 base pair intergenic spacers of the rDNA repeats mediate disjunction (McKee BD et al 1992 Genetics 94:625). ►heterochromatin; Virkki N 1989 Hereditas 110:101.

Collodion: An alcohol and ether solution of pyroxylin (mainly nitrocellulose), used in microtechnical preparations and as a skin protector veterinary procedure.

Collodion Fetus: A variable form of ichthyosis (collodion like) present before and after birth that may or may not heal during later development. Eye defects may be part of the syndrome. Two genes at chromosome 14q11 (defect in keratinocyte transglutaminase, TGM1) and at 2q33-q35 may be involved. ►ichthyosis

Colloid: Colloids are particles with diameters ranging from 0.1 to 0.001 μm , and can exist in fine suspensions (in gas, liquid or solids) or emulsions (in water).

Colobidae (Old World primates, langurs): *Nasalis larvatus* $2n = 48$; *Presbytis cristatus* $2n = 44$; *Presbytis entellus* $2n = 44$; *Presbytis obscurus* $2n = 44$; *Pygathrix nemaeus* $2n = 44$. ►primates

Coloboma: Coloboma appears as a missing or defective sector involving the iris, retina, or the optic nerve (see Fig. C137). It may be associated with brachydactyly, abnormal movements, and retardation. Autosomal dominant or recessive genes may control it but X-linkage has also been suggested for some forms. ►eye diseases, ►cat eye syndrome, ►brachydactyly



Figure C137. Coloboma of the iris. (From Bergsma D (ed) 1973 Birth Defects Atlas and Compendium. By permission of the National March of Dimes Foundation)

Colon Cancer: ►colorectal cancer

Colonization: The evolutionary factor of settling outside the original habitat. ►gene flow

Colony: A group of microbial cells grown at the same spot. They may have originated from a single cell or from several. The shape of the colony for a certain bacterial strain may vary according to the nutrient content and diffusion, the movement and reproduction of the bacteria, and local cell communication. Colony characteristics are used as a criterion for classification.

Colony Hybridization: Colony hybridization involves, first, the cutting up with appropriate restriction endonucleases, of isolated DNA into fragments. A library of the fragments is then established by cloning the fragments with the aid of a cloning vector (e.g. cosmid, YAC, etc.). The bacteria, presumably each carrying the DNA fragments in a chimeric plasmid, are seeded at low density on agar plates so each colony would be separate. After the colonies are formed a replica plate is established from the master plate by pressing over it a membrane filter. After denaturation of the DNA on the nitrocellulose filter, it is hybridized with a labeled DNA or RNA probe. After washing off the unbound probe, the filter is autoradiographed and the colonies containing the desired molecules of DNA are identified. Since the position of the colonies corresponding to the black dots on the photographic film (dot blot) can be identified, the bacteria containing the vector with that specific DNA can be further propagated (see Fig. C138). In the reverse dot blot, the labeled DNA or RNA (the probe) is immobilized on the hybridization filter and the cloning vector is annealed to it. ►cloning vectors, ►cosmids, ►plaque lift, ►cosmid, ►YAC, ►denaturation, ►probe, ►autoradiography, ►DNA library, ►replica plating; Grunstein M, Hogness DS 1975 Proc Natl Acad Sci USA 72:3961.

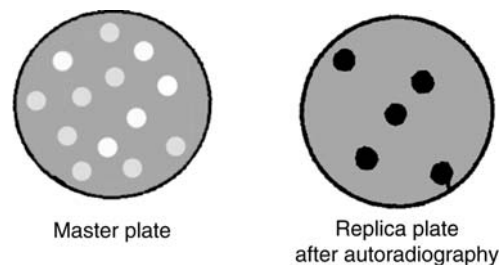


Figure C138. Colony hybridization

Colony Lift: A colony lift is basically similar to a plaque lift. A nylon or nitrocellulose membrane is layered over a growing colony of cells. The colonies stick to the membrane and can be used as a dot blot, and

specific mutants can be identified in the dots with the aid of DNA hybridization.

Colony Stimulating Factor (CSF-1): A cytokine protein activating RAS p21 protein by increasing the proportion of GTP-bound molecules. CSF2 is encoded within the IL-3 gene cluster. ▶CSFR, ▶M-CSF, ▶RAS, ▶IL-3; McMahon KA et al 2001 Biochem J 258[pt2]:431.

Color Blindness: Color blindness exists in different forms. Complete or nearly complete light sensing color blindness (monochromatism or achromatopsia) has prevalence in the 10^{-5} range and it may not involve any alteration in the retina (achromatopsia 1: human chromosome 14, achromatopsia 2: 2q11, achromatopsia 3: 8q21-q22). Adjacent chromosomal areas frequently modulate the X-linked recessive gene. One form of achromatopsia (autosomal recessive) involves also light sensitivity and the affected individuals are bothered by light but have better than average vision under dim conditions (day blindness). Complete achromatopsia involves defects in the retinal cones and, in molecular terms, the α subunit of the cone photoreceptor of a cyclic guanine monophosphate-gated cation channel. This gene (CNGA3 is at human chromosome 2q11. The X-linked incomplete *congenital stationary night blindness* gene CSNB2 encodes at Xp11.23 a retina-specific Ca^{2+} channel α_1 subunit of 48 exons with 1966 amino residues. The complete form of this anomaly was mapped to Xp11.4. Partial color blindness (green color blindness, *deuteranopia*) is also a Xq28-linked recessive and may affect 8% of the males of Western European descent. A cluster of genes that may recombine and undergo gene conversion, explaining the variations and the high frequency of this condition, encodes the green color vision. The red color blindness (*protanopia*) appears to be determined by two X-chromosomal recessive loci (Xq28) with a frequency of 0.08 in males. Another type of color blindness that involves loss of blue and yellow sensors but retains those for red and green (*tritanopia*) may exist in X-linked recessive or autosomal dominant forms (7q31.3-q32). This condition may occur at a very high frequency of 0.02 in some populations, whereas in others it may be lesser by an order of magnitude, or even lower. The blue cone pigment gene displays high homology to that of rhodopsin and substantial homology with the red and green pigments. In the latter form, the rhodopsin receptor may be defective. The great chemist John Dalton suffered from “daltonism” or deuteranopia. ▶hemeralopia, ▶nyctalopia, ▶rhodopsin, ▶eye diseases, ▶color vision, ▶deuteranomaly, ▶ion channels; Neitz J et al 1999 Nature Neurosci 2:884; Crognale MA et al 1999 Vision Res 39:707.

Color Vision: In the human X-chromosome, there is an array of middle (2–7) to long-wavelength (2–4)-sensitive visual pigments. Humans with normal color vision typically have a single long-wavelength gene and two or three middle-wavelength sensitivity genes. The multiple copies probably arose due to unequal recombination and those with more copies may be able to better the differences in hues. Unlike humans, pigeons perceive also ultraviolet light. ▶color blindness, ▶rhodopsin, ▶opsin, ▶unequal crossing over; Yokoyama S, Radwimmer FB 2001 Genetics 158:1697; Yokoyama S 2002 Gene 300:69; Solomon SG et al 2007 Nature Rev Neurosci 8:276.

Colorectal Cancer: Colorectal cancer may be controlled by a large number of genes involved in the “cancer family” syndrome. In many cases, the mismatch repair genes have mutated compared to Gardner syndrome where the APC tumor suppressor is mutant. In colorectal cancer, 40% of the mutations involve the PI(3)K pathway (Parsons DW et al 2005 Nature [Lond] 436:792). Genetic instabilities causing this type of cancer can be dominant involving changes in chromosome number, or if recessive, concerned with microsatellite instabilities. In cancer cells, the telomeres are frequently reduced resulting in anaphase bridges and instability. This may be followed by multipolar mitoses, although multipolarity rarely contributes to clonal cell lines in colorectal cancer (Stewénus Y et al 2005 Proc Natl Acad Sci USA 102:5541).

The common most types of cancers caused are adenocarcinoma of the colon and endometrial (inner mucous membrane) cancer of the uterus; but other types such as breast, ovarian, and brain tumors, as well as leukemia, etc. may be under similar controls (Lynch type I). EphrinB receptors block colorectal cancer progression (Batlle E et al 2005 Nature [Lond] 435:1126). About 75% of the carcinomas show deletions of the short arm of human chromosome 17. This chromosomal segment may be responsible for the transition from the benign to the malignant states of the carcinomas. Nonpolyposis colorectal carcinoma causes 3.8 to 5.5% of the colorectal cases, whereas adenomatous carcinoma contributes to 0.2% and ulcerative colitis to 0.6%. About 1/3 of the alterations involve the RAS oncogene (KIS = Kirsten murine sarcoma oncogen, 12p12.1). Deletions also involve human chromosomes 22, 5, 6, 12q, 15, 17, and 18. The human chromosome 18q21 locus encodes a TGF β -regulated serine/threonine kinase receptor, MADR2. Chromosome 18q24.21 also harbors a susceptibility factor (Tomlinson A et al 2007 Nature Genet 39:984). DCC (deleted in colorectal cancer) is based on a defect in a netrin

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receptor. Netrin is a human homolog of the *Caenorhabditis* gene products UNC-6 and UNC-40 involved in the guidance of neuronal axons (Forcet C et al 2002 Nature [Lond] 417:443). These findings indicate that besides the activation of the major oncogen, it is necessary to inactivate several tumor suppressors. UV light-induced cyclobutane pyrimidine dimers are more readily removed from the transcribed strand of the DNA than from the other (the non-transcribed strand). This is called transcription-coupled repair. Such a repair system seems to be defective in several types of colorectal cancers. About 50% of the Western populations develop this type of cancer by age 70 and 10% of the cases become malignant. An estimated 15% of the cases have a strong dominant hereditary component. NO-ASA (2-[acetyloxy]benzoic acid 4-[nitrooxymethyl]phenylester) is a nitric oxide donating aspirin and appears to inhibit colon cancer hundreds of times more effectively than does aspirin alone by promoting apoptosis (Gao J et al 2005 Proc Natl Acad Sci USA 102:17207). 15-Hydroxyprostaglandin dehydrogenase degrades prostaglandin in normal colon mucosa but it is lost in colon cancer. Knockout of the hydroxylase increases colon tumors in mice 7.6 fold (Myung S-J et al 2006 Proc Natl Acad Sci USA 103:12098). Higher expression of Na^+ /monocarboxylate transporter (SMCT) gene (SLC5A8) is favorable for the prognosis of colorectal cancer (Paroder V et al 2006 Proc Natl Acad Sci USA 103:7270). The location and type of tumor-infiltrating lymphocytes in colorectal and other cancers may predict survival potentials (Galon J et al 2006 Science 313:1960). ▶Gardner syndrome, ▶polyposis, ▶RAS, ▶cancer, ▶p53, ▶p16, ▶DNA repair, ▶hereditary nonpolyposis colorectal cancer, ▶adenomatous polyposis, ▶FAP, ▶PIK, ▶mismatch repair, ▶cyclobutane ring, ▶neuron, ▶Lynch cancer families, ▶PRL-3, ▶mitochondrial genetics, ▶mitochondrial disease in humans, ▶evolutionary clock, ▶RIZ, ▶PMS, ▶plantibody, ▶prostaglandin, ▶CD133; Abdel-Rahman WM et al 2001 Proc Natl Acad Sci USA 98:2538.

Color-Less Testa: Mutations leading to the color-less testa occur in different plant species. These recessive mutations display delayed inheritance because the seed coat is maternal tissue, but in F_3 usually about 1/4 of the individuals uniformly have the recessive seed-coat color. ▶testa, ▶delayed inheritance

Colton (Co): A relatively rare blood type encoded apparently in human chromosome 7. ▶blood groups

Column Chromatography (adsorption chromatography): The separation of (organic) mixtures on sugar, resin, sephadex, silica gel, or other columns established in

glass tubes and eluting the components stepwise with the help of different solvents or solvent mixtures. The eluates collected by fraction collectors can be monitored by spectrophotometry in the samples. ▶chromatography, ▶sephadex, ▶spectrophotometry

Comb: A comb-like device to make wells in the electrophoresis gel (see Fig. C139).



Gel bed comb

Figure C139. Comb

Comb Traits: The comb traits of poultry are determined by two allele pairs and the interaction of their gene products specifies 4 comb types. *RRPP* and *RrPp*: walnut, *RRpp*: rose, *rrPP*: pea, and *rrpp*: single comb in the proportion of 9:3:3:1. ▶Mendelian segregation, ▶epistasis, ▶walnut comb

Combed DNA Color Bar Coding: The combed DNA color bar coding is a technique for the rapid detection of deletions in the DNA. An appropriate genetic sample is stretched out on a treated glass surface and analyzed with fluorescent probes to detect structural changes. (See Gad S et al 2001 Genes Chromosomes Cancer 31:75).

Combination: In a combination generating from n number of individuals, all possible sets contain only x numbers in each set. Mathematically: $= \frac{n!}{x!(n-x)!} : \left(\frac{n}{x}\right)$ ▶binomial distribution, ▶permutation, ▶variation

Combinatorial Chemistry: A method aiming to generate permutations of small molecular building blocks with the goal of finding the most effective pharmaceuticals. This process is then combined with bioassays to find agonists and antagonists of the biochemical process to discover new, effective drugs. The completion of the genome sequencing projects and the developing information on molecular structure facilitate the drug discovery process. ▶agonist, ▶antagonist, ▶chemical genetics, ▶parallel synthesis, ▶chemogenomics, ▶pharmaceuticals, ▶high-throughput analysis, ▶high-content screening; Lehn J-M, Eliseev AV 2001 Science 291:2331; Bhattacharyya S 2001 Curr Med Chem 8:1383, <http://www.combichemistry.com/>.

Combinatorial Diversification: Combinatorial diversification refers to the phenomenon in which, large number of various immunoglobulin genes may enter

into different combinations and generate an enormous array of antibody molecules. ►immunoglobulins, ►antibody, ►junctional diversification, ►affinity maturation, ►somatic hypermutation

Combinatorial Gene Control: The transcription of genes is regulated by the cooperative action of general and specific transcription proteins. It is not known how many such proteins exist but their number can be much smaller than the number of genes, yet they can assure a high degree of specificity. If we just assume that there are a total number (n) of 20 different inducible transcription factors (certainly an underestimated figure) and each gene requires 5 (x), the total number of specificities could be

$$\binom{n}{x} = \frac{n!}{x![n-x]!} = \frac{20!}{5!(15)!} = 15,504.$$

Or if there were 27 inducible transcription factors and 5 were to be used by each gene, the number of specificities $\binom{n}{x} = \frac{27!}{5!22!} = 80,730$ would be enough to regulate all the estimated human genes (ca. 25,000 to 40,000 or according to the latest estimate of about 25,000). ►regulation of gene activity, ►gene number; Darimont BD et al 1998 Genes Dev 12:3343.

Combinatorial Labeling: A cytogenetic method of chromosome analysis using simultaneously more than one fluorochrome-conjugated nucleotide. The number of useful combinations is $2^N - 1$. ►FISH, ►chromosome painting, ►fluorochromes, ►ratio labeling

Combinatorial Library: Antibody heavy and light chain cDNAs are amplified separately by PCR, then ligated and cloned in vectors. Thus a random combinatorial array of constructs is generated. *E. coli* cells infected with the vectors produce both antibody chains. But only the heavy chain contains the variable region, the first constant domain, and the Fab region (see antibody diagram). This protein binds to the antigen but lacks the effector domain. The library can be screened by a radioactively labeled antigen and after washing off the unbound radioactivity, the sought antigen-antibody can be spotted on the plate by the radioactivity fixed. This method permits a very efficient selection among millions of types of antibodies, a selection that appears a thousand fold more efficient than the monoclonal method. The method is further improved upon by using filamentous phages (M13) that display antibodies on their surface. Screening can be done in liquid media and subjected to adsorption chromatographic purification. This procedure is also called epitope screening. ►epitope, ►antibody, ►antigen, ►filamentous phage, ►phage display, ►monoclonal antibody,

►chromatography; Pelletier J, Sidhu S 2001 Curr Opin Biotechnol 12:340; Pinilla C et al 2001 Cancer Res 61:5153.

Combing: ►molecular combing

Combining Ability: A term used in quantitative genetics and animal and plant breeding. *General combining* indicates that a particular stock has better than average performance in any hybrid combinations. *Specific combining ability* indicates a better than average performance only in certain hybrids. From (n) lines $\frac{n(n-1)}{2}$ single crosses and $\frac{[n-1][n-2][n-3]}{8}$ double crosses are possible. ►heterosis, ►hybrid vigor, ►double cross; Henderson CR 1952 In: Gowen J (ed) Heterosis. Iowa State College Press, Ames, Iowa.

Combretastatin: (see Fig. C140). ►angiogenesis

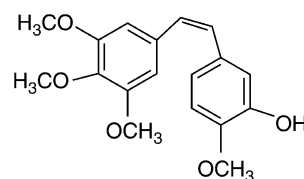


Figure C140. Combretastatin

ComEA: is a membrane-bound double-stranded DNA binding protein in prokaryotes and promotes transformation. Before uptake of DNA one of the strand is degraded. In Gram-negative bacteria, however, the dsDNA passes through the outer membrane with the assistance of secretin.

Comet Assay: The comet assay detects chromosomal lesions by exposing alkaline treated (pH 13) cells to electrophoresis and examining microscopically the comet shape of the destabilized nucleus suffered chromosome breakage by the mutagenic agent. The tail (length of the comet) and the head (diameter) ratios are evaluated (see Fig. C141).



Figure 141. Comet assay

Comm (*commisureless*): *Drosophila* gene counteracts the effects of *Robo*. ►axon, ►Robo

Commaless Code: In 1961, Francis Crick and coworkers (Nature [Lond] 192:1227) predicted the triplet nature of the genetic code from mutation experiments and they concluded that the code is degenerate, not overlapping, and the triplets follow each other in a linear order without interrupted commas. Although

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these were epoch-making conclusions, the discovery of introns in 1977 (Berger SM et al 1977 Cold Spring Harbor Symp Quant Biol 42:523; Broker TR et al 1977 Cold Spring Harbor Symp Quant Biol 42:531) showed that not all genes are contiguous. Also, even in the small DNA virus ϕ X174 several genes overlap and this is a common phenomenon in eukaryotes as well (Boi S et al 2004 Curr Genomics 5:509). ▶degenerate code; ▶ ϕ X174genetic code; Rédei et al 2006 Adv Genet 56:53.

Commensalism: Commensalism is the condition in which, species share the same natural resources without necessarily benefiting or suffering from the relationship. ▶symbiont, ▶pathogenic

Commingling Test: The commingling test analyzes whether the phenotypic distribution in large populations is based on the contribution of a single group or by an admixture of several groups. Such a study may be important for the analysis of quantitative traits, and in genetic epidemiology. (See Khoury MJ et al 1993 Fundamentals of Genetic Epidemiology. Oxford University Press, New York).

Commissure: The joining of corresponding parts of organs, e.g., of the lips of the mouth or vagina or between the axons crossing the midline of the body.

Commitment: ▶determination

Commitment Point: The determination (start) point of the cell division cycle. ▶cell cycle, ▶restriction point

Common Denominator: In mathematics, the term common denominator is used to bring different fractions to a denominator that can be used with all appropriately adjusted nominators to facilitate further manipulations (e.g. additions, subtraction). In molecular biology, the common denominators are the elements shared among different protein isoforms encoded by the same open reading frame. ▶isoform, ▶open reading frame

Common Variant/Common Disease Hypothesis: The common disease hypothesis states that quantitative differences among different alleles may account for common (complex) disease. (See Lee MP 2005 Methods Mol Biol 311:39).

Comorbid: A condition in which, an additional disease occurs along with the primary disease. It may alter the diagnosis and may aggravate the condition.

COMP (cartilage oligomeric matrix protein): A pentameric member of the thrombospondin family. See ▶thrombospondin, ▶pseudoachondroplasia; Oldberg A et al 1992 J Biol Chem 267:22346.

CompP: A *Bacillus subtilis* kinase affecting competence through regulator ComA.

Compaction: The tight binding of cells to each other such as occurs when the blastomeres of the embryo form the morula. ▶morula

Companion Cells: Conductive tissues in plants, associated with sieve tubes. ▶sieve tube

Comparative Anchor Reference Loci (CARL): CARL span the genomes and facilitate comparative genome mapping of different species of mammals. (See for data Lyons LA et al 1997 Nature Genet 15: 47; Margulies EH et al 2005 Proc Natl Acad Sci USA 102:4795).

Comparative Chromosome Painting: Comparative genetic mapping and comparative chromosome painting are suitable means to shed light on the evolution of the chromosome complement. During evolution, chromosome numbers might have increased (polyploidy) or decreased by reciprocal translocations, inversion, insertions, deletions of fusion of chromosomal arms or their parts. Chromosome painting may reveal the homology of the present day species to each other and/or ancestral species. *Arabidopsis thaliana* has five pairs of chromosomes but other related cruciferous plants have a higher chromosome number. *Arabidopsis lyrata* has eight pairs of chromosomes. Analysis of pachytene chromosomes by hybridizing bacterial artificial chromosome-carried *A. lyrata* contigs painted with different fluorochromes revealed their position in the *Arabidopsis thaliana* genome, and permitted the reconstruction of the cytological events that lead to the reduction of chromosome number in *A. thaliana* to five from the ancestral eight still conserved in *A. lyrata* (Lysak MA et al 2006 Proc Natl Acad Sci USA 103:5224). Similar changes are detectable among other plant and animal species. ▶chromosome painting, ▶contig, ▶chromosomal rearrangements, ▶evolution of the karyotype, ▶comparative genomic hybridization, ▶chromosome banding

Comparative Expressed Sequence Hybridization (CESH): CESH is a relatively rapid method, which gives a genome-wide view of chromosomal location of differently expressed genes within tissues. mRNA or cDNA prepared from two different tissues, e.g., healthy or cancerous is differentially labeled with fluorochromes before hybridization. No prior knowledge of genes or cloning is necessary, and minimal amounts of tissue can be used. Expression profiles are achieved in a manner similar to the identification of chromosomal imbalances by comparative genomic

hybridization analysis. The method reveals chromosomal regions where genes are overexpressed as a consequence of drug-resistance, cancer, or other functional differences. ►comparative genomic hybridization; Lu Y-J et al 2001 Proc Natl Acad Sci USA 98:9197.

Comparative Genomic Hybridization (CGH): CGH is a method of cytological localization of a mutant DNA sequence. The normal sequence and the mutant sequence of DNA are labeled by different fluorochromes, and the mixture is used for in situ hybridization. The relative hybridization signals of the bands are monitored by fluorescence microscopy. Alternatively, microarray hybridization can be used for the analysis. This method permits the analysis of DNA sequence dosage (loss or gain) in cancer tissues compared to normal cells. It is also suitable for scanning genomes for evolutionary studies, developmental studies, and for prognosis of cancer. ►fluorochromes, ►in situ hybridization, ►microarray hybridization, ►FISH, ►hyperbranched strand displacement amplification, ►RDA, ►diagnosis; Pinkel D et al 1998 Nature Genet 20:207; Lomax B et al 2000 Am J Hum Genet 66:1516; Lin JY et al 2002 Genome Biol 3:research 0026.1; Pinkel D, Albertson DG 2005 Annu Rev Genomics Hum Genet 6:331, copy number search: <http://bioinfo-out.curie.fr/CAPweb/>, copy number and expression profile: <http://isacgh.bioinfo.cipf.es/>.

Comparative Genomics (sequenced genomes): The prospects for comparable DNA sequences among various prokaryotic and eukaryotic genomes across phylogenetic ranges. The study may involve genic, regulatory and non-coding sequences as well as gaps, fused genes, split genes, and evolved orthologous and paralogous genes. The comparisons may better define the function(s) of genes and non-coding sequences. The proteome of mammals is very similar; generally less than 1% difference exists among mammalian species, but 4% of the *Caenorhabditis* genes have no matches in the *C. briggsae*, a related species. Comparative genomics of primates—about 300 species—is of particular interest because it can shed information on the evolution and function of the human genome. The closest relatives to humans are the hominoids such as the chimpanzee, bonobo, gorilla, orangutan, and gibbon. The Old World Monkeys such as the colobus, baboon, and the rhesus monkey are somewhat further away in the phylogenetic tree. Even further apart are the New World Monkeys: the woolly monkey, the capuchin, and the marmoset. The tarsius, galago and lemur are on the lateral branches. The most likely relationships cannot be determined until complete genome sequences are

available. The classical morphological analysis is not in complete agreement with the limited DNA information. The estimates of the age of divergence are not entirely consistent with the other known data. It appears that the lineage of the closest human relative, the chimpanzee, diverged about 5–7 million years ago (mya), but this estimate may be biased because the effective population sizes as well as the initial gene flow are unknown. The seemingly closest, extinct hominoid species, the Neanderthals apparently split from the human lineages 350,000 years ago. Their mitochondrial DNA is different and their contribution to the human gene pool is uncertain but most likely minimal. Genetic diversity within the human species is much smaller than in other primates despite the larger population size. This fact may indicate recent origin and rapid population expansion. Chromosomal rearrangements, particularly duplications, open opportunities for gene evolution. Transposon and retrotransposons (representing ~45% of the human genome) provide chances for genome evolution. Insertion elements seem to have increased the size of the human genome by about 1%, compared to that of chimpanzee and apparently contributed to the different regulation of the human genome. Insertion and deletions may occur 1/1,000 sequences between humans and chimpanzees. In human chromosome 21 and its chimpanzee homolog (Chr. 22), 68,000 indels were detected in 3.3 million compared base pairs. This resulted in 83% amino acid differences of 231 coding sequences (Watanabe H et al 2004 Nature 429:382). Microsatellite sequences in humans appear 2-bp longer than in chimpanzees (Webster MT et al 2002 Proc Natl Acad Sci USA 99:8748). Mutation rates—especially in the CpG dinucleotides, which are subject to methylation—may vary also between and among related species and have functional consequences. Recombination rates may vary among related species and are a factor in genome evolution. Comparative microarray analysis of the genes reveals expression profiles and species differences. Selectively advantageous alterations in a species can be determined from the Ka/Ks amino acid substitutions; the greater Ka indicates positive selective advantage, and not merely neutral change. ►alignment, ►TWINSCAN, ►GENSCAN, ►SGP, ►SLAM, ►ETOPE, ►browsers, ►dog, ►Trypanosomatids, ►Neanderthal, ►microarray hybridization, ►microsatellite, ►Ka/Ks, ►language; Cliften PF et al 2001 Genome Res 11:1175; Wassenaarman KM et al 2001 Genes Dev 15:1637; Sidow A 2002 Cell 111:13; Kellis M et al 2003 Nature [Lond] 423:241; Miller W et al 2004 Annu Rev Genomics Hum Genet 5:15; Enard W, Pääbo S 2004 Annu Rev Genomics Hum Genet, 5:351; genome sequence alignment and

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annotation database (GALA): Giardine et al 2003 Genome Res 13:732; comparative genomics of model plants: Borevitz JO, Ecker JR 2004 Annu Rev Genomics Hum Genet 5:443; relationship between sequence diversity, specificity and sensitivity of analysis of different genomes: Stone EA et al 2005 Annu Rev Genomics Hum Genet 6:143; <http://www.ncbi.nlm.nih.gov/COG>; comparative regulatory genomics; <http://corg.molgen.mpg.de/>; <http://gib.genes.nig.ac.jp>; comparative plant genomics: <http://plantbpb.uoregon.edu/>.

Comparative Maps: Comparative maps would reveal the evolutionary conservation of genes and nucleotide sequences across phylogenetic boundaries. For this purpose comparative anchor-tagged sequences (CATS) are needed in the species where substantial amount of nucleotide sequence information is available. The information available in various species suggest that 1 to 10 chromosomal rearrangements might have occurred per million years. Conserved sites indicate the functional importance of that DNA sequence. ▶ [comparative anchor reference loci](#), ▶ [unified genetic maps](#), ▶ [mouse](#), ▶ [evolution](#); Smith EJ et al 2001 Poultry Sci 80:1263.

Comparative Regulatory Sequences (CORG): The conserved non-coding blocks of ten vertebrates: <http://corg.eb.tuebingen.mpg.de/cgi-bin/index.pl>.

compartmentalization: Certain groups of cells give rise to clones, which are different by morphology and/or function from their surrounding tissues. Adjacent compartments do not intermingle. The compartment may further differentiate during development. Compartmentalization takes place within the cells as well, by assignment of special functions in a polar fashion or to special subcellular organs. Temporal/diurnal compartmentalization includes the circadian rhythm or various oscillatory functions. ▶ [mRNA targeting](#), ▶ [differentiation](#), ▶ [morphogenesis](#), ▶ [circadian rhythm](#), ▶ [oscillators](#); Helweg-Larsen J et al 2001 J Clin Microbiol 39:3789.

Compass: The protein complex involved in histone 3 lysine 4 methylation is a homolog of human MLL. ▶ [MLL](#), ▶ [histone methyltransferase](#)

Compatibility: Crossing or mating of compatible parents results in (normal) offspring. Also, compatible tissue transplantation does not involve adverse immunological reaction. Simultaneous treatments are compatible if they can be withstood without undesirable consequence(s). incompatibility.

Compatibility Group: Plasmids that may or may not co-exist in the same bacteria.

Compatibility of Organelle and Nuclear Genomes: Compatibility of organelle can be determined in species where biparental transmission occurs and organelles can be transferred between species. Also on the basis of cybrids, it appears that compatibility differences are real, and thus various cytoplasms can be classified. The reciprocal crosses are usually informative. ▶ [plasmid male transmission](#), ▶ [paternal leakage](#), ▶ [ctDNA](#), ▶ [mtDNA](#), ▶ [cybrids](#)

Compensasome: The RNA and protein complex that mediates dosage compensation. ▶ [dosage compensation](#)

Compensatory Mutation: A compensatory mutation mitigates the genetic disadvantage of another mutation. The streptomycin resistance gene in *Salmonella* or *E. coli* endows the cells with great selective advantage on streptomycin media, but under conditions where the antibiotic is not present the primary mutants are disadvantaged because of the modified ribosomes (conveying the resistance) are less efficient in translation. Several passages through streptomycin-free media. the fitness of the bacteria improves without reversion to the wild type gene. The improvement is generally due to mutations that compensate for the shortcoming of the ribosome. ▶ [fitness](#), ▶ [reversion](#), ▶ [second site reversion](#); Guan Y et al 2001 J Virology 75:11920; Kulathinal RJ et al 2004 Science 306:1553.

Competence, Embryonal: A state of being receptive to stimuli for differentiation. It may depend on specific transcription factors, presence of the right signaling molecules, absence of interfering signals, presence of the appropriate receptors and ligands, modifying factors such as kinases, phosphatases, availability of the proper environmental cues, etc., and their complex interactions. (See Duranthon V, Renard JP 2001 Theriogenology 55:1277).

Competence of Bacteria: A physiological state of the (bacterial) cell when transformation (uptake and integration of DNA) is successful. Competence generally coincides with the second half of the generation time or its peak is near the end of the exponential growth phase. Divalent cations and their combination can induce competence. For more than four decades *E. coli* was refractory to transformation, until in 1970 it was discovered that cold CaCl_2 makes possible the uptake of phage DNA. 1 mg supercoiled plasmid DNA yields 10^5 to 10^6 transformations. This frequency can further be increased by two to three orders of magnitude by the use of improved protocols involving also DMSO (dimethylsulfoxide, a wide-range solvent

and penetrant). The bacteria so treated keep their transformation competence if stored at -70°C .

Competence in *Bacillus subtilis* is regulated by the secreted competence-stimulating factor (CSF, 520-720-Da peptide) and the pheromone ComX (the ≈ 10 amino acid C-terminal section of the 55 amino acid peptide). The process of competence development requires transcription factors and specific nutritional conditions. *Bacillus subtilis* has more than 15 proteins for single-stranded DNA internalization that are co-localized at the cell poles along with Rec proteins (Kidane D, Graumann PL 2005 Cell 122:73). In the *Neisseria* bacteria, competence is expressed constitutively. In *Haemophilus influenzae*, arrest of cell division results in competence. In *Streptococcus pneumoniae* and *Bacillus subtilis*, stress signals such as created by certain antibiotics, stimulate competence for transformation. The increased transformability increases the chances of acquiring resistance to new antibiotics and evolution of virulence (Prudhomme M et al 2006 Science 313:89). ▶[transformation genetic](#), ▶[exponential growth](#), ▶[supercoiling](#), ▶[DNA uptake sequences](#), ▶[ComEA](#), ▶[fratricide](#); Grossman AD 1995 Annu Rev Genet 29:477; Peterson S et al 2000 J Bacteriol 182:6192; regulatory circuits in *B. subtilis*: Süel GM et al 2006 Nature [Lond] 440:545.

Competition: The rivalry between or among free-living organisms for available resources. It may be a passive *exploitative* process when one or more competitors use up the resources and for others the facilities or supplies become limited. In *interference*, one organism actively attacks or eliminates another or others by the production of deleterious substances or mechanical obstacles. An *apparent* competition results when an organism of certain genotype evokes a host defense mechanism that prevents others from infecting the same host. ▶[pollen competition](#), ▶[selection](#), ▶[superinfection](#), ▶[frequency-dependent selection](#)

Competitive Exclusion: As per competitive exclusion, two similar species generally do not coexist in the same niche indefinitely. They will either coalesce (be interbreeding) or one will be extinguished.

Competitive Inhibition: The inhibitor competes with the substrate for the active site of the enzyme and its blocking effect can be relieved by an increase in the concentration of the substrate. ▶[regulation of enzyme activity](#); Takahashi Y, Kamataki T 2001 Drug Metab Rev 33:37.

Competitive Regulation: In competitive regulation, besides the minimal enhancer, accessory cis elements are needed to ensure proper gene expression during the different developmental stages.

Competitive Release: Competitive release refers to the phenomenon in which, under conditions when there are limited or no competitive species, races or species are selected for general performance rather than to high adaptive specialization.

Complement: The complement is activated when antigen and antibody form a complex in the Fc domain of the heavy chain of IgG and IgM ▶[antibody](#). The complement has numerous functions, one of the most important of which is mediated through the antibody related lytic pathway and the other is the antibody-independent pathway, outlined. Apart from this, the complement may protect the immune complexes from precipitation, facilitate the solubilization of the immune complex, and make possible its transportation by the circulatory system of the body. The complement (except C5b-9) may interact with surface receptors of the hematopoietic cells of the immune system to stimulate inflammation and to mount an immune response. The complement may promote opsonization by macrophages. Graft rejection may be based on the activation of the complement system. Non-biological, foreign material used during surgery or other medical interventions (various drugs, radiographic contrast media) may activate the complement system. Medical treatments may apply complement deactivating or neutralizing drugs (e.g. aspirin, cobra venom, specific antibodies, and protease inhibitors) in autoimmune or other inflammatory disease. The complement consists of about 30 different proteins that facilitate the destruction of the foreign cells by lysis and activate the leukocytes to engulf the invaders by phagocytosis. Immunoglobulin M (IgM, 950-kDa) and the sub-classes of immunoglobulin G (IgG, 150-kDa) bind complement C1q (459-kDa) components of C1 protein, encoded in human chromosome 1p34-p36.3. The binding causes the sequential activation of C1r (83-kDa, a serine protease encoded at 12p13), C1s (83-kDa is also a serine protease component, encoded at 12p13), C4 (95, 75, 33-kDa, encoded at location of the MHC III in chromosome 6, activator of C2, C3, C5) and C2 (90 to 102-kDa, encoded at the MHC locus), and the cleavage of C3 (185-kDa, encoded at the end of 19q). C2 binds to C4b to form C4b2, which after cleavage by C1s forms the C4b2a complex and then activates C3. There are a number of other proteins that modulate these reactions. C1-inhibitor (C1-INH is a serpin [serine-protease inhibitor], 71-53 kDa, encoded at 11p11.2-q13). C4b binding plasma glycoprotein 570-kDa, encoded in 1q) is an inhibitor of C3 convertase (cleaving protein). IgA, IgE, polysaccharides, and endotoxins can activate the cleavage of complement component

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C3 as well (for structure and function of C3 see Janssen BJC et al 2005 Nature [Lond] 437:505). Proteins B (93-kDa, encoded in the MHC complex), D (24-kDa), P (properdin, 220-kDa, encoded at chromosome Xp), Factor I (dimeric 50- and 38-kDa, serine protease), and a modulator H (155-kDa encoded in chromosome 1q31) are also involved in the cleavage of C3. Conformational change mediates the transition of C3 into C3b (1,560 amino acids in 12 domains) and facilitates the binding of proteins and receptors. Its crystal structure has been revealed (Janssen BJC et al 2006 Nature [Lond] 444:213; Wiesmann C et al 2006 *ibid.* p. 217; Ajees AA et al 2006 *ibid.* p. 221). The largest fragment of C3b then interacts with another protein group, properdin, and participates in a positive feedback system to stimulate the cleavage of C3. Finally, C3b initiates the cleavage of complement components C5 (192-Da, human chromosome 9), C6 (104 to 128-kDa), C7 (92.4 to 121-kDa), C8 (152-kDa, 9q), and C9 (71-kDa). Proteins 6, 7, and 9 are encoded in chromosome 5p, and form the so-called MAC (membrane attack complex). In the so-called *classical pathway*, proteins C1q, C1r, C1s, C4, C2 and C3 are involved. The alternative means of activation follows the “lectin” or *mannose-binding* protein (MBP/MBL) path involving C4, C2, C3, and the mannose binding-associated serine proteases (MASP). This alternative MBP pathway—in contrast to the classical pathway—attacks the foreign proteins without prior antibody synthesis. The majority of the Gram-negative bacteria activate the MBP reactions but some Gram-negatives do not. Activating the binding of the H protein to C3b may prevent the activation. A variety of the components of the cell wall of the pathogens also prevent the initiation of the MBP pathway. The complement components react with cell-specific receptors and some receptors react with more than one complement component. This reaction results in enhanced phagocytosis, antibody dependent cellular cytotoxicity (ADCC), lysis, B-lymphocyte proliferation, etc. Components C1, C4, and C2 attack viral invaders, and their interaction increases permeability. C3a and C5a have anaphylatoxic effects, including the release of cellular histamine, and they regulate humoral immune reactions. The C1q molecules may bind to specific receptors (C1q-R) such as the collectin receptor (60-kDa cC1q-R) or the 100-kDa cC1q-R or the 30-kDa gC1q-R, present in a variety of cells. C3b and C4b bind to surface receptors of several mammalian cells and to bacteria and cause their destruction. According to the “doughnut hypothesis” C5b-C9 components of the complement form transmembrane channels (maximally 10-nm in diameter) through which the lytic components can

penetrate the attacked cells. The target cells may be protected by elimination of the C5b-9 channels. The presence of Ca^{2+} may assist in the (partial) elimination of the channels but Ca^{2+} may also enhance cell death. C5b-9 binding initiates hydrolysis of membrane lipids and in small amounts, C5b-9 may lead also to the synthesis prostaglandins, leukotrienes, growth factors, and a number of cellular proteins. The complement plays a particular role in defense before antibody formation is completed. HIV and human T cell leukemia virus are, however, resistant to the human complement. Gal(α 1-3)Gal terminal carbohydrate antigens are present in the endothelial lining in most mammals, except humans, because human cells do not possess this type of functional galactosyltransferase (although several galactosyltransferases are encoded by the human genome). If the porcine enzyme is transfected into human cells, the retroviruses become sensitive to the human serum.

Immunochemical and hemolytic properties measure the amount of the complement. CH_{50} is a measure of the complement indicating that 50% of the antibody-sensitized erythrocytes release their hemoglobin. Genetically determined deficiencies are known for the complement proteins. Homozygotes may entirely miss a particular protein, whereas heterozygotes may display only a limited quantity. *Lupus erythematosus*, an autoimmune disease, is caused by C2 deficiency. Other deficiencies in the terminal components of the complement pathway may contribute to the symptoms of rheumatoid immune diseases. Susceptibility to various types of infections is also related to deficiencies in the components of the complement proteins. The complement is basically an innate component of the immune system and is complementary to the function of the macrophages, mast cells, T cells, and B cells. The complement can be activated not only by binding of the antibody and antigen, but also by surface structures of microbes and, in an antibody-independent manner, by serine proteases associated with mannan-binding lectin. Hereditary deficiencies have been identified for most complement components. Many of these deficiencies are not lethal per se but make the individuals more susceptible to infections.

► immunodeficiency, ► lupus erythematosus, ► macular degeneration, ► antibody, ► immunoglobulin, ► lymphocytes, ► macrophages, ► opsonins, ► Leiner's disease, ► Reynaud's disease, ► Churg-Strauss vasculitis, ► mast cells, ► humoral antibody, ► HLA, ► endotoxins, ► hemolysis, ► histamine, ► rheumatoid arthritis, ► immune system, ► T cells, ► convertase, ► TAPA-1, ► CD22, ► angioneurotic edema, ► paroxysmal nocturnal hemoglobinuria, ► angioedema, ► glomerulonephritis, ► lectins, ► mannan, ► prostaglandins,

▶leukotrienes, ▶TCC, ▶opsonins, ▶MCP, ▶decay accelerating factor, ▶vitronectin, ▶membrane attack complex, ▶Niemann-Pick disease, ▶anaphylatoxins, ▶allograft, ▶xenograft, ▶hyperacute reaction, ▶CD35, ▶CD21, ▶CD11/CD18, ▶C5a -R, ▶Gala1-3Gal, ▶SIGN-R1; Morley BJ, Walport, MJ (eds) 2000 The Complement Facts Book. Academic Press, San Diego, California; complement minireview: Roozendaal R, Carroll MC 2006 Cell 125:29.

Complement Fixation: A serological measure of the degree of antigen-antibody reaction. ▶antibody detection, ▶complement, ▶CH₅₀

Complementarity: Complementarity of nucleic acid bases means that Adenine pairs with Thymine and Guanine with Cytosine by two and three hydrogen bonds, respectively, and two complementary polynucleotide chains pair in an antiparallel manner. ▶DNA structure, ▶Chargaff's rule

Complementarity Determining Region: ▶CDR

Complementary Alleles: Complementary alleles belong to different gene loci, although partial complementation may occur between alleles that belong to different cistrons of the same gene locus. ▶allele, ▶allelism test, ▶cistron, ▶complementation mapping, ▶complementation test in vitro

Complementary Base (nucleotide) Sequences: Nucleotides can form hydrogen bonds according to the base pairing rules in double-stranded DNA or double-stranded RNA. ▶hydrogen bonding, ▶Chargaff's rule

Complementary DNA: ▶cDNA

Complementary Genes: Homozygosity of recessive alleles located at different loci but controlling functions in the same biosynthetic pathway may be expressed by identical (or very similar) phenotype, and in the F₂ of a double heterozygote is expected to display the phenotypic proportion of 9 wild type and 7 mutants (homozygous for one [3] + for the other [3] + for both [1] of the recessive alleles = 7). This is a modification of the 9:3:3:1 (9/16, 3/16, 3/16, 1/16) ratio. ▶modified Mendelian ratios

Complementary Segregation: ▶complementary genes

Complementary Sex Determination: Complementary sex determination may occur in animals with arrhenotoky. The females are heterozygous for complementary alleles at the sex locus and diploid. There is greater relatedness among sisters of a mother (queen) than between mother and daughters. The normal males are haploid, whereas diploidy in the males is deleterious or lethal. ▶arrhenotoky

Complementation, Donor Strand: The formation of a stable complex by the interaction of two proteins. One such a donor may be a chaperone molecule. ▶chaperones

Complementation, Extracellular: By diffusion, the product of one gene may compensate for the defect in a nearby cell. ▶complementation

Complementation Groups: Recessive mutations that complement in trans-arrangement belong to different complementation groups, i.e., they represent different gene loci, whereas the noncomplementary alleles belong to the same complementation group (see Fig. C142). ▶trans, ▶cis, ▶allelism

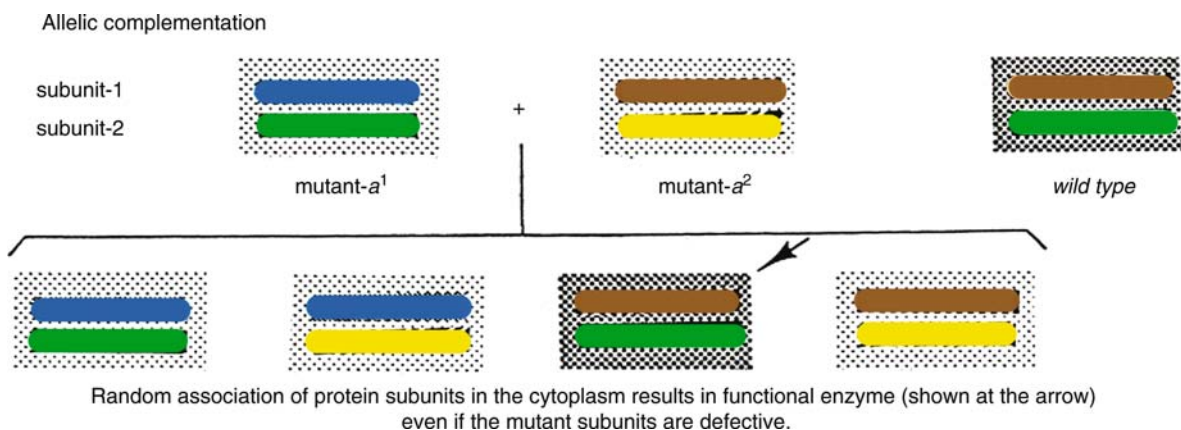


Figure C142. Allelic complementation may be based on random cytoplasmic association of protein subunits of the multimeric enzymes. The mutant subunits may not be functional, yet if they assemble favorably some enzyme molecules can show activity

Complementation Mapping: Complementation mapping is used to determine the pattern of the genetic differences among complementary alleles and the extent of the genetic lesions involved (see Fig. C143).

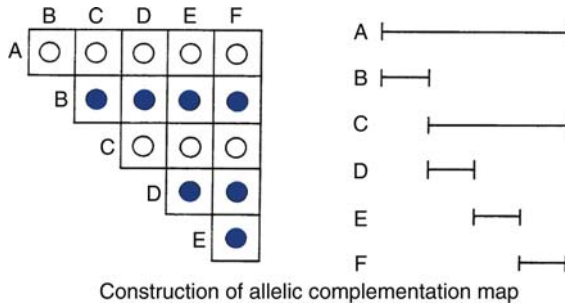


Figure C143. On the basis of partial (allelic) complementation of various alleles of a locus controlling a multimeric enzyme, genetic mapping is possible. This is not necessarily a physical map, rather a functional one and it may not always be therefore linear. Open circles indicate lack of complementation, solid circles stand for complementation of recessive alleles identified here by A, B, C, D, E, and F. (From Catcheside DG 1960 In: Hayes W, Clowes RC (eds) *Microbial Genetics*. Cambridge University Press, Cambridge, UK)

Complementation Test: A test for allelism. Recessive alleles of the same cistron generally fail to complement in trans-arrangement in heterozygotes, e.g., the *Ab/aB* heterozygote is non-mutant if *a* and *b* alleles belong to different loci. If two recessive mutations in the F_1 display mutant phenotype, the two mutants are allelic. ▶ [allelism](#)

Complementation Test, In Vitro: The complementation test is carried out by cell extracts (enzyme assays). This is the most reliable test of complementation because the genes are regulated in vivo and that may boost complementation when the complementation is weak. E.g., 5% of the activity of an enzyme may appear as if it would be of wild phenotype in vivo but in vitro, in the absence of regulation, it can be readily distinguished from 100% activity. ▶ [allelism](#); Loper JC 1961 *Proc Natl Acad Sci USA* 47:1440.

Complementation, Tetraploid: ▶ [tetraploid complementation](#)

Complementation Unit: A cistron. ▶ [cistron](#), ▶ [complementation test](#)

Complete Digestion: In complete digestion, the reaction with a restriction endonuclease is continued until the enzyme cleaves all potential cutting sites in the DNA. ▶ [restriction enzymes](#)

Complete Dominance: In the presence of a completely dominant allele, the phenotype controlled by the recessive allele is not detectable under the conditions of study. ▶ [Mendelian laws](#), ▶ [Mendelian segregation](#), ▶ [Modified Mendelian ratios](#), ▶ [semidominance](#), ▶ [codominance](#)

Complete Flowers: Complete flowers have sepals, petals, stamens, and carpels. ▶ [flower](#), ▶ [differentiation](#)

Complete Linkage: Genes fail to recombine because of their extreme closeness in the chromosome or because of genetic factors interfering with crossing over (chromosomal aberrations), inviability of the recombinants (deficiency or duplication gametes in inversion heterozygotes), or absence of recombination in the heterogametic sex of male *Drosophila* or female silkworm. ▶ [recombination](#), ▶ [linkage](#); Sturtevant AH, Beadle GW 1939 *An Introduction to Genetics*. Dover, New York.

Complete Medium: A complete medium contains all the nutrients that potentially auxotrophic cells may require for growth. ▶ [minimal medium](#), ▶ [auxotroph](#)

Completion: The production of high-quality nucleotide sequence map of both unique and repetitive DNA of a genome. ▶ [high-quality sequence](#), ▶ [genome projects](#), ▶ [finishing](#)

Complex: Complex, as a noun refers to a functional aggregate of molecules without inter-molecular covalent bonds. As an adjective, the function of a complex may not be entirely predictable from the components because it may be qualitatively different than the sum of its components.

Complex Diseases: Multiple genes and diverse environmental factors determine complex diseases and susceptibility to them. Neither statistical nor molecular analyses have been found to facilitate, to an entirely satisfactory extent, the identification of the factors and mechanisms involved, although several approaches are available. ▶ [PAF](#), ▶ [QTL](#), ▶ [correlation](#); Altmüller J et al 2001 *Am J Hum Genet* 69:936.

Complex Heterozygote: Complex heterozygotes are viable heterozygotes for multiple reciprocal translocations A when translocation homozygotes are lethal (see Fig. C144). It is actually a balanced lethal system and heterozygosity is permanent for the genes within the translocation complexes. If there are two multiple translocation complexes, it appears as if there would be only two groups of linked genes even when the basic number of chromosomes is larger. In meiosis, the distribution of the chromosomes is alternate and paternal and maternal complexes always go to opposite poles. Recombination between the complexes is rare but if it occurs it may change the

complexes. The size of the complexes may vary depending upon the number of chromosomes involved in the reciprocal translocation complexes. *Oenothera lamarckiana* carries the seven-chromosome *gaudens* complex (Latin for happy, i.e., the chromosomes do not contain dominant or semi-dominant deleterious genes) and the seven-chromosome *velans* translocation complex (Latin for concealing, since it contains semidominant genes that are responsible for paler color and narrower leaves). *Oenothera hookeri* also has 14 chromosomes but they are not involved in reciprocal translocations. When these two *Oenotheras* are crossed the F_1 is not uniform as in normal Mendelian crosses, instead “twin hybrids” are formed. The maternally transmitted *gaudens* complex makes the hybrids normal in shape and color, whereas hybrids containing the maternally transmitted *velans* complex are pale and have narrow leaves. Thus, because of the two complexes, the F_1 is reminiscent of a testcross involving a pair of heterozygous alleles. In *Oenothera*, these complexes behave differently; some kill the male, others kill the female gametes, and yet others cause zygotic lethality in the homozygotes. Only the complex heterozygotes are found in the sporophytic plants. The light microscope identifies the multiple translocations as translocation rings. Such systems are common among *Oenothera* plants but occur also in other species. ▶translocations, ▶*gaudens*, ▶*Oenothera*, ▶beta complex, ▶zygotic lethal; Cleland 1972 *Oenothera*: Cytogenetics and Evolution, Academic Press, New York.

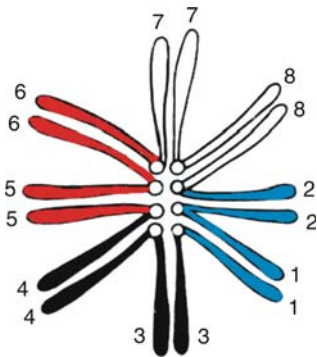


Figure C144. Chromosome pairing multiple translocations

Complex Inheritance: Complex inheritance occurs when multiple loci and interactions are involved in the expression of the gene products. N.E. Morton (Proc Natl Acad Sci USA 93:3471 [1996]) published parametric and non-parametric statistics for estimating linkage, by considering various such pedigrees. ▶polygenic inheritance, ▶multifactorial trait,

▶QTL, ▶complex trait; Zwick ME et al 2000 Annu Rev Genomics Hum Genet 1:387.

Complex Locus: A generally large cluster/complex of functionally related but not entirely similar cistrons and alleles within the locus may show partial complementation (*scute* in *Drosophila*, *t* in mouse, HLA and immunoglobulins in mammals, *R* in maize). Some of the complex loci appeared to be more mutable than other genes because unequal crossing over between the repeated sequences generated new phenotypes. ▶pseudoallelism, ▶allelic complementation, ▶step allelomorphism, ▶Bar, ▶operon; Carlson EA 1959 Quart Rev Biol 34:33; Demerec M et al 1955 Proc Natl Acad Sci USA 41:359.

Complex Promoter: The complex promoter contains—besides the usual promoter elements—an insertion element (e.g., Ty) with its own promoter situated within the long terminal repeat. As a consequence, transcription may initiate from the Ty promoter (δ) located within the interval between the TATA and the UAS sequence, and the transcript of the yeast gene involved may not be functional. The δ promoter also contains binding regulatory elements. ▶promoter, ▶Ty; Pilpel Y et al 2001 Nature Genet 29:153.

Complex Trait: The inheritance of a complex trait is not based on a single dominant or recessive allele but may involve multiple factors. Various environmental effects contribute to the expression of these factors. ▶QTL, ▶complex inheritance; Moore KJ, Nagle DL 2000 Annu Rev Genet 34:653; Glazier AM et al 2002 Science 298:2345; *Drosophila* as model for complex human traits and disease: Mackay TFC, Anholt RRH 2006 Annu Rev Genomics Hum Genet 7:339; <http://www.complextrait.org/>.

Complex Transcription Unit: The transcript of the gene may be processed in more than one way and the translated products vary according to cell- or tissue-specific functions.

Complexin: The proteins of the nerve termini, binding syntaxin. They regulate Ca^{2+} -dependent release of neurotransmitters. ▶syntaxin, ▶neurotransmitter, ▶synaptotagmin; Reim K et al 2001 Cell 104:71.

Complexity of DNA: The complexity of DNA indicates the size of the DNA molecule as determined from the c_0t curve. ▶ c_0t curve, ▶ $c_0t_{1/2}$, ▶kinetics, ▶kinetic complexity, ▶BLAST

Complexity of Function: Complexity can be defined as the number of metabolic steps required for biological function(s). Before different genomes had been sequenced, the assumption that the number of genes determines biological complexity appeared valid. In broad terms, this is still valid because the MS2 phage

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requires only 4 genes whereas the bacterium *E. coli* contains 4,288 protein-coding genes. However, the simple worm, *Caenorhabditis elegans*, has 18,424 genes, whereas the more complex fruit fly, *Drosophila melanogaster*, has only 13,601 and the small plant *Arabidopsis* about 25,498. Therefore, there must be a better way to define biological complexity. Since genes may be spliced in alternative manners, this feature of the genes may boost complexity. Also, the expression of not-housekeeping genes is highly regulated by the recruitment of specific transcription factors and effector proteins. There is apparently a great variety of ways in which, the different proteins can enter into complexes and single polypeptide chains may participate in several functionally different aggregates. Therefore, it appears that the cooperating (enhancing and inhibitory) networks have a major role in determining biological complexity. ▶microarray hybridization, ▶proteome; Szathmáry E et al 2001 Science 292:1315.

Compliant Mutation: Compliant mutation is readily identifiable by genetic testing and reveals the existence of certain risks for disease. ▶genetic testing

Complicon: The complex chromosomal translocation that commonly co-occurs with oncogenic transformation. ▶cancer; Zhu C et al 2002 Cell 109:811.

Composite Cross: In a composite cross, individuals of various genetic constitutions are hybridized in a mass for the purpose of studying the effect of natural selection or to obtain improved varieties.

Composite Promoter: ▶complex promoter

Composite Transposon: A composite transposon carries genes (e.g., antibiotic resistance) beyond those required for transposition. ▶transposon, ▶insertion element

Compound Chromosome: A compound chromosome is the result of the fusion of a telocentric chromosome into a bi-armed monocentric, or of Robertsonian translocation between acrocentric chromosomes, or of translocations, or of intrachromosomal transposition. ▶telocentric, ▶Robertsonian translocation,

▶translocation, ▶transposition, ▶compound X chromosome

Compound Eye: In Arthropods (insects), the eye is composed of several, each structurally complete, elements (ommatidium, about 800 in each eye of *Drosophila*) (see Fig. C145). ▶photo at right, ▶ommatidium, ▶*Drosophila*, ▶CIB

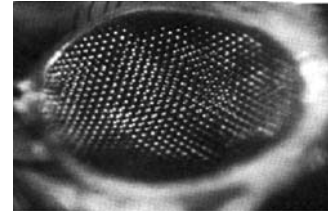


Figure C145. Compound eye

Compound, Genetic: A genetic compound is a heterozygote for 2 mutant alleles of the same gene and may display a phenotype that is intermediate between those of the 2 recessive homozygotes. The loci may be in cis or trans position. ▶cis

Compound Heterozygote: A compound heterozygote carries different (defective) alleles at the same gene locus.

Compound Leaf: The compound leaf is composed of several leaflets (see Fig. C146).



Figure C146. Compound leaf

Compound X Chromosome: In a compound X chromosome, two X chromosomes are fused to the same centromere (see Fig. C147). E. Novitski distinguished the following six types: (i) reversed metacentric or attached X (RM), (ii) reversed acrocentric or double X (RA), (iii) reversed ring (RR), (iv) tandem

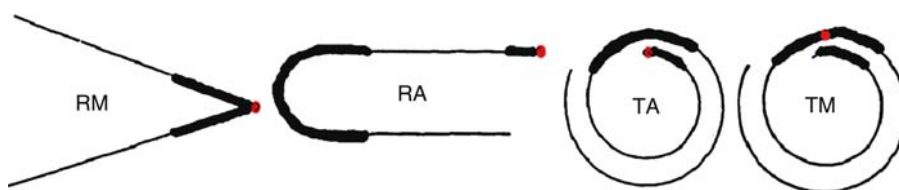


Figure C147. Compound X-chromosomes of *Drosophila*. The heavy lines represent heterochromatic regions; centromeres are red

metacentric or tandem attached X (TM), (v) tandem acrocentric (TA), (vi) tandem ring (TR). (See Novitski E 1954 Genetics 39:127).

Compressions in Gels: In DNA sequencing gels, abnormal intra-strand structures may form and cause anomalous pattern of migration, especially in DNAs with high G + C content. The compression may be avoided by using another DNA polymerase or by 2'-deoxyinosine-5'-triphosphate or 7-deaza-2'-deoxyguanosine-5'-triphosphate. ▶DNA sequencing, ▶deaza-nucleotides, ▶base-calling; Bowling JM et al 1991 Nucleic Acids Res 19:3089.

Compton Effect: According to the Compton effect, as the energy of electromagnetic radiation increases above 0.5 MeV, the radiation of electrons may scatter and recoil depending on the surface hit and the angle of the incidence of the radiation. This may affect the effective dose absorbed by the object and may create hazards if the source is not protected in all directions. ▶X-ray, ▶cathode rays, ▶MeV; van't Veld AA et al 2001 Med Phys 28:738.

Computer Terms (Webopedia): The online dictionary of computers: <http://www.webopedia.com/>.

Computerization of DNA and Protein Sequence Data:

The information of DNA sequences must be entered in a computer file. For proper handling, there may be a need for a *sequence manipulator* that is included with the software. Some programs have an audio feature (e.g. SeqSpeak) that spell out the data as entered. The data entered should be saved in "text files" or ASCII (American standard code for information exchange). The files are supposed to contain the relevant laboratory identification as well. Various software packages use different formats. If the quality of the sequencing gel is good, digitizing pads permit reading the sequence information directly from the autoradiogram. Automated gel readers are available commercially. When a multiplex method is used, a known sequence can be incorporated as an internal standard along with the gel. Automated DNA sequencers use special fluorochrome-tagged primers and no manual work is required for the entire operation. The automated scanners may be equipped with editing features so if a mistake is made it can be manually corrected. To minimize sequencing errors, generally both strands are sequenced and that too, more than once. Also the reading may need to be repeated. Homology Searching can automatically align the data for comparisons. The sequencing programs usually include a means to predict the presumable collinear amino acid sequence of the open reading frames. Programs may detect fragment sequence overlaps in order to generate contigs. The contigs can then be compared with restriction maps, if

available. Some available programs may generate graphic restriction maps. For the identification of functional regions, the detection of repeats, stem-loop structures in DNA or RNA may be used. The GC/AT content may reveal Z DNA or bent DNA structures.

Some programs assist in the identification of likely secondary structures (stem-loop) and folding of the RNA, including base stacking. Programs exist for the design of PCR primers. Gene families with related functions could be revealed by the use of degenerate oligonucleotide probes.

In order to identify protein-coding tracts, each strand is translated in 3 reading frames (6 all together) to obtain a contiguous, uninterrupted open reading frame (ORF). It may be difficult to reveal the possible splice sites, although various programs have this goal. A scoring matrix that quantitates the amino acid changes per 100 amino acids detects evolutionary changes in protein sequences.

The Basic Local Alignment Search Tool (BLAST) permits homology searches even through the Internet. FASTA serves similar purpose through e-mail. Helpful publications and software sources are listed in Ausubel FM et al (eds) 1999 Short Protocols in Molecular Biology. Wiley, New York. ▶proteomics

Conalbumin: An egg white iron-binding protein, encoded by a gene with 17 introns and regulated by estrogen and progesterone.

c-onc (cellular oncogene): A normal gene that loses its ability to limit cell divisions and then initiates cancerous growth. ▶v-oncogene

Concanavalins: Agglutinin proteins, which preferentially agglutinate cancer cells, used also as probes for cell surface membrane dynamics. Concanavalins are also mitogenic. ▶lectins, ▶cell adhesion, ▶mitogen; Wallach DF, Schmidt-Ullrich R 1976 J Cell Physiol 89:771.

Concatamer: Concatamers are repeated phage genomes associated in a linear array of DNA molecules in a head-to-tail fashion, formed during normal replication, and they must be cut to head capacity size for packaging into the capsid by a terminase gene product (endonuclease). ▶headful rule, ▶permuted redundancy, ▶non-permuted redundancy, ▶lambda phage, ▶catenane; O'Donnell R et al 2001 Nucleic Acids Res 29:716.

Concatenane: Interlocked DNA rings or chains (see Fig. C148). ▶knotted DNA



Figure C148. Concatenane

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Conceptacle: A cavity in the fern leaves (fronds) bearing gametangia. ► [gametangia](#)

Conception: ► [fertility](#), ► [fertilization](#), ► [sex hormones](#), ► [hormone receptors](#)

Conceptus (plural concepti): A fertilized egg during its entire development including embryo, and fetus stages, and the extra-embryonic membranes until birth.

Concerted Evolution: In concerted evolution, copies of redundant DNA sequences are rather well conserved in the genomes, although one would have expected divergence by repeated mutations. Ribosomal RNA genes and hemoglobin genes are good examples of concerted evolution (Zimmer EA et al 1980 Proc Natl Acad Sci USA 77:2158); although some exceptions exist (Rooney AP, Ward TJ 2005 Proc Natl Acad Sci USA 102:5084). *Intragenic concerted evolution* may exert more mutational and recombinational pressure on internally repetitive exons of a gene than on the introns. Exons are crucial for the function of the protein product of the gene. As a consequence, extensive homology is observed within species and little homology between related species (such as found in intergenic spacer nucleotides and LINEs). An alternative theory for concerted evolution is the *birth-and-death* evolution, indicating that members of co-evolving genes are lost or new ones emerge, in a dynamic manner. ► [molecular drive](#), ► [LINE](#); Liao D 2000 J Mol Evol 51:305; Gao L-z, Innan H 2004 Science 306:1367; Nei M, Rooney AP 2005 Annu Rev Genet 39:121.

Concordance: The identity of traits within twins or groups of individuals. Among monozygotic twins, the concordance is expected to be ~100%, whereas among dizygotic twins it is between 25 to 50%. Lower concordance is an indication of (substantial) environmental contribution to the phenotype. ► [discordance](#), ► [twinning](#), ► [zygosis](#), ► [monozygotic twins](#), ► [dizygotic twins](#), ► [penetrance](#), ► [expressivity](#), ► [adopted children](#)

Concurrent Control: In an experiment involving certain type of treatment, it is required that an adequate group of untreated individuals will be studied *simultaneously* to permit a reliable comparison and assessment of the effect of the treatment. ► [control](#), ► [historical control](#)

Condensation Reaction: In a condensation reaction, water is released as a byproduct during the formation of a covalent bond.

Condensin: A complex of five protein subunits involved in chromosome condensation in the presence of topoisomerase I during mitosis in association with XCAP-C and XCAP-E. Condensin is activated by phosphorylation using Cdc2 kinase and ATP as phosphate donor. There exist two condensins, I and II and their functions are not entirely overlapping. Aurora B phosphorylates Ser10 on Histone H3 in chromosomal binding of condensin I and in mitotic chromosome condensation (Takemoto A et al 2007 Nucleic Acids Res 35:2403). ► [cohesin](#), ► [XCAP](#), ► [mitosis](#), ► [Cdc2](#), ► [Aurora](#), ► [ATP](#), ► [topoisomerase](#), ► [SMC](#), ► [sister chromatids](#), ► [Mosolov model](#); Hirano T 2000 Annu Rev Biochem 69:115; Kimura K et al 2001 J Biol Chem 276:5417; Kirsten A et al 2003 Nature Rev Genet 4:520; quantitative method to monitor chromosome condensation kinetics in living cells expressing GFP fused to a core histone: Maddox PS et al 2006 Proc Natl Acad Sci USA 103:15097.

Conditional Distribution: In conditional distribution, the distribution of one random variable or the joint distribution of several variables is affected by holding one variable at a fixed value.

Conditional Dominance: ► [dominance reversal](#)

Conditional Lethal: dies under certain conditions (e.g., high, nonpermissive [restrictive] temperature), but is viable under others (e.g., low, permissive temperature). Many auxotrophs are conditional lethal because they survive only when the required nutrient is provided. ► [temperature-sensitive mutation](#), ► [auxotroph](#), ► [conditional mutation](#)

Conditional Mutation: A conditional mutation is expressed only under the condition(s) required. Such mutations may be extremely useful for the study of conditional lethal genes. Conditional expression may also be regulated by agents that affect transcription and/or translation or conformation of the proteins (heat-shock, heavy metals, hormones, repressors, DNA-binding proteins, dimerization of transactivator, signal transduction, etc.). ► [conditional lethal mutation](#), ► [temperature-sensitive mutation](#), ► [auxotrophs](#), ► [and other terms mentioned under separate entries](#); Lewandoski M 2001 Nature Rev Genet 2:743; Genesis vol. 32:49–191 [2002]; Gossen M, Bujard H 2002 Annu Rev Genet 36:153.

Conditional Probability: Conditional probability is not based on absolute frequencies but, e.g., one group is fixed in a matrix. When we have three genotypes AA, Aa and aa, their frequencies add up to one. If one of the groups is fixed then another must be one of the two genotypes. In other words, probability depends

on what events have already taken place. ►Bayes' theorem, ►risk

Conditional Targeting: A gene targeting procedure aimed either at specific tissues or developmental stages or at both. ►targeting genes, ►knock-out, ►knock-in, ►knockdown

Conditionally Dispensable Chromosomes: Same as B chromosomes.

Condom: A rubber shield worn over the penis during sexual intercourse. It prevents pregnancy and also protects both partners from sexually transmitted disease. The effectiveness is not perfect and the failure of protection has been estimated to be 10–20% (Steiner MJ et al 2006 New England J Med 354:2642). The incidence of genital human papilloma virus was 37.8% per-patient years for constant condom use versus 89.3% when in 5% of the time condom was not used (Winer RL et al 2006 New England J Med 354:2645). ►contraceptive, ►papilloma virus

Conductance: In conductance, a non-conjugative plasmid can be transmitted to a recipient cell by cointegration into a mobile, conjugative plasmid. ►plasmid, ►conjugation, ►cointegration

Conductin: An 840-amino acid protein equipped with a β -catenin-, a RGS- (regulator of G protein signaling) and a glycogen synthase kinase-3 β -binding domains. This complex interacts also with various fragments of APC (adenomatous polyposis) tumor suppressor protein. Conductin contributes to the degradation of β -catenin, whereas APC interferes with this degradation. Conductin is homologous to axin and it also capable of similar functions. ►axin, ►catenin, ►RGS, ►adenomatous polyposis, ►GSK; Siderovski DP et al 1999 Crit Rev Biochem Mol Biol 34:215.

Cone: A fruiting structure bearing sporangia, e.g., a pinecone. ►sporangium). Also the retinal cone in the eye is a visual cell. ►retinitis pigmentosa, ►retinoblastoma, ►ommatidium

Cone Dystrophy: A group of dominant diseases involving loss of color vision, photophobia, and reduced central vision acuity occurring at a frequency of $\sim 1 \times 10^{-4}$. Responsible genes have been assigned to 17p12-p13, 6q25-q26, 6p21.1 and Xp21.1-p11.3. The 6p21.1 mutations involve the guanylate cyclase-activating protein. ►ABC transporter; Wilkie SE et al 2001 Am J Hum Genet 69:471.

Cone Pigments: Cone pigments are present in the retina and mediate color vision. ►cone

Cone-Rod Dystrophy: ►ABC transporters

Confidence Intervals: Population parameters can be estimated by *point estimates* and by *interval estimates*. The former specifies the parameter itself; the latter defines the range of values within which, the parameter is expected at a certain level of confidence (probability). If we obtain an average value in a population, we would like to know the range of probability within which, the real, true average might fluctuate by 95% or other confidence of choice. Confidence intervals (C.I.) for reasonably large populations can be determined with the formula: $C.I. = p \pm z \sqrt{pq/n}$ where p and q are the proportions observed ($p + q = 1$), z is the critical value for the normal distribution at a given level of confidence. $z = 1.96$ (for 95%), 2.58 (for 99%), and 3.29 (for 99.9%); it is not very useful to go for even higher z values because then the range will be so wide that it will become almost meaningless. n = the number in the population counted or measured. Example: a population of 140 consists of 2 groups represented by 60 ($p = 60/140 \approx 0.43$) and 80 ($q = 80/140 \approx 0.57$). C.I. for $p = 0.43 \pm 1.96 = 0.43 \pm 1.96 \times 0.04184 = 0.43 \pm 0.08$. Therefore, the frequencies and 0.51 and 0.35 are the 95% confidence limits of the experimentally observed p . Example: a population of 140 consists of two groups represented by 60 ($p = 60/140 \approx 0.43$) and 80 ($q = 80/140 \approx 0.57$). C.I. for $p = 0.43 \pm 1.96 \sqrt{(0.43)(0.57)/140} = 0.43 \pm 1.96 \times 0.04184 = 0.43 \pm 0.08$. Therefore the frequencies and 0.51 and 0.35 are the 95% confidence limits of the experimentally observed p .

Alternatively, the 95% confidence belts can be used. (see Fig. C149); ►inference statistical, ►credible interval

Confidentiality: The code of ethics and many state laws in the US prohibit physicians from disclosing any medical information to a third party, even in court. Some courts permit disclosure if the third party is in imminent danger by a genetic or an infectious disease. ►genetic privacy, ►privacy rules, ►wrongful life, ►counseling genetic, ►paternity test, ►informed consent, ►bioethics; Cohen PE, Wolpert C 1998 In: Haines JL, Pericak-Vance MA (eds) Approches to Gene Mapping in Complex Human Diseases. Wiley, New York, p. 131.

Conflict, Evolutionary: In an evolutionary conflict, the spread of an allele lowers the fitness of the individual or its progeny. In some cases, one allele may be advantageous in one sex but disadvantageous in the other. To neutralize its effect, suppressor genes may evolve. ►meiotic drive

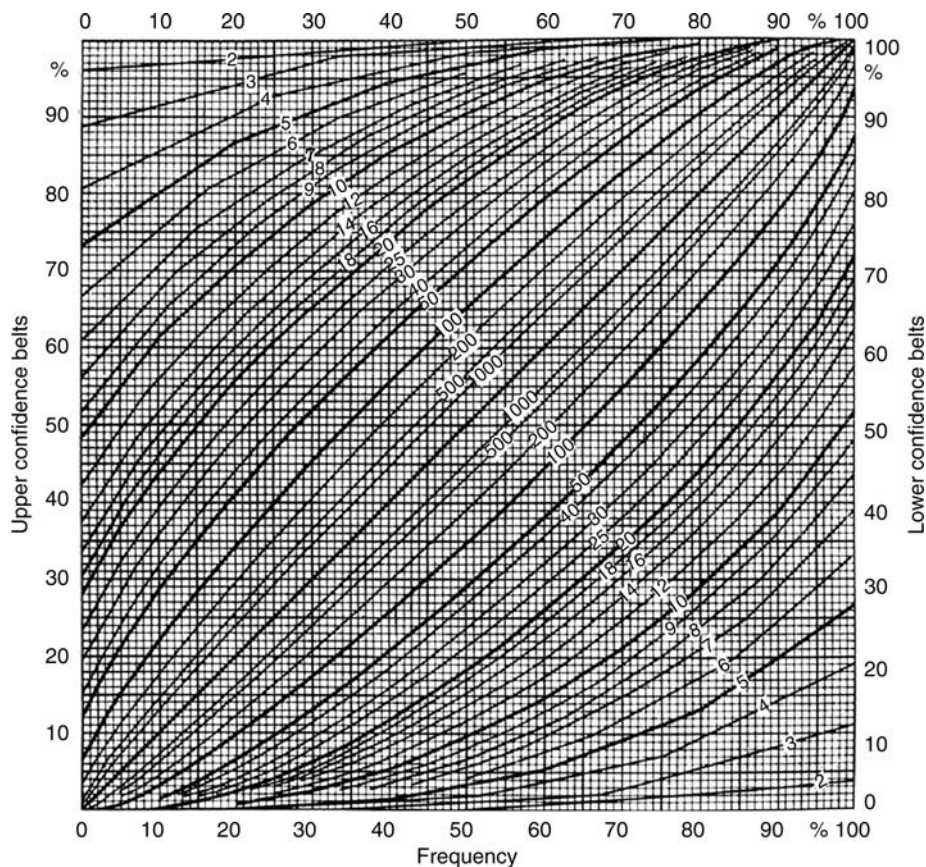


Figure C149. Confidence intervals. Use of the confidence chart: Calculate from the experimental data the frequencies p and q . At the intersections of the vertical line corresponding to “frequency” and the 2 belts (curves) numbered and indicating the size of the sample (population), one can read the percentage of upper and lower confidence. This chart also facilitates an estimate of the (1) repeatability of the fractions obtained, (2) the statistical range of the fractions, and (3) the size of the population where a chosen fraction will be represented by a number of individuals (counts) within the specified range. E.g., the frequency observed is 0.20. The confidence limits at probability 0.95 for a population of 100 will be 29 and 12. Or if the expected frequency is 0.25 and one is willing to accept a latitude of 10% (i.e. a frequency between 0.20 and 0.30), the minimum population size required is 200 at $P = 0.95$ because this latitude is bracketed by the 200 belts. (From Koller S 1956 In: Rauen HM (ed) *Biochem. Taschenbuch*, Springer-Vlg., Berlin)

Confluent: The cell culture that extends over the entire surface of the medium.

Confocal Microscopy: Confocal microscopy permits the formation of a three-dimensional image by focusing laser or other light through a pinhole and with a dichroic mirror to a distinct small area of the object. The fluorescent light emitted from that small focal point is then reflected through another (confocal) pinhole (i.e., this second pinhole is exactly in the focus of that area of the object) and thus a sharp image is received on a detector. The images of the areas not in focus are thus obliterated. Subsequently, the light is focused at several other points and the image of each point is registered on the video screen, thus building

up a three-dimensional integrated picture. If the pinholes are moved in a synchronous manner, a scanning real-time imaging can be obtained. ▶ [microscopy](#)

Conformation: An arrangement of a molecule in space that does not require the severance of any bond because of their freedom of rotation. Point mutations and sequence rearrangements do not substantially alter the original conformation. It has been shown, however, that the nucleotide sequences in the DNA d(CCXGGGACCGG) and d(CCGGTACCGG) crystallize as 4-stranded Holliday junctions. From the 64 permutations of the sequence d(CCnnnN₆N₇N₈GG), evidence was found for B-DNA, A-DNA and

Holliday junctions. ($N_6N_7N_8$ stand for any of the four natural nucleotides and *nnn* are specified to maintain self-complementarity in the sequence, complying with Watson & Crick base pairing). This finding indicates that significant conformational changes result from sequence variations and not from crystal or crystallization effects (Hays FA et al 2005 Proc Natl Acad Sci USA 102:7157). RNAs also fold in special conformation and the native structure is stabilized by peripheral elements tightly bound to the core they surround (Johnson TH et al 2005 Proc Natl Acad Sci USA 102:10176). ►folding, ►chaperone, ►protein structure, ►protein folding, ►morphoein, ►porphyria; Sinha N, Nussinov R 2001 Proc Natl Acad Sci USA 98:3139; conformational changes: <http://molmovdb.org/>.

Conformation Correction: Multimeric proteins may be inactivated by mutation in a subunit that affects the conformation of that polypeptide chain. Another mutation may alter the conformation of another subunit in such a way that the first defect in conformation is corrected and the activity of the enzyme is at least partially restored. It was assumed that some allelic complementation observed is based on such a correction. ►dominant negative, ►allelic complementation; Soto C 2001 FEBS Lett 498:204.

Conformational Diversity: Through conformational diversity, the protein would have the ability to assume more than one conformation, which may enable rapid evolution. ►promiscuous protein; James LC, Tawfik DS 2003 Trends Biochem Sci 28:361.

Conformation-Dependent Immunoassay: The conformation-dependent immunoassay distinguishes between PrP^C and PrP^{Sc} on the basis that a specific epitope is exposed on the surface of the normal prion, but it is hidden in the infectious PrP^{Sc} isoform. It can be used with both the protease-sensitive and the protease-resistant PrP^{Sc} because proteolysis is not required for the assay. ►prion, ►immunoassay

Conformation-Sensitive Gel Electrophoresis (CSGE): CSGE distinguishes DNA segments heterozygous for different sites at a gene. In homozygotes, only a single type of band is formed in the gel, e.g., AB (homoduplex). In heterozygotes, Ab, aB (heteroduplexes) and AA and BB (homoduplexes) are expected.

Confounding: Confounding is the omitting of a particular experimental comparison in order to reduce the error variation. In a factorial design, some, interactive elements are not distinguishable alone but only in combination. Confounding occurs also when the consequence of a specific experimental exposure or genetic condition is not distinguishable from the

effects of other variables that affect the outcome of the treatment. ►factorial experiment

Congeneic: Same as congenic; it is frequently used this way in immunogenetics.

Congener: The term congener refers to an organism/organic substance related to something by origin and/or function, biologically or chemically; or to species belonging to the same genus.

Congenic Resistant Lines of Mice (CR): CR contain a new histocompatibility gene locus introduced from another inbred (or any other) line. Earlier these were called IR (isogenic resistant) lines. Mating inbred line #1 with known histoincompatible line #2 generates such CR lines. The hybrid accepts grafts of #1. In the progeny of hybrids mated inter se, some segregants do not reject transplants of #1. These will be further backcrossed with #1. After 7 backcrosses the "hybrid" will have in over 99% ($1-0.5^7$), the same chromosomes as parent #1.

Upon continued brother-sister matings (usually for 20 generations), an individual may show up that rejects grafts from #1. This is further backcrossed to #1 and the progeny will be selected to resistance against transplants to #1. Such a line is congenic resistant, i. e., almost identical (with the exception of histocompatibility gene) with #1. Some very closely linked genes to the histoincompatibility locus of #2 may not be eliminated, however, from the CR line. Today, the selection may be facilitated by serological assays rather than by expensive transplantation experiments. Also, the desired genes can be transferred by transfection without the need of repeated backcrosses. The development of a large number of CR lines permit the identification of allelism and complementation groups of histocompatibility genes. The serological assays permit the identification of strong and weaker responses, and on this basis major and minor histocompatibility genes can be classified. ►HLA, ►MHC; Fortin A et al 2001 Proc Natl Acad Sci USA 98:10793.

Congenic Strains: Congenic strains are identical, except at one locus or in a very limited region of a chromosome; they are obtained by repeated (10–20) backcrosses. These lines can be used to determine the effect of a particular gene on a selected genetic background. Using eggs obtained by hormone-induced superovulation of prepubertal (three weeks old) mice and in vitro fertilization followed by embryo transfer, the generation time can be shortened to 6 weeks and within a year the desired results may be obtained. ►congenic resistant lines of mouse, ►coisogenic, ►isogenic, ►inbreeding, ►ART, ►substrain, ►subline

Congenital: A congenital condition is a condition one is born with, regardless of whether it is due to direct genetic or developmental causes. ▶familial, ▶hereditary

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Congenital Adrenal Hyperplasia: Congenital adrenal hyperplasia has a prevalence of about 0.0002–0.0001 but in some populations it may occur in a higher frequency. It is based on the deficiency of an enzyme in cortisol (steroid) biosynthesis. The accumulation of the precursor results in virilization of female babies. The condition can be successfully treated by glucocorticoids given to the mother. The autosomal recessive gene(s) are closely linked to the HLA loci in human chromosome 6. Prenatal identification is feasible by linkage with appropriate DNA probes. There are, however, other types of steroid hydroxylase deficiencies encoded in other chromosomes. ▶genetic screening, ▶cortisol, ▶glucocorticoid, ▶HLA, ▶adrenal hypoplasia, ▶adrenal hyperplasia congenital

Congenital Biplasic Aplasia of the Vas Deferens (CBAVD): An autosomal recessive absence of the excretory channel(s) of the testes resulting in azoospermia. ▶azoospermia, ▶cystic fibrosis, ▶vas deferens, ▶P2X

Congenital Disorders of Glycosylation (CDG): CDG Type Ib (15q22-ter) is a defect in mannosephosphate isomerase, and Type Ia (16p13.3-p13.2) is a defect of phosphomanno-mutase-2. The basic problem is the unsatisfactory glycosylation of glycoproteins. The clinical consequences are neurological defects, blood coagulation problems, eye malformations, heart and kidney disease, abnormal transferrin, etc. The symptoms in the Type Ib disease can be alleviated by mannose. Type Ic (1p22.3) is an abnormality in the transfer of glucose to lipid-linked oligosaccharides. Several other variants have also been distinguished.

Congenital Hypothyroidism: The defective development of the thyroid gland causing goiter, mental retardation, deafness, etc. because of deficiency of the thyroid hormone. ▶goiter

Congenital Trait: A trait that is evident at birth and is due to either hereditary or other causes. ▶familial trait

Congression: The assembly of chromosomes in the metaphase plane (see Fig. C150). Septin protein scaffold is required for congression, orderly segregation, and cytokinesis (Spilotis ET et al 2005 Science 307:1781). Mammalian chromosomes can congress to the equator without being connected to the spindle fibers, although that is generally required for proper orientation (biorientation) so the chromosomes

would be properly distributed toward the poles (Kapoor TM et al 2006 Science 311:388). ▶septins, ▶cytokinesis, ▶mitosis, ▶meiosis



Figure C150. Congression. (Photomicrograph is the courtesy of Dr. Arnold Sparrow)

Congruence Analysis: The congruence analysis tests the appropriateness of conclusions reached by different methods in the study of evolutionary trees. ▶homology, ▶xenology

Congruency: Congruency in a genetic or metabolic network indicates the measure of partner sharing.

Congruent Genes: Genes that share sequences in the chromosome.

Conidia (conidiospores; in singular conidium): Asexual, uninucleate fungal spores that appear externally on a hypha by abstriction. Such a hypha is a conidiophore. ▶macroconidia, ▶microconidia, ▶fungal life cycle; Kellner EM, Adams TH 2002 Genetics 160:159.

Conidiophore: (see Fig. C151). ▶conidia

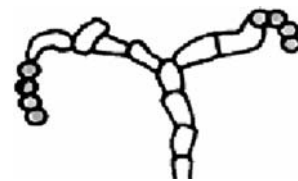


Figure C151. Conidiophore

Conjugate Redox Pair: An electron donor and the corresponding electron acceptor, e.g., NADH and NAD⁺.

Conjugated Protein: A conjugated protein contains prosthetic group(s); e.g., an iron or magnesium heme in hemoglobin and chlorophyll, respectively.

Conjugation, Bacterial: Conjugation generally means mating. In bacteria, conjugation is the physical contact between F⁺ donor and F⁻ recipient cell and the unidirectional transfer of the (Hfr) chromosome

by a rolling circle replication procedure through the conjugation tube (see Fig. C152). Approximately 12 μ m DNA is transferred per minute. The standard genetic map of bacteria is based on the time in minutes required for the conjugational transfer of genes from donor to recipient.

The conjugational transfer may be clockwise or counter-clockwise depending on the orientation of the (Hfr) element in the bacterial chromosome (see Fig. C153).

The transmission of plasmids from one cell to another requires a conjugational mechanism. Conjugation requires cellular contact, controlled by the mating pair formation system (Mpf). In *Agrobacteria*, besides the T-DNA, multisubunit protein complexes are also transmitted to the eukaryotic cell. The Tra and Mpf proteins organize the conjugative pilus. The transforming plasmids that generally lack the *mob* gene required for mobilization of chromosome (genophore) or plasmid are unable to form recombinant

DNA. For some of the plasmids, the mobilization factor can be provided in trans by a helper plasmid (ColK). Col plasmids code for a protein that opens up the circular DNA at the *nic* site close to *bom* (bacterial origin of mobilization). Some plasmids lack the *nic/bom* system and cannot be transferred through conjugation (non-conjugative plasmids). The latter type is favored for containment of recombinants. In the majority of bacteria conjugation is not a standard mode of reproduction, unlike in true sexual organisms. Recent reexamination of the data indicates linkage disequilibrium in bacterial populations.

In *Mycobacterium smegmatis*, the conjugal transfer is mediated by the chromosome rather than by an F plasmid (Wang J et al 2003 Nature Genet 34:80).

Using the RK2 plasmid system, bacterial DNA can be transferred to yeast cells as well as to Chinese hamster ovary cells (Waters VL 2001 Nature Genet 29:375). ▶Hfr, ▶conjugational mapping, ▶bacterial recombination frequency, ▶relaxosome, ▶*ori_T*, ▶*tra* genes, ▶pilus, ▶non-plasmid conjugation, ▶Fplasmid, ▶linkage disequilibrium, diagram of bacterial conjugation, ▶RK2 plasmid, ▶CHO, ▶conjugation *Paramecia*; Ippen-Ihler KA, Minkley EG Jr 1986 Annu Rev Genet 20:593; Frost LS et al 1994 Microbiol Rev 58:162; Lanka E, Wilkins BM 1995 Annu Rev Biochem 64:141; Matson SW et al 2001 J Biol Chem 276:2372; Frost LS et al 2005 Nature Rev Microbiol 3:722; Christie PJ et al 2005 Annu Rev Microbiol 59:451.

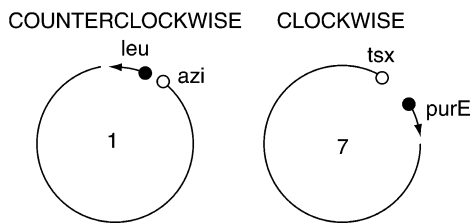


Figure C152. Conjugational transfer

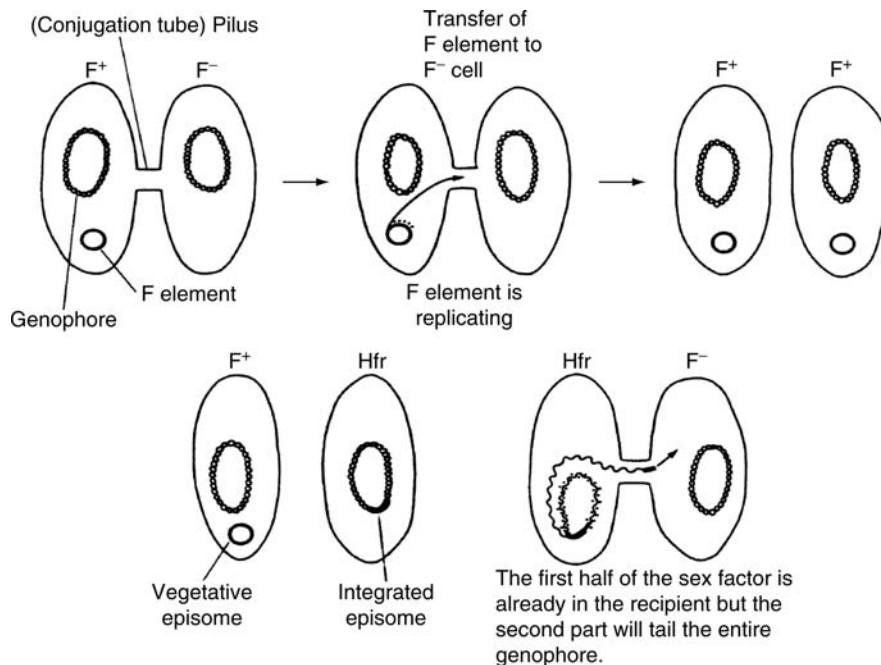


Figure C153. Conjugational transfer

| Markers: | <i>thr</i> | <i>leu</i> | <i>azi</i> | <i>T1</i> | <i>lac</i> | <i>T6</i> | <i>gal</i> | λ | <i>21</i> | <i>424</i> |
|-------------------------|------------|------------|------------|-----------|------------|-----------|------------|-----------|-----------|------------|
| <i>Hfr</i> transfer (%) | | | >90 | 70 | 40 | 35 | 25 | 15 | 10 | 3 |
| Minutes | 8 | 8½ | 9 | 11 | 18 | 20 | 24 | 26 | 35 | 72 |

(On the basis of F. Jacob, and E. L. Wollman, 1961. Sexuality and Genetics of Bacteria. Academic Press, New York.

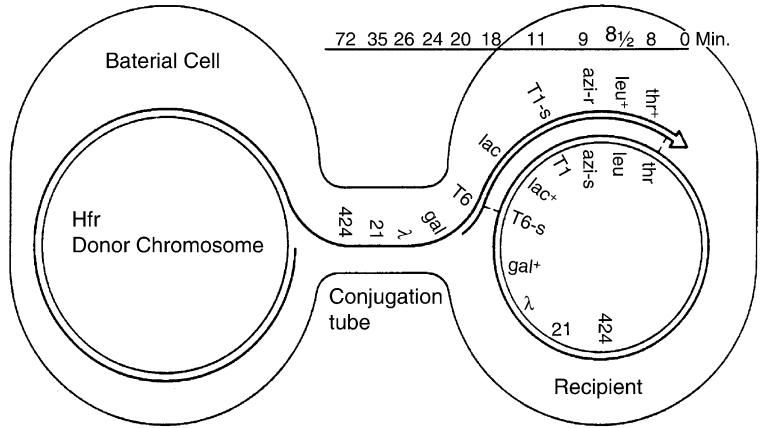


Figure C154. Conjugation mapping

Conjugation Mapping: The transfer and integration of genes of the Hfr chromosome to the recipient in bacteria is measured by interrupted mating and the map is constructed on the basis of minutes required for the linear transfer of a particular marker(s). For the complete transfer ca. 90–100 minutes are required (40–45 kb/2–3 minute intervals). By conjugational recombination, the complementary products of the exchange are not recovered, and the surviving products are the results of double recombination. The single strand transferred becomes double-stranded after entering the recipient (F⁻) cell. (See Fig. C154, ►Hfr, ►conjugation, ►bacterial recombination frequencies, ►F plasmid, ►conjugation bacterial; Jacob F, Wollman EL 1961 Sexuality and the Genetics of Bacteria. Academic Press, New York).

Conjugation, Paramecia: Conjugation in paramecia is the sexual reproduction of these unicellular protozoa that most commonly reproduce asexually by fission (see Fig. C155). During conjugation, two cells of

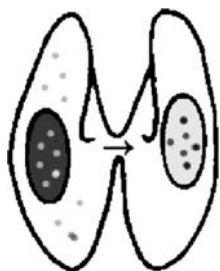


Figure C155. Conjugation, *Paramecia*

opposite mating types appose and meiosis gets underway in the micronuclei. From the four meiotic products, only one survives in both cells and that divides twice by mitosis generating four haploid nuclei in the two cells, each. One of the gametes is then passed over to the other cell through a conjugation bridge in a reciprocal manner, resulting in mutual fertilization and in two diploid conjugants. Subsequently, the pair separates and, *exconjugants* are formed. The macronucleus has only metabolic but no known genetic role and it disintegrates in both cells. Subsequently, the diploid micronucleus undergoes two mitotic divisions, and two of the four mitotic products fuse to regenerate the macronucleus. The remaining two nuclei form diploid micronuclei. *Paramecia* may reproduce also by *autogamy* in the absence of conjugation. Meiosis may take place and four haploid nuclei arise from which again only one survives. The survivor divides again into two, which after fusion generate a diploid homozygote. If the conjugation lasts for longer periods, cytoplasmic elements are also transferred along with the gametes. ►*Paramecium*; Preer JR 1971 Annu Rev Genet 5:361.

Conjugation Tube: ►pilus, ►conjugation bacterial, ►mating bacterial

Conjugative Plasmids: ►conjugation of bacteria, ►plasmid

Connectin: Same as titin. ►titin

Connection Maps: ►genetic networks, ►signal transduction

Connective Tissue Disorders: Connective tissue disorders involve cells with substantial extracellular matrix, which provides structural support, such as bone, cartilage, etc. In the majority of disorders, collagen synthesis is affected. ▶[skin diseases](#), ▶[osteogenesis imperfecta](#), ▶[collagen](#), ▶[Marfan syndrome](#), ▶[Ehlers-Danlos syndrome](#), ▶[Stickler syndrome](#), ▶[Kniest dysplasia](#), ▶[arthritis](#), ▶[Reiter syndrome](#), ▶[pseudoxanthoma elasticum](#), ▶[lupus erythematosus](#), ▶[HLA](#), ▶[autoimmune disease](#)

Connective Tissue Growth Factor (CTGF, 6q23.1): CTGF is a 38-kDa secreted protein, encoded in the vicinity of c-Myc proto-oncogene and it has some homology to insulin-like growth factor. It is required for growth and development, but its upregulation may contribute to tumorigenesis. ▶[angiogenesis](#); Bradham DM et al 1991 J Cell Biol 114:1285.

Connectivity Map: The connectivity map represents gene expression profiles as affected by small molecules (drugs) and diseases (Lamb J et al 2006 Science 313:1929). It can shed light on the mechanisms of action of certain drugs and the responses of physiological processes (diseases) to various treatments.

Connexins: Connexins provide elements of gap junctions; they are built of six polypeptides. All connexins have four membrane-spanning domains, two extracellular loops, a cytoplasmic loop and cytoplasmic amino and carboxyl termini. Connexins may form connexons, the pore of gap junctions. Connexins may have role in heart diseases, infertility, cataracts, deafness, heterotaxy, etc. Mutations in mouse genes coding for connexin26 (Cx26, in human chromosome 13q11-q120) and/or Cx30 (human chromosome 13q12) are linked to approximately half of all cases of human autosomal nonsyndromic prelingual deafness. Cx26 and Cx30 are the two major Cx isoforms found in the cochlea, and they co-assemble to form hybrid (heteromeric and heterotypic) gap junctions. In the absence of the Cx30 gene, Cx26 expressed from extra alleles was found to completely restore hearing sensitivity and prevented hair cell death in deaf Cx30^{-/-} mice. Up-regulation of Cx26 or slowing down its protein degradation might be a therapeutic strategy to prevent and treat deafness caused by Cx30 mutations (Ahmad S et al 2007 Proc Natl Acad Sci USA 104:1337). Connexins are encoded in human chromosomes 1p35, 6q21-q23.2, 13q11, and Xq13.1. ▶[gap junctions](#), ▶[innexins](#), ▶[deafness](#), ▶[erythrokeratoderma variabilis](#), ▶[ectodermal dysplasia](#), ▶[cataracts](#), ▶[Charcot-Marie-Tooth disease](#), ▶[oculodentodigital dysplasia](#); Kelsell DP 2001 Trends Cell

Biol 11:2; Abrams CK et al 2006 Proc Natl Acad Sci USA 103:5213.

Connexon: ▶[connexins](#)

Conplastic: A conplastic strain has the mitochondrial genome of one strain but the nuclear genome is derived from another. Conplastic strains are obtained by at least ten backcrossing of a female by a nuclear genome donor male. The probability that the nuclear genome is of the donor type is $1-0.5^n$, n = number of backcrosses. ▶[mtDNA](#), ▶[mitochondrial genetics](#), ▶[chloroplast genetics](#)

Conradi-Hünemann Disease: ▶[chondrodysplasia](#), ▶[CHILD syndrome](#)

Consanguinity: ▶[coefficient of coancestry](#), ▶[inbreeding coefficient](#), ▶[genetic counseling](#)

Consciousness: Awareness, sensory discrimination of events in the outside world and the body. Consciousness as a field of scientific inquiry evolved from moral, ethical, and religious notions of the ability and choice between right and wrong. Currently science makes efforts to understand the basic mechanisms how the wiring of the nervous system and the concomitant physiological/molecular functions control consciousness. Unfortunately, neurophysiology does not yet have entirely adequate tools to tackle many of the problems involved. Much progress, however, is underway. (See Crick FC, Koch C 2005 Philos Trans Roy Soc Lond B Biol Sci 360:1271).

Consed: One of the frequently used DNA sequence alignment/editing programs. ▶[PHRED](#), ▶[PHRAP](#), ▶[PolyPhrap](#); Rieder MJ et al 1998 Nucleic Acid Res 26:967.

Consensus: Consensus is the existence of basically common (although generally not entirely identical) nucleotide sequence at certain positions among some DNAs or amino acids in proteins. Consensus is indicative of a common functionally important role such as the TATA box, transcription termination signals, etc. On the basis of the organization of consensus sequences, consensus maps may be constructed indicating phylogenetic relationships. ▶[core sequences](#), ▶[CCDS](#)

Conservation Genetics: Conservation genetics is concerned with the population genetics principles involved in the maintenance of feral species. The maintenance of the populations depends on inbreeding, outbreeding, effective population size, deleterious mutation, reproductive success, adaptation to captivity, reintroduction, vagility, outbreeding depression, extinction, etc. (See ▶[terms under separate entries](#), ▶[species extant](#), ▶[admixture](#); Frankham R 1995 Annu Rev Genet 29:305; goals for mammals;

Ceballos G et al 2005 Science 309:603; large *Felidae* [tigers and others]: O'Brien SJ, Johnson WE 2005 Annu Rev Genomics Hum Genet 6:407).

C

Conservative Replication: An early idea of DNA replication suggesting that after replication each double-stranded molecule would contain either two old or two new single strands. ► [semi-conservative replication](#), ► [replication](#), ► [DNA replication](#), ► [replication fork](#)

Conservative Substitution: In conservative substitution, an amino acid replaces another in a polypeptide chain with similar properties. ► [radical amino acid substitution](#)

Conservative Transposition: ► [transposition](#)

Conserved Domain Database: Database of proteins domains and structure: <http://130.14.29.110/Structure/cdd/cdd.shtml>; <http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi>; evolutionarily conserved proteins; <http://www.everest.cs.huji.ac.il/>.

Conserved Noncoding Elements (CNE): CNE do not code for either protein or RNA, yet they occur across many mammalian genomes. Their function is unknown but it is supposed they have important regulatory roles to have been conserved during evolution. ► [non-coding DNA](#); Kamal M et al 2006 Proc Natl Acad Sci USA 103:2740.

Conserved Sequences: ► [consensus](#), ► [comparative maps](#)

Consilience: The search for scientific/philosophical principles that are very widely applicable.

Consinspector: ► [Genome Inspector](#) (Frech K et al 1997 Comput Appl Biosci 13:109).

Consomic: After 10 or more backcrosses of a male to an inbred recipient female strain, all the chromosomes (0.5^{10}) will belong to the recipient strain—at very high probability—except the Y chromosome. ► [con- plastic](#), ► [chromosome substitution](#)

Conspecific: Conspecific refers to individuals, strains or varieties belonging to the same species.

Constant Genome Paradigm: The constant genome paradigm visualized the genetic material in a stable form because insertion or transposable elements were not yet known. The Fluid Genome idea was developed after the discovery of the mobile genetic elements, which are capable of restructuring the genome. ► [transposons](#), ► [transposable elements](#)

Constitutional: It was present in the individual at birth; it was present in one or both gametes and so all cells

of the individual are expected to carry it except when new mutation occurs during development. ► [acquired](#)

Constitutional Translocation: Constitutional translocation between 11q13 and 22q11 in AT-rich regions is presumably the only recurrent translocation besides the Robertsonian translocations. It leads to different types of human hereditary diseases.

Constitutive Cycling: The function of transmembrane proteins such as receptors, channels, and transporters can be rapidly modulated by plasma internalization and release in response to hormones and other regulatory molecules also involving disease. (Royle SJ, Murrell-Lagnado RD 2003 Bioessays 25:39).

Constitutive Enzyme: Constitutive enzymes function at a rather constant level in all cells, all the time. ► [housekeeping genes](#), ► [inducible enzymes](#)

Constitutive Gene: The rate of the transcription of a constitutive gene is not subject to the effect of regulator gene(s). ► [housekeeping genes](#)

Constitutive Heterochromatin: Constitutive heterochromatin is heterochromatic at all stages and in all cells, indicating that these sequences are never transcribed. ► [heterochromatin](#), ► [euchromatin](#)

Constitutive Mutations: Constitutive mutations are those that lost their regulatory element(s) and are always in an “on” position. ► [constitutive gene](#)

Constitutive Splicing: Constitutive splicing of primary RNA transcripts occurs when the exons are spliced together in a single pattern consistent with their order in the gene. ► [alternative splicing](#), ► [introns](#)

Constitutive Triple Response (CTR): CTR is the reaction of plants to ethylene, in which the plumular hook is retained, geotropic response is prevented, and there is reduction of stem elongation. ► [plant hormones](#), ► [plumule](#); Guzman P, Ecker JR 1990 Plant Cell 2:513.

Constrained Elements: Orthologous genomic DNA is enriched in conserved functional elements saved by purifying selection. In the human genome, in ~1.9 Mbp sequence about 3.9 neutral substitutions were found and these cover approximately 5.5% of the human gene loci (Cooper GM et al 2005 Genome Res 15:901). In humans, about 40% of the constrained elements are within coding regions and 20% overlaps with regulatory stretches. ► [orthologous loci](#)

Constriction, Chromosomal: The primary constriction (C) is the centromere and the secondary constriction may tie an appendage to the end of the chromosome by a relatively thin stalk (see Fig. C156). These secondary constrictions are frequently called *satellites* (S) and are associated with the nucleolus

(nucleolar organizer region). The nucleolus contains RNA and till the early 1930s was believed not to contain DNA at all, hence was also known as SAT for *sine acido thymonucleico* (without thymonucleic acid); DNA then being called thymonucleic acid. ▶centromere, ▶satellite



Figure C156. Chromosomal constriction

Construct: A construct is most commonly used for the designation of a specially built plasmid or engineered chromosome.

Consultand: An individual seeking genetic counseling.

Contact Guidance: The physical environment in the tissue may guide the movement of axons. ▶axon

Contact Inhibition: Normal animal cells are anchorage dependent in culture and grow in monolayer because of inhibition by neighbor cells. Cancer cells lose the dependence on anchorage and constraints in growth by neighbors. This is associated also with changes in cell morphology. The oncogenic transformant cells thus, can pile up in an apparently disorganized manner into tumors.

Some *E. coli* strains are also inhibited in growth when they encounter another strain. The inhibitory strain must have a special growth state and the target cells must express pili. In addition, two proteins CdiA and CdiB are required (Aoki SK et al 2005 Science 309:1245). ▶saturation density, ▶cancer, ▶metastasis, ▶pilus; Baba M et al 2001 Oncogene 20:2727.

Contact Map: A contact map represents the proteins that are in contact. (See MacCallum RM 2004 Bioinformatics 20 Suppl. 1:1224).

Containment: A safe place from where hazardous material, including certain type of biological vectors, cannot presumably escape, and thus can be worked with, safely. ▶laboratory safety, ▶biohazards

Context, Genetic: The contribution or effect of genes outside the locus of primary concern. Many genes perform different role in different organs depending upon the effect of other genes active in the different environment.

Contig: A set of (partially overlapping) DNA fragments. A contig includes a complete region of the chromosome without gaps. For the determination of contigs, large capacity vectors are used, e.g., YACs (up to 1–2 megabase), BAC, (~150 kb), P1 plasmid (100 kb),

and cosmids (40 kb). The genome assemblies are characterized by the degree of sequence continuity expressed as N50. The N50 contig length of the Human Genome Project is ~82 kb and that of Celera is ~86 kb. ▶genome project, ▶Celera, ▶N50 length, ▶YAC, ▶BAC, ▶cosmid, ▶anchoring, ▶tiling; Hall D et al 2001 Genetics 157:1045.

Contiguous Gene Syndrome: Deletions resulting in phenotypes consistent with over-lapping functional sequences of more than one gene. It is synonymous with segmental aneusomy. ▶aneusomatic, ▶deletion, ▶Prader-Willi syndrome, ▶Wilms tumor, ▶polyposis adenomatous, ▶retinoblastoma, ▶Miller-Dieker syndrome, ▶Beckwith-Wiedemann syndrome, ▶Alagille syndrome, ▶diGeorge syndrome, ▶Lange-Giedion syndrome, ▶Angelman syndrome, ▶Norrie disease, ▶granulomatous gene syndrome, ▶muscular dystrophy, ▶McLeod syndrome, ▶glycerol kinase deficiency

Contingenci Loci: ▶SSR

Contingency Table: ▶association test

Continuity, Genetic: Genetic continuity is assured by mitotic nuclear divisions. Equal halves of each chromosome (derived by equational division) are shared between the two daughter chromosomes that are identical to those of the maternal cells (barring mutation, chromosomal breakage or accidents). ▶mitosis

Continuous Trait: A continuous trait displays a range of expression (such as weight, height, etc.) rather than an all-or-none appearance (such as white or red). Continuous traits are usually under polygenic control and subject to substantial environmental influence in expression. ▶polygenes, ▶QTL, ▶continuous variation

Continuous Variation: In continuous variation, a trait shows a range of expression forming a quantitative series, without sharply separate classes. The majority of such quantitative traits are based on the collective effects of numerous genes (polygenic systems) that each may have only small effect but cooperatively they may bring about large variations. Traits subject to continuous variation are characterized by their adaptation to the normal distribution or some classes of it. These variations are affected also by environmental factors and the outcome is a continuous or almost continuous series, and from a relatively small to a relatively large phenotypic effect. Continuous variation cannot be classified into discrete categories such as black or white but they have a running spectrum. The characterization is made by counting or measurements or by systems of grading (such as learning scores, disease susceptibility, etc.). The

study of continuous variation requires statistical tools such as mean, variance, standard deviation, tests of significance, correlation, regression, heritability, etc. (See topics mentioned under separate entries, ►**QTL**)

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Contraceptives: ►sex hormones, ►hormone, ►receptors, ►menstruation, ►immunocontraceptive, ►STAT, ►mifepristone, ►RU486, ►eppin, ►ensoulment, ►male contraceptive

Contractile Ring: The contractile ring is made of actin filaments and positioned in the cell equator, and it is instrumental in cutting apart the two daughter cells after the completion of mitosis or fission of bacteria. ►cell cycle, ►cytokinesis, ►Fts Z ring; Pardo M, Nurse P 2003 Science 300:1569.

Contractile Vacuoles: Contractile vacuoles occur in ciliated algae near the base of the flagella. ►flagellum

Contralateral: affects both sides (e.g. both breasts) versus ipsilateral. ►ipsilateral

Contrasélection: In contrasélection, selecting for one desirable trait, e.g., high lactation, may prove negative for the breeder, as consequently, producers may become susceptible to disease or otherwise less vigorous. The selection may affect linked genes or physiological correlation.

Control (check): A standard to which experimental data are compared. The standard must be identical and treated identically to the experimental material except of the special condition (genotype, developmental stage, time, chemicals, etc.) being studied. The *negative control* includes all elements except the

genetic (or other) condition under investigation. The *positive control* is a similar sample, e.g., another DNA [female DNA extract if Y-chromosomal DNA is to be studied], just to see that the experimental system works. *Blind control* is used to test for possible contamination of the reagents, e.g., all the extraction and purification steps are taken without the actual sample material. *No-template control* uses all the DNA amplification reagents except any DNA. Use of appropriate controls is indispensable in the objective evaluation of scientific data. ►concurrent control, ►historical control, ►standard

Control Region: Mitochondrial DNA sequences (~1 kb in vertebrates) devoid of structural genes, but containing replicational and transcriptional signals constitute the control region. Aging has been attributed to increased mutation rate in this region of the mtDNA. ►mitochondria, ►mtDNA, ►aging, ►mitochondrial diseases in humans [for map position]; Howell N, Smejkal CB 2000 Am J Hum Genet 66:1589.

Controlled Mating: The chart shows the percentage of homozygosity in successive generations of controlled mating systems and the limit of eventual homozygosity after an infinite number of generations (see Fig. C157). "Controlled" implies that the mating is not random but is controlled by some plan. Different mating systems have important consequences for the genotypic composition of the population.

Controlled mating is generally used by plant and animal breeders and in all types of genetic experiments.

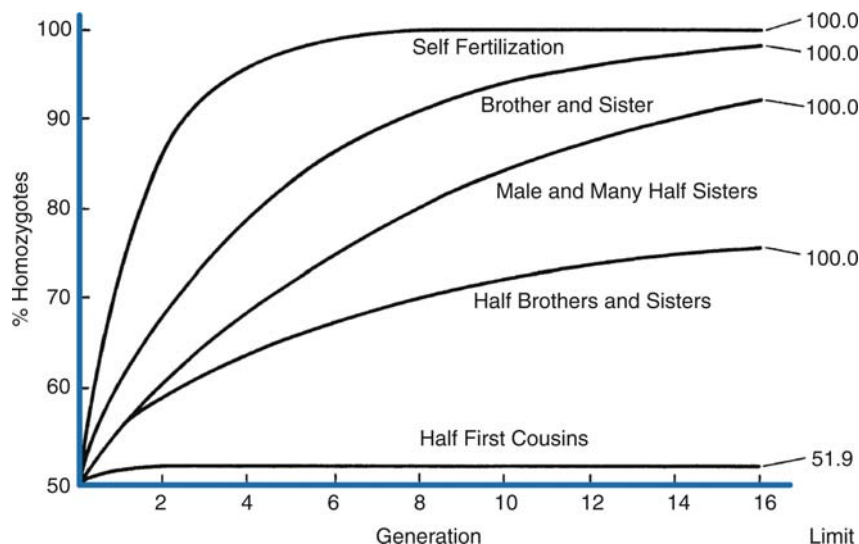


Figure C157. Controlled mating

Controlled mating of humans has been advocated by the discredited negative eugenics movements. The assortative matings based on ethnic, religious, cultural, or other bases within smaller human groups may also be controlled matings with the same biological consequences. Civil and religious laws impose some controlled mating rules involving close relatives. Some state laws prohibited marriage among mentally defective individuals, including even sterilization. Most of the controlled mating laws are no longer enforced in enlightened societies, except for the marriage between close relatives. Controlled mating is very important in animal and plant breeding. Insemination by donor sperm may possibly have some risk since the paternity is generally not known to the offspring and incest may not be prevented. [Chart redrawn after Wright S 1921 *Genetics* 6:167.]
 ▶breeding system, ▶mating system

Controlled Release: Controlled release is an important feature of drugs delivered by porous vehicles that make available the critical substance in a gradient of need.

Controlled Vocabulary: Controlled vocabulary is a term used in bioinformatics for indicating that a standardized form is used in a given application. Enzyme nomenclature is a good example for representing the classes of enzymes according to biochemical reaction. ▶bioinformatics, ▶enzymes

Controlling Elements: The historical term for plant transposable elements that can occupy different positions in the plant chromosome, regulate the expression of various genes, and cause insertional mutations. ▶*Ac-Ds*, ▶*Dt*, ▶*Spm*; ▶*Mu*, ▶*TAM*, ▶transposable elements, ▶insertion elements, ▶insertional mutation

Convection: An alternative term for non-oncogenic transformation of animal cells by exogenous DNA. (▶transformation, ▶transfection)

Convergence: ▶convergent evolution

Convergent Evolution (homoplasy): As per homoplasy, similarity is based not on common ancestry but adaptive values; i.e., species from different lines of descent assume the forms, structure, and function that are most valuable for their survival, e.g., sea mammals (whales, dolphins) are more similar in some traits to fishes than to terrestrial mammals. Convergence at single sites may be achieved by mutation or gene conversion. The regulatory circuits of genetic networks in *E. coli* and *Saccharomyces cerevisiae* indicate convergent evolution (Conant GC, Wagner A 2003 *Nature Genet* 34:264).

▶divergence, ▶gene conversion, ▶genetic networks; Nevo E 2001 *Proc Natl Acad Sci USA* 98:6233.

Conversion: An early, hypothetical step after the first mutational event in carcinogenesis. During this process, the cells become receptive to tumor promotion (propagation of the mutant cell line), and conversion is eventually followed by progression (involving additional stimulatory mutations) and malignancy. ▶progression, ▶malignant growth, ▶carcinogen, ▶cancer, ▶phorbol esters; Boukamp P et al 1999 *Oncogene* 18:5638.

Conversion: In human-rodent fusion hybrid cell lines, only one human chromosome may be retained and in this monosomic condition the recessive allele can be expressed. The human chromosome is thus converted to a haploid state.

Conversion Ascii: ▶gene, ▶conversion. Segregation is not 4:4 as expected without gene conversion (see Fig. C158).



Conversion ascus 5:3 segr.

Figure C158. Conversion ascus

Convertant: ▶gene conversion

Convertase: A large enzyme complex that activates components of the complement. Several enzymes cleave different components. ▶complement, ▶properdin

Convulsions, Benign Familial Infantile (BFIC1, 19q): Dominant epileptic type seizures beginning at age 3 to 12 months. Two additional loci BFIC2 (16p12-q12) and BFIC3 (2q24) have also been identified. ▶epilepsy, ▶ion channels

Cooled Charge-Coupled Imager: The cooled charge-coupled imager is used for FISH images to reduce random noise during long exposure. Modern fluorochromes are recognized, however, by short exposures.

Coolie's Anemia: ▶thalassemia

Coomassie Brilliant Blue (acid blue, anazolene sodium): A stain for proteins and a reagent for quantitative protein determination. It is also an intravenous LD₅₀ for mice is 450 mg/kg. ▶LD₅₀

Coombs Test: The coombs test detects the presence of erythrocyte antigens in blood typing and also in autoimmune and hemolytic diseases. It is called also antiglobulin test (AGT). The polymorphic serum

gamma globulin complex (IgG), present in about 60% of some populations, may interfere with the reaction. ▶immunoglobulins, ▶agammaglobulinemia, ▶gammaglobulin

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Cooperate Stability: Dimmers and interacting proteins are not degraded as easily as monomers. Such nonlinear proteolysis affects the function of genetic networks (Buchler NE et al 2005 Proc Natl Acad Sci USA 102:9559). ▶genetic networks

Cooperation: Cooperation has been an important evolutionary motif in the origin of cells, chromosomal linkage groups, multicellularity, colony formation, differentiation, establishment of genetic networks, etc. Natural selection favors cooperation if $b/c > k$, where b = the benefit of altruistic act, c = its cost and k = the average number of neighbors (Ohtsuki H et al 2006 Nature [Lond] 441:502).

It is possible to construct a synthetic obligatory cooperative system, termed CoSMO (cooperation that is synthetic and mutually obligatory), which consists of a pair of non-mating yeast strains, each supplying an essential metabolite to the other strain. The behavior of the two strains in isolation, however, was found to reveal unintended constraints that restrict cooperation, such as asymmetry in starvation tolerance and delays in nutrient release until near cell death. However, the joint system is shown mathematically and experimentally to be viable over a wide range of initial conditions, with oscillating population ratio settling to a value predicted by nutrient supply and consumption (Shou W et al 2007 Proc Natl Acad Sci USA 104:1877). ▶prisoner's dilemma, ▶tragedy of the commons

Cooperativity: A requisite for the formation of molecular complexes by one ligand promoting the binding of the following. ▶ligand

Cooptation: The re-use of an old function for a new purpose.

Coordinate: A system of numbering in space, e.g., the consecutive numbering of genes in a map or atoms in a molecule.

Coordinate Regulation: Coordinate regulation implies that a group of genes are controlled by common regulatory elements such as is the case in operons and regulons (see Fig. C159). The regulation may be induction or repression. In the past, coordinated regulation was assumed only in prokaryotes but correlated expression of adjacent genes has been detected also in yeast, a eukaryote. Developmental processes are based on the cooperation of many genes by both positive and negative control. ▶Lac operon, ▶Arabinose operon, ▶regulon, ▶SL1, ▶SL2, ▶homeotic genes, ▶correlated expression, ▶development, ▶junction of cellular networks, ▶morphogenesis; Finnegan EJ 2001 Trends Genet 17:361.

Co-Orientation: By the end of metaphase, the bivalent chromosomes or homologous chromatids tend to assume positions so the centromeres would face the opposite poles in anticipation of anaphase (see Figs. C160 and C161). This is sometimes called biorientation compared to co-orientation in anaphase I of meiosis when both centromeres of the two chromatids of a chromosome face the same pole to facilitate reductional division. Resolution of chiasmata in oocytes requires proteolysis by separase (Kudo NR et al 2006 Cell 126:135). Co-orientation is controlled by Aurora B and monopolin (Monje-Casas F et al 2007 Cell 128:477). ▶chiasma, ▶separin, ▶Aurora, ▶monopolin, ▶meiosis, ▶mitosis, ▶Rabl orientation

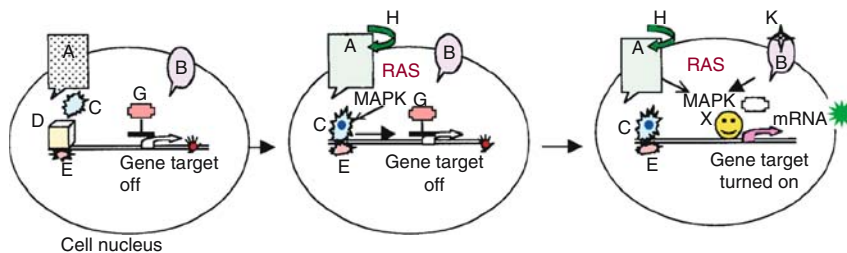


Figure C159. Coordinate regulation. Three stages of a hypothetical scheme leading to the expression of a target gene. The lettered symbols stand for proteins in or entering the nucleus. The double black line represents chromosomal DNA. In the first step, D (cube) and G prevent transcription. In the second step, D is replaced by a modified C, yet it is still insufficient for transcription. In the last step, through the joint action of proteins A + H and B + K, a signal transduction path is activated. When complex X, an aggregate of several proteins (smiley face) reaches the chromatin, inhibitor G is dislodged and inactivated. Thus transcription can proceed. Signs indicate blocks ● or transcription ●



Figure C160. Co-orientation (after M. M. Rhoades)

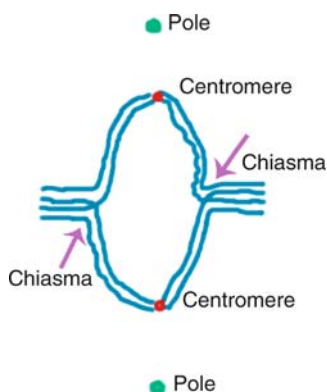


Figure C161. Co-orientation of centromeres

Co-Ortholog: Same as semi-ortholog.

COP1: A 12-subunit ubiquitin ligase protein complex involved in the regulation of photomorphogenesis of plants and lipid metabolism of animals. It is also a negative regulator of p53 (Dorman D et al 2004 Nature [Lond] 429:86). ▶[photomorphogenesis](#), ▶[neddylolation](#), ▶[p53](#), ▶[ubiquitin](#), ▶[obesity](#); Seo HS et al 2003 Nature [Lond] 423:995.

Cop Transport Vesicles: The COPI is built of ARF, coatomer subunits, and a GTPase. mediates the transport within the Golgi apparatus and between the Golgi and the endoplasmic reticulum. The sorting signals are interpreted by GTPase switch ($GTP \rightleftharpoons GDP$) on the COPI vehicles. The COPII vesicles are made of SEC and Sar proteins. Secretory COPII component Sec23a is essential for craniofacial chondrocyte maturation; it mediates traffic between the Golgi apparatus and the endoplasmic reticulum (Lang MR et al 2006 Nature Genet 38:1198). The TRAPPI tethering protein binds Sec23 to the COPII vesicles (Cai H et al 2007 Nature [Lond] 445:941). ▶[clathrin](#), ▶[ARF](#), ▶[Golgi apparatus](#), ▶[endoplasmic reticulum](#), ▶[SEC](#), ▶[SAR](#), ▶[endocytosis](#), ▶[p24](#); Barlowe C et al 1994 Cell 77:895; Lederkremer GZ et al 2001 Proc Natl Acad USA 98:10704.

Cope's Rule: The hypothesis that evolution usually involves increase in body size. The idea does not have general validity.

copia: RETROTRANSPOSON elements occur in all types of eukaryotes; in *Drosophila* they occur generally in 5 – 7 kb sizes with about 300 bp direct and much shorter inverted terminal repeats. They frequently occur in 30–40 families and constitute 5–10% of the genome. The copia elements along with about 30 other insertion and transposable elements are involved in the mutability of the genomes by their movement. The frequency of their rearrangement is within the range of 10^{-3} to 10^{-4} . The long terminal repeats (LTR) encode a viral transposase-like protein. Retrotransposition cycles are initiated from an RNA copy of a transposable element. The transcription begins at the 5' region of the long terminal repeat (LTR) and this transcript is copied into a double-stranded DNA by a reverse transcriptase coded within the transposon. The synthesis of the first DNA strand is primed by the 3'-OH group of a host tRNA that immediately anneals to the LTR (this is called tRNA PBS [primer binding site]).

Integration requires short inverted repeats (4–12 bp) at the end of the LTRs. Integration involves a few bp duplications at the insertional target sites. These duplications are the consequences of the staggered cuts at the target that are filled in by complementary bases after integration. The length of the target site duplications reflects the specificity of the transposon-encoded integrase. *Drosophila* retrotransposons have a number of features corresponding to retroviruses. They contain direct terminal repeats that have the sequences required for the initiation of transcription and polyadenylation. The majority of the *Drosophila* retrotransposons carry short inverted repeats at the end of LTRs. The LTR at one terminus contain TG and at the other CA bases. The majority of the retrotransposons have a purine-rich sequence immediately upstream to the 3'-LTR. These sequences are the priming sites for the second strand DNA (SSP, [second strand primer]). Most *Drosophila* retrotransposons have sequences starting with TGG immediately downstream to the 5'-LTR that is complementary to the 3'-end of the tRNAs (the amino acid acceptor arm). The *Drosophila* retrotransposons have reverse transcriptase (*pol*), and group-specific antigen (*gag*) polyproteins just like the retroviruses of vertebrates. Actually some plant retrotransposon-like elements are also organized in a similar manner but the majority of them are no longer able to transpos because some of their genes were reduced to pseudogenic forms. During retroviral life cycles, extrachromosomal linear and circular DNA elements are formed with one or two LTRs. These features are also retained in some of the copia-like elements. These retrotransposons also produce viral-like elements in the eukaryotic cells quite similar to the real retroviruses. Also, some of the copia-like elements generate

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“strong-stop” DNA elements in cells like retroviruses. These strong-stop DNAs and DNA–RNA heteroduplexes are leftovers of the first and second strand transcription by the reverse transcriptase enzyme. These copia-like elements transpose quite vigorously in both somatic and germline cells and induce mutations in the germline and the soma. Recombination between the multiple copies of the retroposons may cause in the host all types of chromosomal aberrations, such as deletions, inversions, and translocations. Perhaps the movement (insertion) of these elements causes the majority of the spontaneous mutations in the species that harbor transposable elements. The insertions may cause inactivation of exons but more frequently they insert into AT-rich sequences. The major representatives in *Drosophila* are “17.6” (7.4 kb) occurring in about 40 copies per genome and generating a 4-base duplication at the insertion target site, the LTR being 512 bp. “297” (7-kb) has approximately 30 copies. Its LTR is 415-bp and shows 1.7-kb homology between the right-hand ends with 17.6. Its transposition-replication is primed by a tRNA^{Ser}. “412” (7.6-kb), copy number 40, LTR is 481 bp target site duplication of 4 bases. tRNA^{Arg} primes its transposition. “1731” (4.6-kb) is present in about 10 copies and generates a target site replication of 5-bp. Its reverse transcription is primed probably by a fragment of the initiator tRNA^{Met}. “3S18” (6.5-kb) with target site duplication of 5-bp; occurs in about 15 copies. “BEL” (7.3-kb) is present in about 25 copies and the termini are very similar. “blood” (6-kb) occurs in 9 – 15 copies, LTR 400-bp, and generates a target site duplication of 4. The primer may be tRNA^{Arg} similar to elements 412 and *mdg1*. “copia” (5-kb) is present in 60 copies, its LTR 276-bp with 5-bp target site duplication. Its name indicates the “copious” amount of its polyadenylated transcripts in the cells. The initiator tRNA^{Met} primes for the reverse transcription of the copia RNA. Left end of the element: TGTTGGAATA TACTTATTCAA CCTACAAAG TAACGTTAAA, the right end: TATTAAAGAAA GGAAATATAA ACAACA. “gypsy” [synonymous with *mdg4*] (7.3-kb) with 10 copy number has a LTR of 479-bp, and generates 4-bp target site duplication. These elements are associated with many mutations suppressed by *su(Hw)* [suppressor of Hairy wing], the product of this gene binds to an enhancer-like sequence within *gypsy* and affects the expression of adjacent genes including *gypsy*. The phenotype of some of the mutations caused by *gypsy* insertions is affected by *su(f)* [suppressor of forked]. The *gypsy* element is considered to be a retrovirus and its movement is controlled primarily by the X-chromosomal mutation *flam* (flamingo). “H.M.S.Beagle” (7.3-kb) has 50 copies, LTR is 266-bp, and shows 4 base target site duplication. “*mdg1*” (7.3-kb), may be

present in 25 copies, its LTR is 442-bp and creates 4-bp target site duplication; 14/18 of its primer binding sites are identical to that of 412 as well as the 27-bp adjacent to the left LTRs. tRNA^{Arg} is the most likely primer for their reverse transcription. “*mdg3*” (5.4-kb) has LTR of 267-kb and the target site duplications are 4-bp. “*micropia*” (5.5-kb) hybridizes with *copia* in the Y chromosome of *D. hydei*. “NEB” (5.5-kb), “opus” (8-kb). “*roo*” (8.7-kb, formerly called *B104*) has a LTR 429-bp and generates 5-bp target site duplication. “*springer*” (8.8-kb) with LTR 405-bp generates 6-bp target site duplication. ▶retroviruses, ▶retroposon, ▶retrotransposon, ▶transposable elements, ▶transposase, ▶reverse transcription, ▶polyprotein, ▶tRNA, ▶suppressor, ▶*Cin4*, ▶hybrid dysgenesis, ▶*Drosophila*; Bowen NJ, McDonald JF 2001 Genome Res 11:1527; Mejlumian L et al 2002 Genetics 160:201.

Copolymer: A molecule built from more than one type of component, e.g., a nucleic acid made of adenine and thymine units. If the sequence and quantity of the components do not follow a particular system it may be a random copolymer. If the units display periodic repetitions, it is called a repeating copolymer.

Copper Homeostasis Disease: ▶Wilson disease, ▶Menke’s disease

Copper-Inducible System: ▶metallothionein

Copper Malabsorption: ▶Menke’s disease

Coprocessor: An auxiliary processor to assist the main processor in special heavy tasks. Generally, it also speeds up the processing of computers. ▶processor

Coprolite (fossilized dung): Coprolite reveals the diet and food digestion of extinct species or ancestral populations of modern animals. (<http://www.ualberta.ca/~abeaudoi/stuff/dung.htm> <http://www.scirpus.ca/dung.dung.shtml>).

Coprophagy: Coprophagy is the phenomenon where the nymphs of some insects feed on the feces of adults and utilize the nutrients left therein, while simultaneously ingesting their abundant bacterial symbionts. ▶paratransgenic

Coproporphyrria (CPO, 3q11.2): A dominant deficiency of coproporphyrinogen oxidase resulting in excessive excretion of coproporphyrin III, an intermediate in porphyrin synthesis (see Fig. C162). The protein is mitochondrially localized. Deficiency of coproporphyrinogen oxidase causes abdominal pain, neurological problems, and photosensitivity of the skin. Heme arginate administration and high-carbohydrate diet are effective treatments. The gene has been cloned and the crystal structure of the enzyme has been determined (Lee D-S et al 2005 Proc Natl

Acad Sci USA 102: 14232). ►porphyrin, ►porphyria, ►harderoporphyria; Lamoril J et al 2001 Am J Hum Genet 68:1130.

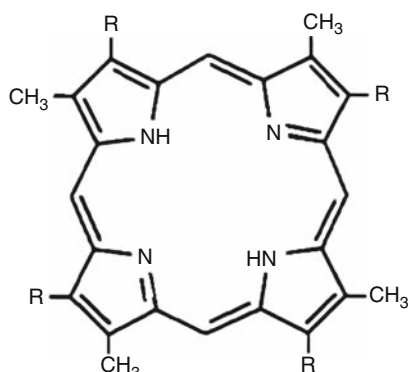


Figure C162. Coproporphyrin III

Coprospecty: Molecular analysis of coprolites. After *N*-phenacylthiazolium bromide cleavage of protein DNA cross-links, various short DNA sequences can be extracted, amplified by PCR, and sequenced. Information may be obtained on thousands of years old animals and their plant food. ►coprolite, ►PCR

Copulation: Sexual intercourse between female and male. Evolutionary selection of characteristics of the process would indicate that leaving more offspring even at the expense of decreased survival might be favored. Actually, this has been shown by the redback spider (*Latrodectus hasselti*) where hungry females frequently cannibalize their mates that copulate longer and thus transfer more sperm and thereby contribute more of their genes to the population. courtship; Koniyoshi H et al 2002 Genetics 162:1775.

Copy Choice: A hypothesis so named in the 1950s. It assumes that in recombination there may be no physical breakage and union between exchanged strands, but rather a replication and choice. This hypothesis bears similarity to Bateson's (1906) reduplication theory and gene conversion (Lindgren 1949). Recently, evidence has been presented that prokaryotic DNA polymerase III holoenzyme may slip frequently during replicating direct repeats. Recombination between RNA viruses may be brought about by template switching during the elongative RNA synthesis by RNA-dependent RNA polymerases. ►gene conversion, ►recombination in RNA viruses, ►breakage and reunion, ►reduplication hypothesis; M-J Kim, Kao C 2001 Proc Natl Acad Sci USA 98:4972; Moumen A et al 2001 Nucleic Acids Res 29:3814.

Copy Number Estimates: In the human genome, the frequency of deleted and duplicated segments of the average 300–400 kb appears as 1:8 and 1:50, respectively, based on mutation frequency of the Duchenne muscular dystrophy region (van Ommen G-JB 2005 Nature Genet 37:333). High-resolution comparative genomic hybridization using oligonucleotide probes can detect many of such alterations in various disease syndromes and also in normal individuals (Urban AE et al 2006 Proc Natl Acad Sci USA 103:4534). ►duplication, ►deficiency, ►genomic variation; Redon R 2006 Nature [Lond] 444:444.

Copy Number Paradox: The copy number paradox is that the genetically functional copies of organellar DNA appear much smaller than the physical copy number estimates. ►mtDNA, ►chloroplasts, ►C value paradox; Jenuth JP et al 1996 Nature Genet 14:123.

Copy Number Variants (CNV): CNVs are genomic segments of 1 kb or larger that were deleted or duplicated in the genomes of the majority of higher eukaryotes. Two human genomes may differ by more than 20 Mb and it is likely that the full extent of CNV still remains to be discovered. Nearly 3000 human genes are associated with CNV. This high degree of variability between two individuals challenges definitions of normality. Many CNVs are located in regions of complex genomic structure (Kehrer-Sawatzki H 2007 Bioassays 29:311). Single nucleotide polymorphism (SNP) represents 83.6%, and CNVs 17.7% of the average total detected genetic variations in gene expression of 14,702 transcripts taken from wide ethnic population samples. Signals from these two types of variation show little overlap (Stranger BE et al 2007 Science 315:848). CNV breakpoint sequences (physical deletion or duplication boundaries) can be determined with the use of a computer program called *BreakPtr*, for fine-mapping CNVs (available from <http://breakptr.gersteinlab.org>, see also Korbel JO et al 2007 Proc Natl Acad Sci USA 104:10110). small duplications: Conrad B, Antronarakis SE 2007 Annu Rev Genomics Hum Genet 8 Sept.

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Copy-Up Mutation: The copy-up mutation initiates runaway replication of the plasmid, i.e., the copy number increases beyond that in the wild type. ►runaway plasmids; Blasina A et al 1996 Proc Natl Acad Sci USA 93:3559; Toukdarian AE, Helinski DR 1998 Gene 223:205.

CoR-BOX: The amino-terminal ligand-binding domain of the thyroid and retinoic acid receptors. ►N-CoR, ►thyroid, ►retinoic acid, ►ligand

C

Cord Blood (umbilical cord blood): ► [stem cells](#)

Cordate: Heart-shaped.

Cordycepin ($C_{10}H_{13}N_5O_3$): A nucleoside analog (3'-deoxyadenosine) that inhibits transcription and polyadenylation. ► [polyadenylation](#), ► [polyA mRNA](#), ► [polyA tail](#), ► [transcription](#)

Core Binding Factors (CBF): Heterodimeric transcription factors. They are essential for normal development and health. ► [transcription factors](#), ► [runt](#)

Core DNA: Core DNA wraps around the histone octamer in the nucleosome. The DNA (chain) winds around the 8 histones' core but does not include H1 histone. ► [nucleosome](#), ► [histones](#)

Core Enzyme: Prokaryotic transcriptase has two identical α and two β ($\beta\beta'$) subunits and to this core a fifth, σ subunit, may be attached that is not essential for transcription but seeks out the position of proper promoters. ► [RNA polymerase](#)

Core Machine: The essential functional unit of protein complexes.

Core Particle: ► [nucleosome](#), ► [core DNA](#), ► [histones](#) (see Fig. C163).

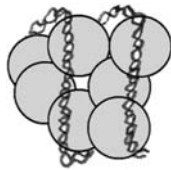


Figure C163. Core particle

Core Polymerase: Core polymerase is composed of only 3/10 subunits of prokaryotic DNA polymerase III (pol III). These subunits are α (polymerase), ϵ (proofreading 3'→5' exonuclease), and θ (enhances the activity of ϵ). ► [DNA polymerases](#)

Core Promoter: The core promoter is the most essential sequence (~100 bp from the transcription start site [TSS]) within a promoter to carry out transcription (see Fig. C164). The core promoter of the eukaryotic RNA polymerase II usually includes the TATA box and may have also an *initiator site* (Inr), enhancer and the TATA box associated general transcription factors, such as the TFIIB recognition element (BRE), and the downstream promoter element (DPE). DPE, when present, is situated 30 nucleotides downstream of the transcription initiation site. Generally the DPE element has Inr but no TATA box. The TAF subunits of TFIID bind DPE and Inr (Burke TW, Kadonaga JT 1996 Genes Dev 10:711). The core promoter is usually situated ± 40 nucleotides

from the transcription initiation site (TATA box). The TATA box is bound by TBP, which is a subunit of transcription factor TFIID.

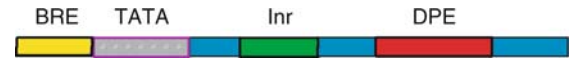


Figure C164. Core promoter

At a distance of -50 to -200 bp from the TATA box there are binding sites for NF-1, CBF, NF-Y. In prokaryotes, the core promoter complex includes only the RNA polymerase holoenzyme and the σ subunit. In eukaryotes, instead of the σ , an assembly of the general transcription factors are found. In addition, the TATA box binding proteins (TBP), TATA box associated proteins (TBA), initiator binding protein (IBP), and enhancer binding proteins (EBP) are usually present. The modulation and regulation of transcription requires series activators, co-activators, and different specific transcription factors. ► [transcription factors](#), ► [open promoter complex](#), ► [TBP](#), ► [TAF](#), ► [transcription unit](#), ► [transcription initiation](#), ► [TSS](#), ► [base promoter](#), ► [null promoter](#), ► [NF-1](#), ► [CBF](#), ► [NF-X](#), ► [PWM](#), ► [DSTF](#), ► [Sp1](#), ► [CAAT box](#); Hamada M et al 2001 Mol Cell Biol 21:6870; Morimoto M et al 2001 Arterioscler Thromb Vasc Biol 21:771; Smale ST, Kadonaga JT 2003 Annu Rev Biochem 72:449.

Core, Protein: The region common to the majority of structures in a superfamily or in a common fold.

Core Proteome: The number of distinct families of proteins within a genome. In *Haemophilus influenzae*, of the 1709 protein-coding genes, 1247 (~73%) do not have sequence relatives within the genome. In yeast, there are ~6241 protein-coding genes and from these 4383 (~70%) represent the core proteome. The core proteome in *Drosophila* and *Caenorhabditis* are 8065 (~62%) and 9453 (~51%), respectively. ► [gene number](#), ► [duplications](#), ► [genome](#), ► [proteome](#)

Core Sequences: Usually invariable short tracts within more or less well preserved consensus sequences of the DNA. ► [consensus](#)

cORF (composite open reading frame): cORF occurs by tandem duplication of genes. ► [ORF](#)

Co-Receptor: CD⁸ and CD⁴ T cell surface proteins along with the T cell receptor recognize MHC I and MHC II molecules. The CD cytoplasmic domains associate with a SRC protein tyrosine kinase. ► [CD⁸](#), ► [CD⁴](#), ► [T cell receptor](#), ► [MHC](#), ► [SRC](#), ► [protein tyrosine kinase](#)

Coremium: ► [hypha](#)

Co-Repressor: A metabolite or protein which, in combination with a repressor protein interferes with transcription and thereby with enzyme synthesis. The

co-repressor may not bind to DNA directly. A co-repressor, when recruited to an activator, may turn the latter into a repressor. ►repressor, ►aporepressor, ►repression, ►regulation of gene activity, ►nuclear receptor, ►cAMP receptor, ►Groucho, ►Tup1, ►N-CoR, ►chromatin remodeling, ►co-suppression, ►co-activator; Yoh SM, Privalsky ML 2001 J Biol Chem 276:16857; Zhang Q et al 2002 Science 295:1895.

Coriaceous: Leathery.

Co-Retention Analysis: Co-retention analysis is used in genetic mapping of mitochondrial genes. More or less large deletions frequently take place in the mitochondrial DNA resulting in simultaneous loss concomitant with simultaneous retention of antibiotic resistance markers. The co-deletion and co-retention frequencies provide converse estimates on linkage. Both co-deleted and co-retained markers must be present in groups indicating their physical position relative to each other. ►linkage, ►physical mapping, ►deletion mapping, ►mitochondrial genetics; Heyting C, Menke HH 1979 Mol Gen Genet 168:279.

Corm: Underground shoots, modified for storage (see Fig. C165).



Figure C165. Corm

Corn: ►maize

Cornflower: ►Echinacea

Cornea Plana: The characteristics of the cornea plana condition are extreme farsightedness (hyperopia) and opacity of the cornea especially at the margins. It exists in autosomal dominant and recessive forms; and is most common in Finland. ►eye diseases

Corneal Dystrophy: Corneal dystrophy has been described in various autosomal dominant and recessive forms involving defects in the keratin filaments in the eye. ►filaments, ►keratin

Cornelia de Lange Syndrome: ►De Lange syndrome

Corolla: The collective term for petals. ►flower differentiation

Corona Virus: ►SARS

Coronary Heart Disease (COD): COD generally involves deposition of lipid plaques within the arteries surrounding the heart (atherosclerosis). Low-density lipoprotein in the blood (above 200 mg/100 mL) increases the risk proportionally. On the other hand, high-density lipoprotein is favorable for avoidance. These account

for the majority of all heart diseases and afflict 6–7% of the populations (predominantly males) in Western industrialized countries. The underlying organic defects vary, and many non-hereditary factors (diet, smoking, drug and alcohol consumption, age, etc.) and independent or concomitant diseases and conditions (blood pressure, diabetes, temperament, etc.) aggravate the condition. In Finnish populations, two likely susceptibility loci were found at 2q21-q22 (LOD score 3.2) and at Xq23-q26. The locus at 15q26 encodes the transcription factor MEF2A that has frequently a 21 bp deletion and (in that case) is responsible for COD and myocardial infarction (Wang L et al 2003 Science 302:1578). Familial hypercholesterolemia, apolipoproteinemia (APOB), sitosterolemia, low level of HDL, Tangier disease, and homocystinuria increase susceptibility to COD. Increased expression of 5-lipoxygenase can also be a factor in COD (ALOX5, 10q11.2; ALOX5AP, 13q12; leukotriene C4 synthase, 5q35) are also contributing factors among others. So far no single decisive gene has been identified. Autosomal dominant early coronary artery disease is predisposed by hyperlipidemia, hypertension, diabetes, and osteoporosis. The genetic determinants of these conditions show linkage to a short segment of chromosome 12p, in which a missense mutation in a low-density lipoprotein receptor gene (*LRP6*) encodes a co-receptor in the Wnt (wingless) signaling pathway (Mani A et al 2007 Science 315:1278). Genome-wide association studies of more 23,000 individuals identified a 58-kilobase interval on chromosome 9p21 that was consistently associated with coronary heart disease. This interval, which is located near the *CDKN2A* and *CDKN2B* genes, contains no annotated genes and is not associated with established heart risk factors such as plasma lipoproteins, hypertension or diabetes. Homozygotes for the risk allele occur in 20–25% of Caucasians and have a ~30–40% increased risk coronary heart disease (McPherson R et al 2007 Science 316:1488). Another study showed similar results. Approximately 21% individuals in a population are homozygous for this variant and they have an estimated 1.64-fold greater risk of suffering myocardial infarction than non-carriers. The corresponding risk is 2.02-fold for early onset cases (Helgadottir A et al 2007 Science 316:1491). ►hypertension, ►angina pectoris, ►cardiovascular disease, ►MEF, ►atherosclerosis, ►familial hypercholesterolemia, ►familial hyperlipidemia, ►hyperlipoproteinemia, ►lipoprotein, ►cholesterol, ►Tangier disease, ►diabetes, ►mucopolysaccharidosis, ►pseudoxanthoma elasticum, ►Marfan syndrome, ►homocysteinuria, ►lecithin: cholesterol acyltransferase deficiency, ►myocardial infarction, ►atherosclerosis, ►wingless; Breslow JL 2000 Annu

Rev Genet 34:233; Watkins H, Farrall M 2006 Nature Rev Genet 7:163.

Coronavirus: Positive-sense RNA viruses of bird and mammals. ▶SARS

C

Corpus: Latin word for body. In information science, it designates a collection of texts regarding a certain area of science or its specified subgroup.

Corpus Callosum: ▶brain

Corpus Luteum (yellow body): The corpus luteum is formed by luteinization of an ovarian follicle after the discharge of an ovum. In case of fertilization of the egg, the corpus luteum increases in size and persists for several months. If there is no fertilization, the CL disintegrates. The CL secretes progesterone. ▶ovary, ▶Graafian follicle, ▶ovum, ▶luteinization, ▶luteinizing hormone-release factor, ▶corticotropin, ▶progesterone, ▶animal hormones, ▶relaxin, ▶abortion spontaneous

Corpuscular Radiation: Corpuscular radiation is emitted by unstable radioisotopes: β particles [electrons] are emitted by ^3H , ^{14}C , ^{32}P , etc. and α particles [helium nuclei] by uranium or fast and thermal neutrons during nuclear fission. ▶physical mutagens, ▶isotopes, ▶ionizing radiation, ▶radiation effects, ▶radiation measurement, ▶radiation hazard assessment, ▶electromagnetic radiation

Correction: ▶DNA, ▶repair

Correlated Expression: In the eukaryote yeast, adjacent genes, irrespective of their orientation in the chromosome, are more likely to be expressed at the same time than non-adjacent ones. Only $r > 0.7$ is accepted as valid indication of correlated expression. The significance of correlated adjacent pairs is determined statistically on the basis of the cumulative binomial distribution by using the formula:

$$p(n \geq n_0) = \sum_{n=n_0}^N p^n (1-p)^{N-n} \left[\frac{N!}{n!(N-n)!} \right]$$

In some cases, only one of the gene pairs carries an upstream activating sequence. Some genes utilize the

same UAS even when they are not immediately downstream from it. On this basis chromosome correlation, maps can be constructed. ▶UAS; ▶coordinate regulation; ▶operon; ▶regulon; Cohen BA et al 2000 Nature Genet 26:183.

Correlation: Interdependence of two variates (see Fig. C166). This relation may be statistical or physiological. The statistical correlation does not necessarily reveal any cause and effect link. The correlation may be positive (when the change of the variables follows the same direction) or negative (when the increase of one variable involves the decrease of the other). Thus, the value of the correlation coefficient may vary between +1 and -1.

The correlation coefficient is independent from the scale of quantitations used, e.g., one can measure the correlation between intelligence and wearing a necktie. For the calculation of the correlation coefficient, *covariance* has to be determined, i.e., the average product of the deviations of two variables from their respective means. It is estimated by dividing the sum of the products of the deviations from their means by the appropriate degrees of freedom. Thus, covariance is: $(w) = \{\Sigma[(x_i - \bar{x})(y_i - \bar{y})]\} / (n - 1)$. For actual calculation, the mathematically equivalent but computationally more convenient equation is used: $(w) = \{\Sigma(X_i Y_i) - [\Sigma(X_i) \Sigma(Y_i)] / n\} / (n - 1)$.

The analysis of covariance has many uses in biology and particularly in genetics. It may be used to separate the genotypic effects from treatment effects. It may reveal the relations among various types of variables. This type of analysis is useful to study the relationships among multiple classifications such as may occur if the experiments involve organisms of different genotypes, in different age groups and developmental stages and environments. In this book it is not possible to work out examples for all these different applications; only the basic procedure is illustrated with step-by-step simple calculations (see Table C6).

The actual use of the formulas can best be shown by a hypothetical example. Let us assume that we measured (*i*) number of variates (in the following case *i* is 1 to 10) in two groups. In the columns x_i and y_i ,

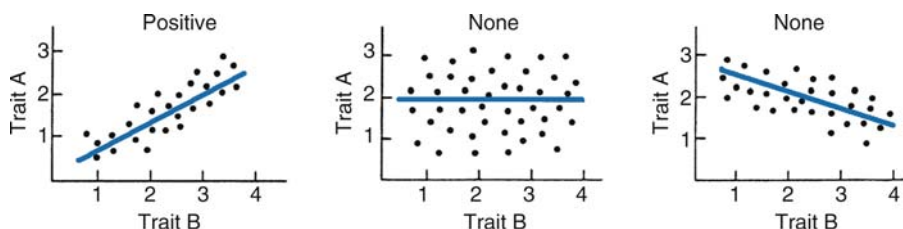


Figure C166. Graphical representation of correlation. The dots correspond to the points of the measured values of two quantitative traits

these measurements are listed from 1 to 10. To make the calculations easier (without changing the outcome) for each measurement, a quantity (the same quantity, close to the means) is subtracted, and we name these X_i and Y_i , respectively, as shown at the top of columns 3 and 4. Column 5 is the product of the lines in columns 3 and 4: $X_i Y_i$. Columns 6 and 7 display the power of values in columns 3 and 4, respectively: $(X_i)^2$ and $(Y_i)^2$.

Indicating that an increase in the values of X involved a positive in the values of Y as shown at the top of columns 3 and 4. Column 5 is the product of the lines in columns 3 and 4, $X_i Y_i$. Columns 6 and 7 display the power of values in Columns 3 and 4, respectively: $(X_i)^2$ and $(Y_i)^2$.

In genetic analysis the coefficient of regression is often used. It measures in quantitative units how much the dependent variable (Y) is changing as a function of the independent variable (X), e.g., we can determine how much the offspring's weight or height regresses to the weight (in kg) or height (in cm) of the parents or to the mother or father. This is in contrast to correlation that could state only plus or minus and strong or weak correspondence but not in actual quantitative units. The coefficient of regression: $b = W/V_x =$ and in the example of the table $b = 20.22/28.71 = 0.704$. For a predictive value, we use the

linear regression equation: $Y = a + bx$ from which $a = Y - bx$, where (a) is the intercept of the straight line on the (Y) coordinate; (b) is the slope indicating how much (y) changes by changes in (x) (see Fig. C167).

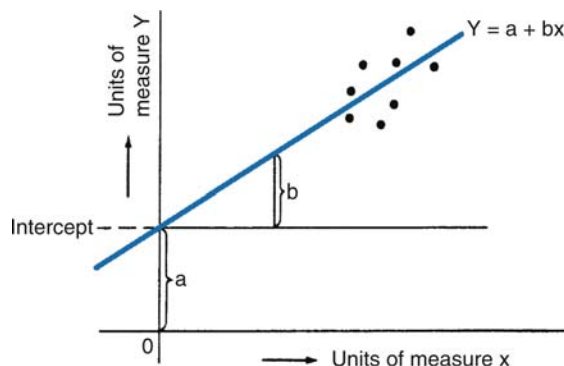


Figure C167. The linear regression line is specified by the equation: $Y = a + bx$. In this function, a is the value of the intercept and b defines the slope of the line, equal to the increase in Y per units of x . The solid circles correspond to the intersections of the values of the two variables. According to the table shown on the preceding page, we can consider the X axis for the units of measures of one of the variates and Y as the axis for the measurements of the other variates

Table C6. Computational scheme for covariance (w)

| (1) | (2) | (3) | (4) | (5) | (6) | (7) |
|-----------------|-----------------|---------------------|---------------------|------------------------|------------------------|------------------------|
| x_i | y_i | $X_i = x_i - 150$ | $Y_i = y_i - 150$ | $X_i Y_i$ | $(X_i)^2$ | $(Y_i)^2$ |
| 148 | 149 | - 2 | - 1 | 2 | 4 | 1 |
| 158 | 152 | + 8 | + 2 | 16 | 64 | 4 |
| 150 | 155 | 0 | + 5 | 0 | 0 | 25 |
| 143 | 142 | - 7 | - 8 | 56 | 49 | 64 |
| 162 | 160 | + 8 | + 10 | 80 | 64 | 100 |
| 150 | 160 | 0 | + 10 | 0 | 0 | 100 |
| 156 | 153 | + 6 | + 3 | 18 | 36 | 9 |
| 160 | 159 | + 10 | + 9 | 90 | 100 | 81 |
| 153 | 158 | + 3 | + 8 | 24 | 9 | 64 |
| 150 | 152 | 0 | + 2 | 0 | 0 | 4 |
| $\bar{x} = 153$ | $\bar{y} = 154$ | $\Sigma X_i = + 26$ | $\Sigma Y_i = + 40$ | $\Sigma X_i Y_i = 286$ | $\Sigma (X_i)^2 = 326$ | $\Sigma (Y_i)^2 = 452$ |

Substituting the values into the covariance formula:

$$W = \{\Sigma(X_i Y_i) - [\Sigma(X_i)(\Sigma(Y_i))/n]/(n - 1) = \{286 - [(26) \times (40)]/10\}/9 = 20.22$$

Variances:

$$V_x = \{\Sigma(X_i)^2 - [\Sigma(X_i)^2]/n]/(n - 1) = \{(326) - [(26)^2]/10\}/9 = + 28.71$$

$$V_y = \{\Sigma(Y_i)^2 - [\Sigma(Y_i)^2]/n]/(n - 1) = \{(452) - [(40)^2]/10\}/9 = + 32.44$$

The coefficient of correlation: $r = W/\sqrt{V_x V_y} = 20.22/\sqrt{28.71 \times 32.44} = + 0.663$, indicating that an increase in the values of X involved a positive change in the values of Y .

After substituting the data of our calculations into the equation:

$a = Y - bx$, since $(\bar{y} = Y = 154)$, and $\bar{x} = X = 153$, and $b = 0.704$; thus, $a = 154 - (0.704 \times 153) = 46.29$. Therefore, if the (x) independent variable is 158 kg, the dependent variable (Y) is expected to be $46.29 + (0.704 \times 158) = 157.52$ kg. When the independent variable is 150 kg, the dependent variable (Y) is expected to be $46.29 + (0.704 \times 150) = 151.89$ kg. The example also testifies for the name of regression. Originally it was observed that large and small parents' children both tend to follow more the population's mean, i.e., they regress toward the mean. The offspring–parent regression is actually a measure of heritability. The linear regression is frequently represented graphically as shown above. ►genetic correlation, ►heritability, ►intraclass correlation

Correspondence Analysis: A computational method for the study of associations between variables. It displays low-dimensional projection of the data into a plane so that both variables simultaneously reveal their association. It is applicable to microarray data of different complexities. ►microarray hybridization; Fellenberg K et al 2001 Proc Natl Acad Sci USA 98:10781.

Cortex: The outer layer of various tissues (egg, brain, kidney, tree bark, etc.).

Cortical Granules: Small secretory vesicles under the egg membrane that by releasing some of their contents protect the egg from being fertilized by multiple sperms. ►fertilization, ►polyspermy

Cortical Inheritance: The cytoplasmic organization may affect the expression of a trait without alteration in the genetic material (see Fig. C168). In *Paramecia*, the movement of the cortically located cilia may be oriented in the same direction. If a piece of the cortical cytoplasm is grafted in the reverse orientation, the graft will beat in the opposite direction and this ciliary movement pattern may be transmitted through generations.



Figure C168. Cortical Inheritance. Gullet and vestibule (→) of *Paramecium aurelia* that can be surgically transferred to another site on the animal and it is then cortically inherited. (Courtesy of Dr. Tracy Sonneborn)

Similarly grafted vestibules may appear as an additional ingestatory apparatus in the progeny. These cortical layers contain no DNA or RNA. The pattern of development seems to be fixed within

the organizational structure. ►epigenesis, ►non-Mendelian inheritance; Beisson J, Sonneborn TM 1965 Proc Natl Acad Sci USA 53:275.

Cortical Reaction: ►fertilization, ►cortical granules

Corticobasal Degeneration: A fronto-temporal dementia generally occurring with parkinsonism caused by mutation in the tau protein. ►tau, ►parkinsonism

Corticosteroid: Corticosteroids are 21-carbon steroids that are synthesized in the outer firm, yellowish layer of the adrenal (kidney) gland. The glucocorticoids regulate carbohydrate and protein metabolism, whereas the mineralocorticoids regulate salt and water traffic. ►animal hormones, ►glucocorticoids, ►transcortin deficiency, ►antitrypsin

Corticotropin (adrenocorticotropin, ACTH): A 39-amino acid peptide hormone of the anterior pituitary that regulates the synthesis of corticosteroid in the adrenal cortex. Its release, e.g., in response to stress, is controlled by the releasing factors of the hypothalamus such as the thyrotropic releasing factor (TRF), the luteinizing hormone releasing factor (LRF), and the corticotropin releasing factor. ►opiocortin, ►corticotropin releasing factor, ►stress; Lin X et al 2001 Mol Endocrinol 15:1264.

Corticotropin Releasing Factor (CRF/CRH): CRF is supposed to be associated with the brain cognitive response. In Alzheimer's disease, CRF is very low although CRF receptors accumulate. CRF mediates endocrine, autonomous, behavioral, and immune responses to stress (alcohol and drug withdrawal, etc.). ►Alzheimer's disease, ►urocortin, ►stress, ►maternal tolerance; Eckart K et al 2001 Proc Natl Acad Sci USA 98:11142.

Cortisol: Cortisol is derived from progesterone (along with aldosterone) in the kidney cortex. It is chemically very similar to cortisone. The production of cortisone is controlled by the pituitary hormone corticotropin and cAMP. Glucocorticoids promote gluconeogenesis and the deposition of glycogen in the liver, inhibit protein synthesis in the muscles, mediate fat and fatty acid breakdown in the adipose tissue, and control inflammatory responses. ►glucocorticoids, ►hydrocortisone, ►abortion spontaneous; Johannsson A et al 2001 J Clin Endocrinol Metab 86:4276.

Cortisone: ►cortisol

Corynebacterium: ►diphtheria toxin, ►biological weapons

cos: cohesive ends (12 bp) of phage λ where linearization and circularization of the DNA take place:

pGGGCGGCGACCT- - - - -
- - - - - CCCGCCGCTGGAp

The sequence shown here represents the *cosN* subsite where cutting takes place. For the proper packaging of the genome, additional *cos* sites (*cosQ*, *cosB*) and proteins are also required (Wieczorek DJ, Feiss M 2003 Genetics 163:11). ▶[lambda phage](#); Wieczorek DJ, Feiss M 2001 Genetics 158:495.

COS Cell (cell, origin, Simian): COS cells are African green monkey cells with a chromosomally inserted Simian virus (SV40) DNA, which is defective in the origin of replication but contain the intact T-antigen (see Fig. C169). COS cells thus replicate multiple copies (small circles) of the harmless viral vector and the inserted passenger DNA independently from the monkey cell chromosome. The foreign DNA in the SV40 vector is transcribed and translated into the appropriate protein with the assistance of the metabolic machinery of the cell. ▶[SV40](#), ▶[African green monkey](#); Gerard RD, Guzman Y 1985 Mol Cell Biol.5:3231.

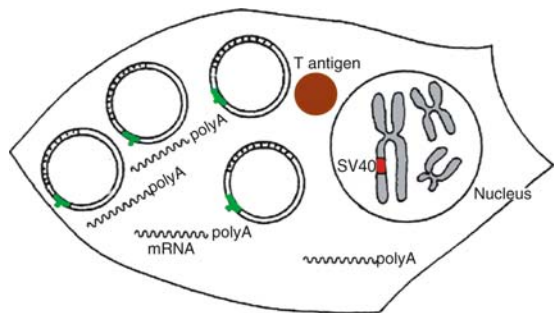


Figure C169. COS cell

Co-Segregation: Analysis for genetic linkage between two different genetic markers, e.g., a visible mutant phenotype and antibiotic resistance.

CO₂-Sensitivity: ▶[symbionts hereditary](#)

Co-Sexual: ▶[hermaphrodite](#)

Cosexuality: In cosexuality, both male and female sexual organs are present within the same individual. ▶[hermaphrodite](#), ▶[monoecious](#)

Cosmetic Surgery: Despite the earlier reservations attached with it, cosmetic surgery has become an accepted medical treatment for psychological problems such as the inferiority complex. The right to cosmetic surgery is part of individual liberty, although in many cases it may be an unnecessary and risky practice.

Cosmic Radiation: Cosmic radiation strikes the earth from interstellar space, partly directly from the radiating bodies, partly (primary) or emanating from the collision of nuclei with cosmic (secondary) radiation in the upper atmosphere. The amount of cosmic radiation varies according to altitude and it is very high at the height at which space vehicles are

located. The amount that falls on the surface of the earth is about 0.028 to 0.045 rad per year and increases substantially at higher altitudes. At 1000 ft it is ~2, at 5000 ft > 20, and at 9000 ft ~70 mrem. One may ingest ~40 mrem from food and water, on an average in the US. These figures should be corrected by a factor of about 0.8 because of protection by housing. For comparison, an average medical diagnostic chest X-ray delivers about 0.2 rad (but the gonads are protected). ▶[isotopes](#), ▶[radiation natural](#), ▶[atomic radiation](#), ▶[radiation hazard assessment](#), ▶[rem](#), ▶[rad](#); Curzio G et al 2001 Rad Prot Dosimetry 93[2]:125.

Cosmids: Approximately 5-kb cloning vectors are derived from phage λ DNA, containing one or two cohesive (*cos*) sites in the same orientation, an origin of replication (*ColEI*), and a selectable marker (*amp^R*). The cloning capacity of the plasmid is about 35–47 kbp because neither substantially smaller nor larger than the λ genome (\approx 49-kbp) can be packaged into the capsid (see in vitro packaging). For cloning, smaller DNAs *charomids* must be used. Into the linearized cosmid, the foreign DNA is ligated at appropriate cloning sites flanked by cosmid sequences. The *concatamer* is cut to head size to fill the capsid, with the assistance of the phage terminase protein (an endonuclease with a specificity of cutting near *cos* sites). After infection from *E. coli*, the cosmid recircularizes within the bacterial cell and due to the presence of the antibiotic resistance marker(s), the bacteria carrying the recombinant cosmid can be isolated. Cosmids can recombine with other plasmids (having homologous sequences) within *recA*⁺-bacterial strains, and the cointegrates can be isolated if both carry independent selectable markers. There may be a problem, however, with rearrangements because of the active *recA*. A number of specially designed cosmids are available and they have been used for particular cloning needs. Cosmid **pJBS** had been used successfully for chromosome walking. After the recombinant cosmid is isolated from a library, the cloned foreign DNA segment can be cut with restriction enzymes without destroying the vector that can be transformed into bacteria and can yield small fragments of potential use as probes for overlapping fragments in the original library. Cosmid **c2RB** carries 2 *cos* sites and ampicillin and kanamycin resistance. Concatenation can be suppressed after insertion of the foreign DNA by phosphatase treatment (that prevents the formation of phosphodiester bonds) or by directional cloning. There are two EcoRI sites in the vector flanking a single BamHI site and this makes it easier to walk from one recombinant site to the next because the two small fragments so generated can be used as probes to re-screen the original library for overlapping clones.

C

Cosmid pcos1EMBL carries tetracycline and kanamycin resistance, and the origin of replication of plasmid R6K (a replicator unrelated to Col1). With these plasmids the screening for recombinants can be carried out in vivo. Special cosmid vectors were developed for the transformation of animal cells. These carry antibiotic markers selectable in eukaryotic cells such as neomycin (*neo*), dihydrofolate (*dhfr*), hygromycin (*hph*), and other eukaryotic genes such as hypoxanthine-guanine phosphoribosyl transferase (*hprt*), thymine kinase (*tk*-), etc. The **pWE** series were used advantageously because of the ease of walking from one cosmid clone to another. They carry the phage T3 and T7 promoters on either side of NotI, an eight-base recognition site (GC↓GCGCGC) restriction endonuclease. The foreign DNA may be cloned into a BamHI site located between the phage promoters. After cloning, the cosmid is cut by restriction enzymes that do not affect the phage promoters. The cleavage products will contain small fragments adjacent to the promoters. The fragments that are downstream of the promoters are then transcribed into labeled RNA. These (radioactive) probes are further used to rescreen the library for overlapping fragments. Since NotI sites are rare in mammalian DNA, on the average about 1500-bp fragments are generated and frequently the NotI digests include the entire cloned fragment. These large fragments facilitate the construction of physical maps and may be useful in transformation because they may include the gene that is to be expressed. Some other pWE vectors may have polycloning sites rather than only the BamHI site. This may make cloning easier but may create problems in the hybridization probes because of background hybridization of the labeled RNAs. Cosmids are also used with plant DNA. ▶**vectors**, ▶**lambda phage**, ▶**charomids**, ▶**Rec**, ▶**library**, ▶**cosmid library**, ▶**directional cloning**, ▶**promoter**, ▶**downstream**; Sambrook KJ, MacCallum P 2006 Molecular Cloning. Cold Spring Harbor Lab. Press.

Cosmid Library: A collection of DNA fragments of a genome cloned in cosmid vectors. ▶**cosmids**, ▶**library**

Cosmid Mapping: Physical mapping of cosmid-contained DNA sequences. ▶**cosmid**, ▶**physical map**

Cosmid Walking: Cosmid walking applies the “chromosome walking” procedure to DNA sequences in a cosmid library. ▶**genome projects**

Co-Speciation: Co-speciation indicates joint evolution of two organisms, e.g., host and parasite. The measure of co-speciation is that the two phylogenies (on the basis of protein or DNA primary structure) are more similar than expected by chance. The simian

foamy RNA virus, a non-pathogenic retrovirus, provides rather strong evidence for co-evolution with Asian and African monkeys and apes based on the viral polymerase and the mitochondrial cytochrome oxidase subunit II structure (Switzer WM et al 2005 Nature [Lond] 434:376). ▶**speciation**, ▶**phylogeny**

Cost-Benefit Analysis: A cost-benefit analysis estimates the tradeoff between expenditure and return in a financial or biological investment.

Costello Syndrome (11p15.5): An autosomal recessive/dominant condition resulting in short stature, skin and hair anomalies, cardiomyopathy, reduced mental abilities, and increased chance of tumors. A deficiency of 67-kDa elastin-binding protein may be one of the basic problems. Mutation in human RAS increases the chance of occurrence of these defects (Aoki Y et al 2005 Nature Genet 37:1038). ▶**RAS**, ▶**cardiomyopathies**, ▶**Marfan syndrome**, ▶**Nonan syndrome**, ▶**cardio-facial-cutaneous syndrome**; Hinek A et al 2000 Am J Hum Genet 66:859.

Co-Stimulator: Cell surface proteins that encourage the interaction between T cell receptors and the antigen-presenting cell. Genes encoding such proteins may be transformed into cancer cells and interleukins, and other cytokines or cytokine-like proteins may reinforce their function. Painting on the tumor cells co-stimulatory proteins is simpler than transfection yet effective in vaccination. The effectiveness may be enhanced by the use of GPI anchors. ▶**CD80**, ▶**CD86**, ▶**CD28**, ▶**CD4**, ▶**CTLA-4**, ▶**tumor vaccination**, ▶**transfection**, ▶**GPI anchor**; Schwartz J-C D et al 2002 Nature Immunol 3:427.

Cost of Evolution: Evolution proceeds by replacing old alleles with new ones and as a consequence some individuals are sacrificed; these pay the cost of evolution according to Haldane. The proportion of eliminated zygotes = sq^2 and the proportion of survivors $\bar{w} = 1 - sq^2$ or in general term the *cost of natural selection*, $C = \int_0^t (sq^2 / \bar{w}) dt$ where s = selection coefficient [$\ln(p_t) - (\ln(p_0))$], q = allelic proportion, \bar{w} = fitness, t = time, dt = integral differentiation. ▶**evolution**, ▶**natural selection**, ▶**fitness**, ▶**selection coefficient**, ▶**allelic frequencies**

Co-Suppression: In co-suppression, when a gene is introduced by transformation into a cell, neither the resident nor the transgene copy of the same gene is expressed (repeat-induced gene silencing) or increasing the gene copy number reduces the degree of expression. Interestingly, in higher plants non-transgenic duplication (polyploidy) does not result in co-suppression. Co-suppression may be complete or incomplete and it may be reversible during development. It may result in sector formation. Co-suppression

was discovered in plants but may occur in other organisms too. The cause of the phenomenon may be methylation of the genes, post-transcriptional degradation of the mRNA, RNAi, special allelic interaction, or antisense RNA. The mechanism might have developed to suppress viral propagation or suppress transposable elements. In *Neurospora*, the *qde-3* encoded RecQ-family DNA helicase is a post-transcriptional silencer. ▶co-repressor, ▶methylation, ▶antisense technology, ▶transgene, ▶RIP, ▶transvection, ▶silencer, ▶paramutation, ▶epigene suppression, ▶quelling, ▶MSUD, ▶imprinting, ▶host-pathogen relationship, ▶QTL, ▶RNAi, ▶repetitive DNA, ▶silencer, ▶post-transcriptional gene silencing, ▶Bloom syndrome, ▶Werner syndrome; De Buck S et al 2001 Plant Mol Biol 46:433; Meza TJ et al 2002 Nucleic Acids Res 30:4556.

$C_{0t}1/2$: The index of the reassociation of nucleic acid molecules when the reaction is half completed. It is proportional to the unique sequences in the reannealing molecules. ▶ C_{0t} curve

C_{0t} Curve (pronounce cot): When single-stranded DNA molecules are mixed they may reassociate, depending on the homology between the two types of strands. The facility of reassociation is determined by the degree of homology of the reactants, their concentration and the time allowed for the annealing. These three parameters are expressed by the C_{0t} curve (see Fig. C170). The reaction depends to a great deal upon the amount of redundant sequences in the DNA and the complexity of the DNAs. Redundant sequences and palindromic DNAs can anneal rapidly because of their similarities. For unique sequences, it takes more time for the complementary sequences to collide.

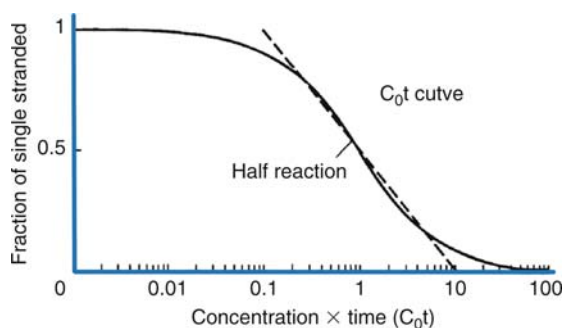


Figure C170. C_{0t} curve. The time course of an ideal second-order reaction illustrates the features of the C_{0t} curve of nucleic acid reassociation. The ordinate corresponds to the fraction of single-stranded molecules. The abscissa denotes the mole value per liter of the material, multiplied by time (usually in seconds) on a logarithmic scale. (Modified after Britten RJ, Kohne DE 1968 Science 161:529)

For the characterization of DNAs of different types, generally the half C_{0t} values are used, i.e., the time when the reassociation is half-completed (see Fig. C171). The reassociation of *E. coli* DNA generally takes place between C_{0t} values of about 0.1 and 10 (ca. 4.7×10^6 bp, mainly unique DNA), whereas for a large and complex genome of rye containing about 80% redundancy in the 7.9×10^9 bp DNA, it is within five orders of magnitude of C_{0t} (between 0.001 to 100) in contrast to the two orders of magnitude in the bacterium. If single-stranded homologous molecules are allowed to reanneal, the process can be represented as $\frac{dc}{dt} = -kc^2$ where c represents the molecular concentration, t = time of the reaction, and k = constant that depends only on the length of the nucleic acid molecules; d means the differential integral. After integration we get:

$\int_t^0 \frac{dc}{c^2} = -kdt$ and hence $\frac{c_0}{c}(-\frac{1}{c}) = -k_t^0(t)$ and $\frac{1}{c} - \frac{1}{c_0} = kt$ and if $t_{1/2} =$ the time when $c = c_0/2$ and $\frac{2}{c_0} - \frac{1}{c_0} = \frac{1}{c_0} = kt_{1/2}$ and if the concentration is expressed as mass (g/L) then:

$c_0 = C_0/M_r$ where the molecular weight (M_r) is in Daltons and the complexity becomes $C_{0t_{1/2}} = \left[\frac{1}{k}\right]M_r$.

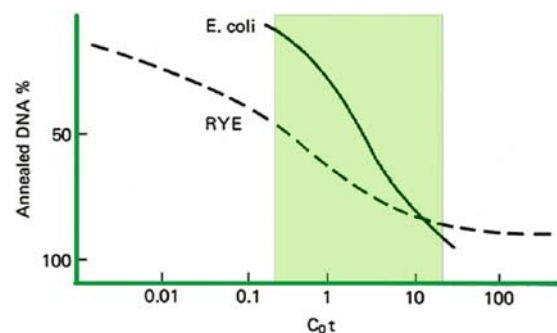


Figure C171. The reassociation kinetics of two genomes (7.9×10^9 bp of rye and 4.7×10^6 *E. coli*) of different complexities. The green shaded area extends to two orders of C_{0t} values and covers most of the range of *E. coli* DNA. In contrast, 11% of the rye DNA reassociated at 0.001 to 100 C_{0t} . The half reassociation value of the non-repeated sequences of rye may be estimated by dividing 7.9 billion by 4.7 million and it is ca. 1,681 and after multiplying this figure by 2.5 (the C_{0t} values at half reaction of the *E. coli* DNA), we obtain $1681 \times 2.5 \approx 4,202$ = the half reassociation value of the non-repeated rye. (Diagram and calculations were modified after Smith DB and Flavell RB 1977 Biochim Biophys Acta 474:82)

Cot Filtration: A procedure for separation of unique DNA sequences from repetitive sequences of the large eukaryotic genomes. The principle of the separation is shown in the entry above. The separated low-copy-number gene-rich fraction then can be cloned and subjected to sequencing, whereas the

highly iterated fraction is rather refractory to routine sequencing (Peterson PD et al 2002 Genome Res. 12:795). ►methylation filtration

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Cot Sequencing: ►cot filtration

C₀t Value: An index of the rate of reassociation of single-stranded DNA molecules. ►C₀t curve, ►kinetics of reassociation

Co-Transcription: ►operon

Cotransduction: More than a single gene is transferred by transducing phage if the genes are closely linked. ►transduction, ►bacterial recombination

Cotransfection: Cotransfection is transformation (genetic) by two or more genetically linked genes simultaneously. In the calcium phosphate precipitated donor DNA granules, non-linked DNA molecules may also be included and integrated into the animal cell simultaneously. ►transformation genetic [transformation of animal cells], ►calcium phosphate precipitation

Cotransformation: In cotransformation, donor DNA molecules containing closely linked genes may be taken up and integrated simultaneously into the bacterial chromosome or into the chromosomes of other organisms. ►transformation mapping, ►co-transfection

Cotranslational Transport: In cotranslational transport, the proteins synthesized on the ribosomes associated with the endoplasmic reticulum (rough endoplasmic reticulum) pass into the lumen of the endoplasmic reticulum during the process of translation. ►protein synthesis, ►endoplasmic reticulum, ►signal sequence; Wilkinson BM et al 2000 J Biol Chem 275:521.

Cotransport: Cotransport occurs when a transporter ferries two solutes simultaneously through a membrane.

Cotton: ►Gossypium

Co-Twin: A pair of twins. ►twinning, ►zygosis

Cotyledon: Seed leaf (actually an imprecise term because the seed before emergence may already have the initials of several leaves). At emergence, the dicotyledonous plants have two cotyledons, which have a nutritive storage role before and for awhile after germination. The monocots have only a single

very small cotyledon that has frequently a digestive role only. In dicots occasionally three or more cotyledons are formed as a developmental anomaly but tri-cotyledony is only exceptionally inherited (see Fig. C172). In zoology, the cotyledons mean the tufts or subdivisions on the placental surface of the uterus.



Figure C172. Di- and tricotyledonous seedlings

Coulomb (C): A unit of radiation measurement; $1 \text{ C/kg} = 1 \text{ R} \times (2.58 \times 10^{-4})$. ►R

Coulter Counters: Electronic equipments for counting cell numbers in a range of sizes.

Coumarin: A plant metabolic product arising from 4-hydroxycinnamate through oxidation (see Fig. C173). It gives rise to dicoumarol, a vitamin K antagonist. These compounds are abundant in some varieties of sweet clover (*Melilotus*) and if the coumarin content is high, the forage value is much reduced because animals may not eat it because of the bitter taste. After fermentation (silage), dicoumarol is formed that is very toxic due to its anti vitamin K and hemorrhagic effects. Plant breeding efforts have successfully reduced the coumarin content of some *Melilotus albus* varieties. Diethylaminocoumarin is a fluorophore. ►vitamin K, ►prothrombin deficiency, ►coumarin-like drug resistance

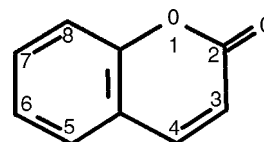


Figure C173. Coumarin

Coumarin-Like Drug Resistance: Due to an autosomal dominant gene some individuals are resistant to coumarin-like compounds such as warfarin, bishydroxycoumarin and phen-indione (anticoagulants).

These compounds are therapeutic agents in certain cases of surgery and in thromboembolic (blood clot forming diseases blocking arteries) diseases. ►blood clotting, ►antihemophilic factors, ►warfarin

Counseling, Genetic: Human geneticists can make predictions about the probability of recurrence risks in families affected by hereditary conditions and diseases such as birth defects, metabolic disorders, developmental problems, neurological or behavioral abnormalities, fertility problems, exposure to hazardous environment, consanguinity, pregnancy beyond age 35, etc. These predictions are based on family histories, cytological, biochemical, and molecular analyses. In Northern Europe, almost 12/1,000, and worldwide about 17/1,000 births are affected by single-gene defects. In Africa—although the rate varies regionally—on an average 7.4/1,000 births involved hemoglobin defects (sickle cell anemia). Consanguinity increases the genetic load substantially.

The completion of the physical mapping of the human genome will greatly improve the potentials of accurate genetic counseling by the availability of appropriate probes and nucleotide sequence information. Genetic counseling should be sought before marriage or procreation in families where risk is indicated. Participation is voluntary. The analyses may involve the prospective parents or the fetus may also be examined by amniocentesis. This procedure surgically withdraws with a syringe amniotic fluids 6–20 weeks following conception and analyzes the sloughed off, floating fetal cells by various methods. Under some circumstances of very high risks, termination of pregnancy may be opted for where there are no moral and/or legal objections. Only the family within the limits of the law can make the decision. The physicians or geneticists provide all the relevant facts but do not recommend the action(s) to be taken. Sometimes the counselor may, however, face the dilemma whether to reveal nonpaternity if this information does not entail health-related problems or if the diagnosis would jeopardize the emotional status of the counseled. From the viewpoint of genetics, selective abortion raises problems. If the families compensate for the aborted fetuses with new pregnancies, the frequency of the deleterious genes will rise in the population because the carriers may transmit the defective alleles and the problems are only postponed. If the carriers of serious hereditary defects refrain from reproduction, the frequency of these genes is supposed to decline eventually. The genetic counselor is a physician thoroughly trained in medicine and genetics and its cytogenetic, molecular, and statistical aspects, and is expected to be familiar with all the relevant techniques involved. Very often, because of the small

family size, penetrance, expressivity problems, variability of the syndromes, difficulties in obtaining candid information of family histories, especially about hereditary diseases with social stigmas, even the best qualified counselor may encounter difficulties. Besides being a good geneticist and an experienced physician, he/she must have sufficient background in psychology and ethics. Genetic and medical facts must be explained in terms easily understood by the families involved, whose level of education may vary from case to case. The counseling may be only limitedly effective because of problems in communication or the inadequate biological/genetical education of the counselee. Counseling is not supposed to follow any eugenic goal and is expected to be nondirective. The clients must be aware that genetic counseling may prevent family trauma, and may offer relief from nagging anxieties in cases when the recurrence risks are low, e.g., in the Downs syndrome and some other aneuploidies secures peace of mind. Also, some anomalies may be phenocopies and the genetics risks involved are practically nil. Since 1981, the American Board of Medical Genetics or the American Board of Genetic Counseling certifies genetic counselors. ►risk, ►genetic risk, ►recurrence risk, ►genetic counseling, ►empirical risk, ►utility index for genetic counseling, ►non-directiveness, ►amniocentesis, ►supportive counseling, ►carrier, ►gene therapy, ►OMIM, ►prenatal diagnosis, ►ART, ►confidentiality, ►genetic privacy, ►wrongful life, ►informed consent, ►bioethics, ►psychotherapy, ►selective abortion, ►genetic screening, ►consanguinity; Mahowald MB et al 1998 *Annu Rev Genet* 32:547; Weil J 2002 *EMBO Rep* 3:590; <http://www.genetests.org/>; Christianson A, Modell B 2004 *Annu Rev Genomics Hum Genet* 5:219; <http://www.geneclinics.org/>.

Count per Minute: ►cpm

Countercurrent Distribution: Countercurrent distribution partitions relatively small molecules between two liquids that are polar to a different extent. Both liquids are moved in a special apparatus in opposite direction between steps of equilibration.

Counter-Ion Condensation: The association of ions with the polyelectrolyte DNA; in B DNA there is about one anionic charge per 1.7 Å distance. In case the line charge spacing changes, the DNA may become unstable. ►DNA types; Fahey RC et al 1991 *Int J Radiat Biol* 59:885.

Count-Location Models: Count-location models consider that chiasmata are distributed uniformly and independently along the length of the chromosome. ►chiasma, ►stationary renewal process, ►mapping functions; Browning S 2000 *Genetics* 155:1955.

C

Counterselection: As per counterselection, in a hybrid population the two parental strains (each resistant, e.g., for a different antibiotic) may not survive in a medium containing both the antibiotics but the recombinants endowed with both of the resistance genes will survive. Thus there is a counterselection for the parental cells or strains. ▶[contraselection](#)

Coupled Reaction: In a pair of coupled reactions, the energy released by one reaction is utilized by the next,

Coupling Phase: In this phase, two or more recessive (or dominant) alleles occur in the same member of a bivalent chromosome (e.g., $\underline{A\ B}$ or $\underline{a\ b}$). Some geneticists call this arrangement *cis*. ▶[re-combination](#), ▶[repulsion](#), ▶[bivalent](#)

Courtship in *Drosophila*: Courtship in *Drosophila* is an extensively studied behavioral trait. Many genes are apparently involved but all appear to be pleiotropic and the mutations recovered affect more than one unrelated function. Some are affected in sex determination, others are visual or olfactory mutants or affect female receptivity or male fertility, or circadian rhythm, and others are involved in the “courtship song” of the flies (generated by the vibration of the wings). One component of the normal courtship is the GR68a pheromone receptor (under the control of the gene for double sex) that senses nonvolatile female pheromones. This receptor is located in about 20 male-specific gustatory bristles on the male foreleg (Bray S, Amrein H 2003 Neuron 39:1019). A better understanding of neuronal function and the availability of selection techniques will promote progress in this field. This as well as other behavioral traits can now be subjected to genetic and neurobiological analyses. ▶[behavior genetics](#), ▶[pheromone](#), ▶[copulation](#), ▶[sex determination](#); Greenspan RJ, Ferveur J-F 2000 Annu Rev Genet 34:205.

Cousin: The child of the sibling of an individual’s father or mother is a first cousin. The child of a first cousin is a second cousin or first cousin once removed. The cousins can be twice..... tenth, and so on removed depending on the steps in the relationship. News services reported that Prince Charles and Diana Spencer are 7th cousins once removed (see Fig. C174).

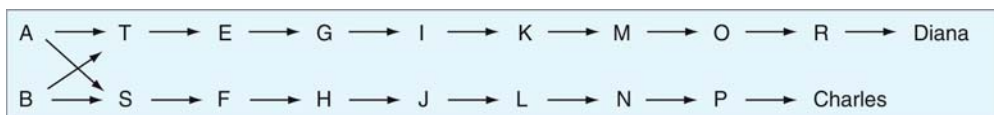


Figure C174. Diagram of the relations of the 7th cousin once removed

Accordingly their pedigree would be as shown. ▶[cousin-german](#)

Cousin-German: A first cousin. ▶[german](#)

Cousin Marriages: Marriages between cousins may increase the chances of defective offspring depending on the coefficient of inbreeding. Infant death rate during the first year of life among children of first cousins is approximately double relative to that in the general population. ▶[coefficient of inbreeding](#), ▶[controlled mating](#). Between 1959 and 1960, 0.08% of the Roman Catholic marriages were inter-first cousins, and among American Mormons during the period 1920–1949, it was 0.61%. In India, the marriages between first cousins, in some communities, were as high as 30% in the not-too-distant past. ▶[inbreeding coefficient](#), ▶[coefficient of coancestry](#), ▶[incest](#), ▶[genetic load](#); Fraser FC, Biddle CJ 1976 Am J Hum Genet 28:522.

Covalent Bond: Chemical linkage through shared electron pairs, e.g., (see Fig. C175).

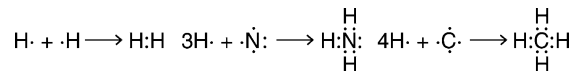


Figure C175. Covalent bond

Covalently Closed Circle: A circular macromolecule (plasmid) in which all the building blocks are covalently linked and thus there are no open ends.

Covariance: ▶[correlation](#)

Covarian Theory: The covarian theory interprets evolution on the basis of varying codons in a lineage-specific manner among the sites. ▶[codon](#), ▶[evolution](#); Penny D et al 2001 J Mol Evol 53:711.

Coverslip: Usually 0.13–0.25 mm thick glass (plastic) covers on microscope slides for flattening of specimens and/or protecting during examination by temporary or permanent seal.

Cowden Syndrome: Multiple hamartomas. ▶[multiple hamartoma syndrome](#)

Cowpea (*Vigna unguiculata*): A food and fodder crop of the tropics and subtropics primarily. All the 170 species have $2n = 2x = 22$ chromosomes.

Cowpea Mosaic Virus: The genome of the cowpea mosaic virus contains B-RNA and M-RNA. The former codes for Vpg in a polyprotein complex at the carboxy terminus. ▶Vpg

Cox: The symbol for cytochrome oxidase and cyclooxygenase proteins and genes. Mitochondrial DNA encodes three subunits and the nuclear DNA codes for 10. Cox-2-derived prostacyclin protects premenopausal mice from atherosclerosis (Egan KM et al 2004 Science 306:1954). Several drugs contain Cox-2 inhibitors to protect from inflammation, arthritis, and other symptoms of disease. Unfortunately, a higher risk of adverse cardiovascular effect and colorectal neoplasias are known to appear after a few years of use (Bresalier RS et al 2005 New Engl J Med 352:1092). ▶cyclooxygenase, ▶cytochromes, ▶menopause, ▶prostacyclins, ▶prostanoid

Cox Proportional Hazards Method: $\ln h(t) = \ln \alpha(t) + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_q x_q$ where h is the hazard, x_1, x_2, \dots, x_q are the variables of concern, and $\alpha(t)$ is the baseline hazard function at t time. The β values are determined by the maximum likelihood of occurrence. The method is generally used when the outcome is censored. ▶hazard, ▶maximum likelihood, ▶censoring; <http://www.medcalc.be/manual/cox-regression.php>.

Coxsackie Viruses (*Picornaviridae*): Coxsackie viruses have ~7,500 base single-stranded RNA genetic materials in particles of diameter 22–30 nm. Humans, monkeys, and suckling mice are susceptible to them and the viruses may cause damage to the nervous system, the respiratory and alimentary tracts, muscles, and internal organs, and may even induce autoimmune disease. Coxsackie B4 viral infection is associated with insulin-dependent diabetes and shares similarity with the Langerhans islet autoantigen glutamic acid decarboxylase. Many coxsackie virus B viruses interact with DAF (decay accelerating factor) and activate Abl kinase triggering Rac-dependent actin rearrangement that facilitates its movement of tight junctions where it interacts with the coxsackie virus and adenovirus receptor (CAR), and thus by permitting changes in the capsid facilitate release of the phage genome. Alternatively, CAR can interact with Fyn kinase and the phosphorylation of caveolin that transports the virus into the cell (Coyne CB, Bergelson JM 2006 Cell 124:119). ▶picornaviruses, ▶diabetes mellitus, ▶Langerhans islet, ▶CAR1, ▶ABL, ▶RAC, ▶DAF, ▶Fyn, ▶caveolin; Wan YY et al 2000 Proc Natl Acad Sci USA 97:13784.

Coyote: *Canis latrans* ($2n = 78$), the North-American canine; it can interbreed with domestic dogs ($2n = 78$) and the wolf ($2n = 78$).

C1p (C/p): A member of the Hsp100 ATPase family. ▶HSP

CP Complex: A nuclear dimer of Cdc68 and Pob3 proteins that regulates gene expression (activation and repression) by interacting with the promoter of budding yeast and modifying chromatin structure, respectively.

CP1: A mammalian transcription factor binding to the CCAAT box. ▶CDP, ▶CAAT box

CP1 (Cbf1/Cpfl): A centromere-binding ([A/G]TCAC [A/G]TG) yeast protein, it is a part of the kinetochore. The protein may affect chromosome segregation and methionine synthesis. ▶kinetochore

C11p11: A DNA probe used for the identification of certain cancer sequences.

CPB: ▶cetylpyridinium bromide

CPBs: mRNA cap-binding proteins. ▶eIF, ▶translation initiation

CPD: Cross-linked adjacent pyrimidine dimers, photo-products. ▶pyrimidine dimers

cpDNA (chloroplast DNA): The size of the cpDNA varies generally between 8 and 13×10^7 Da, it is a circular double-stranded molecule with 20–40 copies per chloroplast in higher plants and 80 copies in the *Chlamydomonas reinhardtii* alga. ▶chloroplasts, ▶chloroplast genetics, ▶Chlamydomonas

CPE (chemical penetration enhancer): CPE aid dermal absorption of cosmetics and drugs. These must overcome the resistance of the epidermis (corneum striatum) by fluidization of the lipid bilayer and should not cause irritation by denaturing the proteins in this layer. ▶drug development; Karande P et al 2005 Proc Natl Acad Sci USA 102:4688.

CpG Motifs (Cytosine-Guanine): CpG motifs of bacteria in unmethylated state induce murine B cells to proliferate and secrete antibodies. In the mammalian genomes these doublets are most commonly methylated. The methylated cytosine may be transmitted epigenetically through the germline. In the human genome, 78% of the promoters have high CpG content (Saxonov S et al 2006 Proc Natl Acad Sci USA 103:1412). ▶B cell, ▶epigenesis, ▶methylation of DNA

CpG Islands: Regions of 500 bp or less or more in 5' upstream of genes with CpG doublets. Their function is regulatory. The human genome has about 29,000 CpG islands. The doublets in these islands (especially

C

in housekeeping genes) are protected from methylation and are instrumental in the transcription of about half the mammalian genes. The CpG islands of imprinted and lyonizing genes may be methylated and silenced. Methylation may increase by aging and *in vitro* culture. The 5'-CpG role in silencing is mediated by the methyl-CpG binding protein (MeCP) that interacts with a histone deacetylase complex. In cancer cells, the tumor suppressor genes appear to be methylated. Hundreds of genes may be promoter-methylated in a single cancer (Jones PA, Baylin SB 2007 Cell 128:683). Some cancer cells contain hypermethylated CpG islands. The hypermethylation may silence the tumor suppressor genes. By computationally mapping all NotI or other methylation-sensitive restriction enzyme sites, methylation events can be defined with single nucleotide precision through the entire genome. The methylation-sensitive enzymes do not cleave the normal recognition site when the C is methylated. Therefore, the methylation status (silencing/expression) can be assessed in a tissue-specific manner (Ching T-T et al 2005 Nat Genet 37:645). ▶isochores, ▶histone deacetylase, ▶methylation of DNA, ▶trichostatin, ▶housekeeping genes, ▶imprinting, ▶lyonization, ▶tumor suppressor, ▶trinucleotide repeats, ▶RLGS; Jones PA, Taki D 2001 Science 293:1068.

CpG Suppression: CpG suppression is actually not a suppression mechanism. Some regions of the genomes are relatively low in CpG sequences and they may be methylated during most of the life of eukaryotes. ▶CpG islands

cPLA₂: cPLA₂ catalyzes the hydrolysis of glycerophospholipids, yielding arachidonic acids ▶fatty acids and lysophospholipids (membrane lipid). It is activated by MAP kinase in the presence of Ca²⁺. ▶integrin, ▶MAP; Blaine SA et al 2001 J Biol Chem. 276:42737.

cpm (count per minute): A measure of radioactivity; 1 μCurie ≅ 1,000,000 cpm. ▶dpm

Cpn: ▶chaperonins

Cpn10: The mammalian homolog of the bacterial GroEs chaperonin in the mitochondria. ▶GroES

Cpn21: A chloroplast chaperonin (homolog of GroES) encoded in the nucleus; it interacts with Cpn60 (homolog of GroEL). ▶GroEL

Cpn60: Mammalian mitochondrial and plant chloroplast analogs of the bacterial GroEL chaperonin. ▶GroEL

CPP32: A proenzyme of apopain. ▶apoptosis, ▶apopain, ▶cysteine proteases, ▶Yama

Cpr: ▶cyclophilins

CPR (cell cycle progression restoration): Cyclin-dependent human genes involved in relieve of cell cycle arrest by pheromones, function as molecular chaperones and transcription factors, control morphogenetic pathways (carcinogenesis), etc.

CPSF (cleavage-polyadenylation protein factor): CPSF mediates the formation of the 3'-end of the mRNA
▶transcription factors, ▶polyadenylation signal, ▶symplekin

cR: ▶CentiRay

CR Lines of Mice: ▶congenic resistant

CRAb (chelating recombinant antibody): An antibody specific for two adjacent and non-overlapping epitopes of a single antigen molecule, generated by chelating. This increases specificity. ▶epitope, ▶antigen, ▶chelation, ▶antibody

CRAC: Calcium release-activated ion channel (Yeromin A et al 2006 Nature [Lond] 443:226; Prakriya M et al 2006 Nature [Lond] 443:230). ▶ion channels

CRAF-1: A protein factor interacting with the CD40 cytoplasmic tail by a region similar to the tumor necrosis factor receptor (TNF-α) associated factors (TRAF). CRAF is required for CD40- binding and dimerization. CRAF has five Zn-fingers and a Zn-ring finger. It participates in signal transduction. ▶CD40, ▶TRAF, ▶TNF, ▶signal transduction, ▶zinc fingers, ▶ring finger; Luttrell LM et al 2001 Proc Natl Acad Sci USA 98:2449.

CRAFT (Cre Recombinase Reporter Assay for Translocation): CRAFT is used to monitor the nucleoprotein VirB/D4 agrobacterial virulence gene transport system to identify translocation into the plant cell. ▶virulence genes of Agrobacterium; Vergunst AC et al 2000 Science 290:979.

Craniofrontonasal Syndrome (CFNS, craniofrontonasal dysplasia/dysostosis, Xq12): CFNS is probably dominant with greater expression in the heterozygous females than in the hemizygous males. It is characterized by several skeletal and facial abnormalities and wiry hair. Mutations in the EFN1 gene, which encodes the ephrin-B1 ligand for Eph receptors, are involved.

Cranio metaphyseal Dysplasia (CMDD, 5p15.2-p14.1): A dominant malformation (outgrowth and sclerosis) of the head bones. Mutation occurs in the ankylosis gene that encodes a 492-amino acid transmembrane protein controlling pyrophosphate level and it is expressed in the joints and in other tissues. A recessive form (CMDR) is encoded at 6q21-q22. ▶head/face/brain defects; Reichenberger E et al 2001 Am J Hum Genet 68:1321.

Cranioorodigital Syndrome (otopalatodigital syndrome type II): An X chromosomal head/face/brain defect, which has symptoms overlapping with those of otopalatodigital syndrome, and is encoded in the same area of human chromosome Xq28. ▶otopalatodigital syndrome, ▶head/face/brain defects

Craniosynostosis Syndromes: Craniosynostosis syndromes occur in a great variety and involve premature closure of the sutures of the skull, resulting in facial malformations. The defect is in one of the fibroblast growth factor receptors (FGFR). Prevalence is in the 4×10^{-4} range. Most of the syndrome types are under autosomal recessive control. Attenuation of FGFR signaling by pharmacological intervention could be applied for the treatment of craniosynostosis or other severe bone disorders (caused by mutations in FGFRs) that currently have no treatment (Eswarakumar VP et al 2006 Proc Natl Acad Sci USA 103:18603). ▶Crouzon syndrome, ▶Chotzen syndrome, ▶Apert syndrome, ▶Pfeiffer syndrome, ▶Marfanoid, ▶Shprintzen-Goldberg syndrome, ▶Gorlin-Chaudhry-Moss syndrome, ▶Muenke syndrome, ▶Antley-Bixler syndrome, ▶MSX; Cohen MM Jr, MacLean RE eds. 2000 Craniosynostosis, Oxford Univ. Press, New York.

Cranium: The skeleton of the head, excluding the bones of the face. It is the container of the brain. ▶brain human; Helms JA, Schneider RA 2003 Nature [Lond] 423:326.

Cranium Bifidum: Cleft or fission on the head. ▶frontonasal dysplasia

Crassulacean Acid Metabolism: Some succulent plants can store large amounts of acids (malate), which are formed during the night and whose level drops during the day. This system of photosynthesis fixes carbon with the aid of phosphoenolpyruvate carboxylase, and generates the C_4 oxaloacetate, as in other C_4 plants, rather than through ribulose-1,5-bisphosphate carboxylase/oxygenase, as in C_3 plants. ▶ C_3 plants, ▶ C_4 plants; Luttge U 2000 Planta 211:761.

CRB: A cell cycle checkpoint protein recruited to DNA breakage sites. It is regulated by methylation of Histone 4 lysine 20. ▶checkpoint; Sanders SL et al 2004 Cell 119:603.

CRE: Cyclic AMP-response elements (TGACGTCA), with DNA sequences ~100 nt (nucleotide) upstream of the TATA box of the transcription unit of genes responding to cAMP. Gene expression by cAMP also requires protein kinase A action on the 43-kDa

accessory protein CREB. ▶CREB, ▶TATA box, ▶cAMP, ▶TORC, ▶protein kinase, ▶Cre/LoxP

Creatine ([N-aminoiminomethyl]-N-methylglycine): Creatine, in the form of phosphocreatine, is a major source of energy generation (kcal/mol = 10.3). Creatine kinase catalyzes the reaction: phosphocreatine + ADP \rightleftharpoons ATP + creatine.

Creatine Deficiency: Guanidoacetate methyltransferase deficiency (GAMT, 19p13.3). Amidinotransferase catalyzes the conversion of glycine into guanidoacetate, and from that GAMT generates creatine with S-adenosylmethionine methyl donor. The clinical symptoms involve postural and locomotive defects due to brain and muscular anomalies and very low creatine excretion. A creatine transport defect (CT1/SLC6A8, Xq28) also generates creatine deficiency. Salamons GS et al 2001 Am J Hum Genet 68:1497.

Creationism: The doctrine about how the universe came into existence based on an oracle, and suggesting that organisms are as we see them at present because they have been so created and ordained. Another important aspect is “that the intellectual soul is created by God at the end of human generation, and this soul is the same time sensitive and nutritive” (Thomas Aquinas, 13th CE). According to the Tertullian (2nd–3rd CE) *transducianism*, both soul and body are conceived and formed at exactly the same time. Some types of creationist ideas exist in many religions, including Hinduism (Hare Krishnas), and native American and Pagan religions. Creationism is not an entirely monolithic view, variations exist but all creationist ideas are united in negating evolution as presented by modern science. Several Christians, Roman Catholics, and Protestants accept evolution by assuming that God could have created the evolutionary mechanism, which led to the development of the biological systems as we experience them. The fossil record is a serious obstacle to the logic of creationism, and posits a difficulty in explaining its divine purpose. It is unfortunate that science be mixed with faith or politics. Of course, scientists may be religious and may assume political views. Karl Popper (The Logic in Scientific Discovery. Hutchinson, London, p. 48) succinctly put forth the essence of science: “...I refuse to accept the view that there are statements in science which we have, resignedly, to accept as true merely because it does not seem possible, for logical reasons, to test them.” ▶evolution, ▶intelligent design, ▶paranormal; Numbers RL 1982 Science 218:538; Evans EM 2001 Cognit Psychol 42:217; Pennock RT 2003 Annu Rev Genomics Hum Genet 4:143; evolution teaching web sites: <http://www.nationalacademies.org/evolution>; <http://evolution.berkeley.edu/>, human evolution: <http://www.talkorigins.org/faqs/homs>.

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Creativity (<http://www.crea.server.de/>): Creativity in research implies the impact of work for the advancement of a particular scientific endeavor. The goals are to identify individuals and institutions, both in Europe and the USA, which have a record of creative research. The aim is to identify knowledgeable experts in targeted categories such as in the fields of human genetics and nanotechnology, and to then ask these experts to nominate highly creative research. The aim is an understanding of the institutional and organizational conditions under which creative researchers have worked. It is hoped that the knowledge gained from the case studies will facilitate recommendations about the design of science policy to support innovative research.

CREB: A CRE (cyclic AMP-response element) binding protein that requires phosphorylation at a serine residue at position 119 or 133 for transcriptional activity. Transactivation of CREB by PK-A requires the glutamine-rich constitutive activator domain (Q2) and the kinase inducible domain (KID, 58 amino acids modulatory sequence), which endow it with independent functions but may work synergistically. KID recognizes PK-A and the transcription complex, and is important for transactivation. There are about 50,000 CREB molecules/cell, mainly bound to chromatin. The CREB family also includes CREM and ATF-1, all subject to phosphorylation by protein kinase A. Active calcium channels also stimulate CREB activity.

CREB apparently activates T lymphocytes involving phosphorylation of CRE and that induces transcription factor AP1, leading to the production of interleukin-2 and to the progression of the cell cycle (see Fig. C176).

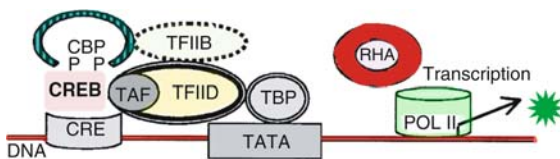


Figure C176. CREB. One of the functions of the CREB protein. CRE (cyclic amp response element) is bound by CREB that is phosphorylated by CBP (CREB-binding protein). TBP (TATA box binding protein) And The General Transcription Factors TFIID, TFIIB as well as TAF130 (transcription-associated protein) congregate at the TATA box. RHA (an RNA helicase) and POLII (RNA polymerase II) are required for transcription. The system may require activation by hormones through G proteins, cAMP, protein kinase A (PKA) and the RAS, RAF, MEK, RSK signal transduction pathways. (Modified after Shaywitz AJ, Greenberg ME 1999 Annu Rev Biochem 68:821)

The CREB kinase is apparently identical with RSK2, a member of the RAS family. Mutations in CREB have been implicated in the Rubinstein-Taybi syndrome, in fusions with the MOZ (monocytic leukemia zinc finger protein) in case of acute amyloid leukemia (AML), and histone acetyl transferase displacement by AP1, leading to transformation. The CREB-binding protein, CBP and p300, by histone acetyltransferase activity, assist the assembly of the transcriptional complex at the promoter. [CRE](#), [CREM](#), [ICER](#), [ATF](#), [TAX](#), [cAMP](#), [CBP](#), [calmodulin](#), [T cell](#), [AP1](#), [cell cycle](#), [immune system](#), [RAS](#), [signal transduction](#), [Rubinstein-Taybi syndrome](#), [leukemia \[AML\]](#), [transactivator](#), [p300](#), [CBP](#), [cAMP](#), [TAF](#), [transcription factors](#), [RHA](#), [PKA](#), [RAS](#), [RAF](#), [MEK](#), [RSK](#), [signal transduction](#), [trinucleotide repeats](#); Shaywitz AJ, Greenberg ME 1999 Annu Rev Biochem 68:821; Vo N, Goodman RH 2001 J Biol Chem 276:13505; Zhang X et al 2005 Proc Natl Acad Sci USA 102:4459; CREB target genes: <http://natural.salk.edu/CREB>.

Credible Interval: The credible interval is similar to the confidence interval; and is calculated on the basis of posterior probability distribution. It indicates the range within which a certain parameter is expected to occur. [confidence interval](#)

Cre/loxP: A P1 phage recombinase system affecting specific target sites. It can also be used in various eukaryotes for mediating site-specific recombination or chromosomal breakage (see Fig. C177). The Cre/loxP system has been successfully exploited for site-specific recombination and the generation of knock-outs. The Cre protein (38-kDa) is a recombinase with specific recognition for the 34 bp *locus of crossing over of P1 (loxP)*, a pair of palindromic sequences and recombination takes place within the 8 base central core (underscored at the sites delineated by red line. Note the inverted repeats left and right from the underscored octad signs (see Fig. C178). When Cre cuts the DNA, a phosphotyrosine intermediate is formed. Eliminating the phosphodiester bonds at \sim allows recombination to take place. The Cre recombinase can be targeted by choosing tissue-specific promoter (Zhou L et al 2002 FEBS Lett. 523:68).

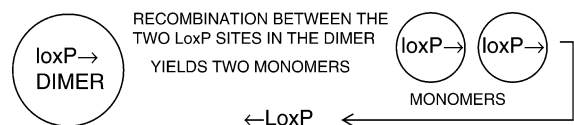


Figure C177. Recombination at loxP

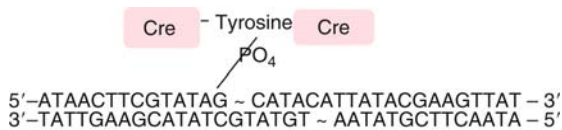


Figure C178. Cre recognition site

In animal cell cultures, the Cre recombinase may induce single and double-strand breaks in the DNA and may slow down cell proliferation. At low concentration, the disadvantageous features can be avoided. ►site-specific recombination, ►Flp/FRT, ►chromosomal rearrangements, ►targeting genes, ►integrase, ►resolvase, ►homing endonuclease, ►ligand-activated site-specific recombination, ►knockout; TAMERE, *Genesis* 2000, 26:99–165; Sauer B 1998 *Methods* 14:381; Zheng B et al 2000 *Mol Cell Biol* 20:648; Van Duyne GD 2001 *Annu Rev Biophys Biomol Struct* 30:87; Loonstra A et al 2001 *Proc Natl Acad Sci USA* 98:9209; Pfeifer A et al 2001 *Proc Natl Acad Sci USA* 98:11450; Seligman LM et al 2002 *Nucleic Acids Res* 30:3870.

CREM a and b (modulator of CRE): CREB-related transcriptional repressors, but CREB is a transcriptional activator. ►CRE, ►CREB, ►ACT

Cremello: A color of horses (see Fig. C179) of *AabbCCDD* genetic constitution.



Figure C179. Cremello

Crenate: has a tooth-like round protrusion.

Crepis: Composite flowers with chromosomes favorable for cytological studies (see Fig. C180). *C. capillaris*, 2n = 6; *C. tectorum* 2n = 8; *C. rubra* 2n = 10; *C. flexuosa* 2n = 14; *C. biennis* 2n = 40.

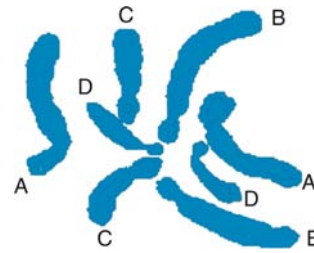


Figure C180. *Crepis parviflora* karyotype

Crest (calcium-responsive activator of transcription): A nuclear protein interacting with CREB-binding protein. It regulates dendrite development in the brain ►CREB, ►dendrite; Aizawa H et al 2004 *Science* 303:197.

Cretaceous Period: 137 to 63 million years ago when the first human ancestors appeared. ►geological time periods

Cretenism: A hereditary or congenital deficiency of thyroid hormone, causing mental and physical retardation. ►goiter

Creutzfeldt-Jakob Disease: A degenerative nerve disorder that begins with forgetfulness and nervousness, most commonly at middle age, and sometimes earlier or later, and after a year or two progresses into jerky movement of the hands, insecure walk, and expressionless face. These symptoms overlap with Gerstmann-Straussler disease and the two are probably identical basically, although within both diseases different types of manifestations have been observed. The diseases are not limited to humans but in sheep (scrapie), goat, and rodents highly similar nerve degenerations have been described. Amyloid protein deposits are found in the brain of afflicted individuals. The biochemical bases of the disorder was attributed to defects in the prion protein (PRP), a 27 to 30-kDa glycolipoprotein. The structural gene of PRP was assigned to mouse chromosome 2, and another gene in chromosome 17 was held responsible for the length of the incubation period of the disease. In humans, the PRP gene is located in chromosome 20p12-pter. It appears that PRP is a normal protein of the nervous system but proteolytic cleavage, amino acid replacements, insertions of 144 to 150 base pairs, and insertions of 5 to 9 or more octapeptide repeats in between the amino acids encoded by codons 51 and 91 may trigger the disease. The most commonly observed Pro→Leu replacement at codon 102 was attributed to the ataxia symptoms, but changes at

codon 117 (Ala→Val), 200 (Gln→Lys) and others were found to be associated with the degenerative phase of the PRP.

The injection of infected brain material into chimpanzees and other animals reproduces the disease. Since the infectious material does not contain any detectable amount of nucleic acid, scrapie, Creutzfeldt-Jakob (CJS), and the Gerstmann-Straussler (GSS) diseases are considered to be the first infectious protein diseases. These diseases occur in a familial manner, and it is not exactly known when and how the genetic determination of the degeneration occurs. It has been detected among all ethnic groups; in some its frequency is much higher than in others. Among the Jews of Libyan origin, the incidence was reported to be 4×10^{-5} , nearly 50 times higher than in the general population. In addition, 41 to 47% of the cases observed were familial whereas in some other populations only 4 to 8% appeared familial. The nv (new variant) CJS is supposed to be the result of human infection by animal encephalopathy inducing prions. Administering first an intracerebral injection of low effectiveness prion protein (SY) to mice, and subsequently an inoculation with a highly aggressive prion, FU, substantially delayed the expression of the disease. (Manuelidis L, Lu ZY 2003 Proc Natl Acad USA 100:5360). This observation appears similar to that involving the prevention of viral superinfection by another strain of the virus.

Between 1983 and 1985 in France, 968 children were treated with human growth hormone contaminated by CJS prions of human brain, and by 2005, 101 had died from the disease and several others infected (Casassus B 2005 Science 307:1711).

►prion, ►kuru, ►encephalopathies, ►Gerstmann-Straussler disease, ►bovine spongiform encephalopathy, ►fatal familial insomnia, ►Alpers progressive infantile poliodystrophy, ►superinfection; <http://www.cdc.gov/ncidod/diseases/cjd/cjd.htm>; <http://www.cjd.ed.ac.uk>.

Cri du Chat (cat cry): A deletion in the short arm of human chromosome 5 involves mewing like voice, mental and growth retardation and other disorders.

Cricket (*Gryllus campestris*): Orthoptera, 2n male = 29, female 2n = 30. The Mormon cricket (*Anabrus simplex*) of North America (see Fig. C181) is a migrating species (traveling 2 km/day); the migration is driven by the need of salt of the large population. The paucity of protein food promotes cannibalism of peers (Simpson SJ et al 2006 Proc Natl Acad Sci USA 103:4152).

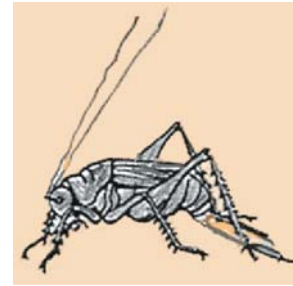


Figure C181. Cricket

Crigler-Najjar Syndrome (bilirubin/uridine glucuronosyl transferase deficiency, UDPGT): A recessive, human chromosome 1q21-q23 defect; causes a non-hemolytic jaundice, hyperbilirubinemia and, in case of total deficiency of UDPGT, early infant death results in case of kernicterus. Phototherapy and liver transplantation are possible treatments. Helper-dependent adenoviral vector (free of viral coding sequences) carrying the UDPGT 1A1 gene transferred to rat disease model and expressed in the liver, has been seen to reduce bilirubin glucuronides from 5 mg/dl to <1.4 mg/dl (wild type level) at negligible toxicity (Toietta G et al 2005 Proc Natl Acad Sci USA 102:3930). Partial deficiency of the enzyme (in type II form) is tolerated. ►uridine diphosphate glucuronyl transferase, ►hyperbilirubinemia, ►Dubin-Johnson syndrome, ►Gilbert syndrome, ►kernicterus, ►gene therapy, ►adenovirus

Criminal Behavior: Criminal behavior may have some genetic component but the overwhelming motivation is provided by the family and social and economic conditions. The use of drugs, alcoholism, broken family ties, poverty, unemployment, etc. are major causative factors. ►behavior in humans, ►behavior genetics

Crinkly-4: A plant TNF/EGF transmembrane receptor. ►TNF

CRIP: A group of proteins with LIM and additional domain(s). ►CRP, ►PINCH, ►LMO, ►LIM

Crisis in Animal Cell Culture: ►Hayflick's limit

CRISPR (clustered regularly interspaced short palindromic repeats): CRISPR are distinctive features of the DNA genomes of most bacteria and archaea. After viral challenge, bacteria integrate new spacers derived from phage genomic sequences. Removal or addition of particular spacers modify the phage-resistance phenotype of the cell (Barrangou R et al 2007 Science 315:1709). ►virus resistance

Criss-Cross Inheritance: Criss-cross inheritance is characteristic for X-chromosome linked recessive mutations. The recessive genes follow the pattern of inheritance of the X chromosome; they are expressed in the hemizygous male but only in the homozygous female (see Fig. C182).

In case the female is heterogametic and the male is homogametic, like in the *Lepidoptera* or birds, the inheritance follows the mirror image of what is shown in the diagram. ▶[sex linkage diagram](#)

Criss-cross inheritance can be observed in humans as well. All the offspring of a red-green color-blind father is expected to be normal but all the male children of a color-blind mother are expected to be affected. Some of the male grandchildren of color-blind grandfathers will be color-blind, although their sons (the fathers of the grandsons) have normal vision.

Cristae: Invaginations of the inner membranes of the mitochondria. ▶[mitochondria](#)

Critical Population Size: Although in a monogenic Mendelian F2 generation, 1/4 of the population is expected to be homozygous recessive, it rarely happens that every fourth individual meets this expectation. Therefore, it may be important to know how many individuals are needed in F2 to find at least one of this desired phenotype. The statistical solution is a device that rules out the case where all the individuals would be of the undesired type (3/4), e.g., $(3/4)^n = 1 - P$ where the (3/4) is the non-recessive class, (n) the number of individuals required in the population, and P = probability. Thus, $(3/4)^n = 1 - 0.95$ must be solved for (n), $n(\log 3 - \log 4) = \log 0.05$,

hence $n = (\log 0.05)/(\log 3 - \log 4) = -1.30/(0.477 - 0.602) = 10.4$, i.e., 11 (because fractions of individuals do not exist and the 0.95 probability is valid for 10.4 or more). Therefore, at 0.95 probability, only 11 individuals give an assurance of finding at least one double recessive. The procedure is similar to that, when we wish to determine the critical population size with a segregation ratio of 15:1 at 0.99; $n = \log 0.01/(\log 15 - \log 16) \approx 72$. Similar calculations are useful for calculating the minimal population size required for the recovery of a mutant individual after mutagenic treatment if we know (or guess) the induced mutation rate. ▶[genetically effective cell number](#), ▶[mutation rate](#); Mather K 1957 The measurement of linkage in heredity, Wiley, New York.

Critical Value: The critical value must be exceeded to reject the null hypothesis in a statistical test.

Criticism of Genetics: The criticism of genetics essentially shares the same elements as those of other scientific fields. In most cases where genetics is criticized, the motivation to do so can be attributed largely to perverse political systems. However, some biologists too deserve to be condemned for their attempts to pursue negative eugenics, racism, experimentation with biological warfare, inappropriate use of atomic energy, careless use of industrial, agricultural and medical chemicals, distortion of population genetic principles applied to environmental problems, cloning of animals and possibly humans, genetic discrimination on the basis of genotyping information, modifying genes of plants, animals and humans by genetic engineering or selecting special

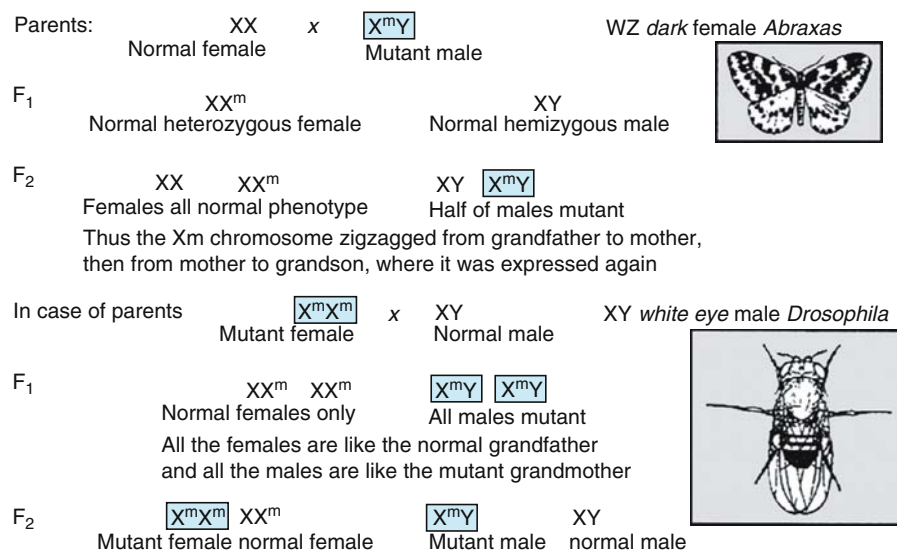


Figure C182. Criss-cross inheritance

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traits on the basis of preimplantation screening, etc. Some of the critiques argue that science cannot be left to scientists and the general public must be vigilant and reserve the decision-making for itself. Some “scientists” also support this view. The problem with this view is that how can the layperson make decisions without being fully familiar with a particular field of science. A solution appears to be to increase the continuous education on the progress of science. The motives behind the accusations are frequently sensationalism and/or attempts to gain political and financial advantage. ►atomic radiation, ►radiation effects, ►chemicals hazardous, ►environmental mutagens, ►biological containment, ►genetic engineering, ►selection conditions, ►mutation, ►eugenics, ►nuclear transplantation, ►ART, ►GMO, ►bioethics, ►ethics, ►informed consent, ►public opinion; Reilly PR 2000 Annu Rev Genomics Hum Genet 1:485; American Society of Human Genetics, Commentary 2002 Am J Hum Genet 70:1; for a biased negativism see Bowring F 2003 Science, Seeds and Cyborgs: Biotechnology and the Appropriation of Life. Verso Books, New York.

Crk: An adaptor protein in a signal transduction pathway, and containing SH2-SH3-SH3 domains. It requires phosphorylation between the two SH3 domains (by the Abl tyrosine kinase). ►signal transduction, ►SH2, ►SH3, ►abl; Feller SM 2001 Oncogene 20:6348.

CRM: Cross-reacting material is a serologically identifiable protein (generally the product of a gene that fails to display enzyme activity). CRM[−] designates a phenotype without an immunologically detectable protein. ►immune response

CRM (cis-regulatory module): ►cis, ►module, ►cis-regulatory module

CRM1/XPO1 (exportin): A nuclear protein, which mediates the export of polypeptides with Leu-rich sequences of the nuclear export signals (NES). It works in cooperation with RanGTP. ►nuclear pore, ►RAN, ►nuclear export sequences, ►nuclear localization complex, ►snRNA; Fornerod M et al 1997 Cell 90:967; structure: Petosa C et al 2004 Mol Cell 16:761.

CRMP-62 (collapsin response mediator protein): A M_r 62 K protein required for axon extension in chickens and *Xenopus*. ►collapsin, ►UNC-33; Ricard D et al 2001 J Neurosci 21:7203.

crRNA: (complementary RNA): A DNA transcript. ►cDNA

Cro repressor: The *cro* repressor of the λ phage, cooperatively with *cI*, regulates lysogeny. ►lambda phage

Crocodile: ►alligator

Crohn Disease (CD, regional enteritis, 14q11-q12): CD, an autosomal recessive inflammation of the bowel, is a familial condition because 10% of the affected individuals have relatives with the same affliction yet the genetic control is unclear. Ashkenazi Jews have increased (2–4 fold) risk to this disease. It is likely that more than a single genetic factor is involved in Crohn disease. A recessive gene for inflammatory bowel disease (IBD1) is located at 16p12-q13. Within this site, mutations in the NOD2/Apaf gene have been identified. The wild type allele of this gene activates NF-κB that senses the presence of bacterial lipopolysaccharides. Some NOD2 variants may alter thus the susceptibility to bacteria. TNF-α has been implicated in the symptoms. Genetic factors for CIBD and ulcerative colitis (UC) have been located also to human chromosomes 3p26, 7q and 21. The 7q region includes the MDR1 (multidrug resistance locus), besides one form of Crohn disease, and the similar but not identical ulcerative colitis (Brant SR et al 2003 Am J Hum Genet 73:1282). Two new bowel diseases have been mapped to 5q31-q33 (Rioux JD et al 2001 Nat Genet 29:223) and 19p13 (Rioux JD et al 2000 Am J Hum Genet 66:1863). At 1p31, the IL23R gene encodes a subunit of the receptor for proinflammatory interleukin-23 (Duerr RH et al 2006 Science 314:1461). GWA revealed involvements also of an intergenic region on 10q21.1 and a coding variant in ATG16L1, which is expressed in intestinal epithelial cell lines and whose functional knockdown abrogates autophagy of *Salmonella typhimurium*, suggesting that autophagy and host cell responses to intracellular microbes are involved in the pathogenesis of Crohn disease. There were also strong associations in the genomic regions encoding the paired-like homeobox (PHOX2B, 4p12), neutrophil cytosolic factor (NCF4, 22q13.1), and a predicted gene at 16q24.1 (Rioux JD et al 2007 Nat Genet 39:596). Some studies indicate the presence of *Mycobacterium paratuberculosis* RNA sequences in the clinical samples obtained from patients. The drinking water may be the source of infection. The cause of the disease is probably the immune system's aggravated reaction to intestinal bacteria (Cominelli F 2004 New Engl J Med 351:2045). ►Apaf1, ►cadherin, ►TNF, ►CIBD, ►CARD, ►NEMO, ►Blau disease, ►multidrug resistance; Parkes M et al 2000 Am J Hum Genet 67:1605; Ogura Y et al 2001 Nature [Lond] 411:603; Lawrance IC et al 2001 Hum Mol Genet 10:445; Sugimura K et al 2003 Am J Hum Genet 72:509; Schreiber S et al 2005 Nat Rev Genet 6:376;

<http://www.niddk.nih.gov/health/digest/pubs/crohns/crohns.htm>.

Cro-Magnon Men: ►Neanderthal people

Crop Plants: Barley, wheat, potato and pea EST and annotations:

<http://pgrc.ipk-gatersleben.de/crest/>; ►legumes, ►plant genomics database, ►EST, individual plants.

Cross: Mating between individuals of not-identical genetic constitution.

Cross Breeding: ►cross-fertilization

Cross Feeding: ►channeling, ►syntrophic

Cross Fertilization (allogamy): Cross fertilization takes place when the sperm and the egg of two different individuals of different genotypes are combined in the zygote.

Cross Fostering: A procedure to test how much of a behavioral trait is hereditary and how much of it is due to the influence of the postnatal environment. Pups are separated from the natural mother and are given to foster mothers belonging to another inbred strain and then the behavioral differences compared with those individuals, which were reared with the birth mother.

Cross Presentation (cross-presentation, cross-priming): The transfer of antigen from antigen-bearing cell to antigen-presenting cell (dendritic cell). It is called cross presentation because the antigens are not directly transferred to the T cells. The process may involve phagosomes and MHC class I- but also class II-restricted antigens. The phagosomal pH is regulated by NOX2 (NSDPH oxidase). In the absence of NOX2, the dendritic phagosomal lumen is acidified, degradation is increased, and cross-presentation is impaired (Savina A et al 2006 Cell 126:205). The result of cross-presentation may be either cross-priming of the cytotoxic T cells or T cell tolerance (cross tolerance). Cross presentation may involve many types of antigens, e.g., tumors, grafts, viruses, and even self tissues or enzymes and other proteins delivered by cell adsorption. A high dose of the antigen is favored. Cross presentation occurs with a few days delay of the host compared what occurs with professional antigen presenting cells. Cross presentation is different from the mechanism used by professional antigen presenting cells. ►antigen presenting cell, ►MHC, ►T cell, ►phagocytosis; Heath WR, Carbone FR 2001 Annu Rev Immunol 19:47; Houde M et al 2003 Nature [Lond] 425:402.

Cross Protection: ►host-parasite relations

Cross-Sectional Study: The assessment of a condition in pairs of monozygotic and dizygotic twins at a particular time. ►longitudinal study

Cross-Species Color Segmentation: In cross-species color segmentation, FISH stained chromosomes (fragments) of one species are hybridized to another species to reveal a cross-species pattern. ►FISH

Cross Sterility: ►incompatibility alleles

Cross Validation: Cross validation tests whether the results from one population can be generalized for another.

Cross-β Spine: The X-ray diffraction pattern shown by fibrils. The fibril is a set of parallel β sheets (with amino acid sequences GNNQQNY and NNQQNY) of protein that are perpendicular to the axis. Amyloid fibers of prions and other amyloid-like fibrils share this general feature. Such stacks are stabilized by side chains protruding from two β sheets, and contribute to the stability of amyloid fibers as well as to their characteristics of self-replication and to the formation of polymorphic structures. ►prions; Nelson R et al 2005 Nature [Lond] 435:773; Krishnan R, Lindquist SL 2005 Nature [Lond] 435:765; Ritter C et al 2005 Nature [Lond] 435:844.

Crossing: Mating of two parental types of different genetic constitution.

Crossing Barrier: ►incompatibility, ►incompatibility alleles

Crossing Over: The process of reciprocal exchange between chromatids. Genes within a pair of homologous chromosomes may be linked in two fashions, either by coupling or by repulsion (see Fig. C183).



Figure C183. Coupling and repulsion

Independent segregation observed by Mendel has the limitation that the linkage and association of genes within a chromosome is not absolute either, because crossing over and recombination may separate genes depending on their genetic (physical) proximity. Chiasmata during meiotic prophase is the physical basis of crossing over (the exchange between chromatids), and this is then detected in the genetic segregation as recombination. Crossing over takes place at the 4-strand stage, i.e., when each of the bivalents is composed of two chromatids associated at the centromere. This is the tetrad stage of the meocyte. A single crossing over between two genes within a tetrad creates two reciprocally

recombinant chromatids for exceptions ► **gene conversion** whereas the other two chromatids remain unaltered (parental). Since 2/4 chromatids are cross-overs, the frequency of recombination caused by a single crossing over event is 50% for that particular tetrad. Each individual heterozygous for linked genes has numerous meocytes and crossing over does not take place in all of them at the same time, therefore, in a population of meocytes the frequency of crossing over may vary from 0 to 50% depending on the genetic distance between the genes. The maximal frequency of recombination in meiosis is thus 50%. Occasionally, recombination higher than 50% has also been observed in apparent contradiction to the principle described. This higher-than 50% value does violate the principle because it is the result of selection during or after meiosis and gametogenesis or fertilization. 1% recombination is considered, by convention, for 1 genetic map unit (m.u) or 1 c.M. (centiMorgan). More than a single crossing over may take place simultaneously within a single meocyte. A single crossing over, however, always produces 50% recombination. If a second crossing over occurs within the same genetic interval, it may prevent the genetic detection of the first crossing over event because the second crossing over may restore the non-crossover type arrangement of the genes. The third crossing over within the same interval restores again the recombinant arrangement of the genes demarcating that interval (see Fig. C184):



Figure C184. Parental, single crossover, second crossover and third crossover

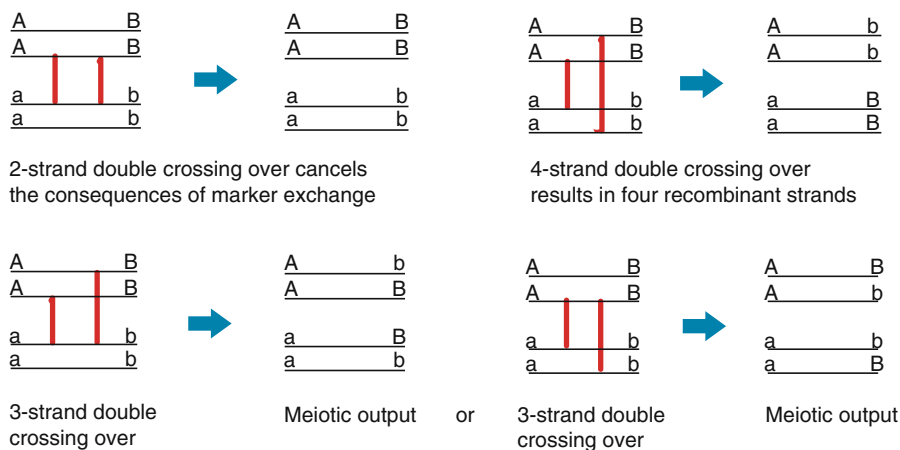


Figure C185. Two-strand, three-strand and four-strand crossing over. Two-strand, three-strand and four-strand crossing over occur normally in the proportion of 1:2:1 (in the absence of chromatid interference). The frequency of recombination by all four types of double crossing over events combined is 50%

Thus each odd numbered crossover generates detectable recombinants and the even numbered ones restore the original linkage phase of the alleles. Since multiple crossing overs are expected to occur at the product of the frequencies, double crossing within a meocytes does not usually affect the other meocytes.

Therefore, if the frequency of a single crossing over is 0.30, double crossing over occurs by 0.30^2 , and triple crossing over by the frequency of 0.30^3 . Thus, if after the first crossing over the frequency of Ab + aB gametes is 0.30, after the second event it may be $0.30 - 0.30^2 = 0.21$, and after the third event $0.30 - 0.30^2 + 0.30^3 = 0.237$. The incidence of crossing overs may not occur as predicted by probability but the first crossing over may hinder the occurrence of a second one (positive interference) or it may stimulate it (negative interference). Double crossing over may involve two, three, or four strands within a meocyte (see illustration next page). In yeast, each bivalent has at least one crossing over and usually not more than two. The probability of non-crossing over is commonly less than 0.1%. Usually crossing overs are not near each other see Fig. C185).

Recombinational interactions are large but only a few of them progress to develop into crossovers (minimization). Non-crossover interactions exceed actual crossovers by a factor of two in *Neurospora*, four in *Drosophila* and based on the number of early recombination nodules in onions, the excess may be 30–40. It appears that the decision about crossing

over is made before the formation of the synaptonemal complex, but the resolution of the Holliday junctions is delayed by or after pachytene.

Crossing over is generally limited to meiosis when the homologous pairs of chromosomes pair.

The chromosomes of some organisms, or under certain circumstance, may pair also during mitoses, and this may result in somatic recombination. Mitotic crossing over resembles the meiotic event but the mechanism of exchange may not be identical. ▶coefficient of crossing over, ▶cytological evidence for crossing over, ▶oblique crossing over, ▶time of crossing over, ▶models of recombination, ▶recombination frequency, ▶mapping, ▶mapping function, ▶mitotic recombination, ▶coincidence, ▶interference, ▶tetrad analysis, ▶chromosome pairing, ▶synapsis, ▶chiasma, ▶meiosis, ▶mitotic crossing over, ▶crossover, ▶sperm typing, ▶recombinational nodule, ▶association point, ▶pachytene, ▶Holliday juncture, ▶Holliday model, ▶recombination mechanism eukaryotes; review of mechanisms in plants: Mézard C et al 2007 Trends Genet 23:91.

Crossing Over Male: ▶male recombination

Crossing Over Modifiers: ▶the various *Rec* alleles

Crossing Over, Oblique: If the duplicated chromosomal region is obliquely paired, recombination may take place in between the segments in the following way (see Fig. C186):

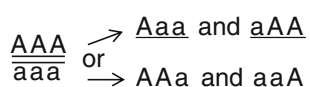


Figure C186. Oblique crossing over

Such an event may also lead to increase or decrease of the chromatin and cause position effect. ▶*Bar*, ▶position effect, ▶unequal crossing over

Crosslink: Various carcinogens and mutagens (nitrogen mustards, mitomycin C, psoralen dyes, cisplatin, etc.) cause DNA inter- and intrastrand crosslinks. These lesions are repaired by ABC excinucleases, which generate dual incisions and repair DNA synthesis. ▶ABC excinucleases, ▶nitrogen mustards, ▶mitomycin C, ▶psoralen dyes, ▶cisplatin

Cross-Linking: Cross-linking is the establishing of bonds between two molecules or linking together by covalent bond nucleotides in the same DNA or RNA. Chemical cross-linking agents are, e.g., bis-(2-chloroethyl)-methylamine and other mutagens and carcinogens (particularly the alkylating agents). The

resulting quaternary structure leads to disruption of DNA functions. UV light can also produce cross-linking within and between nucleic acids and proteins. ▶alkylating agents, ▶DNA repair, ▶pyrimidine dimers; Kuraoka I et al 2000 J Biol Chem 275:26632; De Silva IU et al 2000 Mol Cell Biol 20:7980; Dronkert ML, Kanaar R 2001 Mutation Res 486:1053.

Crossover: Recombinant chromatids, chromosomes, or individuals, originated by genetic exchange between homologous chromosomes through the process of crossing over. The cross-overs can be single or multiple. ▶crossing over, ▶recombination, ▶mapping function, ▶coincidence, ▶crossover fixation, ▶mapping genetic, ▶noncrossover recombinant

Crossover Connection of a Protein: Structural cores are connected by opposite ends of the cores across the surface of the domain.

Crossover Fixation: A hypothesis that explains the relative homogeneity in repeat units of satellite DNA. According to this model, the repeats can undergo frequent unequal crossing overs during short evolutionary periods and then the same unit may be either propagated or eliminated after the recombinational event. If maintained, it can account for the homology of the sequences because there was not enough time yet to accumulate mutations even in the sequences that are not coding and are exempt of selection pressure. ▶crossing over, ▶crossover, ▶satellite DNA, ▶unequal crossing over; Fletcher HL, Rafferty JA 1993 J Theor Biol 164:507.

Crossover Interference: ▶chromosome interference

Crossover Suppressor: During the early days of *Drosophila* genetics, parental inversions were erroneously considered crossover suppressors in the progeny. Actually, in most of the cases the duplication or deficiency strands (generated by recombination within the inversion strands) of the inversion heterozygotes were not transmitted or caused lethality rather than suppressing crossing over *per se*. In the close vicinity of the inversion breakpoints, chiasmata is usually reduced, however, this is a different phenomenon. ▶inversion

Cross-Pathway Regulation: As per the cross-pathway regulation, the biosynthesis of several different amino acids is coordinately regulated in fungi. ▶tryptophan operon, ▶channeling

Cross-Priming: In cross-priming, antigens are obtained from *donor* cells by bone-marrow-derived antigen presenting cells and delivered to cytotoxic T

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lymphocytes (CTL) on MHC class I molecules. Most commonly, CTLs recognize antigens which are localized in the cytoplasm of the target cells. Also, GM-CSF transfected cancer cells may recruit a number of tumor antigen presenting cells to T cells.

►cytotoxic T cell, ►antigen presenting cell, ►HLA, ►tumor vaccination

Cross-Reacting Material: ►crm, ►cross-reaction

Cross-Reaction: The binding of an antibody to an antigen; usually in the case when the formation of the antibody was not stimulated by the antigen but by a very similar substance. ►crm, ►antigen, ►antibody, ►nonspecific binding

Cross-Reactivation: ►marker rescue, ►reactivation

Cross-Resistance: As per cross-resistance, resistance against one agent conveys resistance also against others. ►multidrug resistance

Cross-Talk: The transmission of signals from receiver to sensor molecules between signal transduction pathways. ►signal transduction, ►morphogen, ►epistasis, ►microarray hybridization

Crouzon Syndrome (craniofacial dysostosis): An autosomal dominant phenotype of ossified cartilages and various anomalies of the face, particularly protruding eyeballs. It is allelic to the Jackson-Weiss syndrome and to the Pfeiffer syndrome (see Fig. C187). The basic defect appears to be due to the fibroblast growth factor receptor 2 in human chromosome 10q25-q26. ►eye disease fibroblast growth factor, ►receptor tyrosine kinase



Figure C187. Crouzon syndrome with moderate exophthalmos (protrusion of the eyeballs) and malocclusion (improper position of the lower jaw). (From Tessier P 2000 in *Craniosynostosis* p. 228, Cohen MM, MacLean RE eds., Oxford Univ. Press. By permission)

Crowding, Molecular: Molecular crowding indicates the concentration of diverse molecules within a (cellular) environment, where it may differently affect molecular functions (Sasaki Y et al 2007 *Nucleic Acids Res* 35:4086).

Crown Gall: A tumorous disease (mainly) of dicotyledonous plants caused by the soil-borne *Agrobacterium tumefaciens* (see Fig. C188). (photo courtesy of Dr. A.C. Brown). The tumor development is initiated by the large (200-kb), Ti (tumor-inducing) plasmid containing oncogenes responsible for the production of auxins and cytokinin plant hormones. Removal of the bacteria about two days after infection does not stop the disease, because the genes in the T-DNA part of the plasmids by that time have integrated into the plant genome and are expressed in the plant cells. The infection activates the *Tmr* gene in the plant plastid that encodes an adenosine-phosphate isopen-tenyl transferase and increases cytokine production (Sakakibara H et al 2005 *Proc Natl Acad Sci USA* 102:9972). ►*Agrobacterium*, ►T-DNA; Burr TJ, Otten L 1999 *Annu Rev Phytopath* 37:53.



Figure C188. Crown gall

Crozier: A crozier is a fungal structure formed when the ascogenous dikaryotic hyphae of ascomycetes form a three-cell hook-type growth and in the cell at the tip the two nuclei fuse (karyogamy) to become diploid (see Fig. C189). After that an ascus is formed where meiosis takes place. ►ascus, ►fungal life cycle, ►*Neurospora*



Figure C189. Crozier

7CRP: cAMP receptor protein. ▶cAMP

CRP: Proteins with LIM, LMO domains. ▶LIM, ▶LMO

CRP (catabolite response protein): ▶catabolite repression

CRSP: A transcriptional co-factor complex required for activation of Sp1-TFIID ($M_r \sim 700K$). It has nine subunits with MWs of 30K to 200K. ▶Sp1, ▶transcription factors

Cruciform DNA: Cruciform DNA may be formed as a recombination intermediate between single strands of double-strand DNA (see Fig. C190) ▶Holliday model, and when inverted repeats and palindromes occur in both strands in a double-stranded DNA, and within each strands these palindromes fold back and pair. ▶Holliday model, ▶palindrome, ▶repeat inverted, ▶transposition sites; photo is courtesy of Drs. H. Potter and D. Dressler.

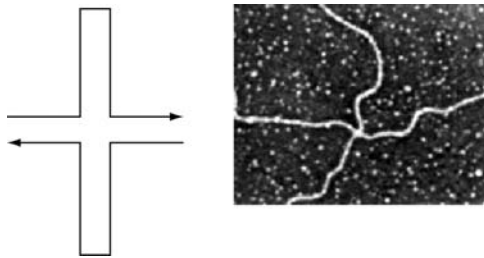


Figure C190. Cruciform recombination intermediate of DNA

Cruzigard: The cruzigard technology is based on a similar principle as in the use of the paratransgenic method. Insect vectors are exposed to different bacterial strains transformed by anti-trypanosomal genes as bait. The insect nymphs feeding on them will release the antibiotic within the insect gut and debilitate the protozoon. ▶paratransgenic, ▶Trypanosoma

crwydryn: A centromere-specific retrotransposon family in grasses. ▶retrotransposon

CRX: Transcription factor regulating photoreceptor outer segment proteins. ▶photoreceptor

Cry9C: A bacterial crystal protein with insecticidal property, used in genetically modified maize (corn). The protein belongs to the family of proteins (Bt) present in *Bacillus thuringiensis*, but it is apparently more effective. Other insecticidal proteins of this family are Cry5A, Cry5B, and Cry6A. According to some claims, it is an allergen for humans. ▶Bacillus

thuringiensis, ▶GMO, Crickmore N et al 1998 Microbiol Mol Biol Rev 62:807.

Cryo-Electron Crystallography: Cryo-electron crystallography permits the analysis of fine structure small biological systems by using electron diffraction. (See Craig T et al 2006 Mol Cell 23:651.)

Cryo-EM (cryo-electron microscopy): Quick-frozen samples obtained by CRYO-EM may permit viewing 3-dimensional structures below a resolution of 10 Å. It may reach beyond nuclear magnetic resonance or X-ray crystallography. ▶X-ray diffraction analysis, ▶nuclear magnetic resonance spectroscopy; reconstruction of single particles: Tao Y, Zhang W 2000 Curr Opin Struct Biol 10:616.

Cryopreservation: Cryopreservation is the maintaining of biological tissues, enzymes, etc. at very low temperatures, below -80°C , or in liquid nitrogen (-195.8°C). Frozen mouse embryos sperm, and ovaries can be now stored, distributed, reconstituted and used for reproduction. Mouse spermatids and spermatozoa kept frozen at -80°C up to a year were found to remain functional in fertilization. Testicular spermatozoa of dead mice kept continuously frozen at -20°C for up to 15 years produced normal offspring after microinjection into oocytes. This technology may make possible the extraction of functional spermatozoa from species preserved in permafrost and that after fertilization of oocytes of extant relatives, the extinct species be revived (Ogonuki N et al 2006 Proc Natl Acad Sci USA 103:13098). ▶sperm bank, ▶artificial insemination, ▶vitrification, ▶stem cells; Ludwig M et al 1999 Hum Reprod 14(Suppl):162; Rall WF 1992 Animal Reprod Sci 28:237; Watson PF, Holt WV (eds) 2001 Cryobanking the genetic resource. Wildlife conservation for the future? Taylor & Francis, London, New York.

Crypsis: The evolutionarily determined ability of animals to evade predators by concealing their through mimicking e.g., a certain shape or color. ▶Batesian mimicry, ▶Müllerian mimicry, ▶mimicry

Cryptic Chromosomal Aberration: A cryptic chromosomal aberration is too small to be detected without special staining techniques, e.g., FISH. ▶chromosomal aberrations, ▶FISH

Cryptic Dominance: A particular situation when recessive alleles of different loci fail to display complementation because of interaction of the gene products. ▶epistasis

Cryptic Element: A cryptic element, such as a plasmid or transposon does not express a particular phenotype.

Cryptic Promoter: An epigenetically silenced and normally inactive promoter. Genetic or extraneous

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alterations may activate it and can lead to the transcription and translation of aberrant peptides. Some cases of carcinogenesis are attributed to activation of cryptic promoters. Cryptic promoters may be responsible for antisense RNA and interfering RNAs. ▶[promoter](#)

Cryptic Plasmids: Do not have a known phenotype; they contain genes only for their maintenance and transmission. ▶[plasmid](#); Burian J et al 1999 J Mol Biol 294:49.

Cryptic Prophage: Can no longer exit from the chromosome of the bacterium and develop into a virion although some its genes are still transcribed. ▶[prophage](#)

Cryptic Satellite: The satellite DNA is not displayed by ultracentrifugation as a separate (band) peak but it is masked within the main band of the DNA. ▶[satellite DNA](#), ▶[buoyant density](#), ▶[ultracentrifuge](#)

Cryptic Simplicity: Cryptic simplicity is found in originally microsatellite regions where many point mutations occur and the repetitiveness breaks down or a few intermixed states are found. These are most common in non-coding regions but may occur in coding sequences too. ▶[microsatellite](#)

Cryptic Splice Site: An unusual juncture where splicing of exons may take place in case the usual site is changed by mutation. ▶[splicing](#), ▶[introns](#)

Cryptobiosis: Suspended life or reversible death.

Cryptochromes: Cryptochromes are linked to plant developmental (photoperiodism, circadian clock) processes under high intensity blue light. Cryptochromes are the blue light photoreceptors of the animal eye and also are modifiers of the circadian rhythm. They display similarities to photolyases. The mammalian cryptochrome genes (CRY) may have light-independent regulatory role. In plant morphogenic responses, cryptochromes cooperate with phytochromes through the Ca^{2+} -binding protein SUB1. Cryptochromes are relevant to various human health problems such as seasonal depression, sleep disorders, jet lag, and even breast cancer. ▶[circadian rhythm](#), ▶[photoperiodism](#), ▶[phytochromes](#), ▶[photolyase](#); Yang H-Q et al 2000 Cell 103:815; Sancar A 2000 Annu Rev Biochem 69:31; Lin C 2002 Plant Cell 14:S207; Liscum E et al 2003 Plant Physiol 133:1429; Lin C, Shalitin D 2003 Annu Rev Plant Biol 54:469; Chen M et al 2004 Annu Rev Genet 38:87; Partch CL et al 2006 Proc Natl Acad Sci USA 103:10467.

Cryptococcus: Several species of the basidiomycete fungus, an opportunistic human and animal pathogen posing a particular risk to immunocompromised populations. The ~20-megabase genomes containing

about 6,600 intron-rich genes of *C. neoformans* (n = 14) have been sequenced. About 5% of the genomes are transposons, accounting for the frequent variations. ▶[basidiomycetes](#); Loftus BJ et al 2005 Science 307:1321.

Cryptogamic Plants: Cryptogamic flowers develop no flowers or seeds and multiply by spores such as ferns, mosses, and algae. ▶[spermatophytes](#)

Cryptogene: Mitochondrial DNA gene with primary transcript subject to pan editing that almost hides the original RNA sequences. ▶[kinetoplast](#), ▶[pan editing](#), ▶[Trypanosoma](#), ▶[RNA editing](#)

Cryptogenic Species: Acryptogenic species is not clearly native in an environment nor is it an introduced one.

Cryptophthalmos: In cryptthalmos, instead of eyelids, the skin of the face covers both of the eyes, or one of the eyes (see Fig. C191). The extent of this developmental anomaly may vary. ▶[Fraser syndrome](#)



Figure C191. Cryptophthalmos

Cryptopolyploidy: Increase in nuclear DNA content among related families with the same chromosome number. ▶[polyploid](#); Sparrow AH, Nauman AF 1976 Science 192:524.

Cryptorchidism: Failure of the testes to descend from the abdominal cavity into the scrotum. This anomaly affects 2% of human births. Mutation in the insulin-like hormone (Insl3) may regulate the growth and differentiation of the gubernaculum (ligament of transient existence connecting the testis and epididymis to the scrotum) and testis descent. In females it may result in sterility. ▶[scrotum](#), ▶[epididymis](#); Kumagai J et al 2002 J Biol Chem 277:31283.

Cryptosporidium: The cryptosporidium protist species are responsible for some types of gastroenteritis and diarrhea and have host specialization. *C. hominis* has ~9.2 million bp genome in eight chromosomes and it has been sequenced (Xu P et al 2004 Nature [Lond] 431:1107). Membrane protrusions are used for entry

sites in infection (Chen X-M et al 2005 Proc Natl Acad Sci USA 102:6338, database: <http://cryptodb.org/cryptodb/>).

Crystal Cells: Hematoidin (hemoglobin-derived bilirubin-like) bodies in the blood.

Crystal Lattice: ▶semiconductor

Crystallins, α -, β -, γ -: Small heat shock proteins occurring in large (700–800 kDa) heteropolymers where they fend off protein denaturation. They are implicated in neuro- and muscle-degenerations and cataracts (opacity of the eye lens). ▶sHsp, ▶eye diseases, ▶desmin; Wang K 2001 Biochem Biophys Res Commun 287:642.

Crystallization: Formation of crystals; a procedure preparatory to X-ray crystallographic analysis of macromolecular structures. ▶X-ray diffraction analysis

Crystals of Protein: Protein crystals have a three-dimensional molecular arrangement (crystal lattice). The components hold a definite position in the lattice by attractive forces yet they may vibrate and assume different characteristic arrangements. Some proteins may not be directly amenable to crystallization due to structural causes. In such instances, appropriate variants can be produced that are more liable to the procedure (Keenan RJ et al 2005 Proc Natl Acad Sci USA 102:8887; Molscript).

Cs (crossovers): Recombinational events

¹³⁷**Cs:** A Cesium isotope emitting β and γ radiation; has a half-life of 33 years. ▶isotopes

CSA: Compartmentalized shotgun assembly. ▶shotgun sequencing

CSAID (cytokine-suppressive anti-inflammatory drug): An inhibitor of cytokine biosynthesis. ▶cytokines, ▶CSBP

CSBP (CSAID-binding protein): Mitogen-activated protein kinases. ▶CSAID, p38.

CSE: A negative regulator element of chromosome segregation in yeast that belongs to the Mediator family. ▶Mediator

CSF: The cytosstatic stability factor (probably the product of c-mos proto-oncogene) stabilizes MPF and thus prevents the exiting of the cell from M phase of mitosis. RSK mediates the activity of CSF. Calcium triggers the exit from meiosis II by targeting the inhibitor, Erp1 of the anaphase-promoting complex (APC). ▶MOS, ▶MPF, ▶proto-oncogenes, ▶mitosis, ▶meiosis, ▶cell cycle, ▶RSK; Shibuya EK, Masui K 1988 Dev Biol 129:253; Rauh NR et al 2005 Nature [Lond] 437:1048.

CSF (CSF-1 at human chromosome 1p21-p13, CSF-2 at 5q31.1, CSF-3 at 17q11.2-q12): The colony stimulating factor, involved in autophosphorylation. The CSF receptor (product of the FMS oncogene) is homologous to the product of the KIT oncogene, a protein tyrosine kinase. ▶KIT oncogene, ▶FMS oncogene, ▶protein tyrosine kinases, ▶colony stimulating factor

CSF1R: The colony stimulating factor receptor, product of the FMS oncogene. ▶FMS oncogene, ▶CSF, ▶KIT oncogene, ▶colony stimulating factor

CSGE (conformation-sensitive gel electrophoresis): CSGE uses gel electrophoresis of PCR fragments for the detection of variations in (mitochondrial) DNA, in order to provide data for evolutionary analyses. ▶gel electrophoresis, ▶PCR; Finnilä S et al 2000 Am J Hum Genet 66:1017.

Csk: A cytoplasmic protein tyrosine kinase; it has two amino-terminal protein-protein interaction domains (Src homology 2 and 3) and a carboxy-terminal catalytic domain. It is necessary for the development of the mouse. In csk⁻ cells, Src, Fyn, and Lyn phosphotyrosine kinase activity is decreased. Csk mediates the selection of T cells and regulates antigen receptors. ▶Src, ▶B lymphocytes, ▶Pyk, ▶Fyn, ▶Lck, ▶protein-tyrosine kinase, ▶SFK; Wang D, Cole PA 2001 J Am Chem Soc 123:8883.

CSL (C-promoter binding factor-1/Suppressor of hairless/LAG-1): A family of transcription factors that mediate transcriptional activation through the Notch receptor (see Fig. C192). Activation of Hes1 and Hes5 may inhibit neurite extension. The Numb, Numb-like and Deltex proteins inhibit Notch signaling and facilitate neurite extension. ▶Notch

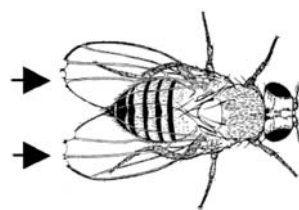


Figure C192. Notched wings of *Drosophila*

cSNP (coding SNP): A single nucleotide polymorphism coding for a different amino acid. ▶SNIPs

Csr: A family of RNAs mimicking mRNAs in glycogen biosynthesis, flagellar motility, and biofilm formation in bacteria and blocking their function (Romeo T 1998 Mol Microbiol 29:1321). ▶RNA regulatory, ▶biofilm

CstF: A cleavage-polyadenylation protein factor; may be associated with RNA polymerase II CTD. ▶poll II, ▶transcription factors, ▶CPSF, ▶CTD; Calvo O, Manley JL 2001 Mol Cell 7:1013.

CTAB ($[\text{CH}_3(\text{CH}_2)_{15}\text{N}^+(\text{CH}_3)_3\text{Br}^-]$): ►cetyl trimethylammonium bromide

CtBP: A C-terminal binding protein, a translational co-repressor that interacts with E1A. It modifies histones and may participate in oncogenesis. Ctbp 1 is encoded at 4p16 and Ctbp2 at 21q21.3. ►E1A, ►co-repressor; Chinnadurai G 2002 Mol Cell 9:213; Shi Y et al 2003 Nature [Lond] 422:723.

CTC: ►cytotoxic T cell

CTCF (CCCTC-binding factor, NeP1): A histone deacetylase and repressor of transcription. A CTCF-dependent enhancer-binding element acts as a chromatin insulator and it may regulate imprinting (Filippova, G et al 2005 Dev Cell 8:31). In mouse, CTCF mediates an interchromosomal interaction, perhaps by directing a distant DNA segment of chromosome 7 to a common transcription factory in chromosome 11. These two sites are involved in imprinting in mouse (Ling JQ et al 2006 Science 312: L269). In the human genome, 13,804 CTCF-binding insulator sites have been revealed (Kim TH et al 2007 Cell 128:1231). ►imprinting, ►insulator, ►boundary element, ►imprinting, ►transcription factories, ►non-coding sequences; Hark AT et al 2000 Nature 405:486; Filippova GN et al 2001 Nature Genet 28:335; Chao W et al 2002 Science 295:345.

CTD (carboxy terminal domain): An example of a CTD is the repeat unit of the largest subunit of RNA polymerases (RNAP), which can substitute for the TATA box in genes that lack TATA sequences. This CTD of the α subunits is the contact site for transcription activator proteins and the upstream promoter element (UP) in *E. coli*. The CTDK kinase, TFIIF, and FCP (yeast) phosphorylate the CTD of the transcriptase. The CTD domains of various proteins have structural and functional specificities. ►RNA polymerase, ►TATA box, ►transcription factors, ►RNA polymerase

ctDNA: Same as cpDNA or chloroplast DNA (see Fig. C193).

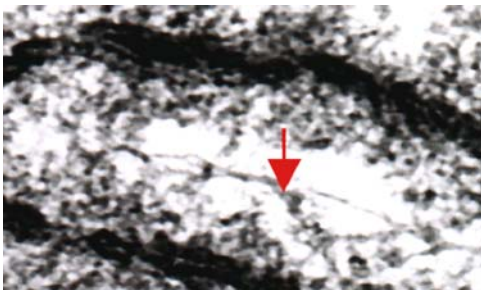


Figure C193. ctDNA. See ctDNA threads at arrow

C-Terminus: The COOH end of the last amino acid in the primary structure of a protein.

CTF: A CCAA motif binding proteins. ►binding proteins, ►cohesion

CTL (cytotoxic lymphocyte): ►T cell

CTLA-4 (cytotoxic T lymphocyte antigen, 2q33): A T cell regulatory molecule along with antigens bound to the major histocompatibility complex (MHC) on antigen presenting cells. CTLA-4 inhibits TCR signaling by binding to its ζ chain and interferes with tyrosine phosphorylation after T cell activation. The autoimmunity Graves disease, hypothyroidism, and type I diabetes are controlled by a non-coding 6.1 kb 3' region of CTLA-4, which displays an alternative splice form (Ueda H et al 2003 Nature [Lond] 423:506). CTLA-4 has signals opposite to the stimulatory proteins CD28, CD80, CD86, and ICOS. CTLA-4 overrides the T cell receptor-induced stop signal required for stable conjugation between T cell and antigen-presenting cell, and thus modulates the threshold for T cell activation and protects against autoimmune disease (Schneider H et al 2006 Science 313:1972). ►T cell, ►autoimmune disease, ►antigen presenting cell, ►MHC, ►CD28, ►CD80, ►CD86, ►ICOS, ►TCR, ►ITAM, ►ITIM, ►goiter, ►diabetes; Chambers CA et al 2001 Annu Rev Immunol 19:565; Egen JG et al 2002 Nat Immunol 3:611.

CTN-RNA (cationic amino acid transporter 2 RNA): CTN-RNA is transcribed from mouse *CAT2* gene using an alternative promoter. In addition to the transporter protein, it encodes a regulatory RNA, which is retained in the nucleus. (Prasanth KV et al 2005 Cell 123:249).

CTR: ►constitutive triple response

Cubitus interruptus (*ci*, 4.0): *Drosophila* gene locus with many different alleles. The cubital vein is interrupted at various lengths in the mutants (see Fig. C194). (See Aza-Blanc P, Kornberg TB 1999 Trends Genet 15:458).

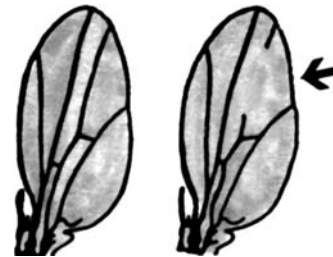


Figure C194. The *cubitus interruptus* phenotype (wild type, left; mutant at right). (Redrawn after Stern C, Kodani M 1955 Genetics 40:343)

Cucurbits: (Cucurbitaceae): *Cucumis sativus* (cucumber) $2n = 14$; *Cucumis melo* (muskmelon) $2n = 24$; *Citrullus lanatus* (water melon) $2n = 22$; *Cucurbita pepo* (summer squash) and other squashes $2n = 40$. ▶crop pants

CUE: A signal or stimulus that initiates or specifies a developmental fate. The *extrinsic signals* may be diffusible molecules (exocrine or paracrine hormones), cell membrane attached proteins, extracellular matrix factors, morphogens, pheromones, or environmental, i.e., light, temperature-related, or other signals. The *intrinsic cues* can be transcription factors, activators, transactivators, signal transducing adaptor molecules, G proteins, etc. The intrinsic cues are considered to be cell autonomous if they are able to affect cell fates irrespective of the surrounding tissue. ▶exocrine, ▶paracrine, ▶transcription factors, ▶activators, ▶transactivation, ▶morphogens, ▶morphogenesis, ▶signal transduction, ▶G proteins, ▶pheromones, ▶chaperone

Cullin (CUL1): A family of proteins involved in ubiquitination of G_1 phase cyclins and cyclin-dependent kinase inhibitors and other proteins. ▶CDC53, ▶cyclin, ▶ubiquitin, ▶cell cycle, ▶DDB1; Schwechheimer C, Deng X 2001 Trends Cell Biol 11:420.

Cultigens: Forms of cultivated plants. ▶cultivar, ▶variety

Cultivar: A genetically distinct variety of crop plants, generally adapted to a region and with some agronomic value for the grower and the consumer. ▶cultigens, ▶variety

Cultural Transmission of Fitness (CTF): A nongenetic transmission of any kind of behavior that affects reproductive success (Heyer E et al 2005 Trends Genet 21:234). When effective family size (EFS) is correlated from one generation to the next (i.e., the number of children per family who reproduce in their native population), there is a measure for the intensity of CTF. Akin to selection, CTF produces an increase in allele frequencies and like drift it has an impact on the whole genome. There are many examples for CTF when cultural or traditional customs affect the population. The general population may be divided into two groups of families: stable families with greater local reproductive success and migrants with lower local reproductive success. This social structure, transmitted from one generation to the next, may lead to the maintenance of a genetic disorder at increased frequency despite a high level of gene inflow from surrounding populations.

A particular Y chromosomal variant in 16 populations throughout a large region of Asia, stretching from the Pacific to the Caspian Sea, was present in very high proportions, in about 8% of the men in this region when its frequency worldwide appeared to be only 0.5%. The pattern of variation within the lineage suggested that it originated in Mongolia <1,000 years ago. Such a rapid spread cannot have occurred by chance. The lineage is attributed to male-line descendants of Genghis Khan, and it appears that to have spread by a novel form selection resulting from their behavior (Zerjal T et al 2003 Am J Hum Genet). ▶fitness, ▶linkage disequilibrium

Culture Collections: Culture collections maintain the cell lines of microbial, viral, and higher organisms and make available specimens for a fee. (See <http://www.ukncc.co.uk>).

Culture Media: For bacteria see Sambrook J et al 2006 Molecular Cloning, Cold Spring Harbor Lab. Press; for plants Murashige & Skoog medium, Gamborg medium; animal cells Butler M 1996 Animal Cell Culture and Technology, IRL/Oxford Univ. Press, New York.

Cumulus Ovaricus: A group of diploid follicular cells surrounding the mammalian egg. Such cells have been successfully used for nuclear transplantation after removal of the resident nucleus, resulting in cloning. ▶nuclear transplantation

Curare: ▶toxins

Curated: A database, which is generated/maintained by human supervision and not merely by mechanical/electronic means. ▶LC, ▶supervised learning

Curcumin (Natural Yellow, diferuloylmethane): A phenolic compound with antioxidant, anti-inflammatory and apoptosis-promoting properties.

Curie: The basic unit of radioactivity contained in 1 g of radium, i.e., 3.7×10^{10} disintegrations per second (dps). Most commonly, 1/1,000th, the millicurie (mCi) or the 1/1,000,000th the microcurie (μ Ci, 2.2×10^6 disintegrations per minute [dpm]) are used in laboratory work. In most equipment only about half of the disintegrations are detectable and thus 1 μ C corresponds to 1,000,000 counts per minute (cpm). Since the Ci unit defines the rate of disintegrations/time unit and the half-life of the different isotope may vary greatly depending on the species, the shorter half-life isotopes lose their isotopic atoms faster. 1 Becquerel = 2.7027×10^{-11} Curie (≈ 27 picocuries). ▶isotopes

Curing: A process of hardening by chemical or physical agents. It also refers to successful medication.

C

Curing of Plasmids: The removal of a plasmid or prophage from a bacterium, e.g., by the use of chemicals (acridine dye, Novobiocin, Coumeromycin) or irradiation. The $[PSI^+]$ form of the yeast prion can be “cured”, i.e., converted into $[psi^-]$ form by treatment with guanidine hydrochloride or methanol, in a reversible process. ▶prion, ▶acridine dye

Currants (*Ribes* spp): All are $2n = 2x = 16$.

Curarino Syndrome (HAS, 7q36): A dominant hereditary sacral agenesis (defect in the formation of the bone just above the hip). The homeobox gene HLXB9 responsible encodes a 403-amino acid protein. (Ross AJ et al 1998 Nat Genet 20:358).

Curvans: ▶rigens

Curvature of DNA: The curvature of the DNA involves deflection(s) of the local helical axis. It causes retardation of movement in the electrophoretic field. (Hardwidge PR, Maher LJ 2001 Nucleic Acids Res 29:2619).

Curvilinear Relationship: A curvilinear relationship indicates that the variations of two variables vary together but not in constant increments.

Cushing Syndrome (mixoma): also called by the acronym NAME (nevi, atrial mixoma, mixoid neurofibromata, endocrine overactivity). Critical features of the disease are adrenal, hypothalamic, pituitary, and lung tumors and hippocampal atrophy as a consequence of overproduction of glucocorticoids (hydrocortisone). ▶nevus, ▶neurofibromatosis, ▶glucocorticoids, ▶adrenal, ▶pituitary, ▶hippocampus, ▶atrophy; Yano H et al 1998 Mol Endocrinol 12:1708.

Cusp: ▶tooth

Custom Testing: Custom testing aims to detect specific mutation or chromosomal aberration, in case family history indicates the potential of the occurrence of a particular anomaly.

Cut-and-Paste: A mechanism of conservative transposition (see Fig. C195). Transposase (e.g., Tn5) and host proteins bind the transposable element and target double-strand DNA breaks at junction in a staggered manner. Insertion follows and the gaps are filled with complementary nucleotides. and (e.g., 9-bp [depending of the nature of the target cuts]). Duplications are generated at the end of the “simple insert”. Cut-and-paste mechanism may be also used in nucleotide exchange repair. ▶transposons, ▶transposable elements, ▶excision repair

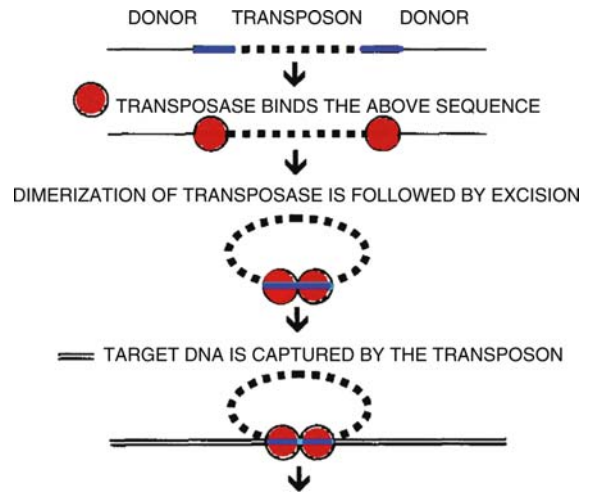


Figure C195. Cut-and-paste model. The catalytically transposon with the aid of an activated water molecule hydrolyzes one strand of the target and liberates a 3'-OH group at the end of the transposon. The 3'-OH end makes a nucleophilic attack on the target and manages transfer of the transposon into a new location. Cut-and-paste model Modified after Davis DR et al 2000 Science 289:77

Cuticle: A layer of substance (collagen) over the surface of epidermal or epithelial cells. ▶collagen

Cutin: A waxy material on the surface of plant cells, slightly permeable to water or gaseous substances.

Cutis Gyrate: ▶Beare-Stevenson syndrome

Cutis Laxa: Cutis Laxa includes autosomal dominant, recessive or X-linked forms. The hereditary forms appear early in life and show loose skin and joints and folding skin. The recessive I form involves, in addition, lung, heart, and digestive tract anomalies. Type II shows bone malformation (dystrophy) and retarded development. Some other forms have the signs of early aging of the skin or emphysema and anemia. The X-linked (Xq12-q13) form causes the formation of bony horns on the foramen magnum (the opening of the cranium to the vertebral canal), deficiency of lysyl oxidase, and disturbance in copper metabolism. ▶skin diseases, ▶elastic fiber diseases, ▶collagen, ▶Ehlers-Danlos syndrome, ▶pseudoxanthoma elasticum, ▶Menkes syndrome, ▶Williams syndrome

CW: Clockwise, ccw (see Fig. C196).



Figure C196. Clockwise

CXCR: Chemokine co-receptor of the CD4 T cells, a member of the serpentine receptor family. CXCR4 and its ligand, SDF-1 (a member of a chemokine family), are involved in hematopoiesis, lymphocyte migration and activation, differentiation of the vascular system, development of neuronal patterning, and acquired immunodeficiency symptoms. CXCR is a seven-transmembrane-spanning G-protein-coupled receptor. ▶CCR, ▶chemokine, ▶CD34, ▶acquired immunodeficiency, ▶SDF, ▶PBSF, ▶serpines, ▶angiogenesis, ▶neuron, ▶seven membrane proteins, ▶G protein, ▶cyclam, ▶metastasis, ▶ZAP-70, ▶gametogenesis, ▶WHIM syndrome; Blanco J et al 2000 FEBS Lett 477:123.

CXR: Chemokine receptor. ▶chemokines

Cxs: Gene conversions accompanied by crossing over. ▶gene conversion, ▶crossing over

Cy (Cy3 [green], Cy5 [red]): Monofunctional cyanine fluorescent labels of different absorption specificities for macromolecules.

Cyanide (HCN): A very powerful inhibitor of cellular oxidation that works by forming a complex with cytochrome oxidase and is thus an extremely dangerous poison. Sodiumthiosulfate and sodium nitrate are antidotes. Cyanides may be present in various foods (almond) and feed (Sudan grass, white clover).

Cyanidine: ▶anthocyanin

Cyanobacteria (blue-green algae): Photosynthetic prokaryotes that contain phycobiliproteins and chlorophyll a. Their genetic material is DNA and can be manipulated in a way similar to that in other prokaryotes. Cyanobacteria harbor phages that exchange genes with the host bacteria. Some phage genes are apparently functional in bacterial photosynthesis (Lindell D et al 2005 Nature [Lond] 438:86). The cyanobacterial circadian clock is different from that of other organisms. A two-component bacterial regulatory system kind mechanism feeds the signals to the clock (Ditty JL et al 2003 Annu Rev Genet 37:513). Cyanobacteria can produce various hazardous toxins (microcystin, nodularin), depending on the species. All known groups seem to produce β -N-methylamino-L-alanine, which upon ingestion may be responsible for neurological disease (amyotrophic lateral sclerosis/parkinsonism-dementia complex) of increased incidence in Guam and other parts of the world where it may enter the human food chain (Cox PA et al 2005 Proc Natl Acad Sci USA 102:5074). ▶phycobilins, ▶phycocyanins, ▶organelle sequence transfer, ▶chlorophyll; genome of *Synechococcus*: Palenik B et al 2003 Nature

[Lond] 424:1037; genome of *Prochlorococcus*: Rocap G et al 2003 Nature [Lond] 424:1042.

Cyanogen Bromide (BrCN): A very toxic, lacrimant gas. It has been used to cleave polypeptides and fusion proteins (at the C-terminal side of methionine) and also as ligand for activated chromatography matrices for Western blotting. ▶ligand, ▶Western blotting

Cyanogenic Glucosides: ▶Insect resistance in plants, ▶lotaustralin

Cyanosis: Bluish discoloration in body areas caused by the accumulation of reduced hemoglobin and methemoglobin resulting from mutation or caused by other factors. ▶methemoglobin

Cy Base: ▶cyclic proteins

Cybernetics: The theory of control and communication such as exists in the nervous system and also in mechanical devices such as the computer. ▶cyborg, ▶genetics digital

Cyborg (cybernetic organism): A futuristic human body modified by substitution of artificial structures for the natural ones, e.g., electronics for the nervous system. Such a system may permit better understanding of the working of an organic system. Also it may correct natural defects in hearing, vision, or muscle control, etc. by the use of microchips (silicon or germanium pieces used in computer circuits, Sequiera S 2001 Trends Neurosci 24:834).

Cybrid: A cybrid contains two different cytoplasm in fused cells. ▶cell genetics, ▶cell fusion

Cyclam: The macrocyclic xylyl-bicyclam (see Fig. C197) blocks HIV entry into the cell by targeting the CXCR4 co-receptor, a seven-helix transmembrane receptor. Several metal ions enhance binding. The Cu-cyclam specifically interacts with tryptophan residues 62, 63, and 123. ▶acquired immunodeficiency, ▶CXXR; Hunter TM et al 2005 Proc Natl Acad Sci USA 102:2288.

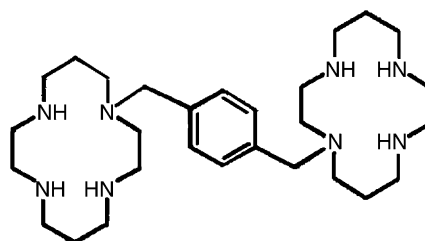


Figure C197. Xylyl-bicyclam

Cycle Cloning: In cyclone cloning, mammalian cell cultures are subjected to multiple rounds of phenotypic

selection in order to isolate cells of certain biological properties. ►MaRX

C

Cyclic ADP-Ribose: Cyclic ADP-Ribose is apparently synthesized from NAD⁺ by ADP-cyclase or by CD38 and serves as a (abscisic acid) signaling molecule when activated by Ca²⁺. The ryanodine receptor, regulating calcium ion channels, may be its receptor. It also regulates calcium signaling in T lymphocytes. ►ABA, ►NAD, ►c-AMP, ►ryanodine, ►CD38, ►T cell

Cyclic AMP: cAMP (see Fig. C198).

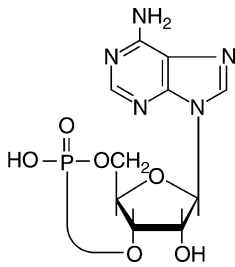


Figure C198. cAMP

Cyclic GMP: ►cGMP

Cyclic Electron Flow: Electrons emanating from *photosystem I* in light returning to their origin. ►photosynthesis, ►Z scheme

Cyclic Nucleotide-Gated Ion Channels: ►ion channels

Cyclic Permutation: ►permuted redundancy

Cyclic Photophosphorylation: In cyclic photophosphorylation, cyclic electron flow drives ATP synthesis. (See cyclic nucleotide phosphorylase: Conti M, Beavo J 2007 Annu Rev Biochem 76:481).

Cyclic Proteins (macrocytic proteins): Natural products with post-translational cyclization such as sex-pilin of bacteria, some bacteriocins, trypsin inhibitors of plants (cyclotides), and θ -defensins of monkeys. These proteins are resistant to proteolysis. See <http://research1t.imb.uq.edu.au/cybase/html/index.php>.

Cyclin (CLN): CLN proteins, synthesized during cell divisional cycles, are responsible players in the process by activating protein kinases (CDKs) and control the cyclic sequence of divisional steps. In *Saccharomyces* yeast cells, there are 22 cyclins that are associated with one of the five CDKs. ►cell cycle, ►CDK, ►CLB; Stein GS et al (eds) 1999 The molecular basis of cell cycle and growth control. Wiley, New York; Loog M, Morgan DO 2005 Nature [Lond] 434:104.

Cyclin A: Cyclin A is similar to cyclin B but appears earlier in the cell cycle. Cyclin A1 is expressed primarily in the germline, in the testes, and in myeloid leukemia cells. Cyclin A1 deficient males are sterile. Cyclin A2 deficiency results in embryo lethality. ►cell cycle, ►CDK, ►CDF, ►LATS; Coverly D et al 2002 Nature Cell Biol 4:523.

Cyclin B: Cyclin B has no known enzymatic activity; it is a part of MPF and has a role accessory to the protein kinase (*cdc2*) subunit. It seems to determine the substrate specificity of MPF. ►cell cycle, ►MPF, ►cdc2, ►CDK, ►CAK; Groisman I et al 2002 Cell 109:473.

Cyclin C: Cyclin C is involved in mRNA processing (Barette C et al 2001 Oncogene 20:551).

Cyclin D (CCND1, 11q13; CCND2, 12p13; CCND3, 6p21): Proteins involved in the G1 phase of the cell cycle. They are of over 50% homology. Cyclin Ds are also oncogenic proteins. CCND1-deficient mice are somewhat resistant to breast cancer mediated by the NEU/ERBB2 and RAS oncogene loci. CCND1 deficiency, however, does not affect the pathway to breast cancer mediated by c-Myc or Wnt-1 oncogenes. ►cell cycle, ►CDK, ►CAK, ►catenins, ►ERBB1, ►RAS, ►c-Myc, ►Wnt, ►breast cancer; Yu Q et al 2001 Nature [Lond] 411:1017.

Cyclin E: A subunit of CDK2. Under normal conditions, it accumulates between G₁ and S phase and is degraded after the S phase. In cancer cells, its level is maintained or increased and may lead to chromosomal instability common in cancer cells. Cyclin E^{T393A} mutation and loss of the p53 pathway associates with increased kinase activity and chromosomal instability, although the mutation itself increased the cyclin stability and had no phenotypic consequences. Ras oncogene was more active in Cyclin E^{T393A} p53^{-/-} cells than in the absence of p53 alone (Loeb KR et al 2005 Cancer Cell 8:35). When Cyclin E is localized to the centrosomes, it can control entry into S phase in the absence of CDK2 (Matsumoto Y, Maller JL 2004 Science 306:885). Coactivator-associated arginine methyltransferase is a positive regulator of *Cyclin E1* gene in mouse fibroblasts (El Messaudi S et al 2006 Proc Natl Acad Sci USA 103:13351). ►CDK2; Moberg KH et al 2001 Nature [Lond] 413:311; Strohmaier H et al 2001 Nature [Lond] 413:316; Payton M, Coats S 2002 Int J Biochem Cell Biol 34:315.

Cyclin F: Cyclin F displays in various protein-protein combinations the F-box motif that recognizes proteins for proteolytic degradation. It also promotes mitosis. ►SCF, ►F-box; Kong M et al 2000 EMBO J 19:1378.

Cyclin G: Cyclin G forms quaternary complex with the B' subunit of phosphatase PP2A, and also binds Mdm2 resulting in the dephosphorylation of the latter. ►PP2A, ►MDM2; Okamoto K et al 2002 Mol Cell 9:761.

Cyclin K: Cyclin K phosphorylates with cdk9, the carboxyterminal of RNA polymerase II (Edwards MC et al 1998 Mol Cell Biol 18:4291).

7Cyclin L: Cyclin L and an associated kinase are involved in the processing of pre-mRNA (Dickinson LA et al 2002 J Biol Chem 277:25465).

Cyclin T: A part of the Cdk9 complex that assists in binding Cdk9 to the Tat lentiviral RNA polymerase cofactor at the 5'-TAR site. ►acquired immunodeficiency, ►PITALRE, ►TEFb, ►CDK; Yang Z et al 2001 Nature [Lond] 414:317.

Cyclin-Dependent Protein Kinases (CDK): CDK, in association with cyclin, phosphorylate proteins and thus promote cell divisional events. In yeast cells, there are five types of CDK enzymes: Cdc28/Cdk1, Pho85, Kin28, Srb10, and Ctk1. The inhibitors of kinase activity may inhibit cell divisions and can be used for therapeutic purposes. ►cell cycle, ►CDK, ►CDK2; Francis D et al (eds) 1998 Plant Cell Division, Portland Press, London, UK.

Cycling Genes: Cycling genes display oscillating expression during embryogenesis.

5',8-Cycloadenosine: 5',8-cycloadenosine (see Fig. C199) and other cyclopurine deoxynucleosides may be generated in the DNA when under hypoxic conditions it is exposed to reactive oxygen. 5',8-cycloadenosine may be formed in stereoisomeric forms as well, and both of them block the 3' to 5' exonuclease function of the DNase III repair enzyme. DNA polymerase η may use them as templates for translesion synthesis, although this enzyme prefers the normal deoxypurine. ►DNA repair, ►translesion; Kuraoka I et al 2001 J Biol Chem 276:49283.

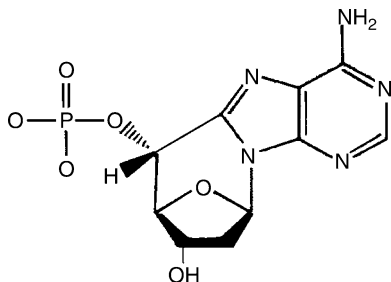


Figure C199. Cycloadenosine

Cyclobutane Dimer: Cyclobutanes have 4 C atoms in a ring. Such a structure may also be formed by cross-linking adjacent pyrimidines in the DNA upon

exposure to UV light. The most common, genetically effective, alteration in ultraviolet light-exposed DNA is the formation of thymine dimers (see Fig. C200).

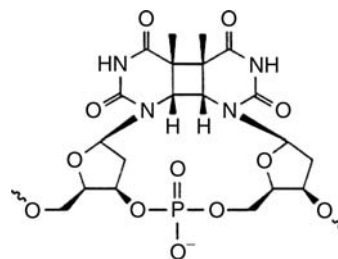


Figure C200. Cyclobutane pyrimidine dimer

The formation of cyclobutane dimers is dependent on the wavelength of the radiation. At 280 nm it is induced almost five times as efficiently as at 240 nm. At 272 nm the mutagen is formed after ~ 1 picosecond following excitation (Schreier WJ et al 2007 Science 315:625). The dimer physically distorts the DNA and interferes with normal DNA replication and incorporation of nucleotides at wrong sites. Substitutions may lead to mutation. Visible light-activated enzymes may split the dimers by light repair. Adenine phosphoribosyltransferase may also repair the damage at both strands of the DNA. ►DNA repair, ►photolyase, ►pyrimidine dimer, ►pyrimidine-pyrimidinone photoproduct, ►glycosylases, ►5',8-purine cyclodeoxynucleosides, ►cis-syn dimer, ►adenine phosphoribosyltransferase; Zheng Y et al 2001 J Biol Chem 276:15786; You Y-H et al 2001 J Biol Chem 276:44688; electrochemistry of the photolyase repair: DeRosa MC et al 2005 Proc Natl Acad Sci USA 102:10788.

Cyclodeoxynucleosides: 5',8-purine cyclodeoxynucleosides.

Cycloheximide: An antibiotic, which blocks the peptidyl transferase on the 80S ribosomes but does not affect protein synthesis on the 70S ribosomes (see Fig. C201). ►antibiotics, ►protein synthesis, ►peptidyl transferase, ►signaling to translation, ►ribosome

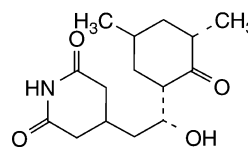


Figure C201. Cycloheximide

Cycloidea Alleles (*radialis*, *rad*): Cycloidea alleles determine the radial symmetry of the flowers of *Antirrhinum* (see Fig. C202). Four genes control

dorsoventral asymmetry (*cyc*, *dich*, *rad* and *div*). *CYC* and *DICH* promote dorsal identity and encode a TCP family transcription factor, which activates *RAD*. The Rad protein contains 93 amino acids and has one MYB domain. *CYC* and *DICH* repress the expression of *DIV*. The three genes also affect posttranscriptional development. Mutation in *CYC* and *DICH* results in radial symmetry of the flowers. *DIV* encodes a MYB family transcription factor and promotes ventral identity (Corley SB et al 2005 Proc Natl Acad Sci USA 102:5068). ▶*peloric*, ▶*snapdragon*, ▶TCP, ▶MYB

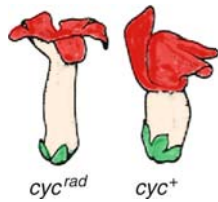


Figure C202. Cycloidea alleles

Cyclooxygenase (COX): An enzyme involved in the synthesis of nitric oxide, eicosanoids, prostaglandins, prostacyclins and thromboxanes from arachidonic acid. This enzyme thus plays an important role in inflammation, pain, fever, and embryo implantation, suppresses immunosurveillance, and stimulates tumorous growth. Inducible nitric oxide synthase specifically binds COX2, S-nitrosylates it, and enhances its catalytic activity. This system is important for inflammation responses (Kim SF et al 2005 Science 310:1966). Resveratrol, a product of grapes and the legume *Cassia quinqueangulata*, acts as a chemopreventive of the tumorigenic effect of cyclooxygenases. The common drug aspirin acetylates both COX-1 (prostaglandin-endoperoxide synthase 1; 9q32-q33.3) and COX-2 (prostaglandin-endoperoxide synthase 2; 1q25.2-q25.3) and irreversibly inactivates COX-2. Acetylated COX-1 has antithrombotic (protection against heart diseases) as well as inflammatory effects (causing heartburn, etc.), whereas shutting off COX-2 is beneficial for immunological and neoplastic diseases. For COX-2 inhibitors, are a new class of nonsteroidal anti-inflammatory drugs (NSAIDs) that provide effective treatment in arthritis but often lead to complications that include cardiovascular disease, myocardial infarction, stroke, and life-threatening skin reactions (Topol EJ 2005 J Am Med Assoc 293:366). Thus, they are no longer marketed. ▶*arachidonic acid*, ▶*lipoxigenase*, ▶*nitric oxide*, ▶*inflammation*, ▶*prostaglandins*, ▶*thromboxanes*, ▶*aspirin*, ▶*IKK*, ▶*thrombosis*, ▶*polyposis adenomatous intestinal*, ▶*MET oncogene*, ▶*implantation*; Smith WL et al

2000 Annu Rev Biochem 69:145; Turini ME, DuBois RN 2002 Annu Rev Med 53:35.

Cyclophilins (Cpr, Cyp, rotamase): Evolutionarily highly conserved peptidyl-prolyl isomerases that catalyze cis-trans isomerization of X-Pro peptide bonds. Peptidyl-prolyl isomerases are encoded at several human chromosomal locations. The cytoplasmic cyclophilin A (18-kDa, 7p13) is bound to and may be inhibited by the immunosuppressive antibiotic, cyclosporine. Cyclosporine bound to cyclophilin inactivates calcineurin. Cyclophilin B and cyclophilin C (each 23 kDa) are found in the secretory pathway. Cyclophilin D (20-kDa, 4q31.3) is mitochondrial and regulates mitochondrial permeability and some necrotic lesions, but not apoptosis (Nakagawa T et al 2005 Nature [Lond] 434:652). Overproduction of cyclophilin D leads to mitochondrial swelling and death, whereas in its absence mice are protected from Ca^{2+} overload and oxidative-stress-induced death (Baines CP et al 2005 Nature [Lond] 434:658). Cyclophilin 40 (40-kDa) is cytoplasmic and usually heat-inducible and seems to participate in heat shock protein-90 and heat shock protein-70 dependent signal transduction. ▶*cyclosporine*, ▶*calcineurin*, ▶*acquired immunodeficiency*, ▶*immunosuppressant*, ▶*mitochondrial import*, ▶*heat shock proteins*, ▶*signal transduction*, ▶*immunophilins*, ▶*PPI*, ▶*peptidyl-prolyl isomerases*, ▶*SCC*, ▶*nina*; Schiene-Fischer C, Yu C 2001 FEBS Lett 495:1.

Cyclophosphamide (cytoxan, endoxan, $\text{C}_7\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}_2\text{P}$): An alkylating carcinogen, clastogen, anti-neoplastic agent, and immunosuppressive drug (see Fig. C203). Preconceptual exposure of male rats to this drug caused embryo loss, malformation, and behavioral deficits in the offspring. Early postfertilization zygotic male pronuclei exposed to cytoxan are hyperacetylated at histones. Male pronuclei are hypomethylated by midzygotic development but female pronuclei are hypermethylated.

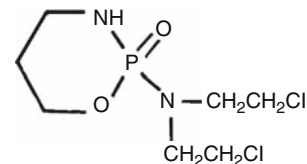


Figure C203. Cyclophosphamide

Thus this anticancer agent disturbs the epigenetic balance and its risks in chemotherapy must be considered (Barton TS et al 2005 Proc Natl Acad Sci USA 102:7865). ▶*aldehyde dehydrogenase*, ▶*oncolytic viruses*

Cyclopia: A developmental anomaly resulting in the formation of only a single eye. The build-up of cholesterol and defective signaling through the sonic hedgehog protein appear to be causative factors.

► [sonic hedgehog](#), ► [holoprosencephaly](#)

Cyclosome: Same as APC, ► [cell cycle](#)

Cyclosporine: A peptide antibiotic. It inhibits the activation of T lymphocytes by blocking the synthesis of IL-2, and it is thus an immunosuppressant (see Fig. C204). Cyclosporine may also become carcinogenic, not only by its immunosuppressive effects but also by boosting the synthesis of TGF- β . ► [immunosuppressant](#), ► [FK506](#), ► [antibiotics](#), ► [calcineurin](#), ► [cyclophilin](#), ► [cyclophosphamide](#), ► [immunophilins](#), ► [TGF](#), ► [immunological surveillance](#), ► [immunosuppression](#)

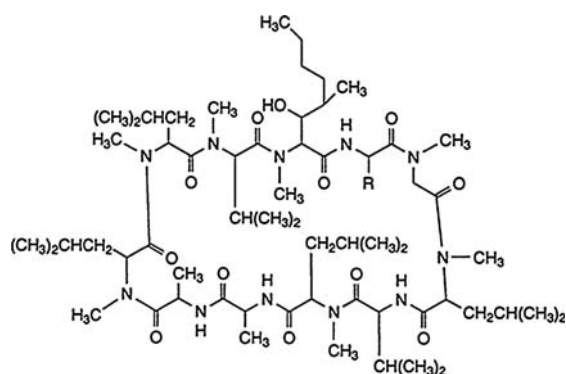


Figure C204. Cyclosporine

Cyclosporine-Binding Protein: ► [cyclophilins](#)

Cyclotides: Naturally synthesized circular plant peptides of ~30 or fewer amino acids occurring in *Rubiacea*, *Viola odorata*, and some other plants. The molecules form a distorted triple-stranded β -sheet and a cystine-knot motif. They are antibiotics and protect against insects. ► [cystine-knot](#); Craik DJ et al 1999 J Mol Biol 294:1327; Jennings C et al 2001 Proc Natl Acad Sci USA 98:10614.

Cyclotron: An accelerator of electrically charged particles and atomic nuclei. It is used to cause transmutations in atomic nuclei, e.g., a normal magnesium into radioactive sodium.

Cylindromatosis (CYLD, turban tumor): A (benign) skin tumor (primarily on hairy areas) caused by rare inactivation of a dominant gene in human chromosome 16q12-q13. The gene encodes a cytoskeleton-associated protein of 107 kDa. The CYLD gene mediates signaling from tumor necrosis factor α

through NF- κ B (NEMO) and I κ B. CYLD is a tumor suppressor and it blocks NF- κ B signaling through BCL-3 (Massoumi R et al 2006 Cell 125:665). As a consequence of reduction in CYLD, deubiquitination of TRAF2—a tumor associated factor—results and apoptosis is inhibited and tumor formation is promoted. ► [NF- \$\kappa\$ B](#), ► [NEMO](#), ► [I \$\kappa\$ B](#), ► [TNF](#), ► [TRAF](#), ► [deubiquitinating enzymes](#); Wilkinson KD 2003 Nature [Lond] 424:738.

Cyme: An inflorescence where the growth of the apex ceases early to the benefit of the branches (see Fig. C205).



Figure C205. Cyme

Cynomolgus: Cynomolgus most commonly means the *Macaca irus* laboratory monkey. ► [Rhesus](#), ► [Cercopithecidae](#)

CYP: ► [cytochromes](#)

Cyp: ► [cyclophilins](#)

Cyritestin: An ADAM family protein regulating the binding and fusion of the membranes of the sperm and the egg. ► [ADAM](#), ► [fertilization](#); Grzmil P et al 2001 Biochem J 357[pt 2]:551.

Cys₄ Receptor: Cys₄ receptor contains four cysteines—zinc domains in eukaryotic transcriptional regulators of α -helix-loop motif. The N-termini of the α helix contacts the nucleotide base, the N-terminal loop binds to the phosphate backbone, and the C-end is the dimerization interface. ► [zinc finger](#), ► [binding proteins](#)

Cyst: In general, bridges (ring canals) connecting a closed cavity in the body or the cluster of germline-derived cells that have undergone only a limited cytokinesis in the cells (see Fig. C206). Spermatogenesis in most animals (except nematodes) takes place in cysts. The oocyte develops within ovarian cysts. ► [fusome](#), ► [gametogenesis](#), ► [morphogenesis in *Drosophila*](#), ► [maternal effect genes](#); de Cuevas MA et al 1997 Annu Rev Genet 31:405.



Figure C206. Cyst

C

Cystathionine β -Synthetase (21q22.3): The excessive expression of cystathionine β -synthetase seems to be linked to decreased atherosclerosis and higher survival rates, if stricken by acute myeloblastic leukemia (AML) in Down syndrome (see Fig. C207). Its anomalies may cause homocystinuria. ▶homocystinuria, ▶AML; Ge Y et al 2001 J Biol Chem 276:43570.

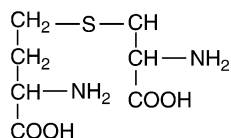


Figure C207. Cystathionine

Cystathioninuria: A recessive (human chromosome 16) deficiency of γ -cystathionase. Consequently, cystathionine cannot be cleaved into cysteine and homoserine, resulting in benign defects. ▶cystinosis, ▶cystinuria, ▶cystin-lysineuria, ▶homocystinuria, ▶amino acid metabolism, ▶aminoacidurias

Cystatine (cysteineprotease inhibitor): The loss of the gene *Cstb* causes myoclonous epilepsy of the Unverricht-Lundborg type and an increase in cathepsin S, C1qB chain of the complement, microglobulin β_2 , glial fibrillary acidic protein, apolipoprotein D, fibronectin 1, and metallothionein II. Cystatin level is an indication of renal function and high cystatin content predicts death by cardiovascular events in older patients (Shlipak MG et al 2005 New England J Med 352:2049). Neurosphere-derived cystatin C promotes growth and differentiation of embryonic stem cells into neurons, astrocytes, and oligodendrocytes (Kato T et al 2006 Proc Natl Acad Sci USA 103:60129). See terms under separate entries; ▶latexin; Lieuallen K et al 2001 Hum Mol Genet 10:1867.

Cysteamine: A decarboxylation product of cysteine. It is a radioprotective compound.

Cysteine ($\text{HSCH}_2\text{CH}[\text{NH}_2]\text{COOH}$): Upon hydrolysis of proteins in air, cysteine is converted to cystine. It is a radio-protective molecule.

Cystein-Histidine Finger: ▶DNA-binding protein domains, ▶zinc finger

Cysteine Knot: The cysteine-rich inhibitory motif of proteins, held together by disulfide bonds.

Cysteine Proteases: ICE, ICH1, NEDD2, ICH2/TX, CPP32/YAMA/apopain, and MHC2 are implicated in apoptosis. ▶apoptosis, ▶caspase

Cysteine-Scanning Mutagenesis: In cysteine-scanning mutagenesis, single amino acid residues in a protein domain are replaced by cysteine and modified by sulfhydryl-specific iodoacetamide derivatives of 7-nitrobenz-2-oxa-1,3-diazolyl dye. The activity of the 'mutated' protein is then determined. ▶site-directed mutagenesis; Kunkel TA 1985 Proc Natl Acad Sci USA 82:488.

Cysteine String Proteins (CSP): CSP contain palmitoylated cysteines on the peripheral membranes involved with the nerve synaptic vessels. ▶fatty acids, ▶synapse

Cystic Fibrosis: Cystic fibrosis is apparently one of the most common serious recessive hereditary defects in humans (human chromosome 7q31-q32), involving fibrous degeneration of the pancreas, bile ducts, the respiratory system, intestinal glands, sweat glands, male genital system, etc. The primary defect is apparently in chloride transport due to alteration of the gene regulating transmembrane conductance, which is caused by membrane lipid imbalance. The electrolyte transport is mediated by syntaxin, and the Munc18 protein blocks the latter. Several genetic modifiers (tissue necrosis factor, transforming growth factor, nitric oxide synthase, glutathione transferase, angiotensin convertase, mannose-binding lectin, etc.) affect the severity of the disease. It afflicts $\sim 1/2,000$ white newborns (the frequency of the responsible alleles may exceed 0.02). In American blacks the prevalence is more than an order of magnitude less and it is even much less common among Orientals. The large CF gene (27 exons) has been cloned (250 kbp). Hundreds of different mutations, including several deletions, have been identified. The manifestation of the disease varies a great deal especially in the lung. Prenatal diagnosis is 98% effective on the basis of determining the high level of immunoreactive trypsin in the serum, characteristic for CF. Sweat test and DNA test can also be used for diagnosis. Inhaling DNase solutions and avoiding respiratory infections may provide pulmonary relief by the use of antibiotics. Replacement and proper diet may alleviate pancreatic symptoms. The intestinal mucilage may be removed by surgery. Cystic fibrosis can be detected on the basis of the pattern of heat inactivation of the enzymes acid phosphatase and α -mannosidase. Homozygotes display practically no activity, heterozygotes 40–60%, and the absence of the defective allele is indicated by 80–100% activity. The testing of γ -glutamyltranspeptidase, aminopeptidase M, and alkaline phosphatase from the second trimester amniotic fluid permits prenatal diagnosis. Genetic screening can be carried out in newborns on the basis of immunoreactive trypsin. The normal allele of the cystic fibrosis gene is involved in the

regulation of sodium and chloride absorption and therefore it has been called cystic fibrosis transmembrane conductance regulator (CFTR, 27 exons), a protein kinase A and ATP regulated Cl^- ion channel. CFTR also affects HCO_3^- transport. A large deletion in the CFTR gene ($\Delta F508$) conditions the deficiency of internalization of *Pseudomonas aeruginosa* bacteria—to which cystic fibrosis patients are hypersusceptible—and because of this, the epithelial cells are unable to clear from the lungs the mucosa by desquamation. *Pseudomonas* infection particularly leads to the production of measurable amount of carbonyl sulfide in the breath and the presence of these bacteria may be revealed by a noninvasive measure of the infection (Kamboures MA et al 2005 Proc Natl Acad Sci USA 102:15762). *P. aeruginosa* infection causes apoptosis by activation of the CD95/CD95-ligand system. The *P. aeruginosa* strains in the CF patients generally carry mutator genes that facilitate the bacterial adaptation to antibiotic treatment. *Salmonella typhi* (the human pathogen) enters the intestinal mucosa through wild type CFTR. The human CFTR⁺ gene, equipped with the rat intestinal fatty acid-binding protein promoter, when transfected into a mouse corrected a lethal intestinal defect. Mice heterozygous for the cystic fibrosis gene secreted 50% of the normal fluid and chloride ions in response to cholera toxin, and thus CF may convey heterozygote advantage in natural selection. It has been suggested that the relatively high prevalence of cystic fibrosis in humans is due to a selective advantage in cases of *Vibrio cholerae* and *Escherichia coli* infection causing diarrhea by their toxin, which stimulates intestinal chloride secretion (Högenauer C et al 2000 Am J Hum Genet 67:1422). Many different mutations exist in the CF genes ranging from nil to only reduced synthesis of CFTR to various types of defects in regulation, in processing, and in altered conductance. CFTR is a member of the multidrug resistance protein family. Defects in CF may be associated with defects in the excretory channel of the testis (congenital bilateral aplasia of the vas deferens), azoospermia, asthma (breathing difficulties), nasal polyposis, and hypertyrosinemia. CFTR protein is also essential for normal sperm function (Xu WM et al 2007 Proc Natl Acad Sci USA 104:9816). Experiments indicate that gene therapy for cystic fibrosis is possible using primarily adenoviral, adeno-associated, and retroviral vectors but the efficiency of local transformation is low <0.1%. 10% efficiency may be required for effective remedy. Liposomal transfers and receptor-mediated gene transfers have also been attempted. The target should be the columnar cells lining the airways. Unfortunately, these cells are rather refractory to gene transfer. It has been shown that DNase I treatment has beneficial

effect on the removal of mucosa from the respiratory channel. Unfortunately, DNase is inhibited by F-actin secreted by the leukocytes that infiltrate the airways in response to infections. Actin-resistant DNase has been engineered that alleviates this problem. ▶cystic fibrosis antigens, ▶syntaxin, ▶munc, ▶genetic screening, ▶gene therapy, ▶infertility, ▶cholera toxin, ▶CD95, ▶azoospermia, ▶polyp, ▶tyrosinemia, ▶CBAVD, ▶multidrug resistance, ▶biofilm, ▶ABC transporters, ▶endoplasmic reticulum, ▶adenovirus, ▶adeno-associated virus, ▶retroviral vectors, ▶liposomes, ▶receptor-mediated gene transfer; Zielenski J, Tsui L-C 1995 Annu Rev Genet 29:777; Sheppard DN, Welsh MJ 1999 Physiol Rev 79: S[1] 23; Mateu E et al 2001 Am J Hum Genet 68:103; Bobadilla JL et al 2002 Hum Mut 19:575; Cutting GR 2005 Annu Rev Genomics Hum Genet 6:237, <http://www.genet.sickkids.on.ca/cftr/>.

Cystic Fibrosis Antigens (calgranulin A and B): Cystic fibrosis antigens are determined by dominant genes in human chromosome 1q12-q22. Homozygosity for the cystic fibrosis gene (7q31-q32) is accompanied by absence of these proteins whereas the symptom-less carriers have an intermediate level. It appears that these independent proteins track the basic defect in cystic fibrosis. Antigen A (also called calgranulin A because it is most abundant in the granulocytes) has a M_r 11,000 and antigen B (calgranulin B) has M_r 14,000. These two proteins are virtually identical with calcium-binding proteins in other sources. ▶cystic fibrosis

Cystine-Knot: A cystine knot is formed when two disulphide bridges link adjacent antiparallel strands of a peptide chain and form a ring that is penetrated by the third. Such cystine knots are found in NGF, TGF- β and PDGF-BB growth factors. ▶TGF- β , ▶platelet derived growth factor; Hymowitz SG et al 2001 EMBO J 20:5332.

Cystine-Lysinuria (diaminopentanuria): An autosomal recessive increase of diamines (cadaverin) in the urine, causing ataxia and mental degeneration. ▶amino acid metabolism, ▶cystinuria, ▶cystinosis

Cystinosis (CTNS): A semi-recessive autosomal hereditary disorder (see Fig. C208) under the control of more than one locus involving up to 100-fold amounts of cystine in the cells (lysosomes). Although it may not involve phenotypically obvious symptoms, it may eventually cause kidney failure, eye defects, growth arrest, and rickets. The heterozygotes can be identified by an increase in cystin in their cells. A cystinosis gene has been assigned to the short arm of human chromosome 17p13. The onset may be early or late.

C



Figure C208. Cystinosis. (Photograph is the courtesy of Dr. D.L. Rimoin, Harbor General Hospital, Los Angeles, CA)

Cystinosis is actually a lysosomal membrane protein (cystinosin) disease. The symptoms may be relieved by cysteamine. Renal transplantation may provide only a transient cure because the metabolic root is not localized to the kidney; kidneys only accumulate cystine. ▶[Fanconi renotubular syndrome](#), ▶[amino acid metabolism](#), ▶[cystinuria](#), ▶[cystin-lysinuria](#), ▶[homocystinuria](#); Touchman JW et al 2000 Genome Res 10:165.

Cystinuria: A recessive disease in several allelic forms, causing variable degrees of cystin deposits in the kidney cysts and in the bladder. Besides the increase of cysteine in the urine, larger than normal amounts of other amino acids (lysine, arginine and ornithine) may also be excreted. High fluid intake may prevent or alleviate the amino acid deposits. Type I is encoded at human chromosome 2p16.3, at the same site as the rBAT transporter protein. Another cystinuria gene was revealed at 19q12-q13.1. ▶[amino acid metabolism](#), ▶[cystinosis](#), ▶[cystine-lysinuria](#), ▶[homocystinuria](#), ▶[rBAT/4F2hc](#); Font M et al 2001 Hum Mol Genet 10:305.

Cystoblast: In the *Drosophila* germarium, the cystoblast divides four times and produces 16 cells (cystocytes), of which one becomes the oocyte, while the remaining 15 become nurse cells. The oocyte develops from one of the two, which are connected to four others. ▶[germarium](#), ▶[maternal effect genes](#)

Cystocarp: A spore-bearing structure formed in red algae after fertilization.

Cystocytes: ▶[cystoblast](#)

Cytidine: A pyrimidine base, cytosine, is associated with ribose or deoxyribose (see Fig. C209).

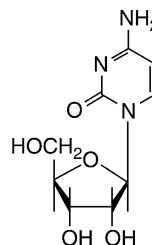


Figure C209. Cytidine

Cytidine 5'-Triphosphate Synthetase (CTPS, 1p34.1):

CTPS mediates the conversion of uridine triphosphate into cytidine triphosphate. Its deficiency may result in mutator effects and multidrug resistance.

▶[multidrug resistance](#)

Cytidylate: The salt of cytidylic acid.

Cytidylic Acid: Cytidine plus phosphate (a DNA or RNA nucleotide).

Cytoblast: The mitotic cell of the germarium in insects.

▶[germarium](#)

Cytochalasins: Toxins that break cellular actin microfilaments, inhibit glucose transport, thyroid secretion, growth hormone release, phagocytosis, and platelet aggregation and are used to evict nuclei from animal cells to produce cytoplasts and karyoplasts (see Fig. C210). ▶[toxins](#), ▶[cytoplast](#), ▶[karyoplast](#), ▶[actin](#), ▶[phagocytosis](#), ▶[nuclear transplantation](#)

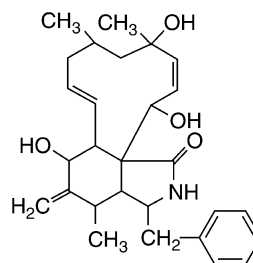


Figure C210. Cytochalasins

Cytochemistry: The chemical analysis of isolated subcellular components, it also employs histochemical techniques for in situ tracing their action.

Cytochromes (CYP): Electron carrier heme proteins with important roles in respiration, photosynthesis, and other oxidation-reduction processes, including the activation of promutagens and procarcinogens. Human mitochondria encode three subunits of

cytochrome oxidase (COX), and 10 are coded by the nucleus. The nuclear SCO genes (22q13, 17p13.1) assist the assembly. In the mitochondria, cytochromes c_1 and c oxidize quinols, and in the chloroplasts, reduce a terminal oxidase, while photosynthetic bacteria cytochromes f and c_6 oxidize quinols and reduce a photo-oxidized reaction center. The cytochrome-b—cytochrome- c_1 complex including heme c_1 , and the Rieske [2Fe-2S] protein and ubiquinol/ubiquinon sites within the mitochondrial inner membrane, play essential roles in electron transfer along with cytochrome oxidase and NADH-dehydrogenase. Cytochrome c nitrite reductase plays an essential role in the nitrogen cycle. Many other roles of cytochromes are also known. When the permeability of the mitochondrial membrane is altered, cytochrome c may be released into the cytoplasm and apoptosis may follow. CYP2D6 (22q13.1) CYP2E1 (10q24.3-qter), CYP3A4, and CYP4A10 are responsible for the metabolism of ~30 drugs used to control debrisoquine-4-hydroxylase activity in the treatment of hypertension. There are hereditary variations among humans in cyclophilin activity and this may seriously affect the response to some drugs. ▶ **promutagens**, ▶ **procarcinogen**, ▶ **activation of mutagens**, ▶ **NADH**, ▶ **dehydrogenase**, ▶ **P450**, ▶ **cyclophilin**, ▶ **porin**, ▶ **carotene**, ▶ **insecticide resistance**, ▶ **Leigh's encephalopathy**, ▶ **SXR**, ▶ **pharmacogenetics**; Berry EA et al 2000 Annu Rev Biochem 69:1005; cytochrome b-transmembrane traffic: Cramer WA et al 2006 Annu Rev Biochem 75:769.

Cytodifferentiation: ▶ **differentiation**, ▶ **morphogenesis**

Cytoduction: The dominant cytoplasmic transmission of a particular hereditary state, such as introduction, e.g., mitochondria into a cell and heterokaryosis in yeast. ▶ **heterokaryon**

Cytofectin GS2888 (dioleophosphosphatidylethanolamine): A transfecting agent for mammalian cells. It is coupled with a fusogenic compound and a cationic lipid (GS2888). It carries plasmids, AS ODNs, etc. into cells efficiently and its toxicity is low. Histidine-rich amphipatic peptide antibiotics also facilitate gene delivery into mammalian cells. ▶ **liposome**, ▶ **fusogenic liposome**, ▶ **AS ODN**, ▶ **transfection**; Axel DI et al 2000 J Vasc Res 37:224; Kichler A et al 2003 Proc Natl Acad Sci USA 100:1564.

Cytogenes: Cytogenes are located in the cellular organelles (plastids, mitochondria) and not in the nucleus. ▶ **mitochondrial genetics**, ▶ **chloroplast genetics**

Cytogenetics: A branch of genetics involving the study of chromosomal structure and behavior in connection with inheritance. It also involves the study of chromosomal anomalies and accompanied pathological conditions, as well as cytological analysis of the

evolution of chromosomes. Integrated cytogenetic and physical maps are available, Trask BJ 2002 Nat Rev Genet 3:769. (See human cytogenetics: <http://www.ncbi.nlm.nih.gov/genemap>).

C

Cytohesins: Brefeldin A-resistant guanine exchange factors (GEF) for ADP-ribosylation factors (ARF) involved in cytoskeletal organization through integrin activation or signaling. Their inhibition by the relatively small molecule SecinH3 causes insulin resistance in the liver (Hafner M et al 2006 Nature [Lond] 444:941; Fuss B et al 2006 Nature [Lond] 444:945). ▶ **brefeldin**, ▶ **GEF**, ▶ **ARF**, ▶ **cytoskeleton**, ▶ **integrin**, ▶ **insulin**

Cytohet: Heterozygosity in cytoplasmic genes (in plastids and mitochondria) when the zygotes receive cytoplasmic material biparentally. ▶ **chloroplast genetics**, ▶ **mtDNA**

Cytokines: Peptides secreted in response to mitogenic stimulation, they participate in intercellular communication and cellular activation. Most of the cytokine receptors invoke tyrosine phosphorylation of cellular proteins. The various cytokine receptors permit the action of different protein tyrosine kinases (PTK) in different cell types. They are instrumental in the induction and regulation of the immune system, cellular differentiation, blood cell formation, apoptosis, and tumor inhibition, and may facilitate cancer metastasis, cell migration, DNA synthesis, etc. The cytokine receptors belong to several superfamilies with some common features within the groups: (1) hematopoietin receptors, (2) interferon receptors, (3) TNF receptors, (4) interleukin-1 receptors and (5) TGF- β receptors, (6) immunoglobulin receptors [M-CSF-R, EGF-R, PDGF-R, etc.], and (7) chemokine receptors. Generally (one of) the α -chains provides the cytokine specificity, whereas a β -chain exerts a boosting effect. Different cytokine receptors may share functions and more than one kind may be involved in the same process. The cytokines may have pleiotropic effects in the signal transduction paths. Different cytokines may recruit various docking proteins and utilize different Janus (JAK) kinases and Tyk2 to increase specificity. Cytokine therapies are hindered by the short half-life of cytokines. A remedy is to fuse the latency-associated protein (LAP) of the transforming growth factor- β 1 (TGF) to interferon- β (IFN) through matrix metalloproteinase (MMP). This fusion product resembles transforming growth factor but stays inert until it is cleaved by metalloproteinase. Cerebrospinal or synovial fluid can activate the construct and the latent construct is more effective in therapy of inflammatory disease because of its prolonged half-life (Adams G et al 2003 Nature Biotechnol 21:1314). ▶ **interleukins**,

►interferons, ►colony stimulating factor, ►PTK, ►TGF, ►M-CSF, ►EGF, ►PDGF, ►signal transduction, ►aminoacyl-tRNA synthetase, ►chemokines, ►lymphokines, ►CIS, ►SOCS-box, ►CSAID; Thompson AW ed. 1998 *The Cytokine Handbook*. Acad. Press, San Diego, CA, USA; Dranoff G 2004 *Nature Rev Cancer* 4:11, www.copewithcytokines.de; <http://csp.medic.kumamoto-u.ac.jp>, cytokine-receptor interactions: <http://bioinf.xmu.edu.cn/software/cytosvm/cytosvm.php>.

Cytokine Storm: The sudden release of cytokines, it may result in strong inflammatory response due to activation of T cells.

Cytokinesis: The division of the cytoplasm after nuclear division leading to the formation of two cells from one (see Fig. C211). In animal cells, a contractile ring composed of actin and myosin and attached to the cell membrane generates a furrow, which separates the mother cell into two daughter cells after the completion of mitotic anaphase. In the mid-zone of the spindle PRC1, a microtubule-associated protein moves to the plus ends of the microtubules during the metaphase–anaphase transition with the assistance of Kif4 motor protein. Phosphorylation of PRC1 by a cyclin-dependent kinase determines the timing of Kif4 action on PRC1 and the eventual formation of the midzone (Zhu C, Jiang W 2005 *Proc Natl Acad Sci USA* 102:343). *Centralspindlin complex* composed of MKLP1 kinesin-like protein (among others) and the Rho guanosine triphosphatase activating protein (GAP) aided by CYK-4 facilitates GTP hydrolysis (Jantsch-Plunger V et al 2000 *J Cell Biol* 149:1391). Cdc5 activates Rho1 (Yoshida S et al 2006 *Science* 313:108). Cytokinesis requires that spindle checkpoint and Aurora B protein are functional. Chromosome segregation is then mediated through microtubule elongation. In the midzone protein “nocut” and anilin-related proteins Boi1 and Boi2 are inhibitors of abscission of the microtubules. When “nocut” senses that the chromosomes are cleared from the midzone and migrated to the opposite cells, cytokinesis (separation) is completed. If the spindle is damaged or “nocut” is inactivated, abscission may take place prematurely and chromosome breakage may ensue (Norden C et al 2006 *Cell* 125:85). ►mitosis, ►cell cycle, ►cell plate, ►midzone, ►cleavage furrow, ►Cdc5; Nan-ninga N 2001 *Microbiol Mol Biol Rev* 65:319; Zeitlin SG, Sullivan KF 2001 *Curr Biol* 11:R514; Heese M et al 2001 *J Cell Biol* 155:239; Glotzer M 2001 *Annu Rev Cell Dev Biol* 17:351; Guertin DA et al 2002 *Microbiol Mol Biol Rev* 66:155; Balasubramanian MK et al 2004 *Curr Biol* 14:R806; proteins mediating animal cytokinesis: Eggert US et al 2006 *Annu Rev Biochem* 75:543.

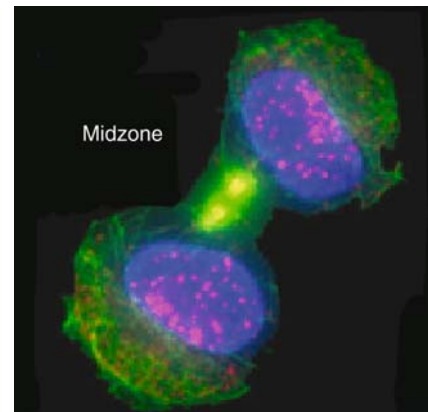


Figure C211. Cytokinesis. (Courtesy Kevin Sullivan and DW Cleveland)

Cytokinins: Cytokinins and auxins are the most important plant hormones regulating plant development. ►plant hormones; Werner T et al 2001 *Proc Natl Acad Sci USA* 98:10487; Hwang I, Sheen J 2001 *Nature [Lond]* 413:383; Mok DW, Mok MC 2001 *Annu Rev Plant Physiol Plant Mol Biol* 52:89; Hutchison CE, Kieber JJ 2002 *Plant Cell* 14:S47.

Cytoline: Cytoplasm replacement (by several backcrosses) generates a new line that is characterized by the identity of the cytoplasm (Allen JO 2005 *Genetics* 169:863).

Cytological Evidence for Crossing Over: The first cytological evidence for crossing over was collected in 1931 in maize by using a line heterozygous for chromosome 9 bearing a large terminal knob and the *C/c* and *Wx/wx* genes. Creighton HB and McClintock

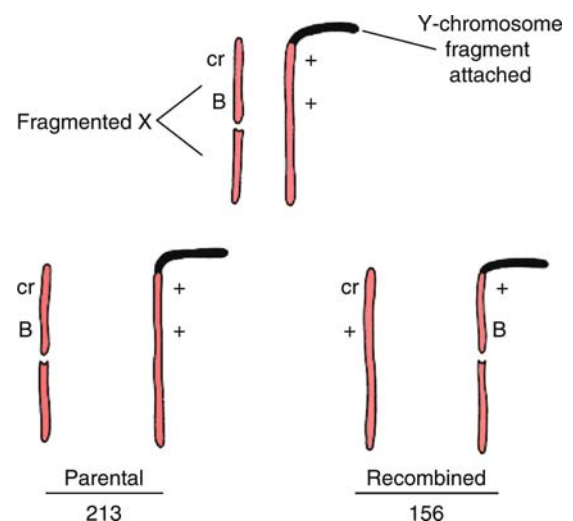


Figure C212. Cytological evidence for crossing over. An outline of one of the *Drosophila* experiments on correspondence between genetic and physical exchange of chromosomes. (After Stern C 1931 *Biol Zbl* 51:547)

B in 1931 (Proc Natl Acad Sci USA 17:492) found that the cytologically detected knob followed the syntenic genetic markers and corresponded to the expectation in the recombinants.

Around the same time, Curt Stern used in *Drosophila* a fragmented X-chromosome marked with *carnation eye* (*cr*) and *Bar eye* (*B*) and another X-chromosome with the wild type alleles and also a fragment of the Y-chromosome attached. Again, the genetically observed recombination was associated with the physical exchange of the cytologically marked chromosomes. (See crossing over, diagram).

Cytological Map: A cytological map shows genetic sites in relation to microscopically visible structures such as chromosome bands, knobs, centromeres, and satellite(s). ▶genetic map, ▶physical map, ▶RFLP, ▶RAPD

Cytological Marker: A unique feature of the chromosome, e.g., knob and satellite, the number of nucleoli in the nucleus, defective plastids, etc., visible by cytological analysis. ▶salivary gland chromosomes, ▶pachytene analysis, ▶knob, ▶satellite

Cytology: The study of structure and related functions of the cell and subcellular elements. See www.cellnucleus.org.

Cytolysin: Cytolysin is secreted by cells to dissolve other cells, e.g., during the immune reaction, during quorum sensing, and during pore-formation by bacteria. ▶streptolysin; Haas W et al 2002 Nature [Lond] 415:84.

Cytolysis: The dissolving of the cells into its chemical components.

Cytomegalovirus (CMV): CMV include the herpes viruses, Epstein-Barr virus, varicella-zoster virus, and the Kaposi sarcoma associated virus. CMV has an icosahedral capsid that is assembled after an internal protein scaffold is cleaved proteolytically (see Fig. C213). Interference with this encapsidation step reduces infectivity by four orders of magnitude (Yu X et al 2005 Proc Natl Acad Sci USA 102:7103). These potentially tumorigenic viruses have double-stranded DNA genetic material and great and diverse mammalian host specificity. US28 chemokine receptor, coupled with G protein and encoded by human CMV, facilitates angiogenesis and contributes to tumor onset and progression (Maussang D et al 2006 Proc Natl Acad Sci USA 103:13068). The name (megalo) comes from the observation that the infection enlarges the host cells. The epidermal growth factor receptor is essential for CMV infection of humans (Wang X et al 2003 Nature [Lond] 424:456). The human cytomegalovirus can produce about 200 potentially antigenic polypeptides, however, the CMV early-expressed gene (gpUL40) may

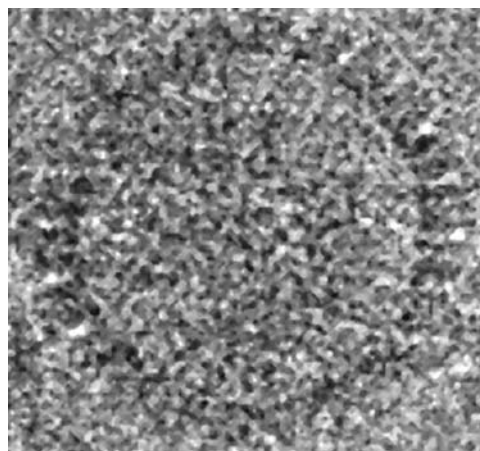


Figure C213. Cytomegalovirus

block antigen presentation by class I MHC molecules (HLA-E), and thus the defense function of CD8⁺ cytotoxic T lymphocytes. In the mouse mutations in proteins, m157 enables the virus to evade natural killer cells of the host (Voigt V et al 2003 Proc Natl Acad Sci USA 100:13483). Phosphorylation of the immediate early (IE) proteins may prevent the interference with antigen presentation and the CTL defense system. The human CMV may cause serious disease in congenitally infected infants and adults with defective immune system. Homosexual males and female prostitutes may frequently (up to 90%) be infected with CMV, depending on the number of sexual partners. The opportunistic CMV disease (most commonly expressed as inflammation and necrosis of the retina) may surface after latent infections in case of AIDS. The latent virus resides in myeloid dendritic progenitor cells and chromatin remodeling leads to reactivation of the virus and pathogenesis (Reeves MB et al 2005 Proc Natl Acad Sci USA 102:4140). Treatment may employ the antisense oligodeoxynucleotide fomivirsen. The human cytomegalovirus may cause site-specific (human chromosome 1q42 and 1q21) breakage due to viral adsorption/penetration but not by expression of CMV genes. It is a common cause of virus-induced birth defects. Several variants have been (~230,000 bp) sequenced. The human virus has ~192 open reading frames (Murphy E et al 2003 Proc Natl Acad Sci USA 100:13585). ▶herpes, ▶Epstein-Barr virus, ▶MHC, ▶antigen presenting cell, ▶T cells, ▶CTL, ▶AIDS, ▶fomivirsen, ▶chemokines; Murphy E et al 2003 Proc Natl Acad Sci USA 100:14976.

Cytoneme: The projection toward the signaling center of the imaginal disk. Cytonemes may transmit signals between the organizing centers and outlying cells. ▶imaginal disks, ▶organizer, ▶signal transduction

C

Cytonuclear Disequilibria Analysis: A method of evolutionary (population genetics) study of the association between nuclear and markers to detect non-random mating, gene flow, population subdivision, mutation, and genetic drift. (See Latta RG et al 2001 Genetics 158:843).

Cytopathic: A cytopathic agent causes pathological changes in the cell.

Cytopenia: The reduction in the number of blood cells. It may occur as a consequence of chemotherapy or disease. ►IVIG

Cytophotometry: Spectrophotometric chemical study of the content(s) of single cells. ►spectrophotometry, ►microscopy

Cytoplasm: All materials enclosed by the cell membrane, including cellular organelles, but excluding the nucleus. ►cell, ►protoplasm

Cytoplasmic Drive: The cytoplasmic drive promotes maternal inheritance by cytoplasmic factors.

Cytoplasmic Incompatibility: Cytoplasmic instability involves the disruption of fertilization or embryogenesis because of bacterial infection in insect species. ►infectious heredity, ►incompatibility, ►*Wolbachia*; Charlat S et al 2001 In Symbiosis: Mechanisms and Model Systems, Seckbach J (ed) Kluwer Academic, Dordrecht, the Netherlands.

Cytoplasmic Inheritance: Cytoplasmic inheritance is determined by non-nuclear genetic factors. Some organelles (plastids, mitochondria) are endowed with independent genetic material, but organelles like the endoplasmic reticulum and the Golgi apparatus do not have independent genetic material. Their transmission to daughter cells requires attachment to the cytoskeleton or actin filaments or they may be also *de novo* synthesized. Their transmission, unlike that mediated by the mitotic spindle, may be asymmetric. ►chloroplast genetics, ►mtDNA, ►mitochondrial genetics; Barr FA 2002 Curr Opin Cell Biol 14:496.

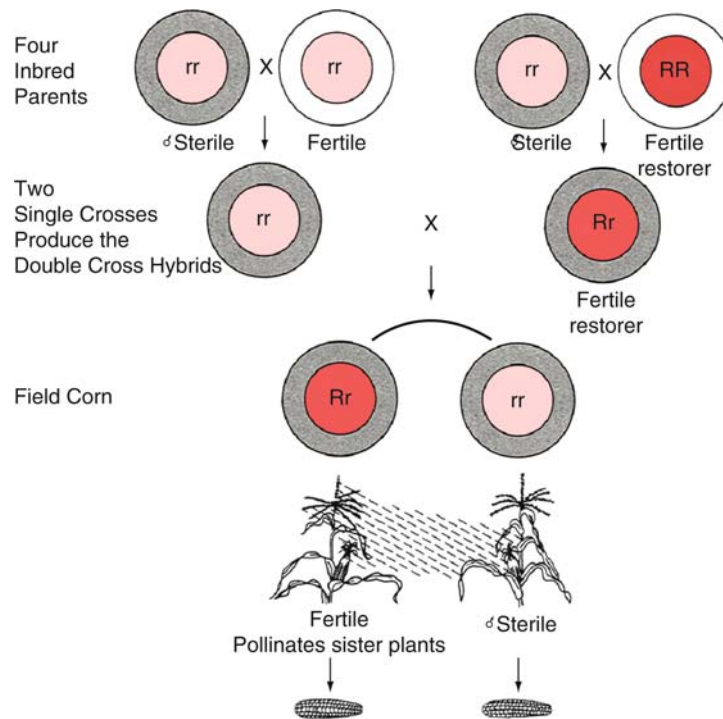
Cytoplasmic Male Sterility (*cms*): In maize, five different mitochondrial genomes have been identified and three of them (*T*, *Texas*; *S*, USDA and *C*, Charrua) control cytoplasmically inherited male sterility. The *Rf* restorer genes restore fertility.

Fertility restoration requires specific nuclear genes or the loss of the *T-urf13* site caused by an intramolecular mtDNA recombination between two 4.6-kb repeats, followed by an intermolecular recombination of a 127-bp repeat, and resulting in a 0.4-kb deletion involving *T-urf13*.

The joint action of *Rf1* and *Rf2* restorer genes is sporophytic, i.e., approximately all (95%) the pollen produced is fertile in the plants heterozygous for these dominant nuclear genes. In the *S* cytoplasm, *Rf3* conveys gametophytic restoration, i.e., in the heterozygotes approximately half of the pollen is fully functional and half is aborted. *Rf4* acts sporophytically also in *S* cytoplasm. Although *cms* has been identified in over 100 maize stocks, all of them fall into the three groups.

The various circular mtDNAs have been physically mapped and their sizes differ (*T* is 540-kb). The male sterility in the *Tcms* stock was attributed to a mitochondrial locus, *T-urf13*, near a 4.7-kb repeat absent from normal mtDNA. Maize mitochondria contain several smaller DNAs besides the main genome.

The loss of mitochondrial linear double-stranded DNA plasmids *S-1* (6,397-bp) and *S-2* (5,453-bp) from the *S* cytoplasm may or may not be required for the restoration of fertility, depending on the nuclear genome (see Fig. C214). In the *cms-S* mitochondrial DNA there are 2-kb recombinational repeats (*R*) at the junctions σ - σ' and Ψ - Ψ' . These repeats may become the sites of recombination between the integrated and the episomal *R* sequences, thus resulting in rearrangements of the mtDNA genomes. The *R* elements carry 210-bp sequences, which are highly homologous (~90%) with the terminal inverted repeats (TIR) of the *S* plasmids. These TIR sequences are sites of frequent recombinations, resulting in complex rearrangements of the mtDNA. The size of the *R* elements varies in different maize stocks. Their homologs in some teosinte lines are named M1 and M2. Some of the nuclear fertility restorer genes (called *Rf* or *Fr* in different species) control the transcription and translation of the *cms* mtDNA. The "reversion" usually represents loss of parts of the *R* sequences and thus it is a permanent, irreversible change. The cytoplasmic male sterility of the *T* type is associated with susceptibility to *Helminthosporium maydis* (*Cochliobolus heterostrophus* Drechsler) blight and to other factors. The *T* cytoplasm conveys susceptibility also to the systemic insecticide methomyl (acetylcholinesterase inhibitor) and the toxin of the fungus *Phyllosticta maydis* (yellow corn leaf blight). The URF13 protein contains 115 amino acids residing in the inner membrane of the mitochondria. URF13 is a receptor of the toxin of the blight pathogens and also for methomyl. When URF13 binds the toxin it forms a mitochondrial pore and uncouples oxidative phosphorylation. *Rf1* restorer gene alters the transcript of the *T-urf13* gene but *Rf2* does not do this although it too inhibits male sterility. The RF2 protein



C

Figure C214. Cytoplasmic male sterility. An outline of the procedure for obtaining double-cross hybrid seed by the use of cytoplasmic male sterile lines of maize. *R* stands for a dominant fertility restorer gene; *r* does not affect cytoplasmic male sterility. The inner circles represent the cell nucleus and a band around it symbolizes the cytoplasm. Shading in the cytoplasm stand for determinants of mitochondrial male sterility. Plants with shaded cytoplasm can produce seed only when fertilized by *R* pollen

is very similar to mammalian mitochondrial aldehyde dehydrogenase. Restoration of fertility does not abolish the susceptibility to the fungal toxins. The elements of these systems are influenced also by the genetic background. In cultured cells *Helminthosporium*-resistant mitochondrial mutations occur that are also male fertile. Cytoplasmic male sterility systems were observed also in several other plant species. The 3.7-kb *pvs* mtDNA sequence in common bean plants is associated with cytoplasmic male sterility. This sequence includes two open reading frames, *orf239* and *orf98*. The 27-kDa protein product of *orf239* localizes in the callose layer and the primary cell wall of the pollen. The mitochondrial *pcf* gene of *Petunia* encodes a 25-kDa protein in the CMS plants, but it is unknown how it affects sterility. Transforming *orf239* into tobacco (*N. plumbaginifolia*) without targeting it into the mitochondria causes pollen disruption. Cytoplasmic male sterility is not based on a single nucleotide change in the mtDNA although nuclear encoded male sterility may be due to point mutations. The majority of the cytoplasmic

male sterility cases are not the direct consequence of deletions.

Transformation of the β -ketothiolase gene (*phaA*) driven by the light-sensitivity promoter (*psbA*) into tobacco chloroplasts was seen to result in male sterility without affecting other functions. Under continuous illumination, the male sterility (caused by collapsed pollen) was entirely reversed and the plants became normally fertile. This procedure, if employed in plant breeding, may facilitate the production of heterotic hybrids. The physiological basis of the ketothiolase action is that it successfully outcompetes acetylcoenzyme-A carboxylase for mediating the conversion of acetyl-CoA into malonyl-coA (required for fatty acid synthesis and normal pollen); instead, acetyl-coA is converted into acetoacetyl-coA, resulting in pollen defects (Ruiz ON, Daniell H 2005 Plant Physiol 138:1232; Khan MS 2005 Nature [Lond] 436:738).

Mitochondrial respiration defects caused by the accumulation of mtDNA induce oligospermia and asthenozoospermia in the mito-mice (Nakada K et al

2006 Proc Natl Acad Sci USA 103:15148). ▶male sterility, ▶mtDNA, ▶mitochondrial abnormalities in plants, ▶symbionts hereditary, ▶heterosis, ▶hybrid vigor, ▶mitochondrial plasmids, ▶mitochondrial genetics, ▶fertility restorer genes, ▶RU maize, ▶cholinesterase, ▶oligospermia, ▶mito-mice; Duvick DN 1965 Adv Genet 13:1; Williams ME, Levings CS III 1992 Plant Breeding Revs 10:23; Budar F, Pelletier G 2001 CR Acad Sci III 324:543; Bentolia S et al 2002 Proc Natl Acad Sci USA 99:10887; general review of methods: Daniell H et al 2005 Methods Mol Biol 286:111; review of plant CMS: Chase CD 2007 Trends Genet 23:81.

Cytoplasmic Transfer: ▶conjugation *Paramecia*

Cytoplasm: An enucleated cell (cell that has lost its nucleus). ▶transplantation of organelles, ▶karyoplast

Cytosine (C): A pyrimidine base in RNA or DNA. ▶pyrimidines

Cytosine Deaminase (CD): Bacterial (gene 1.3-kb) and fungal enzymes transform cytidine into uracil or deoxycytidine into deoxyuridine. Mammalian cells may lack this function. Activation-induced cytosine deaminase (AID) appears to be an RNA-editing enzyme and is however required for somatic hypermutation, class switch recombination, and gene conversion of immunoglobulin genes (Yoshikawa K et al 2002 Science 296:2033). CD also deaminates cytosine arabinoside, an antileukemic drug, into inactive uracil derivatives. CD converts 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU), a more effective anti-cancer drug, by suicidal action. Transformation within the CA gene itself does not affect mammalian cells, but it may increase the sensitivity to 5-FC by 10^2 to 10^4 -fold depending on the type of cancer. The effectiveness of CA gene therapy is determined by the effectiveness of delivering the vector to all cells of the tumor. The cancer cells, which do not incorporate the vector, may reinitiate new tumor growth after an initial regression. The targeting of the vectors is also a problem even when it is equipped with tumor-specific monoclonal antibody. On the other hand, the CA therapy may have a bystander effect. ▶fluorouracil, ▶suicide vector, ▶cancer gene therapy, ▶bystander effect, ▶immunoglobulins, ▶somatic hypermutation; Ueda K et al 2001 Cancer Res 61:6158.

Cytosine-Repressor (CytR): CytR regulates the transcription of at least eight genes of *E. coli* involved in nucleoside uptake and catabolism. All CytR-repressed promoters have a catabolite repressor (CRP) binding site and repression is the outcome of the cooperation between the CytR and the CRP-cAMP complex. ▶catabolite repression, ▶cAMP

Cytoskeleton: The bracing and scaffolding fibers (actin, microtubule and other filaments) in the cytoplasm (see Fig. C215). The cytoskeleton may affect different cellular functions, the progression of the cell cycle, differentiation, diseases, cirrhosis of the liver, highways for intracellular vehicles moved by motor proteins, etc. ▶filaments, ▶intermediate filaments, ▶ARP2/3 complex, ▶cirrhosis of the liver, ▶motor proteins, ▶actin, ▶ankyrin, ▶pollen; Fuchs E 1996 Annu Rev Genet 30:197; Gachet Y et al 2001 Nature [Lond] 412:352; Kost B, Chua N-H 2002 Cell 108:9; bacterial cytoskeleton: Michie KA, Löwe J 2006 Annu Rev Biochem 75:467.

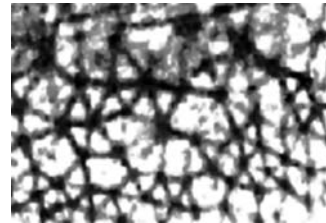


Figure C215. Cytoskeleton

Cytosol: The soluble, non-particulate material of the cell that suspends all cellular structures within the plasma membrane.

Cytostatic: A cytostatic substance hinders cell division.

Cytostatic Factor: ▶CSF

Cytostatic Stability Factor: The cytostatic stability factor maintains MPF at high level during metaphase II and prevents exit from metaphase. ▶MPF, ▶mitosis

Cytotactin: The extracellular matrix protein affecting cell movement.

Cytotaxonomy: Evolutionary studies based on the analysis of the cells and chromosomes.

Cytotoxic: A cytotoxic substance poisons or kills cells, primarily by inhibition of mitosis.

Cytotoxic Ribonuclease: ▶colicins

Cytotoxic T Cell (CTL, CTC): A type of T lymphocytes that destroys infection-carrying cells or foreign antigens. CTLs recognize their targets by the antigenic peptides presented on dendritic cells. CTLs require activation mediated by $CD4^+$ T helper cells (T_H), which have on their surface CD40 or the CD40L (ligand) proteins. CD40 and CD40L alone may be sufficient for activation of CTLs and their presence on the antigen presenting cells (dendritic cells, macrophages and B lymphocytes) enhances the

activation of CTLs. The natural killer cells (NK) lyse various types of cells without the cooperation of the MHC system. CTL and NK cells, however, may cooperate and induce the formation of cytolytic granules and lytic pores. Perforin expression on CD8⁺ T cells and sometimes on CD4⁺ cells plays an important role in this process. The cytolytic granules may contain granulysin, a saposin-like glycoprotein. Saposins are generated by cleavage of the 511-amino acid presaposin and the four types of saposins stimulate the hydrolysis of ceramides by stimulating the particular enzymes. Various leukodystrophies and Gaucher disease are attributed to saposin deficiencies. Another mechanism of action was suggested to rely on the Fas-dependent apoptosis. Actually, these two routes may be used simultaneously. CD8⁺ T cells recognize cytopathic and noncytopathic viruses by presentation of their peptide antigens on MHC I molecules. The killing may also involve the secretion of antiviral lymphokines. Bacterial infections are handled also by activated macrophages, NK cells, T cell receptors, granulocytes, and CD4⁺ and CD8⁺ T cells. IFN γ and perforin

are the fighting molecules. Perforin-dependent destruction of insulin-producing cells seems to be involved in autoimmunity diseases and diabetes mellitus. Graft rejection is caused by the infiltration into the added tissue NK cells, macrophages, and CD4⁺ and CD8⁺ T cells. The latter two recognize MHC II or MHC I differences, respectively. ▶lymphocytes, ▶T cell, ▶T cell receptor, ▶perforin, ▶granzyme, ▶killer cells, ▶apoptosis, ▶CD4, ▶CD8, ▶CD40, ▶antigen presenting cell, ▶dendritic cell, ▶MHC, ▶Fas, ▶macrophages, ▶diabetes, ▶graft rejection, ▶cytomegaloviruses, ▶Gaucher disease, ▶leukodystrophy; Kägi D et al 1996 Annu Rev Immunol 14:297; Raulet DH et al 2001 Annu Rev Immunol 19:291; Moretta A et al 2001 Annu Rev Immunol 19:197; Russell JH Ley TJ 2002 Annu Rev Immunol 20:323.

Cytotoxicity: The ability of any agent to harm, destroy or poison cells.

CytR: ▶cAMP receptor protein

Historical vignettes

Sturtevant AH 1967 Reminiscences of Morgan TH Genetics 159:1 [2001]:

“...if you mix eggs and sperm from the same individual [*Ciona*, an ascidian]. Normally nothing happens. But sometimes self-fertilization does occur. And one of the questions was, Why? What brings this about? How does this happen? And Morgan had a nice hypothesis: maybe the acidity of the water is responsible. And let's see what pH changes will do. But being Morgan he didn't set up measured amounts or concentrations. What he did was to take a dish in which eggs and sperm were present and squeeze a lemon over it. And it worked. Then he studied it in more detail after that. This was one of the most successful experiments in the field.”

Curt Stern recalled his discovery of the cytological and genetical proof of crossing over at the 1st Stadler Genetics Symposium in 1969 and published in vol. 1, p. 24:

“In the context of reminiscences as well as for the benefit of sociologists of science who perhaps may find food for their thoughts, let me recount some aspects of my first report on the cytological proof of crossing over. By the summer of 1931 I had completed the work, had written the paper, which was accepted for publication and had then gone on vacation. At the end of this period I went to Munich to attend the September meeting of the German Genetics Society and to present my results. With me came my fiancée who on the day of my speech presented me with a set of beautifully arranged attached and translocated peppermint canes. I gave my paper with the enthusiasm of a successful youth. Soon after, one of my colleagues from the Kaiser Wilhelm Institut came to me and said: “I didn't want to spoil your fun but while you were on vacation a paper came out written by Harriet Creighton and Barbara McClintock who did experiments in maize equivalent to what you just announced as unique.” May I confess that I am still grateful to my colleague for permitting me the, feeling of triumph for half an hour longer than I would have had it if he had told me about the Creighton-McClintock paper before my talk.”

D

D: The number of restriction enzyme recognition sites per DNA length. ▶restriction enzymes

Δ: The universal symbol for deletions.

d: (dalton): see also the now preferred Da and Dalton.

δ: A yeast transposable element. ▶Ty

2,4-D: (see Fig. D1) ▶dichlorophenoxyacetic acid

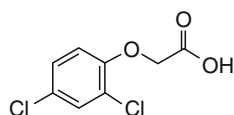


Figure D1. 2,4-D

D Arm: ▶transfer RNA

D Box (destruction box): A recognition sequence (RXXLXXXXN) for the ubiquitin ligase/APC (anaphase promoting complex). ▶APC, ▶ubiquitin, ▶proteasome; Chen F et al 2002 Proc Natl Acad Sci USA 99:1990.

δ Deleting Element (also called ΨJ_α): δ deleting element mediates the deletion of the δ gene from the α gene in the T cell receptor (TCR) site when there is no α gene rearrangement. ▶T cell receptor

D Element: ▶non-viral retrotransposable elements

D-J: ▶immunoglobulins

D Loop: D loop is formed when in replicating small circular DNA (mtDNA) one of the strands is

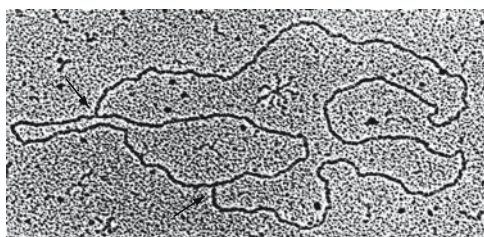


Figure D2. ✓ D loop of mtDNA replication. (Courtesy of Dr. K Wolstenholme)

displaced while the other strand is copied or when in genetic recombination a single-strand DNA invades the RecA protein complex and displaces one strand of a duplex (see Fig. D2). ▶Meselson–Radding model, ▶recombination molecular mechanism, ▶prokaryotes, ▶replication, ▶mtDNA, ▶strand displacement, ▶mitochondrial-control regions; Clayton DA 2000 Hum Reprod 15 Suppl. 2:11.

D2 Protein: A histone-like protein in the nucleosomes of *Drosophila*. ▶nucleosomes

DA: TFIIA transcription factor associated with TFIID–DNA complex. ▶transcription factors

Da: ▶Dalton

DAB: The transcription factor TFIIA associated with TFIIB–TFIID–DNA. ▶transcription factors; Maldonado E et al 1990 Mol Cell Biol 10:6335.

DABCYL Acid: 4-(dimethylaminoazo)benzene-4-carboxylic acid is commonly used in FRET probes of nucleic acids and protease substrates. ▶FRET

DABSYL: 4-dimethylaminoazobenzene-4"-sulfonyl-chloride is used like DABCYL acid. ▶DABCYL acid

Dactylogram: The fingerprint obtained by dactyloscopy (fingerprinting). ▶fingerprints, ▶dermatoglyphics

Dactylogy (cheirolgy): The study of hands, fingerprints. ▶fingerprinting

DAF: DNA amplification fingerprinting. ▶amplification, ▶DNA fingerprinting

DAF: ▶decay accelerating factor

DAF: dauer larva formation. ▶dauer larva

DAG: ▶diacylglycerol

DAI: DAI is an interferon-induced protein and a double-strand RNA activated inhibitor that is involved in kinase function regulating translation. When 25–30% of the factor is phosphorylated protein synthesis is severely inhibited. ▶interferon, ▶kinase, ▶translation

DALA: δ-aminolevulinic acid.

DALI: A three-dimensional protein query program. <http://www.ebi.ac.uk/dali/>.

Dalton (Da): Measurement unit of molecular mass (M_r), generally used to estimate the size of macromolecules, 1 Da = 1.661×10^{-24} g (1/12 of the MW of the C^{12} isotope). 1 MDa is 10^6 Da. 1 pg of DNA is

about 0.60205×10^{12} Da; the M_r of a nucleotide pair is about 650 Da; 1 kbp DNA (Na salt) is about 6.5×10^5 Da. The “average” molecular weight of an amino acid residue in a protein is about 110–120 Da.

DALY (disability-adjusted life year): DALY is the sum of life years lost due to premature mortality and years of life with disabilities adjusted for the severity of the disability. On this basis, congenital anomalies occupy the 10th rank among 17 leading disabilities in the world. ▶ [genetic diseases](#)

Dam: Female mammal. ▶ [sire](#)

dam: The deoxyadenine methylation factor in a GATC sequence. ▶ [methylation of DNA](#)

DAM Methylase: These enzymes are several main groups of methyl transferases (Hha I C5-cytosine methyltransferase, Taq I N6-adenine methyltransferase and the catechol *O*-methyl transferase). The majority of these enzymes use *S*-adenosyl-L-methionine (SAM) as a methyl donor. Their catalytic domain is rather well conserved and the various methylases can transfer methyl groups to DNA, RNA, proteins and other molecules. ▶ [methylguanine-O⁶-methyltransferase](#), ▶ [methyltransferase](#), ▶ [methylation of DNA](#); Cheng X 1995 Annu Rev Biophys Biomol Struct 24:293; Malygin EG et al 2001 Nucleic Acids Res 29:2361.

DAMD (directed amplification of minisatellite DNA): DAMD uses PCR to produce probes for the determination of homologous variations among different species or genetic stocks for DNA fingerprinting, generally by RFLP. ▶ [PCR](#), ▶ [RFLP](#), ▶ [minisatellite](#), ▶ [DNA fingerprinting](#); Heath DD et al 1993 Nucleic Acids Res 21:5782.

D-Amino Acids: Enantiomorphs of the natural L-amino acids. The D and L, respectively, are related to the optical rotation of the molecule, however D or L molecules may have either [+] or [−] optical rotation (see Fig. D3). According to the original Fischer’s model, a D and L amino acid can be represented as shown but other representations are also used. The D forms frequently have inhibitory or antimicrobial effects. The genetic codons of both forms are the same and they are the products by post-translational enzymatic reaction. The inclusion of D-amino acids into vaccines against infectious agents or autoimmune diseases may be advantageous because they last longer and resist enzymatic degradation (Seala M, Zisman E 1997 FASEB J 11:449). An epitope of the mucin2 glycoprotein containing ¹⁵TPTPTGTQTPT²⁵ retained full function after substitution of two D-amino acids at its N-terminal flank and up to three at its C-terminal flank (Tugyi R et al 2005 Proc Natl Acad Sci USA 102:413).

D-amino acids occur naturally in some hemolytic peptides of the skin of frogs, snails, spider venom and in some crustaceans. The D-amino acids are coded by the L form codons and enzymatically converted to the D enantiomorph (Jilek A et al 2005 Proc Natl Acad Sci USA 102:4235). ▶ [amino acids](#), ▶ [mucins](#), ▶ [enantiomorph](#), ▶ [epitope](#)

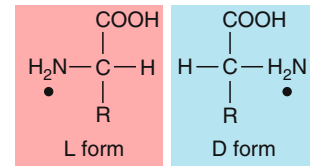


Figure D3. Amino acids

Dandy–Walker Syndrome: A form of autosomal recessive of hydrocephalus with considerable variations. ▶ [hydrocephalus](#)

Danon Disease (Xq24): Danon disease is caused by a deficiency of the lysosomal-associated protein, LAMP-2 and may involve cardiac hypertrophy. ▶ [LAMP](#), ▶ [lysosomal storage diseases](#), ▶ [heart disease](#)

DAP: ▶ [diaminopimelate](#)

DAP Kinases (DA PK): Ca^{2+} /calmodulin-dependent serine/threonine phosphorylases of the cytoskeleton. They mediate apoptosis, metastasis and lymphocyte function. ▶ [apoptosis](#), ▶ [metastasis](#), ▶ [killer cells](#), ▶ [ITIM](#), ▶ [methylation of DNA](#); Cohen O, Kimchi A 2001 Cell Death Diff 8:6; Bialik S, Kimchi A 2006 Annu Rev Biochem 75:189.

DAPI: 4',6'-diamidino-2-phenylindole, a fluorochrome stain for chromosomes. When excited by UV light, blue light is emitted. ▶ [chromosome morphology](#), ▶ [fluorochromes](#), ▶ [chromosome painting](#), ▶ [FISH](#)

Darier-White Disease (keratosis follicularis): An autosomal (12q23-q24.1) dominant keratosis, Darier-White disease is prevalent in areas where sebaceous glands (excreting fatty substances and cellular debris) are located, e.g., on the scalp, face, chest back, armpit and groin. The basic defect is attributed to SERCA2 encoded Ca^{2+} -ATPase regulating calcium signaling in cell-to-cell adhesion and epidermal differentiation. ▶ [keratosis](#), ▶ [SERCA1](#), ▶ [Brody diseases](#); Zhao XS et al 2001 EMBO J 20:2680.

Dark-Field Microscopy: A technique where scattered light arriving from an object illuminated sideways makes it appear bright on a dark background. ▶ [microscopy](#), ▶ [fluorescent microscopy](#), ▶ [phase-contrast microscopy](#), ▶ [Nomarski](#)

Dark Flowering: Plants have limited ability to grow in the dark because they depend on light to meet their need for carbon. Many plants also have a photo-periodic requirement for flower evocation (see Fig. D4). However, *Arabidopsis*, a long-day plant, though sterile, grows and develops flowers and fruits in complete darkness when grown on liquid mineral medium supplemented with sucrose (Rédei GP et al 1974 Stadler Genet Symp 6:135)



Figure D4. Dark flowering

Dark Matter of the Genome: The transcribed but functionally unknown sequences of the genome (Johnson JM et al 2005 Trends Genet 21:93)

Dark Reaction: Light-independent enzymatic reactions that follow the light reactions of photosynthesis and lead to the formation of monosaccharides. ▶[photosynthesis](#)

Dark Repair: The repair of DNA without light (excision repair). ▶[DNA repair](#)

DARPP (dopamine—adenosine 3',5'-monophosphate-regulated phosphoprotein): DARPP is a 32-kDa molecule that in response to dopamine becomes a protein phosphatase (PP-1) inhibitor and thus regulates neurotransmission. It may actually display both serine/threonine phosphatase or kinase inhibitor activity depending on which of the amino acids is phosphorylated by Cdk5. DARPP-32 is required progesterone-mediated sexual receptivity in female rodents. ▶[dopamine](#), ▶[neurotransmitter](#), ▶[PP-1](#), ▶[Cdk5](#), ▶[progesterone](#); Centonze D et al 2001 Eur J Neurosci 13:1071.

DART (direct analysis in real time): DART is a method used in mass spectrometry. It applies electrical potential to a gas (nitrogen or helium) at high ionization potential to form a plasma of excited state atoms and ions to desorb low-molecular weight molecules from the surface of a sample (Cody RB et al 2005 Anal Chem 77:2297). ▶[mass spectrum](#)

DART (database for active regions of the genome): <http://dart.gersteinlab.org/>.

DART (diversity array technology): DNA polymorphism analysis by microarray hybridization. ▶[diversity](#), ▶[microarray hybridization](#), ▶[speciation](#)

darwin: A measure of the rate of evolution = $(\ln[x_2] - \ln[x_1])/n$, where x_1 and x_2 indicate population sizes as they change during n million years (Myr), \ln is the natural logarithm.

Darwinian Fitness: ▶[fitness](#), ▶[neutral mutation](#), ▶[beneficial mutation](#)

Darwinism: The interpretation of evolution as the outcome of natural selection; and survival of the fittest. Charles Darwin published his theory in 1859, in his *Origin of Species*, two decades after he expounded it. The cause of the delay is still unclear; he might have either worried about public response to his revolutionary theory or wanted to accumulate additional data to make it unassailable. On molecular basis, non-synonymous amino acid replacement versus synonymous replacement may be an indication of selective or random events.

“Darwin’s greatest accomplishment is to show that the complex organization and functionality of living beings can be explained as the result of a natural process—natural selection—without any need to resort to a Creator or other external agent. The origin and adaptations of organisms in their profusion and wondrous variations were thus brought into the realm of science” (Ayala FJ 2007 Proc Natl Acad Sci USA 104 Suppl. 1:8563). ▶[natural selection](#), ▶[neo-darwinian evolution](#), ▶[social darwinism](#), ▶[synonymous codons](#), ▶[non-synonymous codons](#), ▶[algorithm genetic](#), ▶[creationism](#), ▶[intelligent design](#); Gould SJ, Lloyd EA 1999 Proc Natl Acad Sci USA 96:11904; complete works of Darwin: <http://darwin-online.org.uk/>; Darwin library, publications on darwinism: <http://darwinlibrary.amnh.org/>; Charles Darwin’s correspondence: <http://www.lib.cam.ac.uk/Departments/Darwin/index.html>.

Darwin’s Finches: ▶[finches](#)

DAS (distributed annotation system): DAS is a program facilitating the comparison of the annotations of different sources. ▶[annotation](#), <http://www.biodas.org/>; helpdesk@ensembl.org, DAS tutorial: http://corg.eb.tuebingen.mpg.de/cgi-bin/DAS_tutorial.pl.

DASH (dynamic allele-specific hybridization): In a well a short single-strand DNA sequence is hybridized with a known DNA probe. Upon pairing the fluorochrome added lights up indicating hybridization, upon denaturation the fluorescent paint fades and from the rate of fading the strength of the hybridization can be estimated. Thus it may reveal single nucleotide differences between the two partners. ▶[SNIPS](#), Prince JA et al 2001 Genome

Res 11:152; Pitarque M et al 2001 *Biochem Biophys Res Commun.* 284:455.

Data Dredging: ►dredging, ►data

Data Model: A set of bioinformatics constructs (sets, relations, objects) suitable to build databases. ►bioinformatics, ►databases

Data Sharing Principles (Fort Lauderdale Agreement): <http://www.genome.gov/10506537>.

Database Management System (DBMS): DBMS interprets the structure of data (schema) for generation of databases in a specified form, e.g., Oracle and Sybase. ►sybase

Databases: (for some addresses and additional information see under **special entries**) Databases provide information of different subjects by electronic means. Addresses frequently change and many have overlapping information, but they can be very helpful. Internet addresses hundreds of databases that are listed each year in the first issue of *Nucleic Acids Research* and accessible through the Internet without charge: <http://nar.oupjournals.org>. Links to several databases follow:

<http://www.biologie.uni-hamburg.de/b-online/e00/links.htm>. Much more information is now available under separate entries in the alphabetical lists. Data management hardware, software and service providers are listed in *Nature* 428:778 (2004)

General Directories (Jump Stations)

National Center for Biotechnology: <http://www.ncbi.nlm.nih.gov/Entrez/>; <http://www.ncbi.nlm.nih.gov>.

National Institute of Health Databases: <http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi?term=>.

SciCentral, Stanford Univ. general and specific information: <http://www.scicentral.com>,

European Bioinformatics Institute: www.ebi.ac.uk.

EBI Services: <http://www.ebi.ac.uk/Tools/web/services/>.

Bioinformatics Directory 2007: http://bioinformatics.ca/links_directory/.

Google: <http://www.google.com>.

Yahoo (www subject directory): <http://www.yahoo.com>.

Infoseek Yellow Pages: <http://www.infoseek.com/>.

AltaVista: <http://www.altavista.com>.

Sherlockhound: <http://www.sherlockhound.com>.

FTP (file transfer protocol): for several databases and free software packages in molecular biology (hard to connect): <ftp://ncbi.nlm.nih.gov/>.

European Bioinformatics Institute: <http://www.embl-ebi.ac.uk/>.

Multiple sequence alignments and hidden Markov models for common protein domains and families: <http://www.sanger.ac.uk/Software/Pfam/>.

BioCatalog “yellow pages”: <http://www.ebi.ac.uk/biocat/biocat.html>.

Bioinformatics Resources: http://bioinformatics.ubc.ca/resources/links_directory/narweb2006/.

GenBank NCBI (National Center for Biotechnology Information): <http://www.ncbi.nlm.nih.gov/>; <http://www3.ncbi.nlm.nih.gov/Entrez>, submission of genome data: <http://www.ncbi.nih.gov/Genbank/>.

GENOMIC AND GENETIC RESOURCES:

<http://www.ncbi.nlm.nih.gov/Sitemap/index.html>.

<http://www.sanger.ac.uk/>.

<http://image.llnl.gov/>.

GenBank - general nucleotide sequence inquiries: <mailto:genbank%life@lanl.gov>.

sequence submission: <mailto:gb-sub%life@lanl.gov>.

DDBJ-general nucleotide sequence inquiries: ddjb@niguts.nig.junet.

submission: ddjbsub@niguts.nig.junet; <http://www.ddbj.nig.ac.jp>.

EMBL-general nucleotide sequence inquiries: datalib@embl.earn, submission: datasubs@embl.earn.

European Bioinformatics, EMBL and WEBIN under separate entries, molecular biology database and server systems: <http://taverna.sourceforge.net/>, nucleotide sequence database: <http://www.ebi.ac.uk/embl>.

EMBL Nucleotide Sequence Database Submissions: Webin—Features & Qualifiers Webin; <http://www.ebi.ac.uk/embl/WebFeat/index.html>.

International Nucleotide Sequence Database Collaboration: <http://insdc.org>.

International Sequencing Consortium: <http://www.intlgenome.org/viewDatabase.cfm>.

Nucleic Acids Folding, Targets: <http://sfold.wadsworth.org/index.pl>.

EST Sequence Information: <http://www.ncbi.nlm.nih.gov/dbEST/index.html>.

STS, GenBank: <http://www.ncbi.nlm.nih.gov/dbSTS/index.html>.

Genome sequences: <http://www.tigr.org/>; <http://nature.com/genomics/>.

<http://www.ncbi.nlm.nih.gov/Entrez/>.

igweb.integratedgenomics.com/GOLD.

Eukaryotic Genes: iubio.bio.indiana.edu/eugenesis

TIGRE Gene Indices: <http://www.tigr.org/tdb/tgi.shtml>,

<http://www.tigr.org/tdb/euk/>; <http://www.ensembl.org/index.html>.

Gene expression, synonyms, references: <http://www.pdg.cnb.uam.es/UniPub/iHOP>.

Gene Ontology: <http://www.geneontology.org>.

Sequence similarity search: <http://www.ncbi.nlm.nih.gov/BLAST>.

- <http://www.ebi.ac.uk/fasta3/>.
 PANDORA (database of interacting proteins): <http://www.pandora.cs.huji.ac.il>.
 Genome Information Broker, Microbial: <http://gib.genes.nig.ac.jp/>.
 DNA databank Japan: <http://www.ddbj.nig.ac.jp/>.
 KEGG (Kyoto Encyclopedia of Genes and Genomes): <http://www.genome.ad.jp/kegg/>.
 DNA and Coding History: <http://www.history.nih.gov/exhibits/nirenberg>.
 Patent Information: <http://www.cambiaip.org>.
 Image Library of Biological Macromolecules: <http://www.imb-jena.de/IMAGE.html>.
 SWISS-PROT (protein information): <http://www.ebi.ac.uk/prosite/>.
 Protein Sequence: <http://www.sanger.ac.uk/Pfam>.
 Protein Structure: <http://scop.mrc-lmb.cam.ac.uk/scop/>.
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Structure>, www.rcsb.org,
 Protein Domains & Functional Sites: <http://www.ebi.ac.uk/interpro>.
 Human Protein Atlas: <http://www.proteinatlas.org/>.
 Structural Classification of Proteins: <http://scop.mrc-lmb.cam.ac.uk/scop/>.
 Protein and Nucleic Acids 3D Structures: <http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/>.
 Interacting proteins: <http://www.doe-mbi.ucla.edu>.
 PepTool (for identifying function from primary structure): <http://www.biotoools.com>.
 Protein structure images: <http://molbio.info.nih.gov/cgi-bin/pdb>,
<http://www.rcsb.org/pdb>.
 Protein Function: <http://www.genome.ad.jp/kegg/>.
 Protein reviews (PROW): <http://www.ncbi.nlm.nih.gov/prow/> Proteome (proteins): <http://www.expasy.ch>.
 Proteome (yeast, *Caenorhabditis*): <http://www.proteome.com>.
 Real time protein information exchange: <http://www.wikiprofessionsl.info>.
 RNA structure, evolution: <http://www.rna.icmb.utexas.edu>.
 Lipids: <http://www.lipidat.chemistry.ohio-state.edu>.
 Homology search: info@ncbi.nlm.nih.gov.
 human-mouse homology: <http://www3.ncbi.nlm.nih.gov/Homology>.
 Meta-MEME (motif-based hidden Markov modeling): <http://metameme.sdsc.edu>.
 Linkage analysis and software: <http://linkage.rockefeller.edu/>.
 ANIMAL GENETICS:
 Online Mendelian Inheritance of Animals (OMIA): <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=omia>; <http://omia.angis.org.au/>.
 Poultry, Pig, Sheep and Cattle genome: <http://www.ri.b.bsrc.ac.uk/>,
<http://www.tigr.org/>.
Caenorhabditis: <http://www.wormbase.org>.
Drosophila: <http://flybase.bio.indiana.edu/>.
 Mouse Informatics Database:
<http://www.informatics.jax.org>.
 Encyclopedia of the mouse genome: <http://www.informatics.jax.org>.
 Mammalian Gene Collection (provides information on human, mouse, rat open reading frames for purchase): <http://mgc.nci.nih.gov/>.
 Induced Mutant Resource Index of Strains of mouse:
<http://www.jax.org/pub-cgi/imrpub.sh?objtype=stridx>.
 Combined Mouse/Human Phenotypes: http://www.informatics.jax.org/searches/allele_form.shtml.
 Zebrafish: <http://depts.washington.edu/~fishscop/>;
<http://zebra.sc.edu>,
 Human Gene Mutation: <http://www.hgmd.cf.ac.uk/ac/index.php>.
 Single Nucleotide Variation: <http://www.ncbi.nlm.nih.gov/SNP/>.
 Disease images, thesaurus: <http://www.brisbio.ac.uk>.
 Locus Link: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>.
 Mendelian Inheritance in Man, online (OMIM): <http://www.ncbi.nlm.nih.gov/>.
 Human Gene Database: <http://gdbwww.gdb.org>.
 GeneCards (human genes, annotations, disease): <http://bioinfo.weizmann.ac.il/cards/index.html>.
 Human Cytogenetic Network: <http://mcndb.imbgu.ku.dk>.
 Human karyotypes: <http://www.pathology.washington.edu:80/CytoGallery/> or
 Human Physical Map: <http://www.ncbi.nlm.nih.gov/genemap99/>.
 Human/mouse gene expression: <http://bodymap.ims.u-tokyo.ac.jp/>.
 Human Mapping Laboratories:
<http://www.genethon.fr/> (information in French)
<http://www.sanger.ac.uk/> (includes also *Caenorhabditis* and other databases)
<http://www.shgc.stanford.edu/> (radiation hybrid maps primarily)
<http://www.well.ox.ac.uk/> (specific proteins, proteome and other information)
<http://www.incyte.com>.
<http://www.genome.wi.mit.edu/> (human and mouse primarily)
 Human Genome Database: <http://gdbwww.gdb.org>.
 DOE Genome Projects: <http://www.ornl.gov/hgmis>.
 Human Cancer Anatomy: <http://www.ncbi.nlm.nih.gov/ncicgap/>.
 Human and primate anatomy: www.eskeletons.org.

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Human embryogenesis: <http://virtualhumanembryo.lsuhsu.edu>.

Human Medical Information: <http://medlineplus.gov>.

Medical Terminology: <http://medical.webends.com>.

Human Disease Gene Database: <http://geneticassocationdb.nih.gov>.

Human genes with disease: <http://hipseq.med.harvard.edu/MEDGENE/login.jsp>.

Human Disease Genetics Home Reference: <http://www.ghr.nlm.nih.gov/ghr/page/Home>.

Drosophila gene homologs of human disease genes: <http://superfly.ucsd.edu/homophila>.

Disease Control and Prevention: <http://www.cdc.gov/health/diseases.htm>.

Rare diseases in six languages: www.orpha.net.

GeneReviews: genetic tests: www.genetests.org; <http://www.geneclinics.org>.

Genetic Counseling: <http://www.geneclinics.org/>.

Medical history: <http://medhist.ac.uk>.

Human body and diseases: www.healcentral.org.

Wild life disease: <http://wildlifedisease.nbio.gov/index.jsp>.

PLANTS:

Gene Indices: <http://www.tigr.org/tdb/tgi/plant.shtml>.

USD, National Agricultural Library: <http://www.nal.usda.gov/index.shtml>.

Comparative Plant Genomics: <http://www.phytome.org/>.

Plant genomes: <http://urgi.versailles.inra.fr/>.

Phylogenomics: <http://greenphyl.cirad.fr/cgi-bin/greenphyl.cgi>.

Ortholog search tool: <http://greenphyl.cirad.fr/cgi-bin/gost.cgi>.

Cereal and grass genomics: <http://www.gramene.org/>.

Mendel Biotechnology: <http://www.mendelbio.com/>.

Forest tree genetics: <http://dendrome.ucdavis.edu>.

Fruits: <http://www.ecpgr.cgiar.org/Networks/Fruit/fruit.htm>.

Botany: <http://sciweb.nybg.org/science2>.

Comprehensive botany: <http://www.nbio.gov/disciplines/botany/index.html>.

Herbarium Species: <http://www.nybg.org/bsci/hcol/vasc>.

Encyclopedia of plants: <http://plants.usda.gov>.

Plant Chromosome Numbers: <http://mobot.mobot.org/W3T/Search/ipcn.html>.

Chromosome numbers for animals and plants: <http://morgan.rutgers.edu/morganwebframes/level1/page2/ChromNum.html>.

Genetic Model Organisms: <http://www.gmod.org/>.

PLANT PATHOLOGY: <http://www.plantpath.wisc.edu/library>; <http://www.apsnet.org/education>.

ENTOMOLOGY: <http://www.ent.iastate.edu/list/>; <http://www.insectimages.org>.

Microbial projects: <http://www.microbeproject.gov>.

EUKARYOTIC MICROBES:

Dictyostelium: <http://www.tigr.org/tdb/tgi.shtml>.

Saccharomyces: <http://genome-www.stanford.edu/Saccharomyces/>.

Saccharomyces Genome Database (SGD): <http://genome-www.stanford.edu> includes also *Arabidopsis*, human data.

Yeast, *Caenorhabditis*, proteome: <http://www.proteome.com>.

Neurospora: <http://biology.unm.edu/biology/ngp/home.html>.

Mycology Online: <http://www.mycology.adelaide.edu.au/>.

Microbes/prokaryotes for classrooms: <http://www.microbelibrary.org>.

PROKARYOTES:

Textbook: <http://www.textbookofbacteriology.net/>.

Comprehensive Microbial Resource (genome annotations):

<http://cmr.tigr.org/tigr-scripts/CMR/CmrHomePage.cgi>.

Genome Information Broker (complete microbial genomes): <http://gib.genes.nig.ac.jp/>.

Haemophilus influenzae, *Methanococcus*, *Mycoplasma*, etc. <http://www.tigr.org>.

E. coli: <http://cgsc.biology.yale.edu> or <ftp://ftp.pasteur.fr/pub/>.

Microbial Genomes: <http://www.tigr.org/tdb/mdb/mdb.html>.

Viruses, structure, biology: <http://www.medicine.wustl.edu/~virology/index.htm>.

Genome Reviews for microbes: <http://www.ebi.ac.uk/GenomeReviews>.

Pathogen Sequences: GeneDB <http://www.genedb.org/>.

MICROSCOPIC GALLERY: <http://www.pbrc.hawaii.edu/~kunkel/>.

Microscopy, histology: <http://www.itg.uiuc.edu/>, www.vcbio.sci.kun.nl/eng.

IMAGE eBANK, free biological structures for instruction:

<http://www.bio.ltsn.ac.uk/imagebank>.

CARCINOGEN: <http://potency.berkeley.edu/>; <http://www.iarc.fr/>.

<mailto:cpdb@potency.berkeley.edu>,

GENETIC TOXICOLOGY (TEHIP): <http://sis.nlm.nih.gov>.

MUTAGENS & TOXIC CHEMICALS: <http://toxnet.nlm.nih.gov>.

Chemical Safety in the Environment: <http://www.inchem.org>.

Radiation related concepts and terms: <http://glossary.dataenabled.com/>.

Biosafety Information: <http://www.cdc.gov/od/ohs>; <http://www.agbios.com>.

Biochemistry textbook: <http://www.indstate.edu/thcme/mwking/home.html>.

Cell Biology and tools: http://www.vlib.org/Science/Cell_Biology/index.shtml.

VIRTUAL CELL (physiological modeling): <http://www.nrcam.uchc.edu/>.

Molecular Structures: <http://www.iumsc.indiana.edu/index.html>.

www.scripps.edu/pub/olson-web/people/gmm/.

RNA structure database: <http://www.rnabase.org>.

Chemical Terminology: <http://www.chemsoc.org/chembytes/goldbook>.

Chemistry Software and Information Resources: <http://www.csir.org/>.

MOLECULAR BIOLOGY ANALYTICAL TOOLS by Internet:

www.MolecularCloning.com.

Biobase regulatory system tools: <http://www.biobase-international.com/pages/>.

United States Science: <http://www.science.gov>.

Office of Biotechnology Activities: <http://www4.od.nih.gov/oba>.

DEVELOPMENTAL BIOLOGY <http://www.luc.edu/depts/biology/dev.htm>.

Plant signaling: <http://www.nature.com/nature/focus/plants/index.html> Teratology: <http://www.teratology.org/jfs/teratologyindex.html>.

Taxonomy: <http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html>.

Biodiversity: <http://www.gbif.net/portal>.

Biodiversity of India, South-East Asia: <http://www.ibin.co.in/>.

Cognitive Sciences: <http://cognet.mit.edu>.

Neuroscience Database: <http://www.sfn.org/ndg/>.

Biology textbook: <http://www.ultranet.com/~jkimball/BiologyPages>.

Education: www.hhmi.org; www.cellbioed.org; <http://www.thenakedscientists.com>.

Education, cell biology: <http://www.bio.davidson.edu/courses/movies.html>.

Genetics Science Learning Center: <http://learn.genetics.utah.edu/>,

Genetics news, questions and answers: <http://www.thetech.org/exhibits/online/ugenetics>.

Biology teacher: <http://www.biosciednet.org/portal>

Human evolution – migration: <http://www5.nationalgeographic.com/genographic>.

Catalog of species: <http://www.sp2000.org>.

National Center for Biotechnology Information news: <http://www.ncbi.nlm.nih.gov/feed/>.

Journal, Reviewer search for suitability: <http://invention.swmed.edu/etblast/etblast.shtml>.

LITERATURE SEARCH: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>.

<http://www.biomednet.com/db/medline/new> National Library of Medicine: <http://www.ncbi.nlm.nih.gov/>.

United Kingdom PubMed Central: <http://ukpmc.ac.uk/>.

Google Scholar Search: <http://scholar.google.com>.

Research Index: www.researchindex.org.

Medical subjects: <http://www.nlm.nih.gov/mesh/MBrowser.html>.

eTBLAST: helps locating topics in MEDLINE database by providing a set of query sentences (e.g., in your abstract and in MEDLINE) and notifies you by e-mail: <http://invention.swmed.edu/etblast/index.shtml>; <http://invention.swmed.edu/etblast/index.shtml>.

EndNote: www.endnote.com.

Connotea (literature organizer): <http://www.connotea.org/>.

MedLine: <http://www.ncbi.nlm.nih.gov/>.

MedLine database organizer: <http://www.hubmed.org/>.

CAS: <http://www.cas.org/>.

ChemPort: <http://chemport.cas.org>.

Finding PubMed clusters: <mailto:vivisimo.com/demos/PubMed@NIH.html>.

PubMed, GenBank alert service: <http://www.pubcrawler.ie>.

Literature mining: <http://bioie ldc.upenn.edu>.

Full-text Papers: <http://www.pubmedcentral.nih.gov/>, >750,000 in full text

<http://highwire.stanford.edu>, www.thescientificworld.com.

some full-text: <http://www.doaj.org>.

Free Medical Journals: <http://www.freemedicaljournals.com/>.

Biosis: <http://www.biosis.org/>.

Journal Name Abbreviations: <http://www.uh.edu/~rmaddock/IRGO/journaltitles.html>.

NATURE Journals: <http://www.nature.com/ng/>.

Nature Publishing Group Journals: <http://www.nature.com/omics>.

Most cited papers in chemistry/biochemistry: <http://www.cas.org/spotlight/index.html>.

Highly cited papers: <http://isihighlycited.com/>.

Influential papers, authors: <http://www.esi-topics.com>.

Biomedical engineering news: <http://www.bmenet.org/BMEnet/>.

Acronyms: <http://www.medstract.org/acro1.0/main3.htm>.

WORDNET (word synonym sets): <http://www.cogsci.princeton.edu/~wn/>.

Statistical assistance: <http://StatPages.org>; <http://www.r-project.org>.

Computing Dictionary: <http://www.foldoc.org>.

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Biodegradation: <http://www.labmed.umn.edu/umbdd>.

Clinical trials in progress: <http://clinicaltrials.gov/ct/gui/c/r>.

Genetics Societies: <http://www.faseb.org/genetics/>.

US Government Research and Development Reports: <http://www.osti.gov/fedrnd>.

Pathways of Discovery: <http://www.britannica.com>.

Nobel Laureates: <http://almaz.com/nobel/alpha.html>.

Historical on DNA, etc.: <http://www.exploratorium.edu/origins>.

Salvador Luria: <http://profiles.nlm.nih.gov/QL/>.

Policy issues: <http://www.genesage.com/professionals/geneletter/index.epl>.

Research integrity: <http://ori.dhhs.gov>.

Encyclopedia of false and superstitious ideas: <http://skepdic.com/>.

Legal Information on privacy, discrimination, cultural and religious issues, genetics, research, ethics:

<http://www.genome.gov/PolicyEthics/>

LegDatabase/pubsearch.cfm?

CFID=4745368&CFTOKEN=7455426.

Playing music from patterns: <http://tones.wolfram.com/>.

PATENTS: <http://www.uspto.gov/>.

Intellectual Property Rights:

<http://ip.nationalacademies.org>.

JOBS: search the home pages of journals or <http://www.careerpath.com>.

or <http://www.ajb.dni.us/>.

Cautionary note: Many symbols have multiple synonyms or single symbols standing for different genes or spelling and capitalization may vary for the same word and various errors may be encountered. Some databases cannot be entered without permission; the conditions for access can usually be obtained from the URL addresses. Addresses frequently change or are decommissioned (http://www-class.unl.edu/biochem/url/broken_links/html). Despite the problems, the databases provide invaluable information on details that could not be included in this book. The information must be critically read just as well as any publication coming from other sources. The addresses given above have been updated shortly before the completion of this book. (See, however, Nature [Lond] 402:722). According to Dellavalle RP et al 2003 Science 302:787 lost Internet site may be recovered through www.google.com; <http://www.altavista.com> or other search engines.

Data Mining: Searching for the biological meaning of nucleotide acid or amino acid sequences. ► [dredging data](#); Baxter SM, Fetrow JS 2001 Curr Opin Drug Discov Devel. 4(3):291; Smyth P 2000 Stat Methods

Med 9[4]:309; Perez-Iratxeta C et al 2002 Nature Genet 31:316; for drug development: Loging W et al 2007 Nature Rev Drug Discov 2007:220.

Data Submission Standards: Provide information on the forms of submission or correction of data as suggested on nucleic acid sequences and proteins by the European Molecular Biology Organization. (<http://www.ebi.ac.uk/Submissions/index.html>)

Date Palm (*Phoenix dactylifera*): One of the 12 species; dioecious, $2n = 2x = 36$.

dATP: deoxyadenosine triphosphate.

Datura: Members of the *Solanaceae* family ($2n = 24$), they have been primarily used for genetic studies involving cytological (trisomics) and cell culture methods. These species are the sources of the alkaloids atropin, hyoscyne, hyoscyamine and scopolamine (see Fig. D5). ► [henbane](#), ► *Atropa*, <http://www.b-and-t-world-seeds.com/Datura.htm>.



Figure D5. *Datura stramonium*

Daubert Rule: A 1993 modification of the principle of the Frye test, it allows the judge in the court to decide whether a scientific method is acceptable and recognized as an effective means to draw valid conclusions. The test in question must have been peer-reviewed and a have demonstrable accuracy. ► [Frye test](#); Klee CH, Friedman HJ 2001 NeuroRehabilitation 16[2]:79.

Dauer Larva: Represents an alternative form of larval development. It becomes semi-dormant at an early stage (e.g., after the second molt the larva of *Caenorhabditis*), if feeding is inadequate or the culture is overcrowded. Under such conditions, daumone (a fatty acid derivative) (see Fig. D6) is synthesized and it controls both development and aging (Jeong P-Y et al 2005 Nature [Lond] 433:541). It is a safety option for survival. Such a larva does not feed and responds only to touch and may stay alive for 30 to 70 days. Normal life cycle may be resumed with new food supply. Dauer larvae do not age

because when they resume the normal life the dauer stage does not affect the post-dauer longevity. Autophagy has an essential role in dauer larva formation (Meléndez A et al 2003 Science 301:1387). Dauer larva formation is under the control of bone morphogenetic (BMP)-like protein, a transforming growth factor (TGF- β) analog, cyclic GMP signals to sensory neurons responding to pheromones and insulin receptor signaling. The orphan nuclear receptor DAF-12 regulates dauer larvae, fat metabolism and longevity of the worms. DAF-9, a cytochrome P450 involved in hormone production, generates two 3-keto-cholestenic acid metabolites (dafachronic acids) (see Fig. D7), which represent DAF-12 activating steroidal ligands. DAF-9 is similar to the CYP27A1 steroidal regulator of humans (Motola DL et al 2006 Cell 124:1209). [▶Caenorhabditis](#), [▶TGF](#), [▶longevity](#), [▶autophagy](#), [▶bone morphogenetic protein](#); Inoue T, Thomas JH 2000 Genetics 156:1035; Houthoofd K et al 2002 Exp Geront 37:1015; Ailion M, Thomas JH 2003 Genetics 165:127.

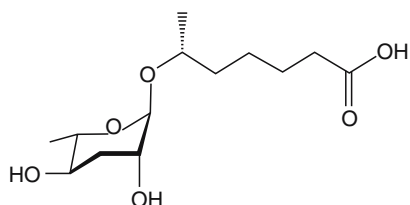


Figure D6. Daumone

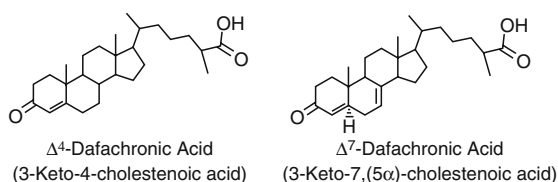


Figure D7. Δ^4 -Dafachronic acid (3-Keto-4-cholestenic acid) and Δ^7 -Dafachronic acid (3-Keto-7, (5 α)-cholestenic acid)

Dauermodification: Induced modification of the phenotype that may be transmitted to the progeny but persists only for a few generations (therefore, it is not a mutation).

Daughter Cells: These are formed after division from the parental one. [▶cell division](#)

Daughter Chromosome: A replicated chromosome has two chromatids. When the chromatids are separated at the centromere during mitotic anaphase they become two single-stranded daughter chromosomes (see Fig. D8). [▶chromatid](#), [▶centromere](#), [▶mitosis](#)

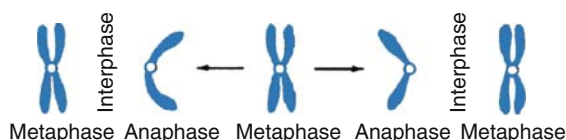


Figure D8. Daughter chromosome formation

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Daughter of Sevenless (DOS): The sevenless (SEV receptor tyrosine kinase) is a protein in the eye developmental pathway. Corcscrew (CSW) is a phosphotyrosine phosphatase in the signaling path and its substrate is DOS, a pleckstrin homology domain protein transmitting light signals for the eye between sevenless and RAS1 in *Drosophila*. In this pathway, Grb2 is an adaptor molecule with the son of sevenless (SOS) guanine exchange factor. The receptor sevenless tyrosine kinase (RTK) triggers neuronal differentiation in the single R7 cells of the ommatidia in response to the BOSS (bride of sevenless) ligand on the neighboring R8 photoreceptor cell. [▶sevenless](#), [▶son of sevenless](#), [▶boss](#), [▶ommatidia](#), [▶RTK](#), [▶pleckstrin domain](#), [▶rhodopsin](#); Bausenwein BS et al 2000 Mech Dev 90[2]:205.

DAX: [▶adrenal hypoplasia](#)

Day Blindness (hemeralopia): Autosomal recessive, defective vision in bright light and total colorblindness. It is the result of defective cone-like bodies of the retina. [▶night blindness](#), [▶colorblindness](#)

Day Neutral: Not responding to photoperiodic treatments. [▶photoperiodism](#)

Days Post Coitum: [▶dpc](#)

Dazla: [▶azoospermia](#)

DBA: Old inbred, grey mouse; it is frequently used for coat color analysis, heart, nerve and autoimmune diseases.

dbEST: A database for expressed sequence tags. [▶expressed sequence tag](#); Boguski MS et al 1993 Nature Genet 4:332.

DBF4: A Cdc7 binding and activating protein and may be required for the initiation of DNA re-plication. [▶Cdc7](#); Ogino K et al 2001 J Biol Chem 276:31376; Jares P et al 2000 EMBO Rep 1[4]:319.

DBL Oncogene: same as MCF2.

DBM Paper: [▶diazotized paper](#)

DBP (DNA binding proteins): These are histones, suppressors, activators, silencers and DNA and

RNA polymerases, transcription factors. separate entries.

DBMS: ►database management system

dbSNP: A single nucleotide polymorphism database.
►SNIPs; <http://www.ncbi.nlm.nih.gov/SNP>.

D

DCC: Deleted colon carcinoma gene involved in cancerous growth. DCC also drives an apoptotic pathway by interacting with caspases 3 and 9. DCC encodes also the main receptor of netrin-1 (Furne C et al 2006 Proc Natl Acad Sci USA 103:4128). ►colorectal cancer, ►tumor suppressor genes, ►pancreatic adenocarcinoma, ►p16, ►caspases, ►apoptosis, ►netrin; Graziano F et al 2001 BMC Cancer 1:9.

dCF (deoxycyformicin): ►ADA; Jehn U, Heinemann V 1991 Anticancer Res 11:705.

dcm: ►methylation of DNA

DCMU (3[3,4-dichlorophenyl]-1,1-dimethylurea): DCMU is an inhibitor of photosystem II. ►photo-synthesis, ►Z scheme

DCP1 (dipeptidyl carboxy peptidase): An angiotensin-converting enzyme. When it is active it may protect against Alzheimer's disease. ►angiotensin, ►Alzheimer disease

Dcp1p: A mRNA decapping nuclease. ►cap

DcR (death decoy receptor): ►FAS

DC-SIGN (dendritic cell-specific ICAM-3 grabbing non-integrin): A protein on the surface of dendritic cells and communicates to the T lymphocytes. It also transfers HIV-1 virus from the mucosa of the cervix or rectum to the lymphnodes where HIV infects the CD4⁺ T cells and eventually by the destruction of the immune system causes AIDS. DC-SIGN responds to different types of pathogens such as Hepatitis C virus, *Helicobacter pylori*, *Mycobacterium tuberculosis*, etc. ►acquired immunodeficiency, ►ICAM, ►acquired immunity, ►integrin, ►dendritic cell, ►Dengue fever; Steinman RM 2000 Cell 100:491.

DCT1 (divalent cation transporter): DCT1 are transporters of metal ions into the cells. ►ion channels

DctB: Bacterial kinase, acting by phosphorylating protein DctD.

dCTP: deoxycytidine triphosphate (di-Na salt, MW 511.13) (see Fig. D9)

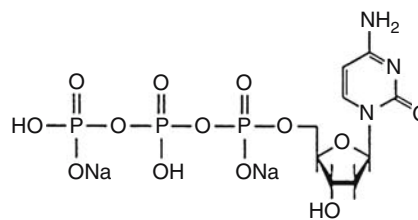


Figure D9. dCTP

DDB (aspartic, aspartic, glutamic acids): DDB appears to be the core motif in various transposases. ►amino acid symbols in protein sequences

DDB (damaged DNA-binding protein): A heterodimer of p127 and p48. Mutations at the xeroderma pigmentosum gene E results in loss of it p48 activity and deficiency in global cyclobutane pyrimidine repair. ►DNA repair, ►cyclobutane dimer, ►xeroderma pigmentosum; Wakasugi M et al 2002 J Biol Chem 277:1637.

DDB1: A core subunit of the Cul4A-based ubiquitin complex. ►Cul; Li T et al 2006 Cell 124:1095.

DDBJ (<http://www.ddbj.nig.ac.jp>): Data Submissions, Laboratory of Genetic Information Analysis, Center for Genetic Information Research, National Institute of Genetics, 111 Yata, Mishima Shizuoka 411, Japan. General inquiries about nucleotide sequence database, e-mail: ddjb@niguts.nig.junet, submission forms: ddjbsub@niguts.nig.junet, telephone: 559 75 0771, <http://gib.genes.nig.ac.jp>.

DD(35)E: Insertion elements characterized by this motif (D = aspartic acid, E = glutamic acid. ►insertion elements; Mahillon J, Chandler M 1998 Microbiol Mol Biol Rev 62:725.

DDT: ►dichlorodiphenyltrichloroethane

De Lange Syndrome (Cornelia de Lange, Brachmann-de Lange syndrome): De Lange syndrome is most likely caused by new autosomal dominant mutations (see Fig. D10). The afflicted individuals do not reproduce. According to a Danish study, its frequency appeared to be 6×10^{-6} . The gene is situated in the area 3q21-qter.

About 30% of the cases are associated with various chromosomal anomalies, including duplication (and possibly deficiency) of the long arm of human chromosome 3. Some of the chromosomal anomalies may be unrelated to the syndrome characterized by the two eyebrows growing across the nose, hairy forehead and neck, long eyelashes, depressed nose bridge and uptilted nose tip, wide spacing of teeth, flat fingers and hands, altered palm print, mental

retardation, etc. The physical anomalies are evident by the end of the second trimester.

Mutations at Xp11.2 involving a cohesin subunit (SMC1L1) affect about half of the De Lange cases (Musio A et al 2006 *Nature Genet* 38:528). ►[mental retardation](#), ►[limb defects in humans](#), ►[head/face/brain defects](#), ►[hypertrichosis](#), ►[cohesin](#)



Figure D10. De Lange syndrome. Note deformed ear, long eyelashes and flat nasal bridge. (Modified from Bergsma, D., ed. 1973 *Birth Defects. Atlas and Compendium*). By permission of the National Foundation of the March of Dimes

De Novo: To start anew (from “scratch”).

De Sanctis–Cacchione Syndrome (xerodermic idiocy): A neurological defect frequently associated with xeroderma pigmentosum; it is due to a deficiency of repair caused by mutation in ERCC6. ►[xeroderma pigmentosum](#), ►[excision repair](#)

Dead-Box Proteins: A family of ATP-dependent helicases, present in prokaryotes and eukaryotes, they can stabilize mRNA and facilitate translation with the involvement of the 43S complex containing eIF4A, eIF4B, eIF4F. The 4Fs have three subunits: eIF4A, eIF4E, and eIF4G. 4B and 4F form a helicase that binds the 5'-end of the untranslated RNA through the 4E subunit. The name DEAD comes from the single letter amino acid symbols of proteins: Asp (D)-Glu (E)-Ala (A)-Asp (D) identifying a sequence present in eIF4A. The Vasa DEAD-box protein of *Drosophila* sharply bends the bound RNA to avoid a clash with the conserved α -helix in the N-terminal domain. This “wedge” helix may disrupt base pairs when an RNA duplex is bound. This mechanism potentiates targeted modulation of intricate RNA structures (Sengoku T et al 2006 *Cell* 125:287). ►[helicases](#), ►[eIF-4A](#), ►[DEAD-box proteins](#), ►[amino acid symbols in protein sequences](#), ►[translation initiation](#), ►[degradosome](#), ►[RNA surveillance](#), ►[ataxia](#), ►[P body](#); de la Cruz J et al 1999 *Trends Biochem Sci* 24:192.

Dead-End Complex: If the required nucleotides are not available for transcription the action of the polymerase is halted and may not be resumed after supplying the needed building blocks, presumably because of

changes in the proper configuration at the 3' end. Transcription may be resumed, however, if RNA hydrolytic proteins are supplied and that leads to redirection of the transcription complex. (Erie DA et al 1993 *Science* 262:867.)

De-Adenylation Pathway: The degradation of mRNA by removal of the poly(A) tail. ►[polyA tail](#); Caponigro G, Parker R 1996 *Microbiol Rev* 60:233; Tucker M et al 2001 *Cell* 104:377.

DEAE-Cellulose: As a membrane, DEAE-cellulose is used for trapping DNA from agarose gels. ►[gel electrophoresis](#)

DEAE-Dextran: A polycationic diethylaminoethyl ether of dextran (a polysaccharide) that stimulates the uptake of proteins and polynucleotides into cells, promotes the infection of cells by viral RNA and DNA, may inhibit tumors in animals, and stimulates reactions to antibody. ►[dextran](#), ►[transformation genetic animal cells](#)

DEAE-Sephacel: DEAE-Sephadex, DEAE Sepharose are ion exchangers used for gel filtration, as ion exchangers and chromatographic media. ►[sephadex](#), ►[sepharose](#), ►[ion-exchange resins](#), ►[gel filtration](#)

Deafmutism: The hereditary loss of hearing and speech with a prevalence of about 0.03–0.04%, and with a recurrence risk of about 12% among afflicted sibs. There are an estimated number of 35 loci capable of causing this anomaly. The spontaneous rate of mutation was estimated to be about 4.5×10^{-4} . The incidence of deafness has a rather large environmental component. ►[Usher syndrome](#), ►[deafness](#)

Deafness: A hearing deficit within a broad range from slight hearing difficulties to complete loss and this may be a progressive phenomenon. By age 90, about half of the human population experiences some degree of hearing loss. It has been estimated that about 1% of all human genes are involved in the control of hearing. About 68 loci are involved with non-syndromic hearing deficit. The sensation of balance and hearing is mediated by the stereocilia (epithelial appendages) of the inner ear hair cells via electrical signals to the brain. Transient receptor potential (TRP) ion channels at the tip of the sensory hair cell bundle initiates perception of sound (Corey DP et al 2004 *Nature [Lond]* 432:723).

About 3/4 of the hearing problems have complete or partial genetic determination and the rest may be environmentally induced. About 5–10% of the population develops hearing problems with advancing age and about 0.001 fraction of newborns are deaf or develop some kind of hearing loss by school age. The first indication of an infant's hearing loss is inability to articulate. About 87% of congenital

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deafmutism is caused by recessive factors. Dominant inheritance determines deafness to some low, middle and high tone sounds, while at other frequencies the hearing may be normal. The Michel syndrome is responsible for a complete lack of the internal ear formation. The hearing problems may have a wide range of organic bases but usually, they are classified as *conductive* (transmission) *hearing deficit* that is caused by defects in the hearing canal or the middle ear. *Sensorineural* defects involve the inner ear and the associated nervous system. This type *non-syndromic* (single phenotype is only deafness) is based on a mutation of the connexin gene (DFNA3) in chromosome 13q11-q12. DFNA2 (1p34) is due to mutations at a complex locus encoding the potassium ion channel KCNQ4 and possibly connexin 31. DFNA5 (7q15) is caused by deletion in intron 7 and premature termination of transcription. Deafness (DFNA15) in human chromosome 5q31 involves mutation in transcription factor POU4F3. The non-syndromic DFNA17 (22q12.2-q13.3) is a mutation in the non-muscle myosin gene, MYH9. DNFA23 (14q21) and DNFA25 (12q21-q24) encode non-syndromic deafness. DFNB1 encodes connexin-26. The Myo7a mutation (DFNB2) is non-syndromic myosin VIIa defect. DFNB3 in human chromosome 17p11.2 (homologous with mutation shaker-2 in mouse) involves a defect in an unusual myosin molecule (Myo15), resulting in short stereocilia ([singular stereocilium] protoplasmic filaments on the ca. 100 hair cells of the inner ear). DFNB4 encodes pendrin. DFNB9 is a mutation in otoferin and DFNB21 involves α -tectorin. DFNB29 gene (21q22.1) encodes the tight junction protein, Claudin-14, DFNB31 is a defect in the protein whirlin of the stereocilia. The non-syndromic DFNA13 (human chromosome 6) is due to mutation in a collagen gene, COL11A2. DFNA1 appears to affect the cytoskeleton through connexin 32. DFNA16 is a dominant non-syndromic deafness is encoded at 2q23-q24.3. Mutation in human chromosome 11q22-q24 (DFNA8, DFNA12) involves α -tectorin, an extracellular matrix protein over the inner ear hair cells. The latter mutation is synonymous with *shaker-1* of mouse chromosome 9. DFNB26 was assigned to 4q31. DFNB37 (6q13) is based on recessive defect(s) in myosin-6 (Ahmed ZM et al 2003 Am J Hum Genet 72:1315). DFNM1 at 1q24 is recessive deafness suppressor. Congenital deafness in some instances in humans has been remedied by cochlear implants at early stage of development. Also in cats auditory nerve synapses have been improved by some and stimulation after cochlear implants (Ryugo DK et al 2005 Science 310:1490).

The classifications may not be absolute because the types may overlap and further complicated in a

number of syndromes. Conductive hearing problems occur in otopalatodigital syndrome, Treacher Collins syndrome, osteogenesis imperfecta, Crouzon syndrome, Turner syndrome. Sensorineural hearing defects are found in Alport syndrome, Jervell and Lange-Nielsen syndrome, Pendred syndrome, Usher syndrome, Stickler syndrome, Refsum syndrome, Wildervanck syndrome, Norrie's disease, albinism (cutaneous), Waardenburg syndrome, LEOPARD syndrome and the Ménière disease. Both conductive and sensorineural defects may be present in the Klippel-Feil syndrome and some other cases. Deletions or mutations in the Xq21 region may also cause deafness (DFN1, Charcot-Marie-Tooth disease, Mohr-Tranebjaerg syndrome, DFN3) in case of (surgical) injuries to the stapes (the stirrup-like bones in the ear) resulting in leakage of the fluid (perilymph) of the inner ear (gusher deafness). The molecular basis of this hearing impairment is in gene Brain Protein 4 (BRN-4/RHS2/POU3F4), encoding a transcription factor with a pou domain. Approximately 6% of the hereditary deafnesses are X-linked and are brought about by different mechanisms such as defects in the iris, cornea or by ocular albinism or other types of albinisms. Thyroid hormone receptor β is essential for the normal development of the auditory function. Maternally determined high sensitivity to aminoglycosides (streptomycin, neomycin, and paromomycin) may result in non-syndromic hearing loss due C1494T mutation in the 12S mitochondrial RNA gene (Zhao H et al 2004 Am J Hum Genet 74:139). A non-syndromic recessive deafness was located to human chromosomes 2p22-p23 and to 21q22. Hereditary deafness occurs among children at a frequency of 5×10^{-4} . Some deaf children may be helped by stimulation of the auditory cortex through implants. The Ames waltzer mouse's deafness is caused by mutation in a protocadherin gene. Genetic testing is feasible for connexin based defects in hearing deficits. By 2001, 77 human gene loci have been identified for non-syndromic deafness (40 autosomal dominant, 30 autosomal recessive and 7 X-linked and defects in mitochondrial RNA). Additional genes are known to affect hearing (15 autosomal dominant, 9 autosomal recessive, 2 X-linked, 5 mitochondrial and more than 32 genes control syndromic hearing deficits). the named syndromes under separate entries, ►mitochondrial diseases in humans, ►stereocilia, ►connexin, ►Charcot-Marie-Tooth disease, ►mucopolysaccharidosis [Hunter and Hurler syndromes], ►Wolfram syndrome, ►Usher syndrome, ►Lange-Nielsen syndrome, ►pou, ►connexin, ►tight junction, ►cadherin, ►otosclerosis, ►mitochondrial diseases in humans; Steel KP 1995 Annu Rev Genet 29:675; Scott HS et al 2001 Nature Genet 27:59; Kelsell DP

et al 2001 *Am J Hum Genet* 68:559; Petit C et al 2001 *Annu Rev Genet* 35:589; Resendes BL et al 2001 *Am J Hum Genet* 69:923; Call LM, Morton CC 2002 *Current Op Genet Dev* 12:343; anatomy, genes, function: Friedman TB, Griffith AJ 2003 *Annu Rev Genomics Hum Genet* 4:341, <http://www.uia.ac.be/dnalab/hhh/>; <http://webhost.ua.ac.be/hhh/>; <http://www.medicality.org.uk/diseases/hereditary-deafness.php>.

Deah-Box Proteins: These are involved in the processing of precursor RNA and may be responsible for silencing of transgenes and transposons. ▶**DEAD-box**; Wu-Scharf D et al 2000 *Science* 290:1159.

Deamidation: The removal of an amide group (NH₂) from a protein introduces a negative charge and may affect the tertiary structure, as well as the biological activity of the molecule. Deamidation of amino acids 52 and 66 of Bcl-X_L antiapoptotic protein disables its attachment to the BH3 domain proteins (PUMA, NOXA) and opens the path to cell death. Thus, it may result in the death of cancer cells. Damage to DNA generally activates the transcription of p53 tumor suppressor resulting in the upregulation of protein p21 and other proapoptotic proteins. Proteins Bax and Bak then mediate the mitochondrial release of cytochrome c and caspases, which cause the tumor cell death by proteolysis. Deamidation may be involved in other regulatory functions too. ▶**Bcl**, ▶**p53**, ▶**p21**, ▶**Bax**, ▶**Bak**, ▶**apoptosis caspase**; Li C, Thompson CB 2002 *Science* 298:1346.

Deamination: The removal of amino group(s) from a molecule. Cytosine is deaminated to uracil at the rate $3 \text{ to } 7 \times 10^{-13} \text{ sec}^{-1}$ in double-stranded DNA, i.e., about 40 to 100 deaminations of this type occur daily in the human genome. Thus C≡G transitions to T=A are apparently of major significance for mutation and evolution. The deamination of 5-methyl-cytosine is 2 to 4 times higher than that of cytosine. In single-strand DNA the rate of deamination is about 140 times higher than in double strands. Mismatched Cs are deaminated 8 to 26 times the rate of normally paired ones. Transcribed strands are about 4 times more likely to show deamination than the non-template strands. Some of the deaminated nucleotides are, however, removed by uracil-DNA glycosylases. ▶**nitrous acid**, ▶**transition**, ▶**DNA repair**

Death: An irreversible stop to vital functions, especially that of the brain and the genetic material (see Fig. D11). The *genetic death* is a population genetics term for lack of reproduction. Lack of reproduction may be due to the presence of deleterious or lethal genes. The probability of survival depends on the number of recessive lethal factors (n), according to e^{-n} , e.g., in case of $n = 2$, $e^{-2} \approx 0.135 = \text{survival}$.



Figure D11. Death

Death Domain: 60–80 amino acids in the cytoplasmic regions of cytokine receptors that engage the apoptosis path. ▶**cytokine**, ▶**apoptosis**, ▶**TNFR**, ▶**scaffold-mediated activation**, ▶**death receptor**

Death Rates: ▶**age-specific birth and death rates**, ▶**apoptosis**, ▶**Hayflick's limit**

Death Receptors: They transduce the apoptotic signals with the aid of cysteine-rich extracellular domains to the intracellular death domains. ▶**FADD/Mort**, ▶**DED**, ▶**death domain**, ▶**FAS**, ▶**FASL**, ▶**PLAD**, ▶**TRAIL**, ▶**mannose-6-phosphate**; Ashkenazi A, Dixit VM 1998 *Science* 281:1305.

Death Signaling: (i) ligands bind death receptors, (ii) trimerization of receptor and initiation of DISC, (iii) recruitment of FADD to DISC, (iv) recruitment of procaspase 8, (v) formation of active heterotetrameric caspase 8, (vi) activation of caspase cascades, (vii) truncation of Bcl/2 molecules, (viii) release of *cytochrome c* and Smac/DIABLO, (ix) cleavage of the death substrates leading to apoptosis. ▶**apoptosis**, ▶**death receptors**, ▶**FADD**, ▶**DISC**, ▶**caspases**, ▶**Bcl**, ▶**cytochromes**, ▶**Smac**, ▶**DIABLO**

Deazanucleotides: Analogs of nucleotides, antiviral agents and used for compression of sequencing gels (see Fig. D12). ▶**compression in gels**, ▶**DNA sequencing**

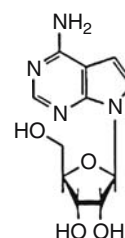


Figure D12. 7-Deazaadenosine

DEB: Diepoxybutane is an alkylating mutagen and carcinogen. ▶**mutagens**

Debranching Enzyme: It converts a nucleic acid loops (lariat) into a linear molecule. ▶**lariat RNA**; Khalid MF et al 2005 *Nucleic Acids Res* 33:6349.

Debrisoquine: An adrenergic-blocking drug used for treatment of hypertension. The response to the drug (human chromosome 22, dominant) depends on

cytochrome P450IID family of proteins. About 1–30% of the populations, depending on ethnicity, may be poor hydroxylators of this and other similar drugs, and may suffer serious side effects upon treatment. ▶cytochromes

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DEC-205: An integral membrane protein, homologous to the macrophage mannose receptor. It appears to have important role in antigen presentation and processing in antigen-capturing (dendritic) T cells. ▶antigen presenting cell; Mahnke K et al 2000 J Cell Biol 151:673.

Decapentaplegic (DPP): DPP is a complex gene/protein involved in dorsoventral and anterior/posterior (wing) differentiation in insects. Its vertebrate homolog is the bone morphogenetic protein (Bmp). An active dpp/Bmp favors ventral differentiation. DPP interacts with a large number of proteins. ▶morphogenesis of *Drosophila*, ▶organizer, ▶bone morphogenetic protein, ▶*Mothers against decapentaplegic*; Hsiung F et al 2005 Nature [Lond] 437:560; Affolter M, Basler K 2007 Nature Rev Genet 8:663.

Decapping: Process of removal of the mRNA cap (encoded by *DCP1* in yeast) and degradation by enzymatic decay in the 5'→3' direction (by exonuclease Xrn1p). It is usually triggered by shortening of the poly(A) tail (←3') but it may be brought about also by other means (Badis G et al 2004 Mol Cell 15:5). Mutation in the 7 *LSM* genes of yeast inhibit decapping and the decapping activator proteins Pat1/Mrt1. Decapping represses translation. The non-translated mRNA accumulates in processing bodies (P bodies). Decapping activators Dhh1p and Pat1p mediate the process; both the deficiency and overexpression of these proteins result in inhibition of translation (Coller J, Parker R 2005 Cell 122:875). ▶mRNA, ▶cap, ▶polyA mRNA, ▶polyadenylation signal, ▶Translation, ▶P body; Tucker M, Parker R 2000 Annu Rev Biochem 69:571; Dunckley T et al 2001 Genetics 157:27; decapping factors: Fenger-Gran M et al 2005 Mol Cell 20:905.

Decarboxylation: The removal of COOH group(s) from a molecule.

Decatenation: The disentangling of the catenated sister chromatids formed during DNA replication with the aid of topoisomerase II. This is a requisite for chromatid condensation during the ensuing phases. Decatenation inhibitors—without DNA damage—arrest cell cycle at mitosis (Skoufias; DA et al 2004 Mol Cell 15:977). ▶catenane, ▶sister chromatid; Downes CS et al 1994 Nature [Lond] 372:467; Deming PB et al 2001 Proc Natl Acad Sci USA 98:12044.

Decay-Accelerating Factor: (DAF, CD55, 1q32): DAF is an erythrocyte membrane glycoprotein along with

MCP and other members of the group control convertase activity. DAF may regulate translation without affecting mRNA in transgenic animals. ▶erythrocyte, ▶MCP, ▶complement, ▶convertase, ▶SMGT; Miyagawa S et al 2001 J Biochem 129:795; Uhrinova S et al 2003 Proc Natl Acad Sci USA 100:4718; Lukacik P et al 2004 Proc Natl Acad Sci USA 101:1279.

Decidua: A membrane lining the uterus during pregnancy that is shed around delivery. ▶embryo-genesis in animals

Decision Tree: A decision tree can assist in exploring conditional probabilities among several possible actions and outcomes (see Fig. D13). It starts out at the left square and connects to new decisions (squares) or uncertainties (circle), which are also called nodes. On the connecting lines (edges) the estimated probabilities can be represented. One may use a large number of branches if necessary. Each probability can be multiplied by a numerical value (percentage or fraction) and at the end the most rewarding or harmful decision can be evaluated. Such a procedure has merits in business or in medicine when different treatments are contemplated. Several software tools are available on the Internet. (Chen HY et al 2007 New England J Med 356:11)

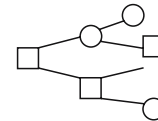


Figure D13. Decision tree

deCODE: genetics research, Reykjavik, Iceland, <http://www.decode.com/>.

Decoding: Although the genetic code intrigued biologists before the nature of the genetic material was firmly determined, the complete genetic code was deciphered between 1961 and 1966. From frameshift mutations, Crick's laboratory concluded that the code is written most likely in triplets of nucleotides. Since 1961 random copolymers of RNA were used. E.g., in a 5A: 1 C copolymer the AAA triplet are expected to be more common the CCC triplets. By chance alone the AAA sequence is expected to have a frequency of $(5/6)^3 = 0.579$ (125/216). ACA is expected to have the frequency of $5/6 \times 1/6 \times 5/6 = 25/216$ (0.116) and CCC is expected in a frequency of $(1/6)^3 = 0.0046$ (1/216). Thus, the 3 triplets' proportions were expected to be 125:25:1. In an in vitro protein synthesis assay, this copolymer promoted the incorporation of lysine the most abundantly. Therefore, the codon of AAA was expected for lysine. The 2A:1C codons could be

AAC, ACA, CAA, therefore additional copolymers were needed for determining their meanings. Repetitive ordered copolymers UUCUUCUUC permitted the incorporation of phenylalanine (UUC), serine (UCU) and leucine (CUU), depending in what register the sequence was read. The sequences GAUAGAUAG directed the incorporation Asp (GAU), Arg (AGA) and then the translation was stopped. Thus UAG was identified as the amber stop codon. The most precise method used ribosome binding. A collection of charged tRNAs were allowed to bind single known sequence triplets. Then tRNAs were charged with radioactively labeled amino acids. Cognate anticodons of a specific charged tRNAs bound only one triplet and thus the codons were identified. The validity of the code was then confirmed also by recombination. At amino acid site 211 in the wild type tryptophan synthetase glycine was identified. One mutation at this site resulted in a replacement by arginine and in another mutant by valine. A transduction experiment between the mutants restored glycine at site 211. This could be achieved if in the wild type there was CCT, and in the mutants GCT and CAT, respectively.

Recombination between the first bases $\frac{GCT}{CGA}$ could produce CCT (glycine), and thus verified the codons for glycine, arginine and valine. In the living cells the tRNAs in association with proteins recognize the amino acid codons on the surface of the ribosomes. ►genetic code, ►code genetic, ►ribosome binding assay, ►synthetic polynucleotides, ►wobble, ►overlapping genes, ►isoacceptor tRNA; Yčas M 1969 The Biological Code, North-Holland, Amsterdam, The Netherlands.

Decoding, Non-Standard: The use of the standard codon or a stop codon for specifying an amino acid other than usual for the majority of living systems. For e.g., some yeasts (*Candida*) use the leucine codon CUG for serine and in this case the special tRNA^{Ser} has a modified G (N1-methylguanosine) at position 37. ►decoding, ►genetic code; Santos MA et al 1997 Mol Microbiol 26:423.

Decoding, Ribosomal: The recognition of the proper mRNA triplet by the charged aminoacyl tRNA on the 30S ribosomal subunit and GTPase activation center on the 50S subunit. This step is called *accommodation* and it involves the moving of the aminoacyl-tRNA inside the ribosome (Sanbonmatsu KY et al 2005 Proc Natl Acad Sci USA 102:15854). Single nucleoside replacement in the tRNA may substantially alter the conformation of the tRNA and its control of the reading frame (Stuart JW et al 2003 J Mol Biol 334:901). Chloroplasts use only 31 anticodons for translation. Mitochondria may employ only as few as

22 anticodons, however, in some organisms the mitochondria use nuclear encoded tRNAs. Note also that the genetic code dictionary in mitochondria varies among different organisms and may be different from the 'universal' code. ►genetic code, ►tRNA, ►isoaccepting tRNA; Agris PF 2004 Nucleic Acids Res 32:223.

Deconvolution: A computer algorithm to remove haze from optical microscopy; a section for clarifying and sharpening images. Deconvolution microscopy provides high-resolution images by computer-assisted reconstruction of cross-sectional images of several planes.

Decoration: Minor protein fold(s) upon the basic structure that allow differences in function.

Decorrelation: Recombination frequencies vary along the length of a chromosome therefore average linkage disequilibrium does not accurately reflect the age of a chromosome during evolution.

Decoy Receptors: Decoy receptors bind various activator ligands, detract them from their normal receptors and may suppress inflammation. Some members of TNF family receptors such as lymphotoxin-β, osteoprotegerin, TNFR2 may alleviate bowel inflammation, arthritis, autoimmune disease, etc. ►TNF, ►autoimmune disease, ►arthritis, ►receptor, ►dumbbell oligonucleotides; Mantovani A et al 2001 Trends Immunol 22[6]:328.

Decoy RNA: It may be used to decrease gene expression by sequestering viral RNA-binding regulatory proteins. ►sequester, ►transdominant molecules; Jayan GC et al 2001 Gene Ther 8:1033.

Decussate: Consecutive leaf nodes in alternating rectangle arrangement (see Fig. D14). ►phyllotaxy



Figure D14. Decussate leaves of mint

DED (death-effector domain): DED of apoptosis proteins like FLICE. ►apoptosis, ►FLICE

Dedifferentiation: The loss of cellular differentiation frequently followed by new cell divisions. It has been generally assumed that terminally differentiated

mammalian cells (in contrast to that of lower animals and plants) are incapable of dedifferentiation. Cancerous transformation is, however, a type of dedifferentiation. Mammalian *msx1* gene can stimulate myotubes to dedifferentiate (in the presence of growth factors), and undergo transdetermination.

►redifferentiation, ►transdetermination, ►myotube, ►redifferentiation, ►regeneration

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Deep Sequencing: An extensive coverage of the DNA sequence; indicating the number of times a tract is sequenced. It may be extended to methylation of histones in the chromatin that affects expression of genes.

Deer: Chromosomally, a very diverse group of Cervidae yet, the American whitetail deer (*Odocoileus virginianus*) is $2n = 70$ and the reindeer (*Rangifer tarandus*) is also $2n = 70$. (Slate J et al 2002 Genetics 160:1587, <http://www.thearkdb.org/browser?species=deer>).

De-Etiolation: Plants grown in the dark usually elongate and fail to synthesize leaf pigments and thus show etiolation. Some mutations, however, show short hypocotyls and green pigment in the dark, i.e., they are deetiolated. The *Arabidopsis* AtDET1 gene homologs are also conserved in animals and encode a c-Jun ubiquitin ligase (Wertz IE et al 2004 Science 303:1371). ►Jun, ►ubiquitin, ►brassinosteroids

Default: A preset instruction followed until new instruction is given.

Defective Interfering Particle (DI): Subgenome-size mutants due to deletion(s) that require homologous virus for replication. They may have advantage in replication over the helper virus and thus secure their maintenance. ►helper virus

Defensin: ►Antimicrobial peptides, ►Paneth's cell. (Salzman NH et al 2003 Nature [Lond] 422:522)

Deficiency, Chromosomal: The (terminal) loss of a piece of the chromosomes ►deletion. Terminal losses of chromosomes can be readily induced by ionizing radiation at first order kinetics ►kinetics and they frequently behave as null alleles. If in a heterozygote the wild type allele is destroyed or removed the remaining recessive may be expressed (pseudodominance). An interstitial loss—if it is of substantial size—may be detected cytologically at meiotic pachytene because the wild type strand bulges out across the lost tract as shown by the diagram. Nutritional or metabolic deficiency may be due to a mutant gene (see Fig. D15) ►deletion, ►deletion mapping, ►duplication, ►duplication – deficiency

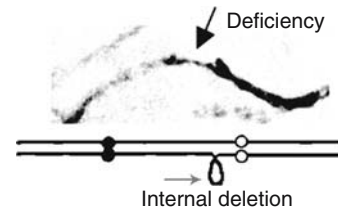


Figure D15. Deficiency, chromosomal

Defined Medium: Contains chemically identified and characterized nutrients.

DeFinetti Diagram: The genotype frequencies are represented as perpendicular lines from a point within an equilateral triangle in such a way as the length of the lines or the area correspond to the frequencies (see Fig. D16). (Li CC 1976 First Course in Population Genetics, Boxwood Press, Pacific Grove, CA.

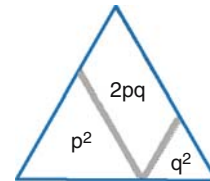


Figure D16. DeFinetti diagram

Deformation: Abnormal development caused by mechanical or physiological restriction(s).

Degeneracy of Lymphocytes: An ability of T cells to recognize and respond to different peptides (epitopes) carried by different MHC complexes despite the renowned specificity for molecules. Some degeneracy may also exist with B cells, which have Igs of low affinity. ►T cell, ►epitope, ►major histocompatibility complex, ►Ig

Degenerate Code: The same amino acid is coded for by more than one type of nucleic acid triplet, e.g., the RNA code word for phenylalanine can be either UUU or UUC; other amino acids may have a single or up to six codons (i.e., 6 codons degenerate [go down] into 1 amino acid). ►code genetic, ►genetic code; Crick FHC 1959 Brookhaven Symp Biol 12:35.

Degenerate Oligonucleotide-Directed Mutagenesis: A degenerate oligo-nucleotide (with several A residues is self-annealed) at the 3' end with an 8-nucleotide palindrome (see Fig. D17). The 3' sequence includes an EcoRI (G↓AATTC) restriction enzyme recognition site. The 5'-end should also encompass another restriction enzyme site (see diagram, Dde I. [C↓TNAD]). The central region is mutagenized (as shown by larger letters and a dot above the new base).

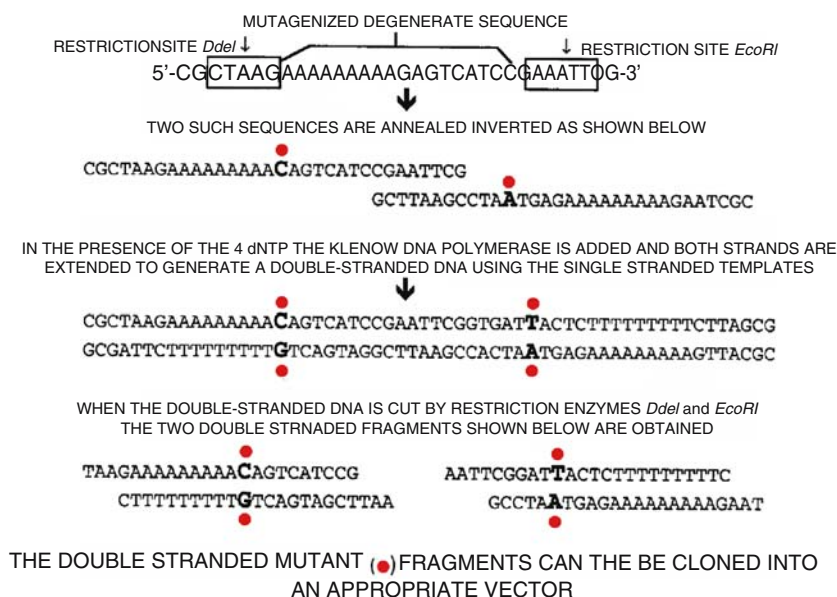


Figure D17. Degenerate oligonucleotide-directed mutagenesis

The construct is treated with Klenow fragment (a fragment of bacterial DNA polymerase I that lacks 5'→3' exonuclease activity) in the presence of the 4 deoxyribonucleotides to extend the nucleotide chains. The system produces two double-stranded mutant oligonucleotides after cleavage at the restriction endonuclease recognition sites with different base pair substitutions. Airaksinen A, Hovi T 1998 *Nucleic Acids Res* 26:576; diagram modified after Hill DE et al 1987 *Methods Enzymol* 155:558.

Degenerin: A member of a family of epithelial sodium channel proteins (interacting with collagen) in *Caenorhabditis* muscle contraction. Mutants uncoordinated (unc-105) have such a defect. Proteins MEC4 and MEC10, defective in mechanical signal transduction in the touch reception system, encode homologous proteins. Other homologs are the epithelial sodium channel (ENaC) genes of mammals. The MDEG1 protein, localized in the taste buds, appears to be a receptor for sour taste. ▶ [Liddle syndrome](#), ▶ [touch-sensitivity](#), ▶ [ion channels](#), ▶ [collagen](#), ▶ [anesthetics](#); Askwith CC et al 2001 *Proc Natl Acad Sci USA* 98:6459; Hamill OP, Martinac B 2001 *Physiol Rev* 81:685.

Degest (Differently Expressed Genes, transcripts, alternative splicing events using EST information): <http://genome.ewha.ac.kr/DEGEST/>. ▶ [alternative splicing](#)

Degradative Plasmids: *Pseudomonad* plasmids that have the ability of degrading salicylate, camphor, octane, chlorobenzoate, 2,4,5-trichlorophenoxyacetic

acid, etc. Cho JC, Kim SJ 2001 *J Mol Microbiol Biotechnol* 3[4]:503.

Degradome: The repertoire of protein-degrading enzymes, proteasome. ▶ [proteasome](#)

Degradosome: A multi-enzyme complex of polynucleotide phosphorylase (exoribonuclease), RNase E (endoribonuclease), RhlB (helicase), DnaK (heat-shock protein) and enolase (glycolytic enzyme) involved in the degradation of mRNA. The process is ATP-dependent. ▶ [ribonuclease](#), ▶ [helicase](#), ▶ [glycolysis](#), ▶ [RNA surveillance](#), ▶ [mRNA](#), ▶ [proteasome](#); Capousis AJ et al 1994 *Cell* 76:889; Blum E et al 1999 *J Biol Chem* 274:4009; Feng Y et al 2001 *J Biol Chem* 276:31651; Dziembowski A et al 2003 *J Biol Chem* 278:1603.

Degree of Freedom: The number of independent comparisons within numerical data; e.g., a 3:1 segregation has 1 degree of freedom because if one of the classes is specified within, say 4, the other can be either 3 or 1, i.e., there is only one choice. In cases where multiple comparisons can be made, e.g., in a segregation of 9:3:4 (recessive epistasis) the degree of freedom is 2 because if one class is specified as 4, the other two classes can be anything within 12/16, thus there is another choice left. In case of 9:3:3:1 segregation, degrees of freedom are 3 because if one class is chosen there are still three more to choose. In some experiments with multiple comparisons, e.g., in a variance analysis careful consideration must be given to the number of independent comparisons before the correct degrees of freedom can be determined. ▶ [analysis of variance](#)

Degree of Relatedness: ►relatedness, degree of

Degron: A signal element in the proteins liable to degradation by ubiquitin-mediated processes. The function of unknown genes can be revealed by their fusion to temperature-sensitive degron constructs that selectively destroys their protein products (Kanemaki M et al 2003 Nature [Lond] 423:720). ►N-degron, ►PEST, ►ubiquitin; Gardner RG, Hampton RY 1999 EMBO J 18:5994.

DegS: *Bacillus subtilis* kinase regulating degradative enzymes through protein DegU. (Kobayashi K et al 2001 J Bacteriol 183:7365)

DEGSAGE (differential gene expression by SAGE): http://genome.ewha.ac.kr/SAGEexpress/SAGEexpress_DEGs.htm. ►DEGEST, ►SAGE

Dehalococcoides ethenogenesis: It dechlorinates the ground water pollutants tetrachloroethene and trichloroethene (industrial solvents, hepatocellular carcinogens) to ethane/ethylene ($\text{CH}_2 = \text{CH}_2\text{CC}$), an anesthetic in higher concentrations. Its sequenced genome of 1,469,720 bp encodes 17 putative reductive dehalogenases. (Seshadri R et al 2005 Science 307:105)

Dehydrogenase: Enzymes mediating removal of hydrogen from molecules.

Dehydroepiandrosterone (DHEA): A multifunctional animal hormone enhancing immune response, and with a possible anti-diabetic, anti-obesity, anti-cancer, neurotropic, memory-enhancing and male anti-aging properties. separate entries; Yen SSC 2001 Proc Natl Acad Sci USA 98:8167; Mazat L et al 2001 Proc Natl Acad Sci USA 98:8145.

Dehydrotestosterone: A key hormone in maleness determination in mammals. It is made by steroid 5α -reductase enzyme from testosterone. Its deficiency causes defects in the development of the external male genitalia and the prostate but the epididymis, seminal vesicles and vas deferens are normal. The affected individuals are less prone to acne and baldness. The enzyme is encoded by two genes (SRD5A1, chromosome 5p15 and SRD5A2, 2p23). The dehydrotestosterone receptor deficiency leads to testicular feminization and Kennedy disease, both located in human chromosome Xq11.1-q12. ►animal hormones, ►testicular feminization, ►Kennedy disease

Deinococcus radiodurans: Gram-positive bacteria with 200-fold higher resistance to ionizing and 20-fold higher resistance to UV than *E. coli*. The genome of two chromosomes of 2,648,638 and 412,348 bp, respectively, a megaplasmid of 177,466 bp and another plasmid of 45,704 bp has been completely

sequenced. The radiation insensitivity has been attributed to the compaction of the DNA that facilitates restitution of radiation-induced breaks. Accumulation of manganese and decrease of iron in the cells facilitates the resistance to radiation (Daly MJ et al 2004 Science 306:1025). Ionizing radiation- and UV-induce hundreds of fragments by double-strand breaks that are readily reassembled into a functional 3.28-megabase genome. DNA repair process takes place in two stages, which involves *extended synthesis-dependent strand annealing* (ESDSA). At least two genome copies and random DNA breakage are requirements for effective ESDSA. Chromosomal fragments with overlapping homologies are used both as primers and as templates for massive synthesis of complementary single strands by DNA polymerase I. Newly synthesized complementary single-stranded extensions become 'sticky ends' that anneal with high precision, joining together contiguous DNA fragments into long, linear, double-stranded intermediates. These intermediates require RecA-dependent crossovers to mature into circular chromosomes that comprise double-stranded patchworks of numerous DNA blocks synthesized before radiation, and connected by DNA blocks synthesized after radiation. Thus, the radiation resistance is based on a highly effective DNA repair (Zahradka K et al 2006 Nature [Lond] 443:569). ►radiation-sensitivity, ►Taq DNA polymerase; White O et al 1999 Science 286:1571; Makarova KS et al 2001 Microbiol Mol Biol Rev 65:44; Levin-Zaidman S et al 2003 Science 299:254.

Dejerine-Sottas Syndrome (DSN, 17p11.2): Hypertrophic neuropathy, slow nerve conduction, abundant Schwann cell and basal lamina onion bulb formation, hypomyelination. Recessive mutations at the PRX locus (19q13.13-q13.2) encoding periaxin L and S are also responsible for DSN. The wild type alleles are required for the maintenance of myelin of the peripheral nerves. DSN is caused also by mutation of the periaxin proteins encoded at 19q13.1-q13.2. ►Schwann cell, ►myelin, ►Charcot-Marie-Tooth disease, ►HNPP, ►HMSN; Boerkoel CF et al 2000 Am J Hum Genet 68:325.

Delayed Early Genes (DE): These are turned on following the immediate early genes, about 2 min after phage infection. They use the early and new middle promoters. Their expression depends on protein synthesis. ►immediate early genes, ►late genes

Delayed Inheritance: The expression of some traits depends on the genotype of the diploid oocyte rather than the genetic constitution of the zygote. In such

cases the reciprocal F₁ generation may be of two types (maternal or paternal), the F₂ may be uniform (because the genetic constitution of the F₁ is identical) and segregation is delayed to the F₃. Similar phenomenon is observed when the phenotype of the male gametophyte (pollen) is determined by the diploid microsporocyte rather than by the haploid nucleus of the microspore or pollen. ▶*testa*, ▶*Lathyrus odoratus*, ▶*Limnaea*

Delayed Mutation: The expression is delayed after cell division following the mutagenic exposure in contrast to the “zero-point” mutation, which is expressed in resting cells. (Demerec M et al 1948 Carnegie Inst Year Book 47:169)

Delayed-Response Gene: It is activated by a growth factor after a lag period (about an hour). ▶*early-response gene*, ▶*early gene*, ▶*late gene*

Delete-A-Gene (deleteagene): A fast neutron mutagenesis method associated with PCR analysis of deletions (Li X, Zhang Y 2002 Functional & Integr Genomics 2:254). ▶*fast neutrons*, ▶*PCR*

Deleterious Mutation: Unfavorable for fitness, the rate of deleterious mutations is not easy to quantitate because small effects are difficult to identify. The statistical estimate for $\hat{U} = \Delta M^2 / (2V_m)$ the mutation rate U (see Fig. D18) where ΔM is the rate of change in the population and V_m is the variance of the mutation. The average homozygous mutation effect $s = 2V_m / \Delta M$. More accurate estimate can be obtained according to Keightl Bataillon TM 2000 Genetics 154:1193, by using maximum likelihood. An alternative formula for the rate of deleterious mutation is $U = 2uGC$ where U is the deleterious mutations, $2uG$ is the rate of mutation in the diploid genome and C the fraction of the sites in the genome subjected to selective constraints. Accordingly, in *Drosophila* U appears to be 1.2 per diploid genome (Haag-Liautard C et al 2007 Nature [Lond] 445:82). ▶*mutation beneficial*



Figure D18. Chromatid deletion (Courtesy of B.R. Brinkley)

Deletion: The loss of a (internal) chromosomal segment; it is generally symbolized with -, or d or Δ or *del.* Small deletions may appear as recessive null mutations or larger deletions may have a dominant phenotype. Deletions are distinguished from mutations by failing to revert to the normal allele and they may affect also the frequency of recombination.

Specifically directed deletions can be obtained in mice by taking advantage of the *loxP* and *Cre* factors of bacteriophage P1 (see Fig. D19) targeting genes. Deletions may be responsible for various human hereditary anomalies. Deletions can be generated in isolated DNAs by cutting the double-stranded molecules with the aid of restriction endonucleases leaving behind complementary single-strand overhangs. These ends then can be sliced back by Bal 31 exonuclease or S1 nuclease before ligation of the free ends. Deletions may be detected with the aid of a light microscope if the chromosomes have clear landmarks such as knobs, or when they display banding patterns such as the salivary gland chromosomes. Or it is revealed by special staining techniques or when the deleted chromosome is paired either during mitosis or meiosis with the normal chromosome. Deletions of the DNA may be detected by electronmicroscopy if a deletion and a normal strand are hybridized in vitro. At the site of the deletion the normal chromosome or the normal DNA strand buckles out because it has no partner segment to pair with.

Complete nucleotide sequences of parasitic prokaryotes indicates extensive losses of genes, which were apparently not needed because the host could supply the compounds such as amino acids, fatty acids, nucleotides, enzyme cofactors and enzymes of the Krebs cycle. Therefore, *Mycoplasma genitalium* has only 479 ORF, and *Mycoplasma pneumoniae* has only 679.

Deletions may be useful for identifying functional domains in the chromosome (see Fig. D20). Generation of deletions by insertion elements or by the Cre/LoxP or FLP/FRT recombinase system are very useful for revealing the functional role(s) of a large array of genes (Parks AL et al 2004 Nature Genet 36:288). In human populations, deletions of one to hundreds of kilobases long contribute to a large part of the variations (McCarroll SA et al 2006 Nature Genet 38:86). In mouse, megabase-size deletions of apparently gene-free regions (deserts) do not seem to affect function or viability (Nóbrega MA et al 2004 Nature [Lond] 431:988). In yeast, deletion of many genes may not result in visible (lethal) phenotype. ▶*deficiency chromosomal*, ▶*cri du chat*, ▶*Wolf-Hirschhorn syndrome*, ▶*retinoblastoma*, ▶*Prader-Willi syndrome*, ▶*Angelman syndrome*, ▶*Smith-Magenis syndrome*, ▶*Beckwith-Wiedemann syndrome*, ▶*Langer-Giedion syndrome*, ▶*Di-George syndrome*, ▶*Miller-Dieker syndrome*, ▶*Wolf-Hirschhorn syndrome*, ▶*contiguous gene syndrome*, ▶*aging*, ▶*deletion mapping*, ▶*pseudodominance*, ▶*duplication*, ▶*nested genes*, ▶*overlapping genes*, ▶*knockout*, ▶*Bal 31*, ▶*S1*, ▶*gene*

number, ► evolution, ► gene number, ► insertion elements, ► insertional mutation, ► Cre/LoxP, ► FLP/FRT, ► copy number estimates, ► homologous recombination; N-terminal truncated mutants generator for cDNA to identify functional protein domains: <http://oblab.cs.nchu.edu.tw:8080/WebSDL/>.

D

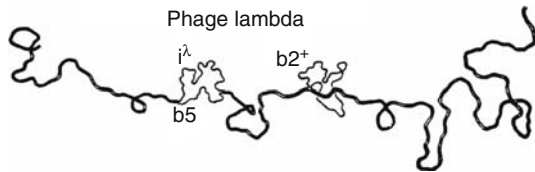


Figure D19. Deletion of phage λ DNA (b2) (Westmoreland, B. et al. 1969 Science 163:1343)

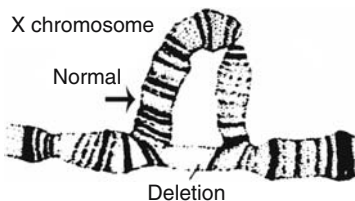


Figure D20. Deletion in the salivary gland X chromosome of *Drosophila* (Painter. T.S. 1934 J. Hered. 25:465)

Deletion 22q11.2 Syndrome: Quite a complex syndrome, it includes several psychiatric diseases and affects dozens of genes. Its prevalence is $\sim 4 \times 10^{-3}$ (Paylor R et al 2006 Proc Natl Acad Sci USA 103:7729), ► DiGeorge syndrome, ► velocardiofacial syndromes, ► autism, ► Asperger syndrome, ► psychoses

Deletion Analysis: Involves a number of diverse procedures, including pseudodominant expression of a recessive allele in a heterozygote when the dominant allele is deleted. Deletion mapping determines the extent of deleted segments on the basis of pseudodominance of linked genes, by genomic subtraction the normal DNA sequence extending over the gap can be isolated by molecular procedures, deletion of components of a gene (e.g., upstream regulatory elements) and their role can be identified,

etc. ► deletion mapping, ► linker scanning, ► genomic subtraction, ► pseudodominance

Deletion Generator: The *deletion-generator* technology may produce losses in defined areas within 60 kb of the insertion sites. For this purpose in *Drosophila*, a double transposable element, $P\{wHy\}$ is available. It contains within a *P* element a *hobo* transposon with flanking *W* (white eye) and *Y* (yellow body) markers. The *hobo* element within the *generator* may recombine with any *hobo* insertion within the genome. The recombination then deletes any gene(s) between the *hobo* insertion and the *generator* insertion points including one of the flanking markers, *W* or *Y*, depending on the orientation of the generator construct in the chromosome. The deletion of the *W* wild type allele produces white eye in the males and the loss of *Y* results in yellow body color. Therefore the deletions can be readily screened. Also a series of nested deletions can be obtained and the function of the unknown deleted genes can be annotated by the phenotype of the deletion animals. ► hybrid dysgenesis, ► annotation; Huet F et al 2002 Proc Natl Acad Sci USA 99:9948.

Deletion Mapping: Used in *Drosophila* and plants on the basis of pseudo-dominance, i.e., deletions of the normal sequences carrying the wild type alleles of syntenic genes identify the length of the deletions in the heterozygotes and determine their relative position (see Fig. D21).

About 2,000 mutants mapped the fine structure of the rII gene of phage T4, about 300 sites, by this principle (see Fig. D22).

Wild type was restored by recombination only between non-overlapping deletions and the crosses with the long deletion indicated that the mutation and the short deletion were both within the range of the long deletion. In an analogous manner transient-silencing genes with RNAi can generate functional maps. Bacteria expressing double-strand RNAs for specific genes can feed *Caenorhabditis*. By such a study 86% of the genes of this organism could be systematically analyzed (Kamath RS et al 2003 Nature [Lond] 421:231). ► pseudodominance, ► deficiency chromosomal, ► deletion, ► RNAi; see diagram; Slizynska H 1938 Genetics 23:291; Benzer S 1961 Proc Natl Acad Sci USA 47:403; Khush GS, Rick CM 1968 Chromosoma 23:452; Glaever G et al 2002 Nature [Lond] 418:387.

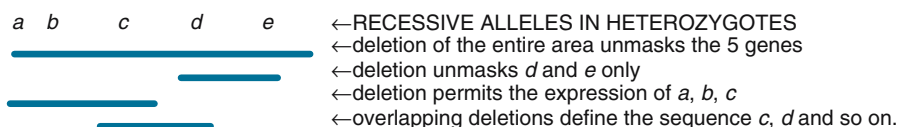


Figure D21. Deletion mapping

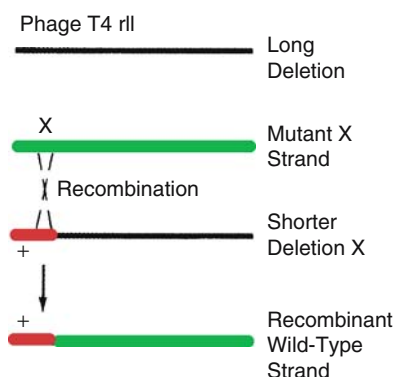


Figure D22. Phage T4 rII

Deletion Mutation: A lack of a portion of the genetic material that may vary in extent from a single to millions of nucleotide pairs. Deletions may be generated by molecular biology techniques using restriction endonucleases and extension of the gaps by exonuclease. Since the restriction enzymes nick at specific locations, they can be used for site-directed deletions. ►deletion unidirectional, ►ionizing radiation, ►radiation effects, ►localized mutagenesis, ►genomic subtraction

Deletion Unidirectional: DNA molecules blocked at the 3'-end by sulphur-containing nucleotides (thionucleotides) are protected from 3'→5' exonuclease action of T4 DNA polymerase are sliced back in the opposite direction in a time dependent extent. After removing the single strands left behind, nested sets of deletions of various lengths are obtained. ►Bal 31

Delila: A database manager program for selection of nucleic acid sequences in a library. <http://www.lecb.ncicrf.gov/~toms/delila/delila.html>.

Delitto Perfetto: A RAD52 requiring technique based on transformation of yeast by unpurified oligonucleotides leading to site-specific mutation in vivo within a window up to 200 bp. ►site-specific mutation; Storici F et al 2001 Nature Biotechnol 19:773.

Delphinidine: ►anthocyanin

Delta Endotoxin: ►*Bacillus thuringiensis*

Delta 1: (TPSD1, 16p13.3): A tryptase serine protease gene in humans.

Delta 88: A 7-kb *Drosophila* transposable element. ►transposable elements

Delta-Like 1 (*Dll* 1, 6q27): A mammalian ligand for Notch receptors. Interactions between *Dll*1 and Notch in trans activate the Notch pathway, whereas *Dll*1

binding to Notch in cis inhibits Notch signaling. *Dll*1 undergoes proteolytic processing in its extracellular domain by ADAM10 (Dyczynska E et al 2007 J Biol Chem 282:436). *Dll*4-specific antibody signaling deregulates angiogenesis and inhibits tumor growth (Ridgway J et al 2006 Nature [Lond] 444:1083).

►Notch, ►ADAM, ►angiogenesis

Demand Theory: Gene expression is determined by negative control when there is a low demand for the product of the gene. In case of high demand positive control is operating. The environment and evolutionary forces determine these cycles. ►negative control, ►positive control

Deme: An interbreeding population (a Mendelian population) without reproductive isolation; it is also used for denoting a natural breeding group with one male and several females.

Demecolcine (*N*-Deacetyl-*N*-methylcolchicine): Demecolcine depolymerizes microtubules and causes mitotic arrest at metaphase without significant effects on other cellular processes. It is used for karyotype analysis. ►colchicine, ►colcemid, ►karyotype

Dementia: Deterioration of mental abilities, dullness of the mind due to innate defects of the brain or developmentally programmed disease (paranoia, schizophrenia [dementia precox], Alzheimer's disease, etc.) or caused by poisonous substances or drugs affecting the nervous system. Both Familial British (FBD) and Familial Danish dementia (FDD) are caused by mutation in the *ITM2B* gene encoding the integral membrane protein 2B (ABRI). The mutation of FBD converts a stop codon to arginine at residue 267, thus extending the protein chain to 277 amino acids. In FDD, there is a 10-bp duplication between residues 265 and 266. In both, some variations exist. The clinical symptoms resemble those of early onset Alzheimer's disease but the amyloid deposits are systemic. *Frontotemporal dementia* is a heterogeneous disease involving human chromosome 3, 9 and 17 and it is characterized by apathy, restlessness, lack of judgment, mutism and dystonia. Onset is in the late 50s. This condition is not associated with β amyloid deposits. One of the G→C mutations involves the acceptor splice site of exon 6 of CHMP2B chromatin modifying protein, part of the ESCRT-1 endosome-sorting complex (Skibinski G et al 2005 Nature Genet. 37:806). ►neurodegenerative diseases, ►furin, ►endosome, ►chromatin remodeling, ►amyloids; Ghiso JA et al 2001 J Biol Chem 276:43909; Kim S-H et al 2002 J Biol Chem 277:1872.

Demethylation: It may take place by demethylase enzymes or by base excision repair. Demethylation can occur independently of replication and it may

require breaking the DNA backbone 3' to methylcytosine in the process of excision repair (Kress C et al 2006 Proc Natl Acad Sci USA 103:11112). Demethylation has significance for developmental controls in which methylation may turn off genes and demethylation may restore activity. In *Arabidopsis* mutation in the recessive gene *ddm1* may reduce the level of methylated cytosine by 70% and the demethylated condition is transmitted also through meiosis (Kakutani T et al 1999 Genetics 151:831). Demethylation results in different developmental anomalies (Finnegan EJ et al 1996 Proc Natl Acad Sci USA 93:8449). The animal spermatozoa are heavily methylated but rapidly dimethylated after fertilization. Demethylation of the egg nucleus is a gradual process after fertilization. In animals, the methylated state is reset in the new generation (Meyer W et al 2000 Nature [Lond] 403:501). De novo methylation is essential for embryogenesis and gametogenesis of mice (Okano M et al 1999 Cell 99:247). The human ICF syndrome is caused by methylation defects (Xu GL et al 1999 Nature [Lond] 402:187). Hypomethylation of DNA caused runted newborn mice, which developed later lymphomas and high frequency of chromosome 15 trisomy (Gaudet F et al 2003 Science 300:489).

The MeCP2 transcriptional repressor recruits histone deacetylases to the chromatin. In contrast MBD2, which binds methylated DNA was suggested to remove the methylation and to activate transcription. MBD2 is a member of the MeCP2 complex and—according to Ng H-H et al 1999 Nature Genet 23:58—does not demethylate DNA and it silences transcription in an alternate manner. Oxidative demethylation can revert methylated DNA bases to the normal state and thus repairs damage. The DNA glycosylase/lyase domain of ROS1 seems to be responsible for demethylation of 5-methylcytosine of DNA in *Arabidopsis* (Agius F et al 2006 Proc Natl Acad Sci USA 103:11796). The nuclear protein Gadd45a (growth arrest and DNA damage-inducible protein 45a) removes gene silencing global methylation signals with the cooperation of XPG repair endonuclease in *Xenopus* (Barreto G et al 2007 Nature [Lond] 445:671). ▶methylation of DNA, ▶trichostatin, ▶histone deacetylase, ▶ICF, ▶ROS; Cervoni N, Szyf M 2001 J Biol Chem 276:40778; Treweek SC et al 2002 Nature [Lond] 419:174; Goll MG, Bestor TH 2005 Annu Rev Biochem 74:481.

Demic Diffusion: Geographic expansion of a small deme into a large area resulting in demographic growth. The diffusion can be traced by analyzing the non-recombinant segment of the Y chromosome, mitochondrial DNA, autosomal microsatellite sequences and the mutations arising in these systems. Computer

models may analyze the front line of the expansion. ▶deme, ▶Y chromosome, ▶Eve foremother, ▶microsatellite; Edmonds CA et al 2004 Proc Natl Acad Sci USA 101:975.

Demography: The study of changes in the human populations by migration, birth, mortality, marriages, health, occupations, education, etc. Genetics became the most important tool of the study of human populations and their origin by the use of data obtained from the analysis of mtDNA, the Y chromosome and single-nucleotide polymorphism. ▶mtDNA, ▶Eve foremother, ▶Y chromosome, ▶SNIPs, ▶mortality; Wakely J et al 2001 Am J Hum Genet 69:1332; ▶out-of-Africa, <http://www.census.gov/ipc/www/idbnew.html>; <http://www.cdc.gov/nchs>.

De Novo Synthesis: The formation of molecules through synthesis from (simple) precursors rather than by cannibalization (recycling) of more complex processes of salvage.

DEN: diethylnitrosamine, an alkylating mutagen and carcinogen. ▶mutagen, ▶carcinogen

Denaturation: A loss of native configuration of DNA (frequently separation of the complementary strands) or of proteins by damaging the non-covalent bonds at elevated temperature or by chemicals, such as alkali, detergents and others (see Fig. D23). The denaturation of the DNA is often reversible (renaturation). The forces between complementary DNA strands can be measured by atomic force microscopy. Adhesive forces between complementary strands of 20, 16 and 12 base pairs was found to be 1.52, 1.11 and 0.83 nN, respectively (1 newton [N] = 1 kg m/s² = 10⁵ dyn). Local denaturation bubbles during gene replication and transcription. ▶atomic force microscope, ▶c₀t, ▶DNA thermal stability, ▶renaturation; Ginoza W, Zimm BH 1961 Proc Natl Acad Sci USA 47:639.

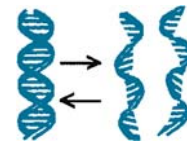


Figure D23. Denaturation

Denaturation Mapping: Electronmicroscopic localization of strand mismatches in DNA. ▶mismatch, ▶deletion, ▶deficiency chromosomal

Denaturing Gradient Gel Electrophoresis (DGGE): DGGE permits the separation of DNA fragments of identical size on the basis of different susceptibility to

denaturation because of mutation even in a single nucleotide. The DNA fragments are electrophoresed in polyacryl-amide gels in which there is an increasing gradient of a denaturing agent such as urea or formamide or both. The increased temperature also promotes separation of the strands of the DNA double helix. The partially denatured fragments migrate at a lower speed in the gel. ►[electrophoresis](#), ►[mutation detection](#); Myers RM et al 1987 *Methods Enzymol* 155:501.

Dendrimer: A branched molecular complex composed of monomers such as a DNA tract with a double-stranded central core and at the two ends four single-stranded, non-complementary tracts. The complex of monomers has the potential to hybridize with complementary oligonucleotides at the open single strands. These structures can then be used as devices for microarray hybridization. Dendrimers have been used as synthetic gene delivery vehicles for in vivo gene therapy. After delivering a special signal the dendrimer may self-destruct leaving the passenger molecule, e.g., an anticancer drug, at the target. ►[endosome](#), ►[PAMAM](#); Stears R et al 2000 *Physiological Genomics* 3:93; Rudolph C et al 2000 *J Gene Med* 2:269; Benters R et al 2002 *Nucleic Acids Res* 30[2]:210; ►[microarray hybridization](#), <http://www.genisphere.com>.

Dendrite: A relatively short branch of neurons that receives information from other nerve cells. ►[nerve cells](#), ►[CREST](#); Häuser M et al 2000 *Science* 290:739.

Dendritic Cell: Heterogeneous leukocytes with the primary role to capture MHC antigens and present them to T cells. Although dendritic cells chew to pieces most of antigens presented to T cells, some antigens are presented intact to B cells (Bergtold A et al 2005 *Immunity* 23:503) (see Fig. D24). The TNF receptor RANK ligand promotes dendritic cell function. The granulocyte macrophage-colony-stimulating factor (GM-CSF) promotes their differentiation. TNF- α and IL-1 β promote their maturation. RAC expression of the mature dendritic cells is required for priming of T cell (Benvenuti F et al 2004 *Science* 305:1150). Antigen capture by dendritic cells is facilitated by actin remodeling through Toll-like receptor (West MA et al 2004 *Science* 305:1153). They travel from the peripheral tissues to the lymphoid organs and promote immunity. Myeloid type dendritic cells may stimulate T lymphocytes whereas the lymphoid dendritic cells may have the opposite effect. Fusion of human dendritic cells with breast carcinoma cells activates cytotoxic T cells against the tumors. The different CD8 α dendritic cells develop from common myeloid progenitors. Dendritic cells can detect

pathogens directly or sense the products of infection such as heat shock proteins or uric acid crystals. Dendritic cells also maintain neuronal circuits. ►[antigen presenting cell](#), ►[plasmacytoid cell](#), ►[T cell](#), ►[TNF](#), ►[IL-1](#), ►[GM-CSF](#), ►[DC-SIGN](#), ►[RAC](#), ►[Toll](#), ►[actin](#); Banchereau J, Steinman RM 1998 *Nature [Lond]* 392:245; Henri S et al 2001 *J Immunol* 167:741; Pulendra B et al 2001 *Science* 293:253; Mellman I, Steinman RM 2001 *Cell* 106:255; and following reviews, Huang Q et al 2001 *Science* 294:870; in immunotherapy: Aragonese-Fenoll L, Corbi AL 2007 *Clin Transl Oncol* 9:77.



Figure D24. Dendritic cell

Dendritic Cell Vaccine: Antigen presenting cells primed with tumor antigens to incite CTLs against tumors. The dendritic cell may be transformed with the antigen gene using viral vectors. ►[antigen presenting cell](#), ►[CTL](#), ►[tumor vaccination](#), ►[cancer gene therapy](#)

Dendrocytes: Wrap nerve axons with myelin sheath. Oligodendrocytes (see Fig. D25) cause clustering of Na channels.

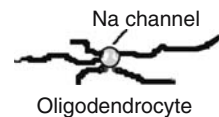


Figure D25. Oligodendrocyte

Dendrogram: A chart showing relationship among entities in a form resembling branches of a tree. ►[evolutionary tree](#), ►[character matrix](#), ►[Euclidean distance](#)

Dengue Virus (DENV, dengue fever): An icosahedral (~ 500 Å), positive strand RNA virus translated into a single 350 kDa polyprotein and causes either the dengue fever or the hemorrhagic dengue. Both of them are debilitating diseases primarily in South-East Asia. Mosquitos transmit the virus. For productive infection, dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN1, encoded by CD209), an attachment receptor of the virus is essential. Variants of CD209 discriminate between severe dengue fever

and dengue hemorrhagic fever (Sakuntabhai A et al 2005 Nature Genet 37:507). A way of protection was worked out involving the transformation of the mosquito (*Aedes aegypti*) by a *Sindbis* virus vector carrying a 567-base antisense RNA of the premembrane coding region of the dengue-2 virus. The transduced mosquitoes cannot support the replication and thus do not transmit the virus. ►biological control, ►antisense RNA, ►ICAM, ►DC-SIGN; Diamond MS, Harris E 2001 Virology 289:297; DENV structure: Pokidysheva E et al 2006 Cell 124:485.

D

Denhardt Reagent: Used to suppress background hybridization in Northern hybridization, RNA probing, single-copy Southern hybridization, annealing DNA immobilized on nylon membrane. It is made of Ficoll-400 (a non-ionic synthetic sucrose polymer), polyvinylpyrrolidone (an insoluble material removing phenolic impurities) and bovine serum albumin at a concentration of 2.5% (or less) each in water. ►DNA hybridization, ►Northern blot, ►BSA

Denoising: The removal of noise and improving the quality in capillary electrophoresis. ►capillary electrophoresis; Perrin C et al 2001 Anal Chem 73:4903.

Densitometry: Optical detection of increased or decreased amounts of a substance in a solution or in solid medium.

Density Gradient Centrifugation: The separation of subcellular organelles or macromolecules on the basis of their density (see Fig. D26). The density of DNA (ρ) increases with increased GC content ($\rho = 1.660 + [0.098 \{G+C\}]$). During buoyant density centrifugation the DNA is positioned at the density of CsCl that corresponds to DNA density. The density of the CsCl solution is determined by refractometry. The nuclear DNA of most eukaryotes has an AT content of about 40%, corresponding to a density of about 1.7 g/mL. The DNA of cellular organelles may have a density different from that of the nucleus and thus form a satellite band(s) in the ultracentrifuge. Single-stranded nucleic acids sediment faster and circular DNA molecules sediment slower. Among cellular organelles nuclei sediment fastest, then chloroplasts and mitochondria occupy the highest position in the centrifuge tube. For the separation of organelles either sucrose or percoll (polyvinylpyrrolidone-coated silica) are used most commonly. ►centrifuge, ►buoyant density centrifugation, ►ultracentrifugation, ►density labeling; Meselson M et al 1957 Proc Natl Acad Sci USA 43:581.

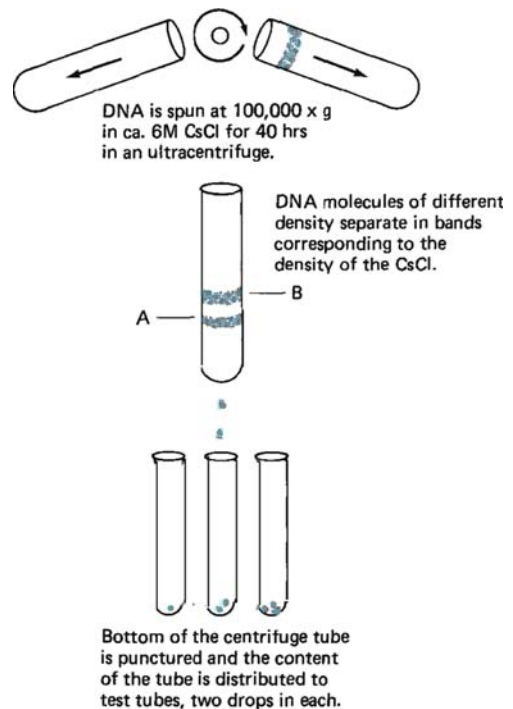


Figure D26. Density gradient centrifugation

Density Labeling: By growing cells first in dense (heavy isotope) medium, e.g., $^{15}\text{NH}_4\text{Cl}$ and then transferring to normal $^{14}\text{NH}_4\text{Cl}$ medium, the heavy and light DNA or recombinant strands can be separated by density gradient equilibrium centrifugation. ►density gradient centrifugation

Densovirus: ►parvoviruses

Dent Disease (Xp11.22): The recessive defect in the CLCN5 chloride ion channel responsible for hypophosphatemic rickets and kidney stones (nephrolithiasis). ►rickets, ►nephrolithiasis

Dental Non-Eruption: Autosomal dominant failure to cut teeth.

Dentatorubral-Pallidoluysan Atrophy (DRPLA, myoclonous epilepsy with choreoathetosis, Haw River disease): It involves involuntary jerky muscle movements, epilepsy, feeble-mindedness, ataxia, brain degeneration due to a chromosome 12p13.31 dominant condition. The mutation causes an abnormal number (49–75) of CAG repeats in the atrophin-1 protein compared to 7–23 under normal conditions. ►fragile sites, ►trinucleotide repeats, ►muscular atrophy

Denticle: Tooth-like extrusion (insects) or pulp stone in the mammalian tooth.

Dentin Dysplasia: In dentin dysplasia the pulp is absent or poorly developed, the root canal is frequently empty and/or enlarged, and the bluish teeth is spontaneously lost. Several forms of autosomal dominant expression have been observed.

Dentinogenesis Imperfecta: The dominant condition is encoded in human chromosome 4q21.3 causing blue-gray or brownish teeth due to dentin defect. The Brandywine type appears to be non-identical. ▶[dentin dysplasia](#), ▶[osteogenesis imperfecta](#), ▶[tooth](#); Xiao S et al 2001 Nature Genet 2001 27:201.

Denver Classification: This classification of human chromosomes in 1960, arranged the chromosomes into 7 groups (A to G) on the basis of decreasing length and arm ratio. ▶[human chromosomes](#), ▶[Chicago classification](#), ▶[Paris classification](#)

Denys–Drash Syndrome: A very severe (dominant negative) mutation in the WT gene ▶[Wilms tumor](#), affecting primarily the female gonads and genitalia, internal male genitalia and kidneys. ▶[Wilms tumor](#), ▶[Frasier syndrome](#), ▶[dominant negative](#)

2-Deoxyribonolactone: Oxidative damage to DNA may produce various modified products of deoxyribose such as 2-deoxypentos-4-ulose and deoxy-ribonolactone (dL) (see Fig. D27). The latter creates problems in repairing the damage because the function of polymerase β is hampered at the AP endonuclease incised dL sites. ▶[DNA repair](#); DeMott MS et al 2002 J Biol Chem 277:7637.

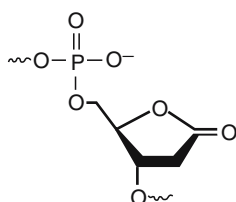


Figure D27. 2-Deoxyribonolactone

Deoxyribonuclease: An enzyme capable of breaking phosphodiester bonds in single- or double-stranded DNA. ▶[DNase free RNase](#), ▶[DNase hypersensitive sites](#), ▶[restriction enzymes](#), ▶[endonuclease](#), ▶[exonuclease](#)

Deoxyribonucleic Acid: ▶[DNA](#)

Deoxyribonucleotides: The building blocks of DNA, they contain only H rather than OH at the 2 position of the ribose, one of the nitrogenous bases (A, T, G, C) and phosphate. ▶[ribonucleotide](#), ▶[nucleotide chain growth](#)

Deoxyribose: ▶[ribose](#)

Deoxyribozyme: The hammerhead ribozymes contain deoxyribonucleotides yet they can cut RNA. Single-stranded DNAs may become $\text{Zn}^{2+}/\text{Cu}^{2+}$ or Pb^{2+} metalloenzymes. The $\text{Zn}^{2+}/\text{Cu}^{2+}$ enzymes may function as DNA ligase. ▶[ribozyme](#), ▶[DNA ligase](#); Carmi N, Breaker RR 2001 Bioorg Med Chem 9:2589; Wang DY, Sen D 2001 J Mol Biol 310:723; Khachigian LM 2000 J Clin Invest 106:1189.

Dependovirus: Dependovirus replicates only in the presence of a co-infecting helper virus, e.g., adeno-associated virus requires helper adenovirus or herpesvirus. ▶[adeno-associated virus](#), ▶[adenovirus](#), ▶[herpes](#)

Depression: A psychological state of sadness, despair, low self-esteem, generally accompanied by lack of appetite and sleeplessness (see Fig. D28). A major genetic factor associated with depression has been located to 12q22-q23.2 (Abkevich V et al 2003 Am J Hum Genet 73:1271). It is frequently associated with glucocorticoid over-production that may lead to hippocampal atrophy. The therapy may involve serotonin re-uptake inhibitor drugs, such as Prozac (fluoxetine). Mood is determined in the forebrain. Low activity of serotonergic neurotransmission results in depression (dysphoria) whereas high activity causes euphoria. Preliminary results indicate that in treatment-resistant depression the subgenual cingulate brain region (the cingulate gyrus is just above the middle of the corpus callosum; see diagram) is metabolically over-active.

Chronic stimulation of the white matter tract adjacent to this area reduced the local cerebral blood flow that resulted in sustained remission, antidepressant effects (Mayberg HS et al 2005 Neuron 45:651). Some mentally ill persons suffering from severe depression contributed a great deal to human culture like Vincent van Gogh the great Dutch painter. The famous painter of the seventeenth century also suffered from melancholy and later bipolar disorder (Schildkraut JJ et al 2007 J Nerv Ment Dis 195:3) (see Fig. D29). The highly acclaimed and yet often rejected great Austrian composer and performer Robert A. Schumann suffered from periodic despair among periods of great achievement and spent the last two and half years of his life in a mental asylum. ▶[glucocorticoid](#), ▶[hippocampus](#), ▶[serotonin](#), ▶[affective disorders](#), ▶[melancholy](#), ▶[bipolar mood disorder](#), ▶[BDF](#), ▶[van Gogh](#); Schafer WR 1999 Cell 98:551; Zubenko GS et al 2002 Amer J Med Genet 114:413; animal models: Flint J 2002 FEBS Lett 529:131.

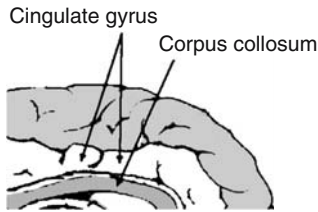


Figure D28. Depression



Figure D29. Vincent van Gogh (1853–1890)

Depurination: The loss of purine from nucleic acids. In mammalian cells both G and A loss and damage may occur at high frequency ($3 \times 10^{-9} \text{ min}^{-1}$) and some of the damage is corrected by enzymatic repair, others lead to mutation in the DNA. Self-catalyzed, site-specific depurination of 5'G residues spontaneously occur across the human genome in short 29–18 sequences. These sequences can form a stem-loop structure and the catalytic intermediate is 5'G-T-G-G-3' bp in the duplex DNA adjacent to a 5'-T-A-3'. At such sites the depurination rate is several-fold higher than in other areas of the genome. The stem-loop structure is associated with superhelical stress and has likely an important biological role in nucleosome positioning, chromosome superfolding and genetic recombination (Osamova O et al 2006 Proc Natl Acad Sci USA 103:4392). ▶[apurinic site](#), ▶[excision repair](#)

DER: A transmembrane hormone-receptor tyrosine-kinase protein of the epidermal growth factor of *Drosophila*. It affects many phases of the development including photoreceptor determination, wing vein formation, etc. The activator ligand is the Spitz

protein (a homolog of TGF- α); Argos is an inhibitor of DER. ▶[EGF](#), ▶[Argos](#), ▶[Spitz](#)

Derepression: The removal of repression (so protein synthesis can go on). ▶[induction](#)

Derivative: Mathematically, it is a function f' of a function f whose value at any point x_1 in the domain of f (see formula) if such limit exists (see Fig. D30).

$$f'(x_1) = \lim_{\Delta x \rightarrow 0} \frac{f(x_1 + \Delta x) - f(x_1)}{\Delta x}$$

Figure D30. Derivative

Derivative Chromosome: Modified by chromosomal rearrangement(s).

Dermatan Sulfate: Glucosaminoglycan; repeating units of disaccharides, generally acetyl-galactosamines linked to an iuduronic acid. ▶[mucopolysaccharidosis](#)

Dermatitis, Atopic (AD, 3q21): A skin inflammation generally associated with itching, frequently evoked by allergic reactions to cosmetics, plants, animals, light, etc. The locus may be involved in paternal imprinting. AD genes are linked to psoriasis loci and may be associated with 1q21, 3p24-p22, 13q14, 15q14-q15, 17q25-q21, and 20p. ▶[skin diseases](#), ▶[imprinting](#), ▶[psoriasis](#); Cookson WOCM et al 2001 Nature Genet 27:372; Bradley M et al 2002 Hum Mol Genet 11:1539.

Dermatoglyphics: The examination of dermal ridges and creases on fingers, toes, palms and soles for the purpose of identification, diagnosis and forensic investigations. ▶[fingerprints](#); Sodhi GS, Kaur J 2001 Forensic Sci Int 120[3]:172.

Dermatome: The cell layer that generates the mesenchymal connective layer of skin.

Dermatomyosities: ▶[polymyosities](#)

Dermatosparaxis: A hereditary disease in cattle. The procollagen peptidase that cleaves a peptide from the N-terminus of the chains is defective causing disorganized, poor fiber formation resulting in extreme brittleness of the hide. ▶[collagen](#)

Deratomyotome: The primordium of the vertebrate skeletal muscles (Gros J et al 2005 Nature [Lond] 435:954)

DES (diethylsulfate, $[\text{C}_2\text{H}_5]_2\text{SO}_2$): A potent alkylating mutagen and carcinogen.

Desaturase: Enzymes—on the endoplasmic reticulum of plants—introducing double bonds into the hydrocarbon portion (cis) of fatty acids in the presence of NADPH, light generated ferredoxin and activated O_2 .

Desaturation of some fatty acids may be desirable for some oil crops and can be accomplished by mutation techniques. Fatty acid desaturase may activate the plant defense system against pathogens. ▶ [fatty acids](#), ▶ [host-pathogen relations](#); Shanklin J, Cahoon EB 1998 *Annu Rev Plant Physiol Mol Biol* 49:611; Kacharoo P et al 2001 *Proc Natl Acad Sci USA* 98:9448.

Descent: Ancestry, the descendants of a person or a family of genetic lineage.

Desensitization: Signal-response systems after prolonged stimulation display reduced responsiveness to stimulation by the same agent. The process is mediated through G protein-coupled receptors and arrestin. ▶ [signal transduction](#), ▶ [arrestin](#), ▶ [pleckstrin domain](#), ▶ [phosphoinositides](#); Lefkowitz RJ, Shenoy SK 2005 *Science* 308:512.

Deserts: Chromosomal regions with a paucity of genes or low frequency of recombination. ▶ [jungles](#), ▶ [recombination frequency](#), ▶ [recombination by replication](#), ▶ [map units](#)

Desetope: The antigen binding site of the MHC molecule. ▶ [antigen](#), ▶ [MHC](#), ▶ [agretope](#)

DESI (desorption electrospray ionization): A technique of mass spectrometry. A fine spray of charged droplets are applied to the surface of a compound from which small and large molecules are picked up, ionized as desolvated ions (release the electrostatically bound water) and are introduced into a mass spectrometer. ▶ [mass spectrometer](#), ▶ [electrospray](#), ▶ [desolvation](#)

Desktop: A computer that has the various menu bars and where the actual work is performed.

Desmin: A muscle filament protein. Desmin-related myopathies (DRM) are neuromuscular diseases affecting skeletal, cardiac and eye lens muscles. Missense mutations in the molecular chaperone α B-crystallin, encoded at human chromosome 11q21-q23, is responsible for one form. Cardiomyopathies may develop in desmin deficiency. In such cases the increased expression of Bcl-2 ameliorates the heart function. ▶ [myopathy](#), ▶ [crystallins](#), ▶ [Bcl-2](#); Weisleder N et al 2004 *Proc Natl Acad Sci USA* 191:769; diseases of filament protein: Omary MB et al 2004 *New England J Med* 351:2087.

Desmocollins: Desmosome attached proteins. ▶ [desmosome](#)

Desmoid Disease, Hereditary (5q21-q22): An infiltrative fibromatosis (tumor-like fibrous nodules) due to mutation in the APC gene distal to the β -catenin domain. ▶ [Gardner syndrome](#)

Desmoplakins: The proteins involved in cell in plakoglobin. Dominant mutation (6p24) in the desmoplakin domain may modify a phosphorylation site of plakoglobin and cause one form of arrhythmogenic right ventricular cardiomyopathy. ▶ [desmosome](#), ▶ [filament](#), ▶ [plakoglobin](#), ▶ [arrhythmogenic right ventricular cardiomyopathy](#); Rampazzo A et al 2002 *Am J Hum Genet* 71:1200.

Desmosome: A protein plaque of cell junctions (between epithelial cells) into what desmin and keratin filaments of cells are tied. Besides mediating cell adhesion, desmosomal cadherins are involved in epithelial morphogenesis. A defect of desmosomes is responsible for various skin diseases. ▶ [junction complex](#), ▶ [cadherin](#), ▶ [pemphigus](#), ▶ [intermediate filaments](#), ▶ [filaments](#), ▶ [plakoglobin](#), ▶ [p63](#), ▶ [skin diseases](#); Runswick SK et al 2001 *Nature Cell Biol* 3:823.

Desmosterolosis: Desmosterolosis involves diverse lethal malformations due to deficiency of 3- β -hydroxysterol- δ -24-reductase. ▶ [chondrodysplasia](#); Waterham HR 2001 *Am J Hum Genet* 69:685; Kelley RI, Herman GE 2001 *Annu Rev Genomics Hum Genet* 2:299.

Desmoyokin: A cell junction protein. (Nie Z et al 2000 *J Invest Dermatol* 114:1044)

Desmutagen: Chemical agents, which can interact and directly inactivates mutagenic molecules.

Desolvation: The release of electrostatically bound water or removal of solvent from polar or nonpolar atoms, removal of solvent adducts from a gas phase ion as a preparation for mass spectrometry. ▶ [mass spectrometer](#)

Destruction Box: Amino acid sequences at the N-terminal of cyclins and other proteins making them targets for ubiquitinylation: **Arg** (Ala/Thr) (Ala) **Leu** (Gly) \times (Ile/Val) (Gly/Thr) Asn. Those in bold are conserved, the others may vary. ▶ [ubiquitins](#), ▶ [amino acids](#), ▶ [N-end rule](#), ▶ [degron](#), ▶ [N-degron](#); Burton JL, Solomon MJ 2001 *Genes Dev* 15:2381.

Desynapsis: The loss of synopsis of the homologous chromosomes (after the completion of the recombination process). The desynaptic gene of maize reduced chiasma frequency in the majority of chromosomes but it increased chiasma frequency in the short arm of chromosome 6 where the nucleolar organizer is situated. ▶ [synapsis](#), ▶ [asynapsis](#), ▶ [sister chromatid cohesion](#), ▶ [chiasma](#), ▶ [nucleolar organizer](#); Dix DJ et al 1997 *Development* 124:4595.

Detasseling: The removal the male inflorescence of maize (see Fig. [D31](#)). ▶ [heterosis](#)



Figure D31. Tassel

D

Detector Proteins: Sense environmental signals (in bacteria) in the periplasmic region. ▶ [periplasma](#)

Detergent: The various types may have different chemical structures but they all have a large non-polar hydrocarbon end that is oil-soluble and a water-soluble polar end. The so-called “soft detergents” are biodegradable. In the laboratory most commonly sodium lauryl sulfate (SDS, sodium dodecyl sulfate, $n\text{-C}_{11}\text{-H}_{23}\text{CH}_2\text{OSO}_3\text{Na}^+$) is used in gel electrophoresis. Detergents are employed also for the solubilization of membrane proteins and lipid components. ▶ [SDS](#), ▶ [polyacrylamide gels](#), ▶ [Tween 20](#), ▶ [nonidet](#)

Determinate Inflorescence: The stem terminates in a flower rather than in an apical meristem. ▶ [meristem](#), ▶ [indeterminate inflorescence](#)

Determination: The establishment of a specific *commitment* to differentiation. It is a biochemical change within cells or tissues whereby they lose options for differentiation in all but one particular way. In plant cells, however, the determination may be reversible. In the processes controlled by homeotic genes transdetermination may overrule the regular pattern. In *Bacillus subtilis* the commitment to spore formation is governed by gene *SpoIIQ* under the control of transcription factor σ^F and *SpoIIP* controlled by both σ^F and σ^E . In the presence of nutrients, the forespore can exhibit rod-like longitudinal growth in the absence of SpoIIQ and SpoIIP, whereas the mother cell can do so when only SpoIIP is absent. Differentiation becomes irreversible when neither the mother cell nor the forespore can grow in the presence of nutrients (Dworkin J, Losick R 2005 Cell 121:401). ▶ [transdetermination](#), ▶ [homeotic genes](#), ▶ [transplantation nuclear](#), ▶ [heritability](#); Glotzer M et al 2001 Annu Rev Cell Dev Biol 17:351.

Determinism, Genetic: A tenuous social theory that crime, immorality, disease, poverty and all social ills are predetermined in families. Behavior genetics shows that inheritance plays a certain, variable role in behavior and by logical extension judgment of human values. Also, the question of the degree of responsibility is opened. If behavior is genetic how much is the role of free will? Ethicists and legal scholars would have difficulties to define “values”. If it is measured can it be valued? The philosopher David Hume remarked: “Good sense and genius beget

esteem: Wit and humor excite love.” The problems certainly exceed the scope of this text although the moral dilemmas are inescapable for the geneticist once Pandora’s box has been opened. ▶ [human behavior](#), ▶ [ethics](#); Alper JS 1998 Soc Sci Med 46:1599.

Deterministic Gene: A certain condition or disease is most likely to occur in its presence.

Deterministic Model: When the changes in a population are based on fixed parameters such as the selection coefficient, mutation pressure, and migration. ▶ [stochastic model](#)

Detoxication: A process by which a toxic agent is made less harmful by the metabolism.

Detoxification: The removal of a toxic agent from a biological system by extrinsic factors.

Detoxification Enzymes: ▶ [glutathione-S-transferase](#), ▶ [paraoxonase](#), ▶ [superoxide dismutase](#)

Detrimental Mutation: A mutant that has low fitness but its rate of survival is not below 10%. ▶ [beneficial mutation](#), ▶ [mutation](#), ▶ [fitness](#)

Detritus: Particulate decay product.

Deubiquitinating Enzymes (DUBs): DUBs cleave the ubiquitin–protein link and thus prevent degradation by protease. ▶ [ubiquitin](#), ▶ [monoubiquitin](#); Richert K et al 2002 Mol Genet Genomics 276:88.

Deuteranomaly: A deficiency of the photopigment, sensitive to middle wavelength yet they retain some trichromatic (three-color) vision, depending on how much short and long wavelength receptors they have. The mildest cases have differences from normal in exon 5 of the X-chromosomal gene. The next mildest anomaly involves exon 2 and either exon 3 or 4 but not both. In the most severe cases the anomaly was commonly in exon 2 but usually not in 3 or 4. Deuteranomaly affects about 5% of the US males but only 0.25% of the females because of X-linkage. ▶ [colorblindness](#), ▶ [night blindness](#)

Deuteranopia: ▶ [color blindness](#)

Deuterium: ^2H , heavy hydrogen (atomic weight: 2.014725), a stable, non-radioactive isotope.

Deuterostome: A taxonomic group characterized by blastopores behind the mouth, such as echinoderms, hemichordates and chordates. ▶ [blastopore](#), ▶ [protostome](#)

Deuterotoky: Unfertilized eggs develop into male or female. ▶ [arrhenotoky](#), ▶ [thelytoky](#), ▶ [chromosomal sex determination](#), ▶ [sex determination](#)

Development: A sequence of events beginning with determination and through differentiation leads to the

various stages of life of the organism. In multicellular organisms it begins with the fertilization of the egg and goes through epigenesis and terminates in death. The zygote grows and at an early stage polarity and segmentation becomes obvious. In animal embryos the cells move into organizing centers (gastrulation) and the development becomes rather rigidly determinate. The germline is laid down and is separated from somatic differentiation. Plant cells maintain high degree of totipotency through development and

movement of cells is restricted by the rigid cell walls. In plants, *meristems* containing totipotent cells are organized and serve as the bases of growth differentiation and development. In animals the *stem cells* assume the functions comparable to that of the meristem of plants. The development is based on a highly regulated cooperation of genes that are turned on, changed in the level of activity and turned off. Although development is potentiated primarily according to the genetic blueprint, the realization of

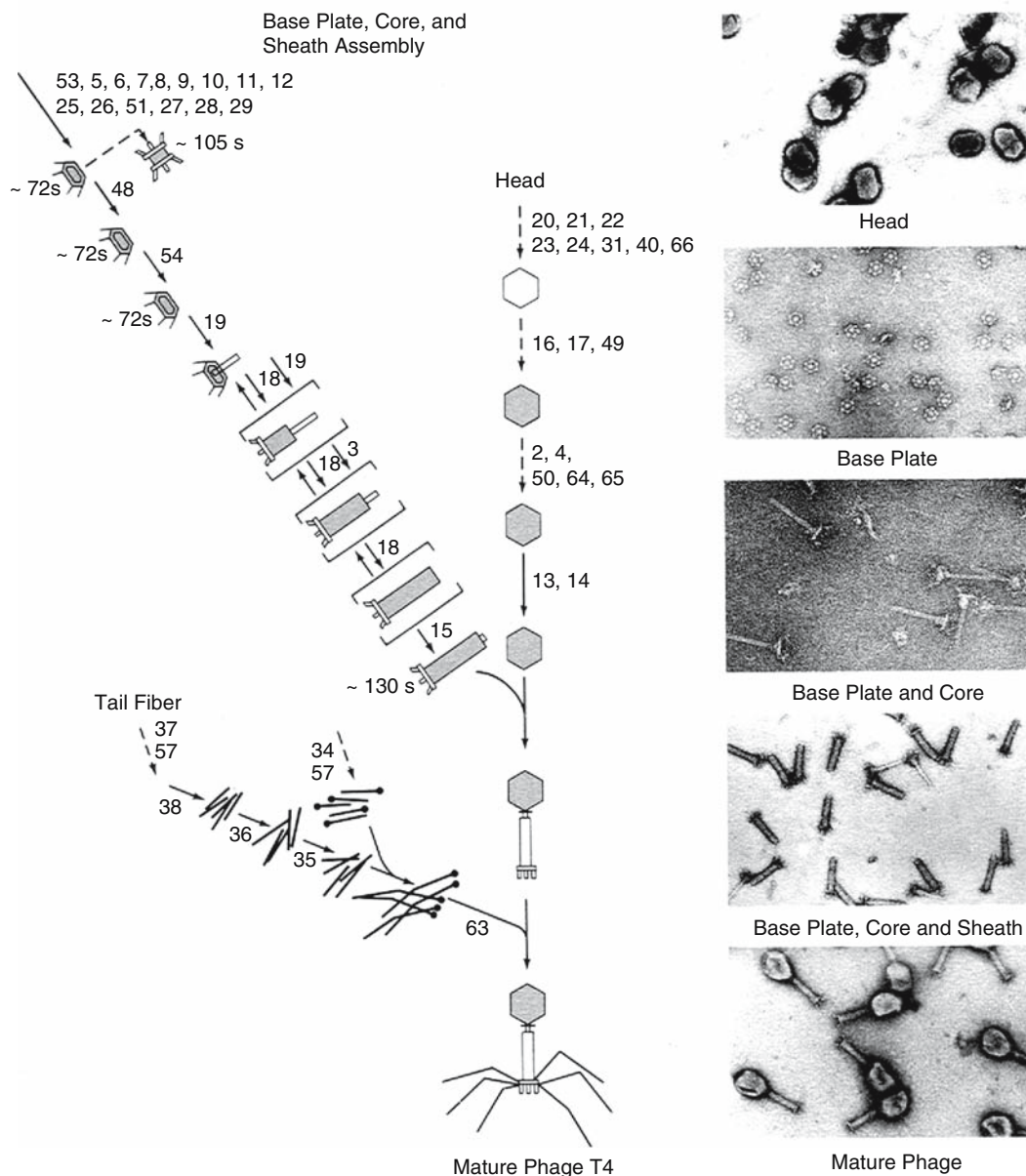


Figure D32. The morphogenetic and developmental pathway of phage T4. The numbers refer to genes. In case of mutation, incomplete phage parts may develop within the host bacteria. Many of these structures are true phage precursors and may form viable phage particles *in vitro* from appropriate mixtures of mutants blocked at key developmental steps. (After Wood WB 1980 Quarterly Rev Biol 55:353, and King J 1971 J Mol Biol 58:69)

the plan generally requires environmental cues. The signal transduction pathways provide the motivation.

Developmental events are the outcome of combinatorial action of a relatively limited number of signals and the expression of regulatory genes. The sensors of these signals may reside within the enhancers of the major genes concerned with the guidance of cellular differentiation. Development is genetically controlled in all organisms. Many genes of the bacteriophages have been identified that control individual steps of differentiation of the structures and their assembly into a mature phage particle (see Fig. D32).

Bone morphogenetic protein (Bmp4) plays an important role in beak development of ducks (see Fig. D33) and chickens (Wu P et al 2004 Science 305:1465).

The phage body is constructed according to the instructions of the viral genes but the cellular metabolism is used for execution of the project. Thus, the cooperation of both host and of the viral genomes is responsible for the product. The simplest developmental pathway of animals is seen in the nematode, *Caenorhabditis elegans*. About 90% of the genes of *Caenorhabditis* involved in the control of development are related to developmental genes of *Drosophila* and vertebrates while only ~50% of the other protein-coding genes are homologous to other taxonomic groups. Developmental mechanisms are of focal interest of research using diverse organisms. The complex interaction of many genes can be monitored by microarray hybridization.

Molecular machines can be inferred and functional relationships of genes and proteins can be studied by evaluating physical interaction (interactome), expression similarity (transcriptome) and phenotypic similarity during development (e.g., embryogenesis). In a nuclear function model 55 genes/proteins in four functional categories (DNA synthesis, histones, chromosome segregation, nucleocytoplasmic transport) were grouped and the relations were graphically represented by weights of the links/lines and size of the individual nodes. The results indicated that early embryogenesis is achieved through the coordination of a limited number of molecular machines (Gunsalus KC et al 2005 Nature [Lond] 436:861).

► *Caenorhabditis*, ► morphogenesis, ► segregation asymmetric, ► heterochronic RNA, ► GeneEMAC, ► see morphogenetic pathways diagram, ► junction of cellular networks, ► signal transduction, ► microarray hybridization, ► coordinate regulation, ► genetic networks; Boys DC et al 2001 Plant Cell 13:1499; Rougvie AE 2001 Nature Rev Genet 2:690; Freeman M, Gurdon JB 2002 Annu Rev Cell Dev Biol 18:515; Rossant J, Howard L 2002 Annu Rev Cell Dev Biol 18:541; Anderson KV, Ingham PW

2003 Nature Genet 33 (Suppl.):285; plant development: Goodrich J, Tweedie S 2002 Annu Rev Cell Dev Biol 18:707; plant development: Bäurle I, Dean C 2006 Cell 125:655; Tomancak P et al 2002 Genome Biol 3:research 0088.1; mathematical modeling of development: Tomlin CJ, Axelrod JD 2007 Nature Rev Genet. 8:331, <http://www.ucalgary.ca/UofC/eduweb/virtualembryo/>; <http://www.fruitfly.org/cgi-bin/ex/insitu.pl>.



Figure D33. A clear example of the genetically programmed development of simple traits of higher animals. Bottom: normal and Top: “Donald Duck” chicken embryos after 8 to 11 days of incubation. The beak anomaly is the result of homozygosity of a recessive gene. The mutants cannot be identified until the eighth day of incubation, and within two days after the onset both lower and upper beaks display the developmental defect. By later stages the condition becomes more pronounced and the afflicted chicks cannot survive. (Courtesy of Abbott UK and Lantz FH 1967 J Heredity 58:240)

Development, Autonomous: The process is independent of the (cellular, tissue) environment.

Developmental Clock: The developmental fate of an organism or structure is determined as a function of time.

Developmental Cycle: The processes during ontogenetic developments in the alternating generations. ► *alternation of generations*, ► *ontogeny*

Developmental Field: A group of cooperating cells destined to a differentiatinal fate.

Developmental Noise: A variation, which cannot be attributed to any verified cause.

Developmental-Regulator Effect Variegation: It shows some similarities to the variegation type position effect but the variegation is induced when the *Polycomb* gene and its response element are inserted at euchromatic sites of *Drosophila*. This variegation is also sensitive to the products of the *trithorax* gene. ▶variegation, ▶position effect, ▶*Polycomb*, ▶*trithorax*, ▶*bithorax*

Developmental Therapeutics Program (DPT): DPT involves information on drug discovery and is accessible: <http://epnws1.ncicrf.gov:2345/dis3d/DTP.html>.

Deviation: Difference from the usual type. ▶standard deviation, ▶variance

Dewar Photoproduct: An UV-induced valence isomer of pyrimidine-pyrimidone 6–4 adduct. It is less mutagenic than the 6–4 adduct (see Fig. D34), which inserts preferentially a G opposite to a 3' T and results in a highly mutagenic T→C transition in ~85% of the replications of *E. coli* cells. The Dewar product leads to a lower frequency but broader range of mutation by SOS repair. The Dewar product leads to insertions of A in 72% across T and 21% of the cases a G and only 13% translesion errors occur. The Dewar product causes less distortion of the DNA structure than the 6–4 photoproduct and therefore causes less hardship for repair DNA polymerase. ▶DNA repair; Lee J-H et al 2000 Proc Natl Acad Sci USA 97:4591.

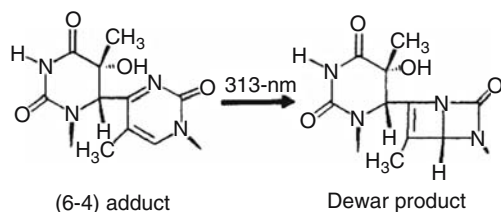


Figure D34. Dewar photo product

Dexamethasone (C₂₂H₂₉FO₅): A long-active synthetic glucocorticoid with antiinflammatory and immunosuppressive action. It is usually an inducer of glucocorticoid receptors in animals but not necessarily in plants. ▶glucocorticoids, ▶GVG

DEXH/D (unwindase): Double-stranded RNA helicase, which disrupts RNA–Protein interaction and reorganizes ribonucleoproteins. These nucleic acid-activated triphosphatases have numerous functions in RNA metabolism (splicing, RNAi, etc.) and RNA unwinding may not be necessary for protein displacement. ▶unwindase, ▶RNA helicase, ▶NPH,

▶TRAP, ▶exon junction complex; Fairman ME et al 2004 Science 304:730.

Dextran: An α-1,6 linked poly-D-glucose, sometimes with α-1,4 or α-1,3 linked branches. It is present in cross-linked form in the gel-filtration and anion exchanger agent Sephadex. It is synthesized by bacterial enzymes and is an important component (along with inorganic salts and lipids) of the dental plaques, responsible for tooth decay (caries) and gum disease. ▶DEAE-dextran, ▶Sephadex

Dextrin: ▶amylopectin

Dextrinosis: ▶glycogen storage diseases (Type III)

Dextrorotatory: Rotates the plane of polarized light clockwise.

Dextrose: same as glucose.

df or d.f. or DF (degrees of freedom): ▶degree of freedom

DFFR: ▶azoospermia

DFI (differential fluorescence induction): of green fluorescent protein gene during FACS. ▶aequorin, ▶FACS

DGCR8 (DiGeorge syndrome critical region 8): A protein which initiates microRNA maturation from primary microRNA (pri-miRNA) in complex with Drosha ribonuclease III (Han J et al 2006 Cell 125:887). ▶DiGeorge syndrome, ▶Drosha, ▶microRNA

DGGE: ▶denaturing gradient gel electrophoresis

dGTP: deoxyguanosine triphosphate (see Fig. D35).

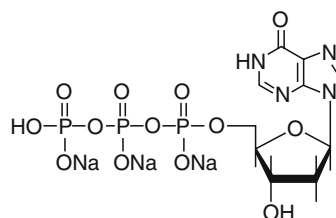


Figure D35. dGTP

DHAC 1 (RPD3): A histone deacetylase. ▶histone deacetylation, ▶histone acetyltransferase

DHFR: dihydrofolate reductase (22-kDa) controls the reaction: dihydrofolate + NADPH + H⁺→tetrahydrofolate + NADP⁺; *dhfr* deficient cells are resistant to methotrexate (amethopterin). Transformation to methotrexate resistance may be beneficial for cancer chemotherapy. The conversion of deoxyuridylic monophosphate to deoxythymidylic monophosphate

requires tetrahydrofolate. ►folic acid, ►methotrexate, ►amethopterin, ►NADP⁺, ►multidrug resistance, ►DM chromosome; Wallace LA, Robert Matthews C 2002 J Mol Biol 315:193; repression by a non-coding RNA: Martianov I et al 2007 Nature [Lond] 445:660.

D

DHR Domain: Same as PDZ domain.

Diabetes: Obesity-dependent diabetes type II (Astrup A, Finer N 2000 Obesity Rev 1:57). The high fructose sweetener consumption perturbs glucose uptake and metabolism and enhances lipogenesis and triglyceride biosynthesis (Basciano H et al 2005 Nutrition & Metabol 2;5). ►fructose

Diabetes Insipidus: An autosomal dominant type, and like all diabetes involve an imbalance in electrolyte control resulting in excessive urination and as a consequence extreme thirst. In the case of the neurohypophysis type, the defect resides within the arginine V2 vasopressin receptor gene and the controlling antidiuretic neurohypophyseal hormone. The kidneys cannot reabsorb large amounts of water and it is released, and may require a 10–15 fold higher than normal water intake (up to 20 L/day). In the autosomal dominant nephrogenic type, upon administration of antidiuretic hormone, cyclic adenosine monophosphate level increases in the urine remarkably. There is also an early onset juvenile insulin-dependent form. This may be recessive or polygenic; a problem hard to resolve because of the high frequency of the gene and the low penetrance. In another syndrome diabetes mellitus, diabetes insipidus and deafness occur together under probably autosomal recessive control. Some of the nephrogenic diabetes insipidus cases are either autosomal dominant or recessive and both encoded at 12q13 or may be encoded at Xq28. The neurohypophyseal type has been assigned to 20p13. Other somewhat less well-characterized complex forms are also known. ►diabetes mellitus, ►kidney disease, ►vasopressin, ►Wolfram syndrome, ►cAMP, ►insulin, ►neurophysin, ►MODY, ►aquaporin; Willcutts MD et al 1999 Hum Mol Genet 8:1303; Pasel K et al 2000 J Clin Endocrin Metab 85:1703; Majzoub JA, Srivatsa A 2006 Pediatr Endocrinol Rev 4 Suppl. 1:60.

Diabetes Mellitus: A recessive hereditary disease most commonly under the control of more than a single gene causing hyperglycemia due to insulin deficiency and other factors, and by defects in glucose transport from the blood to cells. Diabetes of the mother may seriously affect the fetus. The prevalence of diabetes in most human population exceeds 3% and it is increasing in the USA. The recurrence risk among sibs varies depending on the type of genetic control or primarily non-genetic type of diabetes. The

penetrance and onset are variable and dietary and other environmental factors affect it. Even monozygotic twins have less than 100% concordance sibling risk in Type I, and is about 6% higher than among unrelated but in monozygotic twins the risk of concordance is 21–70% higher than in dizygotic twins (Redondo MJ et al 2001 Rec Progr Horm Res 56:69). Type I is associated with chromosome regions 12q24, 12q13, 12p13, 16p13, 18p11 and 4q27 (Todd JA et al 2007 Nature Genet 39:857). In Type II the heritability appears somewhat lower. Environmental factors affect the expression. There is strong association between the HLA class II genes and diabetes. When 392,935 single-nucleotide polymorphisms were tested in a French case–control cohort, markers with the most significant difference in genotype frequencies between cases of type 2 diabetes and controls were found and confirmed in another cohort. Four loci including a non-synonymous polymorphism in the zinc transporter *SLC30A8* (chromosome 8), which is expressed exclusively in insulin-producing β -cells, and two linkage disequilibrium blocks that contain genes potentially involved in β -cell development or function (*IDE-KIF11-HHEX* [chromosome 8] and *EXT2-ALX4*, [chromosome 11q]) were identified (Sladek R et al 2007 Nature [Lond] 445:881). A variant of the transcription factor 7-like 2 gene (*TCF7L2*) conferred the most significant risk to diabetes Type II in Icelandic and other populations. Also, a variant in the *CDKAL1* gene that was associated with Type II (Steinthorsdottir V et al 2007 Nature Genet 39:770). Three loci were found to be associated with Type II—one in a noncoding region near *CDKN2A* and *CDKN2B*, another in an intron of *IGF2BP2*, a third in an intron of *CDKAL1*—and replicated associations near *HHEX* and in *SLC30A8* found by whole-genome association. The same work confirmed association of a SNP in an intron of glucokinase regulatory protein (*GCKR*) with serum triglycerides (Saxena R et al 2007 Science 316:1331). Altogether now at least 10 loci seem to be associated with diabetes Type II in various large populations (Zeggini E et al 2007 Science 316:1336; Scott LJ et al 2007 Science 316:1341).

Treatment involves dietary restrictions and insulin administration in the insulin-dependent diabetes. In common usage, without qualification, diabetes means the mellitus form although several other types of the condition have been identified. Diabetes is characterized by excessive amounts of sugar in the blood, and excretion of large amounts of urine, which may or may not contain excessive amount of sugar. Diabetes can be medically characterized into insulin-dependent or immune-dependent (IDDM, type I) and insulin-independent (NIDDM, type II) forms. NOD

(non-obese diabetic) mouse is a model for Type I diabetes. In NOD mice the insulin/proinsulin epitope appears to be the primary target of the autoantigens rather than the Langerhans islets (Nakayama M et al 2005 Nature [Lond] 345:220; Kent SC et al 2005 Nature [Lond] 435:224). Disruption of the MAK kinase 9 gene (encoding JNK2 protein kinase) decreases insulinitis and slows down the progression of diabetes. JNK2 seems to control of helper T cell (Th1/Th2) balance and the immune response (Jaeschke A et al 2005 Proc Natl Acad Sci USA 102:6931). Allogeneic spleen cell injection with Freund's complete adjuvant or without spleen cell alleviated NOD by stimulating insulin-producing β cell regeneration (Chong AS et al 2006 Science 311:1774; Nishio J et al 2006 Science 311:1775).

Its treatment with donor splenocytes (monocytes of the spleen) restores endogenous insulin secretion and normal glycemia and the return of pancreatic β -cells (Kodama S et al 2003 Science 302:1222). Islet cell replacement is a possibility for treatment of diabetes Type I. There is limited availability of this tissue and a life-long immunosuppression is required to prevent rejection problems. Pancreatic and duodenal homeobox gene 1 (PDX-1) has a central role in regulating adult β cell function. Transient expression of PDX-1 transgene induced functional transdifferentiation in subpopulation of liver cells in mouse. In culture, 50% of the liver cells that expressed PDX-1 activate the otherwise inactive insulin promoter. The transdifferentiated liver cells functioned for prolonged period of time, released and processed insulin in a glucose-regulated manner and ameliorated hyperglycemia upon implantation. This procedure may thus permit cell replacement therapy by using the patient's own insulin-producing system without adverse immunological consequences (Sapir T et al 2005 Proc Natl Acad Sci USA 102:7964).

Recent evidence seems to point to the cause of Type II disease as the imbalance between insulin action and insulin secretion. The insulin receptor apparently acts on two proteins, the *insulin receptor substrates* (IRSs) and the Type II disease IRS-2 may function in an aberrant manner. The IRSs apparently recruit a number of other proteins that are also involved in the pathways of insulin control. In (NOD) mice, it appears that glutamic acid decarboxylase expressed in the β islet cells of the pancreas is required for the activation of T cells, responsible for the development of the autoimmune reaction of Type I diabetes (Greely SAW et al 2002 Nature Medicine 8:399). In IDDM the loss of glucose may cause hunger and great thirst and frequent urination. The glucose loss may involve then increased catabolism of proteins and fat. As a consequence weight loss may follow. When the mobilization of fats

increases and the oxidation of fatty acids becomes incomplete, ketone bodies and acetone may accumulate. The ketones appear in the urine and the acetone may be exhaled, giving the untreated patients a special odor. IDDM is treated with insulin and properly controlled diet. The NIDDM may be caused by a defect in the glucagon receptor in human chromosome 17q25, near-telomeric region. The patients generally are overweight. A susceptibility locus was assigned for Type II at 3q27-qter and 1q21-q24. Another Type II susceptibility locus was found at 5q34-q35.2 (Reynisdottir I et al 2003 Am J Hum Genet 73:323). Recently the NIDDM1 locus was assigned to chromosome 2 and NIDDM2 to chromosome 12. More substantial evidence is in favor of association three protease locations (calpain10, [2q37.3]) carboxypeptidase E/H [chr. 4] and prohormone convertase-1 [5q15-q21] with diabetes NIDDM1. Susceptibility to diabetes Type II has been found linked to chromosome 10q in the vicinity of transcription factor TC7L2 (transcription factor 7-like) assumed to control glucose homeostasis (Grant SFA et al 2006 Nature Genet 38:320).

The calpain linkage was detected in Mexican populations and confirmed in German and Finnish individuals but rarely in other European lineages. In NIDDM obesity is a frequent sign but besides the increased blood sugar content, other symptoms may vary, depending on the cause. The latter type patients do not respond to insulin. The obesity in NIDDM seems to be regulated by TNF- α . The IPF1/IDX1 (insulin promoter factor/islet-duodenum homeobox-1, 13q12.1) factor defect is frequently associated with diabetes Type II. Peroxisome proliferator-activated receptor gamma (PPAR γ), inwardly rectifying potassium ion channel KIR6.2, hepatocyte nuclear factor 4 α , mitochondrial genetic factors, Donohue syndrome, Rabson-Mendenhall syndrome all affect substantially diabetes expression (O'Rahilly S et al 2005 Science 307:370). KLF11/TIEG2, pancreas-enriched transcription factor, is a glucose-inducible regulator of insulin and binds to its promoter in the β cells. Its mutations may be of importance in the development of type II diabetes (Neve B et al 2005 Proc Natl Acad Sci USA 102:4807). Disrupted function of pancreatic acinar cells may lead to diabetes II (Raeder H et al 2006 Nature Genet 38:54).

Chemical chaperones 4-phenyl butyric acid and taurine-conjugated ursodeoxycholic acids normalized hyperglycemia, restored insulin-sensitivity, alleviated stress of the endoplasmic reticulum and appeared effective as a treatment for Type II diabetic mouse (Özcan U et al 2006 Science 313:1137).

The first clinical test for diabetes is the glucose-tolerance test. To fasted individuals about 100 g glucose is given in water orally. In healthy individuals

the blood sugar level returns to normal after 2–3 h but not in the diabetic ones.

Various animals are also afflicted with this condition. Several forms of the insulin-dependent diabetes are associated with HLA antigen DR3/4 or 3 or 4. Diabetic and glucose intolerance symptoms are associated with a large number of syndromes. A gene involved in the control of IDDM7 has been located in human chromosome 2q34. An early onset insulin gene, IDDM2 (human chromosome 11p15.5) seems to be associated with tandemly repetitive DNA sequences that regulate insulin transcription. The principal gene for early onset (IDDM1) appears to be in human chromosome 6p21.3 and 1p although 6 indicated reasonable linkage (lod scores ~3), yet lod scores of 1.0 to 1.8 with 6 other loci were found. Another 1998 study in England also indicated only weak linkage (lod scores) with chromosomes 1p21 (1.8), 4p15 (1.9), 8p24-p21 (1.5), 12p13-pter (1.8), 16p11-q12 (2.2), and 21q11 (2.5). IL-4/IL-13 pathway seems also a modulating factor. The glucokinase gene (GCK) was located to 7p15 is also involved in IDDM. The X-chromosomal (Xp13-p11) IDDM locus is in fragment DXS1068. It was well established in people carrying the HLA-3DR antigen. Generally the male:female ratio is close to 1 at high incidence of IDDM1 but it may be low in low-incidence countries of Asia and Africa. IDDM3 was located to chromosome 15q. IDDM4 appears to be in 11q13, IDDM5 in 6q25 and chromosome 18q harbors IDDM6, IDDM9 is in 3q21-q25, IDDM10 is near the centromere of chromosome 10. The literature reported IDDM locations at 15 different chromosomal regions but an 1998 analysis could verify linkage with highly significant lod scores (<3) only at 6p21.3 and 1p although 6q indicated reasonable linkage, and lod scores of 1.0 to 1.8 with 6 other loci were found.

This is basically a polygenic autoimmune disease brought about by the destruction of insulin-producing β cells in the Langerhans islets of the pancreas by the infiltration of T lymphocytes, B lymphocytes, macrophages and dendritic cells. The variable number of tandem repeats (VNTR) in the insulin genes may contribute to juvenile obesity. The chromosomal locus 6q16.3-q24.2 is associated with childhood obesity and diabetes Type II (Meyre D et al 2005 *Nature Genet* 37:863).

CTL may be activated also either by perforin-granzyme B release or FasL. TNF, lymphotoxin, IFN- γ may also damage the pancreatic β -cells. Protein CD44 and its hyaluronic acid ligand also have an adverse role in diabetes. T_H1 cells seem to play the primary role in the process whereas the T_H2 cells may not have either promoting or protecting effect. There are some indications that retroviral infection may contribute to the expression of diabetes.

The MODY type diabetes diseases, APECED, the human X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy (IPEX/Scurfy; FOXP3; Wildin RS et al 2001 *Nature Genet* 27:18), the mitochondrial tRNA^{Leu-UUR} mutations may also be involved in Type II mellitus and deafness (van den Ouweland JM et al 1992 *Nature Genet* 1:368), familial lipodystrophy, Dunnigan syndrome, aceruloplasminemia, hemochromatosis, hyperproinsulinemia, hypoglycemia, Wolfram syndrome, Friedreich ataxia, are all apparently monogenic.

Diabetes may be responsible for blindness, kidney disease, heart attacks, strokes and for the amputational needs of the lower extremities. Low blood glucose and loss of vision in mice indicates glycemic control in diabetics and retinal diseases is related to metabolic stress as macular degeneration (Umino Y et al 2006 *Proc Natl Acad Sci USA* 103:19541). Genetically engineered non-pancreatic cells carrying the insulin gene under appropriate promoter may eventually cure diabetes. Such constructs would release insulin in a modulated manner like the normal pancreatic β cells and may evade immune destruction. Mitochondrial dysfunction accounts for 0.5 to 1% of the cases of diabetes mellitus caused by loss or defect in pancreatic β -cells and diminished secretion of insulin. ▶diabetes insipidus, ▶insulin, ▶HLA, ▶Hirschsprung disease, ▶autoimmune disease, ▶ion channels, ▶blood cells, ▶calpain, ▶VENTURE, ▶T cells, ▶cytotoxic T cells, ▶Th1/Th2, ▶insulinitis, ▶JNK, ▶glucagon, ▶glycemia, ▶superantigen, ▶polygenic inheritance, ▶Langerhans islet, ▶hemochromatosis, ▶MODY, ▶APECED, ▶lipodystrophy familial, ▶Dunnigan syndrome, ▶Wolfram syndrome, ▶Friedreich ataxia, ▶Wolcott-Rallison syndrome, ▶TNF, ▶IFN, ▶IL-4, ▶IL-13, ▶lymphotoxin, ▶insulin-receptor substrates, ▶PPAR, ▶obesity, ▶HNF, ▶lod score, ▶HLA, ▶CD30, ▶glutamate decarboxylase, ▶neurod, ▶perforin, ▶granzyme, ▶FasL, ▶VNTR, ▶calpains, ▶thiazolidinediones, ▶adiponectin, ▶CTLA-4, ▶histamine; Watanabe RM et al 2000 *Am J Hum Genet* 67:1186; Bach J-F, Chatenoud L 2001 *Annu Rev Immunol* 19:131; *Nature* [Lond] 2001, vol. 414: 782–827; Amer J Med Genet 115, issue 1 [2002]; Florez JC et al 2003 *Annu Rev Genomics Hum Genet* 4:257; diabetes type I: <http://T1Dbase.org>.

Diabetes Type, Type I and Type II: ▶diabetes mellitus

DIABLO (direct IAP-binding protein with low pI): ▶Smac, ▶IAP, ▶pI, ▶caspase, Adrain C et al 2001 *EMBO J* 20:6627.

Diabody: A dimeric association of shorter than normal, variable heavy and light chains of the antibody

(ScFv). Such dimers may be monospecific, i.e., they are formed from two variable A immunoglobulin chains or bispecific when A and B chains are joined by a linker. ▶[bispecific antibody](#), ▶[humanized antibody](#), ▶[triabody](#), ▶[recombinant antibody](#); Kortt AA et al 2001 *Biomol Eng* 18[3]95.

Diagenesis: The physical and chemical alterations that take place in the geological sediments after deposition of organisms.

Diacylglycerol (DAG): A lipid in the cell membrane that activates protein kinase C (PKC). DAG regulates growth and differentiation by its modulated level within the cell nucleus. The level of DAG in the nucleus is regulated by DAG-kinase- ζ (DGK- ζ). PKC phosphorylates DGK- ζ in the MARKCS (myristoylated alanine-rich C-kinase substrate) domain (see Fig. D36). ▶[protein kinase](#), ▶[CD36epiboly](#), ▶[phosphatidate](#)

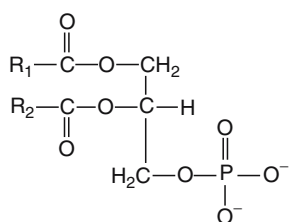


Figure D36. Diacylglycerophosphate

Diagnosis: To determine the nature and cause of a disease. Computational diagnosis is based on comparative genomic hybridization by using biomarkers and bioinformatics. ▶[comparative genomic hybridization](#), ▶[biomarker](#), ▶[bioinformatics](#); bio-informatics in cancer diagnosis: Narayanan R 2007 *Methods Mol Biol* 360:13.

Diagnostic Test: A test carried out to reveal the presence or absence of a suspected anomaly in a fetus or during any time of the life of an individual.

Diakinesis: A nuclear division phase characteristic only for meiosis. It resembles very closely the diplotene stage but the condensation of the chromosomes is further increased. The chiasmata tend to move toward the termini of the chromatids (terminalization) and the paired chromosomes (bivalents) begin their separation from each other as approaching metaphase. ▶[meiosis](#)

Diallele Analysis: The diallele analysis is used in quantitative genetics and (plant) breeding to assess

the breeding value of genetic stocks by crossing them in all possible combinations. The data reveal both nuclear and extranuclear contributions. The great amount of work involved, however, limits the number of stocks that can be studied. From n lines $n(n-1)/2$ single crosses and $[n(n-1)(n-2)(n-3)]/8$ double crosses are possible. Thus from 10 lines, 45 single crosses and 630 double crosses are possible. Similarly, from 40 inbred lines, 780 single crosses and 274,170 different double crosses can be made. Therefore, some geneticists prefer heritability tests involving intraclass correlation. ▶[heritability](#), ▶[intraclass correlation](#), ▶[single cross](#), ▶[double cross](#); Hinkelmann K 1977, p. 719 in *Proc Int Conf Quant Genet*; Pollak E et al eds. Iowa State Univ. Press, Ames, IA.

Dialog Box: It requests further information from the user of the computer or gives some warnings accompanied by a beep sound.

Dialysis: The removal of small molecules through a semi-permeable membrane into water or into lower concentration solutes.

Diaminopimelate (DAP): A (polylysine) peptidoglycan component of the cell wall of many bacteria. *E. coli* strain EK2 (χ 1776), is blocked in its synthesis and prevents the organism to survive in the mammalian gut, was used as a host for genetic vectors for recombinant DNA to assure containment. ▶[biohazards](#), ▶[biological containment](#)

2,6-Diaminopurine: A mutagenic analogue of adenine (see Fig. D37).

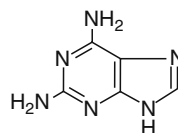


Figure D37. Diaminopurine

Diamond Code: The code suggested in various arrangements to account for the arrangement of DNA and proteins (Gamow G 1954 *Nature [Lond]* 173:318). It was later abandoned, as experimental observations failed to support it.

Diamond-Blackfan Anemia (DBA): Human chromosome 19q13 erythroblastopenia (deficiency of red blood cells) caused by defects (breakage point) in the gene encoding ribosomal protein S19. Mostly neonates and infants are afflicted. The decrease of erythroid precursors is frequently associated with

upper limb, face and other malformations. Allografted bone marrow restores blood cell formation.
 ▶ [ribosomal proteins](#), ▶ [allograft](#)

Diandry: Fertilization of a single egg by two spermatozoa. ▶ [methylation of DNA](#)

D

Diapause: A relatively inactive period in the life cycle of an organism such as during pupation, hibernation, seed stage, etc.

Diapedesis: Exit of corpuscular elements (virus) through intact blood vessels. ▶ [extravasation](#)

Diaphorase: ▶ [NAD](#), ▶ [methemoglobin](#)

Diaphyseal Aclasis: ▶ [exostoses](#)

Diarrhea (diarrhoea): Diarrhea may have diverse origins. A rare autosomal dominant type responded to steroid hormone treatment. Autosomal recessive forms include a defect in chloride absorption and occurs at a frequency of about 7.6×10^{-5} . Another different recessive form was affected in the Na^+/H^+ exchange and a rare X-linked form was found to be very susceptible to infections and other complex problems, eczema, thyroid autoimmunity, diabetes, hyperimmunoglobulinemia D, etc.

Diastase: An enzyme complex that can hydrolyze starch into sugar.

Diastematomyelia: An autosomal recessive disease causing a split in the spinal cord by either fibrous or bony material and each half is wrapped. It is often associated with spina bifida, atrophy of the legs and other defects. ▶ [neuromuscular diseases](#), ▶ [spina bifida](#), ▶ [atrophy](#)

Diastereomer: Stereoisomers, which are not enantiomorphs, i.e., are not mirror images of each other, for e.g., galactose/glucose. ▶ [enantiomorphs](#), ▶ [galactose utilization](#)

Diastole: The rhythmic expansions of the heart cavities and filling it with blood. Diastolic dysfunction is common cause of heart failure. ▶ [systole](#), ▶ [hypertension](#)

Diastrophic Dysplasia (DD): An autosomal recessive (human chromosome 5q31-q33 or q34) anomaly with curved spine (scoliosis), clubbed foot, backward-bending abnormal thumb, abnormal earlobes, premature calcification of rib cartilage, short stature, respiratory and cardiac insufficiencies, etc. The basic defect is in a sulfate transporter. Various hereditary bone diseases share similar symptoms. ▶ [stature in](#)

[humans](#), ▶ [limb defects in humans](#), ▶ [dwarfism](#), ▶ [epiphyseal dysplasia](#), ▶ [atelosteogenesis](#), ▶ [scoliosis](#), ▶ [club-foot](#)

Diatoms: Unicellular photosynthetic algae. The genome ($n = 24$) of *Thalassiosira pseudonana* has (in bp) a nuclear genome of 34×10^7 (~11,242 protein-coding genes), plastid genome 12.9×10^4 (144 protein-coding genes), and its mtDNA is 44×10^3 (40 protein-coding genes), and are sequenced. (Armbrust EV et al 2004 Science 306:79; EST database: <http://avestha.gen.sznbowler.com>)

Diauxy (diauxie): ▶ [glucose effect](#)

Diazotized Paper: A modified filter paper (Whatman 540, Schleicher & Schuell 589 or equivalent) used for nucleic acid transfers and Western blots. The paper is first treated with nitrobenzyloxymethyl pyridinium (NBPC) that leads to the formation of NBM paper that is then reduced with sodium bisulfite ($\text{Na}_2\text{S}_2\text{O}_4$) to aminobenzyloxymethyl (ABM) paper and through a reaction with nitrous acid (HNO_2) the amino group is converted into the diazo group of the DBM (diazotized) paper. NBM and ABM papers are commercially available. The stability of these modified papers depends on the conditions of storage.
 ▶ [Western blot](#)

Dibasicaminoaciduria: An autosomal recessive defect involving accumulation of lysine, arginine and ornithine when protein-rich food is consumed without any increase in cystine. The anomaly may lead to liver and bone defects. ▶ [hyperlysinemia](#), ▶ [argininemia](#), ▶ [citrullinemia](#), ▶ [cystine-lysinemia](#), ▶ [amino acid metabolism](#)

dic (X): dicentric X chromosome. ▶ [dicentric chromosome](#)

Dicentric Bridge: A dicentric bridge is formed when a dicentric chromosome is stretched because at anaphase the two centromeres are pulled in opposite direction (see Fig. D38). ▶ [breakage-fusion-bridge cycles](#), ▶ [paracentric inversions](#), ▶ [dicentric chromosomes](#), ▶ [bridge](#) (for photomicrographs).

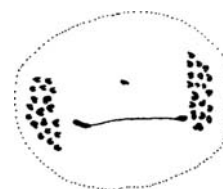


Figure D38. Dicentric bridge

Dicentric Chromosome: This has two centromeres. It is usually an unstable structure because at anaphase the two centromeres are pulled toward opposite poles and that generates a bridge that may be ruptured at any point, leading to unequal distribution of the genes of that chromosome (see Fig. D39).

The dicentric chromosomes usually do not transmit through meiosis by being trapped in between the two poles. In mammals, dicentric chromosomes with short interval (4–12 Mb) between the two centromeres may function as if they would be monocentric because one of the centromeres is inactivated. ▶breakage-fusion-bridge, ▶inversion paracentric, ▶Robertsonian translocation, ▶Turner syndrome; Thrower DA, Bloom K 2001 Mol Biol Cell 12:2800.

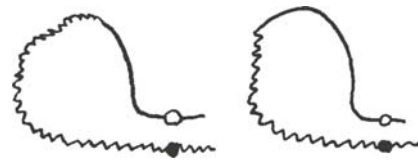


Figure D39. Dicentric chromosomes. Dicentric chromatids result from four-strand double-crossingover within a paracentric inversion

D

Dicentric Ring Chromosomes: These are formed when there is a sister-chromatid exchange in a ring chromosome(see Fig. D40). At mitotic anaphase the sister-centromeres are pulled toward the opposite poles causing the chromatids to break at potential

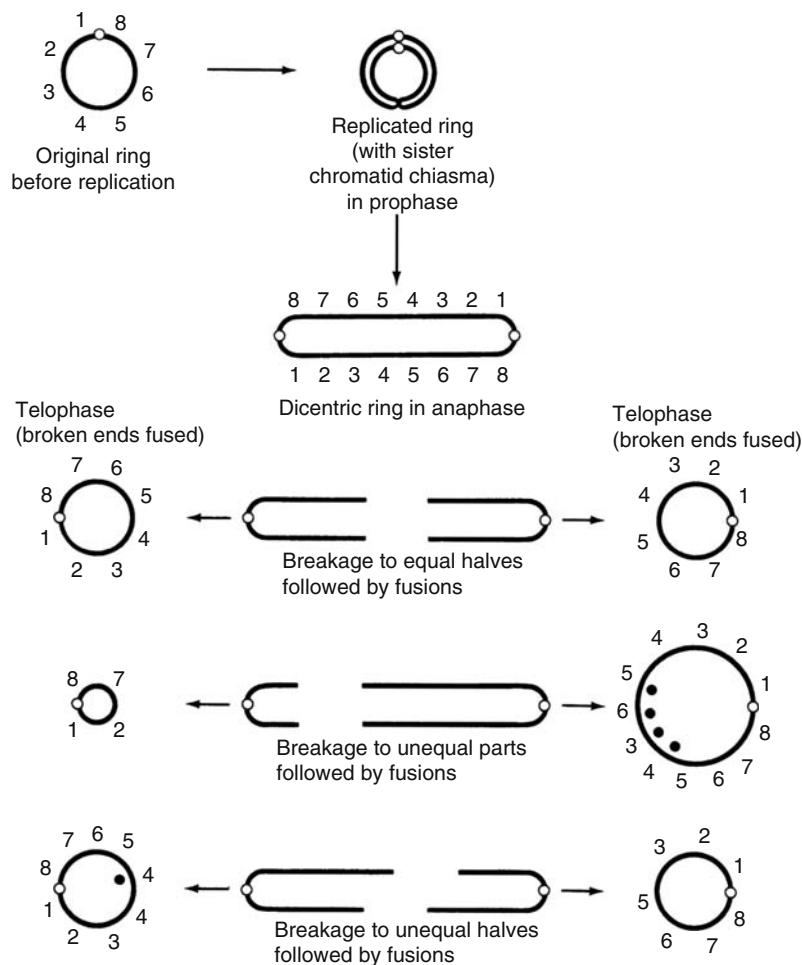


Figure D40. Dicentric ring chromosomes may be a source of genetic instability. If sister chromatid exchange takes place in the following anaphase, double chromatid bridge is formed that may break equally, and in this case the distribution of the genes to the poles is normal. (Numbers represent the genes). The chromatids may break also unequally resulting in unequal distribution of the chromatin (genes) that may be detected if appropriate markers are present. The broken ends usually heal and new dicentric ring chromosomes of different sizes are formed. (After B. McClintock 1941 Genetics 26:542; see also photo below)

points of stress and thus leading to unequal distribution of the genes (duplications and deficiencies in the cells). The broken ends may fuse and the process may continue and the resulting somatic instability is revealed by sectors if appropriate genetic markers are present. ►ring bivalent, ►ring chromosomes, ►translocation chromosomal; see Fig. D41.

D

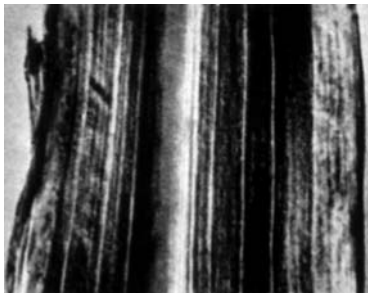


Figure D41. Sectorial maize leaf homozygous for a deficiency and carries a ring chromosome

Dicer (DCR, DCL): RNase type III ribonucleases with somewhat different specificities in different organisms, and preferentially processing single-stranded (DICER-1) (see Fig. D42) or double-stranded RNA (Dicer-2/R2D2). Dicer is important for animal development and in its absence multipotent stem cells cannot be formed and embryonic death occurs. Three domains of the acquired human immunodeficiency (AIDS) virus trans-activating response RNA-binding protein (TAR) are integral parts of the DICER complex (Chendrimada TP et al 2005 Nature [Lond] 436:740). *Arabidopsis* plants normally contain four Dicer enzymes; DCL1 produces microRNA, DCL2 is responsible for some virus-derived siRNA, DCL3 produces RNA-dependent RNA polymerase and DCL4 is the primary processor of endogenous RDR6-dependent trans-acting siRNA (Gascioli V et al 2005 Current Biol 15:1494). DICER interacts with more than a dozen proteins, which determine its specificity in various RNAi and microRNA pathways (Duchaine TF et al 2006 Cell 124:343). ►RNAi, ►microRNA, ►PAZ domain, ►tasiRNA, ►AIDS, ►Drosha, ►RNase III; Lee YS et al 2004 Cell 117:69; *Giardia*; crystal structure of *Giardia intestinalis* Dicer: MacRae IJ et al 2006 Science 311:195.

Dichlorodiphenyltrichloroethane (DDT): An insecticide, now almost entirely avoided in the industrialized countries of the Northern Hemisphere because it

weakened the eggshells of birds preying on insects and due to its accumulation in mammalian fat tissues, etc. (see Fig. D43).

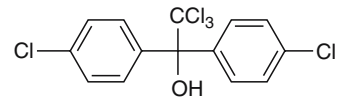


Figure D43. DDT

Some insects developed resistance to it by eliminating HCl from the molecule with the aid of increased levels of DDT dechlorinase enzyme. It is toxic to humans: oral LDLo 6 mg/kg. Although it was suspected to be carcinogenic, the final tests did not confirm this. Recently, it was discovered that main metabolite of DDT, p,p'-DDE is potent anti-androgen by binding to the androgen receptor. It is not in use for over 20 years, it still persists in the environment (its half-life being ~100 years). It is blamed for reduced human sperm counts, increased testicular cancer, and other anomalies of the reproductive system. DDT, thus, became an anathema although it is the most effective weapon against mosquitos, responsible for malaria. In December 2000, the World Health Organization (WHO) allowed the temporary use of DDT in 25 countries with very high incidence of malaria (Kapp C 2000 Lancet 356:2076), and the endorsement of its use is still maintained by WHO in 2006. ►LDLo, ►sperm, ►malaria

2,4-Dichlorophenoxyacetic acid (2,4-D): A synthetic plant growth hormone. ►auxins; for formula see ►2, 4-D

Dichotomous Trait: A qualitative trait, however, its determination may be only partly genetic, and environmental factors have substantial role in its etiology. ►quantitative trait

Dichroic Mirror: It transmits light in one color and when reflected, passes it in another color. ►circular dichroism

Dicistronic Translation: Transcripts carrying internal ribosomal entry sites (IRES) and may be co-translated (expressed) in appropriate gene fusion vectors in the same sequence. ►IRES, ►ribosome scanning, ►picornaviruses

Dicot (dicotyledonous): A taxonomic category of plants with embryos having two cotyledons.



Figure D42. Organization of a human Dicer. (DUF: domain of unknown function; PAZ: PAZ domain; dsRBD: double-strand RNA binding domain)

Dictionary of Biomedical Terms ⇔ **Acronyms:** <http://www.ncbi.nlm.nih.gov/cancerinfo/terminologyresources/>;
<http://www.nlm.nih.gov/medlineplus/plusdictionary.html>.

Dictyosomes: Golgi apparatus.

***Dictyostelium discoideum*:** A haploid ($x = 6$), unicellular amoeba with a genome size of ~33,887,060 bp. They contain also diverse sets of high copy number nuclear plasmids. Its sequenced mitochondrial genome is 54 kb. Diploid cells have also been observed. The cells form colonies that upon starvation differentiate into structures reminding of multicellular organisms. Actually, they form two types of cells, spores and stalk cells. At a stage when they are about 70% pre-spore and 30% pre-stalk they form aggregates that are called slugs, appearing somewhat similar to gastropod animals (Fig. D45). They make during the growth phase about 3,000 to 5,000 different mRNAs and during differentiation between 800 and 2,000, i.e., within the same order as lower animals (see Fig. D44). During the growth phase *Pre-Starvation Protein Factor* (PSF) accumulates and when its level reaches the critical point it serves as a signal for development by activating adenylate cyclase, cAMP receptor and a Gα protein required for signal transduction although development may take place in the absence of camp.

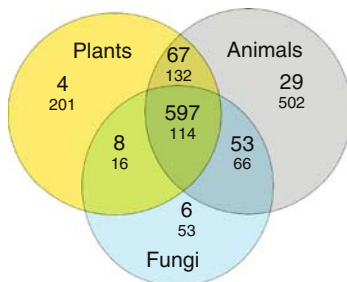


Figure D44. Venn diagram of the distribution of PFAM domain proteins among the major eukaryotic groups. The big numbers indicate presence and the small gray numbers indicate absence in *Dictyostelium*

The steroid *Differentiation Inducing Factor* (DIF) is made by the end of aggregation. The interaction of these two factors leads to culmination and formation of the fruiting body. All the functions required for growth and development involve the regulated expression of about ~12,500 proteins transcribed

and translated from 6 linkage groups of genes. The mean gene length is 1,756 bp and 69% has introns. At the end of each chromosome there is a ribosomal RNA repeat supposedly representing telomeres. The centromere-like structure is represented by clustered repeats. It appears that *Dictyostelium* retained more of the ancestral genome preceding the differentiation of the major eukaryotic forms Eichinger L et al 2005 (Nature [Lond] 435:43). ▶ cAMP, ▶ adenylate cyclase, ▶ signal transduction, ▶ Gα protein, ▶ DIRS, ▶ PFAM, ▶ Venn diagram; Wilkins A, Insall RH 2001 Trends Genet 17:41, <http://www.tigr.org/tdb/tgi>; <http://dictybase.org/>.

Dictyotene Stage: A late prophase stage of meiosis in human females. Meiosis in the oocyte begins by about the fourth month of the fetus but it is completed only before each ovulation (see Fig. D46). Meiotic

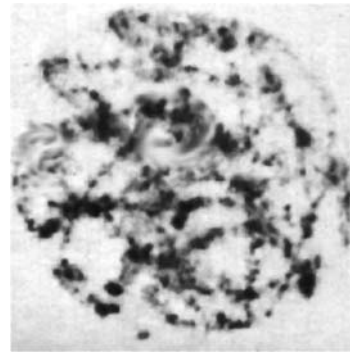


Figure D46. Late meiotic prophase

arrest is mediated by cAMP. With the surge of luteinizing hormone before ovulation meiosis is resumed. Thus, some cells remain in dictyotene for 30–40 years (until the end of ovulation). It has been hypothesized that this prolonged meiotic stage may be responsible for some of the chromosomal anomalies observed as a function of increasing age. In the human males, cell divisions in the germline continue to advanced age and point mutations increase in proportion to the advance of age. ▶ meiosis, ▶ Down's syndrome, ▶ atresia, ▶ chromosome replication, ▶ oogenesis

Dicytoplasmic System: The plastids are uniparentally transmitted (e.g., conifers) by the male whereas the

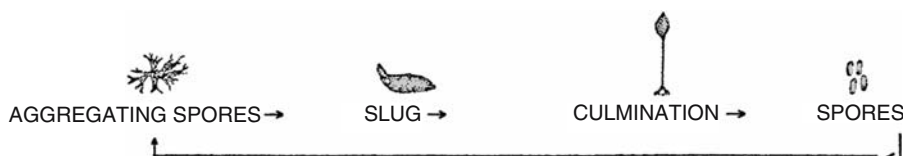


Figure D45. *Dictyostelium discoideum* life cycle

mitochondria are uniparentally inherited through the female.

Dideoxy Fingerprinting: A variation of the single-stranded conformation polymorphism (SSCP) technique that detects single-base or other subtle alterations in the DNA. One lane of the Sanger dideoxy termination reaction is electrophoresed in a non-denaturing gel. Mutations may show up as the presence of an extra segment or the absence of one or by altered mobility. ▶ [single-strand conformation polymorphism](#), ▶ [DNA sequencing](#) (Sanger).

Dideoxy Nucleotides: ▶ [DNA sequencing](#)

Dideoxyribonucleotide: It lacks an O atom at both the 2' and 3' position of the ribose (see structural formulas below) (see Fig. D47) and because of the latter feature; it is incapable of supporting DNA chain elongation that is required for the DNA polymerase to add nucleotides to the chain. Therefore, these molecules can be used for selective chain-terminators in the Sanger method of DNA sequencing. ▶ [DNA sequencing](#), ▶ [formula d](#)

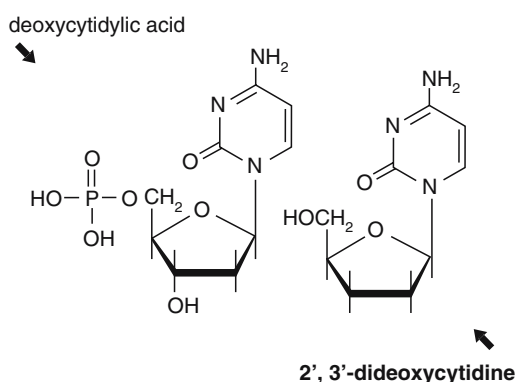


Figure D47. 2',3'-Dideoxycytidine

Diego Blood Group System: It is polymorphic in Mongolian, Chinese and American Indian populations. ▶ [blood groups](#)

Dielectrophoresis: Induced motion of polarizable particles in non-uniform fields, a method for the separation of bioparticles such as cells, viruses and proteins. Dielectrophoresis in a microfluidic device greatly increases the efficiency of marker-specific selection of cells (Hu X et al 2005 Proc Natl Acad Sci USA 102:15757). ▶ [electrophoresis](#), ▶ [cell sorter](#), ▶ [microfluidics](#); Hughes MP 2002 Electrophoresis 23:2569.

Dielectric: The transmission of electric signal by induction and not by conduction. It may shield electrostatic fields and dissipates minimal energy in a medium.

Diencephalon: The part of the brain that includes thalamus, hypothalamus, epithalamus and subthalamus. ▶ [brain](#)

Diepoxybutane: ▶ [DEB](#)

Diethylnitrosamine: ▶ [DEN](#)

Diethylstilbestrol: A non-sterol, yet sterol-like action chemical. It had been used for geese to increase the size of the liver (see Fig. D48). Until 1971, it was a prescription drug to prevent miscarriage in women. In utero exposed female offspring had a high incidence of malformations in their reproductive organs and adenocarcinoma. Estrogen favored carcinogenicity. ▶ [estrogen](#); Newbold RR et al 1990 Cancer Res 50:7677.

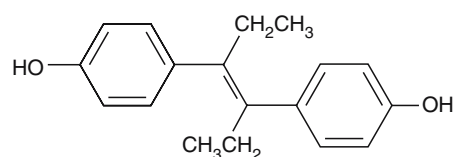


Figure D48. Diethylstilbestrol

DIF (differentiation-inducing factor): A TNF involved in mitogen-promoted blood cell differentiation. ▶ [TNF](#); Kanno T et al 2001 Dev Growth Differ 43:709.

Differrante Syndrome: ▶ [mucopolysaccharidosis](#)

Differential Centrifugation: The partition of particles (cellular organelles) by their different rates of sedimentation in aqueous or organic liquid medium (sucrose, percoll, etc.) during centrifugation. ▶ [centrifuge](#)

Differential Display (DD): Reveals the profile of protein(s) or RNA differently expressed, e.g., in healthy versus diseased states. ▶ [RNA fingerprinting](#); Liang P, Pardee AB 1992 Science 257:967; Pei L, Melmed S 1997 Mol Endocrinol 11:433.

Differential Hybridization Mapping: The tissue-specific expression of genes can be determined by hybridization to DNA, the transcript prepared during different stages of the differentiation or development. ▶ [tissue-specificity](#); Shoemaker DD et al 2001 Nature [Lond] 409:922.

Differential Psychology: The study of behavior differences among individuals and groups that seeks out genetic differences in behavior rather than average characteristics, the object of "experimental psychology". ▶ [IQ](#)

Differential Segment: The region of the X and Y chromosomes that lacks homology and those

chromosomal areas, in general, fail to pair. Also, a particular borrowed chromosomal segment in a congeneric strain. ▶sex linkage, ▶holandric genes, ▶congenic

Differentiation: The morphological and/or functional specialization of originally totipotent cells to meet particular needs of the organisms. Differentiation is determined by morphogen gradients, asymmetric distribution, cell position, etc. The pattern of differentiation is regulated in anterior/posterior, dorsal/ventral and by left/right gradients of the morphogens under genetic control. ▶determination, ▶development, ▶segregation asymmetric, ▶polarity embryonic, ▶morphogenesis, ▶selector genes, ▶morphogenesis in *Drosophila*, ▶mRNA targeting, ▶compartmentalization, ▶primitive streak, ▶inter-cellular immunization, ▶intracellular immunization

Differentiation of Plastid Nucleoids: The SN (scattered nucleoids) in the small plastids are distributed between the thylakoids and grana (land plants and many algae). The CN (central nucleoids) are located at the center of the plastids (red alga, undifferentiated proplastids of higher plants). CL (circular lamellar) types occur as ring-shaped structures within the girdle lamella (brown algae). The PS (peripherally scattered) type lie near the inner plastid envelope and the SP type spreads around the pyrenoid. The proplastids may be of 0.2 µm diameter with 1–2 cpDNA genomes or 2–3 µm in diameter with several cpDNA genomes. The smaller (proplastid precursors) may divide into structures like themselves or form the larger proplastids and change into colorless etioplasts in darkness and the latter upon illumination differentiate into green chloroplasts. In the *Chlamydomonas* alga the 5–6 nucleoids each may have 13–16 cpDNA, while in *Euglena* the number of nucleoids may be 20–34 with 3–15 DNA rings each; in the chloroplasts of higher plants the 12 to 25 nucleoids each may contain 2–5 cpDNAs. ▶chloroplasts, ▶DNA replication in plastids, ▶DNA replication in mitochondria

Diffraction: ▶X-ray diffraction analysis

Diffuse Large B-Cell Lymphoma (DLBCL): A highly morbid disease with less than 50% chance for cure. Microarrays of 6,817 genes in diagnostic tumors treated with cyclophosphamide, adriamycin, vincristine and prednisone (a type of cortisone) classified by supervised learning revealed two potential survival categories (70% and 12%). Thus, there is a predictable target for successful therapy. separate entries; Shipp MA et al. 2002 Nature Med 8:68.

Diffusion: The movement of molecules from a higher to a lower concentration in a solution. Diffusion of proteins within a cell from its origin along an axis can

be determined as $S = (4Dt/\pi)^{1/2}$ where D is the diffusion coefficient and t = time. Examples: D of 10 µm²/S diffuses on average 4 µm in a 1 S period. A membrane-bound protein diffuses <0.8 µm and transmembrane protein <0.25 µm. Cell signals are transduced either by protein—protein binding interactions or by second messenger-mediated interactions between signaling τ = the lifetime of the activated state. If τ = the time by 63% of the proteins to be inactivated then the 2-dimensional $r = (2D\tau)^{1/2}$ and for the 3-dimensional diffusion $r = (3D\tau)^{1/2}$. ▶signal transduction, ▶demic diffusion, ▶diffusion genetic; Teruel MN, Meyer T 2000 Cell 103:181.

Diffusion, Genetic: The distribution in a wave like manner of gene(s) in the function of a variable such as geographic region, infestation by a parasite, etc. The rate of advance per generation under steady state condition is $v = \sigma\sqrt{2s}$ where σ = standard deviation and s = selection coefficient. The length of the wave advance is: $\sigma([1/2]s)^{1/2}$. The rate of advance is obtained by $\sigma(2s)^{1/2}$ and if we arbitrarily substitute $\sigma = 20$ and $s = 0.01$ the km, the spread per generation would be $20(2 \times 0.01)^{1/2} \approx 2.83$ km. ▶cline, ▶legit

DiGE: Difference gel electrophoresis for detecting changes in protein extracts in a single gel using fluorescent tagging. Two-dimensional DiGE using fluorescent protein labels permits classifications of cancer cell signatures and trace metastatic tumors to origin (Seike M et al 2004 Proteomics 4:2776; Unlu M et al 1997 Electrophoresis 18:2071).

Digenic Diseases: The presence of two mutations is required for the full expression of the disease phenotype and one of the independent events alone has no or slight deleterious effect. In retinitis pigmentosa, controlled by 26 genes, heterozygosity, at least two loci results in disease. In the Bardet–Biedl syndrome (6 loci) the disease may be based on triallelic condition, i.e., one of the loci is heterozygous and another is homozygous for the mutation. Deafness controlled by DFNA12 or the connexin 26 encoding locus are also in this category of diseases. Hirschsprung disease (6 genes) is manifested when the RET gene mutation is coupled with mutation in one or the other RET ligands (glial cell-derived neurotrophic factor or neurturin). Similar digenic requirement exists in diabetes. Some of the glaucoma families segregate for two different genes. The Usher syndrome gene USH1B seems to reinforce the expression of USH3. Epidermolysis bullosa may display mutation in both COL17A1 and the β3-polypeptide subunit of laminin 5. Polycystic kidney disease genes PKD1 and PKD2 each may evoke the disease alone but in families segregating for both the symptoms appear more severe. Waardenburg

Syndrome may involve mutation in the MITF (responsible for hearing deficit) and the tyrosinase locus (responsible for defect in pigmentation). The complex holoprosencephaly is close to a polygenic disease that is based on mutations at different loci. the diseases named; Ming JE, Muenke M 2002 Am J Hum Genet 71:1017).

D

DiGeorge Syndrome: An autosomal dominant (human chromosome 22q11.2) defect of thymus and parathyroid formation and a variety of other anomalies (malformed ears, broad nasal bridge, far apart eyes, abnormal U-shaped mouth, small jaws, heart disease, etc.), including immunodeficiency. Apparently autosomal recessive form has also been observed. This anomaly is frequently associated with deletions (1.5 to 3 megabase long) in chromosome 22 and some of the defects in this rather heterogeneous syndrome are due to a deletion in chromosome 10p13. This latter deletion accounts also for hypoparathyroidism associated with the velocardiofacial syndrome (VCFS), sensorineural deafness and renal anomaly (HDR). The 200-kb region involved in HDR contains the GATA3 Zinc-finger transcription factor controlling vertebrate development. In some instances, transplantation of fetal thymus alleviated some of the symptoms. The 22q11 locus has been cloned and includes several components, including WD40 repeats similar to the yeast transcriptional co-repressors Hir1p and Hir2p most likely associated with chromosome remodeling by controlling histone transcription. Their mammalian homolog, HIRA interacts with the Pax3 transcription factor. The DiGeorge syndrome may be a defect in the CDC45 ligand. T box haplo-insufficiency may also elicit parts of the syndrome. The so-called critical region 8 (DGCR8) encompassing about 35 kb upstream of exon 1 mediates microRNA biosynthesis in both humans and *Drosophila* (Landthaler M et al 2004 Current Biol 14:2162). Tumor growth factor β (TGF- β) signal inactivation (controlling the 22q11.2 gene) resulted in DiGeorge symptoms (Wurdak H et al 2005 Genes Dev 19:530). ▶immunodeficiency, ▶deletions, ▶velocardiofacial syndrome, ▶cat eye syndrome, ▶face/heart defects, ▶CATCH, ▶Pax, ▶chromatin remodeling, ▶CDC45, ▶GATA, ▶haplo-insufficient, ▶T box; Jerome LA Papaioannou VE 2001 Nature Genet 27:286; Guris DL et al *ibid.* p. 293, Baldini A 2002 Hum Mol Genet 11:2363.

Digestion: Enzymatic hydrolysis of molecules in vitro or in the digestive tract in vivo.

Digital Karyotyping: Quantitative estimation of DNA copy numbers by isolation and counting short DNA sequence tags of genomic loci. ▶karyotype

Digital Organism: Simulation of self-replication, genome expression, interaction and environmental responses by computer programs in virtual reality. (Lenski RE et al 1999 Nature [Lond] 400:618)

Digitoxin: A cardiotonic alkaloid (glycosid) present in the ornamental-medicinal plants (see Fig. D49), *Digitalis*. ▶ATP-ase



Figure D49. Digitoxin

Diglyceride: ▶diacylglycerol

Digoxigenins: Aglycones of the steroid nucleus digoxin; they are used in non-radioactive forms to label amino acids, DNA and glycoconjugates (see Fig. D50). ▶non-isotopic labeling; Broketa M et al 2001 J Clin Virol 23:17.

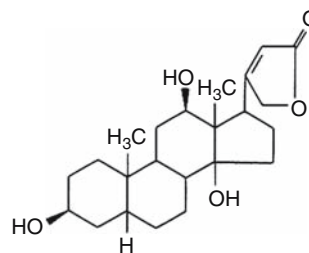


Figure D50. Digoxigenin

Digynic: It has two sets of maternal chromosomes in a normally diploid cell or triploid cell. ▶methylation of DNA

Dihaploid: An individual having half the somatic chromosome number of that of a tetraploid from where it descended. Dihaploid plants are obtained generally by crossing tetraploids by diploids and among the offspring, diploids selected carry some advantageous genes of the tetraploid that were not present in the parental diploid. ▶haploid, ▶autotetraploid

Dihybrid: Heterozygous for two pairs of alleles, e.g., *A/a* and *B/b*. ► [Mendelian segregation](#), ► [modified Mendelian ratios](#), ► [checkerboard](#)

Dihydrofolate Reductase (DHFR): The enzyme synthesizes tetrahydrofolate, an essential precursor in the biosynthesis of thymine, purines and glycine. ► [methotrexate](#), ► [amethopterin](#), ► [DHFR](#); Boehr DD et al 2006 Science 313:1638.

Dihydropyridine Receptor (DHPR): A voltage sensor in the L-type Ca^{2+} ion channels and ryanodine enhances the DHPR function. ► [ion channels](#), ► [ryanodine](#)

Dihydropyrimidine Dehydrogenase (DPYD, 1p22): DPYD mediates the catabolism of uracil and thymine. Its recessive deficiency leads to excessive amounts of pyrimidines in the urine. DPYD may catalyze the degradation of the anticancer drug 5-fluorouracil. DPYD deficiency may result in severe complex reaction to 5-fluorouracil. ► [5-fluorouracil](#)

Dihydrouracil: It may be formed by oxidizing effects and ionizing radiation of nucleic acids (see Fig. [D51](#)).

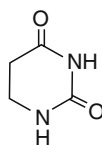


Figure D51. Dihydrouracil

Dihydrouridine (5,6-dihydro-2,4-dihydroxyuracil nucleoside): a post-transcriptionally modified uridine in the tR(5,6-dihydro-2,4-dihydroxyuracil nucleoside): NA. ► [tRNA](#); Bishop AC et al 2002 J Biol Chem 277:25090.

Dihydroxybenzil: synthetic non-steroid ligand of estrogen receptor (see Fig. [D52](#)). (Chockalingham K et al 2005 Proc Natl Acad Sci USA 102:5691)

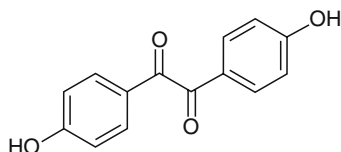


Figure D52. 4,4'-Dihydroxybenzil

3,4-Dihydroxyphenylalanine: ► [DOPA](#)

Dihydrozeatin: A natural cytokinin. ► [cytokinins](#)

Di-Isosomic: in wheat, $20''+i''$, $2n = 42$, [$''$ = bivalent, i = isosomic].

Di-Isotrisomic: in wheat $20''+(i'')1'''$, $2n = 43$, [i = isochromosome, $''$ = disomic, $1'''$ = trisomic]

Dikaryon: A single cell has two nuclei; the nuclei may be genetically identical (homokaryon) or genetically different (heterokaryon). These regularly occur in fungi after fusion of somatic cells and in other eukaryotes if the nuclei do not fuse. ► [fungal life cycles](#)

Dikaryote: Cells with two unfused nuclei. ► [dikaryon](#)

Dimer: The association of two units (e.g., two polypeptides). Dimerization may regulate the function of certain enzymes. (Mellado M et al 2001 Cell Mol Biol 47:575; Lodmell JS et al 2001 J Mol Biol 311:475; Gomes I et al 2001 J Mol Med 79:226)

Dimer 14-3-3: A protein factor that assists dimerization of Raf, an oncogene and a key player in the mitogen signal transduction pathways. ► [raf](#), ► [signal transduction](#), ► [protein 14-3-3](#)

Dimerizer: The system is based on a 'structural' complementation by revealing the function of a gene product, either from the RNA or the protein that it encodes in connection to a particular or a class of molecules (see Fig. [D53](#)). One moiety is a high-affinity ligand for another protein connectable by a chimeric "dimerizer" that facilitates the functional association with an enzyme. The protein components can be, e.g., dihydrofolate reductase that is connected via methotrexate- β -lactam cephalosporin and dexamethasone by a peptide bond (Mtx-cephem-Dex). The dihydrofolate reductase is fused also to the LexA DNA binding domain and to the B42 protein-glucocorticoid receptor activation domain. When the Mtx-cephem-Dex dimerizer assists to establish a non-covalent linkage, the RNA polymerase transcribes and facilitates the expression of the β -galactosidase reporter. In case lactamase is active, the expression of the galactosidase is abolished because dimerization link disintegrates. This is thus a method of chemical complementation independent from the reaction and it is similar to the three-hybrid test. ► [cephalosporin](#), ► [dexamethasone](#), ► [lactamase](#), ► [galactosidase](#), ► [three-hybrid system](#)

Dimethylglycine Dehydrogenase (DMGDH): An enzyme of the mitochondrial matrix involved in the biosynthesis of choline. It causes fish-like body odor, chronic muscle fatigue. The levels of the muscle form of creatine kinase and DMGDH in the serum are elevated. (Binzak BA et al 2001 Am J Hum Genet 68:839)

Dimethylsulfate: ► [DMS](#)

Dimethylsulfoxide (DMSO): A very effective solvent of a wide range of organic chemicals with moderate toxicity. It also protects cells against low temperatures. DMSO may facilitate cellular DNA uptake and

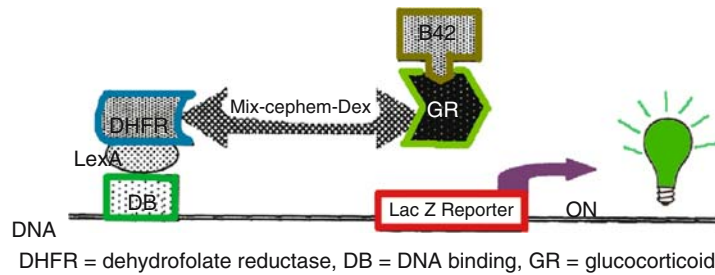


Figure D53. Dimerizer

thus transformation of eukaryotic and prokaryotic cells.

Di-Mon Cross: It involves dikaryotic and monokaryotic fungi. ► [Buller phenomenon](#)

Dimorphic: Dimorphic displays two forms whether the two are chromosomes, cells or organisms.

Dimorphic Fungi: Potential human pathogens, which in the environment (soil, 25°C) display filamentous morphology but upon ingestion by humans (37°C) they switch to yeast-like shape as they become pathogenic (see Fig. D54). The morphological transition is mediated by a hybrid histidine kinase, which also regulates cell wall integrity, sporulation and the expression of virulence genes (Nemecek JC et al 2006 Science 312:583).

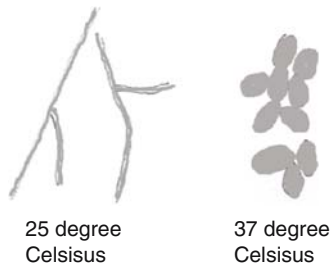


Figure D54. Dimorphic fungi

Δi-mRNA: Fully spliced nuclear mRNA. ► [splicing](#)

2,4-Dinitrophenol: An indicator of pH, wood preservative, and insecticide. It is highly toxic to animals by being an uncoupler of electron transport and oxidative phosphorylation. It blocks ATP formation by respiration. Uncoupling oxidative phosphorylation generates heat in hibernating animals, in those adapted to cold or in newborns.

Dinoflagellates: Members of the marine plankton and may appear as red tide, and by their vast number deplete the oxygen in their habitat and cause the death of sympatric animals. In addition, they may secrete a

neurotoxin which may be ingested by shellfish and may poison other creatures consuming shellfish. Their yellow, brown or red color is due to the pigments of their primitive chloroplasts. These chloroplasts contain a very small number of genes and curiously each of them (~9) appear to be in a separate circular DNA plasmid. The majority of the normally plastid genes are within their nucleus. Some *Pfiesteria* strains are toxic to fish and mammals (Burkholder JM et al 2005 Proc Natl Acad Sci USA 102:3471). ► [chloroplasts](#); Saldarriaga JF et al 2001 J Mol Evol 53:204.

Dinucleotide Abundance: ► [dinucleotide odds ratio](#)

Dinucleotide Odds Ratio: The frequency with which CpG or TpA sequences occur. Statistical survey of sequenced DNAs in different species indicates that the dinucleotide abundance within a species for different classes of DNAs (coding, intron, intergenic) tend to be similar but different in unrelated ones. (Gentles AJ, Karlin S 2001 Genome Res 11:540)

Dinucleotide Repeats: Such GpT/ApC and ApG/CpT may cause genetic instabilities by slipped-strand mispairing and generating deletions or additions. ► [trinucleotide repeats](#); Stalling RL et al 1991 Genomics 10:807; Renwick A et al 2001 Genetics 159:737.

Diode: A simple vacuum tube with an electron-emitting cathode and an electron accepting plate. The cathode emits electrons when it heated by an enclosed filament. Various laboratory equipments contain diodes.

Dieocious: The two sexes are represented by separate individuals like the majority of animals, fungi, and also some plants (<4%) such as spinach, *Asparagus*, date palm, poplar, osage orange, etc. ► [breeding system](#)

Dioxin: A family of carcinogens and (frameshift) mutagens. It may occur as a contaminant in various industrial chemicals and among the products of

burned peat. LD₅₀ orally for mice is 114 µg/kg. There are large differences among animals in the sensitivity to dioxin. If the aromatic hydrocarbon-binding receptor (AHR) has lower binding affinity, there may be 250 fold differences in sensitivity (e.g., between tern [*Sterna hirundo*] bird and chicken [*Gallus gallus*]). Two amino acids (Val-325 and Ala-381) in the ligand-binding domain of AHR of the tern are responsible for reduced activity (see Fig. D55) (Karchner SI et al 2006 Proc Natl Acad Sci USA 103:6252). Dioxin may have anti-estrogenic effects it can as well induce endometriosis and estrogen-dependent tumors. ▶environmental mutagens, ▶estradiol, ▶endometriosis, ▶LD⁵⁰; Ohtaki F et al 2003 Nature [Lond] 423:545; Harper JW 2007 Nature [Lond] 446:499.

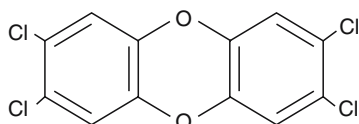


Figure D55. 2,3,7,8-Tetrachlorodibenzo *p*-dioxin

DIP: (Database of Interacting Proteins): <http://dip.doe-mbi.ucla.edu>.

Diphosphoglycerate Mutase Deficiency (7q31-q34): The enzyme controls oxygen affinity in red blood cells by binding to deoxyhemoglobin. Its deficiency leads to a type of hemolytic anemia. ▶anemia

Diphtheria Toxin: A single-chain (535 residue) very potent toxin produced by *Corynebacterium diphtheria* carrying a lysogenic phage. It has applied significance in cancer research because it blocks eukaryotic peptide chain elongation (eEF-2). Rat and mouse are resistant to this toxin because they lack its membrane surface receptor. Humans, guinea pigs and rabbits are, however, sensitive to it. The human sensitivity is encoded in chromosome 5q23. The virulence of the bacterium is a response to the expression of the toxin gene (*tox*) regulated by the toxin repressor (DtxR) activated by transition metal ions. The metal ion (iron, Ni^{II}) triggers the two different DtxR subunits to embrace—at opposite sides—33-bp of the DNA of the *tox* operator. Transformation by the diphtheria toxin gene has been employed for ablation of cells and to inhibit protein synthesis in targeted cells. ▶toxins, ▶biological weapons; Saito M et al 2001 Nature Biotechnol 19:746.

Diploblasts: Animals with only ecto- and endodermic germ layers. ▶ectoderm, ▶endoderm, ▶triploblast

Diplochromosome: It displays 4, (rather than 2) chromatids in each arm because of replication

without splitting of the centromere (see Fig. D56). ▶endoreduplication, ▶salivary gland chromosomes

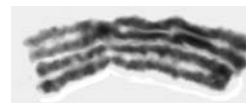


Figure D56. Diplochromosomes

Diplococcus pneumoniae (old name *Pneumococcus*): A member of the genus in the tribe *Streptococceae* and the family *Lactobacillaceae*. This is the most common cause of pneumonia. The lanceolate cells occur in doublets. The virulent forms are encapsulated and form shiny (smooth) colonies; the avirulent forms lack the protective coat (and form rough colonies) and are destroyed by the enzymes of the host cells. Genetic transformation was discovered with this bacterium in 1928. ▶transformation

Diploid: A diploid has two complete basic sets of chromosomes, characteristic for the zygotes and for most of the body cells of the majority of animals and plants, and for the premeiotic phase of several other eukaryotes (fungi, algae, etc.). Some diploids may have only a single sex chromosome in the somatic cells as a normal condition.

Diplonema: The structure of the chromosome thread at the diplotene stage of meiosis (see Fig. D57). ▶meiosis, ▶diplotene, diplotene chromosome picture by courtesy of B John.

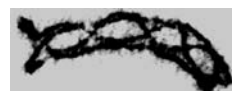


Figure D57. Diplonema

Diplont: A diploid individual (cell).

Diplontic Selection: Competition among diploid cells within multicellular organisms. This can take place only when dominant mutation or other dominant-acting change(s) occur.

Diplophase: The diploid phase of an organism that exists also as a haploid.

Diplospory (apogamety): A non-reduced embryosac develops without meiosis or by restitution. ▶restitution nucleus

Diplotene Stage: The diplotene stage of meiosis is preceded by pachytene when the chromosomes begin to appear as clearly bipartite, doubled threads (diplonema) through the light microscope. The

pairing (synapsis) of the bivalents appears somewhat relaxed but the four chromatids are held together by the chi-shaped (χ) structures of the overlapping chromatids, the chiasmata. The synaptonemal complex is generally the most conspicuous (by electron microscopy) when chiasmata are visible. ▶meiosis, ▶chromatid, ▶chiasma, ▶synaptonemal complex

D

Diplo type: The combination of two haplotypes; it is frequently identical with genotype. The genotype may not reveal, however, the allelic configuration in each of the two strands or the two haplotypes. ▶haplotype; Kitamura Y et al 2002 Ann Hum Genet 66:183.

Dipole: Molecules that have two equal and opposite charges separated in space. A simple dipole molecule is H_2O . ▶protein dipole server: <http://biportal.weizmann.ac.il/dipol/>.

Diquat: It can serve as electron acceptor in photosystem I of photosynthesis. It is also a light-dependent herbicide. ▶photosynthesis, ▶herbicides

Direct DNA Transfer: The incorporation of DNA into plant protoplasts without bacteria using only plasmids or perhaps other “naked” DNA. ▶transformation, ▶naked DNA

Direct Repeats: Adjacent or non-adjacent repeats of identical or similar nucleotide sequences of the same order such as ATG...ATG. These are common at the termini of insertion elements. ▶insertion elements, ▶transposons, ▶transposable elements

Direct Suppressors: They modify the final product of the gene so the mutation is not (fully) expressed. ▶suppressor mutations

Directed Expression: The *GAL4* activator element of yeast can be inserted into any genome at random locations by transformation. The promoter of the target gene drives the expression of *GAL4*. If a gene containing the *GAL4* binding site in its promoter is transduced into the system, it is expressed at any of the *GAL4* locations and permits the study of its effect on development. ▶*GAL4*, ▶transcriptional activator; Brand AH, Perrimon N 1993 Development 118:401.

Directed Mutation: A controversial (Lamarckian) notion that mutations of advantageous phenotype are preferentially induced in an adaptive environment, i.e., mutations would not be random and preferentially selected as required by the ideas of neo-Darwinian theory. Although supportive evidence has been put forth even recently, none of them can be completely defended against the alternative, conservative, classical interpretations ▶acquired characters. In depth analysis of adaptive mutation (directed mutation) in *E. coli* revealed that these adaptive reversions of the *Lac* alleles required *F'* plasmid

transfer replication and homologous recombination involving *F'* plasmid elements that may contain revertant alleles, and may so account for the apparent directed mutations. In bacteria, the so-called *adaptive mutations* took place only in the presence of a functional RecBCD recombinational pathway. Others have pointed out that *Lac* locus may be amplified—to cope with the reduced function due to mutation—and the increased number of copies appear to be responsible for the rise in overall reversions without an increase of mutability in the individual copies. The notion of the existence of true adaptive mutations is thus controversial. Directed mutations can be obtained, however, by manipulating the DNA in vitro using the techniques of molecular biology and transformation. In somatic hypermutation activated BV lymphocytes activate cytidine deaminase resulting in several fold increase in transition of C→T. ▶acquired characters, ▶localized mutagenesis, ▶RNAi, ▶PCR-based mutagenesis, ▶TAB mutagenesis, ▶linker scanning, ▶Kunkel mutagenesis, ▶cysteine-scanning mutagenesis, ▶homologue-scanning mutagenesis, ▶lamarckism, ▶lysenkoism, ▶soviet genetics, ▶neo-darwinian evolution, ▶somatic hypermutation, ▶hypermutation, ▶epimutation, ▶transgenerational effect, ▶staggered extension, ▶RNA-peptide fusion; Xia G et al 2002 Proc Natl Acad Sci USA 99:6597; Zheng Q 2003 Genetics 164:373; Storici F et al 2001 Nature Biotechnol 19:773.

Directional Cloning: Vector DNA termini are ligated with different linkers that produce different cohesive sequence at the two ends after restriction endonuclease cleavage. The passenger DNA (insert) can be ligated thus in a chosen orientation only (see Fig. D58). ▶vectors; Bubler U, Hoffman BJ 1983 Gene 25:263; Ohara O, Temple G 2001 Nucleic Acids Res 29(4):e22.



Figure D58. Directional cloning

Directional Evolution: The biased distribution, e.g., of the different length of microsatellites. ▶microsatellite; Hutter CM et al 1998 Mol Biol Evol 15:1620; Demetrius L 1997 Proc Natl Acad Sci USA 94:3491.

Directional Selection: Alters the population mean in either plus or minus direction. ▶selection types

Directionality: phage λ *chi* sites may enhance recombination more on the left than on its right side or the

transposase may be more functional in one orientation. ► [orientation selectivity](#), ► [lambda phage](#)

Directory: Reveals the contents of the folders (documents generated by the user) in a computer.

Dirichlet Distribution: A beta distribution of a multivariate type $f(x_1, x_2, \dots, x_q) = \frac{\Gamma(\nu_1 + \dots + \nu_q)}{\Gamma(\nu_1) \dots \Gamma(\nu_q)} x_1^{\nu_1-1} \dots x_q^{\nu_q-1}$. The distribution can be applied to the distribution of non-synonymous codon distribution across a sequence during natural selection (Huelsenbeck JP et al 2006 Proc Natl Acad Sci USA 103:6263). ► [beta distribution](#), ► [multivariate normal distribution](#), ► [non-synonymous codon](#), ► [synonymous codon](#)

DIRS: *Dictyostelium* intermediate repeat sequence elements occupy the ends of each chromosome and presumably represent centromeres. In other organisms, similar repeat elements are scattered. ► [Dictyostelium discoideum](#)

DIRVISH (direct visual hybridization): A mapping procedure for DNA sequences using fluoro-chrome-labeled samples hybridized to highly stretched DNA strands and their location is visualized with the aid of fluorescence microscopy. ► [FISH](#), ► [fluorochromes](#); Buckle VJ, Kearney L 1993 Nature Genet 5:4; Aerssens J et al 1995 Cytogenet Cell Genet 71:268.

Disaccharide: Covalently bound two monosaccharides, e.g., sucrose (glucose:fructose).

Disaccharide Intolerance: A collective name for the inability of proper metabolism of sugars. The sucrose intolerance is caused by sucrase–isomaltase malfunction. The enzyme is present but does not function normally, resulting in diarrhea when sucrose is consumed. Sucrose, maltose and starch are well tolerated in lactase deficiency but lactose cannot be reabsorbed and causes bloating, diarrhea and general discomfort because of the high gas production by intestinal microbes. The congenital lactase deficiency (alactasia) is caused by recessive mutations in human chromosome 2q21 (Jarvela I et al 1998 Am J Hum Genet 63:1078). Two types of lactase-phlorizin hydrolase activity are distinguished. One type generally appears as a developmental defect after age 5. Its frequency may be quite variable in different populations. Its frequency is low where dairy farming is prevalent and high where milk is absent from the diet. The lactase persistence (LCT*P, 2q21) to adulthood is controlled by a genetic factors closely associated with the lactase gene locus. A single nucleotide polymorphism (*C-13910T*) in an enhancer element 13.9 kb upstream of the lactase gene (*LCT*) involves *-13910*T*. This allele occurs at very high frequency in northern Europeans as part of a very long haplotype (known as A), and promotes binding

of the transcription factor Oct-1. The frequency *-13910*T* allele is very low in many African milk drinking pastoralist groups where lactase persistence phenotype has been reported at high frequency. In Sudanese populations, there is no association of *-13910*T* or the A haplotype with lactase persistence (Ingram CJE et al 2007 Human Genet 120:779).

Its worldwide distribution follows the availability of dairy product in the diet (Beja-Pereira A et al 2003 Nature Genet 35:311). The frequency of the dominant LCT*P in populations of northern European ancestry is ~0.74–0.78 or higher (except the Finns, 0.59). Several haplotypes for lactose tolerance/intolerance can distinguished based on mutation and recombination of the different alleles. The frequency of the lactose tolerance gene is very low or high, respectively depending on dairy farming. The frequency of lactase persistence decreases across southern Europe and the Middle East (50% in Spanish, French and pastoralist Arab populations) and is low in non-pastoralist Asian and African populations (1% in Chinese, 5–20% in West African agriculturalists). Lactase persistence is common in pastoralist populations from Africa (90% in Tutsi, 50% in Fulani). There is a difference in the expression of this trait due to different modifiers in the populations (Tishkoff SA et al 2006 Nature Genet 39:31). The lactase-persistence gene appeared low in neolithic, European human populations as DNA evidence from skeletal remains indicates (Burger J et al 2007 Proc Natl Acad Sci USA 104:3736).

Taking tablets of microbial β -galactosidase before eating dairy products can alleviate lactose intolerance. A new possibility is gene therapy by oral administration of adeno-associated viral vectors with the good β -galactosidase gene. Rat experiments with such a treatment produced somatic cure for up to 6 months because the vector was readily incorporated across epithelial barriers. The sucrase–isomaltase deficiency gene is at human chromosome 3q25-q26. ► [fructose intolerance](#), ► [lactose intolerance](#), ► [glycosuria](#), ► [phlorizin](#), ► [gene therapy](#), ► [adeno-associated virus](#), ► [stratification](#); Hollox EJ et al 2001 Am J Hum Genet 68:160; Enattah NS et al 2002 Nature Genet 30:233; Swallow DM 2003 Annu Rev Genet 37:197.

Disarmed Vector: Agrobacterial genetic vector from which the oncogenes (encoding phytohormones) have been deleted in the T-DNA (and usually replaced by foreign, desirable genes). ► [Ti plasmid](#), ► [Agrobacterium](#), ► [plant hormones](#), ► [transformation genetic](#)

Disassociation: The separation of the two strands of DNA. ► [C₀t curve](#), ► [Watson and Crick model](#)

Disassortative Mating: The mating partners are less similar in phenotype than expected by random

choice. ▶assortative mating, ▶breeding systems, ▶sexual selection; Reusch TBH et al 2001 Nature [Lond] 414:300.

DISC: ▶disk

DISC: A death-inducing signaling complex of FAS, FADD, and caspase 8. ▶FAS/CD95, ▶FADD, ▶caspase, ▶apoptosis

Discontinuous Gene: The translated exons are separated by introns. ▶introns, ▶exons

Discontinuous Replication: ▶Okazaki fragments, ▶replication fork

Discontinuous Variation: It is caused by qualitative genes and the expression can be classified into discrete groups with relatively low environmental effects. ▶continuous traits

Discordance: Dissimilarity of a trait between individuals because of genetic difference. The term is also used for gene loci carrying two different alleles in a diploid. Monozygotic twins are generally concordant in all traits yet, occasionally, they can be discordant regarding a particular disease. ▶dizygotic twins, ▶twinning, ▶zygosis, ▶monozygotic twins, ▶penetrance, ▶expressivity, ▶concordance

Discriminant Function: Estimates statistically the overlap between two populations and it has uses for classification and diagnosis, for the study of relations between populations and as a multivariate extension of the *t*-test (see Table D1). Example: a single variate *X* is distributed in two populations with means μ_1 and μ_2 ; the standard deviations (σ) are assumed to be the same. To know to which of the two populations does the specimen *X* belong, we classify *X* to population 1 if $X < (\mu_1 + \mu_2)/2$ and to population 2 if $X > (\mu_1 + \mu_2)/2$. If *X* is from population 1, our decision is wrong if $X > (\mu_1 + \mu_2)/2$ or when δ (the distance between the two means) = $(\mu_2 - \mu_1)$. $(X - \mu_1)/\sigma$ follows the normal distribution and misclassification is probable in the tail from $\delta/2\sigma$ and ∞ in both cases. The δ/σ must exceed 3.0 to consider the classification accurate. The δ/σ is also called distance between two populations. Analysis of variance of the discriminant function can be used

Table D1. Discriminant function

| | Sum of Squares | Df* |
|----------------|-----------------|----------|
| Between Groups | $(n/2)D^2$ | 2 |
| Within Group | D | $2n - 3$ |
| Total | $D(1 + [n/2]D)$ | $2n - 1$ |

*Df: degrees of freedom

as follows: where *D* is the difference between \bar{X}_1 and \bar{X}_2 . The significance of the difference can be determined by *z*. ▶multivariate analysis, ▶analysis of variance, ▶recursive partitioning, ▶*z*; Mather K 1965 Statistical Analysis in Biology. Methuen; London; UK; Venables WN, Ripley BD 1994 Modern Statistics, Springer, New York.

Discrimination, Genetic: The use of actual or predictive genetic information for employment or insurance and causing emotional, financial or social disadvantage/ advantage based on genetic constitution alone. In the majority of states in the USA, such discrimination is against the law although the definition of discrimination is not unanimous. On February 17, 2005 the US Senate failed to pass bill S. 306 by a vote of 98 to 0 on genetic information nondiscrimination act. On April 25, 2007 the US House of representatives passed the bill GINA (Genetic Information Nondiscrimination Act) prohibiting discrimination on the basis of medical condition, or hiring, firing or job placement on the basis of genetic information and there is a high chance that the President will sign the bill after Senate approval. By 2007, 35 states have laws against genetic discrimination in employment, and 47 have laws against genetic discrimination in health insurance. However, the state-by-state approach provides an inconsistent framework, and the scope of protection provided by many state laws is extremely narrow (Hudson KL 2007 New England J Med 356:2021). ▶gender discrimination

Discriminator Region: It is in the -10 to +1 region of prokaryotic promoters where in amino acid starving cells 5'-diphosphate 3'-diphosphate (ppGpp) binds (see Fig. D59). The σ subunit contacts the non-template strand of *E. coli* 2 base position downstream of the -10 element within the discriminator region and provides a short-lived complex for the RNA polymerase binding factors of the ribosomal RNA promoter and provides a means of regulation (Haugen SP et al 2006 Cell 125:1069; Bernardo LM et al 2006 Mol Microbiol 60:749). ppGpp (alarmone) and RNA polymerase binding protein DksA are synthesized under starvation conditions, control rRNA protein genes and activate amino acid operons. The ppGpp-repressed promoters are GC rich, the ppGpp-activated promoters are richer in AT in the discriminator region. ▶stringent control; Pemberton IK et al 2000 J Mol Biol 299:859.



Figure D59. Discriminator region

Diseases in Humans: Deviation/deviations from the normal physiological, structural and neural characteristics of the individual body, including a state of infections by virus, bacterium, fungus or protist parasites. The disease may be genetic, congenital or acquired or a combination of all these factors. In the twenty-first century the basis/bases of disease is sought in molecular terms (DNA, RNA, protein and small molecules), unlike in previous epochs when disease was considered in broader terms only. The future is to identify the cause of diseases and disease susceptibility in the genetic constitution of the host (human) and the pathogen and/or environmental factors. Human epidemiological studies indicate that prenatal and early postnatal environmental factors influence the adult risk of developing various chronic diseases, such as cancer, cardiovascular disease, diabetes, obesity and even neural diseases such as schizophrenia (Jirtle RL, Skinner MK 2007 *Nature Rev Genet* 8:253). Increasing evidence accumulates that modifier genes may seriously alter (+/−) the expression of the major genes responsible for disease (Nadeau JH, Topol EJ 2006 *Nature Genet* 38:1095). The symptoms of the diseases are based on the interacting network of factors. Genes associated with similar disorders show both higher likelihood of physical interactions between their products and higher expression profiling similarity for their transcripts, supporting the existence of distinct disease-specific functional modules. It appears that essential human genes are likely to encode hub proteins and are expressed widely in most tissues. This suggests that disease genes also would play a central role in the human interactome. The vast majority of disease genes is nonessential and shows no tendency to encode hub proteins, and their expression pattern indicates that they are localized in the functional periphery of the network (Goh K-I et al 2007 *Proc Natl Acad Sci USA* 104:8685). These findings have important implications for precise and valid diagnosis of syndromic cases and for the development of drugs with serious side effects and point toward the need of individualized medicine.

► [genetic diseases](#), ► [genetic medicine](#), ► [genetic network](#), search for disease gene candidates: Tiffin N et al 2005 *Nucleic Acids Res* 33:1544; Childs B et al 2005 *Annu Rev Genomics Hum Genet* 6:313, genetic bases of susceptibility to infectious human disease: Hill AVS 2006 *Annu Rev Genet* 40:469; CCSB-HI, non-synonymous single nucleotide polymorphism in disease:

<http://gila-fw.bioengr.uic.edu/snp/toposnp/>, disease genes conserved sequences in humans and mouse: <http://dgcst.ceinge.unina.it/>, distribution of communicable diseases: <http://globalatlas.who.int/globalatlas/health/disease/cure> news by radio or Internet:

<http://www.nih.gov/news/radio/index.htm>, candidate gene picking for hereditary diseases: http://www.ogic.ca/projects/g2d_2/.

Disequilibrium: A lack of equilibrium. ► [linkage disequilibrium](#) and [linkage equilibrium](#), ► [Hardy-Weinberg theorem](#)

Dishevelled (Dsh): A protein that mediates dorsal–ventral positioning and polarity in the embryo and the formation of a secondary axis.

Disintegration: The reversal of the integration process mediated by integrase. ► [integrase](#), ► [dpm](#)

Disintegrin: A metalloproteinase controlling cell migration. ► [metalloproteinases](#)

Disjunction: The separation of bivalents (chromosomes) during meiosis I, or of chromatids in mitosis. ► [meiosis](#), ► [mitosis](#), ► [nondisjunction](#)

Disk (disc): A magnetic surface on which information can be recorded and later retrieved by the appropriate command to the computer. The capacity of amount of information stored is expressed in kilobytes (K) or megabytes (MB). The floppy disks (about $9 \times 9 \text{ cm}^2$) can be low-density (400 K, single-sided or 800 K, double-sided) or high-density disks (1.4 MB), the Zip disk can store information up to 100–250 Mb. CDs accommodate 700–800 Mb. The hard disks hold from 20 MB to several GB (gigabyte) or more information. 1 K = 1024 characters, about 170 words in English.

Dislocated Hip (hereditary): Its prevalence in human population is about 0.075% and its recurrence risk among sibs is about 5%. It is autosomal dominant and usually more common among females than males. It occurs sometimes as part of the recessive Marfan and the Ehlers–Danlos syndromes. ► [Marfan syndrome](#), ► [Ehlers-Danlos syndrome](#)

Disome: Two homologous chromosomes.

Disomic: An individual or cell with one specific or any of the chromosomes represented twice. *Maternal or paternal disomic* individuals arise from hybrids in case of nondisjunction for a particular chromosome in translocation heterozygotes (Robertsonian translocations). *Uniparental disomy* may be associated with trisomy when one of the three chromosomes, derived from one of the parents, is lost and the result is homozygosity (disomy) for the other parent's chromosomes. The frequency of human gametic disomy, estimated on the basis of trisomic conceptuses, varies according to chromosomes: X: sperm/ova 0.04/0.04; 16: 0/1; 13, 18: 0/0.17; 21: 0.03/0.40. ► [Beckwith–Weidemann syndrome](#), ► [Prader–Willi syndrome](#), ► [Angelman syndrome](#), ► [Robertsonian translocation](#), ► [trisomy](#)

Dispensability: The feature of a gene conveying limited fitness in a certain environment of a population.

Dispermic Fertilization: When two sperms enter into one egg. ▶[double fertilization](#); Palermo GD et al 1995 Hum Reprod 10 Suppl. (1) 120.

D

Dispersed Genes: These are members of (multi) gene families. ▶[gene family](#)

Dispersed Repeats: ▶[SINE](#), ▶[LINE](#)

Dispersion Index: It indicates the extent by which a set of data deviates from their mean. For the Poisson distribution, e.g., it is determined by a formula (see box). Also $R(t) = \text{Var}(S_t)/E(S_t)$ where S_t = number of amino acid substitutions at any site. Var and E stand for variance and expectation, respectively (see Fig. D60). In case of neutral substitutions the variance to mean ratio, $R(t) \sim 1$, except when the mutations occur premeiotically (i.e., in clusters). In case the variances of the evolutionary rates exceed the expectations on the basis of Poisson distribution, the phenomenon is called overdispersion of the molecular clock. ▶[variance](#), ▶[Poisson distribution](#), ▶[evolutionary clock](#)

$$D = \sum_{i=1}^n \frac{(x_i - \bar{x})^2}{\bar{x}}$$

Figure D60. Dispersion

Dispersive Replication: The polynucleotide strands are a mosaic of old (blue) and newly synthesized (red) sequences (see Fig. D61). This old assumption has not been confirmed experimentally. ▶[semi-conservative replication](#); Delbruck M, Stent GS 1957 In: McElroy WD, Glass B (eds) The Chemical Basis of Heredity. Johns Hopkins Press, Baltimore, MD pp 699.



Figure D61. Dispersive replication

Displacement (t): In population genetics t = the number of standard deviations difference between the mean values of homozygotes AA and aa (arbitrarily assuming that the variance within genotype is the same for each genotype). ▶[genetic variances](#)

Displacement Loop: ▶[D loop](#)

Display Technologies: allow the expression of large pool of modularly coded biomolecules, analyze and select diverse and specific proteins at a very large scale.

▶[phage display](#), ▶[ribosome display](#); Ma D, Li M 2001 J Cellular Biochem 37:34.

Disposable Soma: A theory that the evolution of aging requires the preservation of the body that limits the resources available for reproduction. After reproduction, aging does not affect evolution because the soma is already met its purpose. Aging is caused by wear and tear of the body. Longevity genes are generally involved in energy metabolism. In its simplest form, longevity is favored by producing fewer offspring. The disposable soma applies to higher animals but not to higher plants; somatic tissues of plants can be regenerated into intact individuals. In addition, body parts of hydras can be regenerated into perfect animals with immortal germ line. Somatic embryonic stem cells of higher animals can also give rise to any type of tissue including those of the germline. ▶[aging](#), ▶[stem cells](#), ▶[reprogramming](#), ▶[aging](#), ▶[longevity](#); Lycett JE et al 2000 Proc Roy Soc Lond B Biol Sci 267:31; Rando TA 2006 Nature [Lond] 441:1080.

Disruptive Selection: As a consequence of the process, the population breaks up into two (contiguous) groups with different mean values. ▶[selection types](#)

Dissection, Genetic: It analyzes the mechanism of genetic determination of a process.

Disseminated Sclerosis: ▶[multiple sclerosis](#)

Dissociation Constant: K_d is the equilibrium constant for the dissociation of a complex of molecules (AB) into components (A) and (B); K_a is the dissociation constant of an acid into its conjugate base and a proton. The smaller the K_d value $\frac{(A)(B)}{(AB)}$ the tighter is the binding between the components.

Dissolution: Dissolution processes double Holliday junction-containing recombination intermediates into noncrossover products. ▶[Holliday junction](#), ▶[Holliday model](#); Wu L et al 2006 Proc Natl Acad Sci USA 103:4068.

Distal Marker: It is situated in a direction away from the centromere or another gene, or in bacterial conjugation it is transferred after a particular site. ▶[centromere mapping](#), ▶[conjugational mapping](#)

Distal Mutagen: It is formed when a promutagen through chemical modification is first converted into an intermediate (proximal mutagen) that finally becomes the ultimate or distal mutagen. ▶[mutagens](#), ▶[carcinogens](#)

Distalization Rule: In differentiation when new cells are generated (regenerated), each intercalary cell division produces progressively more distal cells until the circumferential filling of missing values are

completed. ► [polar coordinate model](#); French V 1981 Philos Trans Roy Soc Lond B Biol Sci 295:601.

Distance Matrix: ► [character matrix](#)

Distichiasis: Double eyelashes, lymphedema.

Distorted Segregation: It is seen when the transmission of one of the alleles is not the same as that of the other. The cause of this anomaly can be chromosomal defects, lethal or semilethal mutations or genes like the *Segregation distorter* (*Sd*, map location 2–54) in *Drosophila*. The distortion may reduce either the dominant or the recessive class depending on the linkage phase and map distance of the marker to the factor that disturbs normal phenotypic or genotypic proportions. ► [segregation distorter](#), ► [meiotic drive](#), ► [gametophyte factor](#), ► [certation](#), ► [preferential segregation](#), ► [megaspore competition](#), ► [gene conversion](#); Schimenti J 2000 Trends Genet 16:240; Pardo-Manuel de Villena F; Sapienza C 2001 Mamm Genome 12:331.

Distortion in Cloning: Different DNA fragments, because of their nature, length, etc., may be replicated at different rates in the vectors and may bias the representation of the sequences in the library. ► [library](#), ► [vectors](#), ► [replication](#)

Distribution-Free: An analysis that does not suppose a distribution and it is, therefore, nonparametric. ► [non-parametric tests](#)

Distributions: ► [normal distribution](#), ► [Poisson distribution](#), ► [exponential distribution](#), ► [binomial distribution](#), ► [Bernoulli process](#), ► [trinomial distribution](#), ► [multinomial distribution](#), ► [hypergeometric distribution](#), ► [negative binomial](#), ► [gamma distribution](#)

Distributive Circuit in Signal Transduction: One kinase may initiate multiple responses. ► [signal transduction](#)

Distributive Pairing: In distributive pairing, the chromosomes may recombine during meiosis and are then distributed to the poles normally (*exchange pairing*). Chromosomes that are not involved in exchange display *distributive pairing* and may suffer nondisjunction. A *Drosophila* mutation *nod* (*no distributive disjunction*; map location 1–36) when homozygous, may display high (800 fold) frequency of chromosome loss and nondisjunction of chromosome 4 during meiosis I. Recent information indicates that in the distribution of achiasmate chromosomes the heterochromatin adjacent to the centromere plays an important role. More than 70% of the nondisjunctions are the result of achiasmate meiosis. ► [chromosome pairing](#), ► [achiasmate](#), ► [heterochromatin](#), ► [chromokinesis](#); Hawley RS, Theurkauf WE 1993 Trends Genet 9:310; Grell RF 1985 Basic Life Sci 36:317.

Disulfide Bridge: A covalent bond between two sulphur atoms (–S–S–) of two cysteine residues of a polypeptide chain(s) affecting conformation. DsbA (disulphide bond) is a small periplasmic protein. In the active form, it has two cysteines joined by a disulphide bond. Disulphide bonds are formed with an exchange between the oxidized DsbA and the reduced cysteine residues of the substrate. This results in inactive, reduced DsbA. DsbB reoxidizes the molecule and restores the active form. ► [protein structure](#); Kadokura H et al 2004 Science 303:534.

Ditelo-Monotelosomic: in wheat, $20''+t''+t'$, $2n=43$, [$''$ = disomic, $'$ = monosomic, t = telosomic]

Ditelosomic: in wheat, the chromosome constitution is $20''+t''$ ($2n=42$) [$''$ indicates disomy, t = telosomic]

Ditelotrisomic: in wheat, $20''+(t'')1'''$, $2n=43$, [$''$ = disomic, $'''$ = trisomic, t = telosomic].

Dithioerythritol (DTE): 2,3-dihydroxybutane, Cleland reagent; it protects SH groups.

Dithiothreitol (DTT): DL-threo-1,4-dimercapto-2,3-butanediol; protects SH groups.

Ditype: A tetrad with two kinds of spores. ► [tetrad analysis](#)

Diuretic: It promotes discharge of urine. ► [aquaretic](#), ► [hypertension](#)

Diurnal: A response or behavior displaying daily cycles.

Diuron: A herbicide interfering with photosynthesis.

Divergence: Evolutionary differences in morphology, cytology and/or in the primary structure of nucleic acids and proteins that are believed to have descended from common ancestry. The divergence can be quantitatively estimated on the basis of average chiasma frequencies of the genomes if the species can be crossed. The average frequencies of amino acid substitutions in the proteins or base substitutions in nucleic acids can be used to estimate genetic distance and the time required to achieve it. Some caution may be required in interpreting evolutionary divergence because similarity may be based also on evolutionary convergence and reverse mutation. Mutation, chromosomal rearrangements and recombination may bring about divergence. The recombinational force in *E. coli* appears to be 50 times higher than that of mutation in clonal divergence. ► [convergent evolution](#), ► [genetic distance](#), ► [chiasma](#), ► [chimpanzee](#); <http://Ins00.psi.ch/nobugs2004/papers/paper00099.pdf>.

Divergent Dual Promoter: Juxtapositioned promoters may carry out transcription in opposite directions. ► [promoter](#), ► [divergent transcription](#), ► [catabolite repression](#)

Divergent Transcription: It proceeds from two promoters in opposite orientation. ▶promoter, ▶transcription

Diversification: ▶combinatorial diversification, ▶junctional diversification

D

Diversity (Shannon–Weaver index): $H = (n(\log N - \sum \log n_i))/N$ where H = diversity, N = total number of individuals, n_i = number of individuals of different phenotypes. Molecular genetic diversity (π) can be assessed at the nucleotide level. Based on thousands of human genes π values in the non-translated 5' and 3' regions averaged 0.0003 ± 0.0001 , non-synonymous and synonymous values of π were found to be 0.0001 ± 0.0001 and 0.0005 ± 0.0002 , respectively. Diversity at the protein level is inversely proportional to the number of subunits because the greater functional constraints. Mutation rate, however, is increasing in proportion to the size of the genes because of the larger mutational target although the mutations may be subject to selective screening for survival or even elimination. There are substantial variations among various genes. Diversity also affected by the size of the habitat (Rauch EM, Bar-Yam Y 2005 Proc Natl Acad Sci USA 102:9826). Only a relatively small fraction of the diversity is limited to specific ethnic groups although, in general, the most ancient populations, e.g., Africans display greater diversity than the newer ones. Population size is generally positively correlated with diversity of nuclear genes in animals but this rule does not hold for mitochondrial genes (Bazin E et al 2006 Science 312:570). Locally coexisting species represent α diversity and β diversity means spatial change in composition of species whereas γ diversity indicates regional diversity in species. ▶SNIP, ▶neutral mutation, ▶adaptive radiation, ▶polymorphism, ▶mutation rate, ▶microarray hybridization, ▶DArT, ▶microsatellite, ▶minisatellite, ▶species; Chakravarti A 1999 Nature Genet 21 Suppl. 56, Yu N et al 2002 Genetics 161:269, maintenance of diversity of plant genetic resources: Esquinaz-Alcázar J 2005 Nature Rev Genet 6:946, worldwide distribution of animal habitats: <http://www.worldwildlife.org/wildfinder>.

Dizygotic Twins: They develop from two separate eggs fertilized by separate sperms. Dizygotic twinning seems to be linked to the peroxisome proliferator activated receptor PPARG at 3p25. ▶twinning, ▶monozygotic twins, ▶zygosis, ▶pedigree analysis, ▶PPAR

$\Delta(lac - proAB)$: A deletion for the bacterial *lac* (lactose; map position 8) and *prolineA* and *prolineB* (map position 6 for both; blocks before glutamate semi-aldehyde) genes. ▶*Lac* operon

D-loop: ▶displacement loop

DM: The HLA DMA and DMB gene products that are required to exchange CLIP from Class II major histocompatibility proteins so the T cell can be loaded with the antigen. The DM α and β subunits are similar to the α and β chains of the Class II molecules. ▶MHC, ▶HLA, ▶CLIP

DM (double minute) Chromosome (DM): It has no centromere and can be maintained only under selective pressure for the gene(s) it carries and absent from the rest of the genome. In several types of cancer, oncogenes are amplified either in double minutes or in *homogeneously stained regions* of the chromosomes or both (see Fig. D62).

Sub-lethal doses of hydroxyurea (HU) may cause a loss of DMs and thus the oncogenes. The loss of amplified epidermal growth factor receptor (EGFR) reduces tumor growth. Amplified dihydrofolate reductase genes (DHFR) in DMs in methotrexate-resistant mouse cells were also selectively reduced in the presence of MTX (methotrexate) and HU, but after a week resistance to HU developed and DHFR was reamplified. This type of elimination of extra DNA from the eukaryotic cells may be considered as a functional substitute for the restriction–modification system of prokaryotes (Shimizu N et al 2005 Nucleic Acids Res 33:6296). ▶YAC, ▶homogeneously stained regions, ▶amplification, ▶DHFR, ▶methotrexate, ▶hydroxyurea; Hahn PJ 1993 Bioessays 15:477; Nevaldine BH et al 1999 Mutation Res Genomics 406:55.

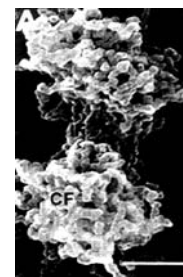


Figure D62. Scanning electron micrograph of a double-minute chromosome with ~30 looping interconnecting 17 nm fibers. The chromatin fibers (CFD) are ~32 nm in diameter. (From P.V. Schoenlein et al 1999 Chromosoma 108:121)

dm: When placed in front of a gene or protein symbol, it indicates *Drosophila melanogaster* homology.

DMBA (9,10-dimethyl-1,2-benzanthracene): A carcinogen standard, a mutagen; forms covalent DNA adducts. ▶carcinogen, ▶adduct

DMC1 (disrupted meiotic cDNA gene): A protein product in yeast controlling meiotic recombination. Similar function is carried out by RAD51, which is required for both meiotic and mitotic recombination and its role is similar to bacterial *RecA*. The Dmc1 protein acts only during meiosis. In humans, the hDmc1 mediates recombination by nucleation into single-stranded DNA to form a helical nucleoprotein filament (Sehorn MG et al 2004 Nature [Lond] 429:433). Dmc1 and Sae4 meiotic proteins are involved in loading Dmc onto the recombination chromosomes (Hayasi A et al 2004 Cell 119:927). Dmc1 is indispensable for repairing double-strand breaks. ▶*RecA*, ▶*RAD51*, ▶*nucleation*; Gupta RC et al 2001 Proc Natl Acad Sci USA 98:8433; Chen Y-K et al 2004 Proc Natl Acad Sci USA 101:10572.

$(\delta\mu)^2$ (delta mu square): A measure of the genetic distance based on the square of the difference (δ) between average repeat size (μ) in two populations. At reproductive isolation mutation and genetic drift in equilibrium within the ancestral and derivative populations indicates the time elapsed since separation. This parameter is highly variable and may be of limited utility. ▶*evolutionary distance*, ▶*coalescent*, ▶*F_{ST}*

$\Delta\mu\text{H}^+$: An energy donor, it promotes translocation through cellular membranes.

DMH (differential methylation hybridization): DMH is used to determine the relative frequencies of methylated and unmethylated cytosine in two DNA samples, e.g., normal and tumor cell DNA. The two DNAs, the normal and tumor cell DNAs, are digested to smaller fragments by the four-base recognizing MseI restriction enzyme (T'TAA) that does not cut CpG and rarely affects CpG islands. The fragments are equipped with priming linkers for PCR. Then using a methylation-sensitive restriction enzyme, the amplified methylated DNA is not digested but the unmethylated is cut and thus, the latter cannot be amplified by PCR. Then the fragments from both sources are labeled, e.g., by Cy3 (green fluorescence) the normal and by Cy5 (red fluorescence) the tumor DNA and co-hybridized onto a microarray glass slide containing CpG island DNA probe. The spots of different color indicate the degree of hybridization. Red spots on the slide indicate hypermethylation, green spots hypomethylation and yellow spots indicate that the extent of methylation was the same in the two DNAs (equal mixture of red and green fluorescence). In cancer cells, the tumor suppressors are hypermethylated (silenced) and the oncogenes are hypomethylated (activated). ▶*methylation of DNA*, ▶*restriction enzymes*, ▶*microarray hybridization*, ▶*fluorescent*; Yan PS et al 2001 cancer Res 61:8375.

DMS: dimethylsulfate, an alkylating agent, mutagenic and carcinogenic. ▶*alkylation*

Dms: ▶*double minutes*

DMSO: ▶*dimethyl sulfoxide*

dna: Bacterial mutations involved in DNA replication.

DNA: deoxyribonucleic acid, the genetic material of all eukaryotes and bacteria and many viruses (see Fig. D63).

The most direct proof for DNA being the genetic material was provided by genetic transformation. DNA is measured either in base pairs (bp) or spectrophotometrically: 1 unit of optical density (OD) of double-stranded DNA (at 260-nm wavelength) is about 50 $\mu\text{g}/\text{mL}$. One OD of single-strand DNA is about 40 $\mu\text{g}/\text{mL}$; 1 $\mu\text{g}/\text{mL}$ DNA contains about 3.08 μM phosphate (▶*DNA types*); 3000 nucleotides are about 1 μm in length, 1 pg DNA is about 0.60205×10^{12} Da [$10^{-12}/(1.6661 \times 10^{-24}$ g)]. DNA types. ▶*Watson and Crick model*, ▶*hydrogen pairing*, ▶*spectrophotometer*, ▶*transformation*, ▶*xDNA*

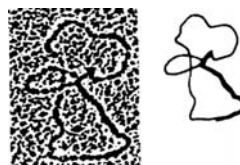


Figure D63. DNA. Electronmicrograph and interpretative drawing of double- and single-strand DNA. (Courtesy of Professor Y. Aloni)

DNA Alignment: ▶*indel*

DNA Amplification: ▶*amplification*

DNA Annealing: The reassociation of two complementary single strands into a double-stranded molecule. ▶*C₀t curve*, ▶*DNA hybridization*

DNA Bank: A collection of safely stored and identified DNA samples that can be used for comparative research or for forensic purposes.

DNA Base Composition: It varies among different organisms (see approximate values in the table). At an early stage of molecular biology, this information indicated that DNA is the genetic material, and it was used for designing the Watson and Crick model of the double helix. The differences between the amounts of A and T, and G and C, respectively, were caused by analytical errors (see Table D2).

DNA Bending: Two distant DNA sites are brought closer together because of the non-straight run of the double helix caused by phosphate neutralization due to

Table D2. DNA base composition

| Species, DNA Base Composition | A | T | G | CΣ |
|---|------|------|------|------|
| Humans | 30.7 | 31.2 | 19.3 | 18.8 |
| Wheat (<i>Triticum aestivum</i>) | 25.6 | 26.0 | 23.8 | 24.6 |
| Budding yeast (<i>Saccharomyces cerevisiae</i>) | 31.3 | 32.9 | 18.7 | 17.1 |
| <i>Escherichia coli</i> | 26.0 | 25.2 | 24.9 | 23.9 |
| <i>Mycobacterium pheli</i> | 16.5 | 16.0 | 34.2 | 33.2 |
| Bacteriophage T4 | 32.4 | 32.4 | 18.3 | 17.0 |
| Bacteriophage φX174 (single-stranded) | 24.3 | 32.3 | 24.5 | 18.2 |

ΣMethylcytosine and hydroxymethylcytosine combined

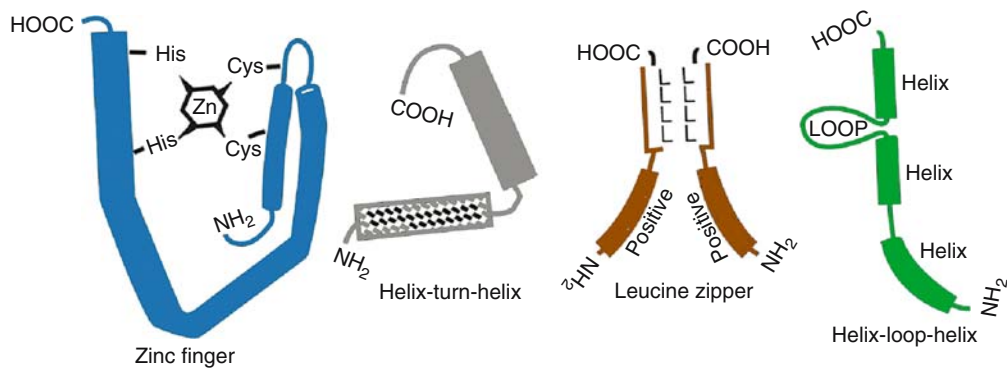


Figure D64. DNA binding protein domains

protein binding. The DNA may also bend by attaching a sequence-specific ligand to two sites separated by say 10 nucleotides. The lambda phage *Cro* repressor binds to three specific operator sites and causes DNA bending. Bending of chromatin may increase the chances of affinity of the TATA box-binding protein by over 100 fold and may also block gene expression. Repair of DNA by MutS also requires bending of DNA. ▶looping of DNA, ▶DNA kinking, ▶lambda phage, ▶TBP, ▶flexer, ▶high mobility group proteins, ▶mismatch repair, ▶inter-chromosomal interaction, ▶looping of DNA; Hagerman PJ 1990 Annu Rev Biochem 59:755; Wu J et al 2001 J Biol Chem 276:14614, *ibid.* 14623.

DNA Binding: *N*-methyl imidazole and *N*-methylpyrrole amino acids can recognize specific base pairs or short base sequences in the DNA and bind to them. There are also many DNA-binding proteins in the cells. Understanding the number, kind and strength of binding of proteins (transcription factors) to DNA reveals a great deal on expression of genes and several methods are available for the quantitative evaluation of binding (Liu Z et al 2005 Nucleic Acids

Res 33:546). ▶DNA-binding protein domains, ▶transcription factors

DNA Binding Protein Domains: There is a variety of DNA-binding proteins and they have some common structural motifs belonging to four major groups: zinc fingers, helix-turn-helix, leucine zipper and helix-loop-helix (see Fig. D64).

Proteins binding to DNA and RNA have important regulatory and potential therapeutic use (Harbison DB et al 2004 Nature [Lond] 431:99). The entire genome can be scanned for binding sites by generating a permuted library of 8–10 base pairs on microarray platform. Fluorescently labeled ligands are applied to the microarray grid to detect binding sites containing the total possible permutations of 8 (=32,896 molecules). Because the binding site size in the majority of metazoans is 6–10 bp, this array represents the genome reasonably well. Evaluation was possible in an unbiased, rapid and unsupervised/noncurated manner (Warren CL et al 2006 Proc Natl Acad Sci USA 103:867).

(See figures and more under the name of individual motifs; ▶DBP, ▶regulation of gene activity,

►hormone receptors, ►binding proteins, ►single-strand binding proteins, ►DNA bending, ►RNA-binding proteins, ►SELEX, ►transcription factor map, ►chromatin immunoprecipitation; microarray hybridization; Karmirantzou M, Hamodrakas SJ 2001 Protein Eng 14:465; Garvie CW, Wolberger C 2001 Mol Cell 8:937).

DNA, Blunted: It lacks (single-stranded) cohesive termini such as the cohesive end and cannot circularize without modification of ends (see Fig. D65).



Figure D65. Blunted, Cohesive

DNA Brushes: DNA monolayers can be used for elucidating charged polymers at interfaces. Their internal ionic microenvironment determines to a large extent their physical behavior. In general, a critical attribute of a ssDNA-modified surface is efficient and reproducible hybridization with target DNA and it is usable at nanoscale. ►ssDNA; Shen G et al 2006 J Am Chem Soc 128:8427.

DNA Chemical Synthesis: the 5'-end of the first nucleotide is protected by dimethoxytrityl (DMT) while a linker to silica attaches the OH end. The reactive groups of all nucleotides are chemically protected. Afterwards DMT is removed by washing and the next nucleotide is activated and attached to the 3'-OH group. Using iodine, the 5' to 3' linkage is oxidized to generate a phosphotriester bond (one of the O of the phosphate group is methylated). The reaction is continued until the desired chain length is reached. About 70–80 residue polymers can be made this way. The process has also automated versions and routine synthetic services are commercially available. (Linkletter BA et al 2001 Nucleic Acids Res 29:2370)

DNA Chimera: A DNA molecule ligated together from originally different molecules.

DNA Chips: It is a combinatorial array of oligonucleotides synthesized on a solid support (modified glass or polypropylene) in situ at specific “addresses” in a checkerboard like arrangement (see Fig. D66). The synthesis requires the use of masks to protect areas of the array. They may use the 4 nucleotides (A, C, G, T) in any sequence length (4^8) up to many thousands. These procedures are expected to be exploited for mass, automated sequence analyses, mutation detection, etc. in a way analogous to the electronic microchip technology. This type of technology can be used to

synthesize a vast array of nucleotide sequences at staggering speed. ►microarray hybridization

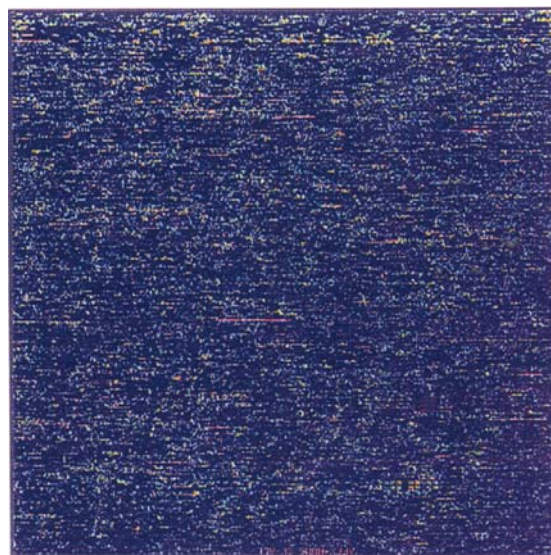


Figure D66. Fluorescent image of an array containing more than 280,000 different 25-mer oligonucleotide probes in an area of $1.28 \times 1.28 \text{ cm}^2$. The array contains probe sets for more than 6,800 human genes, and the image was obtained after overnight hybridization of an amplified and labeled human mRNA sample. (From Fields S et al 1999 Proc Natl Acad Sci USA 96:8825)

The procedure is a modification of the photolithography used by commercial printing for several decades. A mercury light is directed to a photolithographic mask and through it to a solid surface. There it activates at specific areas of nucleotides for chemical coupling. The 5' ends are protected. Subsequent exposure then removes the protection and potentiates the reaction of the end with another nucleotide. The cycle is then continued. The specificity of the nucleotides to be chosen is controlled by the mask. Chips of $1/6 \text{ cm}^2$ can accommodate hundreds of thousands of sequences of $20 \mu\text{m}$. The space occupied by an oligonucleotide sequence of millions of molecules is called a *feature*. Each wafer contains a grid of 49–400 chips. The generation of the chips and the synthesis is mechanically controlled with minimal human labor and the whole process requires about half an hour. When the synthesis is complete, the chips are separated and hybridized with an appropriate fluorochrome-labeled nucleic acid (DNA or RNA) probe. After removal the unhybridized probe sequences, the fluorescence analysis by a confocal microscope required about half an hour. The resolution is going to be improved to $20 \mu\text{m}$ in the future and each chip may permit the resolution of 400,000 probes/chip.

The ~3,000,000,000-nucleotide mammalian genome may require only 10 chips. Detection of single base pair mutations is a much more elaborate process than monitoring the expression of genes.

The cost of the technology is comparable to an automatic sequencer. The DNA chip technology can be extended to mapping gene functions to chromosomal locations and obtaining information on all the genes contributing to a particular function. The total genomic DNA is arranged in fragments over the wafers with a minimum of 20 oligonucleotide probes of 25 base length for each open reading frame of the yeast genome. Probes from the coding sequences were placed in order of their position in the genetic map (chromosome). Mismatches in the hybridization to the same array of the two genetically different strains are detected with aid of a confocal laser scanner on the basis of the fluorochrome used for staining. The location of the chromatid exchanges can be physically identified by color and the information using known genetic markers can be verified by classical tetrad analysis. Since the total nucleotide sequence (representing all the genes) of a large number organisms is already known these new technologies may detect simultaneously the turning on and off of thousands of genes and may distinguish the differences between a healthy and diseased body. The information may lend great help to design more efficient drugs and it should greatly further the knowledge how a cell or billions of cells work together in the body. (For more see Southern EM 1996 Trends Genet 12:110; Nature Genetics 14, No 4, Fodor SPA 1997 Science 277:393; Winzeler EA et al 1998 Science 281:1194; see also ►SHOM, ►photolithography, ►nanotechnology, ►genomics, ►microarray hybridization; www.gene-chips.com, for optical lithography see Ito T, Okazaki S 2000 Nature [Lond] 407:1027; Lockhart DJ, Winzeler EA 2000 Nature [Lond] 405:827).

DNA, Circular: The majority of plasmids, prokaryotic, and organellar (mitochondrial, plastid) DNAs form a covalently closed circle and a circular genetic map. ►genetic circularity

DNA, Circulating: DNA has been detected in the blood plasma of cancer patients and the majority of the maternal blood samples obtained from women carrying male fetuses revealed Y chromosome-specific sequences (Lo YM et al 1997 Lancet 350:485). These circulating DNA molecules have applicational potentials for non-invasive prenatal diagnosis of disease and for the detection of the sex of offspring after 7–16 weeks of gestation (Chiu RW, Lo YM 2002 Expert Rev Mol Diagn 2:32; Sekizawa A et al 2001 Clin Chem 47:1856). ►prenatal diagnosis, ►plasma nucleic acid; Ding C et al 2004 Proc Natl Acad Sci

USA 101:10762; Anker P et al 2003 Int J Cancer 103:149.

DNA Cloning: ►cloning

DNA Complexity: ►C₀t curve

DNA Computer: It is based on the 4 four bases in the DNA. Theoretically, it makes possible to conduct simultaneously several different operations. At present, the technical problems do not allow their practical construction although in theory it is promising. DNA actually meets the requirements of an automaton for managing the cellular processes. A 3-symbol-3-state automaton uses as hardware of two enzymes an endonuclease and ligase and it computes autonomously with superior performance (Soreni M et al 2005 J Am Chem Soc 127:3935). ►Hamiltonian path, ►RNA computer, ►automaton, ►biocomputer; Chen J, Wood DH 2000 Proc Natl Acad Sci USA 97:1328; Sakamoto K et al 2000 Science 288:1223; Joachim C et al 2000 Nature 408:541; Cox JC, Ellington AD 2001 Curr Biol 11:R336; Benenson Y et al 2003 Proc Natl Acad Sci USA 100:2191.

DNA Conformation: ►DNA types

DNA Consensus: ►consensus

DNA Crystals: These may be used to explore molecular structures at the finest scale. Antiparallel-recombinant DNA molecules are tiled in order to generate lattices at periodic patterns. The crystal is an arrangement of molecular units in two- or three-dimensional periodicity. An understanding of the forces involved may assist in the design of special catalysts, enzymes or industrial biochips, etc. ►tiling, ►chip; Packer MJ, Hunter CA 2001 J Am Chem Soc 123:7399.

DNA Damage: ►chromosome breakage, ►DNA repair

DNA Damage Checkpoint Response: The phosphatidylinositol 3-kinase-related protein kinase (PIKK) family members have been shown to be key DNA damage sensors and signal transducers in the checkpoint response. Of these, ATM (ataxia telangiectasia mutated) is mainly responsible for initiation of the checkpoint response elicited by double-strand breaks caused by ionizing radiation or radiomimetic agents. Another PIKK family member, ATR, initiates the DNA damage checkpoint response caused by UV radiation and UV-mimetic agents that produce base damage such as *N*-acetoxy-2-acetylaminofluorene (*N*-Aco-AAF) (Choy JH et al 2007 Proc Natl Acad Sci USA 104:13301). (See review: Tembe V, Henderson BR 2007 Cell Signal 19:1113; polymerases: Lindsay-Boltz LA, Sankar A 2007 Proc Natl Acad Sci USA 104:13213).

DNA Data Bases: ►databases

DNA Dating: ►racemate

DNA Denaturation: The separation of the two strands of DNA duplexes by breaking the hydrogen bonds and the hydrophobic interactions among bases; it results also in reduced viscosity. This is accomplished by raising the pH or the temperature above 70°C or 80°C. The “melting temperature” also depends on the base composition because G=C binds by 3 and A = T by 2 hydrogen bonds. By lowering the temperature below 60°C renaturation may begin. ►denaturation, ►hyperchromicity, ►hypochromicity, ►DNA, ► c_0t , ►DNA thermal stability, ►DNA thermal stability, ►diagram at denaturation

DNA, Denatured: Hydrogen bonds are disrupted between the two strands; thus it is single stranded. ►DNA denaturation

DNA Density: (see Fig. D67) ►density gradient centrifugation, ►ultracentrifugation

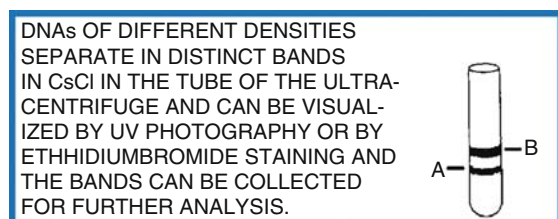


Figure D67. DNA density

DNA Density Shift: This may occur if heavy isotopes (^{13}C or ^{15}N) or 5-bromodeoxyuridine is incorporated into the DNA during replication, replacing the normal atoms or nucleotides.

DNA Dependent Protein Kinase: ►DNA-PK

DNA-Dependent RNA Polymerase: It uses DNA template for the synthesis of RNA. ►transcription

DNA Diagnostics: ►prenatal analysis, ►genetic screening

DNA Driven Hybridization: In the molecular hybridization medium the DNA is in excess relative to RNA. ►DNA hybridization

DNA Extraction: There are a large number of procedures applicable to the major taxonomic groups. Only some basic outlines can be provided here. BACTERIA: 1. Grow bacteria in culture medium of choice to a high density (one to several days). 2. Harvest cells by centrifugation. 3. Lyse cell pellet in TE buffer (Tris-EDTA) containing SDS (sodium dodecyl sulfate) and proteinase K (free of DNase) at 37°C for an hour. 4. Make it 0.5 M for NaCl and add CTAB (cetyl trimethylammonium chloride) to precipitate cell wall,

polysaccharides, proteins, etc. but keep DNA in solution. 5. Add equal volume of chloroform:isoamyl alcohol and centrifuge to remove CTAB and polysaccharides. 6. Save supernatant. 7. Remove protein by phenol:chloroform:isoamyl alcohol and centrifuge. 8. From supernatant precipitate DNA by isopropanol. 9. Wash the precipitated DNA with 70% ethanol. 10. Take up DNA in TE buffer and store it in refrigerator. PLANTS: 1. Use 10–50 g clean young tissue (from plants which have been kept in dark for 2 days to reduce starch). 2. Grind it to powder in liquid nitrogen. 3. Extract DNA in pH 8 Tris-EDTA buffer containing a detergent (SDS or Sarkosyl) for about 1 to 2 h at 55°C. 4. Pellet debris by centrifugation at 4°C (6,000 rpm, 10 min) and collect supernatant DNA. 5. Precipitate DNA from supernatant by 0.6 volume cold isopropanol (–20°C) by centrifugation (8,000–10,000 rpm, 4°C, 15 min). 6. Pellet is taken up in TE buffer. MAMMALIAN TISSUES: 1. Tissue or cell pellet (0.2–1 g) washed clean, and powdered in frozen liquid nitrogen. 2. Lysis of cells (in NaCl, Tris buffer, EDTA, SDS, pH 8, proteinase K). 3. Extraction of DNA in phenol:chloroform:isoamyl alcohol and centrifuge (10 min, 10,000 rpm). 4. To supernatant add 0.5 vol. 7.5 M ammonium acetate and 2 vol. cold ethanol to precipitate DNA by centrifugation (2 min, 5,000 rpm). 5. Wash DNA by 70% ethanol. 6. Suspend DNA in TE buffer. All of the above procedures are very similar. Further purification may be necessary by ultracentrifugation in CsCl. Quantity may be determined on the basis of absorption of ultraviolet light of 260 nm (quartz cuvettes) in a spectrophotometer. In a reasonably pure DNA preparation the ratio of OD260: OD280 is about 2:1. One OD is about 50 µg/mL for double-stranded DNA and 40 µg/mL for single-stranded DNA; 1 pg DNA is about 6.5×10^{11} Da. ►centrifuge, ►ultracentrifuge, ►spectrophotometer, ►SDS, ►Sarkosyl, ►TE buffer, ►EDTA, ►CTAB, ►Tris, ►proteinase K

DNA Fingerprinting: has been developed since the 1980s as a molecular tool for the genetic specification of an individual, a taxonomic, or other related groups (see Fig. D68). DNA fingerprinting is an important tool for the study of evolution, for establishing the degree of relatedness of genetic stocks, and its application is relevant to civil and criminal court decisions requiring identifications with high precision(see Fig. D69). The perfect definition of identity would come from the complete sequencing of the genomes but that is not practical for routine purposes. The best approximation is to use Southern hybridization with some repetitive sequences as probes isolated from minisatellite DNAs of common occurrence in the eukaryotic genomes ►SINE

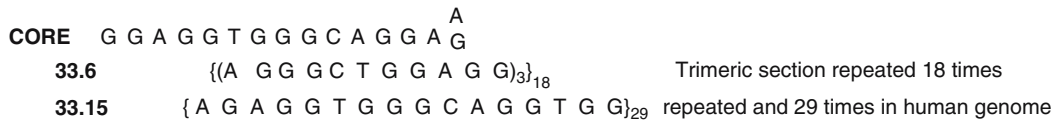


Figure D68. Minisatellite DNAs

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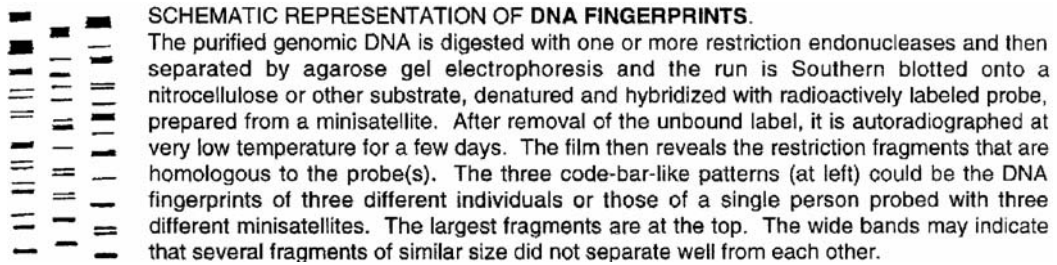


Figure D69. Schematic representation of DNA fingerprints

The first such probe was obtained from the four, 33 basepair repeats in the intron I of the human myoglobin gene. These repeats have a core sequence very similar to the *chi* elements that are responsible for meiotic recombination hot spots. These elements generate unequal crossingover at high frequency but are silent in the somatic cells. Because of this nature, they generate a high degree of specific genetic diversity. Actually, it appears that each individual is different from others (except monozygotic twins or clones). These minisatellite DNA sequences differ from each other but share the highly conserved core.

The minisatellites are distributed widely in the human (and other eukaryotic genomes) within the chromosomes. In addition to the minisatellite probes, microsatellites can also be used.

These are generally mononucleotide to tetranucleotide repeats, occurring very frequently and dispersed in the eukaryotic genomes. When isolated genomic DNA is digested with one or more restriction endonuclease(s), separated by agarose gel electrophoresis, Southern blotted and hybridized to minisatellite probes that are radioactively labeled, the autoradiograms appear similar to the diagram. The total DNA without probes cannot be used because its quantity and complexity is too large and the individual bands cannot be distinguished because many of them share the same or almost the same position in the gel. Such a gel would not appear cross-banded but it would look like a smear. Generally, the bottom of probed gels contains a larger number of small fragments that are barely or not separated (not shown in the diagram). For the analyses, fresh DNA samples are preferred because in older specimens degradation may take place and the larger fragments (closer to the start point [top]) become very weak or

vanish. However, some fingerprinting may be feasible in frozen flesh or in over 2000 year-old mummies. In the same gel, appropriate full range molecular size markers are also run at both sides to facilitate identification of fragment length with appropriate accuracy. The fragment length estimated on the basis of mobility in the gel compared to that of a corresponding size marker might have an error of 3–4%.

If one assumes that apparently co-migrating bands in the gels of A and B individuals represent identical alleles of the same minisatellite locus, the probability x that an allele in A is also present in B is proportional to the frequency of that allele according to $x = 2q - q^2$. If the frequency of the allele in the homozygotes is low then, the mean probability, $\hat{x} \approx \hat{q}^2$. Also if it is assumed that there is little variance among allelic frequencies, then the number of alleles $n \approx 1/\hat{q}$ and the mean homozygosity is approximately $\sum_i^n q_i^2 \approx n\hat{q}^2 = \hat{q}$. A certain propor-

tion of the co-migrating bands in A and B belong to different minisatellite loci, and the estimates of mean allele frequency and homozygosity so estimated are maximal, and the true estimates will depend on the accuracy of the resolution and estimation of the size of the fragments in the gels. The mean probability that all fragments detected by probe 33.15 (see Table D3) is also present in individual B is $0.08^{2.9} \times 0.20^{5.1} \times 0.27^{6.7} \cong 2.78 \times 10^{-11}$. (Note that the probabilities were raised to the power of the corresponding mean fragment number). Because the current population of the earth is about 6×10^9 , about more than 50-fold increase in the current population would be needed to find perhaps two individuals with identical genetic constitution. The precision of the analysis is further

Table D3. In an experiment with 20 Englishmen, the following information was obtained. (Data and methods of calculations after A. J. Jeffreys, et al. 1985. *Nature* 316:76)

| DNA Fragment Size, kb | No. of Fragments M \pm Standard Deviation per Individual | | Probability x That Fragment in A Individual Is Present in B Individual | | Max. Mean Allelic Frequency per Heterozygosity | |
|-----------------------|--|---------------|--|-------|--|-------|
| ↓ | Probes–33.6 | 33.15 | 33.6 | 33.15 | 33.6 | 33.15 |
| 10–20 | 2.8 \pm 1.0 | 2.9 \pm 1.0 | 0.11 | 0.08 | 0.06 | 0.04 |
| 6–10 | 5.1 \pm 1.3 | 5.1 \pm 1.1 | 0.18 | 0.20 | 0.09 | 0.10 |
| 4–6 | 5.9 \pm 1.6 | 6.7 \pm 1.2 | 0.28 | 0.27 | 0.14 | 0.14 |

improved by the use of several probes. In the American forensic laboratory practice four or five probes are used that detect only two allelic variations each, and making the precise reading of the bands easier because only two are shown by each run. This type of analysis still provides 99.9% accuracy for determining the identity of a person. The power of this procedure is also indicated by the fact that 0.5 to 5 μ g DNA (present in a drop of blood, in a few thousands of cells) may be enough for an RFLP test. The procedure described above is the DNA fingerprinting or RFLP (restriction fragment length polymorphism). RFLP has superior analytical value to PCR because the former is based on the entire DNA whereas in the latter only fragments of the DNA are amplified.

If RFLP is coupled with say 200,000-fold amplification of a sample using PCR, its efficiency may be further increased. The DNA sample prior to amplification may be as low as 500 pg (0.5 ng), however, somewhat larger quantities (2 ng) may give better results. The most efficient techniques may permit DNA analysis from palm swabs, briefcase handles or telephone handles, gloves, coffee mugs, etc. A single PCR amplification does not, however, deal with an entire genome-size DNA but only with an extremely small fragment, defined by the two 5'-terminal primers. By the use of Taq DNA polymerase, starting with pg quantities of DNA of 2 kb in length can be increased up to 1 μ g in 30–35 cycles, and after dilution it can be subjected to even further amplification. For RFLP tests, not just larger quantities of the DNA are required but it must be fresh or non-degraded. PCR analysis can be carried out not just with more minute samples, but some degradation may not prevent its suitability for the test. For forensic PCR tests, generally the DNA of the second exon of the human leukocyte antigen (HLA)-DQ- α is used most commonly. Actually one test kit, *Amplitype HLA-DQ-alpha Forensic Kit*, marketed by the Perkin-Elmer Company is commercially available. This procedure has an accuracy of 98–99% but a newer PCR procedure, the *Poly-Marker Test* (PM)

is supposed to have up to 99.7% precision. The PCR methods use dot blot hybridization and fluorochrome labels that eliminate the waiting period involved in exposing the Southern blot to X-ray film. The Amplitype relies on differences in six allelic types (n) that determine 21 different genotypes according to the general formula $[n(n+1)]/2$. The PCR method is less accurate than the RFLP test but its value can approach that of the latter by the use of larger number of probes. In both types of assays, the proper statistical procedure is very important. The power of the statistics depends on databases revealing the frequencies of the allelic variations in the general or ethnic populations, so the genotype of the individual to be tested can be compared to other similar or identical types. In other words, the statistics will tell the probability of how many other individuals may have the same DNA fingerprint as the suspect. In court, then along with the DNA fingerprints, other evidence is considered that may further improve identification (such as dermatoglyphics, alibi, time frame, etc.).

For DNA fingerprinting a variable section of the mitochondrial DNA can also be successfully used. Since the size of this DNA is more limited than that of the nuclear DNA fragments, the potential information to be gained is less.

DNA fingerprinting can identify with great certainty members of a biological family. If the total number of identifiable bands of putative mother (M) and father (F) is T and of that n is shared by offspring (O), then the probability that (O) would share all the bands in common between (M) and (F) is Y^T where $Y = 1 - (1 - x)^2$ [for the definition of x see above]. The probability that (O) would share the specific maternal or the specific paternal fragments is x^{Mf} and x^{Ff} where Mf and Ff are the number of mother- or father-specific fragments. The use of DNA evidence in the criminal courts have been questioned on statistical grounds and because some of the crime or biological laboratory contractors may have based unwarranted conclusions on poorly performed and/or incompetently evaluated DNA tests. The statistical

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arguments brought forward are as follows. If the only evidence is the DNA profile and the probability of match for a particular individual is $1/1,000,000$ but there may be 500,000 individuals who could be responsible for the case if the DNA evidence is not considered. There are then two possibilities: either the suspect is the criminal and he displays a perfect match to the DNA sample collected at the crime scene or another individual among the other 500,000 is the criminal and the DNA analyses match only by chance. The probability for the first case is $1/(500,001) \times 1 = 0.000001999$. The probability for the second case is $500,000 \times (1/500,001) \times (1/1,000,000) = 0.000,000999$. Since the ratio of these two fractions is about 0.5, and $1.5/0.5 = 3$. Thus, the statistical chance that the suspect is innocent is $1/3 \approx 0.33$. These methods are particularly useful to rule out identity, i.e., rule out that the blood, semen or tissue sample left at the crime scene did not come from a particular suspect or that a particular person may not be a relative to an individual. Positive identification is also likely at an extremely high probability. The technology and the experience of the technicians have improved since the 1980s. Also, the removal of contaminants from the specimens (sulfur, dyes of the clothing, etc.) may be facilitated by new procedures of purification of the DNA. Several of the commercial testing laboratories follow the guidelines recommended by the *Technical Working Group on DNA Analysis Methods* (TWIGDAM). The greatest care is still required in the use of these powerful techniques because in murder trials life or death of the suspects may depend on the correct identification. There are still some questions regarding the best procedures and the acceptance of DNA fingerprints and its statistical evaluation as evidence in the different courts of the USA. The best statistical procedures for the criminal justice system should be to determine the ratio of the conditional probabilities (Pr) of the claims of the prosecution (C) and the defense (C') based on the evidence (E) as $Pr(E|C)/Pr(E|C')$. Currently—because of the great facility of accurate identifications—DNA fingerprinting is the most effective identification system in forensic repertory. DNA fingerprinting has wide applicability outside of the judicial system for identification of modern or ancient biological samples.

Comparison of the diploid set of DNA of Craig Venter and the National Center for Biotechnology Information human reference assembly revealed more than 4.1 million DNA variants, encompassing 12.3 Mb. These variants (of which 1,288,319 were novel) included 3,213,401 single nucleotide polymorphisms (SNPs), 53,823 block substitutions (2–206 bp), 292,102 heterozygous insertion/deletion events (indels)(1–571 bp), 559,473 homozygous

indels (1–82,711 bp), 90 inversions, as well as numerous segmental duplications and copy number variation regions. Non-SNP DNA variation accounts for 22% of all events identified in the donor, however, they involve 74% of all variant bases. Genotyping and cluster analysis of 750 unique SNP loci discovered showed that the donor's 99.5% similarity to individuals of European descent and it could be further corroborated by an extensive five-generation family history. The donor was found to be heterozygous for variants in the KL gene that have been associated with a lower risk for coronary artery disease. However, the donor was found to be also homozygous for the 5A/5A in rs3025058 in the promoter of the matrix metalloproteinase-3 that was associated with higher intra-arterial levels of stromelysin and has a higher risk of acute myocardial infarction. Furthermore, the donor displayed heterozygosity for the GSTM1 gene, which may increase susceptibility to environmental toxins and carcinogens. A 4-bp novel heterozygous deletion was found in Acyl-CoA Oxidase 2 (ACOX2) causing a protein truncation. ACOX2 encodes an enzyme activity found in peroxisomes and associates intimately with lipid metabolism and further was found to be absent from livers of patients with Zellweger syndrome. The donor's LCT genotype should confer adult lactose tolerance (Levy S, Sutton G, Ng PC, Feuk L, Halpern AL et al 2007 PLoS Biol 5[10]: e254).

The mammalian mitochondrial DNA D loop is rich in variable base substitutions. In addition, the copy number of this DNA is very large making its analysis rewarding even from samples highly degraded such as in exhumed corpses or ancient DNA. In such instances, DNA amplification is usually required. More recently, techniques are being developed that permit DNA typing from single cells. Essentially the same total DNA procedures have been used for the analysis of feral populations of animals, for anthropological studies, on ancient biological samples, to check the authenticity of cell cultures or plant varieties, etc. DNA fingerprinting has been used for the generation of sequencing-ready large insert BAC or PAC clones (Marra MA et al 1997 Genome Res 7:1072). The inserts are labeled by ESTs and connected by chromosome walking. ►fingerprinting, ►bisulfite reaction, ►minisatellite, ►microsatellite, ►VNTR, ►MVR, ►ceiling principle, ►forensic genetics, ►Southern blotting, ►dot blot, ►nick translation, ►gel electrophoresis, ►PCR, ►RFLP, ►phylogenetic analysis, ►mtDNA, ►probe, ►SINE, ►myoglobin, ►intron, ►chi elements, ►labeling, ►fluorochrome, ►autoradiography, ►electrophoresis, ►molecular marker, ►allelic frequencies, ►HLA, ►feral, ►mtDNA, ►Bayes' theorem, ►conditional probability, ►Romanovs, ►heteroplasmy,

►utility index for genetic counseling, ►Frye test; The Evaluation of Forensic DNA Evidence. Natl Acad Press 1996; Krenke BE et al 2002 J Forensic Sci 47:773.

DNA Flap: A stable 99-nucleotide overlap in the center of the HIV-1 reverse transcription-generated DNA. HIV-1 synthesizes the DNA as two discrete half-genomic segments. A central polypurine sequence initiates the synthesis of the downstream part of the (+)-strand. The upstream tract of the (+)-strand is initiated at the 3'-end of the polypurine, proceeds until the center of the genome and terminates after a discrete strand displacement. This event of the reverse transcription is mediated by the central termination sequence that removes at this stage the HIV reverse transcriptase. Thus, the final product of the (+)-strand replication of the linear DNA has an overlap or flap. The integrity of the polypurine tract and the central termination sequence are essential for the retroviral life and the flap is also involved in the nuclear import of the HIV-1 genome. ►acquired immunodeficiency, ►lentiviruses; Whitwam T et al 2001 J Virol 75:9407.

DNA Forms: Form I is superhelical and circular, II nicked circular, III linear. These conformational states affect electrophoretic mobility in gels. ►nick, ►electrophoresis

DNA Function: Music of Life—representation of transcription, translation, metabolism and replication in musical terms. German composer Thilo Krigar is creating DNA functions in concert: <http://www.dna-in-concert.de>.

DNA, Genomic: Natural and complete nucleotide sequences of genes, introns included.

DNA Glycosylase: ►glycosylase

DNA Grooves: B DNA double helix displays a 3.4 nm pitch including a wider (major) and a narrower (minor) groove (furrow) along its helical structure. Molecules that specifically recognize base pairs in the major or minor groove provide means of regulation of gene activity. The various binding proteins and transcription factors have been and are still thoroughly investigated but so far, no general recognition system between nucleotide base (pairs) and amino acids are known. The four base pairs (A·T, T·A, G·C, C·G) may be distinguished in the major groove on the basis of hydrogen binding properties (see Fig. D70).

Oligonucleotides may recognize the double helix and form triple helix structures but do not provide sufficient single base (pair) specificity. Some antibiotics (such as distamycin [$C_{22}H_{27}N_9O_4$]) modified by replacing the pyrrole (Py) rings with an imidazole (Im) ring provided limited ability to recognize G·C

pairs. Two distamycins effectively recognize, however side-by-side A·T sequences in the minor groove. In 1998, new recognition codes were reported capable of distinguishing all four base pairs in the minor groove: Py/Im→ C·G, Im/Py→ G·C, Hydroxypyrrole (Hp)/Py→ T·A and Py/Hp→ A·T. This development does not provide discrimination among human genes because for that 17 base pairs would be needed. By further progress new approaches may, however be opened not just to gene regulation but also for drug design. ►DNA types, ►pitch, ►Watson and Crick model; Hélène C 1998 Nature [Lond] 391:436; White S et al *ibid.* 468.

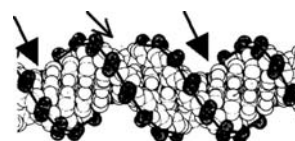


Figure D70. DNA grooves. Two major and one minor groove are shown in this space-filling model of DNA

DNA Gyrase: A DNA-binding protein, a topoisomerase, controlling coiling, site-specific nicking, and it is functional in replication, transcription, recombination and DNA repair. These enzymes are members of the DNA topoisomerase family. ►topoisomerase, ►nick; structure: Costenaro; L et al 2005 Structure 13:287.

DNA, Heavy Chain: The chains of a DNA duplex can be separated and annealed with poly-inosine-guanine (PI-G). The chains rich in cytosine bind more of PI-G and form a heavier band and sediment faster upon ultracentrifugation in CsCl. Therefore, it is called heavy or C chain whereas the complementary chain is called light chain (W). The density of DNA can be increased also by substituting bromodeoxyuridine in place of thymidine or by (N^{15} or C^{13}) heavy isotopes. ►bromouracil, ►ultracentrifuge

DNA Heteroduplex: ►heteroduplex, ►models of recombination

DNA Hybridization: Annealing single-stranded DNA with complementary single-stranded DNA or RNA either for measuring the degree of homology or for labeling it before selective isolation. Either hybridization can be carried out in a solution or with DNA immobilized on a membrane filter (Southern blots) or in situ, in denatured chromosomes or in microbial colonies (dot blots). The material intended for hybridization is labeled either radioactively (3H , ^{14}C , ^{32}P) or with biotin and fluorescent dyes. ►chromosome painting, ►FISH, ►in situ hybridization, ►Southern blotting, ►Grunstein–Hogness screening, ►Benton–Davis plaque hybridization,

►Northern blot; Marmur D, Lane J 1960 Proc Natl Acad Sci USA 46:453; Doty P et al 1960 Proc Natl Acad Sci USA 46:461; Hall BD, Spiegelman S 1961 Proc Natl Acad Sci USA 47:137.

DNA Immunization: ►immunization genetic, <http://www.genweb.com/Dnavax/dnavax.html>.

DNA Index: It reveals the amount of DNA in a cell relative to pre-S phase diploid cell (= 1). ►cell cycle

DNA Isolation: ►DNA extraction

DNA Junction: Three-way or four-way arrangements are generated by recombination (Holliday junction) or repair of the DNA (see Fig. D71).

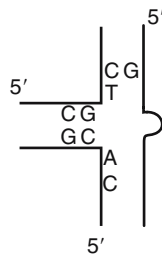


Figure D71. DNA junction. One type of three-way junction. (Modified after Assenberg R et al 2002 Nucleic Acids Res 30:5142)

DNA Kinking: The regulation of transcription depends on protein-induced localized modification of the DNA structure (bending). This modification depends on the nature of the proteins recruited for the tasks and the base sequences in the DNA. The bases stacked in the major and minor grooves ('the rungs') of the helix may cause four major categories of architectural alterations relative to each other: (1) twist [slight rotation of the rung], (2) roll [slightly lifting the broader side of a rung], (3) tilt [uplifting the rung at one side], and (4) rise [slipping the rungs away from each other]. The elastic properties of the DNA determine how it is wrapped around histones in the nucleosomal structure, the packing of phage DNA into capsids, super-coiling, DNA looping, etc. These changes are reversible and depend on the physical environment of the DNA. ►nucleosome, ►super-coiling, ►DNA looping, ►triple helix formation, ►DNA bending; Beylot B, Spassky A 2001 J Biol Chem 276:25243.

DNA Knots: Catenated (interlocking ring) DNA. ►catenated, ►catenene, ►knotted circle; Podtelezhnikov AA et al 1999 Proc Natl Acad Sci USA 96:12974.

DNA Library: A collection of restriction endonuclease-generated fragments, each containing different segments of the genome. ►restriction enzyme, ►fragment recovery probability

DNA Ligases: Enzymes joining DNA termini in the cell nucleus. DNA ligase I (125 kDa) is the most important ligase in animal cells, DNA ligase II (72 kDa) and DNA ligase III (100 kDa) have minor role in mammalian cells. DNA ligase IV mediates joining of the ends of DNA in eukaryotic non-homologous recombination. Other organisms have different DNA ligases. Bloom's syndrome and acute lymphoblastic leukemia are caused by DNA ligase deficiency. ►vectors, ►Bloom's syndrome, ►lymphoblastic leukemia, ►deoxyribozyme, ►non-homologous recombination, ►Ku, ►double-strand break; Bentley D et al 1996 Nature Genet 13:489; Pierce AJ, Jasin M 2001 Molecular Cell 8:1160; DNA ligase I structure: Pascal JM et al 2004 Nature [Lond] 432:473, history of discovery: Kresge N et al 2007 J Biol Chem 282(2):e1.

DNA, Light Chain: ►DNA, ►heavy chain

DNA Likelihood Method: A type of maximum likelihood procedure for the calculation of branch length in evolutionary trees. ►evolutionary distance, ►evolutionary tree, ►unrooted evolutionary trees, ►least square methods, ►neighbor joining method, ►four-cluster analysis, ►minimum evolution methods

DNA Looping: ►looping of DNA, ►LCR

DNA Machine: A short DNA sequence capable of binding to protein/proteins and thus regulating gene expression.

DNA Markers: Special isolated or identified DNA sequences such as restriction fragments, RAPDS, microsatellites, minisatellites, EST and other sequences which can be used as probes or followed by molecular or genetic/molecular analysis. terms under separate entries.

DNA Methylation: ►methylation of DNA

DNA Methyltransferase (DNMT): ►methyltransferase DNA, ►methylation of DNA

DNA Microarray: ►DNA chips, ►microarray hybridization

DNA Mobility Shift: ►gel retardation assay

DNA Modification: ►methylation of DNA, ►restriction enzymes, ►5-azacytidine

DNA Mutation: ►mutation spontaneous

DNA, Native: The hydrogen bonds between the two strands are intact. ▶[Watson and Crick](#)

DNA Nicking and Closing: ▶[topoisomerases](#)

DNA, Non-Genic: ▶[non-genic DNA](#)

DNA, Nonpermuted: A nonpermuted DNA is terminally redundant, e.g., 123456789012 and all molecules have the same sequence. ▶[DNA permuted](#)

DNA Overhang: In a double-stranded DNA one of the chains protrudes at the end as shown. Such a structure is frequently generated by restriction endonuclease cuts (see Fig. D72). ▶[restriction enzyme](#)

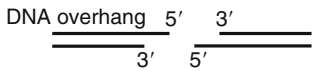


Figure D72. DNA overhang

DNA Packaging: The insertion of a piece of (concatameric) DNA into a phage capsid. ▶[packaging of DNA](#), ▶[packing ratio](#), ▶[condensation of chromosomes](#)

DNA Pairing: The formation of hydrogen bonds between complementary bases of two single-stranded DNA. ▶[DNA](#), ▶[Watson and Crick model](#), ▶[hydrogen pairing](#)

DNA Passenger: ▶[passenger DNA](#)

DNA, Permuted: Phage DNA may be repetitious as the concatameric molecules cut off at different positions but to the same length. Therefore, collections of these molecules may appear (with numbers substituted for nucleotides). ▶[DNA non-permuted](#), ▶[redundant Permuted sequences](#)
123456789012 345678901234 567890123456

DNA Photolyase: It splits pyrimidine dimers during direct repair. DNA repair; ultraviolet light; pyrimidine dimer; cyclobutane dimer; cryptochromes.

DNA Polarity: The first base in a DNA chain has a 5' phosphate (triphosphate) at the beginning and the subsequent bases are added to it at the 3'-OH position (see Fig. D73). From the nucleotide triphosphate, two phosphates are removed and the third one (α group) forms a phosphodiester linkage with the first one. Thus the chain growth is $3' \leftarrow 5'$. The complementary DNA chain also has polarity and the two run antiparallel

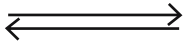


Figure D73. Opposite polarity

DNA Polymerases: prokaryotes and eukaryotes have several DNA polymerase enzymes with polymerase (and exonuclease) functions (see Tables D4 and D5).

DNA pol III holoenzyme forms a particle of 10 subunits, and it is responsible for the replication of the prokaryotic chromosome. The T7 phage DNA polymerase, encoded by gene 5 is 80 kDa. It associates with the bacterial-coded thioredoxin and polymerizes thousands of nucleotides. It also requires the hexameric protein DNA polymerase III holoenzyme and forms a particle of 10 subunits and it is responsible for the replication of the prokaryotic chromosome.

Prokaryotic DNA polymerase III displays no similarity with other polymerases yet the crystal structure of its active site is similar to DNA polymerase β and nucleotidyltransferases (Lamers MH et al 2006 Cell 126:881). The T7 phage DNA polymerase, encoded by gene 5 is 80 kDa. It associates with the bacterial-coded thioredoxin and polymerizes thousands of nucleotides. It also requires the hexameric protein of T7 primase-helicase and a T7 single-strand binding protein that controls at the replication fork the synthesis of the leading and lagging strands. Prokaryotic DNA polymerases IV (DinB) and V (UmuD₂ complex) enzymes have mutator function in the SOS repair pathway. The

Table D4. DNA polymerases of eukaryotes

| pol α | pol β | pol γ | pol δ | pol ϵ |
|---|---|--|--|--|
| 3 subunits 1 80–300 kDa nuclear lagging str. primase & 3' \rightarrow 5' polymerase. no exonuclease | 1 subunit 40 kDa repair nuclear, no exonuclease | 2 subunit ~180–300 kDa polymerase and exonuclease in mitochondria | 1 subunit ~170–230 kDa nuclear leading strand replicase, 3' \rightarrow 5' exonuclease | 1 subunit 250 kDa 3' \rightarrow 5' leading nuclear polymerase & 3' \rightarrow 5' exonuclease |

Table D5. DNA polymerases of prokaryotes

| Pol I | Pol II | Pol III |
|-------------------|----------------------|-------------------|
| 109 kDa | 90 kDa | 1,000 kDa |
| 5'→3' polymerase | 5'→3' polymerase | 5'→3' polymerase |
| 3'→5' exonuclease | 3'→5' exonuclease | 3'→5' exonuclease |
| 5'→3' exonuclease | No 5'→3' exonuclease | None |

majority of the pol IV mutations are small deletions (Kobayashi S et al 2002 J Biol Chem 277:34087). *Saccharomyces cerevisiae* pol δ with a methionine (M) replacing conserved leucine (L) 612 at the polymerase active site has normal processivity and slightly higher polymerase specific activity. The substitution mutant L612M pol δ also has normal 3' exonuclease activity, yet it is impaired in partitioning mismatches to the exonuclease active site, thereby reducing DNA synthesis fidelity. Error rates in vitro for L612M pol δ are elevated for both base substitutions and single base deletions but in a highly biased manner (McElhinny SAN et al 2007 J Biol Chem 282:2324).

Recently, **pol ζ** was discovered in yeast (Rev3, Rev7); it does not have 3'→5' exonuclease function although it is a repair enzyme that can bypass more efficiently thymine dimers than the other polymerases. Pol ζ is error-prone, yet it has an essential role during the development of mouse embryos. DNA **pol η** (encoded by gene RAD30) of yeast has function similar to pol ζ but it is distinct from it.

Pol η bypasses cis-syn thymine dimers efficiently and accurately. **Pol ι** (iota) has a high rate of misincorporation of deoxynucleotides opposite especially across pyrimidines. The human Pol ι requires Hoogsteen base pairing for correct replication (Johnson RE et al 2005 Proc Natl Acad Sci USA 102: 10466). DNA pol ζ immediately follows and extends the misrepair although it alone does not insert mispaired bases. Pol ι also has base excision repair activity. DNA polymerase **pol θ** , cannot bypass thymine dimers or 6-4 photoproducts or abasic sites. Its error rate with deoxyribonucleotides is 10^{-3} to 10^{-4} . It incorporates two adenines opposite the thymine dimer. It is also responsible for C/G mutations during somatic hypermutation of immunoglobulin G genes (Masuda K et al 2005 Proc Natl Acad Sci USA 102:13986). Special DNA polymerases are the telomerase and the terminal nucleotide transferase. **Polymerase κ** is essential for DNA replication of

yeast and humans, along with pol α , δ and ϵ , and it mediates sister chromatid cohesion. Enzyme pol κ , with some homology to pol β , in cooperation with other proteins mediates also in DNA repair. **Polymerase λ** is involved in base excision repair. **Polymerase μ** mediates non-homologous end joining. **Polymerase σ** has a function in sister chromatid cohesion. **REV1** polymerase mediates bypass synthesis and **TdT** is involved in antigen receptor diversity. Pol5 (**DNA polymerase ϕ**) of yeast is localized in the nucleolus and it is involved in the synthesis of rRNA (Shimizu K et al 2002 Proc Natl Acad Sci USA 99:9133). The human genome encodes at least 15 DNA polymerases (see Fig. D74).

The catalytic domains of the DNA polymerases are well conserved although the other structural domains are variable. Improved processivity for PCR can be conveyed to DNA polymerase by fusing the enzymes to double-strand-binding proteins (see Fig. D75) (Wang Y et al 2004 Nucleic Acids Res 32:1197). This modification does not reduce catalytic activity of enzyme stability ▶**pol enzymes**, ▶**DNA replication in eukaryotes and prokaryotes**, ▶**recombination**, ▶**DNA repair**, ▶**mutator genes**, ▶**ABC excinucleases**, ▶**reverse transcription**, ▶**PCNA**, ▶**sliding clamp**, ▶**replication fork**, ▶**replisome**, ▶**telomerase**, ▶**terminal nucleotidyl transferase**, ▶**thymine dimer**, ▶**DNA repair**, ▶**reverse transcriptases**, ▶**cis-syn dimer**, ▶**DNA repair**, ▶**error-prone repair**, ▶**X-family of DNA polymerases**, ▶**Y-family of DNA polymerases**, ▶**sister chromatid cohesion**; Patel PH; Loeb LA 2000 Proc Natl Acad Sci USA 97:5095; Zhang Y et al 2000 Nucleic Acids Res 28:4147; Zhang Y et al 2001 Nucleic Acid Res 29:928; Guo D et al 2001 Nucleic Acid Res 29:2875; Glover BP, McHenry CS 2001 Cell 105:925; Sutton MD, Walker GC 2001 Proc Natl Acad Sci USA 98:8342; Burgers PMJ et al 2001 J Biol Chem 276:43487; Hübscher U et al 2002 Annu Rev Biochem 71:133; Rattray AJ, Strathern JN 2003 Annu Rev Genet 37:31.

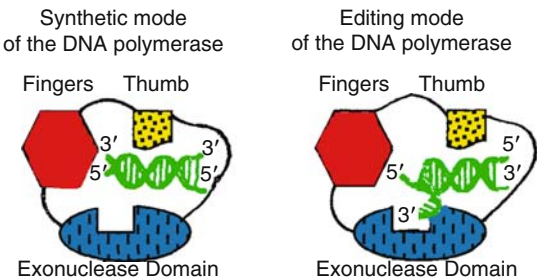


Figure D74. DNA polymerase functions. Abstract, generalized representation of the polymerase and the exonuclease (editing) functions of DNA polymerases. (Modified after Steitz TA 1999 J Biol Chem 274 17395)

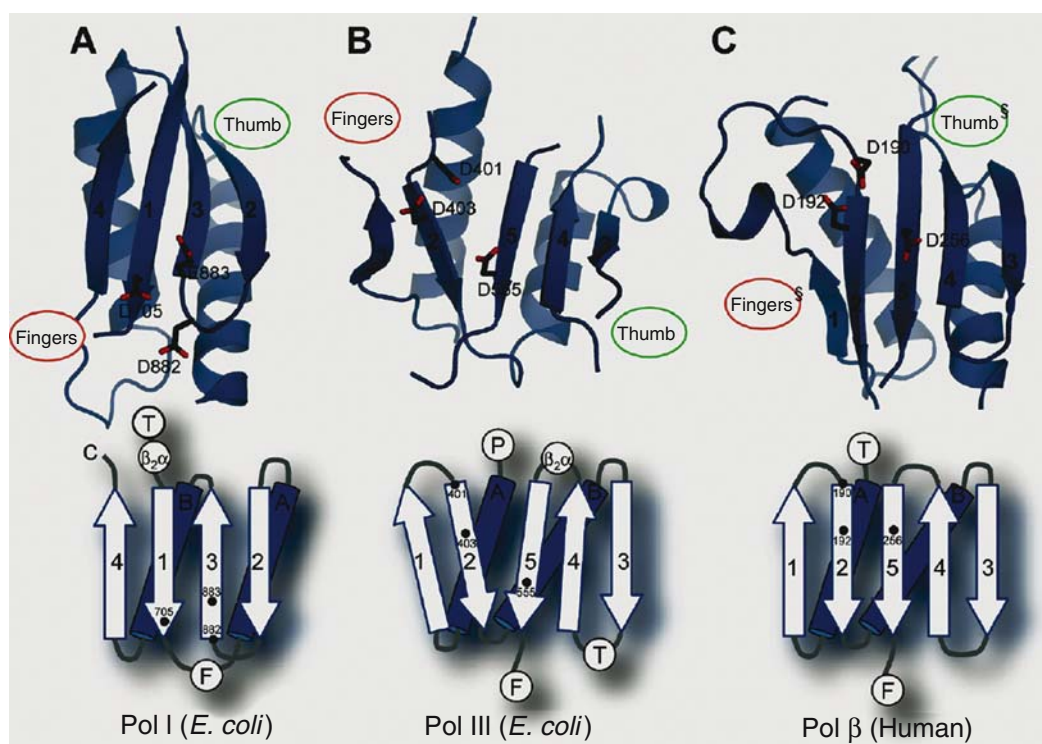


Figure D75. Comparative study of the active sites of *E. coli* DNA polymerase III and human DNA polymerase β . (Courtesy of M.H. Lamers and John Kurijan)

DNA Polymorphism: ▶DNA fingerprinting, ▶RFLP, ▶SNIPs, ▶microsatellites, ▶band-sharing coefficient; Satta Y 2001 Genes Genet Syst 76[3]159.

DNA Primase: ▶primase

DNA Probe: A radioactively or non-radioactively (fluorochrome) labeled single-stranded DNA sequence that anneals specifically to its homologous, complementary DNA or RNA tract and thus, by virtue of the label identifies the homologous strand. ▶Southern hybridization, ▶dot blots, ▶Northern hybridization, ▶heterologous probe, ▶insertional mutagenesis, ▶nick translation, ▶labeling, ▶fluorochrome, ▶FISH

DNA Proofreading: ▶proofreading, ▶DNA repair

DNA Rearrangements: ▶phase variation, ▶mating type determination in yeast, ▶transposons, ▶insertion elements, ▶recombination, ▶immunoglobulins, ▶and chromosome rearrangements

DNA Reassociation Kinetics: ▶ c_0t curve

DNA Relaxing Enzymes: ▶topoisomerase, ▶gyrase

DNA Renaturation: The reannealing of denatured strands. ▶renaturation, ▶annealing, ▶and denaturation

DNA Repair: It may be brought about by different mechanisms. The frequency of single-strand breaks/Gy is about 25 times higher than that of double strands of DNA. The bulk of information is available from prokaryotic systems. The direct repair and the excision repair systems are error free because in the former, no new DNA synthesis is required and in the latter the undamaged DNA strand provides a normal template so there is no increase in errors beyond the normal level for the polymerase involved. The *SOS repair* is an error-prone repair mechanism that is operating when structural distortions block the path of the regular DNA polymerase and the enzyme is stalled and in the distress (lacking appropriate template), incorporates nucleotides in an unorthodox manner thus leading to mutation.

I. DIRECT REPAIR systems remove pyrimidine dimers (cyclobutane dimers) by activating splitting enzymes, photolyases, upon exposure to visible light (Light repair). These enzymes contain chromophore cofactors, such as reduced flavin adenine dinucleotide (FADH₂) and folate to absorb light. The *Bacillus subtilis* spore photoproduct lyase breaks between C–C bonds of 5-thymine-5,6-dihydrothymine, rather than cyclobutane dimers. Another direct repair enzyme is O⁶-methylguanine methyltransferase that

accepts at a cysteine site an O⁶ alkyl group from mutated guanylic acid or other methylated bases and restores the normal purine at the expense of its own inactivation. Direct repair does not involve any “unscheduled” DNA synthesis. Prokaryotes have two, mammals have only one repair methyltransferase.

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II. EXCISION REPAIR SYSTEMS involve various and limited amounts of unscheduled DNA synthesis. 1. *Mismatch repair*: MutS protein binds to various mismatched bases. MutH protein binds to a GATC tract in the DNA and MutL protein links the other proteins into a repair complex. The dam methylase (*dam*) enzyme recognizes the old DNA strand at replication and methylates it at a C site within the 5'-GATC tract. At that time, the nascent DNA strand is still unmethylated. Mismatches are recognized (G–T well, C–C, poorly) and repaired within a 1 kb range of the GATC sequence as long as the new strand is not yet methylated. The MutH protein is an endonuclease that cuts 5' to GATC. The nicked strand then unwinds with assistance of helicase II (*uvrD* gene product). A single-strand binding protein (SSB, *ssb*) braces the site, and the defective single strand is sliced off 3' to 5' by exonuclease I (*sbcB*) through the defect. On the 3' side of GATC the mismatch is removed either by exonuclease VII or *recJ* 5' to 3' exonuclease. Then DNA polymerases (*pol I*, *pol II* or *pol III*) repair the gap and the new ends are ligated (*dnaL*). 2. *Base excision repair* (BER): cutting the N-glycosyl bonds by DNA glycosylases and leaving behind apurinic and apyrimidinic (AP) sites lifts defective bases out. The glycosylases remove deaminated cytosine (= uracil), deaminated adenine (= hypoxanthine) bases alkylated by alkylating mutagens, etc. Hydrolytic deamination of cytosine may occur 100 to 500 times per day in a human cell and 5-methylcytosine may be deaminated about 3-times more frequently (Shen JC et al 1994 *Nucleic Acids Res* 22:972). Genes *ada* and *alkA* of prokaryotes are involved. After the base is removed, AP endonucleases cut out the deoxyribose phosphates and possibly more nucleotides. The BER pathway corrects more than 10⁴ lesions daily in each human cell. In humans, several glycosylases have been mapped ►[glycosylases](#). The gap is filled in by pol I or pol β and ligation completes the repair process. Pol β is a highly error-prone polymerase. In mammalian cells, apurinic/apyrimidinic nuclease (APE1) may correct the process by exonucleolytically removing the incorrect bases from the ends (Chou KM, Cheng Y-C 2002 *Nature [Lond]* 415:655). Some of the uridines in the DNA may be the results of replicational errors or by deamination of C. Uridine nucleotide glycosylase (UNG) also plays important role in generating antibody diversity and cancer (Rada C et al 2002

Current Biol 12:1748). Another enzyme SMUG, with little homology to UNG, also has uracil-DNA glycosylase activity with preference to single-stranded DNA (Haushalter KA et al 1999 *Current Biol* 9:1743). Thymine-DNA glycosylase (TDG) excises from T:G mispairs. In mammalian cells, about a dozen different glycosylases are known. Oxidative damage to guanine may commonly produce 8-oxoguanine, which also requires removal. The MYH DNA glycosylase removes adenine from 8-oxoguanine:A mispairs (Fromme JC et al 2004 *Nature [Lond]* 427:652). Mut T-encoded hydrolase removes 8-oxo-deoxyguaninetriphosphates from the nucleotide pool. 3-methyl-DNA glycosylases (MPG) remove methylated purines, importantly me-A, which is very toxic. Transfer of the methyl group to cysteine residues by a specific methyltransferase repairs the highly mutagenic O⁶-meG. Mammalian cells have dioxygenases, which demethylate 1-methyl adenine and 3-methyl cytosine (Duncan T et al 2002 *Proc Natl Acad Sci USA* 99:16660). Oxidases are known which remove oxidized pyrimidines. The prokaryotic pol I has an intrinsic proof-reading exonuclease activity. The BER repair depends on the relative activities of APE, ARP and POL β , various replication factor proteins in a sequential manner and finally on DNA ligase (Sukhanova MV et al 2005 *Nucleic Acids Res* 33:1222). 3. *Nucleotide excision repair* (NER): damages to the DNA involving longer tracts are cut at two sites by the ABC excinuclease system and the intervening sequences are removed. This complex is encoded by genes *uvrA* (coding for the ATPase subunit of endonucleases), *uvrB* and *uvrC* (coding for the endonuclease subunits) of the excinuclease of *E. coli*. UvrD is a helicase that releases the excised oligomer. DNA pol I carry out repair synthesis and the M_r 75 ligase ties the ends. Excision repair may involve just a few and up to a few thousands of nucleotides. The gaps are filled in by any of the four DNA polymerases of prokaryotes. The human excinuclease complex contains single or combined activities of 16 polypeptides. In humans, BER is the only mechanism to escape UV-caused genetic damage. 4. *Transcription-coupled repair*: is a type of excision repair when the pyrimidine dimers are more readily removed from the transcribed strand than from the non-transcribed strand. This type of repair may be coupled with the more common excision repair system (Svejstrup JQ 2002 *Nature Rev Mol Cell Biol* 3:21). Such a mechanism was first detected in *E. coli* but it turns out that the failure of this mechanism is the most common cause of base mismatches in colorectal human cancer. The vertebrate enzyme DNA polymerase β is involved in excision repair and in the release 5'-terminal

deoxyribose phosphates from incised apurinic-apyrimidinic sites. The repair is confined to the transcribed strand and in mammals to genes transcribed by pol II. In humans, there is a requirement for the transcription–repair coupling protein (TRC). The Cockayne syndrome is a defect of two TRC factors. *E. coli* also requires a TRCF encoded by *mfd* gene. The crystal structure of TRCF sheds light on its function (Deaconescu AM et al 2006 Cell 124:507). The human diseases Xeroderma pigmentosum F and Trichothiodystrophy are excision repair defects. Human DNA excision repair also requires XPA, a zinc finger protein and HSSB, a human single-strand binding protein, RPA another damage-recognition protein, the transcription factor TFIIH with multiple subunits of helicase, Zinc finger, kinase, and cyclin functions. Furthermore XPC, a ubiquitin, XPF (5' cut) and XPG (3' cut) nucleases, RFC an ATPase, PCNA, an auxiliary protein to DNA polymerase δ , repair polymerases ϵ/δ and DNA ligase are used (Sancar A 1996 Annu Rev Biochem 65:43; Wood RD 1996 Annu Rev Biochem 65:135).

III. SOS REPAIR is required when there is extensive damage to the DNA (presence of cyclobutane rings and adducts formed by UV light, cross-linking caused by chemical mutagens, etc.) that prevent the movement of the DNA polymerase III enzyme along the strands and the template cannot lend itself for accurate copying. The repair system is in distress and becomes error-prone. Shortly after the damage has taken place the activity of the RecA protein increases up to 50 times. Next, the LexA repressor is cleaved and that initiates the activity of a series of genes including the excinuclease system, *UmuC* and *UmuD* (repair functions), *hima* (with multiple functions in replication, recombination and regulation). The DinB prokaryotic and eukaryotic homologs make replication by polymerase IV error prone. Rad30A operates the error-free polymerase η that bypasses the UV lesions. Rev1 deoxycytidyl-transferase also assists in the bypass but it is error-prone. LexA repression targets a SOS box (containing a consensus CTG-N₁₀-CAG) in the vicinity of the promoter of its objects. Most commonly, dAMP is inserted opposite the abasic site. Eukaryotic DNA polymerase ζ and η can bypass pyrimidine dimers but pol ζ may be hypermutagenic. The SOS repair usually involves extensive DNA repair synthesis. SOS repair is considered to follow either the pathway of *damage avoidance* (DA), i.e., the complementary strand is used to rescue the blocked replication fork or by relies on *translesion synthesis* (TLS), i.e., the repair enzyme reads through the replication block. The block generated by the DNA-damaging agent determines the route of the SOS repair. In bacteria, the DNA polymerase V in the presence of protein UmuD',

RecA and a single-strand DNA binding protein produce point mutations at a frequency of 2.1×10^{-4} per nucleotide, an increase of ~40-fold over that of the effect of DNA polymerase III holoenzyme. About 53% of the mutations are transversions. ▶*translesion*; Johnson RE et al 1999 Proc Natl Acad Sci USA 96:12224; Sutton MD et al 2000 Annu Rev Genet 34:479; Aartsen A, Michiels CW 2006 Trends Microbiol 10:421.

IV. RECOMBINATIONAL REPAIR makes corrections by exchanging the defects with correct sequences through recombination (gene conversion). In double-stranded human DNA the observed breakage rate 5.8×10^{-3} /Mbp/Gy was found for both 80 and 160 Gy and about 75% rejoined correctly within 2 h (Lobrich M et al 1995 PNAS 92:12050). RecA/Rad51 and Rad52 (in yeast) have pivotal function in homologous recombination repair. Rad52 promotes the end-to-end joining of DNA. Ku70 and Ku80 proteins protect the ends from nuclease degradation. DNA ligase IV, XRCC, Mre11, Rad50 mediate repair of DNA double-strand breaks. Non-homologous DNA end-joining (NHEJ) requires the presence of DNA-dependent protein kinase, XRCC4 and ligase IV. NHEJ is generally necessary for V(D)J recombination in generating the appropriate immunoglobulins. In vertebrates, soon after double-strand breaks, histone H2AX is phosphorylated and this is followed by accumulation of repair proteins. Phosphorylation of H2A is followed by loss of H2B and H3 histones. Histone loss also requires the presence of MRX damage sensor and INO80 nucleosome remodeling complex. MRX and chromatin remodeling are required for efficient recombination (Tsukada T et al 2005 Nature [Lond] 438:379). At this stage nuclease-sensitivity is increased (see Fig. D76).

In *Drosophila*, chromosome breakage, induced by the P transposable element, is repaired by recombination and the efficiency of this repair is up to five times higher when the homologous sequence was syntenic within, at any position, of the X-chromosome rather than somewhere in trans position, in an autosome. In double-strand repair, the DNA remains in a fixed position within the nucleus and 30 min after the breakage the Mre repair enzyme moves to the site of the damage. In bacteriophage T4 DNA replication and double-strand break repair are closely coupled. ▶*histone variants*, ▶*MRX*, ▶*INO80*

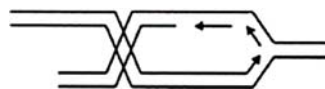


Figure D76. Recombination repair

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V. TRANSCRIPTION-COUPLED REPAIR. When RNA polymerase (RNAP) encounters DNA damage that blocks continuation of transcription the bacterial Mfd protein can remove the RNAP and it recruits nucleotide excision repair proteins to the defective site. Mfd can block transcription to prevent synthesis of RNA that would carry downstream defect. Mfd can also remove proteins that would block transcription and thus represses “roadblocks” and reinstates transcription (Smith AJ, Savery NJ 2005 *Nucleic Acids Res* 33:755).

►recombination, molecular mechanisms in prokaryotes, ►DNA polymerases, ►P element, ►Mre11, ►V(D)J, ►XRCC, ►RAD, ►DNA ligase, ►sister chromatid exchange, ►double-strand breaks, ►histone variants; Cox MM et al 2000 *Nature* 404:37; Cox MM 2001 *Proc Natl Acad Sci USA* 98:8173; George JW et al 2001 *Proc Natl Acad Sci USA* 98:8290; Bleuit JS et al 2001 *Proc Natl Acad Sci USA* 98: 8298; Kuzminov A 2001 *Proc Natl Acad Sci USA* 98:8461; Fukushima T et al 2001 *J Biol Chem* 276:44413.

Retrotransposons or parts of them may be inserted into double-strand breaks and heal the defects. It is not known how frequent such events may be, but most eukaryotic genomes have a large number of retrotransposon elements and this repair function may justify their evolutionary maintenance. Specialized retroposons such as HeT-A and TART of *Drosophila* or the Ty5 yeast element may use their reverse transcriptase and RNA template to heal telomeres in case the telomeres are shortened by aging or if breaks damage them. The repair mechanisms of eukaryotes are much less well understood than in prokaryotes. The numerous *RAD* genes of yeast control radiation responses and are involved in repair. Short-patch DNA repairs (such as damages caused by alkylating agents) requires the function of DNA polymerase β , a ubiquitous housekeeping enzyme. Repair of UV lesions involves DNA polymerase ϵ . For e.g., xeroderma pigmentosum F, a human hereditary condition controlled by several dominant and recessive genes the defect in excision repair of UV lesions may be connected with polymerase ϵ . It has been estimated that each cell under normal conditions loses more than 10,000 bases from the spontaneous breakdown of DNA, and the damaged spots have to be repaired. The efficiency of repair in eukaryotes depends on the time available before the onset of the S phase of the cell cycle. Proteins p53, p21, PCNA and other cellular proteins may have cell cycle-stalling functions. The efficiency of repair varies at different sites within a gene.

Generally, areas near active genes are more efficiently repaired than in inactive regions. The most rapid repair is found in the transcribed strands of

active genes. The DNA repair systems play a role also in the cell cycle and tumorigenesis. In 1994, *SCIENCE* magazine declared DNA repair enzymes the molecules of the year. DNA repair in eukaryotes is complicated by the nucleosomal organization of the chromatin. Progress in DNA sequencing identified ~130 genes involved in human DNA repair. (Wood RD et al 2001 *Science* 291:1284, *Biological Responses to DNA Damage* 2001 Cold Spring Harbor Symp Quant Biol Vol. 65).

Detection of DNA damage is important in mutation analysis, carcinogenesis, cancer therapy, and aging, etc. The nature of the lesions can vary from base modifications, strand breaks to DNA-protein and DNA-chemical crosslinks. Gas chromatography–mass spectrometry, high performance liquid chromatography, immunoassays, etc. have been used for the identification of modified bases. A newer method, using immunochemical recognition and capillary electrophoresis and laser-detected fluorescence detection may identify lesions with a limit of 3×10^{-21} moles is available (Le XC et al 1998 *Science* 280:1066). ►excision repair, ►glycosylases, ►X-ray repair, ►mismatch repair, ►bypass repair, ►radiation sensitivity, ►mutagenesis, ►DNA ligases, ►NA-PK, ►PCNA, ►p53, ►p21, ►xeroderma pigmentosum, ►ataxia telangiectasia, ►Fanconi anemia, ►Bloom syndrome, ►Cockayne syndrome, ►colorectal cancer, ►aging, ►RAD50, ►RAD28, ►Ku, ►NHEJ, ►TRCF, ►retrotransposons, ►retroposons, ►Ty, ►mating type determination in yeast, ►chromatin assembly factor, ►preferential repair, ►alkyltransferases, ►proofreading, ►postmeiotic segregation, ►photoreactivation, ►Mer⁻ phenotype, ►Mex, ►chromatography, ►capillary electrophoresis, ►laser, ►SNIPS, ►male recombination, ►HEI, ►UMU, ►translesion, ►SSB, ►RecA, ►DNA polymerases, ►Gy, ►mtDNA, ►XRCC, ►methylguanine-O⁶-methyltransferase, ►unscheduled DNA synthesis, ►PARP, ►RNA repair, ►SSA; Aravind L et al 1999 *Nucleic Acids Res* 27:1223; Kunkel TA, Bebenek K 2000 *Annu Rev Biochem* 69:497; Sutton MD, Walker GC 2001 *Proc Natl Acad Sci USA* 98:8342; Wood RD et al 2001 *Science* 291:1284; Friedberg EC et al 2002 *Science* 296:1627; Rattray AJ, Strathern JN 2003 *Annu Rev Genet* 37:31; Barnes DE, Lindahl T 2004 *Annu Rev Genet* 38:445, DNA double-strand repair: Wyman C, Kanaar R 2006 *Annu Rev Genet* 40:363, break and disease: McKinnon PJ, Caldecott K 2007 *Annu Rev Genomics Hum Genet* 8:37.

DNA Repair Associated Human Disorders: Ataxia telangiectasia, Bloom syndrome, Fanconi anemia, Breast cancer, Cockayne syndrome, De Sanctis–Caccione syndrome, Fanconi’s anemia, Lynch cancer

families, Rothmund–Thompson syndrome, Trichothiodystrophy, Werner syndrome, Xeroderma pigmentosum, Hereditary Nonpolyposis Colorectal Cancer

DNA Repair Synthesis: ► [unscheduled DNA synthesis](#)

DNA, Repetitive: ► [repetitious DNA](#), ► [trinucleotide repeats](#)

DNA Replication Error: It has been estimated that in bacteria the individual nucleotide replacement error is about 10^{-9} to 10^{-10} per generation. ► [replication error](#), ► [error in replication](#), ► [error-prone repair](#), ► [proofreading](#), ► [diversity](#); Kunkel TA, Bebenek K 2000 *Annu Rev Biochem* 69:497.

DNA Replication, Eukaryotes: The mechanism of replication in prokaryotes is better understood because more simple in vitro assay systems are available for the smaller DNAs. In yeast, the replicational origins are called ARS (*autonomously replicating sequences*). Although the genome of the eukaryote, *Saccharomyces cerevisiae* is only about 4 times larger than that of the prokaryote *E. coli*, the former has 400 replicational origins, each including about 300 bp. The yeast ARS are not identical with each other yet they have a short core sequence that is about 11 repeating A = T units. The single replicon of *E. coli* is over 4,000 kb but the yeast replicons are only about 40 kb. The speed of replication in yeast is about 3.6 kb/min but in *E. coli* it is almost 14 times as fast. In the large amphibian genome, it proceeds at a speed of about 1/7 of that of the yeast. If the replication of the toad DNA proceeds only 500 bp/min, it would take more than 20 years to complete an S phase when actually at the gastrula stage it takes about 4 to 5 h because the large genome relies on more than 15,000 replicons. Replication in eukaryotes just like in *E. coli*, proceeds bidirectionally and electron-microscopic examination detects a large number of replication “bubbles” or replication “eyes” that are actually the replicational origins. As the replication within a bubble nears completion the neighboring bubbles coalesce as replication is completed along the length of the chromosome (see Fig. [D77](#)). The molecular structure and function of the eukaryotic replication fork is best understood in the eukaryotic SV40 virus that has a 5,243-bp chromosome with nucleosomal organization.

Human and other mammalian cellular fractions combine with the large T antigen of SV40 and in a plasmid replicate the viral genome, indicating the similarities of the interchangeable elements of the systems. In the presence of ATP, a double hexamer of the viral T antigen (which is an initiator and a DNA helicase) binds to the viral origin and modifies it. This protein–DNA complex then binds the *cellular replication protein A* (RPA, subunits 70, 34 and

11 kDa). RPA/RFA/HSSB is a single-strand binding protein (SSB) similar in function to the helix-destabilizing proteins and in cooperation with the helicases assists in unwinding of the DNA duplex. The T antigen–RPA complex then binds eukaryotic *DNA polymerase α* (in humans with subunits p180 [polymerase], p70 [assembles the primosome], p58 [stabilizer] and p48 [primase]) with RNA and DNA polymerase functions. The sizes of these subunits may be different in other eukaryotes. (Pol α -primase functions may be inhibited by kinase cyclin A-CDK2. In the human ataxia telangiectasia the phosphorylation may be hindered.) This enzyme (pol α) then generates an RNA–DNA primer at the replicational origin. Initiation of replication in mammalian (and presumably other eukaryotic cells) cells requires specific DNA sequences. The *cellular replication factor C* (RFC, subunits 140, 40, 38, 37, 36-kDa) binds to the 3'-end of the new DNA and brings to the growing point the *proliferating cell nuclear antigen* (PCNA, 29-36-kDa) and DNA-polymerase δ (pol δ , catalytic subunit 125-kDa, plus another 48-kDa subunit) then pol α is replaced by pol δ aggregate proceeds in elongating the leading strand. On the lagging strand pol α /primase complex remains active at the initiation of the Okazaki fragments but after a *switch* the RCF/PCN/pol δ complex elongates also this strand. The elongation of the two strands is a coordinated process. After the Okazaki fragments are completed *RNase H* and 5'→3' *exonuclease MF1* (Fen1 and Dna2 helicase) remove the RNA primer and DNA ligase binds the ends of the Okazaki fragments into a continuous strand. Eukaryotic replication also utilizes topoisomerases in a somewhat similar fashion to *E. coli*. When the replication fork encounters transcription initiation complexes, both in yeast (eukaryote) and prokaryotes (T4 page, *E. coli* bacterium) the progress of replication transiently slows down. Actually, DNA replication depends on the cooperation of a multitude of proteins forming higher orders of domains (factories). An experimental study in mouse cells detected about 22 sets of domains of DNA replication. The replication domains are distinct from the 16 higher order transcriptional domains. The late-firing origins of replication are regulated during S phase also by the Mec1 and Rad53 proteins of yeast. The majority of replication models assume that the replication factories move along the DNA. Alternative models suggest that the polymerases are in a fixed position within the factories and rather the DNA moves along and rotates during the process of replication. ► [replication fork](#), ► [replisome](#), ► [clamp-loader](#), ► [DNA replication prokaryotes](#), ► [processivity](#), ► [replication machine](#), ► [SBD](#), ► [DNA replication mitochondria](#), ► [replication during the cell cycle](#), ► [cell](#)

cycle, ▶reverse transcription, ▶DNA-PK, ▶ARS, ▶MCM, ▶Mec1, ▶Rad53, ▶Rad27/Fen1, ▶ribonuclease H, ▶PCNA, ▶Okazaki fragment, ▶CLB and diagrams, ▶ataxia telangiectasia, ▶steric exclusion model, ▶parental histone segregation; Kelly TJ, Brown GW 2000 Annu Rev Biochem 69:829; Kunkel TA, Bebenek K 2000 Annu Rev Biochem 69:497; Bell SP, Dutta A 2002 Annu Rev Biochem 71:333; Gerbi SA, Bielinsky, A.-K 2002 Current Opin Genet Dev 12:243; Johnson A, O'Donnell M 2005 Annu Rev Biochem 74:283, database of DNA replication origin: <http://www.oridb.org/>, <http://www.oridb.org/about.php#full>.

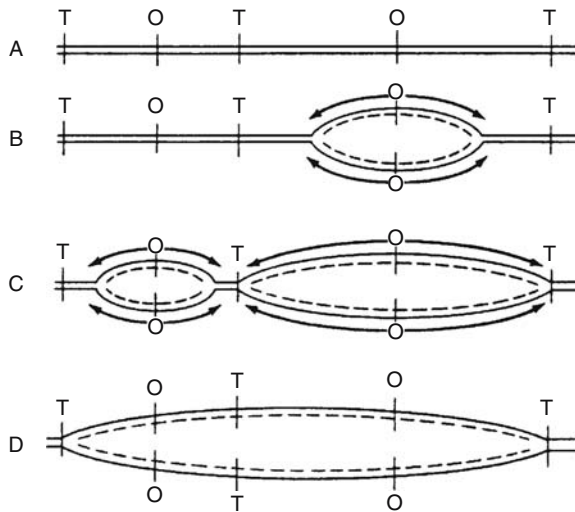


Figure D77. Replication bubbles. Multiple replicons are required for the large eukaryotic genomes. The horizontal lines represent the old DNA strands. The dashed lines show the new, bidirectionally synthesized DNA within the “eyes”. O = origin, T = terminus. Eventually the multiple replication bubbles coalesce. (Redrawn after Huberman JA, Riggs AD 1968 J Mol Biol 32:327)

DNA Replication, Mitochondria: The mammalian mitochondrial DNA is a very short duplex circle (16.5 kbp). In mouse it has two origins of replication, *ori-H* and *ori-L*. Before replication at the *ori-H* site, a displacement loop is formed of the H-strand, apparently to make room for the unidirectional replication. When the H strand loop is about 2/3 complete, replication of the L strand begins. The completion of the replication requires 2 h as it proceeds 270 base/min, i.e., more than two orders of magnitude slower than the process in the *E. coli* chromosome. RNA transcribed on the L strand initiates priming. Replication and transcription appear to be primed by the same process. The transition to L (light)-strand synthesis in human mtDNA is at

the template GGCCG. In the larger mitochondrial DNAs (e.g., in maize the T mtDNA is 540-kbp and N mtDNA is 700-kbp) more *ori* sites are used. The 80-kbp yeast mtDNA has at least seven replicational origins. At the latter, there are 3 shorter G=C rich regions, interrupted by 2 longer A=T rich sequences. In the DNA, ribonucleotides are found, probably leftovers from the RNA primer. The principal replicase enzyme is DNA polymerase γ (180 to 300-kDa) has a very low rate of error (10^{-6}) and this accounts for its high fidelity of replication. Nevertheless, mitochondria accumulate mutations at a higher rate than the nucleus probably because of the high ROS activity. [Note that this is not identical with the γ subunit (52-kDa) of prokaryotic DNA polymerase III coded for by *E. coli* gene *dnaX*]. The *Drosophila* mtDNA does not display D loops. The mtDNA may be divided into the daughter nucleoids either by pinching it off into two approximately equal pieces during the division of the nucleoid (*Physarum*), or, the nucleoid divides into two equal parts at the beginning of splitting of the organelle (*Paramecium*) or the nucleoid divides prior to the beginning of division of the organelle (*Nitella*). Another method of division is that the approximately 30 small mitochondria fuse into a long mitochondrion during the G1 phase of the cell cycle following mtDNA replication. Subsequently, the large mitochondrion divides into two and then fragments further into spherical nucleoids (*Saccharomyces*). Within each nucleoid the number of mtDNA molecules may vary: 3–9 in yeast, 32 in the *Physarum* plasmodium or 2–6 in the mouse nucleoids. The number of mtDNA copies/cell may show substantial variations (≈ 1000 to ≥ 8000). In some fungi (*Candida*), the catenated mtDNA molecules may contain 7 units in a linear array. Most commonly, the mtDNA appears as covalently closed circles yet in some cases (e.g., malignancy), two monomers may be catenated in a double circle or may be double-length chains. The 50 kbp mtDNA of *Tetrahymena* is also linear whereas in the *Paramecia* kinetoplasts mini- and maxicircles occur. ▶DNA replication, ▶DNA polymerases [γ], ▶MRP, ▶CSB, ▶kinetoplast, ▶nucleoid, ▶D loop, ▶R loop, ▶plasmodium, ▶polymerase, ▶catenate, ▶mitochondrial genetics, ▶error in replication, ▶ROS, ▶mitochondrial-control regions; Moraes CT 2001 Trends Genet 17:199; Clayton DA 2000 Hum Reprod 15(2):11; Lecrenier N, Foury F 2000 Gene 246:37; Maier D et al 2001 Mol Biol Cell 12:824; Gensler S et al 2001 Nucleic Acids Res 29:3657; Shadel GS, Clayton DA 1997 Annu Rev Biochem 66:409.

DNA Replication, Prokaryotes: The genetic material must be faithfully replicated to assure heredity.

Unlike in eukaryotes, pyrimidine deoxyribonucleotides are synthesized from ribonucleotide diphosphates rather than triphosphates. The replication takes place in a semi-conservative manner ► **semi-conservative replication**. Although the basic system of the process is very similar from viruses to eukaryotes, variations exist in the mode the final product is made. **Viral DNA REPLICATION**—Some viruses (ϕ X174, G4, M13, fd) contain single-stranded viral DNA (V DNA) and thus the genetic material must be replicated via a complementary strand (C DNA) in the intermediate double-stranded step, the replicative form (RF). All types of DNAs require a replication *origin* (*ori*) to begin the process. A common feature of the origins is that they are rich in A = T to facilitate strand separation required for the semiconservative replication. Not uncommonly in the leading strand there is a prevalence of G over C and T over A in prokaryotes and also in mammals (Touchon M 2005 Proc Natl Acad Sci USA 102:9836). The initiation of replication in the filamentous phage fdV DNA proceeds in opposite direction to the C DNA in the RF from closeby points. In the G4 phage the replicational origins of the V and C strands are widely separated and in its close relative, ϕ X174 there is one origin for the V strand but multiple origins for the C strand. The replication of the about 15 times larger duplex DNA of phage T7 proceeds bidirectionally \leftrightarrow from the origin and so does the *E. coli* duplex DNA that is about 800 times larger.

Since the DNA single strands run antiparallel, simultaneous semiconservative replication has some special requirements (see Fig. D78). This problem is met in a simple way by the 36-kb DNA of adenoviruses: first the replication starts at one of the 3'-ends and when it is completed then the other strand is copied using as template the other OH-end. Here

each 5'-end cytidylic residue of the DNA is bound to a 55 kDa terminal protein. Then an 80-kDa viral protein displaces the end protein and uses the terminal deoxycytidylic acid as the beginning nucleotide template to lay down the first guanosinephosphate.

The 80-kDa protein binds to nucleotides 9 to 18 at the end, and to the next 30 nucleotides host-nuclear-protein factor I is attached. Since the 80-kDa protein had already formed a complex with the polymerase, replication can now proceed.

Replication in *E. coli*—The size of the replicational unit, the *replicon*, in *E. coli* is thus the whole genome (4.7×10^6 bp) whereas in mouse the average length of the about 2,500 replicons is about 150 kb. Despite the large number of replicons in higher eukaryotes the pace of replication is much slower. In *E. coli* about 50 kb/min, but in mouse about 2.2 bp/min.

The single origin in *E. coli* is in the *oriC* locus and the two forks must meet at about half way in the circular DNA. At about 100-kb from this meeting point there are the *ter* (termination) regions of about 23-bp length; *terD* and *terA* signal termination on one of the branches of the fork and *terC* and *terB* on the other. The protein coded by the *tus* gene recognizes the terminators and halts replication after the replication forks passed the *ter* sites. DNA synthesis can be started only if appropriate hydroxyl ends are available because this is a requirement of all DNA polymerases known. In *E. coli* the hexameric *helicase* proteins (330-kDa) are required to unwind the two strands and generate the Y form (see Fig. D79).

This process uses energy liberated by hydrolysis of ATP to ADP. Single-strand binding (SSB) helix-stabilizing proteins that make the bases free to be copied on both old strands assist the unwinding. The unwinding removes the negative supercoiling and may even reverse the original coiling into positive supercoiling. This process has limitations and the tension must be relieved by making single-strand cuts in the still unwound duplex. This nicking is carried out by topoisomerases (swivelases). DNA *topoisomerase type I* enzymes make a single cut in one strand of the helix and then permit the nicked strand to rotate once around the intact strand and then resealing the free ends and relieving negative supercoiling. *Topoisomerases type II* can cut and rejoin both strands of the duplex ahead of the fork and thus remove both negative and positive supercoiling. The latter group of enzymes includes *gyrases*, and can make double cuts and convert positively, supercoiled sections to negatively supercoiled ones. Type II *topoisomerases* can also convert catenated molecules OO into decatenated ones by permitting one duplex ring to slip out from the other \Rightarrow O O. At the bifurcation, one of the templates runs 5' \rightarrow 3' and the other 3' \leftarrow 5' (see Fig. D80).

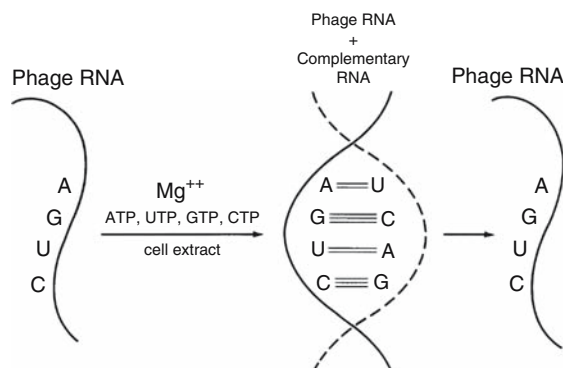


Figure D78. Replication of single-stranded DNA. Broad outline of replication of single-stranded a nucleic acid molecule via a replicational intermediate double-stranded structure. (From August JT et al 1968 Cold Spring Harbor Symp Quant Biol 33:73)

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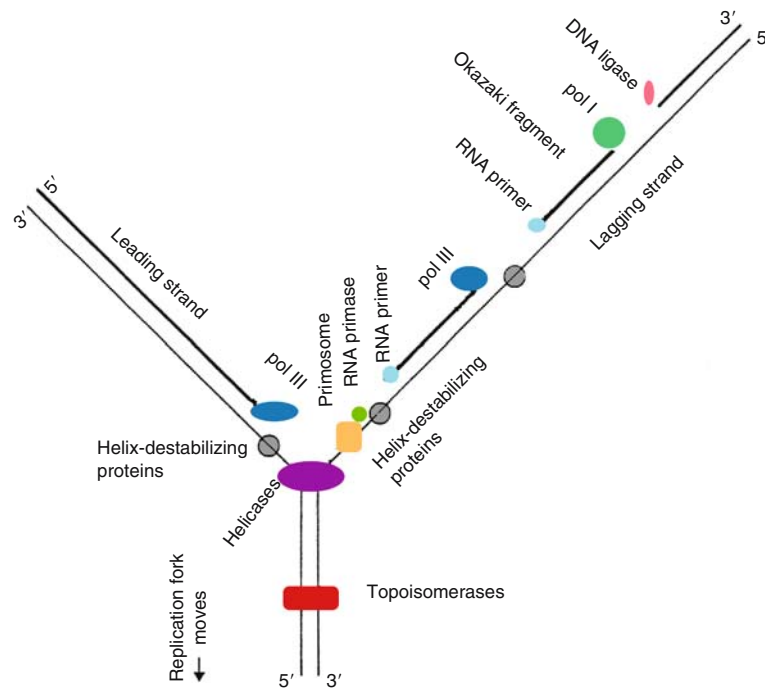


Figure D79. Replication fork. A broad overview of prokaryotic replication fork

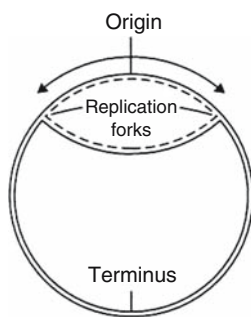


Figure D80. Bidirectional replication

It is simple to proceed with replication of the old strand that faces the fork with its 5'-end because its complementary new strand can be elongated by adding bases to the 3'-OH terminus.

This is called the *leading strand* (left branch of the fork in the diagram). While DNA synthesis (the new strand is shown by the heavier line) is going on, the strands at the fork must be kept separated by the *helix destabilizing proteins* (also called SSB, tetrameric single-strand binding proteins of 74 kDa, shown as small circles). The principal enzyme of replication is *DNA polymerase III* holoenzyme (clamp-loader, 10 to 20 copies per cell). The α subunit of the enzyme (encoded by gene *polC*) carries out polymerization (chain extension) at the 3'-end of both *leading* and

lagging strands (right branch of diagram). The ϵ subunit (gene *dnaQ*) is endowed with a 3' to 5' exonuclease function that reduces errors to 5×10^{-9} from 7×10^{-6} . The two (α and ϵ) together with θ , represent the *pol III core*. The β subunit (gene *dnaN*) apparently keeps the holoenzyme attached to the DNA. Additional polypeptide chains (γ , δ , δ' , ψ , τ and χ) are also part of the huge holoenzyme (≈ 1 MDa).

The holoenzyme may be assembled in different ways under the control of gene *dnaX* products γ and τ . The lagging strand is synthesized in pieces (Okazaki fragments of 1 to 2 kb) because of the lack of a 3'-OH terminus to elongate a continuous strand starting from the base of the fork. Actually, even the leading strand is replicated in a discontinuous manner but it has fewer initiation sites than the lagging strand. The lagging strand requires a primer to be initiated. For primer a short RNA sequence is used. The primosome is a protein complex of helicases (*dnaB*, *dnaC* gene products), pre-priming protein (66-kDa, *dnaT* gene product), *priA* gene product (82-kDa monomer) recognizes primer assembly site and displaces the helix-destabilizing protein, and primase (60-kDa monomer product of gene *dnaG*). The primosome wraps around the DNA Strands. Although this complex is shown only at the base of the lagging strand in the diagram it probably moves along to other locations as its role requires. Since the

lagging strand is synthesized in pieces (Okazaki fragments) that carry RNA at the initiation region (5'), there is a need for other functions. DNA polymerase I (109-kDa monomer product of gene *polA*) serves triple roles. The larger C-terminal domain (68-kDa Klenow fragment, when cleaved by subtilisin) possesses a 5' to 3' polymerase and a 3' to 5' exonuclease functions. It can elongate the 3'-OH DNA or RNA termini by adding 5' nucleotidyl phosphates and can slice off nucleotides in the 3' to 5' direction. The elongation of the new DNA is contingent on the nutritional status of the cell and it is controlled by (p) ppGpp nucleotides (magic spot). Its N-terminal domain (35-kDa) is a 5' to 3' exonuclease, and activity blocked during the polymerization reaction. Thus, pol I can simultaneously extend the Okazaki fragment's 3'-OH end and remove the primer RNA at the 5'-end, and it is capable of the replacement replication (nick translation) that is just needed for making the lagging strand continuous. The 3' to 5' exonucleolytic activity has also the important function of "editing". If it finds "spelling errors" during synthesis, it removes the mismatched base and replaces it with the correct one. Its N-terminal domain reduces replicational errors from 10⁻⁵ to 10⁻⁷ that is about the average spontaneous mutation rate in bacteria. After the Okazaki fragments reach full length they are joined by DNA ligase, an E. Coli enzyme that attaches adjacent 5'-phosphoryl and 3'-OH ends of nucleotide chains in the presence of NAD⁺ (nicotinamide adenine dinucleotide). Most of the details of the information on DNA replication was obtained in in vitro systems where the single components can be added or withdrawn and the role can be established without the complications of the in vivo each chromosomal analyses. In E coli the transcriptionally most active genes are operating in the leading strand. In *Caulobacter crescentus* each chromosomal locus occupies a specific address arrayed linearly along the longitudinal axis of the cell. During replication, these are moved in chronological order to the final subcellular site (Viollier PH et al 2004 Proc Natl Acad Sci USA 101:9257) rolling circle replication and (theta) replication, ▶steric-exclusion model, ▶replication fork, ▶replication machine, ▶magic spot, ▶nucleoid, ▶RNA replication in viruses, ▶DNA chemical synthesis, ▶replication speed, ▶processivity, ▶Okazaki fragments; Wawrzynów A, Zylicz M 1997 In Gething M-J (ed) Guidebook to Molecular Chaperones and Protein Folding Catalysts, Oxford Univ. Press, New York, p. 481; Nossal NG et al 2001 Molecular Cell 7:31; Postow L et al 2001 Proc Natl Acad Sci USA 98:8219; Johnson A, O'Donnell M 2005 Annu Rev Biochem 74:283; polarity of termination: Mulcair MD et al 2006 Cell 125:1309.

DNA Replication Types: These are distinguished as type I and type II (see Fig. D81):

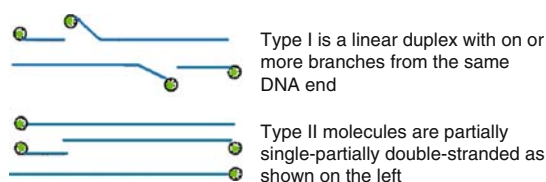


Figure D81. Replication types

DNA-RNA Hybrid: DNA is annealed with RNA in a double helix. ▶annealing

DNA, 7S: It is found in the mitochondria where it facilitates the synthesis of the heavy strand of the mtDNA. In mammals, mtDNA replication proceeds from two promoters the light strand and the heavy strand promoter, respectively. In this region an arrested H strand DNA, the 7S DNA is hybridized to the parental circular mtDNA and forms there a triplex with the displaced replication loop. This 7S DNA is primed by a 7S RNA derived from the light strand DNA. ▶mtDNA, ▶RNA 7S; Lee DY, Clayton DA 1998 J Biol Chem 273:30614; Gensler S et al 2001 Nucleic Acids Res 29:3657.

DNA, Selfish: It has little or no known use for the organism, yet it is of common occurrence such as the repetitive sequences. ▶repetitious DNA, ▶redundant DNA, ▶introns, ▶transposable elements, ▶micro-satellites, ▶minisatellites, ▶SINE, ▶LINE; Crick FHC 1979 Science 204:264.

DNA Sequence Alignment: ▶intel, ▶DNA sequence information

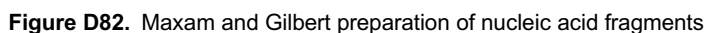
DNA Sequence Comparison Viewers: ▶ACT, ▶Artemis

DNA Sequence Information: (see Fig. D82) ▶databases, ▶Nucleotide sequencing collaboration: <http://www.insdc.org/>, <http://www.ebi.ac.uk/embl/>, about many different species including extinct ones: <http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html>.

DNA Sequencing: It determines the order of nucleotides in DNA fragments. Two procedures have been most widely used: the protocol of Maxam and Gilbert (M&G; see diagram) and one or another modification of the method of Sanger and co-workers. The M&G method can sequence both single and double-stranded DNA.

The P³² end-labeled DNA sample is divided into five aliquots and by different, limited chemical breakage at one or two of the four bases, unique sets of labeled fragments are produced (G, G + A, A + C, C, C + T). From the five batches, fragments are then separated according to length in five lanes in

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Since one end of each fragment in each batch terminates by the same nucleotide(s), according to the breakage mechanism (see figure and box) and in each batch these ends are specific, the sequence of the bases, in the different length fragments, can be read directly from the film of the gel (see Fig. D83).

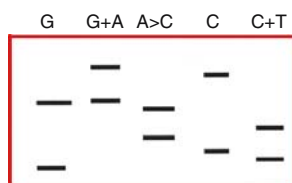
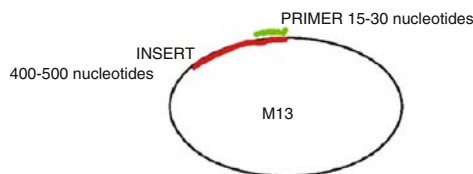


Figure D83. Because no band appears in the **A > C** lane corresponding in position in the **G + A** lane or in the **C** lane corresponding to the **C + T** lane the sequence must be **GTCATAGCA** (read from bottom to top). The maxam gilbert method can sequence both single- and double-strand dnas, and the sequence can be read directly as illustrated below

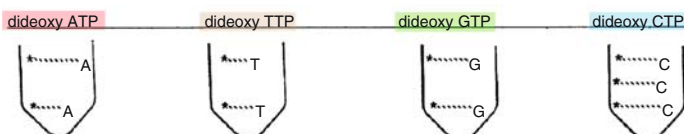
By the *Sanger method* single-stranded DNA is sequenced that has been cloned in M13 (or related) phage vectors (see Fig. D84). A chosen DNA fragment is then replicated in the presence of appropriate primer, α - P^{32} -dATP, limited supply of the four normal deoxyribonucleotide triphosphates and the large subunit of DNA polymerase I (Klenow fragment), or mainly Taq or phage T7 polymerases.

In addition to these common components in four separate vessels, the dideoxy analogs of the four nucleotides (dideoxyATP, dideoxyTTP, dideoxyGTP, dideoxyCTP) are added. These analogs when incorporated into the growing nucleotide chain stop further elongation because they do not have OH at the 3' position where the new nucleotides normally attach during replication. As a result, the chain growth stops and the position of this nucleotide in the chain is marked. The fragments generated by this stopped replication procedures are separated by electrophoresis as described in the M&G procedure and from the results of the sequencing gel, the base sequences can be read directly. Another method called "sequencing-by synthesis" uses iterative addition to the template the four deoxynucleotide triphosphates, and as the DNA polymerase incorporates the complementary nucleotide monophosphate the liberated pyrophosphate is determined. Actually, after addition the nucleotides are enzymatically degraded in the sequence of incorporation. The detection is made possible by a sulfurylase reaction coupled with luciferase. In recent years, great technical advances were made in DNA sequencing by using laboratory equipment and computer technology, and megabase-size DNA stretches can be sequenced in much shorter time. A large number of viral, several prokaryotic, a score of eukaryote (*Saccharomyces*, *Caenorhabditis*, *Drosophila*) genomes have been entirely sequenced and several others nearing completion. The average estimated error rate is $1-3 \times 10^{-3}$ base. The sequencing of DNAs facilitates the understanding of how

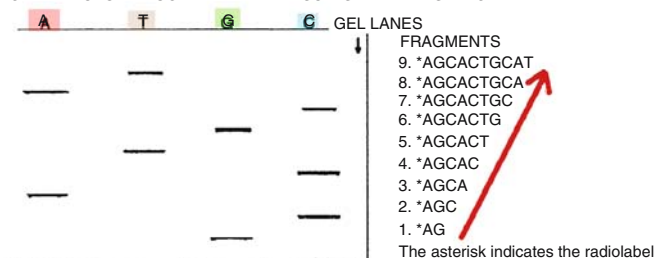
INSERT INTO A CLONING SITE (CONTAINING THE *Lac* GENE) OF THE SINGLE-STRANDED M13 PHAGE. THE INSERTION INACTIVATES *Lac* IN THE PHAGE AND INFECT *Lac*⁻ BACTERIA. THE TRANSFORMANTS DO NOT PRODUCE COLORED PLAQUES ON Xgal MEDIUM.



TO FOUR TUBES, EACH, ADD THE SEQUENCING VECTOR (M13), ³²P-DEOXYRIBOADENOSINE TRIPHOSPHATE, THE NORMAL DEOXYNUCLEOTIDE TRIPHOSPHATES AND A DNA POLYMERASE (EITHER THE KLENOW FRAGMENT OR SEQUENASE) AND IN EACH OF THE FOUR TUBES ADD ALSO ONE OF EACH OF THE FOUR TYPES OF DIDEOXYRIBONUCLEOTIDES:



THE DIDEOXYNUCLEOTIDES ARE INCORPORATED IN PLACE OF THE NORMAL NUCLEOTIDES BUT LACKING THE 3'-OH END, THE CHAIN GROWTH STOPS. THEREFORE, THE SYNTHESIZED FRAGMENTS WILL TERMINATE EITHER WITH AN A or T or G or C, RESPECTIVELY. SINCE NORMAL NUCLEOTIDES ARE ALSO PRESENT, FRAGMENTS OF DIFFERENT LENGTH WILL BE GENERATED ON THE INSERT TEMPLATE ACCORDING TO THE CHANCE WHETHER NORMAL OR BLOCKING NUCLEOTIDES WILL BE INCORPORATED BY THE POLYMERASE. THE FRAGMENTS ARE THEN SEPARATED BY LENGTH BY POLYACRYLAMIDE GEL ELECTROPHORESIS. THE RADIOACTIVE dATP MARKS ONE END OF THE FRAGMENTS AND THEY CAN BE DETECTED IN THE GEL BY AUTORADIOGRAPHY. THE RESULTS MAY BE AS DIAGRAMMED:



THUS THE NUCLEOTIDE SEQUENCE CAN BE READ FROM THE LAST BASE OF FRAGMENT NUMBER 1 TO FRAGMENT NUMBER 9: G C A C T G C A T

THE START OF THE RUN IS AT THE TOP AND THE LONGER IS A FRAGMENT THE SHORTER THE DISTANCE IT MOVES IN THE ELECTRIC FIELD OF THE GEL

Figure D84. Sanger method of DNA sequencing

biological systems work. It opens new approaches to study interacting proteins, facilitates more efficient design of drugs, decipher the mechanisms of cancer and other diseases, provides new tools for forensic analyses, evolutionary and archeological research and it even may identify biological warfare agents. The Sanger method is applicable to fmole DNA samples in a nanoliter-scale microfabricated bioprocessor at 99% accuracy (Blazej RG et al 2006 Proc Natl Acad Sci USA 103:7240). ▶DNA sequencing automated, ▶pyrosequencing, ▶nucleic acid chain growth, ▶sulfurylase, ▶luciferin, ▶BLAST, ▶BLASTX, ▶FASTA, ▶BLOSUM, ▶databases, ▶evolutionary distance, ▶array hybridization, ▶DNA chips, ▶clone validation, ▶computerization of DNA and protein sequence data; Methods in Enzymology 59 & 65; Marziali A, Akeson M 2001 Annu Rev Biomed Eng 3:195; Green ED 2001 Nature Rev Genet 2:573, see diagram for an outline of the

most widely used dideoxynucleotide method of Sanger et al.

The genome projects use either one or the other of the two automated sequencing procedures for large-scale sequence determinations. The hierarchical shotgun sequencing (HS) breaks up the (human) genome into overlapping BAC clones, sequences them and then reassemble them as merging clones. This procedure was used by the Human Genome Project. The Whole-genome shotgun sequencing (WGS) sequences the entire genome and then reassembles the entire collection into contigs and scaffolds. This procedure was designed and used by the Celera biotechnology firm. The two procedures are discussed by Waterson RH et al 2002 Proc Natl Acad Sci USA 99:3712.

A newer method uses four-color DNA sequencing by synthesis on a chip. It employs four photo-cleavable fluorescent nucleotide analogs attached

though 2-nitrobenzyl linker to the 5 position of the pyrimidines and to the 7 position of the purines. The incorporated nucleotides are irradiated then by ~355 nm laser beam for 10 s. Afterward, sequencing by synthesis reaction was carried out a self-priming template on the chip, immobilized by azide-alkyne cycloaddition. The template was generated by PCR, using azido-labeled primer and ligated to the immobilized DNA. Each cycle of this procedure permitted the identification the sequence of 12 continuous nucleotides and then the fluorophores are cleaved off by near-UV. The procedure may be extended to longer tracts of DNA (Seo TS et al 2005 Proc Natl Acad Sci USA 102: 5926). It has been reported that another highly accurate procedure uses epifluorescence microscopy and nonelectrophoretic method. Short DNA fragments are amplified on 1- μ m beads by polymerase chain reaction (PTPCR) and then sequenced at about 1/9th of the cost of the conventional (Sanger) method (Shendure J et al 2005 Science 309:1728). Combination of chromatin immunoprecipitation (ChIP) with massively parallel sequencing permits the identification of specific DNA sequences under different epigenetic conditions (Robertson G et al 2007 Nature Methods 4:651).

►sequatron, ►DNA chips, ►shotgun sequencing, ►genome projects, ►computerization of DNA and protein sequence data, ►contig, ►scaffold, ►pyrosequencing, ►bisulfite reaction, ►massively parallel signature sequencing, ►deep sequencing, ►DNA fingerprinting; some newer procedures' survey: Marziali A, Akeson M 2001 Annu Rev Biomed Eng 3:195; history of progress: Venter JC et al 2003 Nature Genet 33 (Suppl.):219, advanced technologies: Shendure J et al 2004 Nature Rev Genet 5:335, <http://www.sequenceanalysis.com>.

Convenient identification of nucleotide sequences within specific DNA segments is relevant to many biological problems including developmental processes and medicine. Incorporation of a complementary nucleotide into self-primed single-strand DNA attached to the surface of a gold electrode evokes an electrode surface charge perturbation. Such an event is detectable by a voltage-clamp amplifier. It is supposed that the electrode detects proton removal from the 3'hydroxyl group of DNA during the formation of phosphodiester bond when complementary base is provided. Such a method is rapid and does not require special reagents (Pourman N et al 2006 Proc Natl Acad Sci USA 103:6466, DN sequence and physico-chemical property analysis tool: <http://gna.web.gbf.de/FeatureScanHome.htm>).

DNA Sequencing, Automated: The nucleotide sequences on the X-ray film obtained by autoradiography can be read directly or can be scanned with aid of computer

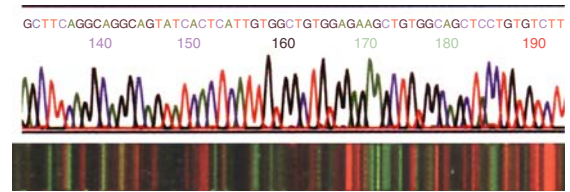


Figure D85. The peaks (in four colors) correspond to the pattern of a sequencing gel. (**Note** the scan is not of the gel shown below it!). The laser scanner feeds to the computer the information according to color that corresponds to specific bases of the DNA

programs (see Fig. D85). The computer can be used also to search for particular sequences, transcription signals, homeoboxes, termination signals and any other type of conserved elements.

In addition, through computer connections to DNA databases, homologies to previously determined sequences can be identified. By the most efficient methods (by year 2000), more than Mb DNA can be daily sequenced at a cost less than \$0.50 per nucleotide in a finished sequence. In recent years, the cost has been reduced and the latest techniques permit a further substantial cost reduction. The genome projects used either a whole-genome shotgun method (Celera Genomics) or 150-kb clones in bacterial artificial chromosomes (International Human Genome Sequencing Consortium).

High-throughput technology reduced the cost to \$1.00 per raw kilobase by 2005. Currently developing systems by using pyrosequencing and sequencing-by-synthesis technologies may drive down the cost to \$1,000 for a 9-billion bp mammalian genome (Service RF 2006 Science 311:1544). In 2007, the sequencing of the whole genome of James Watson cost about \$1,000,000 and was completed in a few months.

Nucleoside triphosphates attached to a fluorophore can be incorporated into DNA through UV photocleavable 2-nitrobenzyl linkers. Such a procedure holds promise for an efficient automated sequencing by synthesis similarly to the Sanger method (Li Z et al 2003 Proc Natl Acad Sci USA 100:414). For great efficiency and scalable, a highly parallel system with raw throughput significantly greater than that of state-of-the-art capillary electrophoresis instruments have been developed.

The apparatus uses a novel fibre-optic slide of individual wells and is able to sequence 25 million bases, at 99% or better accuracy, in 1, 4-h run. This method can achieve an approximately 100-fold increase in throughput over current Sanger sequencing technology. An emulsion method for DNA amplification and an instrument for sequencing by

synthesis using a pyrosequencing protocol optimized for solid support and picoliter-scale volumes were used (Margulies M et al 2005 Nature [Lond] 437:376, note corrigendum Nature [Lond] 441:120). The latter method proved useful for such difficult tasks as the sequencing of the ancient DNA of Neanderthal bones. ▶DNA sequencing, ▶Bermuda standard, ▶shotgun sequencing, ▶pyrosequencing, ▶nanopore technology, ▶capillary electrophoresis, ▶polymerase chain reaction, ▶PTPCR, ▶BAC, ▶MALDI/TOF/MS; Meldrum DR 2001 Science 292:515; Markel S, León D 2003 Sequence Analysis in a Nutshell: A Guide to Common Tools and Databases. O'Reilly Press, Sebastopol, CA.

DNA Shuffling: It is the in vitro homologous recombination in pools of randomly fragmented genes, and reassembly by the polymerase chain reaction in order to test the consequences of the new sequences as evolutionary changes. Such a process may increase the efficiency of genes by hundreds of folds if the DNA sequences are derived from different bacterial or viral species. Shuffling within DNA sequences from one species may also result in several-fold increases in enzyme efficiency. In bacteria, extensive reorganization of the genes may contribute to variable expression (Cardeno-Tarraga AM et al 2005 Science 307:1463). ▶localized mutagenesis, ▶RCR-based mutagenesis, ▶protein engineering; Moore GL et al 2001 Proc Natl Acad Sci USA 98:326; Zhang Y-X et al 2002 Nature [Lond] 415:644.

DNA Silencing: ▶silencer

DNA Splicing: ▶splicing, ▶splicing junction

DNA Structure: ▶Watson and Crick model

DNA Subtraction: ▶genomic subtraction

DNA Supercoiling: ▶supercoiling of DNA

DNA Synthesis: ▶DNA replication, ▶DNA chemical synthesis

DNA Synthesis, Meiosis: During meiosis there is no DNA synthesis, except that may be needed for genetic repair. Before meiosis, synthesis brings the level of DNA in the meiocytes to 4 C level. After the reductional division each cell has 2 C amount of DNA and at the end of meiosis there is 1 C amount in each of the four gametes. ▶C amount DNA

DNA Thermal Stability: Heat may disrupt the hydrogen bonds between the two strands of DNA. The stability depends on the base composition since G≡C are linked by 3 hydrogen bonds whereas A = T by only 2. Generally, at temperatures exceeding 60°C denaturation may begin and upon prolonged exposure to 100°C it is completed. The resulting single strands

have higher UV absorption at 260-nm wavelength than the duplexes (hyperchromicity). ▶DNA denaturation, ▶denaturation, ▶hyperchromicity

DNA Topoisomerases: They are capable of nicking and reclosing single strands of (Type I) or causing scission in both strands and rejoining the cuts (Type II). These enzymes are ubiquitous from bacteria to eukaryotes and have roles in relaxing superhelical configuration, replication, transcription, recombination and repair. (mentioned items under separate entries; Huang WM 1996 Annu Rev Genet 30:79; Champoux JJ 2001 Annu Rev Biochem 70:369).

DNA Tracking: Following the path of the DNA such as the movement of a polymerase along the template after the initiation of transcription or replication.

DNA Translocase: An ATP-driven motor protein complex mediating replication, recombination and DNA transfer between cells. In *E. coli* it (FtsK) may move rapidly (5 kb/s) along the DNA in two directions (Pease PJ et al 2005 Science 307:586).

DNA Transport: It is concerned with segregation of the chromosomes, bacterial conjugation and chromosome transfer, phage infection and assembly into phage particles, transformation etc. DNA is generally transferred in single-stranded form, except in bacteriophages that move across bacterial septa. In bacteria, the SpoIII-like protein family is the most important instrument of the processes. ▶conjugation, ▶infection, ▶phage life cycle, ▶transformation, ▶pilus; Errington J et al 2001 Nature Rev Mol Cell Biol 2:538; Chen I et al 2005 Science 310:1456.

DNA Transposition: ▶transposition

DNA Tumor Virus: It may be integrated into the animal host DNA. The Papovavirus family consists of a variety of types and may be responsible for warts and carcinomas (see Fig. D86). The Hepadnaviruses (hepatitis-B) are responsible for liver carcinomas. The Herpes viruses (Epstein-Barr virus) may cause cancerous transformation of the lymphocytes (Burkitt's lymphoma, and nasopharyngeal cancer). Several RNA viruses belong to the retrovirus groups and may be transcribed into DNA and activate cancerous growth. See mentioned terms under entries; ▶isometric phage

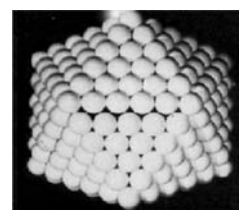


Figure D86. Adenovirus, facultative DNA tumor virus

DNA Twist: The number of base pairs per turn of the double helix. DNA-binding proteins (repressors, histones of the nucleosomes, remodeling of chromatin) can affect the winding of the molecule and alter expression of genes. Nicks of one strand reduces the torsion. ▶DNA bending; Havas K et al 2000 Cell 103:1133.

D

DNA Types: see table D6. ▶xDNA

DNA Typing: determination of the individual specificity of a DNA sample (see Table D6). ▶DNA fingerprinting, ▶DNA sequencing, ▶microarray, ▶multi-locus sequence typing; Burns MA et al 1998 Science 282:484.

DNA, Ultraviolet Absorption: The maximal absorption is at about 260 nm but the solvent and pH may influence the maximum. The maximal absorption of polycytidylic acid is between 270 and 280 nm whereas that of polyguanylic acid may vary between 250–290 nm, depending on the pH. Single-stranded molecules have increased absorption relative to double-stranded DNA. DNA isolated from plant or animal tissues generally has 280/260 \approx 2 absorption ratios. The OD₂₆₀ of 1 corresponds to about 50 μ g/mL double-stranded and 40 μ g/mL single stranded DNA at about pH 8 in TE buffer. ▶O.D., ▶TE buffer, ▶buffer, ▶UV, ▶cyclobutane dimer, ▶physical mutagens

DNA, Unique: DNA sequences that occur only in single copies in the genetic material.

DNA Uptake Sequences (DUS): The genomes of certain bacterial species (but not *E. coli* K12) contain 9-10-mer base sequences, 5'-GCCGTCTGAA-3' repeated in ~1900 copies in *Neisserias* or 5'-AAGTGCGGT-3' sequences in *Haemophilus influenzae* (repeated 1,471 times) and in *Actinobacillus actinomycetemcomitans*. These species are naturally competent for

transformation. Besides, their protein-coding gene's expression is more stable and have better regulated phase variation and better stress responses and DNA repair, recombination, restriction-modification, etc. ▶oligodeoxyribonucleotide gated channel, ▶phase variation, ▶competence of bacteria, ▶DNA repair, ▶restriction-modification; Davidsen T et al 2004 Nucleic Acids Res 32:1050.

DNA Vaccines: ▶immunization genetic, ▶vaccines

DnaA: The DNA replication initiation protein in *E. coli*. It binds to a 9mer consensus the DnaA-box (5'-TT (A/T)TNCACA) and if it complexes with ATP it binds to the ATP-Dna-box (5'-AGatct). ▶oriC, ▶DnaB

DNAase: ▶DNase

DnaB: A hexameric DNA helicase involved in bacterial replication by polymerase III. Besides being a helicase, it regulates the synthesis of the primer and a factor of processivity. ▶DNA replication in prokaryotes, ▶O-some, ▶processivity, ▶DnaA, ▶oriC; Carr KM, Kaguni JM 2001 J Biol Chem 276:44919.

DnaC: A prokaryotic DNA helicase. ▶DNA replication in prokaryotes

DnaE: It encodes the catalytic subunit of bacterial DNA polymerase III. ▶DNA polymerases; Dervyn E et al 2001 Science 294:1716.

DnaJ: A family of chaperone proteins of *E. coli* (375 amino acids), belonging to the Hsp40 family of chaperones/co-chaperones. They also regulate the ATPase and peptide-binding activity of Hsp70. They are present in pro- and eukaryotes, animals, plants and fungi. DnaJ stabilizes the DnaK–protein complexes with the cooperation of GrpE. It assists replication of the DNA by activating RepA helicase binding to the origin of replication in *E. coli*. After the

Table D6. DNA types

| Helix | bp/Turn | Degree of Rotation per Base Pair | Rise per bp (angstrom) | Diameter (angstrom) | Condition of Existence |
|-------|---------|--|------------------------|---------------------|---|
| A | 11 | +32.7 | 2.9 | 23 | 75% rel. hum., Nam K or Ce |
| B | 10.4 | +36.0 | 3.38 | 19 | 92% rel. hum., low ions |
| C | 9.7 | +38.6 | 3.34 | 19 | 66% rel. hum., Li ions |
| D | 8 | occurs only in guanine-free DNA | | | |
| E | 7.5 | occurs only in guanine-free DNA | | | |
| Z | 12 | -30.0 | 3.71 | 18 | left-turned, alternating purines and pyrimidines, high salt |
| P | 2.62 | the phosphate backbone is inside 75% longer than B DNA | | | |

bp = base pair, rel. hum. = relative humidity

transcription of Hsp70, the complex may separate the heatshock-specific σ^{32} subunit from the RNA polymerase and reactivates the heat aggregated and thus inactivated regular σ^{70} subunit. ▶chaperones, ▶HSP, ▶Hsp70, ▶DnaK, ▶GRP, ▶Rep, ▶ σ^{70} , ▶CbpA, ▶RcsG; Rüdiger S et al 2001 EMBO J 20:1042.

DnaK: An *E. coli* chaperone protein of the Hsp70 family with high homology to eukaryotic Hsps. In cooperation with DnaJ and GroE it carries out the main functions of controlling heat responses, protein folding, transport and degradation in concert with proteases, initiation of bacterial, plasmid and phage replication, flagella synthesis, etc. DnaK synthesis is regulated by a specific σ^{32} subunit a bacterial RNA polymerase. Severe oxidative damage inactivates DnaK and activates the redox-regulated Hsp33 chaperone. Upon return to non-stress conditions Hsp33 is inactivated and DnaK is reactivated to protein folding function (Winter J et al 2005 Mol Cell 17:381). ▶chaperones, ▶Hsp70, ▶GroEL, ▶flagellum, ▶RNA polymerase, ▶ σ , ▶Ydj1, ▶Sis1, ▶Zuotin, ▶Anj1, ▶Ldj, ▶Tid50, ▶Hdj2, ▶HsJ1, ▶auxilin, ▶Mtl1, ▶Hip, ▶trigger factor, ▶translcon; Kedzierska S, Matuszewska E 2001 FEMS Microbiol Lett 204:355.

DNA-PK (DNA-dependent protein kinase, 8q11): A phosphatidyl inositol kinase family (PI[3]K) protein has a role in transcription, replication, immunoglobulin gene switching, cancer and DNA repair. In cells deficient in DNA-PK non-homologous end-joining is preferred whereas homologous recombination is reduced (Convery E et al 2005 Proc Natl Acad Sci USA 102:1345).

The sequence-specific enzyme complex works only when it is in cis-position to the site of phosphorylation. The Ku autoantigen, a transcription factor, attracts DNA-PK to specific DNA sequences. Ku binds to a specific negative regulatory element (NRE1) — in the long terminal repeat—and keeps in check inappropriate expression of the glucocorticoid-induced transcription of mouse mammary tumor virus (MMTV). Ku can bind also to other DNA sites although it displays preference to DNA ends and to the MMTV glucocorticoid receptor and octamer transcription factor 1 (Oct-1). DNA-PK phosphorylates in vitro glutathione S-transferase-Oct-1 fusion protein and the glucocorticoid receptor. Phosphorylation by DNA-PK was contingent on the presence of the glucocorticoid receptor and Oct-1 binding sites. DNA-PK is required also for immunoglobulin (V[J]D) recombination and activation of innate immunity. DNA-PK mediates also the binding of p53 protein to the DNA and thus, may or may not play a role in the mammalian DNA damage control pathway. DNA-PK also functions as an RNA-dependent protein kinase and regulates RNA

processing and transport (Zhang S et al 2004 Nucleic Acids Res 32:1). ▶mouse mammary tumor virus, ▶Oct-1, ▶autoantigen, ▶p350, ▶Ku, ▶immunoglobulins, ▶RAG, ▶XRCC4, ▶p53, ▶ligase DNA, ▶non-homologous end-joining, ▶double-strand break, ▶PIK, ▶innate immunity; Smith GCM; Jackson SP 1999 Genes Dev 23:916; Bryntesson F et al 2001 Radiat Res 156:167; Chechlacz M et al 2001 J Neurochem 78:141; Goiytisolo FA et al 2001 Mol Cell Biol 21:3642; Soubeyrand S et al 2001 Proc Natl Acad Sci USA 98:9605; Mårtensson S, Hammersten O 2002 J Biol Chem 277:3020; DNA-PK structure: Rivera-Calzada A et al 2005 Structure 13:243.

DnaQ: A bacterial gene encoding the proofreading ϵ subunit of DNA polymerase III. ▶proofreading, ▶DNA polymerases

DNase: Enzymes degrading DNA. ▶restriction enzymes, ▶endonuclease, ▶exonuclease, ▶DNA polymerases

DNase-Free RNase: It may be prepared by different procedures such as affinity chromatography on agarose 5'(4-aminophenylphosphoryl)-uridine-2'(3')-phosphate, by adsorption on Macaloid, by heating in the presence of iodoacetate. Commercially available preparations so labeled may not always be trustworthy. ▶RNase-free DNase, ▶DNase, ▶RNase, ▶Macaloid

DNase Hypersensitive Site (HSS/DHS): In the DNA, HSS is very easily attacked by nucleases probably because they are unprotected by proteins (histones); their presence correlates with expression of adjacent genes. The generation of hypersensitive sites alters the nucleosomal structure of the chromatin. Hypersensitive sites are located in the vicinity of promoters or a promoter and enhancer, suppressors and insulators. Computational method were developed to detect common DNA structural motifs in a large collection of HSSs that are found in the ENCODE regions of the human genome. HSSs have common DNA structural motifs that show no apparent sequence consensus. One such structural motif is much more highly enriched in experimentally identified HSSs that are in CpG islands and near transcription start sites (TSSs), compared to HSSs not in CpG islands and farther from TSSs, suggesting that DNA structural motifs may participate in the formation of functional regulatory elements (Greenbaum JA et al 2007 Genome Res 17:940). By cloning HSS sequences, regulatory systems can be identified globally and in various tissues, developmental stages and disease susceptibility. ▶IN11, ▶integrase, ▶promoter, ▶enhancer, ▶nucleosome, ▶antitrypsin, ▶chromatin remodeling; Crawford GE et al 2004 Proc Natl Acad Sci USA 101:992, <http://www.gene-regulation.com/>.

DNASIS: A computer program for DNA base sequence analysis.

DNASP: A software package for the analysis of DNA sequence polymorphism. www.ub.es/dnasp.

DNA-Templated Organic Synthesis and Selection

(DTS): DNA-templated synthesis generates labeled libraries for screening small synthetic compounds, macrocycles. The DNA-macrocyclic conjugates were screened for protein affinity. The procedure is sensitive for detection of small biological molecules. The procedures enable selection of libraries of 10^6 peptides for therapeutic or chemical applications. (Gartner ZJ et al 2004 Science 305:1601; Halpin DRT, Harbury PB 2004 PLoS Biol 2(7):e17). ▶[macrocycle](#)

DnaX: is one of 10 different subunits of the prokaryotic DNA polymerase holoenzyme. ▶[DNA replication in prokaryotes](#); Song M-S, McHenry CS 2001 J Biol Chem 276:48709.

DNA-Zymes (DNA enzymes, deoxyribozymes): These are catalytic single-strand DNA molecules that have been isolated in the laboratory by in vitro selection in random oligonucleotide pools (see Fig. D87). They are thus not “natural enzymes” unlike ribozymes. They can cleave and make phosphoester bonds and also catalyze other reactions (porphyrin metallation). They do not have the 2'-hydroxyl group of RNA yet can carry out the reactions very effectively. The so called 10–23 DNA-zyme digests a specific motif of nucleotide sequences. The 15-nucleotide catalytic core of this DNA-zyme is flanked by two substrate recognition sequences that bind to complementary RNA by hydrogen bonds. It cleaves the phosphodiester bonds between unpaired purines and pyrimidines and generates 2',3'-cyclic phosphate and 5'-hydroxyl ends. A DNA-zyme-based catalytic beacon can detect uranium oxide (UO_2^{2+}) in < 2 min at ambient temperatures with 11 parts-per-trillion (45 pM) sensitivity and > 1-million-fold selectivity over any other metal ions (Liu J et al 2007 Proc Natl Acad Sci USA 104:2056) although similar methods also exist for the detection of Pb^{2+} . Such methods have application for the detection of metal pollution and for medicine. ▶[ribozyme](#), ▶[phytoremediation](#), ▶[soil remediation](#); Breaker RR 2000 Science 290:2095. (Diagram after Nowakowski J et al. 1999 Nature Struct Biol 6:151)

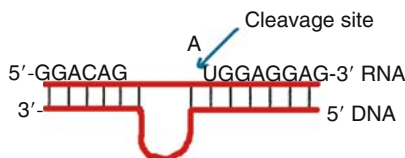


Figure D87. DNA-zyme

DNP: deoxyribonucleoprotein; also dinitrophenol.

dNTP: deoxyribonucleotide triphosphate of any of the nucleic acid bases.

DOC (APC10): A cell cycle protein. ▶[APC](#)

Doc Element: ▶[non-viral retrotransposable elements](#)

Dock Web Site: Provides information on docking (interacting) molecules. (<http://dock.compbio.ucsf.edu/>; <http://blaster.docking.org/zinc>)

Docking Proteins: The signal-mediating proteins at the cell membrane or inside the cell facilitating the cooperation of other proteins. ▶[signal transduction](#); Hadari YR et al 2001 Proc Natl Acad Sci USA 98:8578; Wei BQ et al 2002 J Mol Biol 322:339.

Dodder (*Cuscuta*): Parasitic plants recognizing the volatile compounds emitted by other plant species and exploiting their nutrients (see Fig. D88). They do not develop sufficient roots or photosynthetic leaves and depend on hosts for survival. The dodders can discriminate among the host species on the basis of the volatiles they emit; dodders are agriculturally obnoxious, especially for legumes. ▶[kairomones](#); Runyon JB et al 2006 Science 313:1964.



Figure D88. *Cuscuta* orange/yellow, host green

Dodecamer: 12 units, composed of two hexamers.

Dodecyl Sulfate, Sodium Salt (SDS): An anionic detergent ($\text{CH}_3[\text{CH}_2]_{11}\text{OSO}_3\text{Na}$). It is used to separate membrane proteins from the lipid layers because the detergent replaces the lipids at the hydrophobic tract of the membrane protein. It is used also for SDS-acrylamide-gel electrophoresis where the unfolded proteins move according to their size rather than by charge. Synonym: laurylsulfate Na salt. ▶[membrane proteins](#), ▶[electrophoresis](#)

DODO: ▶[parvulins](#)

Dog (*Canis familiaris*, $2n = 78$, ~2.5 Gb/genome): Molecular data indicate its origin from wolves. Because of the high diversity in the mtDNA in both species, dogs apparently originated by more than a single event of divergence although the difference between dog and gray wolf DNA is only 0.2%. Dogs

and wolves are not isolated sexually. Dogs have been domesticated about 15,000 years ago and over 350 to 1,000 different breeds may exist. Among 85 domestic pure-breeds, about 99% of the individual animals could be identified correctly to breed on the basis of microsatellite genotypes (Parker HG et al 2004 Science 304:1160). A high-quality draft of the genome sequence became available by 2005 (Lindblad-Toh K et al Nature [Lond] 438:803). The major conclusions about the dog genome and its comparison with other mammalian genomes indicate that the average transposons insertion rate is lowest in dogs, deletion rate is highest in mouse and the lowest nucleotide substitution rate is in humans (see

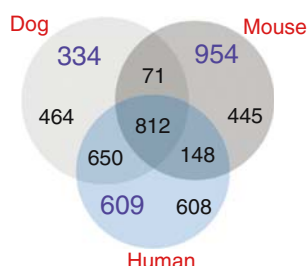


Figure D89. Total length (Mb) of aligned and unique sequences in euchromatin. Overlapping portions are orthologous ancestral sequences. Lineage-specific interspersed repeats are shown in larger fonts and in purple color (After Lindblad K et al. 2005 Nature [Lond] 438: 803)

Fig. D89). About 5.3% of the functional elements in dogs and humans underwent purifying selection. Most of these elements are also preserved in mouse, indicating common sequences across mammalian genomes. Half of the highly preserved non-coding sequences are clustered in about 200 gene-poor regions, including transcription factors or axon guidance receptors. Linkage disequilibrium (LD) within breeds of dogs includes several megabases but among different breeds, LD extends only to tens of kilobases. The patterns of LD display two principal bottlenecks; one indicates early domestication and the other reflects recent breeding events. Haplotypes within breeds are long and include 3–5 alleles per locus. Some may involve 100 kb and may be shared to a variable extent across breeds. SNP frequency within breeds is about 1/900 bp and among breeds about 1/1,500. Functionally related genes reveal evolutionary patterns in dogs and humans. The sequence information permits construction of evolutionary trees.

Body size variations are larger in dogs than in other terrestrial mammals and it is under the control of a major QTL in chromosome 15. Near this QTL there is a *IGF1* (insulin-like growth factor) single-nucleotide polymorphism locus, which is common to all small breeds and nearly absent from giant breeds, suggesting that the same causal sequence variant is a major contributor to body size in all small dogs (Sutter NB et al 2007 Science 316:112) (see Fig. D90).

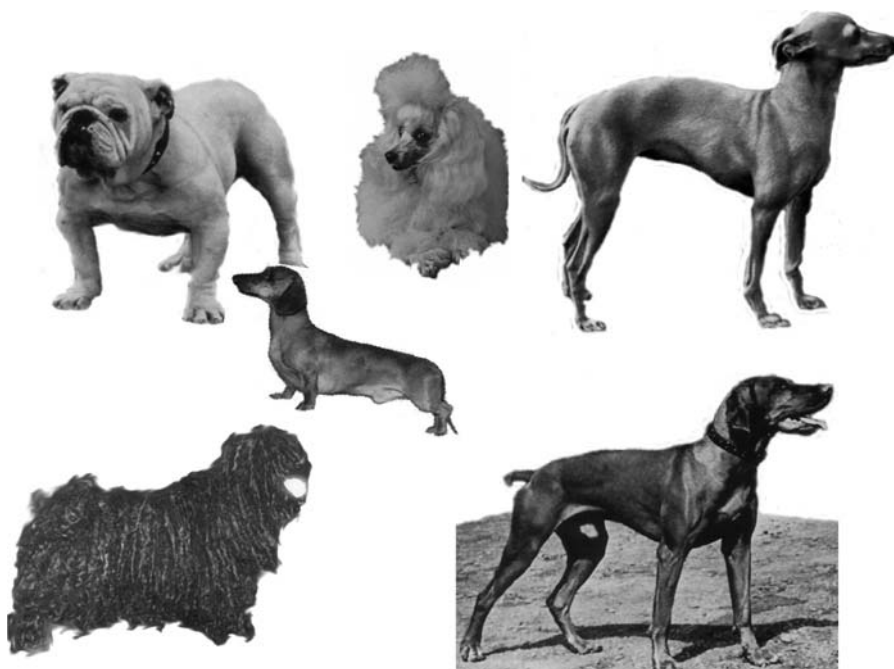


Figure D90. Dog breeds show great variation in size, color and morphology. Top left to right: English Bulldog, Poodle, Italian Greyhound. Below left to right: hungarian Puli, Dachshund, Hungarian Vizsla

D

About 370, mainly recessive genetic diseases have been identified by 1999 and many of them (~58%) have homologs in humans. In 2005, cloning of two Afghan hounds by nuclear transfer from adult skin cells into oocytes that had matured in vivo has been reported (Lee BC et al 2005 Nature [Lond] 436:641). The validity of this paper has been questioned after the same laboratory fabricated reports on human cloning for the purpose of stem cell production ►stem cells. Further investigation confirmed, however, the validity of this paper (Cyranowski D 2006 Nature [Lond] 439:123). ►microsatellite, ►prairie dog, ►insulin-like growth factors, ►QTL, ►Waardenburg syndrome; Ostrander EA et al 2000 Trends Genet 16:117; Breen M et al 2001 Genome Res 11:1784; Savolainen P et al 2002 Science 298:1610; A 3;270 radiation hybrid map: Guyon R et al 2003 Proc Natl Acad Sci USA 100:5296; review of dog genetics; human disease homologs: Sutter NB, Ostrander EA 2004 Nature Rev Genet 5:900; genome sequence: Kirkness EF et al 2003 Science 301:1898; wolf; fox.

Dog Rose: ►*Rosa canina*

DOGS: (dioctadecylamidoglycylspermine): A lipopolyamine used for delivering exogenous DNA into cells. ►liposomes

Dollo Parsimony: It posits that it is harder to acquire a new feature during evolution than to lose it. It is named after the Belgian evolutionist Louis Dollo who in 1893, apparently, first announced the principle as “An organism is unable to return, even partially, to a previous stage already realized in the ranks of its ancestors”. Farris and Felsenstein mathematically defined this law about a century later. (Felsenstein J 1979 Systematic Zool 28:49)

Dolly: ►nuclear transplantation

Dolphins: *Lissodelphis borealis* 2n = 44; *Orcinus orca* and other species are 2n = 44.

Dolycephaly: The head being abnormally long. It is a characteristic of several hereditary diseases.

Domain: The defined segments of proteins (with a characteristic tertiary structure that folds independently and usually represents specific functional properties), or cellular structures (chromosomes), e.g., DNA binding domain of transcription factors. DNA sequence units or exons are also considered as domains. Shared domains of macromolecules reveal evolutionary histories among organisms. It appears that the majority of eukaryotic proteins consist of two or more domains. Some domains may be shared among several different proteins of different functions. Hidden Markov model-based statistics are used for domain recognition. Protein domain contents allow reasonably good inferences on phylogenesis (Yang S et al 2005

Proc Natl Acad Sci USA 102:373). ►domains of antibodies, ►exon, ►protein domains, ►genome domain, ►SMART, ►genetic network, ►hidden Markov model; Coin L et al 2003 Proc Natl Acad Sci USA 100:4516; <http://scop.mrc-lmb.cam.ac.uk/scop/>; <http://ekhidna.biocenter.helsinki.fi:9801/sqgraph/pairsdb>; conserved domains: <http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi>.

Domain Swapping: Generates from monomers of proteins dimeric structures (see Fig. D91). (Hohl M et al 2007 Nucleic Acids Res 35:3053)



Figure D91. Domain swapping

Domains of Antibodies: These are segments of light and heavy-chain polypeptides separable by chemical treatments. ►antibody

Dombrock System Blood (DO): About 64% of northern Europeans are Do(a⁺) blood type; it is coded in the short arm of human chromosome 1. ►blood groups

Domestication: The taming and breeding of animals under human supervision and for human use began in the Neolithic (stone) age, about 10,000 years ago. The evolution of the domesticated animal breeds was a gradual process. There is evidence for numerous MHC *DRB* alleles that are present in modern domestic mammals implying that substantial backcrossing with wild ancestors, either accidental or intentional, has been important in shaping the genetic diversity of our domesticates (Vilà C et al 2005 Trends Genet 21:214).

Cultivation of plants started at about the same time. Fig plants (*Ficus carica*) in the Jordan Valley were apparently domesticated about a thousand years earlier than cereals as indicated by archeological finding of carbonized fruits (Kislev ME et al 2006 Science 312:1372). An estimated 1200 genes of maize was affected by selection during evolution from teosinte (Wright SI et al 2005 Science 308:1310). ►major histocompatibility complex; Cowan CW, Watson J 1992 The Origins of Agriculture. Smithsonian Inst., Washington, DC; Salamini F et al 2002 Nature Rev Genet 3:429; morphological, genetic and archeological evidence for the course of domestication of plants and animals; Zeder MA et al 2006 Trends Genet 22:139.

Domestication Bottleneck: It reduces genetic variation relative to wild ancestors.

Dominance: The property of an allele to be expressed in a heterozygote (heterozygote) in the presence of any other allele at a gene locus. In the majority of species, dominant mutations are much less common than the recessive ones. In humans, however, the known dominant mutations seem to exceed the recessives but many traits cannot be classified to either group. One must keep also in mind that the term dominance was conceived before biochemical characterization of gene expression became feasible. Usually, at a finer level of analysis both the “dominant” and the “recessive” alleles are expressed in the heterozygotes. The degree of dominance is sometimes expressed as the *coefficient of dominance*. In human or larger mammal pedigrees, because of few offsprings, it may be difficult to distinguish between dominant and recessive pattern of inheritance. The probabilities can, however, be analyzed statistically. Let us assume that 8 affected males have 6 affected female offspring and 5 unaffected male progeny. For non-dominant inheritance we would expect the probability to be $(0.5)^6 + (0.5)^5 = (0.5)^{11} \approx 0.00049$ (1/2048). One must also consider the problems of penetrance and environmental factors. ▶codominance, ▶semidominance, ▶dominance reversal, ▶penetrance

Dominance, Evolution of: R.A Fisher suggested in the 1930s that dominance evolves through the acquisition of modifier mutations that convert gradually the original recessive mutations into dominant ones. The basis of this idea was that under feral conditions the majority of alleles are dominant while the majority of new mutations are recessive. Sewall Wright (1934), J.B.S. Haldane (1930) and H.J. Muller (1932) hypothesized that dominance occurs by mutation as such and the rare advantageous dominant ones have the selective advantage of masking the deleterious recessive alleles in the populations. According to the molecular evidence since then, the majority of the mutations (except the loss of genes) show codominance when their function can be determined with greater precision. The development of dominance has been attributed to the control of processes regulating metabolic pathways, to the “flux” by changes in activities of controlled enzymes, by the changes in enzyme concentration and in enzyme kinetics ▶dominance, ▶co-dominance; Bourguet D 1999 Heredity 83:1; Hurst LD, Randerson JP 2000 J Theor Biol 205:641; Bagheri HC, Wagner GP 2004 Genetics 168:1713.

Dominance Hypothesis: It attributes the superior value of hybrids (hybrid vigor, heterosis) to the accumulation of favorable dominant genes. ▶hybrid vigor, ▶overdominance, ▶superdominance; Rédei GP 1982 Cereal Res Commun 10:5.

Dominance Reversal: A change of environment or developmental stage may alter and reverse the dominance–recessivity relationship of alleles (see Table D7). The *co* (*CONSTANS*) mutation flowers earlier than the Columbia wild type but under long daily illuminations, its onset of flowering was delayed. The F1 hybrid was dominant at short days but recessive at long days. The transcription of this gene was regulated by the FLAVIN-BINDING, KELCH REPEAT, F-BOX protein (FKF1). This protein controls the cycling Dof transcription factor (CDF1). FKF1 seems to determine the daily expression of *CO* in part by degrading a repressor (CDF1) of *CO* transcription, depending on the length of daily illumination (Imaizumi T et al 2005 Science 309:293). ▶epistasis, ▶conditional lethal genes, ▶temperature-sensitive mutation, ▶dominance, ▶F-Box; Shiffriss O 1947 Amer Soc Hort Sci 50:330.

Table D7 Reversal of dominance in flowering of *Arabidopsis*

| | Short Days | Long Days |
|------------------|------------|------------|
| wild | 27.4±0.72 | 11.1±0.48c |
| <i>co</i> | 20.0±0.54 | 15.7±0.03 |
| <i>co</i> × wild | 21.0±0.52 | 9.8±0.15 |

(From Rédei, G.P. 1962 Genetics 47:443)

Dominance Theory: ▶dominance hypothesis

Dominance Variance: (in quantitative genetics) This occurs due to the expression of dominant alleles. ▶genetic variances, ▶additive genes

Dominant Allele: It is expressed fully in a diploid (polyploid) even in the presence of recessive allele(s). ▶dominance, ▶semi-dominant

Dominant Individual: Occupying a higher rank in an animal society and better access to food and mates than the rest of the individuals.

Dominant Lethal Assays in Genetic Toxicology: Generally, rodents are treated with mutagens during various stages of spermatogenesis. Subsequently they are mated with untreated females. After about two weeks of pregnancy the females are sacrificed and the number of lethal implantations are classified and counted. ▶bioassays in genetic toxicology, ▶implantation, ▶autosomal dominant mutation

Dominant Negative (dominant-negative): The inhibition of the activity of a normal (wild type) protein when its subunits are mixed with mutant polypeptide

subunits, which alter the conformation and thus render it inactive. ▶ [conformation correction](#), ▶ [allelic complementation](#), ▶ [tetralogue](#), ▶ [RET oncogene](#), ▶ [osteogenesis imperfecta](#), ▶ [Marfan syndrome](#), ▶ [Denys-Drash syndrome](#), ▶ [gain-of-function mutation](#)

D

Donkey: *Equus asinus* 2n = 62. The domestication apparently took place in northern Africa and from more than a single progenitor race of the wild (see Fig. D92). Although in the Western world donkeys are neglected animals today, in medieval times (and in the underdeveloped world even today) they had/have prominent role. The illustration is adopted from the mid-fourteenth century *Biblia Pauperum*. ▶ [hinny](#), ▶ [mule](#); Beja-Pereira A et al 2004 Science 304:1781.



Figure D92. Donkey in a medieval codex

Donohue Syndrome (Leprechaunism, 19p13.2): It is a defect in the insulin receptor. Growth retardation, face anomalies, protuberant ears, abdomen, genitalia, hand, feet enlargement, excessive hair on skin, acanthosis nigricans, hepatocyte vacuolization. ▶ [insulin](#), ▶ [insulin receptor protein](#), ▶ [dwarfism](#)

Donor: A donor provides genetic material (F^+) to the recipient (F^-) by bacterial conjugation or any other means of genetic transfer (including eukaryotes). Blood type O that is acceptable to any individual with other alleles of the ABO blood group or other antigenic substances compatible to other serotype is also called a (universal) donor. ▶ [conjugation](#), ▶ [ABO blood group](#), ▶ [serotype](#)

Donor Site: The original position in the DNA (map) of a non-replicative transposable element from where it may move to another position within the genome, to the *recipient site*. ▶ [transposable elements](#)

Donor Splicing Site: ▶ [introns](#)

Dopa: 3,4-dihydroxyphenylalanine, an intermediate in melanin synthesis; the derivative dopa-mine is a neurotransmitter. ▶ [neurotransmitter](#), ▶ [phenylalanine](#)

Dopamine: A catecholamine formed by decarboxylation of dopa and it is a precursor of epinephrine, norepinephrine and melanine. Dopamine hydroxylase converts dopamine into epinephrine (see Fig. D93). Dopaminergic means an activation or site of effect by dopamine. Regulation of dopamine D2 class receptors involves Akt protein kinase, arrestin $\beta 2$ and protein phosphatase 2A (Beaulieu J-M et al 2005 Cell 122:261). ▶ [dopa](#), ▶ [animal hormones](#), ▶ [neurotransmitter](#), ▶ [DARPP](#), ▶ [memory](#), ▶ [Akt](#), ▶ [arrestin](#), ▶ [phosphatases](#), ▶ [Parkinson disease](#)

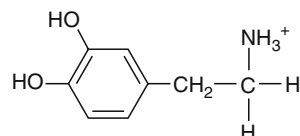


Figure D93. Dopamine

Dope: ▶ [lipids cationic](#)

Doping Nucleotides: Process in which a short nucleotide string is synthesized where some codons in the first strand have any of the four natural nucleotides and at the third position they have either G or C. In the second strand at the positions corresponding to the above named codons there will be inosines. The rest of the codons correspond to the usual amino acids. When such an insert is added to a vector, a variety of random mutations may occur in the protein domain coded by the sequence and yields a library of proteins with different amino acids at critical regions. ▶ [directed mutation](#), ▶ [protein engineering](#), ▶ [hypoxanthine](#) [for inosine]; Balint RF Larrick JW 1993 Gene 137:109; Hutchison CA et al 1986 Proc Natl Acad Sci USA 83:710.

DOP-PCR (degenerate oligonucleotide-primed polymerase chain reaction): DOP-PCR amplifies short chromosomal sequence and thus facilitates the detection (by fluorescence) of chromosome copy number in aneuploidy cancer cells. ▶ [FISH](#), ▶ [PCR](#); Tsubosa Y et al 2005 Cancer Genet Cytogenet 158:156.

Doppelgänger: ▶ [prion](#)

Dorfin: An RNA-finger ubiquitin ligase protein. ▶ [RNA finger](#)

Dormancy: A state of low metabolic activity. In plants seed dormancy requires the hormone abscisic acid whereas gibberellic acid relieves dormancy. Two basic-helix-loop-helix proteins seem to suppress germination of seeds (Tsiantis M 2006 Curr Biol 16 (1):R25). ▶ [plant hormones](#), ▶ [DNA binding protein domains](#); Alonso-Blanco C et al 2003 Genetics 164:711.

Dorsal: Relating to the back position of a body or upper surface of a structure or organ. Dorsal–ventral cell fate specification in the *Drosophila* embryo is initiated by *Dorsal* and is partly under the control of an autoproteolysis cascade determined by genes *GD*, *Snk*, *Ea* and the nerve growth factor ligand Spätzle (Dissing M et al 2001 EMBO J 20:2387). *Dorsal* represses the Zen (*zerknüllt*) homeobox by a 600 bp *ventral repression element* (VRE) containing 4 *Dorsal*-binding sites. There are 15 regions in the *Drosophila* genome that contain three or more binding sites within up to 400-bp sequences (Markstein M et al 2002 Proc Natl Acad Sci USA 99:763). About 100 genes mediate the dorsal–ventral nuclear gradient in *Drosophila* (Levine M, Davidson EH 2005 Proc Natl Acad Sci USA 102:4936; Biemar F et al 2006 Proc Natl Acad Sci USA 103:12763)

Dorsal Closure: Dorsal closure after gastrulation of the embryo establishes the dorsal ectoderm by stretching—without proliferation—the lateral ectoderm over a transient epithelial structure (amnioserosa). This is a complex process, mediated by the products of several known genes in *Drosophila*.

Dorsal Lip: ►blastopore

Dorsalization: The formation of dorsal elements is preferentially enhanced at the expense of ventral development during morphogenesis and embryo development. ►morphogenesis

Dorso-ventral: Back-abdomen directional arrangement of anatomical structures. (Stathopoulos A et al 2002 Cell 111:687)

Dosage Compensation: A single dose of a gene has the same phenotypic effect as two or more. Examples for this abound in X-chromosome-linked genes where the phenotype for such genes is practically identical in the XY males and XX females or in the WZ females and ZZ males or XO males and XX females. Such dosage compensation may occur with various doses of the X-chromosome and to some extent, it may occur in various aneuploids. MSL (male-specific lethal, *msl-1* 2.53.3, *msl-2* 2.90) and MLE (maleless, *mle-2*.55.2) proteins appear to be involved in dosage compensation in *Drosophila* by hypertranscription in the single male X chromosome. The MSL1 protein binds to more than 700 locations in the X chromosome and cover more than half of the genes. High level of dosage compensation involves the most essential genes. The binding favors the 3'-end of the transcription units and exons and coding sequences (Gilfillan GD et al 2006 Genes & Development 20:858). The MSL effect is also global not just directed to specific sites (Legube G et al 2006 Genes & Development 20:871). MSL is responsible for the

presence of a monoacetylated histone H4 in the male X chromosome of *Drosophila* and this results in remodeling of the active chromatin (Sass GL et al 2003 Proc Natl Acad Sci USA 100:8287). MOF, a histone H4 lysine 16-specific acetyl transferase protein interacts with the MSL and with several components of the nuclear pore complex (Mendjan S et al 2006 Mol Cell 21:811). MLE also seems to attach to the male X-chromosome two non-coding RNA (roX1, roX2) that may upregulate the transcription of genes in the X. In mammals, however, the non-coding Xist RNA mediates X-chromosomal inactivation in the female. *Sex lethal* (*sxl*, 1-19.2, with many different alleles), controls both sexual dimorphism and dosage compensation through its 39-kDa-protein product and promotes alternative splicing of *msl-2* RNA transcripts. Females with X:A (sex chromosome:autosome) ratio of 1 synthesize this protein and permit the transcription of both X-chromosomes. Males of X:A of 0.5 do not make the SXL protein and increase the expression of the majority of the X-linked genes. SXL permits the normal transcription of *Sxl* and *tra* in the females but in males, it inserts stop codons into these two transcripts. There are binding sites for SXL in the 3' untranslated region (UTR) in the *msl-1* transcripts and these may cause down-regulation in the females. There are both 5' and 3' UTR binding sites in the *msl-2* transcripts in the females and thus other potentials for regulation. Msl-2 seems to be the main target and instrument of X-regulation. The SXL protein is suspected to have another function, down-regulating some X-chromosomal genes in the female flies. In the hermaphroditic XX females of *Caenorhabditis*, X-chromosomal genes are expressed at about the same level as in the normal XO males (hypotranscription; Meyer BJ 2000 Trends Genet 16:247). In *Drosophila*, the single X-chromosome is hypertranscribed to achieve dosage compensation. In mammals, only one of the two or more X-chromosomes remains active. Some of the (*sdc*) genes affect both sex determination and dosage compensation. In the males XOL1 prevent the assembly of the dosage compensation complex in contrast to the XX females (hermaphrodites) where it activates the assembly. In *Caenorhabditis* a 793-bp sequence recruits the dosage compensation complex to the X-chromosome and from one or more sites its effect spreads along the chromosome (Csankovszki G et al 2004 Science 303:1182). The *rex* recruitment elements occurring in promoters, exons and introns in the X-chromosome of *Caenorhabditis* control dosage compensation. Mutations in these elements may abolish dosage compensation (McDonel P et al 2006 Nature [Lond] 444:614). Other genes (dumpy series [*dpy*]) affect only dosage compensation. The DPY-27 protein is associated with

the X-chromosomes in the hermaphrodites of *Caenorhabditis*. DPY-27 like proteins are present in other organisms too and control chromosome condensation and segregation. The DPY-26 locus affects Dpy-27 and Dpy-30 proteins for dosage compensation and Sdc2 and Sdc3 for the coordination of dosage compensation and sex determination. SDC-1 is a 139-kDa protein with Zn fingers. This family of proteins has some structural features characteristic for motor proteins. SDC-3 regulates sex determination by its ATP-binding domain and a Zn finger-like domain seems to affect dosage compensation. Actually, both series are cooperating in reducing the level of X-chromosomal gene expression in the hermaphrodites. A more recently discovered gene, *Pof* (painting of the fourth chromosome) involves heterochromatinization of the X chromosome in *Drosophila busckii* when translocated from *D. melanogaster* where it is located in the fourth chromosome. In birds, observations on dosage compensation are not entirely unequivocal although some of the genes seem to follow the rules in mammals. Dosage compensation may be either by X-chromosomal inactivation or by imprinting (Reik W, Lewis A 2005 Nature Rev Genet 6:403). It has been suggested that X-chromosomal inactivation and imprinting might have evolved from a defense mechanisms that silences unpaired DNA (Huynh KD, Lee JT 2005 Nature Rev Genet 6:410).
 ▶sex determination, ▶lyonization, ▶*Msl*, ▶*Mle*, ▶killer genes, ▶spirochetes, ▶segregation distorter, ▶hypertranscription, ▶splicing, ▶introns, ▶Zn finger, ▶motor protein, ▶neo-X-chromosome, ▶MSL, ▶numerator, ▶*Xic*, ▶*Xist*, ▶*Tsix*, ▶*Xol*, ▶epigenesis, ▶imprinting, ▶JIL-1; Stuckenholz, Z inactivation, C. et al. 1999 Trends Genet. 15:454; Meller VH 2000 Trends Cell Biol 10:54; Avner P, Heard E 2001 Nature Rev Genet 2:59; Park Y Kuroda MI 2001 Science 293:1083; McQueen HA et al 2001 Curr Biol 11:253; Stuckenholz C et al 2003 Genetics 164:1003; Lucchesi JC et al 2005 Annu Rev Genet 39:615; Straub T, Becker PB 2007 Nature Rev Genet 8:47.

Dosage Effect: Phenomenon in which the number of alleles of a certain type determines the degree of expression. ▶gene titration, ▶quantitative gene number, ▶quantitative trait, ▶mapping by dosage effect

Dose Fractionation: Occurs when irradiation is delivered not in a single burst but there are intervals between the doses. This may permit intermittent repair. ▶radiation effects

Dose, Permissible: ▶radiation hazard assessment

Dosage Quotient (DQ): It is used to determine whether a particular exon was deleted or duplicated in

a multiplexed PCR reaction where U stands for the unknown and C for control. The exons 4 and 17 are chosen arbitrarily. (Formula after Dabora SL et al 2001 Am J Hum Genet 68:64; ▶exon, ▶PCR multiplex

Dose Rate Effects: Usually at low dosage, the correlation between the frequency of mutations and mutagen (ionizing radiation) is linear but at higher doses the response curve follows second or higher order kinetics because of the multiplicity of effects (hits) on the genetic material. ▶radiation effects, ▶kinetics

Dosimeter Film (badge): It contains photographic emulsion that can detect β , γ and X-radiation by blackening when developed. The films are used within the range of 20 keV for X rays and 200 keV for β radiation. ▶radiation measurements

Dosimeter, Pocket: It contains an ion chamber and detects ionizations due to X or γ radiation. The direct reading types are held against light to make a reading against a precharged value. Its useful range is generally 0 to 200 mR. Sometimes they may display false readings. ▶radiation measurement

$$DQ = \frac{\text{Area Locus exon 4(U) / AREA Locus exon 17(U)}}{\text{Area Locus exon 4(C) / Area Locus exon 17(C)}}$$

Dosage quotient

DOT: Department of Transportation (USA) regulates shipment of certain substances. ▶mutagens, ▶carcinogens, ▶environmental mutagens

Dot Blot: ▶colony hybridization

Dot Matrix: A method for aligning complex sequences. The two sequences are placed along the vertical and horizontal axes of a square (see Fig. D94). The matching residues form a diagonal, which may be discontinuous if mutation, deletions or insertions

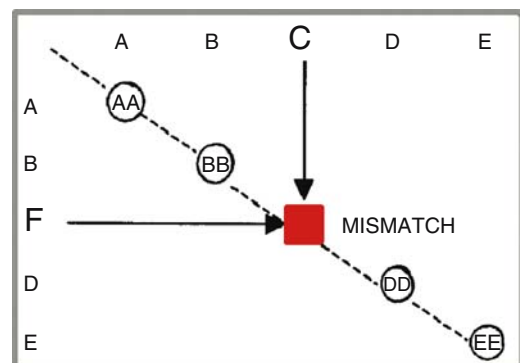


Figure D94. Dot matrix

distinguish the two sequences. Such an arrangement is actually similar to a checkbox or Punnet square of classical genetics. ► [Punnet square](#); Sonnhammer EL, Durbin R 1995 Gene 167 [1–2]:GC1.

DOTAP: ► [liposome](#), ► [lipids cationic](#)

DOTMA: ► [lipids cationic](#)

Dotted: ► [Dt gene](#)

Double-Blind Test: Neither the subjects nor the experimenter knows who received the treatment and who received the placebo. ► [placebo](#), ► [open-label trial](#)

Double Bridge: It is visible at anaphase I if four-strand recombination occurs in paracentric inversion heterozygotes or in the case of sister-chromatid exchange in ring chromosomes. ► [bridge](#), ► [inversion](#), ► [dicentric ring chromosome](#)

Double Cortex: Human Xq21.3-q24 brain defect of the thinner cortex and disorganized neurons resulting in mental retardation and seizures. ► [mental retardation](#), ► [seizures](#)

Doublecortin (DBX): DBX and doublecortin-like (Dclk) kinases control mitotic proteins associated with neuronal development and neuronal migration (Shu T et al 2006 Neuron 49:25; Koizumi H et al 2006 Neuron 49:55).

Double Cross Hybrids: These were extensively used for the commercial production of hybrid corn. The seed companies produced the seed of single crosses (1) and (2) and crossing the two single crosses according to the scheme yielded the seed for the farmers to produce corn for food, feed or industrial raw material (Fig. D95). Currently, most of the corn hybrids are single-crosses. ► [hybrid vigor](#), ► [heterosis](#), ► [cytoplasmic male sterility](#)

single cross (1) [A x B] x [C x D] single cross (2)
DOUBLE CROSS SEED ←

Figure D95. Derivation of Double Cross Hybrids

Double Crossing Over: A single recombination changes the synteny of linked markers (see Fig. D96). The frequency of double crossing over is expected to equal the product of the frequency of the single crossing overs. 2-strand double crossing over within

an inverted segment generally has no harmful effect in inversion heterozygotes and two normal and two inverted chromosomes are recovered in the gametes. 3-strand double crossing over within the inversion produces 1 acentric, 1 dicentric, 1 functional recombinant chromosome with a piece of the inverted segment and 1 functional (inverted or non-inverted chromosomes). 4-strand double crossing over within a paracentric inversion heterozygote leads to the formation of double bridges (two dicentric chromosomes) and two acentric fragments and most likely no viable gametes. In pericentric inversions bridges do not occur but the gametes receiving the exchange strands (except the two strand double cross overs) will be duplicated or deficient and most likely non-viable. Double crossing over in translocation heterozygotes, depending on their site, may damage most of the gametes and reduces the fertility below 50%. ► [crossing over](#), ► [inversion](#)

Double Dummy Trial: Clinical test where patients take two sets of medicine (experimental or placebo) for treatment A and treatment B and neither the patients nor the experimenter know who received A or B until the evaluation has been completed.

Double Exchange: ► [double crossing over](#)

Double Fertilization: It occurs in plants when one of the generative nucleuses of the pollen fuses with the haploid egg and gives rise to the zygote whereas the other fuses with the two polar nuclei and initiates the development of the triploid endosperm. In a *cdc2* mutant *Arabidopsis* the pollen tube contains only a single sperm and that fertilizes the egg, yet minimal endosperm (and mainly aborted seeds) developed indicating the transfer of a positive signal to the two nuclei of the future endosperm that normally is triploid after fertilization by the second sperm (Nowack MK et al 2006 Nature Genet 38:63). ► [gametophyte](#), ► [embryogenesis in plants](#), ► [heterofertilization](#), ► [semigamy](#), ► [apomixis](#), ► [polyembryony](#), ► [adventive embryony](#), ► [parthenocarp](#), ► [xenia](#), ► [metaxenia](#), ► [CDC2](#), ► [pollen tube](#)

Double Flowers: ► [flower differentiation](#), ► [petal](#), ► [Matthiola](#)

Double Helix: Two deoxyribonucleotide chains formed by phosphodiester linkages are joined in a helical arrangement through hydrogen bonding between bases

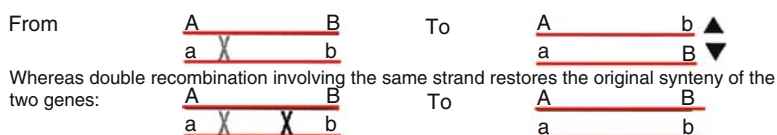


Figure D96. Double crossing over

as determined essentially by the Watson and Crick model (see Fig. D97). The two DNA strands form plectonemic coils (wound around each other) that can be partially and locally released during replication by the helicase and topoisomerase enzymes. ▶DNA types, ▶Watson and Crick model, ▶helicase, ▶topoisomerase, ▶plectonemic coils; Nature (2003) 421:395–453.



Figure D97. DNA double helix

Double Heterozygote: Heterozygous at two gene loci.

Double Homozygote: Homozygous at two gene loci.

Double Infection: A bacterial cell may be infected with two different genotypes of the same or compatible bacteriophages and this may provide an opportunity for phage recombination. ▶multiplicity of infection

Double Lysogenic: A bacterium carrying a normal lambda phage, side-by-side with a λ dg. This lambda-defective-galactose phage lost a piece of its genetic material but acquired the bacterial *ga*⁺ gene and is thus capable of specialized transduction if another phage compensates for its defect. When such a phage is induced (to switch from prophage to vegetative phage) it produces a *high frequency lysate* and high *specialized transducing* ability. ▶transduction, ▶lysogen

Double Minutes (DMs): Extrachromosomally amplified chromatin containing a particular acentric chromosomal segment (gene). The homogeneously stained sites in the chromosomes indicate their incorporation. They occur frequently in cancer cells. ▶cancer, ▶homogeneously stained sites, ▶fragile sites, ▶YAC, ▶DM chromosome, ▶amplification; Zimonjic DB et al 2001 Cytogenet Cell Genet 93:114.

Double Muscling: ▶myostatin

Double Negative Cell: Lymphocytes in the thymus without CD4 or CD8 proteins.

Double PCR and Digestion: A procedure intended to enrich mutant DNA sequences in the amplified mtDNA. During the first PCR step both mutant and wild type DNA is amplified. Then a restriction endonuclease is applied which degrades the wild type but not the mutant DNA. A subsequent PCR step then amplifies the full-length mutant sequence. ▶polymerase chain reaction, ▶mtDNA

Double Positive Cell: It expresses both CD4 and CD8 proteins but may die within the thymus. ▶T cell, ▶lymphocytes

Double Reciprocal Plot: ▶Lineweaver-Burk plot

Double Recombination: Two recombinations in between two strands (chromatids, DNA) within a determined interval (see double crossing over). It is genetically detectable only if there are multiple markers in the chromosome.

Double Reduction: A chromatid segregation, which may occur when in a trisomic or tetrasomic individual recombination takes place between a gene and the corresponding centromere (see Fig. D98). Consequently, in a duplex, double recessive gametes are produced and e.g., an *AAa* individual produces *aa* gametes. The chromosome mechanism leading to double reduction in case of tetrasomy is represented at the entry *alpha parameter*. ▶trisomic analysis, ▶autopolyploid, ▶centromere mapping in higher eukaryotes, ▶alpha parameter

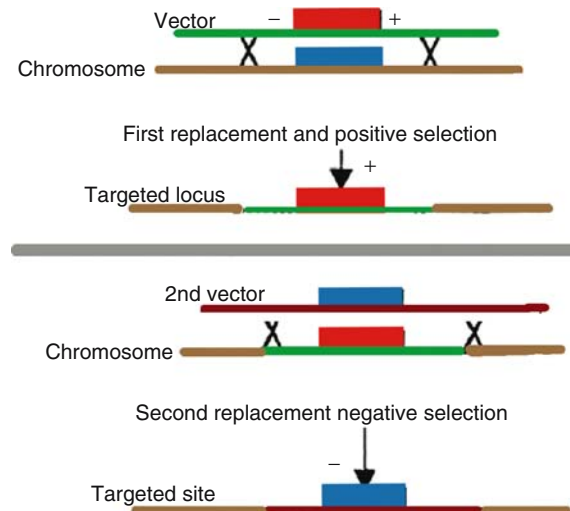


Figure D98. Double replacement targeting

Double Replacement Targeting: It can be used for the insertion very small changes within a gene locus. The procedure is suitable for the HPRT marker where both positive and negative selections are practical. The first replacement is followed by a second step with another vector homologous to the same target and carrying the negative selectable gene, which then screened. (Moore RC et al Biotechnology 1995 13:999; see diagram).

Double Restriction: The DNA is cleaved by two restriction enzymes. ▶restriction enzymes

Double Stranding: The sequencing of both strands of the DNA to minimize errors.

Double-Copy Vector: A transgene, including its promoter, is inserted into the 3'-LTR. After replication (since the 3'-LTR is the template for the 5'-LTR) the

transgene + promoter + the regular 5'-LTR promoter are present in the new construct that is expected to display high activity of the transgene because of the duplications. The transgene may be inserted in either forward or in reverse orientation. In the former case, it may slow down the expression from the downstream copy. In the reverse orientation this may not happen but the transgene may not find its own polyadenylation signal. Nevertheless, its stability may not suffer because the signal may be provided by adjacent cellular gene(s). ►retroviral vectors, ►SIN vectors; Wiznerowicz M et al 1997 Gene Ther 4:1061.

Doubled Haploid: A diploid line arising by doubling the chromosome number of a haploid. Therefore, they are expected to be homozygous at all gene loci until mutation occurs. ►haploid

Doubleisotrismic: In wheat, $20'' + (i + i)1'''$, $2n = 43$, [$''$ = disomic, $'''$ = trisomic, i = isochromosome]. ►disomic, ►trisomic, ►isochromosome

Doublemonoisosomic: In wheat, $20'' + i' + i'$, ($2n = 42$), [$''$ = disomic, $'$ = monosomic, i = isosomic]. ►disomic, ►monosomic, ►isosomic

Doublemonotelosomic: In wheat, $20'' + t' + t'$, $2n = 42$, [$''$ = disomic, $'$ = monosomic, t = telo-chromosome]. ►disomic, ►monosomic, ►telosome

Double-Strand Breaks (of the chromosomes): They occur frequently as a consequence of ionizing radiation of the nuclei, exposure to various chemicals (mutagens, carcinogens), free oxygen radicals, cellular enzymes, etc. Palindromic “at-risk sequence motifs” (ARMs), trinucleotide repeats, arrest of the cell cycle, meiotic recombination, mating type switch, intron homing may all cause such breaks. Double-strand breaks (and repair) are requisites for meiotic recombination or for any segmental interchange of the chromosomes. Apparently, when double-strand breaks occur the broken sites tend to congregate and thereby translocations are facilitated (Aten JA et al 2004 Science 303:92). In the budding yeast, mitochondrial DNA sequences may be incorporated into chromosomal DNA in the vicinity of the LTRs of retrotransposons.

The frequency of spontaneous DSB formation have been inferred from inviability, chromosome loss or cytogenetic phenotypes of cells lacking DNA repair proteins, some of which affect processes other than repair. These estimates range from 0.2–1 per genome replication in *Escherichia coli* and 50 per human genome (Vilenchik MM, Knudson AG 2003 Proc Natl Acad Sci USA 100:12871). Single-strand breaks occur 15–20 times more frequently. For repair of the breaks Ku70, Ku80, DNA-dependent protein kinase, XRCC4 and DNA ligase IV are required.

Double-strand breaks may be repaired by gene conversion. *E. coli* mutants in base excision repair because of defects in glycosylase activity are less susceptible to double-strand breaks but overproduction of glycosylases results in more DNA lesions. The DNA breaks occur when the glycosylase attempts to remove the damaged DNA. In higher eukaryote cells more than 8 double-strand breaks may occur daily. Double-strand breaks may be repaired by up to 20% efficiency with targeted oligonucleotides (Storici F et al 2003 Proc Natl Acad Sci USA 100:14994). In yeast histone H2A, phosphorylated at Ser129 is recruited to the site of the break and additional protein factors such as Arp4 and NuA4 and other chromatin remodeling proteins are also directed to the site for repair (Downs JA et al 2004 Mol Cell 16:979). Post-replicative break repair require the presence of cohesin along both arms of the chromosomes. DNA checkpoint kinases Mec1p and Tel1p phosphorylate histone H2AX and this generates a domain for cohesin binding and Mre1 and Scc2p enable binding (Ünal E et al 2004 Mol Cell 16:991). Proteasome subunit Sem1/DSS1 is also required for double-strand break repair by both homologous and non-homologous end joining repair (Krogan NJ et al 2004 Mol Cell 16:1027). Double-strand breaks are sensed in mammalian cells by the Mre11–Rad50–Nijmegen breakage syndrome 5 complex (MRN) and it recruits ataxia telangiectasia mutated (ATM) to the broken ends and cell cycle arrest, apoptosis and DNA repair are activated (Lee J-H, Paull TT 2005 Science 308:551).

RNA nucleotides complementary to DNA may serve as templates for repairing double-strand break in yeast using DNA polymerases α and δ (Storici F et al 2007 Nature [Lond] 447:338). ►palindrome, ►ROS, ►trinucleotide repeats, ►intron homing, ►chromosomal aberrations, ►chromosomal instability, ►end-joining, ►non-homologous end-joining, ►LTR, ►retrotransposon, ►Ku, ►PARP, ►X-ray repair, ►ATM, ►RAD50, ►RAD51, ►terminal deoxynucleotidyl transferase, ►DNA repair, ►glycosylases, ►DNA-PK, ►DNA ligases, ►Arp, ►NuA, ►chromatin remodeling, ►XRCC, ►X-ray caused chromosome breakage for illustration, ►V(D)J, ►gene conversion, ►Mac, ►Tel, ►histones, ►Mre, ►Scc, ►cohesin, ►Szostak model, ►mismatch repair, ►delitto perfetto, ►telomerase; Haber JE 2000 Trends Genet 16:259; Paques F, Haber JE 1999 Microbiol Mol Biol Rev 63:349; Blaisdell JO, Wallace SS 2001 Proc Natl Acad Sci USA 98:7426; Hopfner K-P et al 2002 Current Opin Struct Biol 12:115; double-strand break repair in human cells: O'Driscoll M, Jeggo PA 2006 Nature Rev Genet 7:45; Su TT 2006 Annu Rev Genet 40:187; double-strand break repair review: Downs JA et al 2007 Nature [Lond] 447:951.

Double-Strand-Break Repair Model of Recombination:

►Szostak model, ►double-strand breaks

Double-Strand RNA: ►RNA double-stranded

Doublestranding: The sequencing of both complementary strands of particular DNA stretch in order to minimize errors. ►compression in gels, ►base calling

Doublet: A double band in the salivary gland chromosome or a double band in an electrophoretic gel (see Fig. D99). Also, *Paramecia* that share a common endoplasm and a single macronucleus. ►salivary gland chromosomes, ►gel electrophoresis, ►*Paramecium*

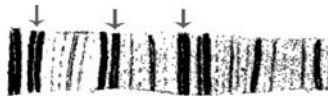


Figure D99. Doublet

Double-Targeting Vector: It increases transformation efficiency by using selective CAR-specific adaptor proteins for special cells and specific promoters for transcription of the desired gene. Such an approach may enhance efficiency many folds. ►CAR, ►retroviral vectors, ►gene therapy

Doubletelotrisomic: In wheat, $20'' + (t+ t) + 1'''$, $2n = 43$, [$''$ = disomic, t = telochromosome, $'''$ = trisomic]. ►disomic, ►telosome, ►trisomic

Doubling Dose: The amount of a mutagen that doubles the spontaneous rate of mutation. Since mutation rate depends on the organisms, its genotype, developmental stage and environmental factors, the estimates arrived at by different investigators may not be identical. From mouse experiments it had been estimated that 1 R chronic ionizing radiation produces a mutation rate of 2.5×10^{-8} per locus per generation and the spontaneous rate was considered to be 1×10^{-6} , hence $(1 \times 10^{-6}) / (2.5 \times 10^{-8}) = 40$ R was assumed to be the doubling dose of ionizing radiation for humans too. Other estimates considered the doubling dose for recessive mutations 32 R and for dominant ones 20 R. More recently, the doubling dose for radiation has been estimated as 100 cGray (1 Rad). The majority of the data are systematically biased, depending on the genes used because the range of inducible mutations in mouse may vary within a range of about an order of magnitude and therefore, the samples used may not be true "average representatives". The doubling dose may have important meaning for the estimation of genetic radiation risks. Assuming that the average human dominant mutation rate is 10^{-5} to 10^{-6} , the chances

for the occurrence of a human dominant mutations at 100 R dose (1 R = ca. 93 erg/wet tissue) exposure may be 32×10^{-5} to 32×10^{-6} , i.e., 1/3,125 to 1/31,250. Actually, these estimates may not be very accurate but direct data cannot be readily obtained in human populations. Another problem is that the mutant gametes may not compete successfully and the absolute genetic damage may be much larger than these estimates. An additional problem is that in human populations the mating is random (or almost random) therefore homozygous recessives may not appear most of the time unless the marriages are consanguineous. Atomic radiations in Hiroshima and Nagasaki substantially increased the incidence of cancer and teratogenesis in the generation exposed, but an increase in human mutations in the following generation was not clearly detectable except by altered sex ratio. Based on the Hiroshima and Nagasaki human data of 31,500 children of parents exposed to the bombs within a 2-km range of the epicenter, James Neel estimated the doubling dose for low-level chronic radiation to be 3.4 to 4.4 Sv equivalent. On the basis of various mouse irradiation data the average doubling dose in mouse he estimated as 1.35 Gy. This latter figure was derived by pooling of recessive lethals (1.77), recessive visibles (3.89), dominant visibles (0.16), deletion or mutation of the dominant allele in male mice at 7 loci (0.44), protein loci (0.11), etc. studied in different mouse strains. The Chernobyl atomic power plant accident in 1986 has shown, however, genetic effects and increase in cancer caused by atomic radiation. A medical X-ray machine may deliver 0.04 to 1.0 rem (100 rem = 1 Sievert [Sv]) to the organ or structure routinely examined. Although the gonads are generally shielded during these examinations, some general risk remains, particularly for carcinogenic effects. Molecular techniques developed to detect mutations in DNA base and amino acid sequences have also been used to ascertain doubling doses. ►radiation effects, ►mutation in human populations, ►radiation hazard assessment, ►relative mutation risk, ►coefficient of inbreeding, ►atomic radiation, ►teratogenesis, ►RBE, ►Rem, ►Rad, ►Sievert, ►BERT, ►specific locus mutations assay, ►mutation detection; Sankaranarayanan K, Chakrobarty R 2000 Mutation Res 453:183.

Doubling Time: The time required for the completion of a cell division, measured in minutes, hours or days for specific cell types under defined conditions. ►cell cycle

Doubly Uniparental Inheritance: It is displayed by the mitochondria of some marine mollusks (*Mytilidae*). They have two types of mitochondria: one (F) is transmitted by the females to both female and male

offspring, and the other (M) is transmitted by the males only to the male offspring. ►mitochondria, ►uniparental inheritance, ►paternal leakage; Southerland B et al 1998 Genetics 148:341.

Douglas Fir (*Pseudotsuga menziesii*): Primarily a forest timber tree with $2n = 2x = 26$.

DOVAM-S (detection of virtually all mutations—single strand conformation polymorphism): A rapid method with very high efficiency. ►single-strand conformation polymorphism; Liu Q et al 1999 Biotechniques 26:932, 936, 940.

Dowex Resins: Ion exchangers and used also for gel filtration and chromatography. ►ion exchange resins, ►gel filtration, ►chromatography

Down Promoter: It slows down the rate of transcription.

Down-Regulation: decreasing activity by regulation. ►up-regulation, ►regulation of gene activity

Down's Syndrome: It is caused by primary trisomy or translocation of human chromosome 21 or 21q21–22.3. Robertsonian translocations occur in 5% of the patients, most commonly with 14q21q (Berend SA et al 2003 Am J Hum Genet 72:488). Older literature calls Down syndrome by the unfortunate term of *mongoloid idiocy*. The incidence of this condition varies from less than 1/1,000 at maternal age around 20 years to close to 100/1,000 live birth when the mother approaches menopause.

Trisomy 21 may affect only part of the body in a mosaic pattern. The transmission of disomic gametes is about 91% through the females and 9% through the males. The fertility of the afflicted persons is reduced (especially males) and the afflicted females is less than 50%. The most important phenotypic transmission risk by signs in humans involve a relaxation of the muscles (hypotonia) controlling the eyefold, protruding tongue, flat face, shorter than expected height, two third displays the

simian fold in the palm (see Fig. D100, Fig. D101), generally (but not always) reduced mental abilities (IQ 25 to 50 although with proper training they can learn to read and write and enjoy life and usually are quite sociable and affectionate.

This trisomy is associated with a series of other anomalies such as heart disease, susceptibility to megakaryoblastic leukemia. For leukemia and other tumors the SIM2 (Single Minded) gene encoding a basic helix-loop-helix motif within chromosome 21q22.2 is responsible. SIM1 in human chromosome 6q16.3-q21 is similar to SIM2. SIM2 exists in long and short forms due to alternative splicing (DeYoung MP et al 2003 Proc Natl Acad Sci USA 100:4760).

Prenatal cytological examination of fetal cells in the amniotic fluid and sampling chorionic villi may reveal if the fetus has this condition. Unfortunately, amniotic cells may display anomalies that do not occur in the normal cells of the fetus. There is a correlation between the low level of maternal α -fetoprotein (MSAFP) and fetal Down syndrome. The interpretation of the clinical analysis is further sharpened if unconjugated estriol (α -hydroxylation product of estradiol) and gonadotropin levels are also measured. Ultrasonic analysis may also indicate Down syndrome prenatally if heavy skin fold on the neck (nuchal translucency test, NT), excessive fluid accumulation, narrow small intestines or short bones are indicated. First-trimester NT screening for Down syndrome enables a significant number of women over age 35 to lower the risk for chromosome 21 trisomy several fold and avoid the risks of invasive testing (see Fig. D102). However, despite significant reductions in age-specific mid-trimester risks, a relatively high proportion of women over 35 years of age still opt for invasive testing (Caughey AB et al 2007 Prenatal Diagn 27(2):119). A newer, non-invasive technology is digital PCR SNP, which analyzes the fetal nucleic acids in maternal plasma. The use of digital PCR determines the allelic imbalance of a SNP on PLAC4 mRNA,

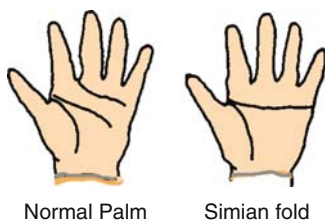


Figure D100. In a normal individual the palm creases do not go all the way from one side to the other (left). In Down syndrome and some other congenital disorders the typical Simian folds present. In addition, the hands may be shorter and the little finger crooked



Figure D101. Down's syndrome

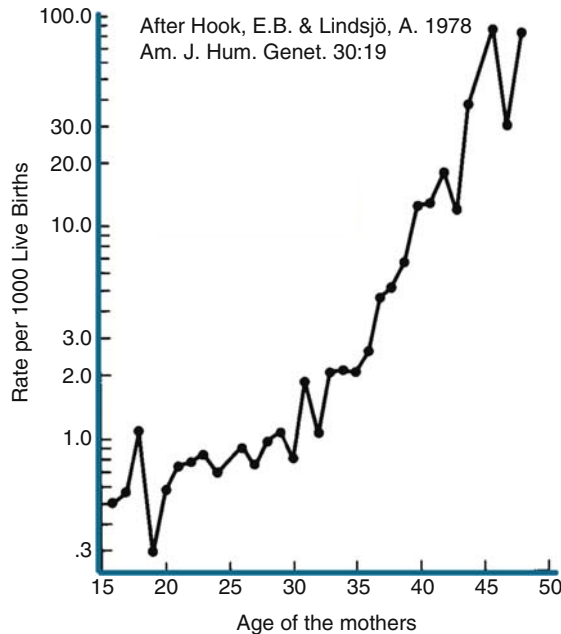


Figure D102. Down's syndrome, Sweden 1968–1970

a placenta-expressed transcript on chromosome 21, in the maternal plasma of women bearing trisomy 21 fetuses. The procedure appears to be accurate (Lo YMD et al 2007 Proc Natl Acad Sci USA 104:13116). The recurrence risk of trisomy is very low unless the family has a history of non-disjunctions and heterozygous for translocations involving chromosome 21. In the expression of the bone characteristics of this trisomy, the ETS oncogene and transcription factor (human chromosome 21) may play the major role. The *DSCR1* (Down syndrome critical region) gene at 21q22.1-q22.2 encodes a proline-rich inhibitor of calcineurin protein phosphatase, which is highly expressed in the fetal brain and other organs (Fuentes JJ et al 2000 Hum Mol Genet 9:1681). The brain of DS individuals has fewer neurons and abnormal neuron differentiation. Apparently, several genes are overexpressed in the critical region of human chromosome 21 and the corresponding mouse region (Amano K et al 2004 Hum Mol Genet 13:1333). The expression of some chromosome 21 genes is however lower or are at normal level or highly variable among individuals (Yahya-Grayson EA et al 2007 Am J Hum Genet 81:475). In mouse, the human 21 chromosome genes are distributed among three chromosomes, 16, 21 and 22. In addition, the neurons become apoptotic earlier and predispose them to Alzheimer syndrome symptoms. These defects have been attributed to elevated levels of lipid peroxidation. The defects in the

nervous system are attributed also to *DYRK*, a dual-specificity tyrosine phosphate regulated kinase (Martinez de Lagran M et al 2004 Neurobiol Dis 15:132). Folate deficiency and hypomethylation due to defects in methylene tetrahydrofolate reductase and methylene synthase reductase may favor the nondisjunction involved. Many thousands of genes are involved in trisomy and even in smaller duplications, the number of genes can be several hundreds. Therefore, the precise molecular cause of the clinical symptoms is difficult to interpret (Vacik T et al 2005 Proc Natl Acad Sci USA 102:4500). Screening, using several tests, from the first trimester of pregnancy is highly effective (Malone FD et al 2005 New England J Med 353:2001). NFAT transcription factor is crucial for animal development. Two genes of mouse *DSCR1* (*Down syndrome critical regulator*, inhibitor of calcineurin) and *DYRK1A* (a nuclear serine/threonine kinase acting on GSK3) synergistically hinder the nuclear occupancy of NFATc transcription factors and this leads reduction in activation of NFAT-depending genes. This fact explains the cognitive deficits and muscular hypotonia and other symptoms of trisomy 21 (Arron JR et al 2006 Nature [Lond] 441:595). ▶nondisjunction, ▶trisomy, ▶trisomic analysis, ▶MSAFP, ▶I.Q., ▶amnion, ▶estradiol, ▶fetoprotein, ▶translocation, ▶prenatal diagnosis, ▶homocystinuria, ▶amniocentesis, ▶Alzheimer disease, ▶apoptosis, ▶triple test, ▶mongolism, ▶NFAT, ▶calcineurin, ▶GSK3, ▶PCR; Hassold PA, Jacobs PA 1984 Annu Rev Genet 18:69; Hunt PA, LeMaire-Adkins R 1998 Curr Top Dev Biol 37:359; Kahlem P, Yaspo M-L 2000 Gene Funct Dis 1:175; Epstein CJ 2001 In: Scriver JR et al (eds), The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, p. 1123; Gardiner K et al 2002 Genomics 79:833; Patterson D, Costa ACS 2005 Nature Rev Genet 6:137.

Downstream: In the direction of the 3' terminus of the polynucleotide; the nucleotide chain grows downstream because the nucleotides are added to the 3' OH end of the preceding one.

Downstream Box: A downstream enhancer of prokaryotic translation of mRNA. It appears that it is not acting by binding to the 16S rRNA (anti-downstream box) as previously suggested.

Downtag: ▶bar-code genetic

Doxorubicin (adriamycin): An antineoplastic agent, immunosuppressant, inhibitor of reverse transcriptase and suspected a carcinogen (see Fig. D103). A single recessive gene in chromosome 16 of mouse determines doxorubicin susceptibility and a modifier exist in chromosome 9. The susceptibility is correlated

with renal disease. (Zheng, Z et al 2005 Proc Natl Acad Sci USA 102:2502). ►angiogenesis

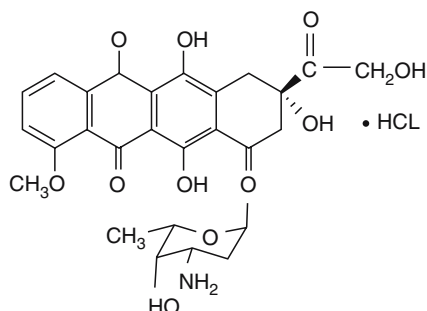


Figure D103. Doxorubicin hydrochloride

Doxycycline: An analog of tetracycline (see Fig. D104).
►tetracycline

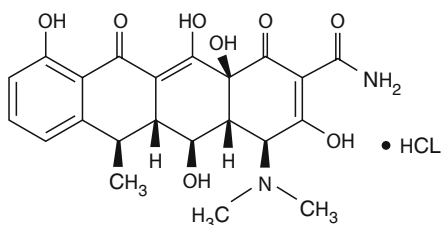


Figure D104. Doxycycline

Doyme Honeycomb Retinal Dystrophy: ►macular degeneration

DP1: A transcription factor activated by MDM2.
►MDM2, ►E2F1

DPA (DNA pairing activity): A protein (120-kDa) that promotes the formation of heteroduplexes in yeast.
►recombination mechanisms eukaryotes

DPC4 (deleted in pancreatic cancer at human chromosome 18q21.1): A gene missing in about 50% of the pancreatic cancer cells. It is homologous to the *Drosophila* mad (many abnormal [imaginal] discs, 3–78.6) gene, member of the *dpp* (decapentaplegic) family, encoding a transforming signal related to TGF. ►morphogenesis in *Drosophila*, ►tumor suppressor genes, ►TGF, ►SMAD, ►imaginal disc

dpc also d.p.c. (days post coitum): The time after mating has taken place (in embryonic/fetal development).

DPE (downstream promoter element): ►core promoter, ►DSTF

dpm (disintegration per minute): The number of disintegrations per 1 g radioactive radium = 1 μ Ci = 2.2×10^6 dpm but usually about half as many counts

per minute (cpm) are shown in the equipment that generally work at about 50% efficiency. ►Curie

DPN (diphosphopyridine nucleotide): Current name NAD (nicotinamide adenine dinucleotide).

dpp (decapentaplegic): ►morphogenesis in *Drosophila* {17}

DPT: ►developmental therapeutics program

DQ Antigen: Antigen encoded by the DQ segment of the HLA complex. ►HLA

DR (death receptor): ►TRAIL, ►death domain, ►apoptosis

DR Antigen: Antigen encoded by the DR alleles of HLA. ►HLA

DRADA: A dsRNA-dependent adenosine deaminase; an RNA editing enzyme in mammals; the same as dsRAD. ►RNA editing, ►dsRNA

Draft Genome Sequence: An assembly of scaffolds into a nucleotide sequence map, which still has some gaps and other deficiencies. ►scaffolds in genome sequencing; Katsanis N et al 2001 Nature Genet 29:88; ►human genome

DRAP: ►DSTF

Dras: *Drosophila* homolog of *ras*. ►RAS oncogene

DRB (5,6-dichloro-1- β -D-ribofuranosylbenzimidazole): A potent inhibitor of eukaryotic mRNA synthesis in crude in vitro transcription system but not with purified polymerase II. ►transcript elongation, ►P-TEFb

DREAM (downstream-regulatory element antagonist modulator): A transcriptional repressor. When its calcium binding sites “EF-hands” are occupied by Ca^{2+} it comes off from the DRE element of the gene and transcription may be facilitated. ►CREB, ►calmodulin; Ledo F et al 2000 Mol Cell Biol 20:9120.

Dredging, Data: The finding tendencies within the set of data unforeseen at the outset. ►data mining

DRES: *Drosophila*-related expressed sequences.

DrFP583: A fluorescent protein that may change color from green to red after some elapse of time and may be used to monitor of gene expression in function of time. ►aequorin

Drift, Genetic: A change in gene frequencies caused by a sampling error in the gametic array of random mating populations. Such a change, due to chance, is most likely when the effective population size (the number of breeding individuals) is small. Genetic drift may occur repeatedly in a population and can cause substantial changes in the frequency of several

genes. The change does not reflect the adaptive value of the alleles involved. ►effective population size, ►founder principle, ►genetic drift, ►hitchhiking, ►mutation neutral, ►Muller's ratchet, ►antigenic drift, ►antigenic shift; Wright S 1921 *Genetics* 6:111; Pritchard JK 2001 *Am J Hum Genet* 69:124; Frost SD et al 2001 *Proc Natl Acad Sci USA* 98:6975.

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Drip (ARC [activator required cofactor]): A transactivation complex of ~16 subunits in the chromatin. ►transactivator, ►chromatin; Taatjes DJ et al 2002 *Science* 295:1058.

DRIP (defective ribosomal products): About 30% of the proteins produced suffer translational error and chopped up by proteasomes, the quality control system of the cell. The amino acids are then recycled. Similar fate is waiting for some of the viral proteins forced upon the cells by the viral genetic material after infection. Aging cells may also be destroyed by apoptosis when their mission is completed. Viral proteins are disposed of mainly with the assistance of the major histocompatibility system class I (MHC I) that displays the peptide fragment of the surface of the cell. The MHC class II molecules similarly handle extracellular bacterial protein pieces. The MHC molecules reside inside the cells and the peptides are transported into the endoplasmic reticulum by TAP to meet the MHC system. The undesirable peptides are then loaded there onto the MHC molecules, which ferry them to the cell surface. The circulating T cells intercept the MHC—undesirable peptide complex and trigger an immune reaction. ►proteasome, ►apoptosis, ►MHC, ►TAP, ►T cell, ►immune system

Driver Excess Hybridization: ►subtractive cloning

DRK: A downstream receptor kinase of the *Drosophila* light signal transduction pathway. Its vertebrate homolog of GRB2 and it is equipped with SH2 and SH3 domains and it is frequently called a mediator protein in signal transduction. ►GRB2, ►SH2, ►SH3, ►signal transduction

Droe1: 24 kDa *Drosophila* mitochondrial homolog of GrpE. ►Grp

Drosha: Double-stranded RNA-specific type III RNase, and produces a precursor of miRNA with 5' phosphate and 2-nucleotide 3' overhang. For its activity, an RNA binding protein is also required (Tomari Y, Zamore PD 2005 *Current Biol* 15:R61). ►microRNA, ►mirtron; Elbashir SM et al 2001 *Genes Dev* 15:188.

Drosophila: Species of dipteran flies. Genetically most thoroughly studied is the cosmopolitan *D. melanogaster*, (n = 4). The species are reproductively isolated, i.e., they may intermate if the opposite sex

from the same species is not available but the F1 offspring is sterile. The sterile eggs may be recognized by the lack of filaments (see diagrammatic life cycle in Fig. D105). The size of the eggs is about 0.5 mm. Within less than a day, it hatches into the first instar stage larva. (The instar is a larval growth stage in between moltings). The larvae shed their cuticle by the process of molting. Three instar stages are distinguished. The larvae are very voracious feeders and reach a size of about 4.5-mm. The cuticle of the third instar darkens and hardens and becomes the puparium four days after hatching, and in another four days the metamorphosis completed and from the larva the imago (2-mm) emerges. (The imago is a fully differentiated adult form.) This adult type emerges by the process of eclosion through the anterior (fore) end of the pupa. Within a day its color darkens, the wings expand and the abdomen becomes rotund.

There is no further growth after emergence. Within two days the imagoes may be copulating after a mating courtship and may start laying eggs. The adult males live for about 33 days while the females die on the average after 26 days.

Sexing (determining the gender) of *Drosophila* can be made by looking at the metatarsal segment of the fore leg that carries a structure called *sex comb* in the male only (see Figs. D106 and D107). Sexing is possible also on the basis of the genitalia viewed from the ventral side of the abdomen. The abdominal segmentation is also different in the two sexes. After copulation the female stores the sperm in the spermatheca (located above the uterus) and in the uterus. Once the female had been mated it may keep the sperm for a long time, therefore for each genetically controlled mating generally virgin females are used. The eggs are fertilized just before laying. *Drosophila melanogaster* has XX (female) or XY, XO (male) sex chromosomes and three pairs of autosomes. The X-chromosome (chromosome 1) is acrocentric (has one arm) has a genetic length of about 73 map units; chromosomes 2, 3, and 4 have genetic lengths of about 110, 111 and 3 map units, respectively. The Y chromosome has the *KL* male fertility complex on the long arm and the *KS* male fertility complex on the short arm and no other "visible" genes. The X-chromosome contains the nucleolar organizer region in a tandem array of repeats at the *bb* (*bobbed*) locus, coding for the 5.8S, 18S and the 28S ribosomal RNAs. The polytenic X-chromosome is divided into 20 regions; first is at the tip and the 20th at the centromere. It displays about 1000 bands. The Y chromosome does not display polyteny. The second chromosome contains 20 sections in the left arm (21 at the tip and 40th at the centromere) including about 869 to 927 bands and the right arm starts at the centromere with section 41

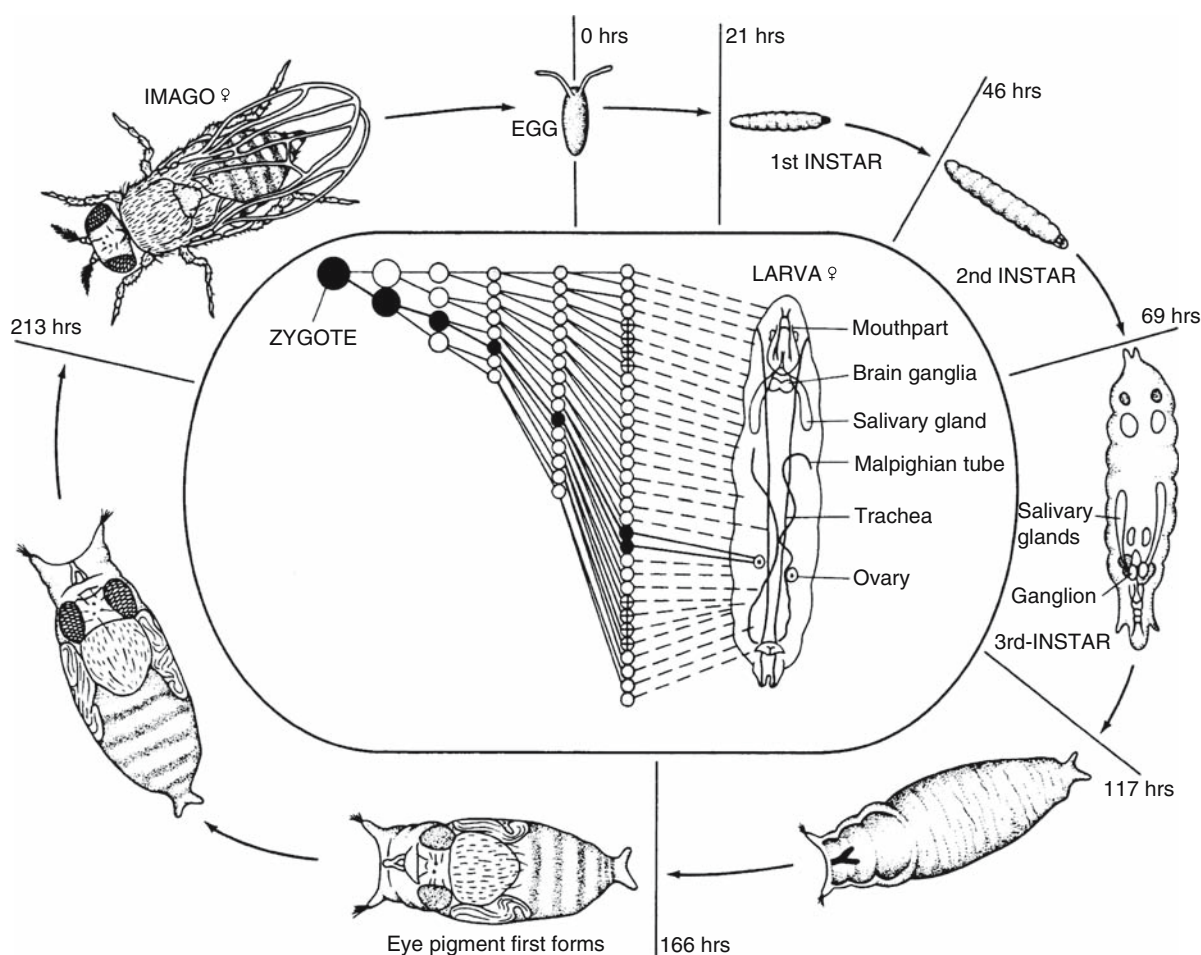


Figure D105. The life cycle of *Drosophila*. The female deposits more than a hundred filamentous eggs (0.5 mm). The hatching maggots (instars) burrow into the food where they undergo two molts. The emerging larvae develop into pupae. The adults (imago) are about 2 mm long when they emerge from the pupal case. The average lifetime of the females is about 4 weeks; the males may live a little longer. The organs of the adults develop from the imaginal discs, present at the 1st instar stage. In the center (insert) the development of the germline is shown

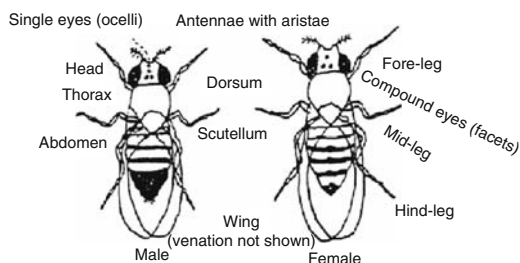


Figure D106. The major areas of the body of *Drosophila melanogaster*. Surface appendages (bristles, hairs) and wing venation are not shown here. (see more at figures in morphogenesis in *Drosophila*)

and ends with section 60 at the other telomere including 1009 to 1152 bands depending on the classification of doublets and singlets. Chromosome 3 appears the longest. The left arm begins with

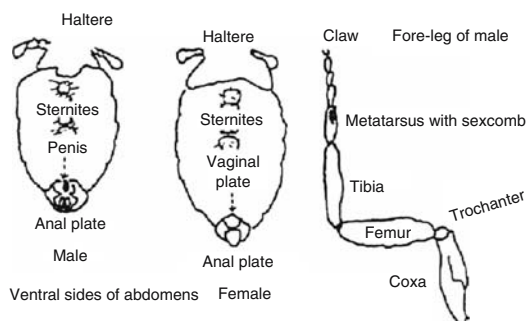


Figure D107. Sexing of the flies is by inspection of the sexcomb present only on the metatarsus of the fore-leg of the male and the genitalia, visible on the posterior ventral part of the abdomen. For examination, the flies are anesthetized for 5–10 min with ether or other suitable times and placed under the dissecting microscope

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section 61 at the tip and section 80 at the centromere including 884 to 1032 bands. The right arm starts with section 81 at the centromere through section 100 at the other end, containing about 1147 to 1233 bands depending on the classification. Chromosome 4 is extremely short and does not display very clear polyteny and does not contain more than about 40 to 50 bands. It is divided into sections 101 and 102, proximally and distally to the centromere, respectively. Each section is further subdivided into A, B, C, D, E, F subsections by vertical lines positioned left to conspicuous bands. Within lettered subdivisions individual bands are numbered. The size of the nuclear genome is ca. 180 Mb and the circular mitochondrial genome contains 19,500 bp. The total euchromatin is ~121 Mb. The origin of replication of the mtDNA is within an AT rich tract. The replication of the first strand is completed before the replication of the 2nd strand begins. It codes for ribosomal RNA and 22 tRNAs. It encodes also cytochrome b, cytochrome c oxidase, two subunits of ATPase and for 7 subunits of the NADH reductase complex. These genes are crowded next to each other with very few nucleotides keeping them apart. They contain no introns. Translation is initiated with ATA, ATT and ATG codons. TAA is the most common termination codon. Codon TGA spells Try (tryptophan) rather than a stop like in the universal codon dictionary. ATA means Met rather than Ile, and AGA is a Ser codon rather than Arg. Codon usage is influenced by the predominance of AT pairs in this genome. "Infectious heredity" is also known in *Drosophilas*, caused by the (RNA) picornaviruses (DAV, DPV, DCV), and the vesicular stomatitis virus-like agent (sigma virus), and the sex-ratio (SR) condition (females do not produce male offspring) caused by spirochete-like protozoa. In *Drosophila melanogaster* more than 4,000 genes and 9,000 chromosomal rearrangements are more or less well characterized. The genome has been almost completely sequenced and more than 13,600 genes have been found yet substantially less than expected.

Alleles at a locus are generally distinguished by superscripts. Recessive alleles in a predominantly dominant allelic series are designated by capital letters but a superscript *r* is added, alternatively in a recessive series of alleles the dominant allele may be identified with lower case letters but with a *D* superscript their dominant expression is identified. The wild type alleles may be designated also by a (+) superscript, and an *rv* superscript and a number indicates revertants of recessive alleles.

Revertants of dominant mutations are considered deficiencies and are symbolized as *Df* with a distinguishing number, e.g., *Df*(1)1-*D1* is a deficiency of chromosome 1 (X-chromosome) and the latter part of

the symbol is explained by words. A number symbolizes alleles specifying the absence of a protein with an *n* superscript and possibly by a number. *Proteins* are frequently designated by three Roman capital letters. Loci moved to new locations by transposable elements are enclosed in brackets followed by the new site in parenthesis, e.g., [*ry*⁺] (*sd*) or [*Cp16*] (*52D*) indicates that the chorion protein gene was inserted by transformation into cytological site *52D*. *Mimics* (different loci but similar phenotype) are designated as e.g., *tu-1a*, *tu1b*, *tu-2* or by arbitrary numbers: *Sgs3*, *Sgs7* or by polytenic location *Act5C*, *Act42A* or by molecular weight *Hsp68*, *Hsp70* added to the letter symbols. *Modifier genes* such as suppressors or enhancers are symbolized with *e* or *E* and *Su* or *su* followed by the symbol of the gene acted upon in parenthesis, e.g., *su* (*lz*³⁴), suppressor of a *lozenge* allele. *Translocations* are symbolized with *T*, e.g., *T*(1;Y;3) indicates an X- and Y-chromosome interchange that may be followed by a number of other symbols. Chromosome rings are indicated as *R*(1)2 where *R* stands for ring, (1) for the X-chromosome and 2 for ring #2. *Inversions* are identified by *In* and additional specifications, e.g., *In* (2*L*)*Cy* indicates an inversion in the left arm of chromosome 2 involving the dominant wing mutation *Curly* or *In*(3*RL*) stands for a pericentric inversion of chromosome 3. Additional specifications may also be applied. *Transpositions* are defined as three-break rearrangements (two are needed for excision and one at the target site). *Tp*(3;1)*ry* designates the movement of a third chromosomal *rosy* allele to the X-chromosome.

Duplications are identified by *Dp* and additional information, e.g., *Dp* (1; 1)^{*y*^{bl}} designates a duplication in the X-chromosome containing the *yellow bristle* marker. When the duplication is a free fragment the designation is *Dp* (1;*f*) and it may further be specified by gene or band symbols added. *Dp*(1;1;1) indicates triplication. *Deficiencies* are defined by *Df*, irrespective whether a chromosomal segment or an entire chromosome (hypodiploid, 2*n* - 1) is involved, e.g., *Df* (2*R*) *vg* is a deficiency of the *vestigial* gene in the right arm of chromosome 2. Complex chromosomal rearrangements can also be symbolized but generally, they require detailed descriptions. Deviations from the euploid, normal chromosomes change the phenotypic sex because the balance of the sex chromosomes and autosomes affects sex in *Drosophila*.

The metafemales have the chromosomal constitution X/X/X;2/2;3/3;4/4, the triploid metafemales are X/X/X/X;2/2/2;3/3/3;4/4/4 (or 4/4 only). Metamales are X/Y;2/2/2;3/3/3;4/4/4. Intersexes may be X/X;2/2/2;3/3/3;4/4/4 with a Y chromosome either present or absent and the numbers of chromosome 4 may vary. Tetraploid females have been observed. Triploids are

X/X/X;2/2/2;3/3/3;4/4/4 (or the sex chromosomes may be either (X/X/X/Y or attached XX/X or XX/X/Y). Haploids of X;2;3;4 are known. Aneuploids nullo-X (Y/Y;2/2;3/3;4/4), nullo-X nullo-Y (0/0;2/2;3/3;4/4), tetra-four (X/X;2/2;3/3;4/4/4/4), triplo-4 (X/X;2/2;3/3; 4/4/4), haplo 4 (X/X;2/2;3/3;4), X0 male (X;2/2;3/3;4/4), XXY female (X/X/Y;2/2;3/3;4/4), XXYY female (X/X/Y/Y;2/2;3/3;4/4), XYY male (X/Y/Y;2/2;3/3;4/4) and YYYY male (either X/Y/Y/Y or attached XY/Y/Y plus normal autosomes) are also known. About 20% of the *Drosophila* genome consist of repeated sequences and display four satellite bands (1.672, 1.686, 1.688, 1.705) upon CsCl density gradient centrifugation [not amplified in the salivary glands]. Other repeated sequences, SINE (0.5 kbp) and LINE (5–7 kbp) 1572 transposable elements were identified. Detailed genetic information on 4,000 gene loci and 9,000 chromosomal aberration (including references) are described in THE GENOME OF DROSOPHILA by D.L. Lindsley and G.G. Zimm, 1992, Academic Press, San Diego, California. Upon sequencing the genome 13,676 genes were estimated in 2000. This number since has increased as the result of improved annotation. The total number of protein-coding genes appears to be ~14,000 (Yandell M et al 2005 Proc Natl Acad Sci USA 102:1566). The number of pseudogenes is small, 17. Some of the genes are overlapping. About 20% of the mRNAs are alternatively spliced. The *mdg4* gene generates 29 transcripts and *Dscam* more than 38,000. *Drosophila* because of its well-manipulated genome and abundance of mutations can be used even for modeling human diseases. A 63% of the predicted *Drosophila melanogaster* proteome has been cataloged (Brunner E et al 2007 Nature Biotechnol 25:576). ▶salivary gland chromosomes, ▶polytenic chromosomes, ▶fruit fly, ▶morphogenesis, ▶imaginal disk, ▶reproductive isolation, ▶instar, ▶molting, ▶puparium, ▶metamorphosis, ▶eclosion, ▶courtship, ▶virgin, ▶nucleolar organizer, ▶infectious heredity, ▶allele, ▶suppressor, ▶translocation, ▶inversion, ▶duplication, ▶deficiency, ▶triploid, ▶aneuploid, ▶tetraploid, ▶transposable elements, ▶P element, ▶hybrid dysgenesis, ▶SINE, ▶LINE; Adams MD et al 2000 Science 287:2185; Rubin GM, Lewis EB 2000 Science 287:2216; Celniker SE, Rubin GM 2003 Annu Rev Genomics Hum Genet 4:89; comprehensive information resources; Matthews KA et al 2005 Nature Rev Genet 6:179; or <http://flybase.org>; <http://flybase.bio.indiana.edu>, *Drosophila* gene homologs of human disease genes; <http://superfly.ucsd.edu/homophila>, tissue-specific genes; FlyAtlas, *Drosophila* genes/development: <http://www.sdbonline.org/fly/ai/main/1aahome.htm>, RNAi;

http://flyrnai.org/cgi-bin/RNAi_screens.pl *Drosophila* species database; <http://insects.eugenes.org/DroSpeGe/>.

Drosopeterin: A bright red eye pigment in insects (*Drosophila*) and related pigments are common in other animals. The *se* (*sepia*) mutants of *Drosophila* (chromosome (3–26.0) accumulate a yellow pigment (a dihydropteridine) but unable to synthesize drosopeterin or iso-drosopeterin because of the defect in PDA (2-amino-4-oxo-6-acetyl-7,8-dihydro-3H,9H-pyr-imido[4,5,6]-[1,4] diazepin) synthetase. ▶pigmentation of animals; Wiederrecht GJ et al 1981 J Biol Chem 256:10399.

Drought Resistance: Soil moisture deficit is a common limiting factor of agricultural crop yield especially in arid regions. Reduced transpiration can conserve water and large root system may better utilize the water content of the soil. Overexpression of vacuolar H⁺-pyrophosphatase in transgenic tomato plants increased root mass, improved cation transport into roots and enhanced the recovery of the plants from episodes of water deficit under laboratory conditions (Park S et al 2005 Proc Natl Acad Sci USA 102:18830). The stress-responsive gene *SNAC1* of rice enhances drought resistance by 22–34% by controlling stomatal closing without reducing photosynthetic function (Hu H et al 2006 Proc Natl Acad Sci USA 103:12987). ▶stress tolerance, ▶salt tolerance

DRP (dynamin-related protein): DRP plays a major role in mitochondrial fission. ▶dynamin; Osteryung KW, Nunnari J 2003 Science 302:1698.

DRPLA: ▶dentatorubral-pallidoluysian atrophy

Drug Combinatorial Treatments: Many diseases are the end results of several genetic (QTL) or metabolic defects and in such cases the administration of more than a single drug is most effective without very detrimental side effects. In a mouse model human adenomatous polyposis (FAP), a non-steroid anti-inflammatory drug (sulindac) and an inhibitor of epidermal growth factor receptor (EKI-569) was quite effective (Torrence CJ et al 2000 Nature Med 6:974). Similarly, the amyotrophic lateral sclerosis model of mouse responded better to a combination of minocycline (lipid-soluble semisynthetic tetracycline) and creatine than either treatment alone (Zhang W et al 2003 Ann Neurol 53:267). Medicine cocktails successfully treat the stubborn cases of acquired immunodeficiency. A combination of ribonucleotide reductase inhibitors (trimidox) and didanosine (reverse transcriptase inhibitor) successfully inhibits retrovirus-induced splenomegaly, hypergammaglobulinemia, activated B-splenocytes and lost splenic structure in

mice (Mayhew CN et al 2005 Antiviral Res 65:13).
 ►epistasis; properties of ~4,100 drugs; <http://redpoll.pharmacy.ualberta.ca/drugbank/>; Wishhart DS et al 2006 Nucleic Acids Res 334:D668.

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Drug Development: Genetic information can reveal the mechanisms of disease mechanism and its metabolic bases and can indicate potential targets for drug development. Model animals play important role in drug design and testing. Unfortunately, animal models may not always respond to drugs the same way or to the same extent as humans. Large scale and targeted mutagenesis and mutation testing in mice and other animals can reveal models for monogenic and complex human diseases. Tissue culture offers unique potentials for drug development because of ethical problems with human experimentation. According to estimates, there are about 3,000 human genetic alterations that can offer potential drug targets, i.e., are “druggable.” G-protein coupled receptors, various ion channels, kinases and phosphatases can be targeted, however without great specificity and precision serious side effects may be encountered in the patients because these molecules affect simultaneously multiple metabolic processes. Peptidomimetics (structurally modified, unnatural, peptides structurally modified molecules) and engineered antibodies with modified variable regions are newer types of potentially potent “drugs.”

Some genes may have substantial impact on the health of human population despite the fact of low penetrance and variable expressivity. In such cases, the precise mechanisms involved are difficult to validate and pose difficulties for drug development. Many human diseases are rather complex, e.g., schizophrenia, diabetes, heart diseases, cancer and a large number of diverse metabolic anomalies may be involved that are hard to clinically decipher and prescribe drugs for in an unambiguously helpful manner. An additional problem is that the majority of human diseases appear as syndromes based on defects of apparently unrelated genes, which affect complex genetic networks at different steps yet the phenotypic consequences can be quite similar. Different mutational sites in the same gene may respond to drugs as either agonists or antagonist of a process. Some of the drugs have multiple effects, some specifically alleviating one health problem and the same time aggravating another. Gain of function mutation in the proprotein convertase subtilisin gene (PCSK9, 1p34.1-p32) results in hypercholesterolemia by destruction of low-density lipoprotein receptor (Maxwell KN et al 2005 Proc Natl Acad Sci USA 102:2069) whereas loss-of-function mutations in PCSK9 lower the LDL cholesterol level by 40% (Cohen J et al Nature Genet 37:328). Thus,

mutations in the same gene can have different effects on the metabolism. The very simple hydrochlorothiazide drug can reduce hypertension is also a diuretic and may cause dizziness and other problems.

Protein defects may be targeted by interacting proteins or even with small molecules. Gene therapy and cancer gene therapy provide non-drug defense against disease. The advantages of these somatic treatments is that the therapeutic genes can be regulated at a natural, physiological level within the receiving organisms in contrast to drugs that are delivered in fixed quantities at ingestion. Therapeutic genes may also be equipped with special receptors, which may be subject to regulation by drugs.

In the *Drosophila* hybrid dysgenesis factor, the P element is being explored to study transgene responses to drugs. The proteome analysis and combinatorial chemistry open new avenues to design more effective medicine. The direct assays of side effects of potential drugs by biological means are difficult and time consuming. Efforts are being made to use toxicology assay chips for the early elimination of unsuitable compounds (Lee M-Y et al 2005 Proc Natl Acad Sci USA 102:983). Systems biology has special relevance to drug discovery, optimization and development of new pharmaceuticals (Butcher EC et al 2004 Nature Biotechnol 22:1253).
 ►PCR-mediated gene replacement, ►hybrid dysgenesis, ►genomic medicine, ►SAR by NMR, ►DNA grooves, ►developmental therapeutics program, ►lineage addiction, ►proteome, ►combinatorial chemistry, ►microarray hybridization, ►phage display, ►pharmaceuticals, ►ethnicity, ►CPE, ►SADR; Nature Rev Drug Discovery 2002 1(1); Zambrowicz BP, Sands AT 2003 Nature Rev Drug Discovery 2:38; ►Lipinski' rule; Allen TM, Cullis PR 2004 Science 303:1818; ►ligands; Stockwell BR 2004 Nature [Lond] 432:846; Lipinski C, Hopkins A 2004 Nature [Lond] 432:855; comprehensive review of human monogenic disorders as drug targets; Brinkman RR et al 2006 Nature Rev Genet 7:249; problems of drug approval; Wood AJJ 2006 New England J Med 355:6128; variation in human genes and drug responses; <http://www.PharmGKB.org>, drug targets: <http://redpoll.pharmacy.ualberta.ca/drugbank/>; G protein ligands in drug discovery; <http://gdds.pharm.kyoto-u.ac.jp/services/glida/>; potential drug targets by docking; <http://www.dddc.ac.cn/tarfisdock/>.

Drug Interaction: A very serious problem in medicine and it is not always easy to foresee how various simultaneous treatments may affect the intended cure. Some compounds may be buffering, activating or non-interacting with others. Natural food may also influence the uptake or metabolism of drugs

► **grapefruit**. These interactions can be represented in functional networks (Yeh P et al 2006 *Nature Genet* 38:489). In recent years, increased concerns developed for many drugs that had to be withdrawn from the markets after they were approved and widely used. The fifteenth century savant Paracelsus/Theophrastos of Hohenheim has already recognized that “poison is in everything, and nothing is without poison. The dosage makes it either a poison or a remedy.” ► **epistasis**, ► **multidrug resistance**, ► **multiple drug resistance**; 3D interactions; <http://bioserv.rpbs.jussieu.fr/cgi-bin/Frog>.

Drug, Personalized: ► **metabonomics**, ► **SADR**

Drug Resistance: In cancer therapy protein kinases appeared ideal targets. Unfortunately, resistance to these treatments appears (Daub H et al 2004 *Nature Rev Drug Discovery* 3:1001). The clearing of the drug from the target cells may cause resistance. This problem may be overcome by administering simultaneously the drug and appropriate antidrug-antibody. Genes that control absorption, distribution, metabolism and excretion may affect response to drugs (Carter TA et al 2005 *Proc Natl Acad Sci USA* 102:11011). A dynamic drug pool may be established by reversible dissociation of the drug and the antibody. The free drug may be gradually eliminated but the free drug pool is continuously replenished from the drug-antibody complex. If such a procedure is successful, it may provide a clinically useful technique to prolong appropriate drug level for a prolonged period (O’Hear CE, Foote J 2005 *Proc Natl Acad Sci USA* 102:40). Dominant drug-sensitive variants of poliovirus interfere with the growth of non-defective virions and may be useful for antiviral therapy with reduced risk of drug resistance (Crowder S, Kirkegaard K 2005 *Nature Genet* 37:701). ► **multiple drug resistance**, ► **resistance transfer factors**, ► **antimetabolite**; Gottesman MM 2002 *Annu Rev Med* 53:615.

Druggability: A molecular target, which can be altered in such a way that it may become a drug.

Drum Stick: ► **Barr body**

Ds: (*Dissociator*): A defective transposable element of maize that can move only when *Ac* provides the transposase function. Its name came from the observation that it was frequently associated with chromosome breakage. ► *Ac*, ► **controlling elements**, ► **transposable elements**

DSB: A double-strand break.

DsbA: A 21.1 kDa monomeric *E. coli* periplasmic protein with strong oxidizing ability. DsbB reoxidizes it. DsbC has similar function. DsbD and DsbE are

thiodisulfide reductases. ► **thioredoxin**, ► **glutaredoxin**, ► **PDI**

Dscam: A *Drosophila* gene, which regulates synaptic specificity of neurons by generating potentially more than 38,000 mRNA isoforms by alternative splicing (Chen BE et al 2006 *Cell* 125:607). ► **alternative splicing**, ► **synapse**

dsDNA: Double-stranded DNA (see Fig. D108).



Figure D108. dsDNA

DSE: Distal sequence element. ► **Hogness box**

DSIF: Regulatory dimeric (~14 and ~160 kDa subunits) protein of transcript elongation. It seems to be a target of DRB. The large subunit is homologous to the bacterial NusG. ► **transcript elongation**, ► **TEFb**, ► **DRB**, ► **NELF**, ► **nusA**; Renner DB et al 2001 *J Biol Chem* 276:42601.

DSP (dual specificity protein phosphatase): One of its active sites dephosphorylates serine, threonine, tyrosine in a protein whereas the deeper active site is specific only for tyrosine.

DsrA: A short (87 base) RNA with three stem-loop motifs modulating transcriptional regulators H-NS (inhibitory) and RpoS (stimulatory). One of the stem-loop binds and stabilizes RpoS mRNA and the second sequesters the H-NS mRNA. (Lease RA Belfort M 2000 *Mol Microbiol* 38:667)

dsRAD: ► **DRAD**

dsRNA: Double-stranded RNA. ► **RNA interference**

DSS (dosage-sensitive sex reversal): An approximately 160-kb duplication in the short arm of the X-chromosome upsets normal male gonad formation in XY individuals. Deletion of the same region however does not affect gonadal differentiation although the hypogonadism results in infertility. Defect in the *DAX-1* gene enhanced the expression in the expression of the aromatase enzyme encoded by the *Cyp19* gene of mice. This enzyme converts testosterone to estradiol in the Leydig cells. ► **sex reversal**, ► **sex determination**, ► **Wolffian duct**, ► **testosterone**, ► **estradiol**; Wang ZJ et al 2001 *Proc Natl Acad Sci USA* 98:7988.

DST1: The yeast gene encodes the 38-kDa strand transfer protein (STP α). ► **recombination mechanism**, ► **eukaryotes**

DST2: The yeast gene encodes the STP β protein (identical to Sep 1). ► **recombination mechanism** **eukaryotes**

DSTF (DPE-specific transcription factor): DSTF facilitates the transcription by DPE promoters and represses the TATA box-driven promoters by binding to the TBP of the transcription factor TFIID. DSTF activity is associated with a 43 kDa (NC) and a 22 kDa (Drap) proteins. ▶core promoter, ▶DPE, ▶NC, ▶Drap, ▶TBP, ▶TFIID; Kutach AK, Kadanaga JT 2000 Mol Cell Biol 20:4754.

dsx (*double sex*): Abnormal location 3–48.1; regulates sexual differentiation in somatic cells of *Drosophila melanogaster*. The null allele converts males and females into intersexes. ▶*Drosophila*, ▶sex determination; Erickson JW 2001 Developmental Cell 1:156.

DT40: A chicken cell line with as high as 10 to 100% homologous recombination in non-isogenic DNA without high selection pressure. It provides an opportunity of high efficiency gene transfer in vertebrate, including human cells. (Thompson LH, Schild D 2001 Mutation Res 477:131; <http://genetics.hpi.uni-hamburg.de/dt40.html>).

Dt Gene: It is actually a transposable element that may be situated in several locations in the maize genome (see Fig. D109). It causes the colorless *a1-m* allele to produce anthocyanin-containing dots in the triploid aleurone tissue, depending on the dosage of the *Dt* elements containing a transposase. It may also cause reversions to the *A* allele in the germline. *Dt*, like other transposable elements, induces also chromosome breakage and can newly arise through chromosomal breakage. The first *Dt* allele, *Dt1* was located to the initial position of the short arm of chromosome 9. *Dt2* (chromosome 6L-44), *Dt3* (7L), *Dt4* (4), *Dt5* (in the vicinity of *Dt1*) and *Dt6* (in the short arm of the chromosome 4) not far from the centromere were identified subsequently. ▶transposable elements; Brown JJ 1989 Mol Gen Genet 215:239.

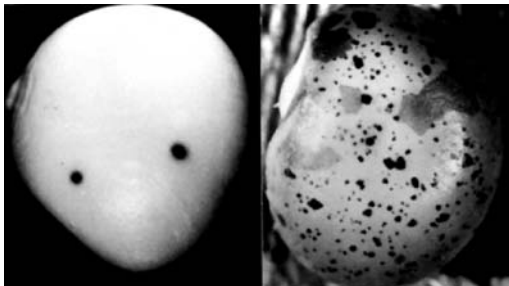


Figure D109. *Dt* gene. Maize kernels *aaa* (left) and *aaa^m Dt Dt* (right) constitution. (Courtesy of M.G. Neuffer)

dTAF_{II}: ▶transcription factors

DTH (delayed types hypersensitivity): DTH may cause acute rejection of allografts and autoimmune reactions due to non-specific T cell responses. ▶autoimmune, ▶T cell, ▶hypersensitivity, ▶allograft; Jager D et al 2001 J Clin Path 54 [9]:669.

DTT (dithiotreitol, Cleland's reagent): A protective agent for SH groups. ▶mercaptoethanol

Dual-Gene Operons: Synthetic constructs carrying two selected structural genes driven by a single promoter. Within the operon and within the untranslated 5' and 3' regions various regulatory elements (restriction enzyme sites) can be placed. Hairpin structures at the 3'-end may protect against exonuclease attack and transcription termination. Such systems permit the analysis of the differential expression of both genes under various controlled conditions. ▶operon; Smolke CD, Keasling JD 2002 Biotechnol Bioeng 78:412.

Dual-Specificity Phosphatases: It recognize more than a single phosphorylated amino acid in a protein and have an important role in signal transduction pathways and differentiation/development, epigenesis. ▶serine/threonine kinase, ▶epigenesis

Dual-Topology Proteins: They can insert into membranes in two different orientations. Frequently, the positively charged amino acids are oriented toward the cytoplasmic side of the inner membrane. Duplication permits specialization, i.e., the pairs may display opposite orientation (Rapp M et al 2006 Nature Struct Biol 13:112). ▶duplication

Duane Retraction Syndrome: A defect of moving the eyeball (globus), encoded in the region 2q31. The Duane Radial Ray (Okhiro syndrome) is due to mutation in SALL4 at 20q13. SALL4 is 1053 amino acid organ-specific transcription factor with eight Zn-finger domains. About 5% of the strabismus cases show similar defect. ▶strabismus, ▶eye diseases; Al-Baradie R et al 2002 Am J Hum Genet 71:1195.

Dubin-Johnson Syndrome (hyperbilirubinemia II, DJS, 10q24): A recessive disease with a relatively high frequency (8×10^{-4}) among Iranian Jews. It involves jaundice, hyper-bilirubinemia, melanin-like deposits in the liver. It is a defect of the detoxification mechanism of the liver. Detoxification is mediated by conjugation with glutathione, glucuronides or sulfates, resulting in negatively charged amphiphilic compounds that can be effectively secreted into the urine. The excretion is carried out with the assistance of canalicular (tubular) multispecific organic anion transporter (cMOAT). Hyperbilirubinemia is also caused by the Gilbert syndrome (synonymous with Arias type hyperbilirubinemia and the Crigler-Najjar syndrome type II defects in the UDP-glucuronosyl-transferase) in human chromosome 2 and deficiency

of Factor VII in human chromosome 13q34. The Rotor syndrome is apparently the same as DJS. ▶hyperbilirubinemia, ▶glutathione-S-transferases, ▶antihemophilic factors, ▶Crigler-Najjar syndrome

Dubinini Effect: The change of dominance in alleles (variegation) because of transposition (of heterochromatin) in *Drosophila*. ▶position effect, ▶heterochromatin, ▶dominance reversal; Dubinin NP, Sidorov BN 1934 Amer Nat 68:377; Locke J, Tartof KD 1994 Mol Gen Genet 243:234.

Dubowitz Syndrome: A fetal-newborn physical and mental retardation complex under autosomal recessive control. The symptoms may resemble to those in fetal alcohol syndrome (non-genetic) and the autosomal recessive Fanconi anemia. ▶alcoholism, ▶Fanconi's anemia

Duch (DH blood group): It is extremely rare and has been identified in Aarhus, Denmark. ▶blood groups

Duchenne Muscular Dystrophy: ▶muscular dystrophy

Duck (*Anas platyrhynchos*): $2n = 78-80$.

DUE (DNA unwinding element): A part of the autonomously replicating sequence (ARS). ▶ARS

Duffy Blood Group, (Fy) Alleles: In human chromosome 1q12-q21 control a red blood cell antigen, frequently used as genetic markers in population studies; 99% of the Chinese and 65% of the Caucasians are positive, whereas 95–99% of the black Africans are of the negative type (Fy^{-}/Fy^{-}). Individuals lacking these antigens [$Fy(a^{-}b^{-})$] are protected against the African malaria-causing *Plasmodium vivax* protozoan. ▶blood groups, ▶ethnicity; Hamblin MT et al 2002 Am J Hum Genet 70:369.

Dulbecco's Medium (PBS): A minimal animal tissue culture solution containing buffered sodium pyruvate, streptomycin, glucose and calcium chloride and penicillin and various nutrients may be added. (Lawson MA, Purslow PP 2000 Cells Tissues Organs 167[2–3]:130; Baust JM et al 2000 In Vitro Cell Dev Biol Anim 36[4]:262)

Dumbbell Oligonucleotides: These are short double-stranded DNA or DNA–RNA with closed loops at both ends. Ring-shape “dumbbells” are created by the fusion of two hairpins. They are very resistant to nucleases and can bind to very specific sequences and block transcription factor access. They may carry antisense RNA or antisense DNA, or may include sequences within the stem (in between the loops) where specific transcription factors can bind and exert interference with transcription this way. Dumbbell technology may have therapeutic value against viral infection. ▶decoy receptor, ▶antisense technologies;

Clausel C et al 1993 Nucleic Acids Res 21:3405; Park WS et al 2000 Biochem Biophys Res Commun 270:953.

Dumping: The transfer of the contents of nurse cells to the oocyte via cytoplasmic bridges. ▶oocyte, ▶nurse cell

‘Dumposome’: Protein Pdd1 of *Tetrahymena* that may be targeted to DNA degradation within cells of organisms. ▶apoptosis

Duncan Syndrome (X-linked lymphoproliferative disease): An Xq25 immunodeficiency with immediate hypersensitivity to various allergens, caused by higher than normal levels of IgE. The affected individuals are particularly sensitive to Epstein-Barr virus infections, and usually die of lymphoma or aplastic anemia. ▶immunodeficiency, ▶immunoglobulins, ▶Epstein-Barr virus, ▶lymphoma, ▶aplastic anemia, ▶anaplastic lymphoma, ▶lymphoproliferative diseases X-linked

Dunnigan Syndrome (1q21.2, 3p25): A dominant lipodystrophy with onset after puberty when the fat tissue is much reduced in the extremities and relocated to face, neck or other body parts. It manifests itself more conspicuously in females. Among many other symptoms, it involves insulin-resistant hyperinsulinism and diabetes. ▶lipodystrophy familial, ▶diabetes; Cao H, Hegele RA 2000 Hum Mol Genet 9:109.

Duodenum: A 12-fingerbreadth long section of the digestive tract between the pylorus (distal opening of the stomach into the duodenum) and the jejunum (small intestine extending from the duodenum to the ileum, next to the appendix, cecum).

Duplex: In a polyploid (e.g., *AAaa*) or triploid or trisomic (e.g., *Aaa*), duplex carries two dominant alleles at a locus and the other allele(s) at the same locus are recessive. ▶autopolyploid

Duplex DNA: It is double-stranded. ▶Watson–Crick model

Duplicate Genes: They convey the same (or very similar phenotype) but segregate independently, therefore, in F_2 the phenotypic proportions are 15 dominant: 1 recessive. The assumptions are that duplicate genes provide functional backup or regulatory role or gene dosage function. However, experimental studies in yeast suggest that the most important role of duplicate genes is that they provide means for gene evolution. The evolving gene—although has overlapping function with the original—it allows for the development of new metabolic tasks for the paralogue (Kuepfer L et al 2005 Genome Res 15:1421). In yeast and *Caenorhabditis* silencing duplicate genes does not have as serious have serious consequences as

silencing singletons. In mouse, based on study of ~3,900 knockouts, single copy and duplicated genes are almost equally essential indicating the duplicates rapidly acquire needed function (Liao B-Y, Zhang J 2007 Trends Genet 23:378). ►modified Mendelian ratios

D

Duplicate Ratio: ►duplicate genes

Duplication: A eukaryotic chromosomal segment is repeated side-by-side (tandem duplication) or may be repeated at another location within the chromosome or in another chromosome (see Fig. D110). The duplication is cytologically detectable in duplication heterozygotes if it is of sufficient length. In prophase, when paired with the non-duplicated strand, it bulges out because the normal counterpart cannot pair with the extra chromosomal tract:

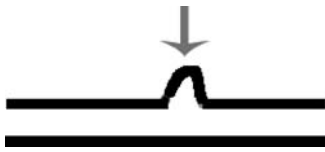


Figure D110. Duplication

The duplication may be direct →→ or inverted →←. After insertion of transposable elements, duplications may occur at the target sites. Transposable elements generally carry in addition terminal direct or inverted repeats. Duplications and deficiencies are generated by crossing over within the inverted segments of para- and peri-centric inversions, breakage-fusion-bridge cycles, crossing over between sister chromatids of ring chromosomes, unequal crossing over, adjacent I and adjacent II distribution of chromosomes in the meiosis of translocation heterozygotes, etc. Duplications may have evolutionary significance because the extra piece of DNA may be modified to carry out a new function(s) or may be used as a backup for the original gene (Kuepfer L et al 2005 Genome Res 15:1421). Molecular evolutionary studies provide many examples of duplications followed by differentiation and divergence. Complex genes are more likely to be preserved by evolution than simple ones because they offer greater chances for the development of new functions (He X, Zhang J 2005 Current Biol 15:1016). It was suggested that reduction in alternative splicing increases the chances of duplications during evolution in providing starting material for evolution (Su Z et al 2006 Genome Res 16:182).

More than 97% of human proteins have a history of duplication of some part of their length, and 80% of the proteins show relationships to more than one other protein in different regions, reflecting an

ancient composite structure. The latter information was obtained from the KGMV library, which consists only of proteins of known function, showing that these conclusions apply to working proteins. KGMV (for known genes maximum variant) library included 13,298 members (Britten RJ 2006 Proc Natl Acad Sci USA 103:19027). It has been estimated that the α and β chains of the human hemoglobin, after duplications, separated about 500 million years ago. Subsequently, from the β chain the γ and δ chains evolved. (The rhesus monkey, however, does not have the δ chain). Similarly, the protein superfamily of trypsin, chymotrypsin, elastase, thrombin, kallikrein, plasmin and bacterial trypsin all have structural similarities indicating common ancestry. Complete nucleotide sequence data of prokaryotic genomes revealed unexpected extensive duplications. In *Bacillus subtilis* more than 1/4 of the genome indicates duplications of recent origin. In *E. coli* there are about 80 transport proteins of common origin. In *Haemophilus influenzae* 284/1709 (~17%), in *Saccharomyces cerevisiae* 1858/6241 (~30%), in *Caenorhabditis elegans* 8971/18424 (~49%) and in *Drosophila melanogaster* 5536/13601 (~41%) of the protein-coding genes appear to have arisen by duplication. The progress of sequencing of the human genome also revealed several duplications (8595 duplicated regions of more than 5000 bp), mainly in the pericentromeric and telomeric heterochromatin of the same or different chromosomes (Bailey JA et al 2002 Science 297:1003). In humans and mouse, more genes moved to the X chromosome from autosomes than to autosomes from the X chromosome. In addition, more duplication occurred within the X chromosome than in the autosomes (Emerson JJ et al 2004 Science 303:537). In *Drosophila*, the duplicated genes appear dispersed although a cluster of 17 paralogous genes of not yet known function has been identified. In *Caenorhabditis* there is some clustering of seven-transmembrane domain paralogous genes. Almost 30% of the *Drosophila* proteins are orthologous with those of *Caenorhabditis* and ~20% of the fly and worm genes also share common origins with yeast. About half of the fly and about 36% of the worm's genes/proteins may have some similarity to that of humans, depending on the stringency of the comparisons. Seven hundred and forty four families or domains of proteins were judged common to all three of these lower eukaryotic organisms. The flies, worms and humans seem to have 300, 500 and more than 600 protein kinases and 85, 185 and > 300 protein phosphatases, respectively. There are 450 and 260 peptidases in the fly and worm, respectively. The numbers of multidomain proteins in fly, worm and yeast are 2130, 2261 and 672, respectively. The number of G protein-coupled receptors (GPCR) are

very high in the worm (~1100) while in flies (160) and humans (~700) fewer were identified. The number of olfactory receptors in the mouse is ~1000 while in the fishes there are only ~100. Of the 289 human genes where the molecular/cytological basis of a disease is known, 177 had orthologs in *Drosophila*, and 68% of the oncogenes also had apparently orthologous fly counterparts by year 2000. The flies do not have breast cancer gene or leptin orthologues. During evolution polyploidization may be followed by loss of genomic sequences (Bowers JE et al 2003 Nature [Lond] 422:433). Similar situation was found in *Saccharomyces cerevisiae*, which apparently arose by complete duplication of the genome of *Kluyveromyces waltii* and the subsequent loss of the one of the representative sequence in 95% of the cases (Kellis M et al 2004 Nature [Lond] 428:617). In yeast, the divergence is increased more after the initial duplication event than during its later evolution. The original and the duplicated forms evolve at different rates (Gu X et al 2005 Proc Natl Acad Sci USA 102:707). Sister regions are scattered along the genome. Many cell cycle, cytoskeleton, cell adhesion, cell signaling, apoptosis, neuronal signaling, cell defense (immunity) genes of *Drosophila* have counterparts in the lower animals. In human chromosome 12 duplications (>greater than 90% identity) constitute 2.66% of this chromosome whereas in the entire human genome 6.37% (Scherer SE et al 2006 Nature [Lond] 440:346). About 27% of the duplications in the human genome terminate within Alu repeats indicating a role of this element in their origin (Bailey JA et al 2003 Am J Hum Genet 73:823). Some of the duplications evolved not by tandem repeats but they were recruited to a certain function from other locations, first probably by gene sharing then to carry out a structural role because of their desirable stability, e.g., the crystallin eye protein genes, α , β and δ , which probably acquired the structural function before duplication (Piatigorsky J, Wistow G 1991 Science 252:1078). Genes determining hereditary disorders are frequently flanked by duplicated regions and indicate that copy number polymorphism favors instability by facilitating non-homologous recombination (Sharp AJ et al 2006 Nature Genet 38:1038).

The SVA family of retrotransposons has increased to 3,000 copies in the human genome. Similar to LINE elements, SVA elements are supposed to rely for transcription on RNA polymerase II and have the ability to transduce downstream sequence. This means that RNA transcription machinery sometimes (in ~10% in humans) skips the element's own weak polyadenylation signal and terminates transcription by using a downstream polyadenylation site located in the 3' flanking genomic sequence. The transcript

containing the retrotransposon along with the extra genomic sequence is subsequently integrated back into the genome through retrotransposition, a process called *3' transduction*. The experimental results indicate retrotransposon-mediated sequence transduction is one mechanism for gene duplication and the creation of new gene families as well as of exon shuffling (Xing J et al 2006 Proc Natl Acad Sci USA 103:17608) ▶ [evolution and duplications](#), ▶ [concerted evolution](#), ▶ [Alu](#), ▶ [paralogous loci](#), ▶ [orthologous loci](#), ▶ [deficiency](#), ▶ [chromosomal aberrations](#), ▶ [duplication-deficiency](#), ▶ [redundancy](#), ▶ [deletion](#), ▶ [heterochromatin](#), ▶ [polyploidy](#), ▶ [gene number](#), ▶ [core proteome](#), ▶ [gene numbers](#), ▶ [olfactogenetics](#), ▶ [oncogenes](#), ▶ [cancer](#), ▶ [breast cancer](#), ▶ [leptin](#), ▶ [immune system](#), ▶ [protein domains](#), ▶ [dual-specificity proteins](#), ▶ [pseudogenes](#), ▶ [subfunctionalization](#), ▶ [copy number estimates](#), ▶ [polyploidy](#), ▶ [Paramecium](#), ▶ [exon shuffling](#); Rubin GM et al 2000 Science 287:2204; Gu X et al 2002 Nature Genet 31:205; Conant GC, Wagner A 2002 Nucleic Acids Res 30:3378; Wolfe KH, Li W-H 2003 Nature Genet 33 (Suppl.):255; duplication and divergence; Taylor JS, Raes J 2004 Annu Rev Genet 38:615; theories of gene evolution by duplication: Hughes AL 2005 Proc Natl Acad Sci USA 102:8791; Bailey JA, Eichler EE 2006 Nature Rev Genet 7:552 [corrigendum to this paper in Nature Rev Genet 7(11)].

Duplication-Deficiency: Cells are produced by adjacent-1 and adjacent-2 distribution of chromosomes in translocation heterozygotes, in para- and pericentric inversion heterozygotes when crossing over takes place within the inverted segment. They may occur in case there is a sister chromatid exchange in ring-chromosomes and all other cases when dicentric chromosomes are produced (breakage fusion-bridge cycles), unequal crossing over, etc. ▶ [inversion](#), ▶ [translocation](#), ▶ [dicentric ring chromosome](#), ▶ [genomic variation](#)

Duplicons: These are chromosome-specific low-copy repeats at multiple areas of the human genome. Homologous recombination between duplicons may lead to chromosomal aberrations such as duplications, deletions and inversions. Such alterations may occur at a frequency of about 10^{-3} and cause genetic diseases. ▶ [chromosomal rearrangements](#); Ji Y et al 2000 Genome Res 10:597.

Durum Wheat: A member of the allotetraploid series with AB genomes. ▶ [Triticum](#)

DUST: A computer program designed to identify low-complexity regions in DNA sequences.

Duty Ratio (duty cycle): Duty ratio indicates the frequency of the time when a motor protein is attached to its filament, it is supposed to move. ▶ [motor protein](#)

Dwarfism: It is caused by several *dominant* genes in apparently different human autosomes. The distinguishing features include (i) narrow vertebrae, (ii) thickening of the tubular bone associated with farsightedness, lower than normal level of blood calcium, (iii) low birth-weight, stiff joints and eye defects, (iv) Myhre syndrome involving pre- and postnatal growth retardation, anomalies of face morphology, poor mobility of joints, defects in sex organs, heart and hearing. Some *autosomal recessive* dwarfism, (v) like the Dubowitz syndrome involves intrauterine growth retardation, mental and hearing defects, sex organ anomalies, unusually high or low voice, no response to growth hormone, etc. (vi) Various other types are accompanied by mental retardation, heart anomalies, hip dislocation, very short arms and digits and the absence of fibula (the smaller bone of the leg). ▶**pituitary dwarfism**, ▶**achondroplasia**, ▶**hypochondroplasia**, ▶**Ellis-von Creveld syndrome**, ▶**thanatophoric dysplasia**, ▶**macromelic dwarfism**, ▶**dyschondrosteosis**, ▶**spondyloepiphyseal dysplasia**, ▶**chondrodysplasia**, ▶**cleidocranial dysplasia**, ▶**pseudohypoparathyroidism**, ▶**osteogenesis imperfecta**, ▶**Kniest dysplasia**, ▶**Williams syndrome**, ▶**animal hormones**, ▶**somatotropin**, ▶**corticotropin**, ▶**growth retardation**, ▶**Pygmy**, ▶**SHORT syndrome**, ▶**stature in humans**, ▶**Mulibrey nanism**, ▶**Seckel' dwarfism**, ▶**Donohue syndrome**, ▶**limb defects**, ▶**diastrophic dysplasia**, ▶**Langer-Nielsen mesomelic dwarfism**, ▶**Laron type dwarfism**, ▶**Moore-Federman syndrome**, ▶**dyssegmental dysplasia**, ▶**GHRH**, ▶**GHRHR**

Dwarfism also occurs in plants. This condition in plants may be remedied in some cases by the supply of gibberellic acid or ethylene. Some of the gibberellin-insensitive dwarf mutants of plants are defective in G proteins that have key role in signal transduction. Agromically advantageous semi-dwarf rice plants with normal grain yield have been generated by the expression of a gibberellin oxidase gene under the control of a leaf and stem specific promoter (Sakamoto T et al 2003 Nature Biotechnol 21:909). Auxins, ethylene and brassinosteroids are also regulators of plant cell elongation. Defect in auxin transport class of P-glycoproteins results in dwarf habitus in *Arabidopsis*, maize and sorghum. In the latter species the *dw3* mutations are tandem duplications and because of unequal crossing over an unusually frequency of reversions occur (Multani DS et al 2003 Science 302:81). ▶**plant hormones**, ▶**brassinosteroids**, ▶**de-etiolation**, ▶**ABC transporter**, ▶**unequal crossingover**

Dyad: Chromosome with two chromatids, also the two cells (dyads) formed by the first meiotic division. ▶**chromatid**

Dyads, Spaced: ▶**spaced dyads**

Dye Primer and Dye Terminator Chemistry: During DNA sequencing it may correct errors due to gel compression or base-calling. ▶**compression in gels**, ▶**base-calling**, ▶**doublestranding**

Dyggve-Melchior-Clausen Dysplasia: A bone formation defect with morphological similarity to Smith-McCort dysplasia. The diagnostic difference that DMC involves retarded physical and mental development. Both diseases are under the control of apparently the same gene (18q12-q21), only the mutations appear different. ▶**osteochondrodysplasia**; Cohn DH et al 2003 Am J Hum Genet 72:419.

Dynactin: A dynein regulating protein with the role of moving organelles, and it may interact with the kinetochore and anchors there dynein. ▶**dynein**, ▶**spindle**; Muresan V et al 2001 Mol Cell 7:173.

Dynamic Allele-Specific Hybridization (DASH): DASH has been designed to detect SNIPS. Two DNA sequences are hybridized initially at low stringency. A fluorescent marker that binds only double-stranded DNA and only then emits the signal monitors the hybrid DNA. When the temperature in the reaction well is raised, the SNIP areas lose the signal because they no longer form hybrid and the mismatch is identified. ▶**SNIP**, ▶**allele-specific probe**; Prince JA et al 2001 Genome Res 11:152.

Dynamic Instability: This may occur when microtubules oscillate between growth and shortening during mitosis along with treadmilling. ▶**treadmilling**

Dynamic Molecular Combing: The physical method for mapping distances between fluorochrome-labeled DNA molecules stretched out on the surface of microscopic cover slides. ▶**physical mapping**; Michalet X et al 1997 Science 277:1518.

Dynamic State: The biochemical concept stemming from the realization that the constituents of the living body, irrespective whether they are metabolic or structural, are in a steady state of flux.

Dynamic Time Warping (DTW): A quadratic time algorithm to determine the smallest distance and optimal alignment between two numerical sequences, possibly of different length: <http://bioinformatics.bc.edu/clotelab/BTW/>. (Kruskal JB and Liberman M 1999 The symmetric time-warping problem: from continuous to discrete In: Kruskal JB, Sankoff D (eds) Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison. Stanford CSLI Publications, pp. 125–161)

Dynamin: ~100 kDa proteins with guanosine triphosphatase activity, are associated with other proteins, play an essential role in coated vesicle formation and are localized at the plasma membrane around the neck

of emerging coated pits (see Fig. D111). Several forms of dynamins are known and they display tissue-specificity. They are involved in vesicle recycling, nerve terminal depolarization, etc. ▶coated pits, ▶endocytosis, ▶synaptojanin, ▶synaptogamin, ▶clathrin, ▶synaptic vesicles, ▶GTPase, ▶DRP, ▶apoptosis, ▶myopathy; Hinshaw JE 2000 Annu Rev Cell Dev Biol 16:483.



Figure D111. Dynamin ring

Dyne Unit of Force: It is needed so that a body of 1 g can be accelerated one centimeter per second per second.

Dynein: A multisubunit protein (1.2 MDa), associated with bundles of microtubules (axoneme) in cilia and flagella and assists their movement in an ATP-dependent process (see Fig. D112). Dynein is supposed to move the microtubules toward the centrosome. Dynein is also involved in the development of left-right asymmetry along the axis of the body and it mediates the breakdown of the nuclear membrane. Several motor neuron diseases are dynein defects. ▶microtubules, ▶tubulin, ▶flagellum, ▶cilia, ▶axoneme, ▶kinesin, ▶dynactin, ▶ankyrin, ▶spectrin centrosome, ▶situs inversus viscerum, ▶left-right asymmetry, ▶amyotrophic lateral sclerosis, ▶spinal-bulbar muscular atrophy, ▶spinal muscular atrophy, ▶Kartagener syndrome, ▶asthenozoospermia; Lee IH et al 2001 Mol Biol Cell 12:2195; Burgess SA et al 2003 Nature [Lond] 421:715; Hafezparast M et al 2003 Science 300:808; Mallik R et al 2004 Nature [Lond] 427:649; review; Oikawa K, Sakakibara H 2005 Current Opin Cell Biol 17:98; Diagram substantially modified after Hirokawa N 1998 Science 279:519.

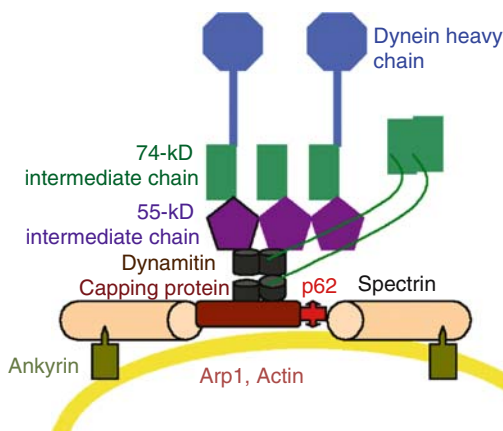


Figure D112. Dynein and associated proteins on the cargo membrane

Dynia Factor: A blood factor controlling the antihemophilic factor. ▶blood clotting pathways, ▶antihemophilic factors, ▶hemostasis

Dynodes: A set of auxiliary electrodes that amplify electrons as they are hit by an electron beam. Dynodes are used in various types of photomultipliers and mass spectrometers, employed in proteome research. ▶proteomics

Dynorphin: An opiate receptor ligand. ▶opiate

Dysarthria: A speech disorder caused by nerve or neuromuscular defect.

Dysautonomia (FD, 9q31): The malfunction of the central nervous system resulting in hypertension, emotional instability, cold hands and feet, excessive sweating and red skin spots. Generally, the prospect of survival to age 40 is poor. It is caused by a defect in splicing of the RNA transcript of IKBAP (inhibitor of κ light chain polypeptide). This protein is part of the IKK complex that includes the NF- κ B-inducing kinase, IKK- β (inhibitor of κ -B kinase β), IKK- α (inhibitor of κ -B kinase α), NF- κ B/RelA and protein IKAP (IKK complex associated protein). Its prevalence is high ($\sim 2-3 \times 10^{-4}$ in Ashkenazy Jewish populations. ▶neuropathy, ▶Riley-Day syndrome; Anderson SL 2001 Am J Hum Genet 68:753; Slaugenhaupt SA, Gusella JF 2002 Current Op Genet Dev 12:307; Cuajungco MP et al 2003 Am J Hum Genet 72:749.

Dysbetalipoproteinemia: A defect in apolipoprotein E. ▶apolipoproteins, ▶hyperlipoproteinemia

Dyscalculia: A brain defect manifested in difficulties handling numerical problems.

Dyschondrosteosis (Leri-Weill syndrome): A dominant dwarfism of the forearms with about four times as high occurrence in females than in males. It may be caused by p22-q12 X-Y translocations or a large deletion at the Xp22.3 region involving the SHOX gene. The same gene is involved in the Langer mesomelic dwarfism. ▶dwarfism, ▶achondroplasia, ▶hypochondroplasia, ▶stature in humans, ▶pseudautosomal, ▶short syndrome

Dyscrasia: A pathological condition of different manifestations in the blood or plasma, plasma proteins.

Dyschromatosis Symmetrica Hereditaria (1q21.3, 6q24.2-q25.2): It occurs mainly in Japan and Korea at a frequency of about 1.5×10^{-5} as a dominant, harmless pea-size hyper and hypopigmented spots on the upper side of the hands and feet or other parts of the body (see Fig. D113). It is caused by mutation in adenosine deaminase. ▶adenosine deaminase

deficiency, ►LEOPARD syndrome, ►xeroderma pigmentosum; Miyamura Y et al 2003 Am J Hum Genet 73:693; photo courtesy of the March of Dimes Foundation.



Figure D113. Dyschromatosis

Dysequilibrium Syndrome: Autosomal recessive cerebral palsy, mental retardation, muscular insufficiency, poor motor control, etc. based on a malfunction of dopamine- β -hydroxylase activity.

Dyserythropoietic Anemia (HEMPAS for hereditary erythroblastic multinuclearity with positive acidified serum test): An endopolyploidy apparently limited to the bone marrow cells. As a consequence anemia appears. The basic defect seems to be a deficiency in the enzyme *N*-acetyl-glucosaminyl transferase II affecting the biosynthesis of glycoproteins. GATA1 mutations result in this disease and thrombocytopenia. ►GATA, ►thrombocytopenia

Dysferlin: A protein defective in both limb-girdle muscular dystrophy 2B and Myoshi myopathy. Dysferlin defect causes disruption of the repair of muscle fibers. ►muscular dystrophy, ►Miyoshi myopathy; Liu J et al 1998 Nature Genet 20:31; Bansal D et al 2003 Nature [Lond] 423:168.

Dysfibrinogenemia: In contrast to fibrinogenemia, where the synthesis of fibrinogen is reduced, these individuals fail to assemble the fibrinogen monomers into normally functional molecules. This human chromosome-4 dominant condition most commonly is not associated with heavy bleeding but may suffer from periodic clot formation in the blood vessels (thrombosis). ►antihemophilic factors, ►afibrinogenemia, ►fibrin-stabilizing factor

Dysgenesis: A mechanism or process producing dysgenic individuals. ►dysgenic, ►hybrid dysgenesis

Dysgenic: Deleterious, undesirable genetic trait ►hybrid dysgenesis

Dyskeratosis (DKC, Xq28; DKBI 4q35): The autosomal dominant forms involve hyperpigmentation of the skin, pre-cancerous skin lesions, poor bone and nail development, no dermal ridges (fingerprints). The benign form does not affect much the individual's well-being. The autosomal recessive form is

also similar. The Xq28 linked form afflicts primarily males who may be also affected by testicle atrophy, anemia, cancer, and lacrimation because of defects in the lacrimal ducts. The DKC1 gene product, dyskerin (514 amino acids), is a nucleolar protein and suspected to have a role in ribosomal function (Mochizuki Y et al 2004 Proc Natl Acad Sci US 101:10756). DKC1 encodes a pseudouridine synthase that modifies ribosomal RNA. In Dkc1tm mutant mouse the defect involves the internal ribosome entry site (IRES) and impairs translation of mRNAs with IRES element such as p27^{Kip}, Bcl-xL, XIAP inhibitors of apoptosis (Yoon A et al 2006 Science 312:902). Dyskerin is also associated with telomerase RNA function and by shortening the telomeres, it may hinder the proliferation of the human somatic cells in the epithelium and blood. Short telomeres, even in the presence of normal telomerase function, result in mice similar tissue development phenotypes as in human dominant dyskeratosis (Hao L-Y et al 2005 Cell 123:1121). The dominant intraepithelial benign dyskeratosis (HBID) is caused by duplication at 4q35 and it is responsible for red eye and other superficial lesions. A large, 821-bp deletion of the 3'-end of a dyskerin gene, encoded at 3q, involves the RNA component of the telomerase enzyme. ►keratosis, ►keratoma, ►skin diseases, ►fingerprints, ►telomeres, ►IRES, ►p27^{Kip}, ►BCL, ►IAAP; Marciniak RA et al 2000 Trends Genet 16:193; Vulliamy T et al 2001 Nature [Lond] 413:432.

Dyskerin: ►dyskeratosis

Dyskinesia: Involuntary movements beyond self-control.

Dyslexia: A highly variable difference in the central nervous system causing difficulties in reading and understanding or tiredness of reading. In some forms, it appeared to be associated with left-handedness and speech defects. Dyslexia may not necessarily be associated with deficiencies of the general intelligence (IQ) and can be compensated for by tutoring type of education. It has been suggested that a dominant gene (DD) in human chromosome 6p22.2 determines some specific forms of it with preferential penetrance in males. Its heritability according to twin studies is very high. Chromosome 15 also harbors a gene for dyslexia. Several QTLs in different chromosomes determine dyslexia. A major QTL has been assigned to 18p11.2 (Fisher SE et al 2001 Nature Genet 30:86). Complicated orthography aggravates the condition whereas it is less serious in near-phonetic languages. ►mental retardation, ►hyperlexia, ►IQ, ►QTL; Wysman EM et al 2000 Am J Hum Genet 67:631; Paulesu E et al 2001 Science

291:2165; Temple E et al 2003 Proc Natl Acad Sci USA 100:2860; genetic factors: Paracchini S et al 2007 Annu Rev Genomics Hum Genet 8:57.

Dyslipidemia: Abnormally high (cholesterol, low-density lipoprotein and triglycerides [LDL]) or low high-density lipid (HDL) content of the blood. High LDL and low HDL content involves risks of heart disease, diabetes, hypothyroidism, kidney and liver anomaly, etc., may be indications of other diseases or metabolic alterations or disorders.

Dysmelodia: An apparently autosomal dominant gene with low penetrance causes reduced musical ability. There is also another autosomal dominant gene (perfect pitch) enabling the individual to remember and play a tune. ▶ [Bach](#), ▶ [musical talent](#)

Dysmorphology: Abnormal morphological change. (Baraitser M, Winter RM 2001 London Dysmorphology Database London Neurogenetics Database & Dysmorphology Photo Library on CD-ROM (Windows). Oxford Univ. Press, New York). (http://www.lmdatabases.com/about_lmd.html)

Dysostosis: A defect in ossification ▶ [bone formation](#)

Dysplasia: Abnormal organization of the cells within the tissue. ▶ [malformation](#)

Dysploidy: The basic chromosome number varies within a population either because of the presence of B-chromosomes or because of Robertsonian translocations or misdivision at the centromere. The change in number does not involve an increase or decrease of an integer of the basic chromosome set. ▶ [polyploidy](#), ▶ [aneuploidy](#), ▶ [B chromosomes](#), ▶ [misdivision](#), ▶ [Robertsonian translocation](#); Baldwin BG, Wessa BL 2000 Am J Bot 87:1890.

Dyspnea: Difficulty in breathing due to various genetic or other causes.

Dyspraxia, Developmental Verbal (SPCH1, 7q31): A dominant expressive and receptive speech, grammar and language defect without substantial sensory or neurological impairment. It is caused by defect in a putative transcription factor including the gene FOXP2, which encodes a polyglutamine tract and a DNA-binding forkhead domain. ▶ [FKH](#), ▶ [speech and grammar disorder](#); Lai CSL et al 2001 Nature [Lond] 413:519.

Dysreproductive Genes: These impair fertility of the individual because of lowering or adversely affecting the reproductive system either by structural and developmental defects or as subvitals, semi-lethals and lethals.

Dyssegmental Dwarfism (dyssegmental dysplasia): Autosomal recessive phenotype involving abnormal

development of the vertebrae. It is accompanied with various other symptoms such as dwarfism, cleft palate, hydrocephalus, etc. A defect in the normal formation of collagen is suspected. The DDSH gene (Silverman-Handmakers disease, 1p36.1) involves defect in the synthesis of perlecan (heparan sulfate proteoglycan), a component of the basement membranes. ▶ [dwarfism](#), ▶ [cleft palate](#), ▶ [hydrocephalus](#), ▶ [collagen](#), ▶ [basement membrane](#), ▶ [Schwartz-Jampel syndrome](#); Arikawa-Hirasawa E et al 2001 Nature Genet 27:431.

Dystasia (areflexic dystasia): ▶ [claw-foot](#)

Dystonia: The lack of muscle coordination caused by a dominant factor at human chromosome 9q32-q34 in the region of the dopamine-β-hydroxylase locus. The prevalence of the disease (torsion dystonia) in Ashkenazy Jewish populations is high, $2-5 \times 10^{-4}$, and the penetrance is about 30%. The torsin gene encodes an endoplasmic reticulum and nuclear envelope protein, torsin A. Increased localization of torsin to the nuclear envelope is one cause of dystonia (Goodchild RE, Dauer WT 2004 Proc Natl Acad Sci USA 101:847). Some dystonias respond favorably to DOPA. Autosomal recessive expression (or possibly mitochondrial origin) may be accompanied by visual defects. In some X-linked forms, the symptoms include deafness. The hereditary progressive DOPA-responsive dystonia in human chromosome 14 is caused by a deficiency GTP cyclohydrolase I. This enzyme controls bipterin biosynthesis required for dopamine. ▶ [neuromuscular diseases](#), ▶ [dopa](#), ▶ [bipterin](#), ▶ [idiopathic torsion dystonia](#), ▶ [myoclonous](#), ▶ [sarcoglycan](#), ▶ [Munchausen syndrome](#); Tarsy D and Simon DK 2006 New England J Med 355:818.

Dystroglycan: A part of the dystrophin-associated protein complex. It participates in the formation of the extracellular matrix in cells contacting basement membranes. It promotes the assembly of the acetylcholine receptors and the neuromuscular junctions. It is the receptor of *Mycobacterium leprae* and some arena viruses. ▶ [acetylcholine receptor](#), ▶ [basement membrane](#), ▶ [sarcoglycan](#), ▶ [Mycobacteria](#), ▶ [animal viruses](#), ▶ [muscular dystrophy](#); Michele DE et al 2002 Nature [Lond] 418:417; Kanagawa M et al 2004 Cell 117:953.

Dystrophin (DRP): The muscle protein that anchors muscle membranes to actin filaments in the myofibrils. The Xp21.2-chromosomal gene contains 79 exons spanning 2,300 kb and the transcription requires about 16 hours. Utrophin is also a dystrophin type protein (DRP1, 6q24) and DRP2 another dystrophin gene has been mapped to human chromosome Xq22. ▶ [muscular dystrophy](#), ▶ [gene size](#), ▶ [exon](#), ▶ [actin](#), ▶ [myofibril](#), ▶ [sarcolemma](#), ▶ [caveolin](#)

Dystrophy: Inadequate nutrition (of the muscles). **DZ:** Dizygotic twin. ▶twinning
▶muscular dystrophy, ▶atrophy

Dyszoospermia: An anomaly involving the formation of spermatozoa. ▶spermatogonia, ▶gametogenesis, ▶spermatid, ▶azoospermia

D

Historical vignettes

Henry Borsook noted in the *Journal of Comparative Cellular Physiology*. Suppl. 1:283 (1956) his recollections from the late 1920s.

Edwin Cohn, the physical chemist asked TH Morgan, the first Nobellaureate geneticist what his plans are. And Morgan's answer was "I am not doing any genetics. I am bored with genetics. But I am going out to Cal Tech where I hope it will be possible to bring physics and chemistry to bear on biology."

Shortly after Morgan arrived to Cal Tech Einstein visited the place and posed about the same question. The answer was about the same as before. Einstein shook his head and said, "No, this trick won't work. The same trick does not work twice. How on earth are you ever going to explain in terms of chemistry and physics so important a biological phenomenon as first love?"

Paul Doty told me that shortly after lapel buttons came in he was in New York and to his astonishment saw one with 'DNA' written on it. Thinking it must refer to something else he asked the vendor what it meant. 'Get with it, bud' the man replied in a strong New York accent, 'dat's the gene'. Crick also remembered "An even odder incident happened when Jim [Watson] came back to work at Cambridge in 1955. I was going into the Cavendish one day and found myself walking with Neville Mott, the new Cavendish professor [Bragg had gone on to the Royal Institution in London]. 'I'd like to introduce you to Watson' I said, 'since he's working in your lab.' He looked at me in surprise. 'Watson?' he said. 'Watson? I thought your name was Watson-Crick'.

(Crick F 1978 How to live with a golden helix. *The Sciences* 19[7]: 6–9.)

E

E1 (Ubc1): Ubiquitin-activating protein. ►ubiquitin, ►SCF

E2 (Ubc2): A ubiquitin carrier and ubiquitin-conjugating enzyme. Ubc2/Rad6 in yeast has dual functions of proteolysis and DNA repair. E2-C is involved in the degradation of cyclin B in cooperation with the APC/cyclosome. E2-C has been detected in many eukaryotes except *Saccharomyces cerevisiae*. ►ubiquitin, ►SCF, ►UBC, ►UbcD1, ►APC, ►cell cycle

E3 (Ubc3): A family of ubiquitin ligases includes 4 types of proteins: (i) acting on the N-end rule proteins (~200-kDa); (ii) E6-AP (papilloma virus E6 oncoprotein-associated protein, ~100-kDa), it includes also *hect* proteins (homologous to E6-AP); (iii) the cyclosome/APC associated enzyme acting on mitotic cyclins, anaphase inhibitors and spindle apparatus proteins; (iv) enzymes acting on the Bim mitotic motor proteins. ►ubiquitin, ►E2, ►SCF, ►N-end rule, ►Angelman syndrome, ►APC, ►cell cycle, ►Bim

E Box (Ebox): Genes controlling endogenous rhythm (circadian oscillators) or other regulators are equipped by promoters containing the conserved core 5'-CACGTG-3' or 5'-CACATG-3' to which the transcriptional activators of clock (and of other) genes bind. Myc, Max, Mad, Mxi, and related basic helix-loop-helix/leucine zipper proteins (TFE-3, TFE-B) preferentially bind to E boxes flanked by 5' C and 3' G but do not bind if the flanks are 5' T or 3' A. E box motifs may reside at the exon-intron 1 junction and regulate transcription and splicing. Some of the E boxes are highly conserved in intron sequences, others are not and thus shed some light on evolutionary paths of gene regulation. ►endogenous rhythm, ►clock genes, ►circadian rhythm, ►LCR, ►Myc, ►MAD/MAX, ►MXI/MAX, ►TFE, ►DNA-binding protein domains, ►brassinosteroids, ►transcription factors; Comijn J et al 2001 Mol Cell 7:1267; Kim C-H et al 2001 J Biol Chem 276:24797; Haggerty TJ et al 2003 Proc Natl Acad Sci USA 100:5313.

EC: Teratocarcinoma-derived pluripotent embryonal carcinoma cell. ►stem cells, ►cancer stem cell

EC: Enzyme classification number. ►enzymes

E. coli (*Escherichia coli*, Colon bacillus; Enterobacteriaceae): Most predominant bacterium in the intestinal flora of mammals (see Fig. E1). In year 2000, ~28%

of beef cattle in the USA was infected by *E. coli* (Elder RO et al 2000 Proc Natl Acad Sci USA 97:2999). Normally it is not pathogenic, but some strains (0157) may cause Winckel's disease (a possibly fatal jaundice of newborns), diarrhea, intestinal bleeding, and urinary infections. Also, the B2 group of the bacteria encodes a non-ribosomal peptide-polyketide synthase. *E. coli* expressing this genotoxin causes double-strand DNA breaks, activate DNA damage checkpoint pathway and can cause cell death (Nougayrède J-P et al 2006 Science 313:848).

The size of single cells of *E. coli* is about 1000 × 2400 nm, and its mass is about 2 pg. Its genome is 4,639,221 bp, containing 4,288 protein-coding genes but about 1/3 have no known function so far. 2,357 of the genes are on the replicational leading strand and 1,929 are on the lagging strand. The size of the *E. coli* chromosome may vary in the different isolates, from 4.5 to 5.5 Mb because of acquired DNA sequences in various locations of the genome (Bergthorsson U, Ochman H 1998 Mol Biol Evol 15:6). Detailed analysis of *E. coli* found that genes in a pair tend to be separated by integral multiples of 117 kb along the genome and positioned in a 117-kb grid of genomic locations. In addition, the most pair-dense locations coincide with regions of intense transcriptional activity and the positions of top transcribed and conserved genes (Wright MA et al 2007 Proc Natl Acad Sci USA 104:10559). By multiple deletions of nonessential genes the genome size of the K-12 strain can be reduced by ~15%. The smaller genome size may increase stability if transposable elements were eliminated, and facilitated electroporation (Pósfai G et al 2006 Science 312:1044). Transport and binding-protein genes (281) represent the largest group (6.55%). For DNA replication, recombination, modification, and repair 115 genes (2.68%) are allocated. Transcription, RNA synthesis, and modification require 55 genes, whereas translation and post-translational modification involve 182 genes (4.38%). Phage, transposons, and plasmids occupy 2.03% of the genome. There are various groups of repeated sequences of different length. It can harbor a variety of plasmids, and it can be a lysogen. At 37°C its generation time is about 20 min. *E. coli* is a genetically and biochemically most thoroughly studied organism. By 1997, the genome of the K-12 nonpathogenic laboratory strain has been completely sequenced almost independently in the USA and Japan. The enterohaemorrhagic strain 0157:H7 has also been sequenced by 2001. The sequence revealed the existence of 1,397 new genes of different functions organized in specific clusters (Fig. E2). ►conjugation, ►conjugation mapping, ►bacterial recombination frequency, ►recombination molecular mechanisms prokaryotes, ►electroporation, ►transposable elements,

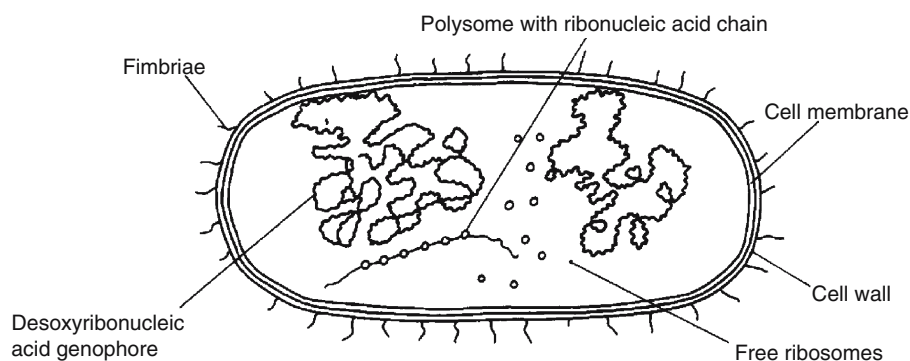


Figure E1. *E. coli* cell

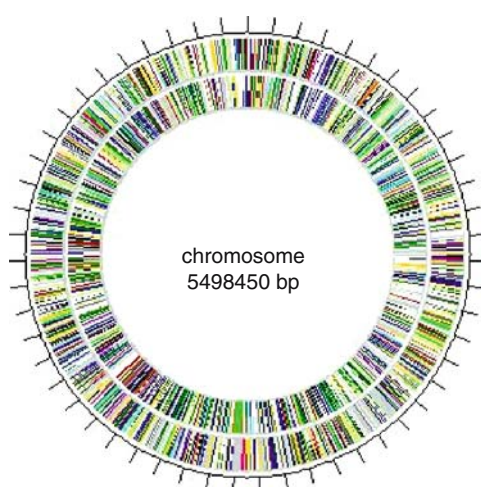


Figure E2. Physical map of *Escherichia coli* chromosome. Open reading frames color-coded by functional categories. (Courtesy of. Masaki Fumoto, see also <http://gib.genes.nig.ac.jp>)

►**genophore**; Blattner FR et al 1997 Science 277:1453; Riley M, Serres MH 2000 Annu Rev Microbiol 54:341; Perna NT 2001 Nature [Lond] 409:529; Schaechter M et al 2001 Microbiol Mol Biol Rev 65:119; Fumoto M et al 2002 Nucleic Acids Res 30:66; genetic techniques: Shuman HA, Silhavy TJ 2003 Nat Rev Genet 4:419; databases: <http://cgsc.biology.yale.edu> or <http://gib.genes.nig.ac.jp/>; <http://ecocyc.org/>; <http://ecoli.aist-nara.ac.jp>; predicted protein interaction database: <http://www.pdg.cnb.uam.es/i2h/>; regulatory systems: <http://regulondb.ccg.unam.mx:80/index.html>; post-genomics: <http://www.ecoli-york.org/>.

⌘ **Element**: At the 5'-end of the viral RNA minus strand it facilitates synthesis and encapsidation of the genome into the viral core. ►**retroid virus**

E Region of GTP-Binding Proteins: The E region interacts with effectors (amino acids 32–42 in RAS). Mutation

in this region may abolish oncogenic-transforming ability without affecting GTP-binding. ►**oncogenes**, ►**RAS**, ►**GTP**, ►**GTP binding protein superfamily**

E Site (exit site): The E site is on the ribosome to where the deacylated tRNA moves from the P site after the peptidyl-tRNA-mRNA complex moves from the A to the P site. The process may be reversible. The elongation factor EF-T mediates the regeneration of the active EF-Tu-GTP from EF-TU-GDP. Thus, besides the initially identified A and P sites, this third E site is now known. In contrast to the A and P sites, the E site may not be a permanent structure, rather it is just a transient intermediate stage of the peptide elongation process. ►**EF-TU-GTP**, ►**protein synthesis**, ►**ribosome**, ►**amino acid activation**

E Value: The e (expectancy) value in an alignment match (by BLAST) that is equivalent or better than expected by chance alone. The lower the E value, the better the score. ►**alignment**, ►**BLAST**

E Vector (self-inactivating vector, Ψ vector): A construct of large direct flanking repeats around the encapsidation signal (E/Ψ) that may bring about very high frequency of template switching of the reverse transcriptase. As a consequence, the viral (spleen necrosis virus, mouse leukemia virus) encapsidation protein may be deleted in 99% or even higher frequency and the virus thus inactivated. Also, suicide genes or other DNAs can be reconstituted by the same mechanism. Such a vector, when it includes selectable markers (e.g., neo), can be efficiently selected for in the presence of G418 antibiotic in gene therapy by retroviral vectors. ►**G418**, ►**neo**, ►**SIN vector**; Julias JG et al 1995 J Virol 69:6839; Delviks KA, Pathak VK 1999 J Virol 73:8837.

E1A: An adenovirus oncoprotein; it can reverse the growth-inhibitory effect of the transforming growth factor (TGF-β). E1A moves cells into the S phase by interacting with the retinoblastoma (Rb) and the p300

proteins. Rb recruits histone deacetylase and p300 attracts histone acetyltransferase. Both Rb and p300 are activated by phosphorylation at the G1/S checkpoint. ▶TGF, ▶T cells, ▶adenovirus, ▶cell cycle, ▶retinoblastoma, ▶p300, ▶chromatin remodeling, ▶histone deacetylase, ▶histone acetyltransferase, ▶CtBP; Fuchs M et al 2001 Cell 106:297.

E2A: An immunoglobulin enhancer-binding factor and basic helix-loop-helix protein encoded in human chromosome 19p13. (DNA binding domains; immunoglobulins).

EEA (excitatory amino acids): Glutamate and aspartate particularly can activate neurotransmitters. ▶neurotransmitter

Eadie-Hofstee Plot: In a coordinate system $v/(S)$ is plotted against v , where v is the enzymatic reaction velocity and (S) is the substrate concentration. ▶Michaelis-Menten equation, ▶Lineweaver-Burk plot

EAR (extra annual risk): The extra annual increase of incidence of cancer compared to (radiation) unexposed population. ▶risk, ▶ERR, ▶Armitage-Doll model

Earlobes Attached (at right, dominant is at left): Attached earlobes are generally, a recessive human trait (see Fig. E3).

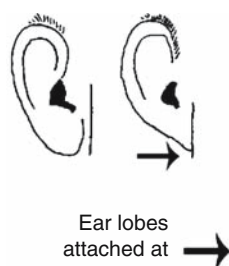


Figure E3. Earlobes attached

Early Genes: Genes transcribed early during development; they are involved in the infection process of the virus, and before replication begins. ▶early-response gene, ▶late gene, ▶delayed-response gene

Early-Response Gene: The early-response gene is activated by growth factors within a few minutes without a pre-requisite for protein synthesis. ▶early gene, ▶delayed-response gene, ▶late gene

Earwax (cerumen): The product of ceruminous apocrine glands and in humans it is determined by a Mendelian factor at 16p11-q12.1. This is also the site of the ABC transporter, the ABCC11, ABCC12 multidrug resistance protein 8 (MRP8) variants. The earwax can be either sticky, brown, wet type, controlled by AA

homozygosis (at a single nucleotide polymorphism G/A538), or the dry type determined by GA heterozygotes or GG homozygotes. The dry type actually lacks cerumen. The dominant A allele involves lower excretion of cyclic guanosine monophosphate than the G. The dry type is predominant (80–95%) among East Asians whereas among Europeans and Africans it is rare (~3%). (See Yoshiura K-I et al 2006 Nat Genet 38:324; ▶apocrine gland, ▶multidrug resistance).

E3B1: A signal transducer between RAS and Rac. ▶EPS8, ▶Rac, ▶RAS, ▶signal transduction

EBF (early B cell factor): Transcription factor specific for B cells and expressed at antigen-independent stages. It regulates the immunoglobulin α chain. ▶B lymphocyte, ▶T cell

ebgA⁰: A gene of *E. coli* (map position 67) that through two mutations permits galactose utilization, although this newly evolved galactosidase is immunologically distinct from the *LacZ*-encoded β -galactosidase enzyme. ▶lactose operon; Hall BG 1999 J Bacteriol 180:2862; Hall BG 2001 Mol Biol Evol 18:1389.

EBNA: Epstein-Barr virus antigens and transactivating oncoproteins. This protein—along with latent membrane proteins (LMPs)—is required for the latent maintenance of the infection. ▶oncogenes, ▶Epstein-Barr virus, ▶transactivator, ▶transactivation response element; Hochberg D et al 2004 Proc Natl Acad Sci USA 100:239.

Ebola Virus (EBOV): A member of the filamentous filoviridae, a negative-stranded, enveloped, nonsegmented RNA virus of 18,958 nucleotides, encoding 7 structural and 1 nonstructural proteins. It is a very dangerous hemorrhagic pathogen of humans and other primates. In recent years the virus seems to have killed 5,000 gorillas and many chimpanzees in Gabon and the Congo (Bermejo M et al 2006 Science 314:1564). Ebola virus-like particles (ebola glycoprotein + matrix protein) appear immunologically active enough to afford effective protection against the virus when used as a vaccine in mice (Warfield KL et al 2003 Proc Natl Acad Sci USA 100:15889). Endosomal cysteine proteinases are required for processing viral glycoproteins and for infectivity. Cathepsin B and Cathepsin L enzymes are effective facilitators in viral entry and their inhibitors may be effective as means of protection. Transcription of the highly pathogenic Ebola virus depends on VP30, a nucleocapsid-associated Ebola virus-specific transcription factor. The transcription activator VP30 was shown to play an essential role in Ebola virus replication, most likely by stabilizing nascent mRNA. The crystal structure and the mutagenesis results

revealed a potential pocket for small-molecule inhibitors that might prevent VP30 activity and thus virus propagation as it has been shown by peptides, which interfere with VP30 homooligomerization (Hartlieb B et al 2007 Proc Natl Acad Sci USA 104:624). ►animal viruses, ►negative-strand viruses, ►cathepsin, ►Marburg virus; Burton DR, Parren PW 2000 Nature [Lond] 408:527.

E

E-Box: The minimal DNA element (CANNTG, where N is any nucleotide) required for binding HLH and b/HLH/Z transcription factors. ►HLH, ►bHLH, ►helix-loop-helix

EBP: Enhancer binding protein. ►enhancer, ►C/EBP

4E-BP1 (PHAS-1): A binding protein of eIF-4E. After it is phosphorylated it stimulates the activity of eIF-4F cap-binding protein, required for the beginning of translation. It appears that phosphorylation of 4E-BP1 releases eIF-4E from the inhibition by 4EGI-1. The formation of the eIF4E/eIF4G initiation of translation complex is inhibited by 4E-BP. ►eIF-4F, ►eIF-4E, ►translation initiation, ►4EGI-1; Heesom KJ 2001 et al Curr Biol 11:1374.

EBV: ►Epstein-Barr virus

EC: Embryonal carcinoma cells. ►carcinoma

EC₅₀ (endpoint concentration 50): Concentration of a chemical that causes half of the individuals to reach an endpoint, e.g., anesthesia.

ECAF: Endothelial attachment factor.

Ecdysone: A steroid-molting hormone of insects produced by the prothoracic gland. Ecdysone signaling is important also for mid-embryonic development. 20-hydroxyecdysone initiates major developmental transitions and insulin family molecules control growth and development. Actually, ecdysone impedes growth by insulin signaling to transcription factor FOXO and to the translation inhibitor 4E-BP (Colombani J et al 2005 Science 310:667). It apparently stimulates transcription and activates puffing at different locations in the salivary gland chromosomes of *Sciara*, *Drosophila*, and other dipteran flies. This hormone and its variants apparently also regulate development in crayfish, arthropods, schistosomes, and nematodes. Similar compounds (β-ecdysones) occur in plants as well. Ecdysone does not play a natural role in mammals, yet the ecdysone receptor transgene controls ecdysone response. In *Drosophila* hydroxyecdysone—the active hormone—is produced after 6 h before entering the prepupal stage and again 10 h after pupariation. The production of the waves of these steroids is accompanied by distinct

morphogenetic developments. The ecdysone, EcR (ecdysone receptor), and USP (*ultraspiracle* 1-[05]) complex (homologous to human retinoid receptor) then turns on various genes. Some of the gene products' (E75, DHR3) feedback inhibit the complex and at the same time regulate (through mid-prepupal protein, βFTZ1) the onset of the second, smaller wave of ecdysone synthesis by these and another set of proteins. EcR and ecdysone defects may extend insect life span (Simon AF et al 2003 Science 299:1407). The complete ecdysone response element (EcRE) is palindromic; some other response elements are homologous although they display variations of the basic sequence (see Fig. E4). Muristerone is an agonist of ecdysone and it occurs in animal and some plant tissues. ►puffs, ►salivary gland chromosomes, ►animal hormones, ►steroid hormones, ►brassinosteroids, ►retinoic acid, ►insulin, ►eIF4A, ►eIF4E, ►FOX; Segraves W 1998. In: Dickson RB, Solomon DS (eds) Hormones and growth factors in development and neoplasia. Wiley-Liss, New York; Koolman J (ed) 1989 Ecdysone, Georg Thieme, Stuttgart, Germany, Arbeitman MN; Hogness D 2000 Cell 101:67; Takeuchi H et al 2001 J Biol Chem 276:26819; Petryk A et al 2003 Proc Natl Acad Sci USA 100:13773.

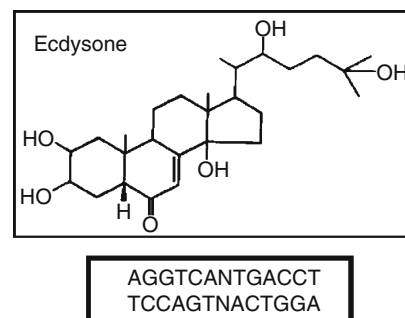


Figure E4. Ecdysone and ecdysone response element

ECE: Extrachromosomal element, such as a plasmid. ►plasmid

Eceriferum Loci: in the eceriferum loci in various plant species determine the cuticular waxes or lack of them (see Fig. E5). In barley, a particularly large number of loci in different chromosomes have been analyzed genetically and biochemically. There is an amazing specific wax pattern associated with the mutations that are correlated with the biosynthetic relations among β-diketones, hydroxy-β-diketones, alkan-1-ol, and alkan-2-ol esters. In the Arabidopsis *cer5* mutation deficiency of an ABC transporter fails in cuticular lipid export (Pighin JA et al 2004 Science 300:702). ►fatty acids, ►ABC transporter; Wettstein-Knowles VP 1975 Molec Gen Genet 144:43.

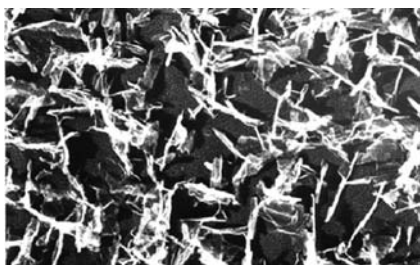


Figure E5. Eceriferum loci. The scanned electron micrograph is courtesy of Dr. Penny von Wettstein-Knowles

ECGF: Endothelial growth factor.

Echinacea (cornflower): Species *E. angustifolia*, *E. pallida*, and *E. purpurea* (see Fig. E6); perennial composite wild flowers of North America and Mexico and attractive garden ornamental flowers with some supposed medicinal value of the dried aerial parts and roots. Its basic chromosome number is $n = 11$. It has a mild fragrance and initially sweet taste, which becomes bitter later. It contains pyrrolizidine alkaloids, yet it is not considered toxic. Herbal medicine supports the oral administration of its extracts against cold, respiratory and urinary infections by attributing to it immunostimulatory effects. It is recommended also for external use in wound healing. Some persons may be allergic to it. Contraindications are for treatment of AIDS, tuberculosis, and autoimmune diseases. A recent clinical study indicated ineffectiveness of *E. angustifolia* root extracts against rhinovirus infections (Turner RB et al 2005 New England J Med 353:341). Another report confirmed antioxidant effects and favorable immune response to *Echinacea* tablets (Agnew LL et al 2005 J Clin Pharm Ther 30(4):363). A survey of 322 articles of the effects of *Echinacea* treatment for cold are equivocal and controversial (Caruso TJ, Gwaltney JM Jr 2005 Clin Infect Dis 40:807).



Figure E6. *E. purpurea*

Echocardiography: An ultrasonic examination of the structure of the fetal heart as part of a repertory of prenatal diagnosis of congenital defects in anatomy.
▶ prenatal diagnosis

Eclampsia/Preeclampsia: Hypertension, edema, proteinuria, kidney failure in the latter part of pregnancy with a prevalence of 2–5%, caused by etiological and genetic factors presumably at chromosome 2p12/2p25; another is at 9p13 in Scandinavian populations and a fourth at 10q22 among Dutch females (van Dijk M et al 2005 Nat Genet 37:514; reexamination of these findings led to the conclusion that the STOX1 gene at 10q22 is not involved [Iglesias-Platas I et al 2007 Nat Genet 39:279; van Dijk M et al 2007, Nat Genet 39:280, claim that polymorphism may be involved but the original report is still correct]). Preeclampsia, early stage of eclampsia, causes complications—possibly fetal and maternal death—in pregnancy by inadequate blood supply to the trophoblasts on the uterus. It appears that if the mothers are lacking all or most of the natural killer cell (NKC) immunoglobulin receptors (KIR), and the fetus possessed HLA-C2 group antigens (contributed to the fetus by the father), there is nonimmune physiological reaction, which causes problems in placental development (Hiby SE et al 2004 J Exp Med 200:957). There are two types of KIR; the A type is inhibitory whereas the B group is stimulatory to NKCs. It seems that the soluble receptor for the vascular endothelial growth factor (VEGF), sFlt1, binds VEGF and the placental growth factor and interferes with blood supply to the placenta. The heterodimer of angiotensin-1 receptor for angiotensin II and the B₂ receptor for bradykinin increased the susceptibility to preeclampsia by four- to five-folds. These and other factors may threaten the survival of the baby or the mother or both. ▶ killer cell, ▶ trophoblast, ▶ HLA, ▶ angiotensin, ▶ kininogen, ▶ mother-fetus incompatibility, ▶ vascular endothelial growth factor, ▶ FLT oncogene; Moses EK et al 2000 Am J Hum Genet 67:1581; Abdalla S et al 2001 Nat Med 7:1003; Redman CW, Sargent IL 2005 Science 308:1592.

Eclipse: The (latent) period between viral infection of a bacterium and the burst of the new phage particles even if burst is induced. ▶ one-step growth, ▶ burst, ▶ induction of a lysogenic bacterium; Anderson TF, Doerman AH 1952 J Gen Physiol 35:657; Abedon ST et al 2001 Appl Environ Microbiol 67:4233.

Eclosion: The hatching of the adult form (imago) of insects from the puparium. ▶ pupa

ECM: ▶ extracellular matrix

EcoCyc: ▶ *E. coli*

Ecodeme: A population adapted to a particular ecological condition. See marine ecological genomes: <http://www.megx.net/>.

Ecogenetics (ecological genetics): Ecogenetics studies the genetically determined responses of organisms to environment(s). ▶adaptation, ▶adaptive radiation; Hoffmann AAS et al 1995 Annu Rev Genet 29:349.

Ecological Interference: The joint outbreak of two infectious diseases may be negatively correlated because of the death of susceptible individuals from the pool after an acute infection. High mortality rate caused by one type of infection thus lowers the recruitment rate of susceptibles to another disease. (See Rohani P et al 2003 Nature [Lond] 422:885.)

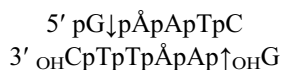
Ecological Race: A distinctly adapted group of an organism without sexual isolation from the ancestral form. ▶sexual isolation

Ecology: The study of the relationship of living systems and their environment. Examples: the increase of CO₂ concentration in the atmosphere and geosphere due to an increase of burning fossil fuels may increase the number of mitochondria in plants and alter the thylakoid structure in the chloroplasts. The temperature change that has been claimed may alter the habitats of all organisms and affect biodiversity. The ecology involves the networks of species that interact directly or indirectly in a complex manner (Montoya JM et al 2006 Nature [Lond] 442:259). ▶ecogenetics, ▶biodiversity, ▶inversion

Ecomorph: A species or group particularly adapted to a microhabitat (microenvironment).

Ecores: Orthologous coding sequences/evolutionarily conserved regions in genomes. ▶orthologous

EcoRI: Type II restriction endonuclease with a primary recognition site.



Å indicates potential base to be methylated, arrows indicate sites of cut.

The staggered cuts have a receding OH and a protruding p end -----OH

-----p

Although the above 6-nucleotide sequence is the primary recognition site, alternate recognition sites with different preferences are also known. These secondary activities (named EcoRI* [star]) depend on the composition of the incubation mixture. ▶restriction enzymes

EcoSeq: A database of a collection of DNA sequences of *E. coli* obtained from various sources.

Ecosystem: The relationship of living organisms to each other and to all environmental factors. Human

consumption has profound effects on the ecosystem (Imhoff ML et al 2004 Nature [Lond] 429:870). ▶species extant; Whitham TG et al 2006 Nat Rev Genet 7:510.

Ecotropic Retrovirus: An ecotropic retrovirus replicates only in the cells of the species from which it has been originally isolated. This specificity is determined by envelope glycoproteins that require specific receptors in the host. ▶amphotropic

Ecotype: A population adapted to a particular ecological condition. Besides the main genes determining the adaptive trait(s), the population may not be genetically homogeneous; usually it is not an isogenic line. ▶adaptation, ▶isogenic stocks

ECR: An evolutionarily conserved region revealed by comparative genome analysis.

Ectoderm: The surface layer of the embryo that develops into epidermis, skin, nerves, hair, nails, ears, eyes, enamel of teeth, internal mouth, and anal tissues. Transforming growth factor-β signals to the mesoderm and endoderm for homeostatic proliferation. For the formation of ectoderm attenuation of TGF-β is required. This task is performed by the protein ectodermin, a member of the Smad4 ubiquitin ligase family (Dupont S et al 2005 Cell 121:2). ▶gastrulation, ▶TGF, ▶smad, ▶ubiquitin

Ectodermal Dysplasia (EDA): Several *autosomal dominant forms* involve complex skin alterations and may eliminate the dermal ridges and alter palmar prints ▶fingerprints. In ectodermal anhidrotic dysplasia patients do not sweat and have a cleft lip and palate; in the hypohidrotic form sweating ability is only reduced whereas the hidrotic form shows normal sweating (see Fig. E7). The trichoodontochoial form is accompanied by deficiency of tooth, hair, breast and nipple formation. The *EEC* (ectrodactyly [missing fingers]) *ectodermal dysplasia* has most of the symptoms mentioned above plus abnormal tear ducts. The *autosomal recessive* ectodermal dysplasias include also complex features such as sweat gland tumors (eccrine tumors and ectodermal dysplasia), also anhidrotic type (due to mutation in connexin-30) dysplasia (HED or Coulson syndrome, 13q12) with neurosensory deafness, dysplasia with cleft lip and palate, mental retardation, syndactyly, hypohidrosis-hypothyroidism, hypohidrosis-hypothyroidism-lung disease. The human chromosome 2q11-q13 locus has both dominant and recessive mutations with hypohidrotic ectodermal dysplasia.

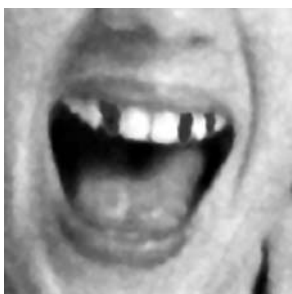


Figure E7. Ectodermal dysplasia. Missing teeth in hypohidrotic ectodermal dysplasia. Usually the teeth are also irregular

An *X-linked recessive* (Xq11-q21.1) ectodermal dysplasia is anhidrotic, shows reduction in hair and tooth development, hyperpigmentation around the eyes, short stature, etc. The Xq13.1 locus involves hypohidrotic ectodermal dysplasia (HED) and incontinentia pigmenti and the mutation is due to IKK-gamma (NEMO). The hypohidrotic ectodermal dysplasia with immunodeficiency is defective in switching from IgM to other classes of immunoglobulins. The latter gene is normally required for the activation of NF- κ B and its defect results in immunodeficiency. The X-linked ectodysplasin-A2 receptor (XEDAR) is different from the EDA-A1 receptor by the insertion of two amino acids. These receptors belong to the tumor necrosis receptor (TNFR) superfamily. In anhidrotic/hypohidrotic ectodermal dysplasia the Sonic hedgehog and its effectors, antagonists of the Wnt (wingless) and the bone morphogenetic (BMP) proteins as well as NF- κ B signaling pathway on lymphotoxin- β are involved (Cui C-Y et al 2006 Proc Natl Acad Sci USA 103:9142). ▶*dermatoglyphics*, ▶*fingerprints*, ▶*ectoderm*, ▶*anhidrosis*, ▶*connexin*, ▶*cleft palate*, ▶*cyst*, ▶*polydactyly*, ▶*EEC syndrome*, ▶*TNFR*, ▶*IKK*, ▶*BMP*, ▶*BMP*, ▶*Wingless*, ▶*NF- κ B*, ▶*incontinentia pigmenti*, ▶*NEMO*, ▶*skin diseases*, ▶*antibody gene switching*; Döffinger R et al 2001 Nat Genet 27:277; Jain A et al 2001 Nat Immun 2:223.

Ectokinases: A group of enzymes phosphorylating extracellular proteins and external domains of membrane proteins affecting cell interactions (Rodríguez F et al 2005 Proc Natl Acad Sci USA 102:4718).

Ectopic Antibody: An antibody molecule introduced exogenously into the cell. It may be genetically modified and specifically targeted. It may function as an effector or suppressor.

Ectopic Expression: The organ-specific expression of a gene is altered by fusing the structural gene to a promoter with different or no organ-specificity of expression. In more general meaning, ectopic expression is the displaced condition of an organ or function. ▶*promoter*, ▶*transformation*, ▶*allotopic expression*, ▶*orthotopic*

Ectopic Integration: The insertion of transforming DNA takes place at a target site different from that of the original position of the transforming DNA. ▶*transformation*, ▶*orthotopic*

Ectopic Pairing: The association between sites in nonhomologous chromosomes due to intercalary heterochromatin. ▶*chromosome pairing*, ▶*heterochromatin*; Aragon-Alcaide L, Strunnikov AV 2000 Nat Cell Biol 2:812.

Ectopic Pregnancy: An abnormality of ~1.2–1.4% incidence when the fertilized ovum develops outside the uterus. Risk factors are pelvic inflammation, *Chlamydia* infection, smoking, tubal surgery, endometriosis, etc., but a role for chromosomal aberrations could not be verified (Coste J et al 2000 Fertil Steril 74:1259).

Ectopic Recombination: The recombination between non-allelic but homologous chromosomal sequences or between a normal chromosomal site and an insert at a nonhomologous site. Recombination between dispersed repetitive DNA such as ribosomal RNA genes, multicopy transposable elements (e.g., Alu), multigene families, transgenes, centromeric and telomeric DNA elements. Ectopic recombination may result in chromosomal rearrangements, aneuploidy and the formation of nucleotide repeats causing various human diseases. There appears to be a selective restraint against such events. ▶*homologous recombination*, ▶*illegitimate recombination*, ▶*intrachromosomal recombination*, ▶*trinucleotide repeats*, ▶*Alu*, ▶*transgene*; Goldman AS, Lichten M 2000 Proc Natl Acad Sci USA 97:9537; Goebel P et al 2001 J Exp Med 194:645; Lam K-WG, Jeffries AJ 2006 Proc Natl Acad Sci USA 103: 8921.

Ectoplast: The cytoplasmic membrane surrounding the protoplast.

Ectrodactyly: Split foot and hand, absence of fingers/polydactyly. It is most likely under autosomal recessive control. Cleft lip and palate, skin, teeth, hair, nail defects and closure (atresia) of the lacrimal ducts may accompany it. The autosomal dominant gene (2q11-q13, ED3) and the (Xq12-q13, ED1) mutations also involve hypotrichosis, hypodontia, and hypohidrosis. Cleft lip and/or palate, EEC3 is at 3q47, Limb-Mammary syndrome is at 3q27,

E

ankyloblepharon-ectodermal defects-cleft lip/palate at 3q27, Adult's syndrome (acro-dermato-ungual-lacrima-digit) at 3q27, split-hand/foot malformation at 3q27. The symptoms are shared partly by a score of other syndromes involved in mutations of the p63 tumor-suppressor protein encoded at 3q27. The Rosselli-Gulienetti syndrome is at 11q23-q24, the EEC1 gene is at 7q11.2-q21.3. ▶[adactyly](#), ▶[polydactyly](#), ▶[split hand/split foot malformation](#), ▶[p63](#), ▶[Rapp-Hodgkin syndrome](#)

Ectromelia: Bone underdevelopment; also poxvirus causing disease of mice involving defect of the limbs and necrosis of visceral organs.

Eczema: Eczema refers to an itchy inflammation of the skin; it may be scaly or oozing and may be caused by various factors even as simple as drying of the skin in winter, food allergy or infections, or Kaposi sarcoma, etc. Loss of function of the filaggrin gene (in about 9% of European populations) is a predisposing factor to ichthyosis vulgaris as well as to asthma (Palmer CN et al 2006 Nat Genet 38:441). Filaggrin is the protein controlling the terminal differentiation of the epidermis. ▶[dermatitis](#), ▶[skin diseases](#), ▶[Wiskott-Aldrich syndrome](#), ▶[Kaposi sarcoma](#), ▶[acquired immunodeficiency syndrome](#), ▶[allergy](#), ▶[ichthyosis](#), ▶[asthma](#)

EDG (endothelial differentiation gene): The EDG, when overexpressed, enhances cell aggregation and an increase in the expression of cadherins, depending on the RHO protein and activation by sphingosine-1-phosphate (SSP). ▶[cadherins](#), ▶[sphingosine](#); Marletta MA 2001 Trends Biochem Sci 26:519; Robert P et al 2001 J Mol Cell Cardiol 33:1589.

Edges: Edges are interactions in genetics networks between nodes. ▶[networks](#)

Edible Vaccines: ▶[plant vaccines](#)

Editing: Some DNA polymerases, aminoacyl tRNA synthetases, aptamers also have nuclease functions and eliminate replicational mistakes or prevent translational errors. ▶[antimutator](#), ▶[DNA polymerases](#), ▶[error in aminoacylation](#), ▶[aptamer](#), ▶[RNA editing](#), ▶[mtDNA](#), ▶[string edit distance](#), ▶[editosome](#), ▶[ADAR](#)

Editosome: The complex which determines the selection of RNA bases for editing. The determination may involve a protein or RNA. In the mitochondria of *Arabidopsis*, 8% of codons are edited (5,285 codons) and 16 were edited twice. The specificity of selection of the correct cytosine residue may require only 2–8 nucleotides. ▶[RNA editing](#); Giegé P, Brennicke A 1999 Proc Natl Acad Sci USA 96:15324.

Edman Degradation: A procedure for protein sequencing. The reagent phenylisothiocyanate causes the formation of phenylthiohydantoin and cleavage of the terminal residue. This amino acid can then be identified. The same process can be repeated many times and the amino acid sequences of the entire macromolecule can be determined, step by step. The commercially available automatic protein sequencers use the same principle in an efficient way. (See Edman P, Begg G 1967 Eur J Biochem 1:80).

EDRF (endothelium-derived relaxing factor): EDRF is nitric oxide. ▶[nitric oxide](#)

EDTA (ethylenediaminetetraacetic acid): A chelating agent and as such an inhibitor of DNase. It is an anticoagulant and is also used for plant nutrient media for improving the solubility of iron, etc. ▶[DNA extraction](#), ▶[embryogenesis somatic](#), ▶[DNA fingerprinting](#), ▶[versenes](#)

Edward VII: King of England, one of the three sons of Queen Victoria who did not inherit the hemophilia gene. ▶[hemophilias](#)

Edward's Syndrome: Trisomy for human chromosome 18 with serious debilitating consequences or of prenatal or postnatal death within a few months; at most may survive up to a few years. Generally, the head is elongated, the ears are set low, eyelids are abnormal, fingers clenched, hypoplasia of nails, and almost all organs are affected. Its incidence is about 1 in 7,500–10,000 births with a predominance of females among the afflicted. The disomic chromosome is maternally contributed in 95% of the cases, and 95% of the incidences fail to survive till birth. Increased maternal age and meiosis II errors are factors in the incidence. ▶[trisomy](#), ▶[trisomic analysis](#), ▶[hypoplasia](#)

EEA-1 (early endosomal autoantigen 1): EEA-1 binds phosphoinositide-3-phosphate (PtdIns[3]-P) and Rab5 to the endosomes and mediates endosome fusion with the cooperation of phosphatidylinositol-3-OH kinase. ▶[endocytosis](#), ▶[phosphoinositides](#), ▶[Rab](#)

EEC Syndrome (ectrodactyly, ectodermal dysplasia, cleft lip/palate): An autosomal (3q27) dominant abnormality. The mutation involves the gene encoding p63, a homolog of p53, and it maps to a location identical with that of the Limb mammary syndrome. Components of the EEC syndrome are parts of the defects attributed to mutations at Split-hand/foot malformation syndromes 7q21.3-q22.1 (SHFM1), Xq26 (SHFM2) and 10q24-q25 (SHFM3). These human anomalies occur at an approximate frequency of 1.8×10^{-5} . ▶[ectrodactyly](#), ▶[ectodermal dysplasia](#), ▶[cleft lip](#), ▶[cleft palate](#), ▶[limb defects in humans](#),

►syndactyly, ►polysyndactyly, ►Pallister-Hall syndrome

eEF Eukaryotic elongation factors of peptide chain. Some of them recruit the aminoacyl-tRNA to the ribosome while others control the translocation of the ribosome on the mRNA. ►Spt; Negrutskii BS, El'skaya AV 1998 Prog Nucleic Acid Res Mol Biol 60:47.

eEF-1A (eEF-1 α): Eukaryotic translation factor, binds amino acid-tRNA; also a GTPase and regulates cytoskeletal (microtubule) rearrangements. It occurs in two isoforms encoded by two genes with tissue-specific expression. It is similar to prokaryotic EF1A. ►protein synthesis, ►EF1A; Hotokezaka Y et al 2002 J Biol Chem 277:18545.

eEF-1 β (eEF1B or eEF-1 $\beta\gamma\delta$): Mediates GTP-GDP exchange on eEF-1 α in eukaryotic translation. It is similar to prokaryotic EF1B. ►protein synthesis, ►EF1B

eEF-1 γ : Mediates GTP exchange with the aid of eEF-1 β in translation. ►protein synthesis

eEF-2: Eukaryotic translation factor; stimulates peptide chain translocation on ribosome. When phosphorylated it may slow elongation rate. It is also a GTPase. It is similar to prokaryotic EF-2 ►GTPase, ►translocation, ►protein synthesis, ►EF-2

eEF3: A unique fungal translation factor without exact homologs in other taxonomic categories. ►structure; Andersen CBF et al 2006 Nature [Lond] 443:663.

EEG (electroencephalogram): A record of the electric current developed in the brain, measured after electrodes are applied to the scalp, to the surface of the brain, or into the brain material. It reveals the functional state of the central nervous system. The EEG pattern depends on a number of factors, but also has a hereditary component indicating psychological responses of the family.

EF-2 (EF-G): A ~77-kDa translation elongation factor in prokaryotes; it catalyzes translocation on ribosomes. Although the reaction derives energy by the hydrolysis of guanosine triphosphate, the tRNA-mRNA-ribosome complex of prokaryotes may alone provide energy for the peptidyl transferase (Fredrick K, Noller HF 2003 Science 300:1159). ►protein synthesis

EF1A (EF-Tu): A (44 kDa) prokaryotic GTP-binding peptide chain elongation factor. It mediates the aminoacylated tRNA binding to the ribosomes. E-Tu and flagellin activate defense signaling in *Arabidopsis* against *Agrobacterium* infection (Zipfel C et al 2006 Cell 125:749). ►flagellin; LaRiviere FJ et al 2001 Science 294:165.

EF-1 α : A translation initiation factor in eukaryotes. ►protein synthesis

EF1B: (Ef-Ts): A prokaryotic translation factor.

E2F1: A family of transcription factors, activated by RB and MDM2 oncogenes. High E2K level may be reached by mutation in RB, and then MAD2 is overexpressed leading to aneuploidy, a common feature of oncogenic transformation (Hernando E et al 2004 Nature [Lond] 430:797). They are involved in the regulation of the cell cycle, apoptosis, neoplasia, etc. E2F interacts with cyclinA/Cdk2 and it is phosphorylated by the latter thereby down-regulating its DNA binding and transcription activation (Rubin SM et al 2005 Cell 123:1093). E2F also regulates p53. E2F1 also regulates p73 protein and apoptosis by T cell receptor activation induced cell death even in the absence of p53. ►MDM2, ►ARF, ►retinoblastoma, ►p53, ►p73, ►DP1, ►pocket, ►cancer, ►EMA, ►histone deacetylase, ►histone methyltransferases, ►retinoblastoma, ►CDF, ►CDC14, ►cell cycle; Takahashi Y et al 2000 Genes Dev 14:804; Wu L et al 2001 Nature [Lond] 414:457; Ogawa H et al 2002 Science 296:1132.

e1F-2B: A translation factor involved in GTP-GDP exchange. ►protein synthesis, ►GTP

$$E = \sum_T w_T H_T$$

Effective Dose of Radiation (E): Where w_T = is the weighting factor varied according to the tissue absorbing, and H_T = equivalent dose to tissue. ►stochastic detriment, ►radiation hazard

Effective Mutagen: An effective mutagen causes all types of mutations (including chromosomal changes) at high frequency. ►efficient mutagen

Effective Number of Alleles The number of alleles that are maintained in the population. ►effective population size

Effective Number of Loci: The number of loci involved in a quantitative trait; also called segregation index. ►gene number in quantitative traits

Effective Population Size (N_e): The number of individuals that leave offspring in a population. Although, from several viewpoints (economic, agricultural, ecological, demographic, insurance, welfare), the total number of individuals may be the most important, geneticists are concerned primarily with that fraction of the population that passes on genes to future generations. The *genetically effective size of the population* is represented as (N_e). If the effective population size is small (even if the mating is random), the allelic and genotypic frequencies may be biased. In cases when unequal numbers represents

the two sexes the effective population size will be lower than the sum of the males and females. Each individual has a 0.5 chance to contribute a particular allele to the offspring (through the egg and sperm) and the chance of contributing two of the same allele is $0.5 \times 0.5 = 0.25$. The probability that the same female contributes two alleles is:

$(1/N_f)(1/4)$ and for a male it is: $(1/N_m)(1/4)$, where N_f and N_m are the number of females and males, respectively. Therefore, the probability that any two alleles of the population comes from the same individual is: $\frac{1}{4N_f} + \frac{1}{4N_m} = \frac{1}{N_e}$ hence $N_e = \frac{4N_mN_f}{N_m+N_f}$. Fluctuations in population size from generation to generation as well as the nonrandom distribution of family size may affect the allelic sampling.

The sampling variance of the alleles is equal to: $\sigma^2 = \frac{q(1-q)}{2N}$.. and hence $\sigma = \sqrt{\frac{q(1-q)}{2N}}$... where q is the frequency of one of the alleles and N is the population size. If the frequency of the a allele is 0.5 and $N = 25$, the standard deviation of the frequency of the a allele becomes: $\sigma = \sqrt{\frac{0.5 \times 0.5}{2 \times 25}}$.. $= \sqrt{0.005}$... ≈ 0.071 . This indicates that chance alone can modify the frequency of the a allele in a small population. And 31.74% of the loci (because according to the normal distribution 68.26% of the population is supposed to be within $M \pm 1\sigma$) may carry the allele with frequencies more extreme than 0.429 to 0.571 rather than 0.5 ($0.50 \pm$ standard error). In other words, this also means that if the population is broken up into smaller breeding units, 31.74% may have gene frequencies in the range of 0.429 and 0.571. In cases of polygeny, the N_e is reduced as determined by the formula: $4MF/(M + F)$ where M and F are the number of males and females, respectively. The N_e for autosomal and Y populations is dependent on the ratio of mating men and mating women (R), and $N_e \approx (2 + 2R)/R$.

The effective number of breeding individuals can be estimated also from the number of heterozygotes, in excess of expectation, on the basis of the Hardy-Weinberg equilibrium, because when the number of breeders is small, by chance, the allele frequencies will differ in the males and females. This procedure is applicable only to polygamous or polygynous populations with few breeders and many loci with multiple alleles (Luikart G, Cornuet J-M 1999 Genetics 151:1211).

Any shift in the gene frequencies brought about by the random fluctuation in gametic sampling is called *random genetic drift*. The drift is completely accidental. Such events may take place in the population in any breeding season if the number of breeding individuals is reduced. Once such a sampling bias of gametes (in mating) has taken place, the

process may continue in either direction but there is a definite chance that the allelic composition of the small population permanently changes. A special case of the random drift is the *founder effect*. A small number of individuals (immigrants) introduced into new habitats may not represent accurately the genetic constitution of the population of their origin. Their descendants then may form the basis of a divergent trend from the norm of their ancestors. Such a phenomenon is not uncommon if animal or plant species migrate to new parts of the world or to regions that are spatially isolated from their old homeland.

Organelle DNAs (mitochondrial and chloroplast) have smaller genetically effective population sizes than the nuclear DNAs because they are inherited uniparentally and are effectively haploid (Birky CW Jr et al 1989 Genetics 121:613). Also, their genetic diversity is more limited and evolves faster because of these facts. [►speciation](#), [►isolation genetic](#), [►standard error](#), [►normal distribution](#), [►F_{ST}](#), [►gamma selection parameter](#), [►polygamy](#), [►polygeny](#), [►Amish](#); Anderson EC et al 2000 Genetics 156:2109; Wall JD 2003 Genetics 163:395.

Effector: A small molecule which assists either in activating or deactivating a molecular event. Interaction of the RAS protein with effectors uses 32–40 amino acids, the effector region, varying in conformation in GTP- and GDP-bound RAS. Effector lymphocytes are activated to destroy the foreign antigens. [►GTP](#), [►RAS](#), [►signal transduction](#), [►lymphocyte](#); Alto NM et al 2006 Cell 124:133.

Effector Cell: An activated B cell or T_H cell that mediates the adaptive immune system. The activation results in an increase in antigen-specific killer cells. After an episodic infection the effector CD8 T cells may migrate to nonlymphoid tissues and become long-lived memory cells. Effector memory T cells are more potent in immunotherapy of cancer because of higher lytic ability and because of the release of more TNF- γ . This property has relevance for the development antitumor vaccines (Klebanoff CA et al 2005 Proc Natl Acad Sci USA 102:9571). [►immune system](#), [►B cell](#), [►CCR](#), [►CD34](#), [►killer cell](#), [►memory immunological](#), [►tumor vaccination](#); Gazitt Y 2000 Stem Cells 18:390.

Effector Domain: The effector domain of an antibody contains the region that recognizes specifically the cognate antigen. [►antibody](#), [►antigen](#)

Effector Gene: An effector gene encodes an enzyme that, in combination with other molecule(s), functions as an effector. [►effector](#)

Efficient Mutagen: An effective mutagen produces primarily point mutations and relatively low amount

of chromosomal alterations. ►effective mutagen, ►point mutation

Efflux Systems: Efflux systems carry out energy requiring active pumping of harmful agents from the cells.

EF-G: A translation factor and a motor protein that is also a GTPase. It mediates the GTP-dependent transfer of peptidyl-tRNA-mRNA complex from ribosomal A site to P site. Its domain IV has some structural similarity to the elongation factor. ►protein synthesis, ►ribosome, ►aminoacylation, ►EF-Tu

EF-Ts: A prokaryotic translation factor protein involved in GTP-GDP exchange. ►protein synthesis

EF-Tu.GTP: An active prokaryotic elongation factor of protein synthesis in which EF-Tu interacts with aminoacyl-tRNA and promotes the translocation of the peptidyl-tRNA from the ribosomal A to B site and the release from the ribosome of the deacylated tRNA. ►aminoacylation, ►protein synthesis, ►ambiguity in translation, ►tRNA; Frederick J et al 2001 Science 294:165.

E.GDP: A bound (inactive) form of guanosine diphosphate in signal transduction. ►E region of GTP-binding proteins

EGF: An epidermal growth factor, binds to receptors such as the protein coded for by the protooncogene ERBB, triggering growth-promoting signals. The *v-erbB* viral oncogene encodes a truncated EGF that continuously binds to a ligand and provides a constitutive supply of growth signals. EGF controls a wide range of cellular processes. ►growth factors, ►oncogenes, ►TGF; Iressa Daub H et al 1997 EMBO J 16:7032; Pierce K L et al 2001 J Biol Chem 276:23155; signals: VivekanP, Rebay I 2006 Annu Rev Genet 40:139).

eGFP (enhanced green fluorescent protein): Different variations exist, all depending on engineered amino acid replacements in the *Aequorea* GFP. The point mutations alter the emission peaks (color) and the added nucleotide sequences assure high expression and maximize signal intensity and are suitable for dual color (blue and yellow) detection. Some expression vectors are commercially available. ►ae-*quorin*; Yang T-T et al 1998 J Biol Chem 273:8212.

EGFR (epidermal growth factor receptor): The EGFR has been localized in the nucleus of different cells. Its localization and stability are mediated by ubiquitination of the Lysine 6-linked polyubiquitin chain in its kinase domain (Huang F et al 2006 Mol Cell 21:737). It has been found in association with the promoter of cyclin D1 indicating that it is a transcription factor. The EGFR family includes ErB2, ErB3, and ErB4 proteins. Its inhibitor, Iressa, is a potential anticancer

agent. ►ERBB1, ►RTK, ►LDL receptor; Bogdan S, Klämbt C 2001 Curr Biol 11:R292; Lin S-Y et al 2001 Nat Cell Biol 3:802; down-regulation mechanism: Landau Met al 2004 Structure 12:2265; Herbst RS et al 2004 Nat Rev Cancer 4:956.

Egg (ovum): The final haploid product of female meiosis. The eggs are huge cells (ca. 100 µm in diameter in humans) (see Fig. E8) compared to the other ones in the body (about 20µm). The egg cytoplasm contains yolk, a very condensed store of nutrients, especially in organisms that lay outside the eggs. In mammals, the yolk is comparatively minimal. (A generalized composite drawing is given in the diagram.) In mammals, the zona pellucida membrane surrounds the egg. In lower vertebrates there is a *vitelline layer* and also other ones. In birds there is the *egg white* and before laying the egg the *shell* is added in the oviduct. The vitelline layer of the insects is covered by the so-called *chorion*, secreted by the *follicle cells* of the *ovary*. In the layer under the plasma membrane (*cortex*) are the *cortical granules*. Their content protects the egg from fertilization by more than one sperm. During fertilization the sperm is attracted to the egg by chemotactic peptides causing changes in the voltage of the membrane and in altering the concentration of cAMP, cGMP, Ca²⁺, and K⁺ ion channels. In mammals, parthenogenesis is normally absent, yet in immature and mature mouse oocytes, by appropriate expression of the *Igf2* and *H19* genes with major roles in imprinting, fulltime development of offspring from two maternal nuclei was successful (Kono T et al 2004 Nature [Lond] 428:860). ►oocyte, ►ovary, ►gametogenesis, ►menopause, ►fertilization, ►imprinting, ►parthenogenesis, ►polyspermic fertilization, ►RPTK, ►sperm

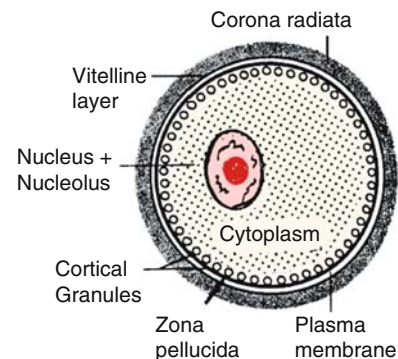


Figure E8. Human egg

Egg Cylinder: A very early mammalian embryonal structure, including the cells that will form the fetus and the embryonal sacs (amnion, allantois), some extra embryonic tissue that form the outer embryo sac (chorion), and the trophoblastic tissues of the placenta.

E

Egg Donation: The providing of eggs for in vitro fertilization for research or assisted reproductive technology. The donor female takes a gonadotropin-releasing hormone agonist to delay ovulation. Then administration of follicle-stimulating hormone facilitates the production of several egg-containing follicles. Another hormone is used for maturation of eggs, which are retrieved surgically from the ovary through the vagina. The procedure is not without risks for the donor. ▶GnRHA, ▶gonad, ▶stem cells, ▶ART

Egg Number in Humans: Each of the two human ovaries contains more than 200,000 primary oocytes yet only about 400 eggs develop to maturity during the period from puberty to menopause. In mammals, the production of egg stem cells was thought to be completed before birth. It appears, however, that proliferative female germ cells may exist in the postnatal ovary just as it is the case in the male gonads (Johnson J et al 2004 Nature [Lond] 428:145). The size of a human egg is comparable to a period in this print. ▶puberty, ▶menopause, ▶oogenesis, ▶oocyte, ▶egg, ▶dictyotene

Egg Plant (*Solanum melongena*): A tropical-subtropical vegetable with $2n = 2x = 24$ chromosomes. (See Doganlar S et al 2002 Genetics 161:1697 and 1713).

Egl-1 (Eglin): A proteinase inhibitor, it controls the proapoptotic caspase-9 and other proteins. ▶caspases; Komiyama T, Fuller RS 2000 Biochemistry 39:15156.

4EGI-1 (eIF4E/eIF4G interaction inhibitor): 4EGI-1 (see Fig. E9) inhibits complex formation between translation initiation factors eIF4E and eIF4G (Moerke NJ et al 2007 Cell 128:257).

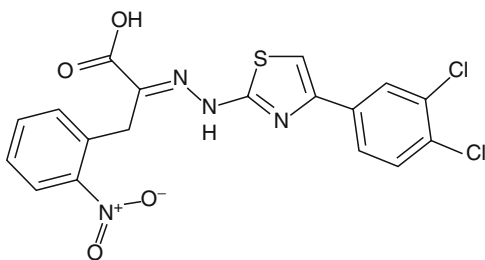


Figure E9. 4EGI-1

Egr-1: A mitogen-induced transcription factor, a serum-inducible nuclear phosphoprotein with zinc finger. Egr2 is a Zn-finger protein regulating cell proliferation. Egr-3 (NGFI-C) is essential for muscle spindle development. ▶NGFI-A, ▶TIS8, ▶platelet derived growth factor, ▶zinc finger, ▶Krox; Calogero A et al 2001 Clin Cancer Res 7:2788.

E.GTP: The bound (active) form of guanosine triphosphate in signal transduction. ▶E region of GTP-binding proteins

Ehlers-Danlos syndrome (EDS): An extremely complex and usually a dominant disorder involving loose joints that stretch excessively, excessive stretchability of the skin that is bruised easily, and characterized by frequent appearance of pseudo-tumors after some trauma (see Fig. E10). The anomalies are caused either by a deficiency of procollagen peptidase (recessive EDS type VII) or the lack of a collagen type. EDS I is deficient in COL5A2 and 5A1 encoded at 2q31 and 9q34.2, respectively.



Figure E10. Ehlers-Danlos symptoms: Genu recurvatum (hyperextension of the knee or back knee), deformed toes, tumors under the ankle and on the front part of the foot. (From Bergsma D (ed) 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

EDS II is the most common form of the disease and is also deficient in COL5A1 and COL5A2 encoded at 9q34.2-q34.3. COL1A1 is encoded at 17q21.3-q22. Low hydroxylysine content of the connective tissue prevents effective cross-linking. EDS type VII (dermatosparaxis) is recessive/dominant at 5q23 and has a deficiency of procollagen protease and lysyl oxidase (LOX). Type VIA (encoded at 1p36.3-36.2) is deficient in lysyl hydroxylase whereas in type VIB the hydroxylysine level is normal. Lysyl oxidase level is reduced in the individuals afflicted by EDS types

VI, VII, and IX. Type IV (2q31, dominant) suffers from mutation in type III procollagen and increases the risk of aneurysm. Type V disease has a defect in the α chain of collagen mapped to human chromosome 9q34, but a type EDS V is X-linked and is caused by lysyl oxidase deficiency. EDS VIII (12p13) is involved in periodontal disease (Rahman N et al 2003 Am J Hum Genet 73:205).

The EDS has many different variations, from mild to severe, and its incidence may be estimated to be in the $1-2 \times 10^{-4}$ range. Type X (2q34) involves platelet abnormality and it is due to the deficiency of fibronectin. ▶collagen, ▶skin diseases, ▶fibronectin, ▶connective tissue disorders, ▶cardiovascular disease, ▶Menkes syndrome, ▶aneurysm, ▶periodontal disease; Schwarze U et al 2000 Am J Hum Genet 66:1757; Wenstrup RJ et al 2000 Am J Hum Genet 66:1766.

Ehrlich ascites: ▶ascites

EI: EI is ethyleneimine (C_2H_5N), a powerful alkylating mutagen and carcinogen. ▶alkylating agent

Eicosahedron: A 20-faceted body (see Fig. E11). ▶DNA tumor viruses



Figure E11. Eicosahedron

Eicosanoids: Eicosanoids are mammalian autocrine signaling molecules affecting muscle contraction, platelet aggregation, pain, and inflammation. They are produced at the expense of phospholipase-degraded phospholipids. Eicosanoid is the systematic name of arachidonic acid. ▶fatty acids, ▶signal transduction, ▶autocrine, ▶platelet, ▶phospholipase, ▶leukotrienes, ▶prostaglandins; McMahon B et al 2001 Trends Pharmacol Sci 22[8]:391.

eIF: An eukaryotic initiation factor of protein synthesis. ▶IF; Karim MM et al 2001 J Biol Chem 276:20750; functions of the eIF initiation complex: Gilbert RJC et al 2007 Proc Natl Acad Sci USA 104:5788.

eIF-1: A 12.7-kDa (human) and 12.3-kDa (yeast) translation factor stimulating the 40S ribosomal subunit preinitiation complex. It interacts primarily with eIF-3. ▶protein synthesis, ▶ribosome scanning

eIF-1A (eIF-4C): A ribosome dissociation factor (17–22 kDa) and 40S preinitiation complex-stimulating protein in translation. It shows ~20% homology with the prokaryotic IF1 (Petroulakis E, Wang E 2002 J Biol Chem 277:18718).

eIF-2: A heterotrimeric (α , β , γ) translation elongation factor mediating the GTP-dependent Met-tRNA binding to the 40S ribosomal subunit. It may repress protein synthesis if its α subunit is phosphorylated. ▶protein synthesis, ▶ribosome, ▶GTP, ▶aminoacylation; Kimball SR 1999 Int J Biochem Cell Biol 31:25.

eIF-2A (eIF2 α): A heterotrimeric translation elongation factor controlling AUG-dependent Met-tRNA-GTP binding to the 40S ribosomal subunit. It is inactivated by phosphorylation through the hemin-regulated inhibitor kinase (HRI, PKR, PEK/PERK). eIF-2 phosphorylation of serine/threonine by RNA-dependent protein kinase (PKR, 68 kDa in humans) is induced by Interferon α/β in response to infection by a double-stranded RNA virus. In addition, PKR can phosphorylate tyrosine 101, 162, and 293. Tyrosine phosphorylation assures binding to dsRNA, dimerization, kinase activation, and eIF2 α phosphorylation and viral resistance by inhibition of translation (Su Q et al 2006 Proc Natl Acad Sci USA 103:63). Dephosphorylation can be inhibited by salubrinal (see Fig. E12) and prevents stress of the endoplasmic reticulum (Boyce M et al 2005 Science 307:935). GCN2 is activated by amino acid starvation. GCN4 activates the transcription of more than 30 amino acid synthesizing enzymes. ▶protein synthesis, ▶aminoacyl-tRNA synthetase, ▶essential amino acids, ▶GCN4, ▶HRI, ▶PEK, ▶PKR; Ito T et al 2004 Structure 12:1693.

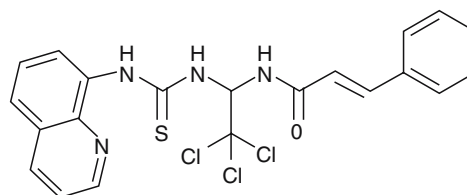


Figure E12. Salubrinal

eIF-2B: A heteropentameric guanine nucleotide exchange factor (GEF) involved in translation by controlling phosphorylation of eIF2. Its defect may lead to leukoencephalopathy with vanishing white matter. (See Leegwater PAJ et al 2001 Nat Genet 29:383; van der Knaap MS et al 2003 Am J Hum Genet 73:1199).

eIF-2C (Co-eIF-2A): A translation initiation factor stabilizing ternary complexes (eIF2•GTP•tRNA) of translation. ▶protein synthesis, ▶ternary

eIF-3: A ~750-kDa, ~12 subunit, five-lobed mammalian elongation initiation factor; it is activated by phosphorylation in translation. It stimulates the formation of the 40S ribosomal preinitiation complex. ▶ribosome, ▶protein synthesis; Siridechadilok B et al 2005 Science 310:1513.

eIF-3A: A translation factor affecting ribosome dissociation by binding to the 60S ribosomal unit.

eIF-4A: An eukaryotic translation (mRNA cap-binding proteins, eIF4E) factor (46-kDa), RNA-dependent ATP-ase, helicase (eIF4A), which stimulates mRNA binding to ribosome. Several isoforms exist. Phosphorylation reduces its affinity for capped mRNA. ▶protein synthesis, ▶ATPase, ▶helicase, ▶mRNA surveillance, ▶FLAG, ▶DEAD-box proteins, ▶isoform, ▶oskar; Gingras A-Cet al 1999 Annu Rev Biochem 68:913; Scheper GC et al 2002 J Biol Chem 277:3303; Bordeleau ME et al 2005 Proc Natl Acad Sci USA 102:10460.

eIF-4B: An eukaryotic translation initiation factor (mRNA cap-binding protein, 69 kDa in humans); elongation initiation of translation upon phosphorylation. A helicase which stimulates mRNA binding to ribosomes. ▶protein synthesis, ▶ribosome, ▶helicase, ▶mRNA, ▶ribosome, ▶4E-BP

eIF-4C: The eIF-4C function is similar to that of eIF-1A and it appears to be synonymous with it.

eIF-4D: Probably the same as eIF-5A.

eIF-4E: A translation factor involved in binding of the circularized (by eIF-4G) capped mRNA to the 40S ribosomal subunit. It may exist in different forms. Loss of a specific eIF-4E isoform (IFE-2) that functions in somatic tissues reduces global protein synthesis, protects from oxidative stress, and extends lifespan in *Caenorhabditis elegans* (Syntichaky P et al 2007 Nature [Lond] 445:922). ▶cap, ▶ribosome, ▶protein synthesis, ▶4E-BP, ▶P body, ▶microRNA, ▶ecdysone, ▶longevity

eIF-4F: A heterotrimeric (including eIF-4E, eIF-4G and eIF-4A) key element of translation initiation; it recognizes the mRNA cap. It is a helicase, an elongation initiation factor and when phosphorylated may lead to overexpression and cancerous growth. Viral genes using IRES may not absolutely depend on the eIF-4F-cap complex. ▶protein synthesis, ▶translation initiation, ▶ribosome, ▶helicase, ▶cap, ▶cancer, ▶Pab1p, ▶IRES, ▶picornaviruses, ▶CDC 33

eIF-4G (eIF-4γ): Comprises two translation initiation factors (I, 171 kDa, and II, 176 kDa) for the 40S eukaryotic ribosomes. It functions as an adaptor between the cap-binding proteins eIF-4A, eIF-4E, eIF-3, and also it may bind to the PolyA tail-binding protein. The latter has been shown to involve translation stimulation. ▶protein synthesis, ▶cap, ▶IRES, ▶FLAG, ▶Pab1p; Gallie DR, Browning KS 2001 J Biol Chem 276:36951; Niedzwiecka A et al 2002 J Mol Biol 319:615; Gingras AC et al 1999 Annu Rev Biochem 68:913.

eIF-4H (25 kDa, monomeric): The stimulatory function of eIF-4H resembles that of eIF-4B.

eIF-5: Consists of 48.9-kDa (human) and 45.2-kDa (yeast) translation factors which promote the joining of the small and large ribosomal subunits into the 80S ribosome. It is crucial for the assembly of the preinitiation complex and its carboxy-terminal domain interacts with the eIF-1, eIF-2, eIF-3 and eIF-4G (Yamamoto Y et al 2005 Proc Natl Acad Sci USA 102:16164). It is a GTPase activator. ▶ribosome, ▶protein synthesis, ▶preinitiation complex

eIF-5A: Assists in the formation of the first peptide bond during translation. ▶protein synthesis, ▶peptide bond

eIF-5B: A homolog of prokaryotic IF-2. It interacts with eIF-2 and promotes the hydrolysis of GTP and generates the 80S initiation complex. Casein kinase-2 is essential for its function (Homma M et al 2005 Proc Natl Acad Sci USA 102:15688).

eIF-6 (p27^{BBP}, anti-association factor): eIF-6 is similar to eIF-3A. The 25-kDa protein dissociates the 80S ribosome and facilitates protein synthesis by maintenance of the 60S subunit. (See Ceci M et al 2003 Nature [Lond] 426:579.)

eIF-D: eIF-D is similar in function to eIF-5A.

Eigenvalue: Literally, this hybrid (German–English) word means proper value, and it is usually used (in physics) in the sense of a characteristic value.

Eincorn: (see Fig. E13). ▶Triticum A genome



Figure E13. Eincorn wheat. Eincorn (*Triticum monococcum*). Courtesy of Drs. G. Kimber & M. Feldman

Ejaculate: ▶sperm

EK2: The laboratory strain of *E. coli* defective in the synthesis of thymine and diaminopimelate. ▶thymine, ▶diaminopimelate, ▶*E. coli*

EKLF (erythroid Krüppel-like factor): A Zn-finger homolog of the *Drosophila* Krüppel gene, involved in blood β-globin and blood non-globin gene transcription regulation. ▶morphogenesis in *Drosophila*, ▶LCR, ▶Krüppel, ▶zinc fingers, ▶globins; Huber TL et al 2001 Curr Biol 11:1456.

Elastase: A proteinase released by the lysosomes of blood granulocytes upon inflammation. It breaks down collagen if not inhibited by protease inhibitors. ▶lysosome, ▶neutropenia

Elastic Fiber Diseases: Elastic fibers, components of the extracellular matrix, have many roles in normal health. Mice lacking a lysyl oxidase-like protein do not deposit elastic fibers into the uterine tract postpartum and develop pelvic prolapse, enlarged airspace in the lungs, loose skin and vascular abnormalities. The function of lysyl oxidase (LOX) is to maintain elastic fibers, cross-linking enzymes, and to provide a scaffold for elastin. The mammalian genome contains at least five LOX and LOX-like (LOXL) genes. ▶[elastin](#), ▶[emphysema](#), ▶[cutis laxa](#), ▶[Marfan syndrome](#), ▶[supravalvular aortic stenosis](#), ▶[Williams syndrome](#), ▶[Hurler syndrome](#), ▶[Costello syndrome](#), ▶[gangliosidosis](#), ▶[pseudo-xanthoma elasticum](#), ▶[ABC transporters](#), ▶[Menkes syndrome](#); Urbán Z, Boyd CD 2000 Am J Hum Genet 67:4; Liu X et al 2004 Nat Genet 36:178.

Elastin ($M_r \cong 70$ K): A rubber-like, cross-linked, glycine- and proline-rich, fibrous protein present primarily in the blood vessels near the heart, but also in the ligaments; modest amounts are present in the skin and tendons. It controls arterial development and proliferation of smooth muscles. Its defect may cause aortic stenosis. ▶[supravalvular aortic stenosis](#), ▶[coarctation of the aorta](#), ▶[Williams syndrome](#)

ELAV (embryonic lethal abnormal vision system): A member of the evolutionarily conserved RNA-binding protein family. Four ELAV-like proteins (HuB, HuC, HuD, HuR) are known in vertebrates. Three of them are specific for neural tissues and the fourth has rather general occurrence. ▶[AU-rich elements](#); Good PJ 1995 Proc Natl Acad Sci USA 92:4557; Pascale A et al 2005 Proc Natl Acad Sci USA 102:12065.

ELC: Expression-linked copy. ▶[Trypanosoma](#)

ELDI (electrospray-assisted laser desorption/ionization): Neutral molecules are desorbed from an ambient surface by nitrogen laser and use the charged droplets for post-desorption ionization of the ablated neutral molecules. Mass spectra of intact protein can be obtained without the use of a matrix. It is suitable for the analysis of the complex cytochrome c and illicit drugs or other complex proteins (Shiea J et al 2005 Rapid Commun Mass Spectrometry 19:3701). The TON (tungsten oxide nanowire) fiber variation permits the analysis of extremely small samples (Jeng J et al 2005 Anal Chem 77:8170). ▶[electrospray](#), ▶[mass spectrum](#)

Electrical Biochip: An electrical biochip detects biomolecular interactions by redox recycling of ELISA, metabolites, DNA microarray, viral infections, etc. ▶[ELISA](#), ▶[microarrays hybridization](#); Albers J et al 2003 Anal Bioanal Chem 377:521.

Electroblotting: The transfer of macromolecules in an electric field from a (polyacrylamide) gel onto a membrane.

Electrocardiography: Electrocardiography records the changes of the variations in the electric potentials of the heart muscles. The first deflections, denoted by P, are due to the excitation of the atria. The QRS indicates the depolarization phase of the excitation of the ventricles. The T wave indicates the complete repolarization of the ventricles. These intervals are measured in fractions of a second. The long Q-T (LQT) interval (see Fig. E14) may indicate abnormal function of either the potassium or sodium ion channel(s) or some other anomaly. The upper graph represents the normal QT. ▶[Jervell and Lange-Nielsen syndrome](#), ▶[HERG](#), ▶[Ward-Romano syndrome](#)



Figure E14. Electrocardiogram, partial

Electrochemical Gradient: An electrochemical gradient moves ions through biomembranes depending on their concentration and charge, at the two sides.

Electrode: The positive (+) anode or negative (−) cathode terminal of an electricity conducting system. ▶[microelectrode](#)

Electroelution of DNA: The procedure is as follows: separate DNA by electrophoresis in agarose gel containing 0.5 µg/mL ethidium bromide, locate band by long-wavelength UV light, cut out the band and place it into dialysis tube filled with 1 x TAE buffer. Let the slice sink to the bottom of the tube, seal, and turn on current in 1 TAE buffer (4–5 V/cm) for 2 to 3 h. Remove tube from apparatus and collect the buffer content of the tube containing the eluted DNA. ▶[electrophoresis](#), ▶[electrophoresis buffers](#)

Electroencephalogram: ▶[EEG](#)

Electrofusion: Cell fusion induced by electrical impulses.

Electrokinetic Enhancement of DNA Uptake: ▶[electroporation](#)

Electrolyte: A substance capable of dissociating into ions and then becoming a conductor of electricity. ▶[ion](#), ▶[polyelectrolyte](#)

Electromagnetic Radiation: The genetically effective range includes UV light, X-rays, and gamma rays. Under conditions of sensitization by various chromophores it may extend into the visible range. Some of the radiations may have contaminating components with potential genetic effects. Extremely low frequency electromagnetic fields (EMF) such as generated by power lines and household appliances have also been suspected to stimulate gene activity (MYC) and increase cancer risk. The experimental data are, however, insufficient to definitely rule in or out such an effect. ▶radiation protection, ▶radiation hazard assessment, ▶terahertz radiation, ▶illumination, ▶light intensities, ▶MYC; see Fig. E15.

Electromorph: A genetically determined variation that can be revealed by electrophoresis. ▶electrophoretic polymorphism

Electron: A small, negatively $[(4.80294 \pm 0.00008) \times 10^{-10}$ absolute electrostatic units] charged particle; its mass is 1/1837 of the H nucleus and its diameter is 10^{-12} cm. All atoms contain one nucleus and one or more electrons. Cathode rays and Beta rays are electrons. ▶cathode rays, ▶beta particles, ▶excitation

Electron Acceptor: An electron acceptor takes up electrons and therefore becomes reduced whereas the *electron donors* provide electrons to other molecules and become oxidized. ▶electrons

Electron Density Map of Proteins: The electron density map of proteins is determined by X-ray analysis and the results are interpreted by the Fourier method (see Fig. E16). The image represents the electron scattering by critical atoms in the molecule and reveals important structural properties. ▶protein structure, ▶X-ray diffraction analysis, ▶FT-IR; Vagin AA, Isupov MN 2001 Acta Crystallogr D Biol Crystallogr 57 [pt 10]:1451.



Figure E16. Electron density pattern, partial

Electron Microscopy: In the light microscope, the resolution of the objects is limited by the wavelength (within the 350–750 nm range) of the light used for illumination. The wavelength of electrons accelerated at high voltage (100 KV) may become only 0.004 nm. Because of aberrations of the lenses available, this minimum cannot be attained yet. Even with the best equipment, a resolution of about 0.1–2 nm, i.e., about 100–1,000 higher than with the light microscope,

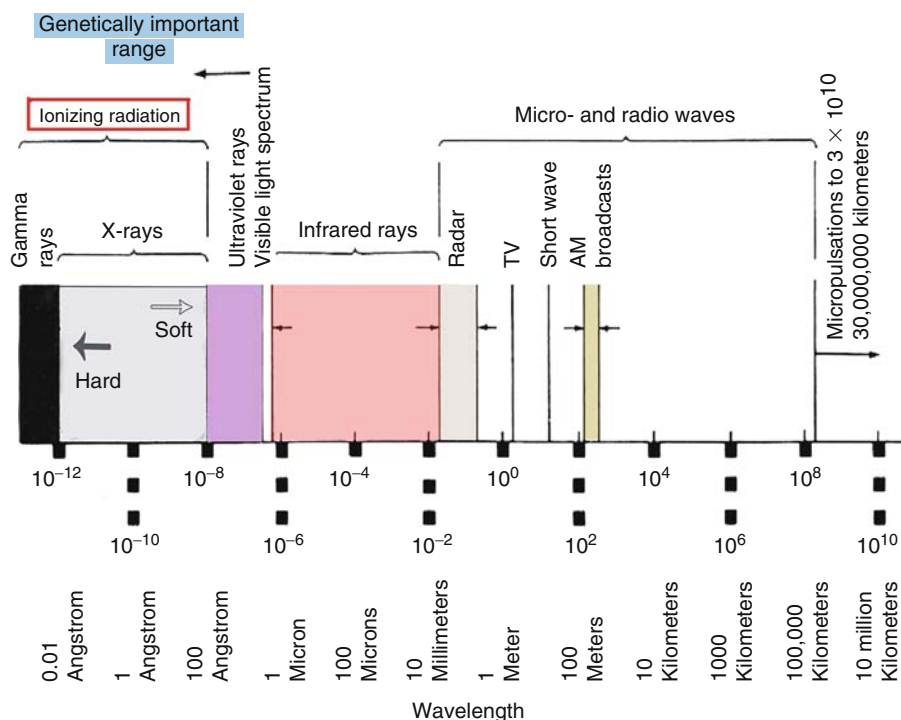


Figure E15. Electromagnetic radiation. (After Lerner and Libby, 1976 Heredity, Evolution and Society, Freeman, San Francisco)

may be possible. In the *transmission electron microscope*, instead of visible light the extremely thin (50–200 nm) specimen, specially fixed and stained, is placed on a grid and is exposed to electron beams accelerated in a vacuum tube. The areas where the specimens reduce the focused electron flux, an image appears that can be viewed or photographed and enlarged by procedures similar to light microscopy. Electron microscopic specimens are usually prefixed in buffered 3% glutaraldehyde and postfixed in 1% buffered osmium tetroxide, then dehydrated and embedded in a propylene oxide-resin mixture that requires polymerization before sectioning by glass or diamond microtomes. The sections are placed on a circular copper grid of 3-mm diameter, covered by a carbon or plastic film. Either before or after sectioning, the biological specimen is treated usually by uranium or lead to assure contrast. Electron-microscopic specimens may be exposed also to substrates of enzymes in order to localize an electron dense precipitate if the enzyme is active. The specimens may also be coupled with specific fluorescent dyes or with colloidal gold, which may be recognized by an antibody, and thus its site is revealed. The material may also be *shadowed*—by spraying in an angle with other thin layers of metals (platinum, chromium)—for obtaining an apparent three-dimensional image. Macromolecules may also be studied by *negative contrast*. The solution in 1% phosphotungstate (or uranyl acetate) is thinly spread on a carbon film and when dried, an electron-dense layer is formed. At the position of the protein molecule there will be no tungstate. Thus a negative image is generated. A special technique in electron microscopy is *freeze-fracture*, which can provide images of the internal organization of delicate structures such as biological double membranes. This freezing technique does not require fixation that usually denatures the material. The specimen is frozen in liquid nitrogen in the presence of a cryoprotectant (glycerol, dimethylsulfoxide) to prevent the formation of ice crystals. The frozen material is then fractured with a knife to crack the double membrane between the two layers. The surface so generated is shadowed with a metal, and after the organic material is dissolved and removed, the remaining metal replica is examined. This replica is a negative image of the biological structure. A similar procedure is *freeze-etching*. Again, the frozen sample is cracked, the moisture is removed by lyophilization, and the inner and outer structures exposed are shadowed. A four-dimensional ultrafast electron microscope has also been designed (Lobastov VA et al 2005 Proc Natl Acad Sci USA 102:7069).
 ▶ [scanning electron microscopy](#), ▶ [microscopy](#), ▶ [freeze-drying](#); Maunsbach AB, Afzelius BA 1998

Biomedical Electronmicroscopy: Illustrated Methods and Interpretations. Acad Press, San Diego, CA.

Electron Paramagnetic Resonance (EPR): EPR can be used to measure the radiation exposure in human or mammalian populations. When paramagnetic substances are placed in a stationary magnetic field and exposed to electromagnetic radiation they register the field of strength and the frequency of the radiation. Paramagnetic substances contain molecules or atoms whose electrons move and produce weak magnetic fields. This method can then be used for the determination of the concentration of radiation-induced radicals in, e.g., hydroxyapatite, present in teeth and bones. The tooth enamel is 97% hydroxyapatite and does not metabolize ^{90}Sr , a common product of atomic fallout. Dentine, which is made up of only 70% from hydroxyapatite, metabolizes this isotope. Therefore, ^{90}Sr will be found mainly in the dentine. The isotope emits short-range β -rays (0.6–1 mm path). One study showed that humans with chronic radiation disease received 1 Gy (gray unit) whereas the dentine showed 5.5 Gy γ -radiation. Thus, it is possible to determine whether the radiation came internally or externally. ▶ [radiation measurement](#), ▶ [radiation hazard assessment](#), ▶ [fallout](#); Swenberg CE et al 1994 Adv Space Res 14(10):181.

Electronic PCR: Searches for EST in DNA sequences. ▶ [PCR](#); Rostmistrovsky K et al 2004 Nucleic Acids Res 32(WEB Server Issue):W108.

Electron Transport: The movement of electrons toward the lower level of energy by electron carriers. The mitochondria and other organelles have important roles in the process.

Electron Volt (eV): $1 \text{ eV} = 1.60207 \pm 0.00007 \times 10^{-12} \text{ erg}$. ▶ [erg](#)

Electronic PCR: STSs can be amplified and defined by a pair of PCR primers and used with the aid of an appropriate computer program to locate the STS to existing genetic or physical markers in a map without performing any experiment. ▶ [EST](#), ▶ [STS](#), ▶ [PCR](#); Schuler GD 1997 Genome Res 7:541.

Electrophile: An electrophile is eager to accept electrons and can covalently bind nucleophiles. ▶ [electron](#), ▶ [nucleophile](#), ▶ [nucleophilic attack](#)

Electrophoresis: Separating charged molecules (such as polypeptides or polynucleotides) between the two poles of an electric field (see Fig. [E17](#)). The material is generally contained in a support medium (cellulose, starch, agarose polyacrylamide) and bathed in an appropriate buffer, and may also contain specific stains. The basis of the separation of the components of a mixture is the relative charge, shape or molecular

size of the components. Larger nucleic acid molecules are generally separated in agarose gels of various concentrations, depending on the size of the molecules. Smaller nucleic acid fragments are separated in polyacrylamide gels. SDS-PAGE electrophoresis treats the proteins with the detergent sodium dodecyl sulfate (SDS) and separates them by polyacrylamide gel electrophoresis (PAGE). The detergent breaks the noncovalent bonds of the proteins and when β -mercaptoethanol is added the disulfide bonds are also eliminated. The proteins so treated migrate in the gel according to their molecular weight rather than by their charge. Nucleic acids have uniform charge, thus their separation is based on their molecular size. Ultrathin gel electrophoresis permits the use of higher voltage without deleterious heat effect because of the increased heat transfer. Also, it increases the speed of separation by an order of magnitude although it may decrease resolution and read length, and it is under experimental study. Another innovative approach is the matrix-assisted laser desorption and ionization method (MALDI) which permits single charged ions from proteins as large as 300-kDa to be produced and analyzed. Mass spectrophotometry MALDI (MALDI-MS) is capable of discriminating length difference in short oligonucleotides due to a single base. ▶pulsed field electrophoresis, ▶isoelectric focusing, ▶gel electrophoresis, ▶two-dimensional gel electrophoresis, ▶dodecyl sulfate sodium salt, ▶capillary electrophoresis; Rickwood D, Hames BD 1990 Gel electrophoresis of nucleic acids: A practical approach. IRL Press, New York; Hames BD, Rickwood D 1990 Gel electrophoresis of proteins: A practical approach. IRL Press, New York.

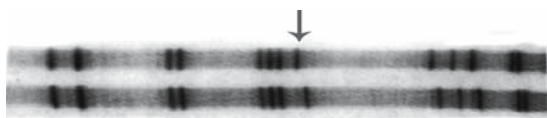


Figure E17. Electrophoretic gels

Electrophoresis Buffers: TAE (Tris-acetate EDTA), TPE (Tris-phosphate EDTA), TBE (Tris-borate EDTA), alkaline 50 mM NaOH-1 mM EDTA are commonly used.

Electrophoretic Karyotyping: Separation of small chromosomes by pulsed field gel electrophoresis according to size. ▶pulsed field; Geiser DM et al 1996 Curr Genet 29:293; Shin JH et al 2001 J Clin Microbiol 39:1258.

Electrophoretic Polymorphism: Protein or DNA variations in a population affecting charge or size. In proteins it may be detectable on the bases of amino

acid (glutamic, and aspartic acid, lysine, histidine, arginine) substitutions by altered electrophoretic mobility or by size of polypeptides. Restriction enzyme digests of DNA provide such information after gel-electrophoresis or by PCR analysis. ▶electrophoresis, ▶isozyme, ▶SDS-polyacrylamide gels, ▶RFLP, ▶PCR; van der Bank H et al 2001 Biochem Syst Ecol 29(5):469; Zhu X et al 2001 Electrophoresis 22:1930.

Electroporation: The transport of DNA across cellular membranes with the aid of electric current pulses; the genes may display transient expression in the target cells. It is also a means of genetic transformation, the conditional regulation of gene expression from electroporated plasmids in the postnatal rat retina and the embryonic mouse brain. For temporal regulation of electroporated genes, Cre/loxP-mediated inducible expression vectors can be used in combination with a vector expressing a conditionally active form of Cre recombinase, which is activated by 4-hydroxytamoxifen. The timing of 4-hydroxytamoxifen administration regulated the onset of gene expression. By using promoters specific for rod photoreceptors, bipolar cells, amacrine cells, Müller glia or progenitor cells, the transgenes were spatially regulated (Matsuda T, Cepko CL 2007 Proc Natl Acad Sci USA 104:1027). ▶transformation, ▶microfusion, ▶Cre-LoxP, ▶Tamoxifen, ▶amacrine cell, ▶glia; Neumann E et al 1982 EMBO J 1:841; Fromm ME et al 1986 Nature [Lond] 319:791; Tsong TY 1991 Biophys J 60:297; Golzio M et al 2002 Proc Natl Acad Sci USA 99:1292.

Electrospray MS (tandem mass spectrometry, ESI): A procedure for determining the molecular weight of unknown proteins and for the study of non-covalent interactions between proteins and other large molecules, thus facilitating their location and identification with the aid of databases. The nanoelectrospray is a low-flow device equipped with a needle of $\sim 1\text{-}\mu\text{m}$ internal diameter and delivers a mixture of molecules, e.g., peptides, into a mass spectrometer. The peptides are separated in the first step and are subsequently fragmented (in this tandem process). The fragmentation in the mass spectrometer is achieved by collision with gas molecules. The fragments obtained from the NH_2 end of the protein are called “b” and those from the COOH terminus are “y” ions. Another procedure involves the initial separation of the peptides by liquid chromatography and then sequencing as they are passed into the electrospray ion source. The fragments are sorted by the molecular mass of one amino acid. This way the location of the amino acid is then revealed in the peptide. Two amino acids with known location (called *peptide sequence tag*) suffice to fish out the

peptide in large sequence databases. The extreme sensitivity of the procedures for 50–100 ng or even smaller amounts of proteins (femtomole range) may be analyzed. The method determines the mass-to-charge (m/z) of the polar molecules and the signal intensity is displayed by the algorithm used in discrete peaks. Some of the procedures are automated. ▶laser-capture microdissection, ▶mass spectrum, ▶laser, ▶MALDI, ▶genome projects, ▶STM, ▶proteome, ▶chromatography; Null AP et al 2001 Anal Chem 73:4518; Takáts Z et al 2004 Science 306:471.

Element, Chromosomal: Conserved sequences (genes) within chromosomes.

Elephants: *Elephas maximus* $2n = 56$; *Loxodonta africana* $2n = 56$. The small pygmy elephants that lived in the Mediterranean islands and have been extinct for 10,000 years appear to have evolved from mammoths—according to new DNA evidence—rather than from the present-day elephants. Earlier, based on mitochondrial cytochrome evidence, the dwarf elephant, *Palaeoloxodon antiquus falconer*, appeared to be closer to *Elephas* than *Loxodonta* or *Mammuthus* (Poulakakis N et al 2002 J Mol Evol 55:364). (See Roca AL et al 2001 Science 293:1473; mammoth).

Elephant Man: A person with abnormally enlarged body parts. The cause of Joseph Merrick's anomaly has been attributed to neurofibromatosis and to Proteus syndrome, but the real cause remains unclear. It is different from elephantiasis, a tropical infection of the lymphatic nodes, limbs, genitalia, etc., causing inflammation and hypertrophy as the result of the obstruction of the lymphatics by several species of nematodes. ▶neurofibromatosis, ▶Proteus syndrome

Elicitor: ▶host-pathogen relation, ▶immune system

ELISA (enzyme-linked immunosorbent assay): ELISA is capable of detecting vg quantities of protein per gram tissue by the use of an antibody attached to a particular enzyme such as alkaline phosphatase (or peroxidase, urease). The + antibody complex binds to the protein antigen present in the reaction vessel and the cleavage of a chromogenic substrate (e.g., *p*-nitrophenyl phosphate) by the enzyme results in the development of color (absorbance detected by spectrophotometer) that is proportional to the amount of the antigen protein. ▶immunoglobulins, ▶antibody, ▶immune reaction, ▶immunoprecipitation, ▶immuno-labeling, ▶IRMA; Davis LG et al 1986 Basic Methods in Molecular Biology. Elsevier, New York.

Elite Plants: Elite plants were specially selected and reproduced under the control of the plant breeder.

ELK (oncogene): ELK1 (human chromosome Xp11.2) and ELK2 (14q32.3) are expressed in human lungs and testes. These oncogenes show homology with the ETS oncogenes. (see Fig. E18).

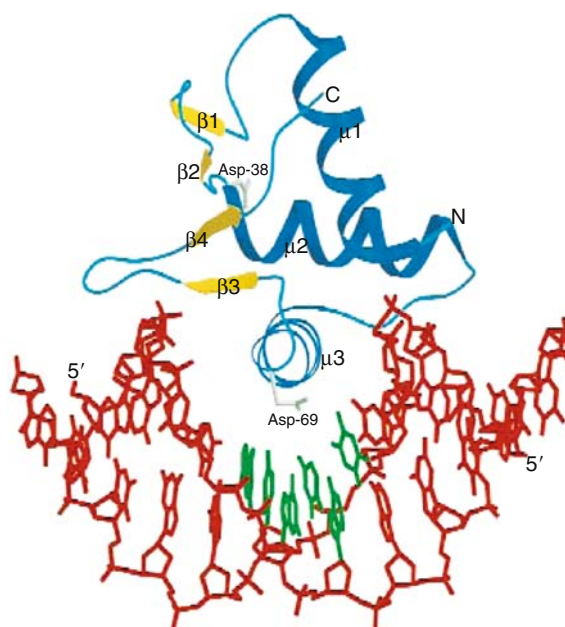


Figure E18. Elk-1 protein structure (top) complexed with DNA (below). (Courtesy of Marmorstein, R. From Mo Y et al 2000 Nature Struct Biol 7:292)

The ELK proteins bind to the SRE element of the chromosomes and, after phosphorylation, may activate transcription. ▶oncogenes, ▶ETS, ▶signal transduction, ▶SRE, ▶SAP-1; Cesari F et al 2004 Genesis 38:87.

ELKS (12p13): A 105-kDa subunit of IκB and required by NF-κB. It is named ELKS because ~44% of the protein is built of E (glutamic acid), L (leucine), K (lysine), and S (serine). Some tumors show ELKS/RET fusion. ▶NF-κB, ▶RET oncogene; Ducut Sigala JL et al 2004 Science 304:1963.

ELL: Human RNA polymerase II elongation factors in chromosome 19-13.1. ELL1 is ~620 and ELL2 is ~640 amino acid size. They increase the rate of transcription after initiation as they suppress pausing of the polymerase along the DNA. Functionally they are similar to ELONGIN, another transcription elongation factor controlled by the von Hippel-Lindau tumor suppressor gene and the MLL gene products of leukemias (encoded at 11q23) by binding to the A subunit of ELL. The ELL proteins may also hinder initiation by hindering interaction of polymerase II with TBP. The ELLs have a conserved region homologous to the zonula occludens protein sequences that bind MAGUK. ▶von Hippel-Lindau

syndrome, ▶elongin, ▶elongation factors, ▶MLL, ▶transcript elongation, ▶PITSLRE, ▶TEFb, ▶TBP, ▶zonula occludens, ▶MAGUK, ▶leukemias; Luo RT et al 2001 Mol Cell Biol 21:5678; Eissenberg JC et al 2002 Proc Natl Acad Sci USA 99:9894; regulators of ELL: Kong SE et al 2005 Proc Natl Acad Sci USA 102:10094.

E

Elliptocytosis (ovalocytosis): The shape of the erythrocytes (red blood cell) is not round as in normal, but elliptic, indicating an often fatal autosomal dominant hemolytic anemia (see Fig. E19). In the *Camelidae*, elliptocytosis is a normal condition. Mutations in spectrin (SPTA1, 1q21) frequently lead to defects in the formation the $\alpha\beta\sim\alpha\beta$ tetrameric spectrin molecules. This may be the basic cause and a variety of this condition has been described. Some forms may be correlated with protection against malaria. The α -spectrin gene was assigned to human chromosome 1q21 (Rhesus-unlinked type elliptocytosis). The Rhesus-linked type was assigned to 1p34-p33. An atypical elliptosis is apparently recessive. ▶anemia, ▶spectrin, ▶ankyrin, ▶spherocytosis, ▶poikilocytosis, ▶erythrocyte; Wandersee NJ et al 2001 Blood 97:543.

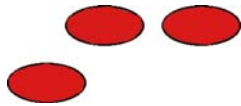


Figure E19. Elliptic red blood cells

Ellis-van Creveld Syndrome: A human chromosome 4p16 recessive. At this locus, the evolutionarily and highly conserved two genes *EvC* and *EVC2* are in head-to-head configuration, and their mutation is responsible for the varied phenotypes (Ruiz-Perez VL et al 2003 Am J Hum Genet 72:728). It involves dwarfism, polydactyly, short extremities, heart malformation, dystrophy of finger nails, “partial hare lip”, teething by birth, heart defects, etc. It is quite common in some Amish populations. ▶Amish, ▶face/heart defects, ▶polydactyly, ▶hare lip, ▶dystrophy, ▶Weyers acrocardial dysostosis, ▶McKusick-Kaufman syndrome, ▶achondroplasia

ELMS (expected maximum lod score): ELMS is computed by weighting the sum of lod scores by their probability. ▶lod score

ELOD: ▶interval mapping, ▶lod score

Elongation Factors (EF): Elongation factors are proteins assisting translation on the ribosomes; see individual factors (eIF) separately listed. Factors eIF-2, eIF-3, eIF-4A, eIF-4B, eIF-4F, and ATP are required for the formation of the *elongation initiation complex I*, which is unstable. The addition of eIF-1 and eIF-1A

to complex I results in the formation of the stable *elongation initiation complex II*. The biosynthesis of many proteins in response to intracellular, attenuation environmental factors (e.g., heat shock) are regulated at the level of transcription. The prokaryotic proteins carry out similar functions as the eukaryotic ones but they are structurally different. ▶protein synthesis, ▶transcription shortening, ▶transcription factors, ▶transcription termination, ▶attenuation, ▶rm, ▶TIIFS, ▶promoter clearance, ▶translation termination, ▶ELL, ▶eIFs, ▶transcript elongation; Sonenberg N et al (eds) 2000 Translational Control of Gene Expression. Cold Spring Harbor Lab. Press, Cold Spring Harbor, NY.

Elongators (ELP): Elongators are proteins associated with the hyperphosphorylated carboxyl domain of RNA polymerase II and their activity is correlated with histone acetyltransferases. The complex replaces the Mediator complex, which is associated with the unphosphorylated Pol II during the initiation phase of transcription. ▶histone acetyltransferases, ▶mediator complex, ▶transcript elongation, ▶Spt, ▶RNA polymerase; Li Y et al 2001 J Biol Chem 276:29628; Hawkes NA et al 2002 J Biol Chem 277:3047.

Elongin: A three subunit (A, B, C, ~770, 118 and 112 amino acids, respectively) protein stimulatory to in vitro RNA transcript elongation. The A subunit has the major role and B and C reinforce A. The elongin-von Hippel Lindau-cullin complex may play a ubiquitin ligase role and target genes for degradation by the proteasome. ▶ELL, ▶elongation factors, ▶transcript elongation, ▶von Hippe-Lindau syndrome, ▶cullin, ▶proteasome; Luo RT et al 2001 Mol Cell Biol 21:5678.

ELSI (ethical, legal, social implications of genetics): ▶ethics, ▶bioethics, ▶copyright, ▶patent, ▶risk, ▶genetic screening, ▶genetic discrimination

ELSI: ▶ROSI

Elston-Stewart Algorithm: A computer-based linkage analyses in general pedigrees. The data are first “clipped” to small nuclear families in a large population and then the information is collapsed to one of the parents or other close relatives whose sibship is analyzed. The procedure is continued iteratively until all the information is collapsed to the proband. Usually a small number of markers are considered. ▶collapsing data, ▶iteration, ▶proband, ▶Lander-Green algorithm; Elston RC, Stewart J 1971 Hum Hered 21:523.

Eluate: That flows off a chromatographic column.

Elutriation: The sedimentation or separation of particles from suspensions. The heaviest particles settle first and the light ones may float. *Centrifugal elutriation*

employs a special centrifuge in which a flow is generated in the direction opposite to the rotation. The latter can handle large volumes fast. ►[centrifuge](#)

EMA (E2F-binding site modulating activity): EMA is 2.4-kb DNA translated into a 272-amino acid protein. EMA binds to transcription factors DP-1 and DP-2. It recognizes better the TCCCGCC rather than the TCGCGCC core sequences of the E2F binding sites. EMA is a transcriptional suppressor. ►[E2F1](#); Koziczak M et al 2000 Mol Cell Biol 20:2014.

EM-Algorithm: A principle that can be applied for the calculation of recombination frequencies in special cases.

Emanuel Syndrome (Opitz-Frias syndrome, deletion at 22q11.2): It involves dominant or recessive hypertelorism (abnormal distance between organs), neuromuscular defects, defects of the esophagus (alimentary tube) throat, hypospadias (defect of the urinary tube in the penis), cryptorchidism (failure of the testes to descend into testicular pouch), and problems with the anus (end of the intestinal tract).

E-MAP (epistasis miniarray profile): The determining of genetic networks on the basis of epistatic interaction of genes (Schuldiner M et al 2005 Cell 123:507). The yeast chromosome biology E-MAP involves 743 proteins (Collins SR et al 2007 Nature [Lond] 446:806). ►[genetic networks](#), ►[transcriptome](#)

EMAPII (endothelial monocyte-activating polypeptide): Stimulates leukocytes, monocytes, chemotaxis and myeloperoxidase, tissue factor and TNF α synthesis. EMPAII domains are evolutionarily conserved and their homologs occur at the C-terminal domain of aminoacyl-tRNA synthetases for one or more amino acids (Eubacteria and Caenorhabditis: Met; Yeast: Met, Gln; Mammals: Tyr, Glu, Asp, Met, Pro, Glu, Arg, Lys); in yeast and mammals other homologies may also be found. Tyr-tRNA synthetase along with cytochrome c, released from the mitochondria, prepare the cell for the apoptotic process. Secreted Tyr-tRNA synthetase in mammals undergoes proteolysis and is converted into an N-terminal catalytic fragment with IL-8 properties and into C-terminal cytokine-like fragment. EMPAII migrates also to the sites of inflammation. ►[aminoacyl-tRNA synthetase](#), ►[IL-8](#), ►[cytokine](#); Shalak V et al 2001 J Biol Chem 276:23796.

Emasculation: ►[castration](#)

EMB Agar: ► [\$\beta\$ -galactosidase](#)

Embden-Meyerhof Pathway: An anaerobic process of glycolysis. The six-carbon sugars are converted into glucose-6-phosphate and through a number of steps to glyceraldehyde-3-phosphate, and eventually to pyruvate. An oxidation step generates NADH and pyruvate is further oxidized to form the acetyl units of acetyl coenzyme A that may be oxidized in the citric acid cycle, and become the core reactions of both carbohydrate and fat metabolism.

Embedding: Microscopic specimens requiring thin sections for examination may be surrounded (infiltrated) by paraffin wax, resins or other suitable material before sectioning by microtomes. ►[microtomes](#), ►[sectioning](#)

Embedded Gene: A gene within the boundary of another. ► [\$\phi\$ X174](#)

EMBL (<http://www.ebi.ac.uk/embl/index.html>): EMBL stores databases for macromolecular sequences (without sequence limit since 2004). European Molecular Biology Data Library, P.O.B. 10.2209, D-6900 Heidelberg, Germany, telephone: 011-49-6221-387-258, EMBL Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SD, UK, telephone: + 44 1223 494444. E-mail, general inquiries: datalib@ebi.ac.uk; for submissions and forms: datasubs@ebi.ac.uk; <http://www.ebi.ac.uk/embl/Submission>; <http://www.ebi.ac.uk/embl/Documentation/>; completely sequenced genomes and predicted proteomes with cross-links to protein structure and statistical analysis: <http://www.ebi.ac.uk/integr8>; microarray information: <http://www.ebi.ac.uk/arrayexpress>; nucleotide sequence: <http://www.ebi.ac.uk/embl/>.

EMBL3: A lambda DNA vector carrying polylinkers at both sides of the *red* and *gam* sites and, if equipped with adjacent promoters, the RNA polymerase can directly transcribe genes cloned into the “stuffer” region without subcloning. ► [\$\lambda\$ DASH](#), ► [\$\lambda\$ FIX](#), ►[GeneScribe](#), ►[Lambda phage](#), ►[stuffer region](#)

Embryo: The differentiated zygote; in mammals up to about a 1/5 of the normal time of gestation. In plants, the embryo stage is considered to last up to the maturing and germination of the seed. ►[embryogenesis](#), ►[fetus](#), ►[embryo culture](#)

Embryo Culture: When developing plant embryos are lifted from the ovaries about 10–14 days after fertilization, they can survive and mature in aseptically cultures.

This procedure may be applied for the rescue of hybrid embryos that may not survive in their natural

environment because of the collapse of the endosperm, the nurturing tissue, or the overgrowth of the nucellus. Although this technique itself does not overcome hybrid sterility, viable seedlings can be produced that may become fertile after doubling the chromosome number (with colchicine).

Plant ovaries for embryo culture (in ear or fruit) require disinfection by calcium hypochlorite ($\text{Ca}[\text{OCl}]_2$ 5%, for 8–10 min and several rinses in sterile H_2O).

E2 culture medium mg/L H_2O , final conc.: $\text{NH}_4\text{-NO}_3$ 400, KNO_3 200, and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 100, $\text{CaH}_4(\text{PO}_4)_2$ 100, KH_2PO_4 100, K_2HPO_4 50. Before use add 2.5 mL/L chelated iron ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ 556 mg or diethylenetriamine pentaacetic acid 786.4 mg, H_2O 100 mL). Supplement it with 3% sucrose and add agar to solidify without making it too hard (about 0.6%) and autoclave.

Embryonic stem cells of mammals may also be cultured successfully although it is more difficult to maintain totipotency of these cells and to obtain viable embryos. ▶[in vitro](#), ▶[embryo](#), ▶[ovary](#), ▶[nuclear transplantation](#), ▶[tetraploid embryo complementation](#); Rappaport J 1954 Bot Rev 20:201; Nagy A et al 1993 Proc Natl Acad Sci USA 90:8424.

Embryo Node: A temporary structure located at the anterior tip of the primitive streak ▶[organizer](#) in birds, reptiles, and mammals. It is the starting point of the organization of the gastrula. ▶[gastrula](#), ▶[primitive streak](#)

Embryo Rescue: ▶[embryo culture](#)

Embryo Research (human): NIH recommendations: embryos (14) 18 days or older are not acceptable. Unacceptable procedures: transfer human embryos to animals for gestation; transfer research embryos or parthenotes (unfertilized eggs) to humans; separation of blastomeres for generating twins; cloning by nuclear transplantation; creation of any type of chimera (human–human, human–animal); creation of embryos in the lab from stem cells; cross-fertilization by human gametes with the exception of clinical laboratory sperm penetration tests with animal eggs; embryo transfer to cavities other than the uterus; sex selection with the exception of preventing sex-chromosome-linked disease; use of sperm or egg without consent; use of sperm or egg from donor who was paid more than reasonably expected. The embryo research policies vary in different countries, and may/may not permit the use of embryos/tissues for studying infertility, contraception, genetic screening, gene therapy, cloning, construction of chimeras, interspecific implantation, sex-selection, etc. Embryo culture and embryo

transfer had minimal effects on postnatal growth when compared with in vivo development with an equivalent litter size in mice. However, embryo culture, and to a lesser extent embryo transfer, led to an enhanced systolic blood pressure at 21 weeks compared with in vivo development independent of litter size, maternal origin, or body weight. Moreover, activity of enzymatic regulators of cardiovascular and metabolic physiology, namely, serum angiotensin-converting enzyme and the gluconeogenesis controller, liver phosphoenolpyruvate carboxykinase, were significantly elevated in response to embryo culture and/or embryo transfer in female offspring at 27 weeks, independent of maternal factors and postnatal growth (Watkins AJ et al 2007 Proc Natl Acad Sci USA 104:5449). ▶[stem cells](#), ▶[ART](#), ▶[phosphoenolpyruvate](#), ▶[gluconeogenesis](#), ▶[angiotensin](#)

Embryogenesis in Animals: Fertilization generally takes place in the oviduct and the zygote is implanted into the uterus. In the preimplantation embryo several maternal genes are expressed. After fertilization the oocyte-stored mRNAs are degraded in about 90% by the two-cell stage of mice. After that the zygotic genome is activated in stages. A major wave of gene activation takes place at the eight-cell stage of mice and that establishes blastomere polarity (see Fig. E20).

After the two-cell stage polarity develops; one cell forms the inner cell mass, which is pluripotent (able to develop into multiple cell types). At this stage several transcription factors are expressed. OCT4, the leukemia inhibitory factor (Lif, it is interleukine-6 cytokine) and a HOX transcription factor (NANOG) are essential for the determination of the embryonic stem cells. CDX2 is essential for regulation of the expression of OCT4 and NANOG and trophoblast development. The ascidian *Ciona intestinalis* body consists of only ~26,000 cells and its genome includes only 16,000 genes, yet its body plan is similar to that of vertebrates. Localized expression of 76 regulatory genes in 3,000 combinations facilitated to reveal the control of embryonic cell lineages (Imai KS et al 2006 Science 312:1183).

Eomes mediate differentiation at the blastocyst stage and blastocyst activity is required for implantation into the uterus. Endocannabinoids (anandamide) and the MAPK pathway are important signals for implantation. Implantation is controlled by several protein factors. A large number of proteins are required for further function of the uterine even at later stages in adulthood. Progesterone and oestrogen and their receptors are essential for implantation in the majority of mammals. HOX10 is involved in the formation of the decidua. The HEDGEHOG-PATCHED-GLI and

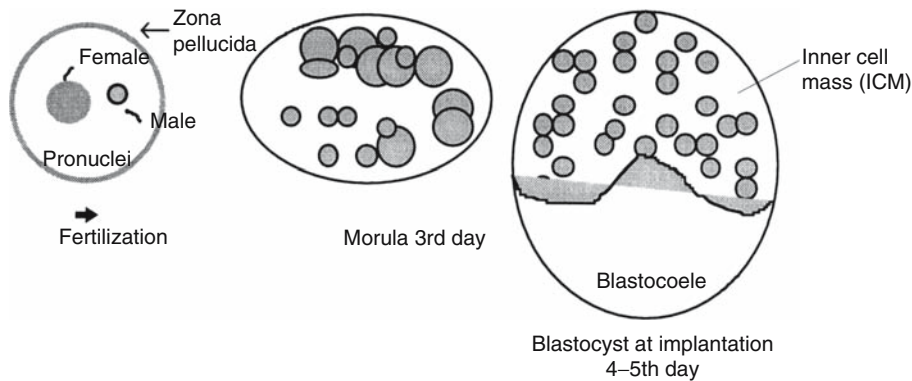


Figure E20. Embryogenesis in mouse.

other proteins are essential for embryo development. Formation of the deciduas and the endometrium assures the appropriate nurture of the embedded embryo (see Fig. E21). Vascular endothelial growth factor and ancillary proteins secure the appropriate blood supply to the fetus. Preeclampsia may result in abortion. (See terms among the alphabetically listed entries, ▶ART, ▶stem cells; Wang H, Dey SK 2006 Nature Rev Genet 7:185; history of ideas on evolution and embryogenesis: Horder TJ 2006 Nature Rev Genet 7:892.

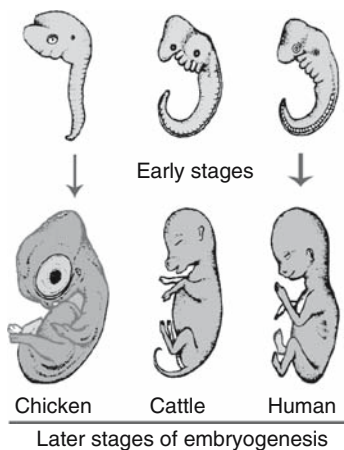


Figure E21. Embryogenesis in vertebrates. (This widely accepted model of Ernst Haeckel has been seriously challenged recently)

Embryogenesis in Plants: Takes place after the sperm within the embryo sac has fertilized (see Fig. E22) the egg. The embryo sac is located within the ovule. The pattern of embryogenesis of higher plants is shown below. The steps are genetically controlled and numerous mutations have been identified that are responsible for the different morphogenic steps.

The information regarding the molecular mechanisms involved in plants is studied less than that in animals. The seed coat is an entirely maternal tissue and, therefore, the inheritance of seed-coat traits is “delayed”. The endosperm develops from the fertilized fused “polar cells” and is generally triploid. In the majority of dicots, by the time the seed matures, the endosperm tissue is generally insignificant in amount or entirely absorbed. In the majority of monocots, the endosperm constitutes the bulk of the seed. In common language the monocot fruit is also called a seed but its proper designation is kernel. The outermost layer of the kernel is the maternal pericarp. Just under the pericarp there is the membrane-like seed coat. The outer layer of the endosperm is called aleurone. The scutellum of the monocots corresponds to the cotyledons of dicots. Seed size and growth form evolved in a coordinated manner and large differences exist in seed size (Moles AT et al 2005 Science 307:576).

While the cotyledons emerge from the seed during germination, the scutellum does not. The “germline” of plants is not set aside during development as in animals, yet the cells of the plant meristems form cell lineages that can be traced if visible genetic differences occur during ontogenesis. The size of the sectors formed permits an estimate on the time when the genetic alteration has taken place during development. Large sectors indicate early event and small sectors show late mutations. ▶megagametophyte, ▶microgametophyte, ▶phyllotaxy, ▶morphogenesis, ▶Drosophila, ▶development, ▶gametogenesis, ▶embryo culture, ▶gametophyte, ▶gametogenesis, ▶endosperm; Chaudhury AM et al 2001 Annu Rev Cell Dev Biol 17:677.

Embryogenesis, Somatic: Plant somatic embryos can be obtained by the techniques of tissue culture. The diagram shows embryogenesis in suspension culture

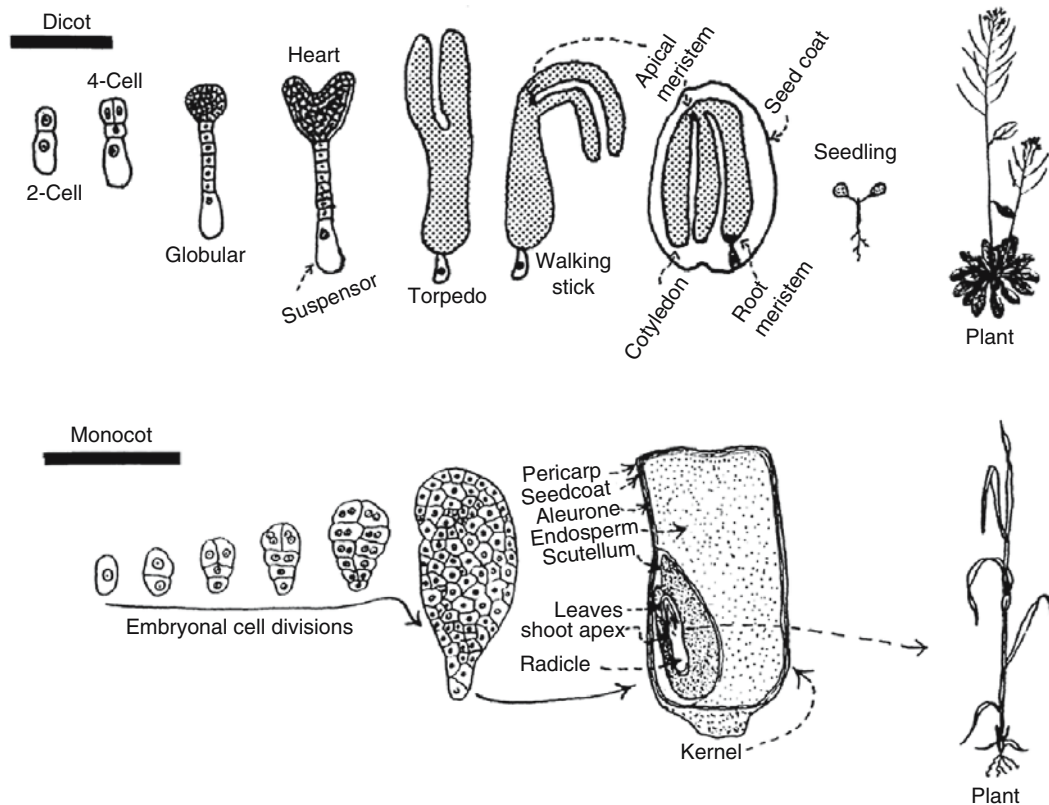


Figure E22. Embryogenesis in plants. The pattern of embryogenesis in plants is different in dicots from that in monocots. Additional variations exist within these two groups. The dicot pattern is exemplified by the crucifer *Arabidopsis* and the monocot pattern is generalized on the basis of maize and wheat

and compares it with *in planta* embryogenesis (see Fig. E23). In most species it is not necessary to go to protoplasts and embryos may develop from other tissue cells on regeneration media. Several nutrient media have been developed in various laboratories (see Murashige and Skoog; Gamborg 5). For tobacco and *Arabidopsis* the following protocol is quite effective. **R4 Medium:** **I.** Major mineral salts, mg/500 mL H₂O: NH₄NO₃ 1,800, KNO₃ 800, MgSO₄·7H₂O 100, CaH₄(PO₄)₂ 100, KH₂PO₄ 100, K₂HPO₄ 50. **II.** CaCl₂ 15g/100 mL. **III.** KI 75 mg/100 mL. **IV.** Microelements mg/500 mL: H₃BO₃ 6,200, MnSO₄·H₂O 16,900, ZnSO₄·7H₂O 8,600, NaMoO₄·2 H₂O 250, CuSO₄·5 H₂O 25, CoSO₄·7H₂O 29.54. **V.** Chelated iron: in 100 mL H₂O FeSO₄·7H₂O 556 mg, diethylenetriamine pentaacetic acid 786.4 mg. **VI.** Vitamins, mg/50 mL: myo-inositol 5,000, thiamin 500, nicotinic acid amide 50, pyridoxine.HCl 50. Final solution: **I.** 50 mL. **II.** 290 µL. **III.** 100 µL. **IV.** 50 µL. **V.** 500 µL. **VI.** 100 µL, pH 5.6, sucrose 3 g. Fill up to 100 mL, agar about 600 mg (varies according to batch) or Gellan gum 180 mg (must be separately dissolved in distilled water on hot plate (with magnetic stirrer). The culture generally requires

5 stages with hormones added in µg/mL: R4-1 (callus initiation) 9RiP 1.5, 2,4-D 0.025–0.050, R4-2 (callus growth and regeneration) 9RiP 2.0, NAA 0.1, R4-3 (leafy callus) 9RiP 1.5, NAA 0.1, R4-4 (shoots appear) BAP 1, NAA 0.1, R4-5 (rooting), BAP 0.0005, NAA 0.05. After R4-4, *Arabidopsis* can be transferred to E2 medium *in vitro* (see ►embryo culture) where they produce seeds even in the absence of roots. Alternatively, after R4-5, the seedlings can be transferred to soil or commercial soil substitute. (RiP = isopentenyl adenosine, 2,4-D = dichlorophenoxy acetic acid, NAA: α-naphthalene acetic acid, BAP: benzylamino purine). Heat stable components are autoclaved, and vitamins and hormones are filtered. ►embryo culture, ►cell genetics, ►tissue culture, ►ART

Embryoid: An embryoid develops through somatic embryogenesis. ►embryogenesis somatic

Embryoid Body: Such as endoderm, ectoderm, neurons, yolk, cartilage, muscle cells and ovary-like structures formed from embryonic stem cells. ►stem cell, ►endoderm, ►ectoderm

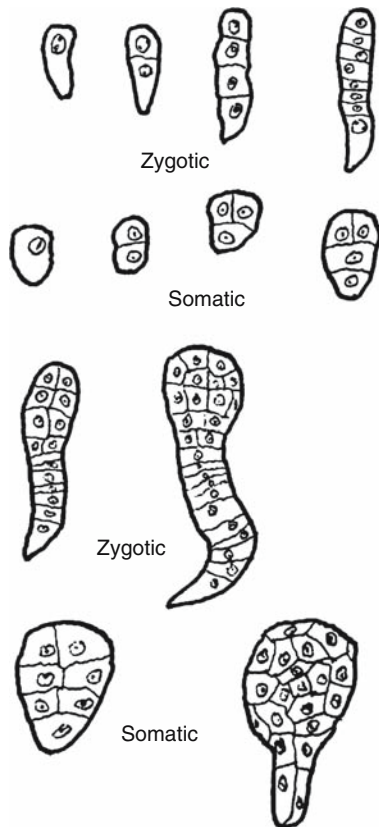


Figure E23. Zygotic and somatic embryogenesis at comparable stages in *Daucus carota*. (Redrwan after Stree, H.E. & Withers, L.A. 1974 in Tissue Culture and Plant Science. Acad. Press, London, UK)

Embryology: The study of embryogenesis from fertilization until the birth (hatching) of an animal, or to the maturation of seeds of plants by genetic, morphological, and molecular techniques ►embryogenesis, ►cell lineages, ►fate map

Embryonal Disk: ►imaginal disk, ►*Drosophila*

Embryonic Induction: The interaction between and among tissues leading to tissue differentiation in the embryo. Vg-1, activin, bone morphogenetic factor, fibroblast growth factor, etc., have been isolated from various sources and found to be effective in regulating embryonic differentiation in animals by binding to receptors, by being restricted in diffusion through the extracellular matrix, affecting signal transduction pathways, etc. ►embryogenesis, ►morphogenesis

Embryonic Lethal: Death occurs before birth.

Embryonic Polarity: The directional determination of the cells in the embryo along longitudinal, vertical, or other directions. The anterior/posterior axis of development is influenced by the sperm-derived centrosomes and the subsequent development of the microtubules. (See Schier AF, Talbot WS 2005 Annu Rev Genet 39:561).

Embryonic Stem Cell (ES): Cells of the early embryo capable of continuous growth and differentiation of animals. They are comparable to the meristems of plants. They represent cells that have not undergone differentiation into somatic cell lineages. These cells can be maintained in vitro in this stage for prolonged periods. They can be reintroduced into preimplantation embryos and thus chimeric animals may be generated. They are suitable for transfection by transgenes and can be used to generate in vitro mutations and are amenable to a variety of modifications such as gene trapping. Several gene products have been identified that are required for the maintenance of self-renewal (Ivanova N et al 2006 Nature [Lond] 442: 533). ►meristem, ►gene trap vectors, ►trapping promoters, ►stem cells

Embryo Sac: The embryo sac of plants develops after meiosis from one of the (generally the basal) megaspores (see Fig. E24). The role of the three antipodals is unclear. The diploid polar cell is fertilized with one of the sperms and gives rise to the triploid zygote and embryo. The synergids (flanking the egg) probably have an early role in nurturing the egg and zygote. The photo shows clearly only 4 nuclei (which were in the same plane) in the embryo sac ►gametophyte, ►embryogenesis, ►gametogenesis

EMC: ►enzyme mismatch cleavage, ►mutation detection

EMC: Encephalomyocarditis virus with RNA genetic material.

Emerin: A 254 amino acid serine-rich integral membrane protein encoded by the STA gene, responsible for the Emery-Dreifuss muscular dystrophy. (Emery-Dreifuss muscular dystrophy, Wolff N et al 2001 FEBS Lett 501:171)

Emery-Dreifuss Muscular Dystrophy: ►muscular dystrophy, ►emerin, ►laminopathies

EMF (extremely low frequency electromagnetic fields): ►electromagnetic radiation

EMG Syndrome: ►Beckwith-Wiedemann syndrome

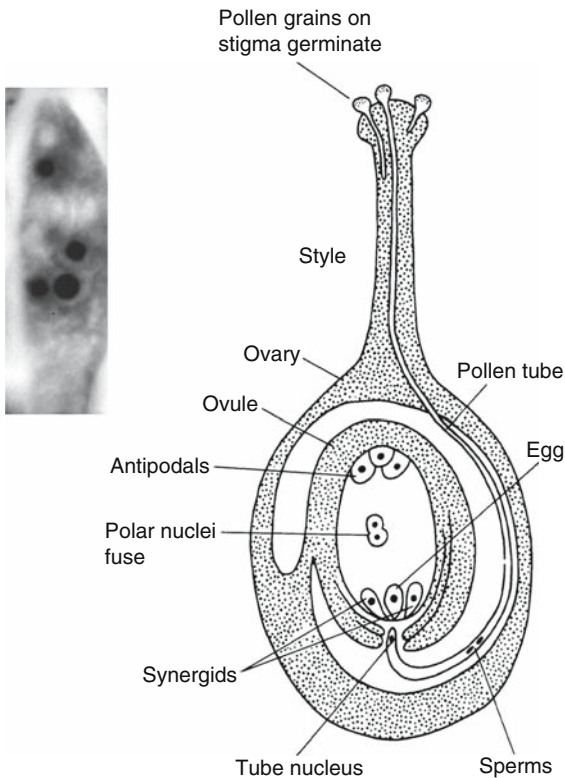


Figure E24. Plant ovule with embryosac diagram at right, photomicrograph of the embryosac with 4 nuclei at left

EMI1 (early mitotic inhibitor of mitosis): A zinc-binding F-box protein that controls the anaphase-promoting complex (APC) by binding to CDC20. ▶F-box, ▶APC, ▶CDC20, ▶Evi oncogene; Reimann JDR et al 2001 Cell 105:645.

EMLS (expected maximum lod score): The sum of lod scores weighted by their probability. EMLS for sharing values of Y (= probability of allele sharing) varies according the size of the population studied. ▶allele sharing; Risch NJ 2000 Nature [Lond]: 405:847.

EMMA: The European Mouse Mutant Archive in Monterotondo, Italy, maintains mutant mouse/frozen embryos for research. ▶mouse

Emmer Wheat ▶Triticum

EM-MS: (electron monochromator-mass spectrometer): An analytical technique especially useful for the analysis of complex biological samples, including complex mutagens and carcinogens of the environment. It applies the electron resonance energy spectrum in the analysis (Havey CD et al 2006 J Phys Chem A Mol Spectrosc Kinet Environ Gen Theory 110:4413).

Emotion: ▶stress

Emphysema, Pulmonary: Pulmonary emphysema is characterized by pathological inflation of the lungs and possible atrophy of the tissues. It appears to be due to autosomal dominant genes or to environmental causes (smoking). Emphysema may show up in infancy as a complication of other ailments. Emphysema develops in case of deficiency of α -antitrypsin. It can be medicated by regular supply of antitrypsin. The heme oxygenase (HMO1, 22q12, inducible; HMO2, 16p13.3, constitutive) genes may regulate susceptibility to chronic pulmonary emphysema (CPE) with lung antioxidant influence. ▶antitrypsin, ▶serpin, ▶elastic fiber diseases

Empirical Risk The occurrence or recurrence of certain genetic defects cannot be predicted on the basis of theoretical principles or mathematical formulas because the genetic mechanisms and their control are not known. Some observations in larger populations indicate, however, a certain tendency of recurrence in families that have had an afflicted individual in the pedigree. The calculation may take into consideration the empirical experience of onset of a disease with both genetic and age components. For example, 100 families have 40 afflicted children older than 50 years, and 170 unaffected who are still in the age group of 20–50. Experience indicates that usually the age of onset begins at 50 and about half of the offspring of afflicted parents eventually expresses the condition. The empirical risk for the still healthy individuals then is $(170 \times 0.5)/210 = 0.41$. ▶genetic risk, ▶risk, ▶recurrence risk, ▶clinical genetics, ▶inbreeding coefficient

EmrE: A family of small multidrug resistance transporters composed of 105–120 amino acids of four transmembrane helices. EmrE confers resistance to antibiotics (tetracycline), ethidium and tetraphenylphosphonium. Crystal structure of this multidrug transporter has been determined (Pomillos O et al 2005 Science 310:1950). ▶multidrug resistance

EMS: A very potent alkylating mutagen and carcinogen. ▶ethylmethanesulfonate

EMSA (electrophoretic mobility shift assay): EMSA detects in vitro the formation of protein complexes by changing the mobility of the complex in the electric field (Fried M, Crothers DM 1981 Nucleic Acids Res 9:6505).

En Blood Group: The En blood group is apparently limited only or mainly to individuals of Finnish descent; it is very rare. ▶blood groups

ENA-78 (epithelial cell-derived neutrophil attractant): A 78-residue chemokine of epithelial cells, monocytes,

neutrophils, fibroblasts, platelets, and some cancer cells. ► [chemokines](#) and other separate entries

ENaC (epithelial sodium channel): ► [ion channels](#), ► [hypoaldosteronism](#)

Enantiomorphs: Enantiomorphs are stereoisomers, molecules with structures that are mirror images of each other. In some instances, only one of the enantiomorphs supports normal metabolism. Interestingly, in nature, L amino acids and D sugars predominate. It has been suggested that the amino acid proline is historically the source of the asymmetry, which was advantageous in the early prebiotic environment and evolution preserved the left-handedness in amino acids. Chirality (enantiomorphs) in the mixture of common insecticides makes a great difference in degradation (an environmental concern) and the toxicity to target and nontarget organisms (Liu W et al 2005 *Proc Natl Acad Sci USA* 102:701). ► [D-amino acids](#), ► [chirality](#), ► [racemate](#); Norden B 1978 *J Mol Evol* 11:13; asymmetric amplification based on solid-liquid phase of amino acid solutions: Klusmann M et al 2006 *Nature [Lond]* 441:621.

Encephalitis: Brain inflammation. ► [Rasmussen encephalitis](#), ► [encephalopathies](#), ► [viral encephalitis](#)

Encephalomyelitis: Brain and spinal cord inflammation. ► [encephalopathies](#)

Enkephalon: Brain; prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon/telencephalon (hindbrain) are distinguished. ► [brain](#)

Encephalopathies: Usually recessive degenerative brain diseases. The childhood recurrent (autosomal dominant) form involves impaired muscular coordination and speech troubles. The Gerstmann-Sträussler disease (GSD) is also an autosomal dominant encephalopathy with late onset (around age 50) and involves feeble-mindedness. The central nervous system shows myeloid plaques, similar to those in the Creutzfeldt-Jakob disease (CJD). The bovine spongiform encephalopathy (BSE) is responsible for the fatal "mad cow disease" which bears similarities to scrapie in sheep and it was believed that a virus induces it. Current views do not support the viral origin; rather it is attributed to an infectious protein (PrP^{Sc}). Recent observations, however, demonstrate 25-nm virus-like arrays in two cell lines productively infected with either sheep-derived scrapie or human-derived CJD agents passaged in mice. Comparable particles were not found in uninfected controls. This data, along with other drug and PrP immunogold binding studies here, lend further credence to the actuality of a transmissible spongiform encephalitis (TSE) virion that is structurally independent of

pathological PrP in the intact cell (Manuelidis L et al 2007 *Proc Natl Acad Sci USA* 104:1965).

In mice that have a null allele for the PrP^C gene, i.e., they are Prn^{P0/0}, even large doses of prions do not cause brain damage. There may be an undetermined chance that these encephalopathies are transmitted to humans from animals by consumption of meat. Most encephalopathies usually have late onset. The incubation period for BSE may be several years. There apparently is evidence now to show that humans are infected by BSE in the form of a new variant of the Creutzfeldt-Jakob disease (Scott MR et al 1999 *Proc Natl Acad Sci USA* 96:15137). It is also known that mice can be infected with scrapie. The major outbreak of BSE is attributed to the feeding of infected sheep offal to cattle. Infectivity can be abolished only by heating the animal products at high temperature and by some solvents. There is no sufficient data on whether milk or eggs or poultry meat would transmit any source of infective material. After decisive control measures, the BSE cases are on a decline since the 1992 peak. An estimated 1 million cattle was infected by BSE and about 160,000 died of the disease in England. The BSE risk to humans is reduced when cattle of over 30 months of age are excluded from consumption. BSE infection through processed meat (brain tissues) can be diminished by orders of magnitude when the infected animal tissue is exposed to several short, high-pressure pulses at temperatures of 121–137° (Brown P et al 2003 *Proc Natl Acad Sci USA* 100:6093). For the complete eradication of the encephalopathies threatening the human populations too, prion-resistant animals may have to be produced. It is known that sheep homozygous for Arg at position 171 in the protein escape scrapie. The kuru, BSE and some forms of the Creutzfeldt-Jakob disease, scrapie transmissible mink encephalopathy, and the feline spongiform encephalopathy are transmitted horizontally whereas the Gerstmann-Sträussler disease and the Creutzfeldt-Jakob disease are transmitted vertically. The hepatic encephalopathy is an apparently nongenetic neuropsychiatric disorder caused by exposure to ammonia. Certain cyclic tetrapyrroles (deuteroporphyrin IX 2,4-bis[ethylene glycol] iron III, phthalocyanine tetrasulfonate) may inhibit the formation of the protease-resistant prions. Prions are not inactivated by nucleases, UV irradiation, psoralen dyes that cross-link DNA, divalent cations, metal chelators, by pH between 3 and 7, hydroxylamine, formalin, boiling and by proteases. The human prions are not contagious like microbial or viral infections but they are transmitted by prion-containing animal residues or by prion transgenes.

Brain tissues (particularly the outermost membranes, the dura mater) are richest in prions but

infection by human blood is controversial although rodent blood seems to transmit it. Peripheral nerves, lung and liver seem to have low infectivity; skeletal muscles, milk, blood, bone, hair, and urine may not transmit prions. There is also some risk that humans may develop a variant of the Creutzfeldt–Jakob disease (vCJD) by ingesting industrial (e.g., gelatin, polysorbate) or medical (e.g., heparin, insulin) products made of or with infected animal material. There is a risk of transmission by inadequately sterilized surgical instruments and particularly by brain tissue specimens, even by aerosols generated by autopsy or through wounds penetrating the gloves during dissection. Fixation of tissue samples in formalin does not abolish infectivity. Autoclaving for 4.5 h at 132°C, denaturing in 50% phenol, guanidine isothiocyanate or hydrochloride at > 4 M, or exposure to 1 N NaOH for 24 h or 2 N NaOH for 2 h inactivates prions. Animal assays for animal prions are generally very slow. Transgenic mice expressing the bovine prion (PrP) may respond faster. The incubation period after infection by a BSE agent is much affected by genetic factors of the recipient mouse. Immunoassays (ELISA) or Western blots for PrP^{Sc} (the scrapie protein) are effective in detection of the condition but their sensitivity is low. Conformation-dependent immunoassay based on the difference between the α -helical PrP^C and the β -sheet component of PrP^{Sc} may be quite efficient. Ovine encephalopathy protein can now be propagated in vitro (Villette D et al 2001 Proc Natl Acad Sci USA 98:4055). In neural cell cultures, specific CJD attenuated the effects of scrapie-derived protease-resistant prions in the absence of an effective immune system (Nishida N et al 20056 Science 310:493).
 ▶prion, ▶scrapie, ▶Gerstmann-Sträussler disease, ▶Creutzfeldt-Jakob disease, ▶kuru, ▶fatal familial insomnia, ▶neurogastrointestinal encephalomyopathy, ▶porphyria, ▶Seitelberger disease, ▶chronic wasting disease

Enchondromatosis: Cartilage tumor(s) regulated by a parathyroid hormone-related protein and Indian hedgehog signals. ▶parathormone, ▶hedgehog; Hopyan S et al 2002 Nature Genet 30:306.

Enciphering: The information regarding the nature of a protein, such as a prion, is contained in its tertiary structure rather than in a nucleic acid. ▶prion

ENCODE (Encyclopedia of DNA Genetic Elements): Pursues the identification and localization of all functional elements such as promoters, transcriptional regulators, replicational origins, etc. The promoter associated region is frequently called ENCODE region. Detailed analysis of a targeted 1% of the human genome indicates that the DNA is generally transcribed

and the majority of the bases are present in transcripts even of noncoding sequences; there is new light on transcriptional start sites and regulation (ENCODE Consortium 2007 Nature [Lond] 447:799). The 2007 data shed new light on the functional organization of the genes. ▶human genome, ▶gene, ▶pseudogene; Science 306:636 [2004], Genome Research ENCODE 17(6), issue 2007; <http://www.genome.gov/10005107>; <http://genome.ucsc.edu/ENCODE>; unified portal of ENCODE: <http://research.nhgri.nih.gov/ENCODedb/>.

Encyclopedia of the Mouse Genome: It contains genetic and cytogenetic information on mouse, electronically obtainable through File Transfer Protocol (FTP), Gopher or World Wide Web Software (WWW) in Sun (UNIX) or in Macintosh versions. ▶mouse, ▶databases

End: Bacterial genes coding for DNA-specific endonucleases.

End Labeling: The Klenow fragment of bacterial DNA polymerase I can add α -P³² dNTP to the 3'-OH end of a nucleotide (polynucleotide). Or transferring the γ -phosphate of ATP to the 5'-OH end of DNA or RNA (forward reaction) or by exchanging the 5'-P of a DNA (in the presence of excess ADP) by the γ -P of radiolabeled ATP, using T4 bacteriophage polynucleotide kinase. This 5'-labeling is used for the Maxam & Gilbert method of DNA sequencing or in any other procedure when 5' labeling is required.
 ▶Klenow fragment, ▶DNA sequencing

3'-End of Nucleic Acids: The OH at the 3' C atom on the ribose or deoxyribose. ▶nucleic acid chain growth

5'-End of Nucleic Acids: The first nucleotide in the chain retains the three phosphates whereas the subsequent ones form phosphodiester bonds with one phosphate between the 5' end and the 3' -OH position of another.
 ▶phosphodiester bond, ▶nucleic acid chain growth

Endangered Species: ▶species extant, Convention on International Trade of Endangered Species (CITES) 1973 Public Law 93–205.

Endemic: Indigenous to a population rather than introduced; confined to a population or area.

Endergonic Reaction: An endergonic reaction consumes energy.

End-Joining: The restoration of broken chromosome ends, or fusion of broken chromosomes, e.g., in translocation or other type of breakage. ▶translocation chromosomal, ▶double-strand break, ▶nonhomologous end-joining; Smith J et al 2001 Nucleic Acids Res 29:4783.

Endocannabinoids: ▶cannabinoids

Endocardial Fibroelastosis (Barth syndrome, cardiomyopathy with neutropenia and abnormal mitochondria, BTHS): A human Xq28-linked recessive thickening of the heart wall muscles due to collagen proliferation (Type I). In Type II methylglutaconic aciduria, besides the defects in the heart muscles, neutropenia (decrease in the number of neutrophilic leukocytes) morphological anomalies of the mitochondria was detectable by electron microscopy. Barth syndrome may be caused by tafazzin acetyl transferase associated with altered metabolism of mitochondrial phospholipid cardiolipin. Tafazzin mutation in *Drosophila* can serve as an animal model for BTHS (Xu Y et al 2006 Proc Natl Acad Sci USA 103:11584). ▶heart disease, ▶neutropenia, ▶neutrophil, ▶collagen, ▶methylglutaconic aciduria, ▶cardiolipin; Bione S et al 1996 Nat Genet 12:385.

Endocarp: The inner layer of the fruit wall of plants such as the stony pit of peaches, cherries.

Endokaryosis: The acquisition of a nucleus by ingesting another organism during evolution.

Endocrine: Hormone-producing glands which, in response to peptide activators within an organism, secrete their product into the blood stream without the reliance on a special duct. ▶endocrine network; <http://endonet.bioinf.med.uni-goettingen.de/>.

Endocrine Neoplasia, Multiple (MEN): The autosomal dominant MEN 1 (11q13) involves endocrine adenomas in several tissues (stomach, lung, parathyroid, pituitary, colon, pancreas, etc.). The MEN1 gene has 10 exons and it is translated into a 610 amino acid protein, menin. The dominant MEN2 and MEN2A, involving also phaeochromocytoma and amyloid-producing medullary thyroid carcinoma, are apparently in chromosome 10q11.2. The latter is the location of the RET protooncogene. MEN2B is similar to MEN2A but frequently shows neural

hyperplasias of the mouth area and in the colon as well. All of these cases involve receptor-like tyrosine kinases. MEN3, also dominant, was located in the vicinity of MEN2A; it also shares the same symptoms and displays neural tumors. The prevalence is $1-10 \times 10^{-5}$. ▶adenoma, ▶phaeochromocytoma, ▶RET oncogene, ▶protein-tyrosine kinase, ▶menin

Endocrinology: The study of hormones, other biological secretions, and their physiological roles. ▶reverse endocrinology, ▶endocrine, ▶animal hormones

Endocycle: A specialized cell cycle involving genomic replication without cell division and resulting in polyploidy. ▶cell cycle, ▶polyploidy, ▶endomitosis, ▶endoreduplication

Endocytosis: An uptake mechanism of cells involving invagination of the cell membrane and then cutting off the (clathrin-coated) vesicle (endosome) so formed inside the cell (see Fig. E25). Some endocytotic pathways do not require clathrin. The cargo receptor transmembrane proteins recognize various molecules by some sort of specificity. To one terminus of the cargo proteins, an *adaptin* molecule (assembly protein; including arrestin, ARNO, AP2, NSF, MDM2) is attached, that in turn recognizes clathrins. Then clathrin-coated vesicles are formed. When the clathrin and adaptin molecules separate from the membrane, a membrane-bound vesicle is formed enclosing the cargo molecules. The adaptins are multisubunit adaptor molecules that can recognize the (Tyr, X, Arg, Phe) peptide signals near the carboxyl end of the receptor, reaching into the cytosol. The carboxyl end of phosphorylated M6P proteins are also recognized by the adaptin molecules in the Golgi apparatus. The M6P proteins are named as such by the mannose-6-phosphate groups that are linked to the amino ends of lysosomal enzymes.

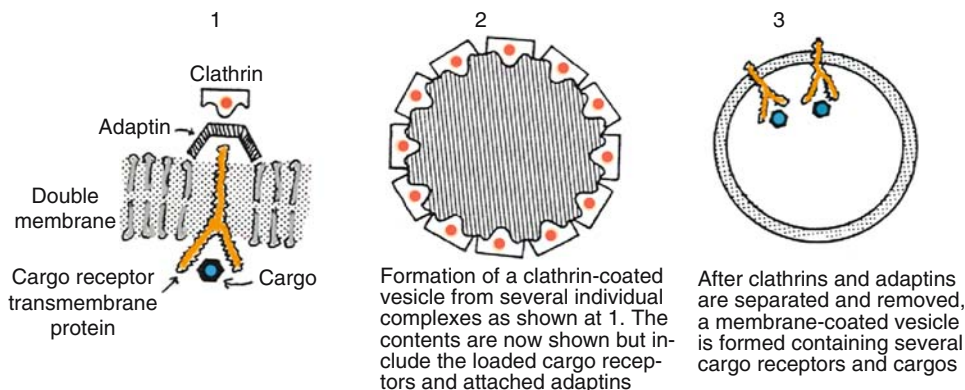


Figure E25. Endocytosis

E

The M6P transmembrane proteins bind lysosomal hydrolases and assist in packaging them into transport vehicles that fuse with endosomes that transport molecules into lysosomes. The endosomal sorting-complex (ESCRT) involves several proteins and its crystal structure and regulatory roles have been determined (Teo H et al 2006 Cell 125:99; Kostelansky MS et al 2006 Cell 125:113). The endosomes are membrane-enclosed transport vesicles, carriers of material to the lysosomes. An endocytotic compartment of the B cells may accumulate class II type MHC molecules and antigens. The unique lipids in the internal membranes of the endosomes sort insulin-like growth factor 2, mannose-6-phosphate ligands, and lysosomal enzymes. These lipids are specific antigens for the antibodies of the antiphospholipid syndrome. The endocytotic pathway also has a signaling function. In addition, endosomes can be used for delivering DNA into cells. Usually a photosensitizer is added to the delivery system that destabilizes the endosomal membrane. A ternary complex composed of the core of DNA, packaged with cationic peptides and enveloped in the anionic dendrimer, phthalocyanine, is used to provide photosensitizing function. This construct assures the uptake of the DNA after laser irradiation and the internalization of the cargo (Nishiyama N et al 2005 Nat Mater 4:934). ▶caveolae, ▶raft, ▶clathrin, ▶triskelion, ▶lysosome, ▶antigen processing, ▶MHC, ▶insulin-like growth factors, ▶lysosome, ▶antiphospholipid syndrome, ▶coatamer, ▶Sec, ▶ARF, ▶SAR, ▶Golgi, ▶COP, ▶adaptin, ▶arrestin, ▶dendrimer, ▶gene delivery, ▶ARNO, ▶AP2, ▶NSF, ▶MDM2, ▶endoplasmic reticulum, ▶receptor-mediated gene transfer; Ungewickell E 1999 Proc Natl Acad Sci USA 96:8809; Itoh T et al 2001 Science 291:1047; D'Hondt K et al 2000 Annu Rev Genet 34:255; Katzmann DJ et al 2001 Cell 106:145; Di Fiore PP, De Camilli P 2001 Cell 106:1; Brodsky FM et al 2001 Annu Rev Cell Dev Biol 17:517; Pelham HR 2002 Curr Opin Cell Biol 14:454; Conner SD, Schmid SL 2003 Nature (Lond) 422:37; Bonifacino JS, Traub LM 2003 Annu Rev Biochem 72:395; Kaksonen M et al 2005 Cell 123:305; coordinating role of endocytosis: Polo S, Di Fiore PP 2006 Cell 124:897; molecular biology and networks: Schmid EM, McMahon HT 2007 Nature [Lond] 448:883.

Endoderm: The internal cell layer of the embryo from which the lung, digestive tract, bladder and urethra are formed. ▶ectoderm

Endodermis: The endodermis in plants is composed of heavy-walled cells and without intercellular space among them; they are found around the vascular system particularly in roots. ▶root

Endoduplication: Endoduplication is basically similar to what is called endomitosis but it was first used to denote the diploidization of androgenetic or gynogenetic embryos. ▶endoreduplication, ▶androgenesis, ▶gynogenesis, ▶c mitosis

Endogamy: Mating within a group, a sort of inbreeding. ▶inbreeding

Endogenote: The tract of the recipient bacterial genome that is homologous to the donor DNA paired with it. In this merozygous condition homo- and heterogenotes can be distinguished, depending on whether the donor sequences are identical or genetically different from that of the recipient. ▶exogenote, ▶merozygote, ▶conjugation bacterial

Endogenous Rhythm: The periodical (oscillatory) changes in cells that occur without external influences. ▶E box

Endogenous Virus: The endogenous virus is integrated into the host chromosome. Endogenous retroviruses may affect the transcription of genes where they are located. The development of superantigens responsible for autoimmune diseases has been attributed to HERV (human endogenous retrovirus) within the HLA gene cluster. The HERV elements retain the long terminal repeats but lack the functional viral envelope gene and are usually not expressed although they are capable of expression. HERVs may constitute ~1–2% of the human genome. HERVs have been used as phylogenetic markers by comparing the integration site polymorphism and for orthologous comparison of the changes in their nucleotide sequences. In vivo and in vitro experiments show that the envelope of a particular class of endogenous retrovirus of sheep, Jaagsiekte sheep retroviruses (enJSRVs), regulates trophectoderm growth and differentiation in the preimplantation conceptus (embryo/fetus and associated extraembryonic membranes). The enJSRV envelope gene is expressed in the trophectoderm of the elongating ovine conceptus after day 12 of pregnancy. If the endovirus is blocked the pregnancy may end (Dunlap KA et al 2006 Proc Natl Acad Sci USA 103:14390). ▶provirus, ▶temperate phage, ▶retroposon, ▶retrotransposon, ▶retrovirus, ▶HLA, ▶superantigen, ▶orthologous, ▶LINE, ▶SINE; HERVd: <http://herv.img.cas.cz>.

Endoglin: A homodimeric receptor glycoprotein on the vascular endothelial cells for the transforming growth factor β , encoded in human chromosome 9q34.1. ▶telangiectasia familial hemorrhagic, ▶vascular targeting, VEGF; Paquet ME et al 2001 Hum Mol Genet 10:1347.

Endolysin: Bacteriophage muralytic (wall-lysing) enzymes for degrading bacterial cell walls. ▶holin

Endomesoderm: A mesoderm layer originating from the endoderm of the early embryo. ▶[endoderm](#), ▶[mesoderm](#)

Endometrium: A three-layer mucous membrane lining the uterus. ▶[uterus](#), ▶[tamoxifen](#)

Endometriosis: A relatively common (10–15%) cause of female infertility due to poorly understood physiological anomaly of the ovaries. It involves excessive menstrual pain (dysmenorrhea) and pelvic pain with coitus (dyspareunia) or upon defecation (dyschezia) or chronic pelvic pain due to endometrial tissue outside the uterus. Gonadotropin-releasing hormone agonists can alleviate the pain because of receptor down-regulation, reduced pituitary gonadotropin secretion, and estrogen production (Berkley KJ et al 2005 Science 308:1586). Comparative genomic hybridization revealed losses in several human chromosomes, particularly in 1, 7 and 22 (Gogusev J et al 1999 Hum Genet 105:444). The presence of abundant plasma cells in endometriosis that produce IgM, and macrophages that produce BLYS/BAFF/TNFSF13B, a member of the TNF superfamily implicated in other autoimmune diseases, were detected. B lymphocyte stimulator (BLYS) protein was found elevated in the serum of endometriosis patients (Hever A et al 2007 Proc Natl Acad Sci USA 104:12451). ▶[comparative genomic hybridization](#), ▶[ovary](#), ▶[Müllerian duct](#), ▶[immunoglobulins](#), ▶[lymphocytes](#), ▶[TNF](#), ▶[autoimmune disease](#)

Endomitosis: Chromosome replication not followed by cell division resulting in polyploidy. In *Schizosaccharomyces* it was found that gene *rum1*⁺ overexpression permits repeated starts of the cell cycle without mitoses in between them, and deletion of the gene allows successive mitoses without an S phase in between them. It appears as if *rum1*⁺ would regulate CDC2, which apparently has two functional forms. Overexpression of *rum1*⁺ would lock CDC2 in the form when it promotes the synthetic (S) phase and deletion of *rum1*⁺ would switch CDC2 into the mitosis-promoting form. ▶[endoduplication](#), ▶[endoreduplication](#), ▶[c mitosis](#), ▶[polyploid](#), ▶[cell cycle](#), ▶[licensing factor](#), ▶[CDC27](#)

Endonuclease: An enzyme that cuts DNA or RNA at internal positions. ▶[exonuclease](#), ▶[restriction enzymes](#), ▶[homing endonuclease](#), ▶[abasic endonuclease](#)

Endonuclease III: Endonuclease III removes from the DNA oxidized pyrimidines such as 5,6-dihydrouracil, 5,6-dihydrothymine, and thymine glycol. ▶[glycosylases](#); Katcher HL, Wallace SS 1983 Biochemistry 22:4071.

Endonuclease IV: Endonuclease IV belongs to a class of trinuclear zinc metalloenzymes; they are apurinic/aprimidinic endonucleases involved in DNA repair in prokaryotes and eukaryotes (Ivanov I et al 2007 Proc Natl Acad Sci USA 104:1465).

Endonuclease V: T4 endonuclease V is called T4-pdg, T4-pyrimidine dimer glycosylase/AP lyase. Endonuclease V is a common base excision repair enzyme of prokaryotes. ▶[glycosylases](#), ▶[pyrimidine dimer](#), ▶[DNAS repair](#); Feng H et al 2005 Biochemistry 44:675; Fuhrmann M et al 2005 Nucleic Acids Res 33(6):e58.

Endonuclease VIII: A bacterial enzyme, which removes from the DNA oxidative-damaged bases by glycosylase/lyase function. ▶[DNA repair](#); Burgess S et al 2002 J Biol Chem 277:2938.

Endonuclease G: A mitochondrial enzyme (~28 kDa) that, upon apoptotic stimuli, moves to the cell nucleus and degrades their DNA independent from the caspase pathway. ▶[apoptosis](#), ▶[CAD](#), ▶[CED-3](#); Parish J et al 2001 Nature [Lond] 412:90; Li LY et al ibid. 95.

Endopeptidase: Proteolytic enzymes cleaving internal bonds at cysteine, serine, aspartic, metallic, or other residues.

Endophilin: A lysophosphatidic acid acyl transferase. It is an effector of dynamin and probably facilitates the invagination of membranes and the formation of synaptic-like microvesicles used in neurotransmission. ▶[lysophosphatidic acid](#), ▶[dynamin](#), ▶[neurotransmitter](#), ▶[synaps](#); Ramjun AR et al 2001 J Biol Chem 276:28913.

Endophenotype: A term used primarily in experimental neurology for describing the characteristics of human diseases (e.g., affective disorders such as schizophrenia) under multigenic control that cannot be defined by any single trait, but rather a collection of traits that vary among the individuals and that have variable expressivity according to age and environmental conditions. ▶[phenotype](#), ▶[neurodegenerative diseases](#)

Endoplasmic Reticulum (ER): The internal membrane system within the eukaryotic cell with secretory channels (see Fig. [E26](#), Fig. [E27](#)).



Figure E26. Endoplasmic reticulum in *Arabidopsis*

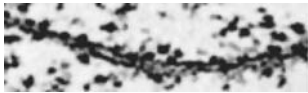


Figure E27. A portion of plant endoplasmic reticulum with ribosomes

Within these membrane-bound compartments proteins and lipids are synthesized, and glycosylation, sulfation of secretory and membrane-bound proteins, proteoglycans and lipids take place. The rough endoplasmic reticulum has attached ribosomes causing the non-smooth appearance (*rough endoplasmic reticulum*). Many nascent peptide chains are transferred to the ER where the synthesis of the proteins is completed and the proteins are folded. If the folding slows down the unfolded protein response (UPR) stimulates the transcription of ER-resident proteins. The Hac1 basic leucine zipper protein is a transcription factor that binds to the UPR element in the promoter of the UPR genes. Splicing that bypasses, the spliceosome is mediated by the presence of a tRNA ligase protein. After the completion of the synthesis the proteins are translocated with the aid of the Hsp70 chaperones. The energy is provided by associated ATP, UDP, GDP and CMP nucleotides. Within the endoplasmic reticulum quality control takes place by selecting the ones which have the proper conformation. The folding is mediated by BiP, lectins calnexin and calreticulin, and protein disulfide isomerase, GRP, and other ER chaperone proteins. The enzymes UDP-5'-diphosphate-glucose—glycoprotein, glucosyl-transferase and glucosidases—also play a role in substrate binding and release of ER proteins. Free cysteines participate in forming interchain disulfide bonds and aggregate and facilitate retention. These ER factors prevent the release of the proteins until their synthesis and folding is completed. The improperly folded polypeptides are degraded and only the correct ones are secreted to the cytosol through the Golgi. The structural surveillance in the ER prevents the release and then degrades some of the structurally mutant α_1 -antitrypsin molecules although they would be capable of function. In cystic

fibrosis the misfolded transmembrane conductance regulator protein may be degraded before it could be transported to the plasma membrane although, under conditions conducive to proper folding, some function may be recovered (see Fig. E28). In other instances the folding defect may cause precocious release of, e.g., β -lactoglobulin polypeptide. The released proteins may be transported with the aid of the cargo receptor to the Golgi apparatus where further processing may take place. A defect in the chaperones in terminally differentiated neurons leads to protein accumulation and stress in ER resulting in neurodegeneration as seen in Alzheimer's and Parkinson's diseases (Zhao L et al 2005 Nature Genet 37:974).
 ▶chloroplast endoplasmic reticulum, ▶signal peptide, ▶signal-sequence recognition particle, ▶cell structure, ▶protein synthesis [translation], ▶Sec61 complex [and other Sec proteins], ▶Hac1, ▶Hsp70, ▶TAP, ▶SsA, ▶SsB, ▶Ydj1, ▶architectural editing, ▶BiP, ▶calnexin, ▶calreticulin, ▶GRP, ▶lectins, ▶antitrypsin gene, ▶aggresome, ▶Golgi apparatus, ▶endocytosis, ▶COP transport vesicles, ▶inclusion body, ▶cystic fibrosis, ▶folding, ▶protein folding, ▶unfolded protein response, ▶endoplasmic reticulum-associated degradation; Parodi AJ 2000 Annu Rev Biochem 69:69; Yamamoto K et al 2001 EMBO J 20:3082; Lehrman MA 2001 J Biol Chem 276:8623; Glick BS 2001 Curr Biol 11:R361; Nicchita C 2002 Curr Opin Cell Biol 14:412; Hampton RY 2002 Curr Opin Cell Biol 14:476; Sitia R, Braakman I 2003 Nature [Lond] 426:891.

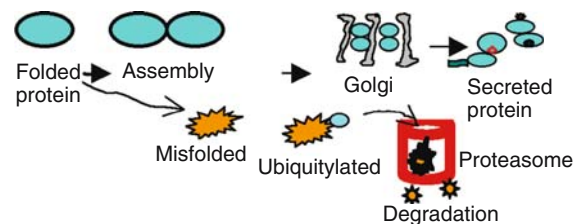


Figure E28. Quality control by ER

Endoplasmic Reticulum-Associated Degradation: Transmembrane and secretory proteins may enter the endoplasmic reticulum through the Sec61 channel. There they fold and may be oligomerized and then transferred to the Golgi apparatus. The status of glycosylation is critical for appropriate degradation. Misfolded proteins can be returned to the endoplasmic reticulum and finally to the cytoplasm where their degradation takes place. AAA-ATPases of the 19S proteasome may provide the energy for the transport. The protein may be ubiquitinated and degraded by the proteasome. Larger protein aggregates that occur in neurodegenerative diseases such as Huntington's

chorea and Parkinson's disease may not be ubiquitinated (Bennett EJ et al 2005 Mol Cell 17:351) and these are shuttled to the lysosomes for degradation by autophagy (Bjørkøy G et al 2005 J Cell Biol 171:603). ▶unfolded protein response, ▶AAA-ATPase, ▶CDC48, ▶Golgi, ▶ubiquitin, ▶proteasome, ▶autophagy; Römisch K 2005 Annu Rev Cell Dev Biol 21:435; Bukau B et al 2006 Cell 125:443.

Endopolyploid: A cell with increased chromosome number because of endomitosis, i.e., the chromosomes have replicated but cell division was skipped. Such phenomena commonly occur repeatedly in cultured plant and animal cells. ▶endomitosis, ▶endoduplication, ▶polyploidy

Endoproteases: A family of enzymes involved in the processing of proteins, e.g., the large peptide hormone precursors, large secreted proteins, pheromones, etc.

Endoreduplication: When the chromosome replication is not followed by centromere and cell divisions and therefore multistranded (polytenic) chromosomes are formed. The mechanism of this phenomenon requires the prolongation of the S phase and suppression of the M phase. Polytenic chromosomes are present in the salivary gland cells of some flies (*Drosophila*, *Sciara*, etc.), but they occur in some plant tissues too, e.g., the endosperm of cereals, in some cells (chalaza, antipodal) of *Allium ursinum*, *Aconitum ranunculifolium*, etc. In animals, the E2F-like proteins, and, in plants, the DP-E2F-like proteins regulate the process (Vlieghe K et al 2005 Curr Biol 15:59). Endoreduplication has been attributed, in plants, to the activities of topoisomerase II and topoisomerase VI during the mitotic cycles (Sugimoto-Shirasu K et al 2005 Proc Natl Acad Sci USA 102:18736). ▶polytenic chromosomes, ▶endoduplication, ▶chalaza, ▶antipodal cells, ▶replication during the cell cycle; Edgar BA, Orr-Weaver TL 2001 Cell 105:297.

Endorphins ("endogenous morphine"): Endorphins are neuropeptide ligands of opiate receptors in the brain pituitary gland and peripheral tissues of vertebrates. Their physiological effects mimic morphines. They have potential therapeutic use in nervous disorders, pain perception, etc. Introducing the β -endorphin gene into the cerebrospinal fluid may mitigate pain for longer periods than drugs. The prodynorphin opioid neuropeptide precursor might have played an important role in human evolution and in separation from the ape line (Rockman MV et al 2005 PLoS Biol 3(12):e387). ▶opiocortin, ▶pituitary, ▶morphine, ▶brain human, ▶POMC, ▶pain, ▶enkephalins; Coventry TL et al 2001 J Endocrinol 169:185.

Cope: A medical instrument for external examination of internal body cavities.

Endosome: ▶endocytosis

Endosomolysis: The disruption of the endocytotic vesicles and liberation their contents. ▶endocytosis

Endosperm: The nutritive tissue within the seed developed from the fertilized polar cells in the embryo sac. In some plants the endosperm develops to a substantial mass and persists as the bulk of the seed (the majority of the monocots). Alternatively, it may be gradually consumed and only traces are visible by the time the embryo fully develops because that function is relegated to the growing cotyledons (majority of dicots). In monocots the surface layer of the endosperm is called *aleurone*. Normally, the embryo is diploid and the endosperm is triploid. Some mutations may permit the development of the endosperm without fertilization of the fused polar nuclei. In species crosses, the 2:3 proportion may be altered with deleterious consequences for the embryo. By crossing a diploid female with a tetraploid male, the embryo will be triploid and the endosperm will be tetraploid (3:4), but by crossing a tetraploid female with a diploid male the number of genomes in the embryo remains the same (3n) but the endosperm will be pentaploid (3:5). Thus the gene dosage in the endosperm is usually different from that in the embryo. Some species of plants have different developmental patterns beginning with the embryo sac. ▶embryogenesis in plants, ▶embryo sac, ▶embryogenesis in plants; Olsen O-A 2001 Annu Rev Plant Physiol Mol Biol 52:233.

Endosperm Balance Number: The term was suggested for the unusual observations that within some species the tetraploids do not effectively fertilize other tetraploids (4x) but may do so with diploids (2x). When their chromosome number is doubled (8x) they may be crossed with tetraploids, except the progenitor tetraploid. Thus a curious chromosome balance is observed. ▶endosperm

Endosperm Mother Cell: The fused polar cells of the endosperm (2n) that when fertilized by a sperm give rise to the triploid endosperm tissue in the seeds of plants. ▶embryosac, ▶gametogenesis

Endospore: A dormant bacterial cell, resistant to most treatments that normally kill active cells. The process of sporulation has been extensively studied in *Bacillus subtilis*. *Clostridium tetani* and *Bacillus anthracis*, etc., also produce endospores. A fungal spore within a cell is also called an endospore. ▶forespore

Endostatin: A collagen XVIII C-terminal, ca. 20-kDa domain which, along with an angiostatin, can regulate angiogenesis and metastasis and may block

cancerous growth by denying the blood supply to tumors. Endostatin-integrin interaction is relevant to angiogenesis. More recent evidence questions the antitumor effectiveness of endostatin. ►angiogenesis, ►angiostatin, ►collagen, ►cancer, ►metastasis, ►integrin; Sim BK et al 2000 Cancer Metastasis Rev 19:181; Rehn M et al 2001 Proc Natl Acad Sci USA 98:1024; Kuo CJ et al 2001 Proc Natl Acad Sci USA 98:4605.

E

Endosteum: The lining of the bone medullary cavity, the endosteal lining.

Endosymbiont: An organism that lives within the cell of another. ►infectious heredity, ►mutualist, ►nucleomorph

Endosymbiont Theory: An evolutionary idea suggesting that plastids and mitochondria were originally free-living microorganisms, later captured by nucleated cells (archaebacterium) and which then became cellular organelles in eukaryotes see Margulis L 1993 in General references (Evolution). It appears that all photosynthetic plastids have a common origin as indicated by the analysis of the red alga *Cyanidoschizon merolae* (McFadden GI, van Dooren GG 2004 Current Biol 14:R514). This old hypothesis is supported by DNA sequence analyses primarily of organellar and eubacterial and archaebacterial rRNA genes. It appears that the plastid rRNA core sequences resemble that of Gram-positive cyanobacteria and the mitochondrial rRNAs indicate descents from eubacteria. The dispute among evolutionists regarding the monophyletic or polyphyletic endosymbiotic origins of these organellar genomes is still extant.

Secondary endosymbiosis is believed to occur when a eukaryote is ingested and retained by other eukaryotes with chloroplasts. In these cases four-layer membranes may enclose the organelles. The "old" endosymbiotic theory fails to interpret the fact that there are eukaryotes without mitochondria or hydrogenosomes. (In hydrogenosomes pyruvate is metabolized by pyruvate:ferredoxin oxidoreductase rather than by a pyruvate dehydrogenase complex.). Archaebacteria do not have evidence for structures homologous to those of eukaryotes. Also, mitochondrion-free eukaryotes seem to have genes, which resemble mitochondrial DNA sequences. Recently, the *hydrogen hypothesis* has been advanced (Martin W, Müller M 1998 Nature 392:37). According to the latter, an autotrophic archaebacterium host entered a symbiotic relationship with a eubacterium capable of respiration. This symbiont produced molecular hydrogen as a waste product of its heterotrophic metabolism that served well the host, thus forging

a stable relationship. In this system, from the symbiont hydrogenosomes, eventually mitochondria evolved. The symbiont transferred genes to the host for organic metabolism, enzymes, and ATP generation. Thus, from autotrophy heterotrophy evolved and the complex organism could utilize also the organic molecules. Eventually, more complex cellular structures evolved giving origin to eukaryotic cells. The obligate intracellular parasites of proteobacteria, *Rickettsia*, *Anaplasma* and *Ehrlichia* genomes appear to be closest to the mtDNA of animals. ►chloroplasts, ►mitochondria, ►nucleomorph, ►rRNA, ►Rickettsia, ►hydrogenosome, ►symbionts; Lang BF et al 1999 Annu Rev Genet 33:351; Wernegreen JJ 2004 PloS Biol 2:307.

Endosymbiosis: ►endosymbiont

Endosymbiotic Gene Transfer: ►organelle sequence transfer

Endothelin: The veins and inner tissues of the heart secrete this peptide hormone. It controls heart muscle functions, hypertension, including myocardial infarction, protein kinase A (PKA) and chloride, potassium and calcium ion channel functions. Mutation in the endothelin may lead to hereditary hypoventilation. Endothelin mutations may account for the Hirschsprung disease and the Shah-Waardenburg syndrome. The endothelin receptor (EDNRB) is required for melanoblast migration and development of the neural crest. Mast cells control endothelin level and limit its toxicity (Maurer M et al 2004 Nature [Lond] 432:512). Red wine reduces the synthesis of endothelin-1 and thus protects against coronary heart disease (Corder R et al 2001 Nature [Lond] 414:863). ►PKA, ►ion channels, ►Hirschsprung disease, ►Shah-Waardenburg syndrome, ►Alzheimer's disease, ►melanocyte, ►neural crest; Hunley TE, Kon V 2001 Pediatr Nephrol 16:752.

Endothelium: The layer of epithelial cells of mesodermal origin, and lining organ cavities.

Endothermic: A chemical reaction that takes up heat.

Endotoxins: Endotoxins are bacterial lipopolysaccharide toxins, attached to the outer membrane and secreted only inward in the cell and released only when the cell disintegrates. Endotoxins release large amounts of tumor necrosis factor (TNF) and interleukin-1 (IL-1). They may present a serious hazard to humans (diarrhea, bleeding, inflammation, increase of white blood cells, etc.) ►toxins, ►TNF, ►IL-1

Endpoint: In chemistry it indicates the highest dilution during titration that still gives a detectable reaction with another substance. In genetic toxicology it is the method of identification of the lowest effective dose of a mutagen or carcinogen that causes point mutations, chromosome breakage, unscheduled DNA synthesis, etc. ▶[bioassays of genetic toxicology](#), ▶[unscheduled DNA synthesis](#)

End-Product Inhibition: ▶[feedback control](#)

End-Sequence Profiling (ESP): ESP reveals genomic rearrangements by mapping sequence-tagged connectors. ▶[sequence-tagged connector](#); Volik S et al 2003 Proc Natl Acad Sci USA 100:7696.

Ends-In, Ends-Out Recombination: Site-specific, targeted recombinations (see Fig. E29). (See diagram, ▶[targeting genes](#); Gong WJ, Golic KG 2003 Proc Natl Acad Sci USA 100:2556)

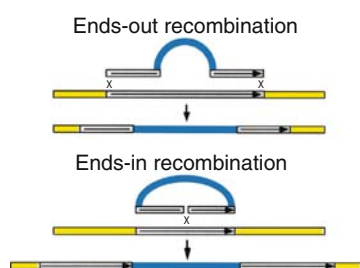


Figure E29. Ends-in, Ends-out recombination. The shaded blocks represent homology. (From Gong WJ, Golic KG 2003). Ends-out, or replacement gene targeting in *Drosophila*. Proc Natl Acad Sci USA 100:2556–61. Copyright 2003 National Academy of Sciences, U.S.A.)

Ene: A Kaposi's sarcoma-associated herpesvirus polyadenylated nuclear RNA containing a 79-nt cis-acting element, which allows intronless polyadenylated transcripts to accumulate to high nuclear levels by protecting them from rapid degradation (Conrad NK et al 2007 Proc Natl Acad Sci USA 104:10412).

Enediynes: Enediynes are anticancer antibiotics. They cleave the DNA by generating benzenoid diradicals when activated. They cleave the DNA backbone by extracting from it hydrogen atoms. ▶[neocarzinostatin](#); Lode HN et al 1998 Cancer Res 58:2925; Liu W et al 2002 Science 297:1170.

Energy Charge: $[(ATP) + 1/2(ADP)] / [(ATP) + (ADP) + (AMP)]$; i.e., it measures the phosphorylating capacity of the adenylate system. The energy charge is 0

if only AMP is available and it is 1 if all AMP is converted to ATP. ▶[AMP](#), ▶[ATP](#)

Energy Coupling: The transfer of energy from one reaction path to another.

Enfuvirtide: Enfuvirtide is used for the successful infection of cells of the HIV virus; the surface glycoprotein complex is fused with the cell membrane. Peptides derived from the HR2 (heptad repeat) region of viral gp41 have been shown to have potent antiviral activity. Enfuvirtide (ENF/T-20/DP-178), the first approved fusion inhibitor for HIV, is a 36-aa peptide derived from this region. Novel fusion inhibitors that are active against ENF-resistant viruses and exhibit a higher genetic barrier to resistance are in development (Dwyer JJ et al 2007 Proc Natl Acad Sci USA 104:12772). ▶[acquired immunodeficiency](#)

Engrafting: Adding another tissue by surgical means, and if it is established it is engrafted. ▶[grafting](#)

Engailed (*en*, *Drosophila* gene, map location 2–62): Among a variety of phenotypic consequences: half of the larval body segments are deleted and the remaining ones are duplicated (see Fig. E30). ▶[morphogenesis in Drosophila](#), ▶[groucho](#)

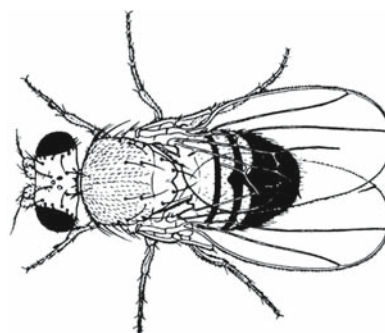


Figure E30. *en*

Enhanceosome: A protein complex of special gene activators and HMG proteins involved in enhancing the activity (transcription) of interferon and other genes in response to various signals and cues (see Fig. E31). The enhanceosome includes histone acetyl transferases, CREB-binding proteins, and associated activators (GCN5).

HMGs are structural proteins facilitating their assembly after acetylation. Acetylation by CBP at lysine-65 destabilizes the complex but acetylation by GCN5 at lysine-71 stabilizes the complex, facilitates transcription, and fends off acetylation by CBP. ▶[enhancer](#), ▶[interferon](#), ▶[activator proteins](#), ▶[HMG](#), ▶[CREB](#), ▶[CBP](#), ▶[GCN5](#); Carey M 1998 Cell 92:5; Munshi N et al 2001 Science 293:1133.

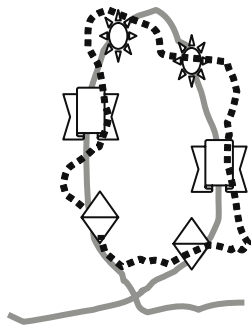


Figure E31. Enhanceosome. DNA loop (continuous grey) is wrapped around the enhanceosome

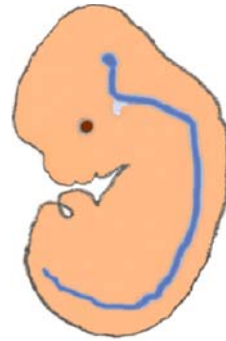


Figure E32. MycCM3 enhancer directs LacZ expression in the neural tube • (Redrawn after Hallikas, O. et al. 2006 Cell 124:47)

Enhancer: Enhancers are cis-acting positive regulatory elements positioned (frequently near Z DNA) either upstream or downstream (by several kb) of the initiation of transcription. The enhancer may be located also within the transcription unit. Supercoiling of the DNA may facilitate enhancer activation of genes at a distance over 2,500 bp. It alters chromatin structure to facilitate transcription by binding special proteins (see Fig. E32). A single short or many short enhancer modules, which are bound by transcription factors, can control a single gene promoter. In case of multiple modules, the gene may be expressed in all tissues where one or more of the modules are active (Michelson AM 2002 Proc Natl Acad Sci USA 99:546). The enhancers may activate a gene for transcription or may increase the basal rate of transcription by two orders of magnitude. Enhancers (one or more) are present in all eukaryotic genes. The size of the enhancers varies from 50 bp to 1.5 kbp. Prokaryotes usually do not use enhancers, however, some σ^{54} subunits of RNA polymerase make this enzyme enhancer-responsive (Rappas M et al 2005 Science 3007:1972). Some of the clustered genes (e.g., HOX) may share enhancers. The prokaryotic enhancer element may also be situated upstream or downstream of the gene. For more about enhancers see Simian virus 40. On the basis of transcription factor-binding specificities a computational tool of enhancer element locator (EEL) has been developed. The method permits the genome-wide identification of multiple tissue-specific enhancers of genes/transgenes involved in control of growth and tumorigenesis (Hallikas O et al 2006 Cell 124:47).
 ▶G box, ▶silencer, ▶TAF, ▶activator, ▶regulation of gene activity, ▶octa, ▶core promoter, ▶POU, ▶homeotic genes, ▶transcription factor map; Bellen HJ 1999 Plant Cell 11:2271; Xu Z et al 2001 Gene 272:149; Liu Y et al 2001 Proc Natl Acad Sci USA 98:14883; enhancer browser: <http://enhancer.lbl.gov>.

Enhancer Competition: The imprinted genes *H19* and *Igf2* share the same enhancer, but *H19* is expressed in the maternal chromosome whereas *Igf2* is favored in the paternal chromosome and the two chromosomes were supposed to be in competition for the same enhancer. Newer evidence indicates that the differential control resides in ~2-kb region upstream from *H19*, the so-called ICR site (imprinting control region). ICR is apparently an allele-specific methylation-sensitive insulator, a boundary element. The conserved zinc-finger protein (CTCF) specifically binds to CG dinucleotide repeats, which occur in that region. ▶imprinting, ▶boundary element, ▶insulator; Cai HN et al 2001 Development 128:4339.

Enhancer Shuffling: The rearrangement of enhancer elements during development can account for differences in transcription. (See Kermekchiev M et al 1991 Gene Expr 1:71).

Enhancer Trapping: ▶gene fusion

Enhancesome: ▶enhanceosome

En-I (Enhancer-Inhibitor): A system of transposable elements of maize. ▶Spm

Enkephalins: Endogenous opioid peptides regulating pain, stress response, aggression, and dominance behavior. The pre-proenkephalin gene, encoding the precursor of Met-enkephalin, introduced by herpes simplex viral vector into the mouse afferent nerves may mitigate pain sensation for a longer term than analgesics. Enkephalin knockout mice displayed increased fear. Enkephalins regulate many neuronal and immunological functions. ▶opiates, ▶pain, ▶endorphin, ▶knockout

Enl: A serine- and proline-rich protein (encoded in human chromosome 19p13); in chromosomal translocations it may be responsible for acute lymphocytic leukemia. ▶leukemias

Enol Form: The form of a molecule that contains an OH group whereas the keto form has C = O (see Fig. E33). These may undergo enol-keto tautomerism; the enolic form may be subject to proton shift.
 ▶tautomeric shift, ▶hydrogen pairing

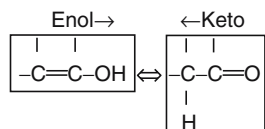


Figure E33. Enol and keto forms

Enolase (phosphopyruvate hydrolase, PPH, ENO): Enolase catalyzes the conversion of 2-phosphoglycerate into phosphoenolpyruvate; ENO1 is encoded in human chromosome 1pter-p36.13. The neuron-specific enzyme (ENO2) is encoded in human chromosome 12p13, and the muscle specific ENO3 is encoded in chromosome 17pter-p12.

Ensembl: An automated annotation program for some eukaryotic genomes and free software. (See series of articles in Genome Res [2004] 14:925 ff; <http://www.ensembl.org/>).

Ensoulment: A religious concept regarding the acquisition of soul by the human embryo. According to the current view of the Roman Catholic Church, ensoulment takes place at conception and that is the stage when life begins. Saint Thomas Aquinas, the thirteenth-century theologian and philosopher, entertained the view that ensoulment occurs during a later stage of embryonic development. The view on the stage of the beginning of life affects some doctrines on contraceptives, birth control, abortion, sanctity of life, and even criminal justice.

Entamoeba histolytica: A protist responsible for intestinal amoebiasis, a bloody diarrhea with high mortality in some underdeveloped areas of the world (see Fig. E34). Its infection generally stems from poor sanitation and feces-contaminated drinking water or raw vegetables, fruits and improper food handling, but it can spread by physical contact between infected persons or toilets. The organism does not contain mitochondria. Its genome contains 23,751,783 base pairs and 9,938 predicted genes. Its chromosomes do not condense and their number is uncertain. Apparently, lateral gene transfer from prokaryotes affected its evolution. ▶*Giardia*, ▶*Trichomonas*, ▶protozoa; Loftus B et al 2005 Nature [Lond] 433:865.



Figure E34. *Entamoeba* cell with ingested red blood cells

Entelechy: The vitalists postulated an inner force of organisms that is responsible for life and growth. In modern morphogenetic theory, it is the basis of the internal program of development.

Enterobacteria: A large group of gram negative bacteria with very wide distribution in insects, higher animals and plants, represented by *Escherichia coli*, *Salmonella*, *Shigella*, *Serratia*, *Klebsiella*, *Proteus*, *Shigella*, *Erwinia*, *Yersinia*, etc. Many of them are pathogenic, some are saprophytes, and others are facultative pathogens. (See genome annotation: <https://asap.ahabs.wisc.edu/asap/logon.php>).

Enterococcus faecalis V583: A gram-positive opportunistic pathogen bacterium. It has been sequenced and has 3,218,031 bp in the chromosome and the three plasmids are 66,320, 57,660 and 17,963 bp. It encodes 3,182 proteins, 12 rRNAs, 68 tRNAs, and 2 structural RNAs. More than one quarter of its genome is represented by mobile elements. ▶mobile genetic elements; Paulsen IT et al 2003 Science 299:2071.

Enterokinase Deficiency: An autosomal recessive defect in the activation of pancreatic proteolytic proenzymes (such as chymotrypsinogen, procarboxypeptidase, proelastase) by this intestinal enteropeptidase, and resulting, consequently, in hypoproteinemia and general weakness. ▶trypsinogen deficiency

Enteropeptidase: Same as enterokinase.

Enterotoxin: Enterotoxin is produced by enteric (intestinal) bacteria. ▶toxins

ENTH Domain: An epsin N-terminal homology domain that interacts with phospholipids of membranes. ▶epsin; Ritter B, McPherson PS 2006 Proc Natl Acad Sci USA 103:3953.

Enthalpy (H): The heat content or energy of a system.

Enthalpy Change (ΔH): The difference between the energy required for disrupting a chemical bond and the energy gained by forming a new one(s).

Entner-Doudoroff Pathway: In bacteria, from 6-phosphogluconate → 2-keto-3-deoxy-6-P-gluconate an aldolase generates pyruvate and triose phosphate.

Entoderm: Same as endoderm. ▶endoderm

Entomology: The study of insects. (See for plant health related data: <http://www.ent.iastate.edu/list/>).

Entomophagous: The feeding on insects.

Entomophagous Bacteria (entomopathogenic bacteria):
 ▶ *Bacillus thuringiensis*, ▶ *Photorhabdus luminescens*; de Maagd RA et al 2003 Annu Rev Genet 37:409.

E

Entrapment of mRNA: The molecule is kept inactive by a ternary complex. (See Schlax PJ et al 2001 J Biol Chem 276:38494).

Entrapment Vector: ▶ gene trapping vector

Entrainment: The exact match between the shift of an endogenous oscillator and the periods evoking the circadian rhythm. ▶ circadian rhythm, ▶ oscillator

Entrez (<http://www.ncbi.nlm.nih.gov/Entrez/>): The source of nucleotide and protein sequence information. Batch Entrez allows the retrieval of several sequences at once from a database and which after downloading can be analyzed on the local computer. Retrieval computer software and databases are distributed on CD-ROM. The software is public and available in Macintosh or IBM PC (Windows) formats. General questions through INTERNET: ▶ info@ncbi.nlm.nih.gov or ▶ net-info@ncbi.nlm.nih.gov. ▶ database, ▶ GenBank

Entrez Gene: Provides information on genes defined by sequence and/or NCBI's Map Viewer. It replaces LocusLink, and can be queried by names, symbols, accessions, publications, GEO terms, chromosome numbers, EC numbers and the products they encode, and by some other features. ▶ ENTREZ, ▶ Map Viewer; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>; gene statistics of >3,500 taxa: http://www.ncbi.nlm.nih.gov/projects/Gene/gentrez_stats.cgi.

Entrez Programming Utilities (E-Utilities): These tools support a uniform set of parameters used to search, link between, and download from the Entrez databases, and use in another environment (http://www.ncbi.nlm.nih.gov/entrez/query/static/eutils_help.html).

Entropic Trap Array: A nanofluidic device for the separation of 5,000 to 160,000 bp long DNA molecules. ▶ pulsed field electrophoresis

Entropy: The measure of energy unavailable for use within a system. The entropy increases by the natural processes of aging. The principle of entropy maximization can be applied to identification of the gene interaction network with the highest probability of giving rise to experimentally observed transcript profiles. Analysis of microarray data from genes in *Saccharomyces cerevisiae* chemostat cultures exhibiting energy metabolic oscillations identifies a gene

interaction network that reflects the intracellular communication pathways that adjust cellular metabolic activity and cell division to the limiting nutrient conditions that trigger metabolic oscillations. The success of the present approach in extracting meaningful genetic connections suggests that the maximum entropy principle is a useful concept for understanding living systems, as it is for other complex, nonequilibrium systems (Lezon TR et al 2006 Proc Natl Acad Sci USA 103:19033). ▶ genetic network

ENU (*N*-ethyl-*N*-nitrosourea): An ethylating agent; (see Fig. E35) one of the most potent point mutagens in mouse (mutation rate/locus 6.6 to 15 × 10⁻⁴). In *Arabidopsis*, within the concentration range of 0.25 to 1.25 mM (18 h exposure of seeds), it causes embryo lethals from 2.8 to 85.1% of the plants. (See Balling R 2001 Annu Rev Genomics Hum Genet 2:463; Herron BJ et al 2002 Nature Genet 30:185).

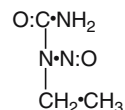


Figure E35. ENU

Enucleate: A cell without a nucleus. ▶ enucleation, ▶ nuclear transplantation, ▶ cytoplasm

Enucleation: The removal of the cell nucleus (see Fig. E36). (▶ nuclear transplantation, ▶ cytochalasin).

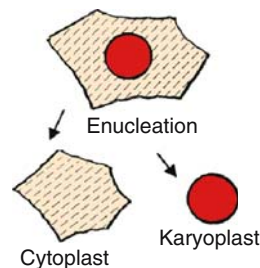


Figure E36. Enucleation

Env Z: A phosphorylating enzyme (kinase) on the bacterial membrane envelope.

Envelope: Envelopes are generally double-layer membranes (surrounding organelles) in the cell. The glycoprotein viral envelope surrounds the capsid of some viruses. ▶ virus

Environmental Deviation: Quantitative characters are manifested in a phenotypic value, called P that can be partitioned into a genotypic value G and an

environmental deviation, E, i.e., $P = G + E$ where P is measured as the mean value of a population. The value of G can be determined by heritability estimates. ► [heritability](#)

Environmental Effects: Environmental effects are of significant importance for the expression of genes. The genetic constitution provides the blueprint but the realization frequently has a variable environmental component. The genotype had been identified as providing a programmed *reaction norm*, but the temporal sequence and intensity of gene expression is determined by the internal regulatory DNA elements and the environment. Among the endless good examples are, the expression of inducible enzymes, the immune reactions, the switching from fetal hemoglobin ζζ in the early embryo to ααGγAγ by the 8th week then to ββδδ shortly before birth and by six months postnatal when it switches to ααββ with about 2% ααδδ. In plants, the onset of the flowering in many species requires vernalization and/or appropriate photoperiodism. Sometimes, environmental effects persist through meiotic events. ► [dauermodification](#), ► [delayed](#), ► [inheritance](#), ► [maternal](#), ► [effects](#), ► [epigenesis](#). The environment exercises greatest effect on the expression of quantitative genes. Many environmental factors are mutagenic, these may include food and feed additives, cosmetics, drugs, medicines, industrial and agricultural chemicals, natural food products, radioactive fallout. ► [quantitative traits](#), ► [heritability](#), ► [environmental mutagens](#), ► [salt tolerance](#), ► [cold-regulated genes](#), ► [case-case design](#); Xiong L et al 2002 Plant Cell 14:S165; human disease: Hunter DJ 2005 Nature Rev Genet 6:287.

Environmental Load: Some specific environmental conditions may favor and maintain alleles that convey inferior fitness to the individuals under usual, average conditions. The alleles so maintained represent the environmental load of the population. ► [genetic load](#)

Environmental Mutagens/Toxins: Carcinogens and teratogens occur in the laboratory, industry, and agricultural environment. According to the estimates of the U.S. National Research Council, approximately 70,000 chemicals are in use and their number is increasing steadily. Their biological effects are not completely known. A survey of about 80 products of engineered protein did not appear toxic (with the exception of interferon) and one humanized antibody + linker might have had some genotoxicity (Mutation Res. 436:137). Many potentially mutagenic agents are present in every household, in the industry and in the research laboratories. The response to these potentially hazardous agents is determined or influenced by the genetic constitution of the individuals

(susceptibility and resistance genes) and a number of factors in the environment besides the few agents named here. A very incomplete list follows:

- Acetaldehyde: An intermediate of organic solvents, preservative of certain food products; it may be present in small quantities in the sweet smell of ripening fruits.
- Acridine dyes: Laboratory chemicals and may be present in some antimalaria drugs.
- Acrylamides: Used for gel electrophoresis and are absorbed through the skin. They are present in some highly heated food but do not seem to pose a cancer risk because of the low amounts.
- Actinomycin D: An antibiotic used to block transcription in the laboratory is a carcinogen.
- Aflatoxins: About a dozen different natural products of *Aspergillus* fungi detectable on peanuts, grains and other feed and food and cause mutation as well as liver cancer.
- Allylthiocyanate: Present in cruciferous vegetables, mustard condiments, and horseradish.
- 3-Aminotriazole: A herbicide that is largely undetectable by mutagen assays, yet it is a powerful carcinogen.
- Aramite: An insecticide used some time ago for fumigation of greenhouses.
- Asbestos: A heat insulator and filtering agent, present in many buildings and can cause malignant mesothelioma (malignancy of the pleura [membrane of the thoracic cavity and lung], peritoneum [membrane of the abdominal wall] and pericardium [envelope of the heart]).
- Atabrine: An antimalaria drug.
- Atrazine: A herbicide that may be activated into a mutagen by the metabolism of plants.
- 5-Azacytidine: Interferes with DNA methylation.
- Benzimidazole: May be present in pharmaceuticals, preservatives and insecticides.
- Benzidine: A laboratory reagent.
- Benzo(a)pyrene: Regularly formed during combustion of many organic materials (in fire-places, automobile exhaust fumes, grilled-charcoal-broiled meat, tobacco smoke), refined mineral oils, and commercial wax products.
- Bisphenol A: Used for manufacturing resins and plastic coating of various containers. Bis-phenols are estrogenic endocrine-disrupting chemicals (EEDC) mimicking the action of estradiols. They affect (sexual) development and responses to diseases.
- β-Propiolactone: Used as plasticizer, in wood processing, tobacco processing, as an additive in leaded gasoline, and insecticides.
- Boric acid: Used for numerous industrial purposes and also as an insecticide and fungicide.

E

- Bracken fern extracts: Bracken ferns may be eaten by grazing animals and they are then exposed to mutagenic and carcinogenic compounds of this plant.
- Cadmium: In nickel-cadmium batteries, paints; an inhibitor of DNA mismatch repair.
- Caffeine: Caffeine itself is not mutagenic or carcinogenic, but it interferes with genetic repair mechanisms.
- Captan: A fungicide.
- Carbontetrachloride: A solvent and seed fumigant.
- Chloral hydrate: A microtechnical reagent and a sedative.
- 2-Chloroethanol: A polymerizing agent, insecticide, and herbicide. It is present in some sedatives.
- Chloroform: A laboratory solvent, found in some office supplies. It may be formed in chlorinated drinking water.
- Chloroprene: Chloroprene is present in elastomers and adhesives.
- Chlorpromazine: Present in some tranquilizers.
- Coal tar: Present in soot, roofing tar, and asphalt (bitumin).
- Colchicine: Used for polyploidization; it is very toxic.
- Cycasin: Present in cycade plants.
- Cyclosporin: An immunosuppressant and antibiotic drug.
- Diamines: Contained by some hair dyes.
- Diazomethane: A laboratory reagent.
- Dichlorvos: An insecticide.
- Diepoxybutane: An industrial polymerization agent; may be present in some pharmaceuticals.
- Diethylene glycol: An industrial chemical; has been used for pharmaceutical products as a counterfeit glycerol substitute and caused fatal poisoning.
- Diethylsulfate: A supermutagen.
- Dimethylsulfate: An industrial methylating agent of cellulose, a polymerizing compound, insecticide, and stabilizer.
- Dioxin: A contaminant in some herbicides and deodorant soaps (now banned).
- Dithranol: Present in some antidermatosis and ringworm drugs.
- EDTA (ethylenediamine tetraacetic acid): A chelator and antioxidant in laboratory and industry.
- Epichlorohydrine: Present in some epoxy resins, gum, paint, varnish, nail polishes, manufacturing crease-resistant fabrics, paper processing, and waterproofing.
- Epoxides: Precursors of ethylene glycol, dioxane, carbowax, monoethanolamine, acetonitrile, plastics, and gaseous sterilants. Epoxides may be trapped in the products or any material in contact with them and may be contaminated.
- Estrogen (β -estradiol): A fertility hormone used in ART and is indirectly carcinogenic. Estrogen-like substances in the environment may adversely affect the reproductive system.
- Ethidium bromide: Used as a nucleic acid stain and as a mutagen for mitochondrial DNA.
- Ethylmethane sulfonate: One of the most widely used and most potent laboratory mutagens.
- Some methanesulfonates are now banned ingredients of older prescription drugs.
- Ethyleneimine: Used for the manufacture of flame-retardant clothing, in crease-resistant and shrinkage controlling of fabrics, in insecticides, soil-conditioners, and synthetic fuels. It is a supermutagen.
- Ethylenedibromide: A fumigant for grain storage.
- Ethylmercuric chloride: A fungicide.
- Fats (after oxidation in rancid food): Such fats may become mutagenic and carcinogenic.
- Formaldehyde: A disinfectant, preservative of museum specimens of animals and organs, fixative, in adhesives, a crease-, crush-, and flame resistance aid in automobile exhausts.
- Fumes: Released by outdoor burning, defective wood-burning fireplaces, and coal furnaces.
- Glycidol: May be present in glycerol; it is used for manufacturing water-repellent fabrics and food preservative. It is a very powerful mutagen.
- Hair-dyes: Certain types are mutagenic/carcinogenic.
- Hydrazines: Found in photographic materials, rocket fuels, preservatives, solvents, and gasoline additives.
- Hydrogen peroxide: Used for bleaching flour, starch, paper, tobacco, cosmetics (hair lightener) stabilizers and plasticizers.
- Hydroxylamine: Used in nylon manufacturing, photographic materials, adhesives, and paints. It converts, specifically, cytosine into a thymine analog.
- Hydroxyurea: Breaks heterochromatin in the chromosomes and is present in some antileukemic, dermatological drugs.
- Isotopic tracers for emitting β and γ radiations.
- Lindane: A fungicide.
- Methylene chloride (dichloromethane): An industrial solvent; also used in food processing.
- Nicotine: An addictive component of tobacco; smoking is a major cause of human cancer.
- Nitrosoamines: Extremely powerful mutagens, but present in small quantities in nitrite treated meat products; formed from nitrites by the action of stomach acids and intestinal microbes.
- Nitrofurans (AF-2): A onetime widely used preservative in Japan for fish and soybean products.
- Nitrogen mustards: Used as anticancer drugs; they are powerful radiomimetic agents.

- Nitrosoguanidines: Extremely potent laboratory mutagens.
 - Nitrous acid: Widely used preservative for meat products, nitrous acid is a direct mutagen and can be converted by mammalian metabolism into nitrosoamines.
 - Organomercurials: Were widely used in fungicides.
 - PCB (polychlorobiphenyls): Present in electric transformers.
 - Perchlorate: A possible pollutant of rocket fuels, which may decrease the level of thyroid hormones and adversely affect brain development.
 - Perfluorooctanoic acid (PFOA/C8): A suspected carcinogen released from some food packaging material (popcorn bags) and overheated Teflon pot lining and other plastics.
 - Peroxides: Bleaching agents, disinfectants; they may be formed from tryptophan under UV.
 - Phenol: Used in DNA extraction. Phenol is extremely toxic and causes vesicles on skin; possibly mutagenic.
 - Phenylmethylsulfonyl fluoride (PMSF): Used in pulsed-field gel electrophoresis. It is very toxic and absorbed through the skin.
 - Phthalates: Plasticizers used in some cosmetics and nail polish.
 - Polybrominated diphenyl ethers: Flame retardants and developmental toxins (neurotoxins) and possible carcinogens.
 - Polychlorinated biphenyls: Once used for various industrial processes and in pesticides.
 - Polycyclic aromatic hydrocarbons: These include volatile, semivolatile and particulate material.
 - Propane sultone: May be present in detergents and dyes.
 - Pyrrolizidine alkaloids: Occur in several species of plants like *Senecio*, *Crotalaria*, etc.
 - Quinacrine: An antimalarial drug.
 - Safrrole: A food additive and coloring agent; it is also present naturally in root beer.
 - Sodium azide: A laboratory reagent and powerful mutagen in some organisms but not in others.
 - Sodium bisulfite: A preservative in fruit juices, wine, and dried fruits.
 - Sodium nitrite: A common preservative of cold cuts, fish and cheese, and can be converted in the body into nitrosoamines.
 - Soot: Contains hydrocarbons such benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene.
 - Streptozotocin: A prescription drug used against athletes' foot fungus; an alkylating agent.
 - Styrene: In reinforced plastics, resins and insulators. It is a clastogen.
 - Tetramethylenedisulphotetramine: Banned rat poison, yet there are sporadic human exposures
 - Thiotepea: Used as a flame retardant, in crease-resistant and water-proof fabrics, and in manufacturing dyes, adhesives and drugs.
 - Trichloroethylene: A weak mutagen that may be present in dry-cleaning agents, degreasing fluids, paints, varnish and food-processing solvents.
 - Triethylenemelamine: A cross-linking agent, used for finishing rayon fabrics, waterproofing of cellophane, insect chemosterilant and in anticancer drugs.
 - Trimethylphosphate: A gasoline additive, insecticide, flame retardant, polymerizing agent, and insect chemosterilant.
 - Tri(2,-3-dibromopropyl) phosphate: A flame retardant.
 - Ultraviolet radiation: May cause skin cancer (melanoma) and mutation in tissues close to the surface; may also be hazardous through the peroxides generated. Wear protective goggles.
 - Urethanes: Used by the plastic industry for manufacturing resins, fibers, textile finishes, herbicides, insecticides, and drugs.
 - Vinyl chloride: The monomer of polyvinyl plastics. May be liberated from the polymers by heat (in a locked-up car) and may contaminate the surface of plastic sheets, bags, water hoses. The monomer is a powerful carcinogen and mutagen requiring metabolic activation. It forms the adduct N²-3-ethenoguanine.
- Many of the mutagens and carcinogens require metabolic activation for effectiveness. There is an inter-individual variability of susceptibility particularly at low degrees of exposure. It has been suggested that the majority of "environmental mutagens" are not the primary cause of mutagenesis/carcinogenesis, rather the endogenous pre-mutations are selected by these agents (Thilly WG 2003 Nature Genet 34:255). UV light, cigarette smoke may be, however, acting directly.
- Ames test, ► mutagen essays, ► bioassays for environmental mutagens, ► mutagenic potency, ► activation of mutagens, ► adduct, ► pseudo-cholinesterase deficiency, ► choline esterase, ► carcinogens, ► air pollution; Waters M et al 1999 Mutation Res 437:21; Albertini RJ et al 2000 Mutation Res 463:111; Johnson FM 2002 Env Mol Mutagen 39:69; <http://toxnet.nlm.nih.gov>, structure-searchable toxicity database: <http://www.epa.gov/nheerl/dsstox>; 1485 compounds of potential carcinogenic potency: <http://potency.berkeley.edu/cpdb.html>, geographic distribution of toxic substances released: ► toxmap; genes and environment initiative: <http://genesandenvironment.nih.gov/>, <http://nationalchildrensstudy.gov/>.
- Environmental Variance:** ► genetic variance, ► environmental deviation

Enzootic: An infection that may be present among animals all the time but which shows up only sporadically or flares up only under certain conditions.

Enzyme: A protein (+ cofactor) that catalyzes (biological) reactions. ► [catalysis](#), ► [enzymes](#)

E

Enzyme Design: The replacement of amino acids in a protein may generate a new biological function (plasticity). Simultaneous incorporation and adjustment of functional elements by insertion, deletion, mutation, and substitution of several active sites into an existing protein scaffold causes new catalytic activity. The introduction of β -lactamase activity into a metallohydrolase scaffold of glyoxalase II resulted in the creation of a new metallolactamase that lost its original activity but catalyzed the hydrolysis of cefotaxime and increased the resistance of *E. coli* to this antibiotic by ~ 100 fold. (Park H-S et al 2006 Science 311:535). Genuinely new enzymatic activities can be created de novo, without the need for prior mechanistic information, by selection from a naive protein library ($>10^{12}$) of very high diversity, with product formation as the sole selection criterion. Ligases have been selected this way with rate enhancements of more than two-million-fold (Seelig B, Szostak JW 2007 Nature [Lond] 448:828). ► [protein engineering](#), ► [glyoxal](#), ► [cefotaxime](#); Dwyer MA et al 2004 Science 3004:1967; divergent evolution of enzymes: Yoshikuni Y et al 2006 Nature [Lond] 440:1078.

Enzyme Induction: Requires the presence of the substrate or substrate analog. ► [Lac operon](#), ► [Arabinose operon](#)

Enzyme-Linked Immunosorbent Assay: ► [ELISA](#)

Enzyme Mimic: A catalytic antibody.

Enzyme Mismatch Cleavage (EMC): An EMC uses the resolvase enzyme of bacteriophages to recognize and cut at mismatches in double-stranded DNA that has been amplified by PCR. The PCR-amplified DNA is expected to have matching and nonmatching strands if there was mismatched in the original double-stranded DNA. This way heterozygosity or mutation may be detected after gel electrophoresis. ► [resolvase](#), ► [mismatch](#), ► [mutation detection](#)

Enzyme Replacement Therapy: Gaucher disease is caused by deficiency of the enzyme glucocerebrosidase/glucosylceramidase. In patients, the infusion of macrophages carrying the enzyme one to four times a week or twice a month, significantly improved most of the symptoms (Barton NW et al 1991 New

Engl J Med 324:1464; Weinreb NJ et al 2002 Am J Med 113(2):112). Clinical trials are underway for Fabry disease (Schiffmann R et al 2001 J Am Med Assoc 285:2743), mucopolysaccharidoses (Kakkis ED 2002 Expert Opin Investig Drugs 11:675), Pompe disease (Amalfitano A et al 2001 Genet Med 3(2):132), and other lysosomal storage diseases. Research is underway for the treatment of phenylketonuria with recombinant phenylalanine hydroxylase (Gamez A et al 2004 Mol Ther 9:124). ► [Gaucher disease](#), ► [Fabry disease](#), ► [mucopolysaccharidosis](#), ► [glycogen storage diseases](#), ► [phenylketonuria](#), ► [gene therapy](#), ► [blood-brain barrier](#)

Enzymes: Enzymes, in general, are protein molecules. Some ribonucleic acids and DNAs also have enzymatic functions (ribozymes, DNA-zymes). The protein part of the enzyme is the apoprotein or apoenzyme. Their catalytic function may require cofactors, such as metals (Cu^{2+} , Fe^{2+} , K^{+} , Mg^{2+} , Mn^{2+} , Mo^{3+} , Zn^{2+} , etc.) or organic compounds (vitamins, nucleotides, etc.) called coenzymes, also called the prosthetic group of the enzymes. The complete enzyme (apoenzyme + prosthetic group) is the holoenzyme. Enzymes are organic catalysts; they mediate biochemical reactions without becoming parts of the reaction products, and enhance the reaction rates by $\sim 10^{10}$ to 10^{15} fold. The site(s) of the enzyme molecule interacting with the substrate (the molecule to be acted on) are the active sites of the enzymes. Enzymes carry out gene functions. RNA is transcribed on the DNA and the RNA is translated into a protein. Enzymes are named by adding “ase” to either the name of the substrate or to the name of the reaction, e.g., DNase, phosphorylase. The International Union of Biochemistry (*Enzyme Nomenclature*, 1972, Elsevier, Amsterdam) classified enzymes into six major groups and assigned code names to them. The six groups are 1. *oxidoreductases* (transfer electrons); 2. *transferases* (catalyze molecular group transfers); 3. *hydrolases* (cleave covalent bonds and transfer H and OH, respectively to the products); 4. *lyases* (form or remove double bonds); 5. *isomerases* (rearrange molecules internally); 6. *ligases* (mediate condensations by forming C-C, C-N, C-O and C-S bonds while cleaving ATP). In technical descriptions, enzymes are identified by EC (enzyme classification) numbers where the first digit refers to the number of one of the above groups and the following digits specify more closely the nature of the reaction mediated, thus DNA polymerase I of *E. coli* has the EC number 2.7.7.7, whereas restriction endonuclease Eco RI is 3.1.21.4., bovine RNase is 3.1.27.5 and glucose-6-phosphate dehydrogenase is 1.1.1.49. Some enzymes are modular, i.e., they may have interchangeable components with other enzymes

or may be components in different catalytic complexes. ►protein synthesis, ►inhibition, ►repression, ►induction, ►allosteric control, ►competitive inhibition, ►effector, ►Michaelis Menten equation, ►Lineweaver Burk equation, ►Eadie Hofstee plot, ►regulation of enzyme activity, ►subunits, ►recombination mechanisms, ►restriction endonucleases, ►ribozymes, ►enzymes multifunctional, ►DNA-zyme, ►BRENDA; Nature (Lond) 409 [2001]:225 ff on biocatalysis, action theory: Garcia-Viloca M et al 2004 Science 303:186; kinetics and energetics: Kraut DA et al 2003 Annu Rev Biochem 72:517; nomenclature database: <http://www.expasy.ch/enzyme/>; amino acid interactions, ligands (substrate, cofactors, inhibitors, etc.): <http://precise.bu.edu/>; catalytic mechanisms: <http://mbs.cbrc.jp/EzCatDB/>; <http://www.ebi.ac.uk/thornton-srv/databases/MACiE/>.

Enzymes, Multifunctional: During the 1940s, the then revolutionary one gene-one enzyme theory was proposed. Since then it has been recognized that the attachment of different prosthetic groups and altering of active sites, using different promoter sites, alternate processing, post-translational modifications, etc., may contribute to the production of different proteins from the same DNA sequence (Perham RN 2000 Annu Rev Biochem 69:961).

Eomes (comesodermin): ►eomesodermin

Eomesodermin (Eomes): A transcription factor attaching to a T box (see MAR) and regulating trophoblast and mesoderm development in mice. Eomes and T-bet are 74% identical in their T-box region. T-bet is a key factor of activation of effector CD8⁺T lymphocytes defending against viruses, intracellular microbes, and tumors. Translocation involving human chromosomes 3p and 10q leads to microcephaly and other brain defects (Baala L et al 2007 Nature Genet 39:454). ►trophoblast, ►mesoderm, ►T cell, ►T-bet, ►T-box, ►memory immunological; Pearce EL et al 2003 Science 302:1041.

Eosinophil: The white blood cells (readily stainable by eosin dye) generally display a bilobal large nucleus. They modulate allergic and inflammatory reactions of the animal body and mediate the destruction of parasites(see Fig. E37). ►granulocytes, ►blood



Figure E37. Eosinophil

Eotaxin: A C-C type chemokine. ►chemokines

EP: Effector proteins stimulate the conversion of E.GTP into E.GDP. ►GTP, ►GDP

EP (early pressure): Early pressure in zebrafish gynogenetic embryos is produced by exposing early embryos, fertilized by UV-inactivated sperm, to high hydrostatic pressure immediately after fertilization to suppress the second meiotic anaphase. A heat shock, 15 minutes after fertilization, suppresses the first mitotic division and leads to gynogenesis. ►gynogenesis, ►zebrafish, ►UV

EPA: RAP1.

e-PCR (electronic PCR): An electronic PCR can be used to search for matches to STS primer pairs in the UniSTS database (forward e-PCR) or to estimate the genomic binding site, amplicon size and sets of primer pairs by searching against genomic and transcript databases of some major genetic organisms (reverse e-PCR). ►PCR, ►STS, ►UniSTS, ►amplicon; <http://www.ncbi.nlm.nih.gov/sutils/e-pcr>.

Ependymoma: The brain or spinal chord covering membrane neoplasia.

EPH (ephrin): A family of receptor tyrosine kinases involved in axon guidance and synaps regulation of integrin, cell migration, embryo differentiation and indirectly signals to the cytoskeleton. The EPH proteins guard against mixing of different cell types (rhombomeres) during early embryonal development of animals. They form two subclasses, EphA and EphB. The EphA receptors are connected by ephrin-A ligands (glycosyl-phosphatidylinositol) to the cell membrane. The EphB receptors use ephrin-B ligands. EphB receptors regulate excitatory synapses by interacting with NMDA receptors. Alternative splice forms of a tyrosine kinase receptor control adhesion or repulsion of cells during embryogenesis. These ligands have different names in different organisms and tissues. The Ephrin-A/Eph-A receptor signaling negatively regulates brain size of mice by apoptosis; loss of Eph-A function reduces apoptosis of neural progenitor cells and increases cortical size of the brain and sometimes exencephalic outgrowth (Depaepe V et al 2005 Nature [Lond] 435:1244). EphrinB receptors coordinate migration and proliferation in the intestinal stem cell niche (Holmberg J et al 2006 Cell 125:1151). EphrinB2 specifically binds the attachment glycoprotein of the Nipah virus (paramyxovirus) and facilitates its infection of a wide range of mammals, including humans. In humans, the virus causes encephalitis with a 70% fatality (Negrete OA et al 2005 Nature [Lond] 436:401). ►tyrosine protein, ►kinase, ►receptor, ►tyrosine kinases, ►netrin, ►neurogenesis, ►synaps, ►rhombomeres,

► **integrin**, ► **NMDA receptor**, ► **paramyxovirus**; Drescher U 2000 *Cell* 103:1005; Wilkinson DG 2001 *Nature Rev Neurosci* 2:155; Cowan CA, Henkemeyer M 2001 *Nature [Lond]* 413:174; Takasu MA et al 2002 *Science* 295:491; Kullander K, Klein R 2002 *Nature Rev Mol Cell Biol* 4:475; Foo SS et al 2006 *Cell* 124:161.

E

Ephedra (ephedrin): A plant alkaloid used as a dietary supplement for weight control. Unfortunately it is not entirely safe because it may cause hypertension, increased heartbeat (tachycardia), stroke and occasionally death. Dietary supplements containing Ephedra were ordered off the markets in November 2004 by the FDA (Federal Drug Administration USA).

Ephelides: ► **freckles**

Ephrim: ► **EPH**

Epiallele: A developmentally changed allele usually without DNA alteration; it may also arise as the result of mitotic gene conversion or recombination. ► **epigenesis**, ► **epimutation**; Rakyen VK et al 2002 *Trends Genet* 18:348.

Epiblast: The precursor of the ectoderm and other embryonal tissues. The epiblast of the inner cell mass of the pre-blastocyst is a good source of stem cell isolation, although the stage of the stem cells may have different developmental potentials (Tesar PJ 2005 *Proc Natl Acad Sci USA* 102:8239). ► **ectoderm**, ► **organizer**, ► **blastocyst**, ► **stem**, ► **cells**

Epiboly: The first embryonic cell movement whereby the upper portion of the yolk bulges in the direction of the animal pole, resulting in the formation of a dome. The blastoderm cells begin spreading dorsally over the yolk until the cell sheet meets at the ventral midline. During zebrafish epiboly, the chimerin family Rac-GAP (Rac-GTPase activating protein) modulates epiboly. Essential modules are involved with GTPase activity and binding of the lipid second messenger diacylglycerol and phorbol esters (Leskow FC et al 2006 *Proc Natl Acad Sci USA* 103:5373). ► **morphogenesis in *Drosophila***, ► **notochord**, ► **RAC**, ► **diacylglycerol**, ► **phorbol**; Marsden M, DeSimone DW 2001 *Development* 128:3635.

Epicanthus: Vertical skin folds near the eyelid; it is a normal characteristic for some oriental human races and some syndromes affect it also. ► **Down syndrome**, ► **ptosis**, ► **Forkhead**

Epichromosomal: Outside the chromosomes; an epichromosomal vector does not integrate into the chromosome and thus does not cause insertional mutation, but it may not be able to replicate continuously.

► **vectors**, ► **insertional mutation**; Rajcan-Separovic E et al 1995 *Hum Genet* 96:39.

Epicotyl: The stem section immediately above the cotyledons of plant embryos and seedlings.

Epidemiology: The study of the distribution, cause and modifying factors of diseases and genetic defects in human and other populations. ► **population genetics**, ► **founder effect**, ► **genetic drift**, ► **inbreeding**, ► **occupational hazard**, ► **mutation detection**, ► **genetic toxicology**, ► **case-case design**, ► **infection**; Ioannidis JP et al 2006 *Nature Genet* 38:3; Human Genome Epidemiology Network (HuGENet): <http://www.cdc.gov/genomics/hugenet/default.htm>, Western Australian resources: <http://www.wager.org.au>.

Epidemiology, genetic: Genetic epidemiology studies the distribution of genetic variations of hereditary diseases, using primarily molecular tools such as blood groups, RFLP, and SNP. ► **blood groups**, ► **RFLP**, ► **SNIP**, ► **linkage**, ► **disequilibrium**, ► **epidemiology**; Bonassi S, William WA 2002 *Rev Mut Res* 511:73.

Epidermal growth factor: ► **EGF**

Epidermis: The nonvascular outer cell layer, derived from the embryonal ectoderm of animals; the surface cell layer of plants. In mouse, epidermal cells deletion of the guanosine triphosphatase Rac1 stimulates terminal differentiation and depletes stem cells required for the maintenance of interfollicular epidermis, hair follicles and sebaceous glands. This effect of Rac1 takes place by negative regulation of c-Myc though p21-activated kinase, PAK2. In this regulation cell adhesion and the cytoskeleton play an important role (Benitah SA et al 2005 *Science* 309:933). In higher animals there is an integument, the stratum corneum (a horny [calloused] layer of dead cells), and in insects, the cuticle for the protection of cell layers beneath. Wounding by microbes provokes an immune response to neutralize the infection and activate nuclear genes involved in protection against pathogens and healing the defect. In plants (*Arabidopsis*), the epidermis controls shoot growth and it is mediated by the presence of brassinosteroid receptor or brassinosteroid synthetic enzymes that are not present in the vasculature (Savaldi-Goldstein S et al 2007 *Nature [Lond]* 446:199). ► **RAC**, ► **PAK**, ► **Myc**, ► **CAM**, ► **cytoskeleton**, ► **brassinosteroids**; Mace KA 2005 *Science* 308:381.

Epidermoblast: Gives rise to the epidermal cells.

Epidermolysis: The dissolution of the skin in spots resulting in blisters (bullae) such as ichthyosis, keratosis, pemphigus, acrodermatitis, porphyria, etc. (see Fig. E38).



Figure E38. Epidermolysis bullosa. (From Bergsma D ed. 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

It is a characteristic symptom of many hereditary skin diseases. The epidermolysis bullosa simplex is encoded in human chromosome 8q24.13-qter and it is caused by mutation in plectin, whereas a similar disease of mouse is associated with a defect in integrin. Junctional epidermolysis bullosa may be due to mutation either in collagen (Col17A1) or laminin protein subunits or in both. Epidermolysis bullosa is a very complex disorder due to defects at 1q32, 1q25-q31, 3p21.3, 10q24, 12q13, 17q11-qter, 17q12-q21. ▶skin, ▶diseases, ▶collagen, ▶intermediate, ▶filaments, ▶plectin, ▶integrin, ▶collagen, ▶laminin; Fine JD et al 2000 J Am Acad Dermatol 42:1051; Ortiz-Urda S et al 2005 Science 307:1773.

Epididymis: A narrow pouch-like structure attached to the testis; it serves for storage, maturation, and forwarding the spermatozoa into the vas deferens during ejaculation. ▶cryptorchidism

Epifluorescence: Epifluorescence is used by special microscopy when the high intensity UV, blue, yellow, or red light is transmitted to the specimen through the objective rather than directly. Only the reflected excitatory light is filtered providing much higher intensity through the eyepieces of the microscope. The techniques generally use appropriate filters and fluorescent dyes for histology, microbiology, and molecular biology.

Epigene conversion: If the gene is introduced into the genome in an additional copy (by transformation of plants) that is hypermethylated, the other copy is silenced by transcription because the methylated promoter is, presumably, imposed on the unlinked promoter. ▶co-suppression, ▶silencer

Epigenesis: The process by which differentiation takes place from undifferentiated cells as programmed by the genome, without any mutational event (base substitution). It is sometimes defined as the mechanism of different types of gene expression from the same nucleotide sequences due to structural changes

in the chromatin and cooperative effect of transcription factors, other regulatory elements and methylation of the gene(s). Typical examples are the different functions of neurons and hepatocytes or plant roots and petals despite the identity of their genome. Epigenetic regulation is somewhat different from the controls of transcriptional activators and repressors that may be subject to great fluctuations. Epigenetic alterations are more stable, involving covalent modifications of the nucleotides and histones—for e.g., by methylation—that are submitted from cell to cell during mitosis and sometimes persist through meiosis. Movement of transposable elements is often considered an epigenetic event despite the fact that it may reorganize and alter the genome. Some mechanisms of gene silencing and activation, such as acting on methyl transferases, histone deacetylases including the action of siRNA are also considered epigenetic (Egger G et al 2004 Nature [Lond] 429:457). It is expected that during meiosis the epigenetic alterations would be erased and, subsequently, reversion take place at the embryonic stage. In fission yeast the mating type conversion genes (*mat*) are, however, transmitted not just mitotically but meiotically too. Similar examples in higher organisms are the paramutant state, imprinting, the position type variegation and paramutation. Meiotic transmission of the epigenetic state has been observed in fission yeast and *Drosophila* that do not methylate DNA much. Hyperacetylation of histone 4 (H4) may be involved in the transmission of the epigenetically activated state. Upregulating genes may have therapeutic value but may have complex and unforeseeable deleterious effects. Epigenetic alterations have decisive roles in carcinogenesis and in the development of various human diseases. CpG island promoter hypermethylation represses tumor suppressor genes, and hypoacetylated and hypermethylated histone H4 transcriptionally silences these genes. Tumor suppressor p21^{WAF1}/CDKN1A and some other tumor suppressors may not even need the CpG hypermethylation for their silencing. In cancer cells H4 lysine 16 residue is acetylated and Lys20 is trimethylated as a general feature of the tumorous condition (Fraga MF et al 2005 Nature Genet 37:391). The epigenetic state of genes can be mapped. Lysine 4 and lysine 27 trimethylation effectively discriminates genes that are expressed, poised for expression, or stably repressed, and therefore reflect cell state and lineage potential. Lysine 36 trimethylation marks primary coding and noncoding transcripts, facilitating gene annotation. Trimethylation of lysine 9 and lysine 20 is detected at satellite, telomeric and active long-terminal repeats, and can spread into proximal unique sequences. Lysine 4 and lysine 9 trimethylation marks imprinting control regions. The chromatin state can be read in an

allele-specific manner by using single nucleotide polymorphisms (Mikkelsen TS et al 2007 Nature [Lond] 448:553). ▶preformation, ▶reaction norm, ▶position effect, ▶imprinting, ▶bivalent, ▶promoter, ▶uniparental disomy, ▶mating type determination, ▶CpG motif, ▶methylation of DNA, ▶PAD4, ▶prion, ▶RIGS, ▶co-suppression, ▶peloric, ▶paramutation, ▶RIP, ▶MIP, ▶RIGS, ▶RNAi, ▶RdRP, ▶histones, ▶histone methyltransferases, ▶histone deacetylases, ▶histone, ▶demethylase, ▶histone variants, ▶p21, ▶histone code, ▶heterochromatin, ▶phenocopy, ▶morphosis, ▶RLGS, ▶reprogramming, ▶CpG, ▶islands, ▶lyonization, ▶insulator, ▶Polycomb, ▶SET motifs, ▶non-coding DNA, ▶noncoding RNA, ▶Beckwith-Wiedemann syndrome, ▶Prader-Willi syndrome, ▶Angelman syndrome, ▶Albright hereditary osteodystrophy, ▶Rett syndrome, ▶immunodeficiency [ICF], ▶ATR-X, ▶Rubinstein syndrome, ▶cancer; Lindroth AM et al 2001 Science 292:2077; Jones PA, Takai D 2001 Science 293:1068; Martienssen RA, Colot V 2001 Science 293:1070; Schreiber SL, Bernstein BE 2002 Cell 111:771; epigenesis in plants: Henderson IR, Jacobsen SE 2007 Nature [Lond] 447:418; epigenesis in mammalian development: Reik W 2007 Nature [Lond] 447:425; epigenetic bases of human disease: Feinberg AP 2007 Nature [Lond] 447:433; human epigenome project: <http://www.epigenome.org/>.

Epigenetic: A phenotypic change that may not be inherited because it is not based on changes in the genome. It is within the range of expression of genes. Much of epigenetic phenomena are based on differential methylation of the DNA during the life of the cell or organism or alteration in chromatin structure. Some of the methylation may be transmitted, however, by either the maternal or both maternal and paternal mouse parents (Rakyan VK et al 2003 Proc Natl Acad Sci USA 100:2538). DNA methylation at *cis*-regulatory sequences determines whether gene expression is on or off. Stable inheritance of these expression states is required in bacterial pathogenesis, cancer, and developmental pathways. In *Escherichia coli*, the *agn43* gene (encoding an outer membrane protein, antigen 43 involved in biofilm formation) exercises control. Systematic disruption of this system shows that a functional switch requires the presence of several, rarely occupied, intermediate states that separate the “on” and “off” states. Cells that leave the on and off state enter different intermediate states, where there is a strong bias that drives cells back to their original state. The intermediate states act as buffers that prevent back and forth switching (Lim HN, van Oudenaarden A 2007 Nature Genet 39:269). ▶reaction norm, ▶cortical inheritance, ▶epimutation, ▶histones,

▶histone code, ▶soft inheritance, ▶RLGS, ▶nucleolar dominance, ▶X chromosome inactivation, ▶paramutation; Surani MA 2001 Nature [Lond] 414:122; Petronis A 2001 Trends Genet 17:142; Richards EJ 2006 Nature Rev Genet 7:395.

Epigenetic Landscape: The course of development of different cell types from the fertilized egg without changes in the base sequences in the DNA. ▶epigenesis

Epigenetic Memory: Cells may propagate for many cell divisions and maintain an “on-state” of gene expression in the absence of conditions that induced them. Thus, cells can inherit the differentiated state of the same cell lineage and may cause developmental abnormalities after somatic cell nuclei are transferred to enucleated oocytes. Normally about 1% of differentiated amphibian cells yield feeding tadpoles and less than 3% of the mammalian cloned embryos develop into live birth. The incomplete reprogramming of the epigenetic state can cause developmental abnormalities and premature death (Ng RK, Gurdon JB 2005 Proc Natl Acad Sci USA 102:1957). Histone 4 K29me is mediated by enzyme PRE-SETZ and Histone 3 K27me is mediated by EZH2 enzymes, respectively. These methyl sites are not demethylated and have good chance for transmission through meiosis (Trojer PO, Reinberg D 2006 Cell 125:213). *Plasmodium falciparum* has about 60 *var* genes for antigens at various locations within their chromosomes; however, parasite isolates contain different complements of *var* genes and, thus, the gene family is enormous with a virtually unlimited number of members. A single *var* gene is expressed by each parasite in a mutually exclusive manner and control of *var* gene transcription and antigenic variation is associated with a chromatin memory that includes methylation of histone H3 at lysine K9 as an epigenetic mark. This epigenetic mechanism contributes to evasion of the host defense system (Chookajorn T et al 2007 Proc Natl Acad Sci USA 104:899). ▶nuclear transplantation, ▶histones, ▶*Plasmodium*, ▶antigenic variation; Ringrose L, Paro R 2004 Annu Rev Genet 38:413.

Epigenetic Shift (epigenetic drift): The identity of monozygotic twins tends to be reduced during the process of aging due to different methylation of DNA, chromatin remodeling, changes in the position of transposable elements, increase in the relative proportion of memory T cells and, to a lesser degree, by somatic mutation. ▶Twinning; Martin GM 2005 Proc Natl Acad Sci USA 102:10413.

Epigenetics: The area of study of epigenesis, epigenetic phenomena, and epimutation. Conrad Waddington argued for the term in 1942 although Theodore

Boveri had already concluded in 1903 that “*alle essentiellen Merkmale...epigenetisch sind und daß die Determinierung ihrer Specialität durch den Kern erhalten*” (i.e., “all traits are epigenetic and the determination of their characteristics is derived from the nucleus”). In modern terms it means the study of the changes in the chromatin (or in prion proteins) which permit different patterns of gene expression from the same nucleotide sequence of the genome. Epigenetic changes do not alter the nucleotide sequence, yet the alterations may be transmitted through mitosis and meiosis. Epigenetics is important for both development and for disease. ►epigenesis, ►imprinting, ►paramutation, ►chromatin remodeling, ►methylation of DNA, ►heterochromatin, ►histones, ►histone code, ►RNAi, ►reprogramming, ►mating type determination in yeast, ►prion, ►stem cells, ►acquired characters, ►developmental-regulator effect variegation; Rubin H 2001 Science 294:2477; Shilatifard A 2006 Annu Rev Biochem 75:243; Ruthenburg AJ et al 2007 Mol Cell 25:15; Cell review issue 2007 Vol 128 ([4]).

Epigenome: The differentiated genome, including epigenetic changes. The epigenetic changes are mediated primarily by methylation/demethylation of cytosine and modification of histones (Bernstein BE et al 2007 Cell 128:669). ►epigenesis; Brena RM et al 2006 Nature Genet 38:1359.

Epigenomics: ►genomics

Epigyny: The plant ovary being embedded in the flower receptacle, with other flower organs above it. ►flower differentiation, ►receptacle

Epilepsy: Suddenly recurring impairment of consciousness, involuntary movements, nervous disturbances occurring simultaneously or separately, caused by acquired or genetic factors. Epilepsy is a very complex paroxysmal disorder affecting 1–2% of the world's population. Some seizures may occur in early infancy while others are triggered by light (photogenic epilepsy) or by reading. According to one study, among 27 monozygotic twins, 10 pairs were both affected (concordant) and 17 pairs were not, and among 100 dizygotic twins, only 10 pairs had it both. Thus some epilepsies appear to have a strong genetic component (heritability, $h^2 > 0.40$). *Grand mal* epilepsy is a severe form of seizures occurring in 4–10% of epileptics and it generally develops fully by adult age. *Petit mal (absence)* epilepsy is a milder form and it is less frequent. In mouse a similar mutation in the γ subunit of a Ca^{2+} ion channel (VS.) is responsible for the *stargazer* epileptic phenotype. The *autosomal dominant nocturnal frontal lobe epilepsy* (ADNFLE, human chromosome 20q13.2-q13.3) is caused by mutation in the neural nicotinic

acetylcholine receptor $\beta 2$ subunit. *Idiopathic epilepsy* is not associated with detectable brain lesions, whereas *symptomatic epilepsy* (acquired epilepsy) may be the consequence of a definable brain injury or disease. Idiopathic epilepsy is caused by mutation in the GABA_A receptor $\gamma 2$ -subunit (Baulac S et al 2001 Nature Genet 28:46). The same molecular defect is responsible for the “childhood absence epilepsy”, CAE and “febrile seizures” (Wallace RH et al ibid. p 49). Recessive single gene mutation can cause infancy-onset mutation in the GM3 gene GM3). Some seizures or spasms are associated with a number of genetic maladies (phenylketonuria, epiloia, Zellweger syndrome, Menke's syndrome, ceroid lipofuscinosis, adrenal hypoplasia, multiple sclerosis, glycogen storage diseases, lysosomal storage diseases, myoclonic epilepsy, porphyria, glutamate decarboxylase deficiency, rickets, galactosemias, Friedreich ataxia, West syndrome, Lesch-Nyhan syndrome). A gene for partial epilepsy was located to human chromosome 10q. *Familial partial epilepsy with variable foci* (FPEVF) was assigned to 22q11-q12. The rare recessive *pyridoxine dependent epilepsy* has been mapped to 5q13; it responds favorably to pyridoxine. The underproduction of γ -aminobutyrate (GABA, 5q31), a molecule with an important role in neurotransmission, may also lead to epileptic seizures and encephalitis. A rare but severe form of childhood epilepsy is caused by autoantibodies that turn against the brain's glutamate receptors. A homologue of this gene is found at 8q24. A voltage-gated sodium ion channel $\beta 1$ subunit gene mutation in human chromosome 19q13.1 is one of the causes of *generalized epilepsy with febrile seizures plus* (GEFS⁺). A second (GEFS⁺) locus was found at 2q24-q33. Febrile seizures were associated also with chromosome 8q13 region. Myoclonus epilepsy with ragged red fibers (MERRF) is determined by mitochondrial defects. The myoclonic epilepsy (EPM1) in human chromosome 21 is based of repeat insertions. *Idiopathic epilepsy* is characterized by seizures, which apparently show no metabolic, structural cause, yet has a relatively high heritability. *Benign familial neonatal convulsion* (BFNC) diseases are attributed to defects in human chromosome 20q13.3, encoding a potassium channel (KCNQ2/KCNQ3). *Benign adult familial myoclonic epilepsy* is at 8q23.3-q24.1. *Familial recessive idiopathic myoclonic epilepsy of infancy* maps to 16p13. About 40 different types of epileptic syndromes have been described. Epilepsy also occurs in animals; in chickens it is controlled by a single recessive gene with reduced penetrance. The *unc (uncoordinated)* mutants of the nematode, *Caenorhabditis* are also affected in GABA-mediated functions. Many famous people, Julius Caesar, Bonaparte Napoleon, the great Russian novelist Fedor

Mikhailovich Dostoyevski, and the famous French novelist Gustave Flaubert suffered from the disease (Gastaut H et al 1984 *Epilepsia* Oct 25[5]:622). (See disease mentioned under the specific entries, ►mitochondrial disease in humans, ►autoimmune diseases, ►seizures, ►glutamate decarboxylase deficiency disease, ►ion channel, ►GABA, ►paroxysmal, ►myoclonic epilepsy; Meisler MH et al 2001 *Annu Rev Genet* 35:567; Haug K et al 2003 *Nature Genet* 33:527; Leppert M F, Singh NA 2003 *Annu Rev Genomics Hum Genet* 4:437; synaptic transmission: Fukata Y et al 2006 *Science* 313:1792; <http://www.epilepsyfoundation.org/gene/>; <http://www.carpedb.ua.edu>).

Epilobium: A herbaceous plant species ($2n = 36$) in the family of *Onagraceae* distributed widely in Europe, Asia, and Africa. It became a favorite organism for the study of nonnuclear inheritance since the early decades of this century. A variety of cytoplasmic mutations were discovered in the different species that were transmitted maternally. The identity of the cytoplasmic genetic material (plasmon) was preserved even when *Epilobium luteum* \times *E. hirsutum* was backcrossed with *E. hirsutum* for 25 generations and less than 3×10^{-8} chance remained for the presence of *E. luteum* genes in the nucleus. Some of the information indicated, however, an interaction between nuclear genes and cytoplasmic genetic elements (plasmon-sensitive genes). Some of the cytoplasmic elements were assigned to the plastids and the others were presumably present in the mitochondria. These nonnuclear genes affected pigment variegation, male and female fertility, and a number of morphological changes of the leaf, plant height, etc. From the developmental patterns of the cell lineages (sector formation and sector size), the number of plasmon and plastome (chloroplast-coded elements) were estimated. It was a tragic fact that after the retirement and death of the primary research worker, Peter Michaelis, the majority of the *Epilobium* mutants were lost because of the lack of an organized system for their maintenance. *Epilobium* species also attracted pharmacological interest. ►*Oenothera*; Michaelis P 1965 *Nucleus* 8:83; Battinelli L et al 2001 *Farmaco* 56[5-7]:341; <http://plantsdatabase.com/genus/Epilobium/>.

Epiloia (tuberous sclerosis, TSC): Epiloia is caused by more than one dominant gene; human chromosomes 9q34.3 (TSC1), 3p26 and 12q23, 16p13.3 (TSC2) have been implicated (see Fig. E39). Its prevalence is about 2×10^{-4} . Characteristic symptoms are seizures, mental retardation, papules on the face, low pigmented spots on the trunk and limbs, etc. Inactivation of either TSC1 or TSC2 results in increased cell size. TSC2 coordinates AMPK and GSK3 mediated

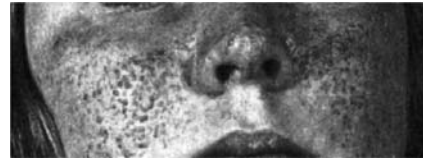


Figure E39. Epiloia

phosphorylation and regulates cell growth (Inoki K et al 2006 *Cell* 126:955). In mutant cell lines the level of Cyclin E and Cyclin A is higher and that disturbs the cell cycle (Tapon N et al 2001 *Cell* 105:345). The symptoms may vary substantially, yet mental retardation is apparent in 50% of the afflictions. Brain nodules may be revealed by tomography for diagnosis even in individuals who are otherwise non-symptomatic. The majority of the cases are due to new mutations, thus sibs may have no risk of recurrence. When the anomaly is present in the pedigree the recurrence risk may approach 50% although the penetrance may be incomplete. The TSC1 encoded protein, hamartin, is about 130 kDa. TSC2 encodes the 200-K protein tuberin. The two proteins apparently affect the insulin-signaling pathway. TSC1-TSC2 inhibit ribosomal protein kinase S6 and activate the eIF-4E-binding protein (4E-BP1), an inhibitor of translation initiation. Phosphorylation of TSC by ERK may inhibit TOR signaling and oncogenic cell proliferation (Ma L et al 2005 *Cell* 121:179). In breast cancer cells, Akt-1 phosphorylates TSC2 resulting in reduced Rho-GTPase activity and reduced focal cell adhesion, motility, and invasion. Overexpression of TSC2 results in increased cell motility and metastasis indicating that oncogenes and tumor suppressors effects are expressed in cellular context. These facts must be considered in therapy (Liu H et al 2006 *Proc Natl Acad Sci USA* 103:4134). ►mental retardation, ►tomography, ►S6 kinase, ►ERK, ►TOR, ►eIF-4E, ►tuberous sclerosis, ►Akt, ►RHO, ►oncogene, ►AMPK, ►GSK3; Dabora SL et al 2001 *Am J Hum Genet* 68:64; Inoki K et al 2002 *Nature Cell Biol* 4:648, [photo by courtesy of Dr. C. Stern, after Dr. V. McKusick].

Epimastigote: ►*Trypanosoma*

Epimers: Stereoisomeric compounds that differ at one asymmetric configuration, e.g., glucose and mannose or ribulose 5'-phosphate and xylulose 5'-phosphate; they are reversibly interconverted by epimerase enzymes. ►enantiomorph

Epimorphosis: A cell-division-requiring regeneration of surface structures of animal cells. ►morphallaxis, ►regeneration in animals

Epimutagenic: A physiological factor that causes epigenetic alteration. ►[epigenesis](#)

Epimutation: An epigenetic change during development without change in the DNA sequence. Usually, the epimutation, based on methylation of certain segments of the DNA, is erased by passing through the germline. Epimutation in the somatic cells may be reverted during aging (Bennett-Baker PE et al 2003 Genetics 165:2055), yet in some instances it may be transmitted through meiosis (Frevel MA et al 1999 J Biol Chem 274:29331).

The somatic epigenetic state of the agouti A^{vy} allele is affected by in utero methyl donor supplementation only when the allele is paternally contributed. Exposure to methyl donor supplementation during mid-gestation shifts A^{vy} phenotypes not only in the mice exposed as fetuses, but in their offspring too. This finding indicates that methyl donors can change the epigenetic state of the A^{vy} allele in the germ line, and that the altered state is retained through the epigenetic resetting that takes place in gametogenesis and embryogenesis. Thus, a mother's diet may have an enduring influence on succeeding generations, independent of later changes in diet (Cropley JE et al 2006 Proc Natl Acad Sci USA 103:17308). Epimutation has also been reported in humans; it is generally difficult to prove its transmission to following generation(s) (Horsthemke B 2007 Nature Genet 39:573). "Heritable germline epimutation" describes an atypical epigenetic state that occurs in all tissues of an individual (hence the adjective "germline") and one that is detected in more than one generation. "Transgenerational epigenetic inheritance" is the direct transfer of epigenetic information across generations. Heritable germline epimutation may or may not be the result of transgenerational epigenetic inheritance (Chong S et al 2007 Nature Genet 39:574). ►[epigenesis](#), ►[epiallele](#), ►[imprinting](#), ►[transgenerational effect](#), ►[methylation of DNA](#), ►[peloric](#), ►[directed mutation](#); Suter CM et al 2004 Nature Genet 36:497.

Epinasty: The downward bending of a plant organ because of the more rapid division of the upper cell layer(s) (see Fig. E40). Hyponasty is the opposite phenomenon.

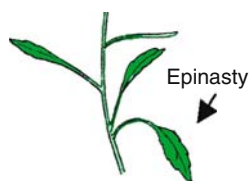


Figure E40. Epinasty

Epinephrine (adrenaline): An animal hormone, produced by the kidney (adrenal medulla). When it binds to specific transmembrane receptors of the G_s proteins, they may be phosphorylated to the G_{sa} - GTP form facilitating the activation of the adenylate cyclase enzyme which produces 3', 5' cyclic AMP. cAMP mediates the function of protein kinase A, setting into motion a cascade of protein phosphorylations and resulting in the activation of glycogen synthase, phosphorylase b kinase (causing glycogen breakdown), acetyl coenzyme A, carboxylase (required for the synthesis of fatty acids), pyruvate dehydrogenase (oxidation of pyruvate to acetyl-CoA), triacylglycerol lipase (resulting in mobilization of fatty acids in the mitochondria and plant peroxisomes), phosphofructokinase and fructose-2,6-bisphosphatase (involved in glycolysis and gluconeogenesis). ►[G_s](#), ►[adenylate cyclase](#), ►[phosphorylase a](#), ►[β-adrenergic receptor](#), ►[axon guidance](#), ►[neurotransmitter](#), ►[animal hormones](#)

Epiphyseal Dysplasia, Multiple (MED): Human chromosome 20q13.3 dominant defect in the α -chain of type IX collagen that involves early-onset of osteoarthritis, walking defects and short stature. It is a sulfate transporter. A recessive form is caused by mutation in the diastrophic dysplasia (5q32-q33.1) sulfate transporter. There is apparently a dominant MED gene at 2p24-p23 encoding matrilin 3, an oligomeric protein of the cartilage matrix containing a von Willebrand factor A type protein domain. Several different mutations have been identified at multiple loci for collagen and thus cartilage defects. ►[collagen](#), ►[arthritis](#), ►[diastrophic dysplasia](#), ►[von Willebrand disease](#); Chapman KL 2001 et al 2001 Nature Genet 28:393; Czarny-Ratajczak M et al 2001 Am J Hum Genet 69:969.

Episomal vector: ►[yeast episomal vector](#), ►[transformation genetic](#)

Episome (plasmid): The dispensable genetic element in bacteria that can exist in a free state within the cell or be integrated into the main genetic material, comprising a couple of thousand to a few hundred thousands of nucleotides. A typical episome is the bacterial sex plasmid (F); the temperate phages also behave like episomes. Originally, the term was coined for a hypothetical chromatin attached to the *Drosophila* chromosome. Plasmids of prokaryotes and eukaryotes are also considered as episomes. Some plasmids may be diluted during division of the cells but the self-replication-competent plasmids may reach high levels in the cells. ►[mitochondrial plasmids](#), ►[F element](#), ►[plasmids](#); Jacob F, Wollman EL 1958 C.R. Hebd Séances Acad Sci Paris 247:154.

Epistacy: Quantitative interaction among the products of more than one allelic pair. The term, originally suggested by R.A. Fisher in 1918, has been usually replaced by epistasis.

Epistasis: The interaction between products of nonallelic genes, resulting in modification or masking of the phenotype expected without epistasis. The majority of single gene yeast mutations affect the expression of other genes. The segregation ratios in F_2 may be altered depending on the type of epistasis involved. At *recessive epistasis* (a recessive allele of a locus is epistatic to another recessive allele of another independently segregating locus) the phenotypic classes in F_2 are 9:4:3, at *dominant epistasis* 12:3:1, rather than the common 9:3:3:1. Epistasis may be brought about by modification of gene function due to alterations in the signal-transducing pathway. *Synergistic epistasis* reinforces the consequences of other epistatic factors, e.g., deleterious mutations may enhance each other's detrimental effects. *Negative epistasis* reduces fitness in individuals with deleterious mutations; the epistatic genes are more deleterious in combination than separately (Butlin R 2002 Nature Rev Genet 3:311). Epistasis may take place between/among protein modules and form an epistatic network (Segrè D et al 2005 Nature Genet 37:77). *Indirect epistasis*, in contrast, is not an intracellular phenomenon. A pregnant mother with some metabolic defect may exert a deleterious effect on the genetically normal (heterozygous) developing fetus by placental transfer of harmful metabolites. Similarly, breast-feeding by such mothers may elicit the symptoms of the disease in the nursing babies. Such a situation may exist in case of phenylketonuric and myasthenic mothers. The problem of epistasis is of interest for quantitative genetic analysis and it may require sophisticated statistics to separate additive effects from interactions. Epistasis thus has significance for animal and plant breeding, as also for human genetics, to determine the role of genes in the development of cancer and other traits under multiple controls and interaction of drugs. Actually, the majority of genes do not operate independently of each other. Microarray hybridization of mutant transcripts permits quantitative estimation of the phenotypes due to interaction in the expression on a global scale (Van Driessche N et al 2005 Nature Genet 37:471) and on this basis E maps (epistatic interaction maps) can be constructed (Schuldiner M et al 2005 Cell 123:507). ▶[signal transduction](#), ▶[phenylketonuria](#), ▶[myasthenia](#), ▶[modified Mendelian ratios](#), ▶[interaction deviation](#), ▶[synergism](#), ▶[recombinant congenic](#), ▶[two-hybrid method](#), ▶[suppressor gene](#), ▶[cross-talk](#), ▶[genetic network](#), ▶[morphogen](#), ▶[epistacy](#); Bateson W 1907 Science 26:649;

Mcmullen MD et al 2001 Genome 44:667; epistasis in populations: Carlborg Ö, Haley CS 2004 Nature Rev Genet 5:618.

Epistasis group: Non-allelic genes with protein products, which may affect each other's function(s). ▶[complementation group](#), ▶[allelism](#)

Epistatic selection: Consecutively occurring mutations may decrease fitness synergistically. ▶[fitness](#), ▶[selection](#)

Epistemology: The study of the nature and limitations of science.

Epithelial branching: A common theme in organogenesis of epithelial tubes, for the lung, liver, or kidney. The later morphogenesis of these branched epithelia dictates the final form and function of the mature tissue. Epithelial branching requires the specification of branch cells, the out-folding process itself, and, frequently, patterned morphogenesis produces branches of specific shape and orientation. ▶[epithelial cell](#); Hatton-Ellis E et al 2007 Proc Natl Acad Sci USA 104:169.

Epithelial cells: Epithelial cells form a tightly organized cover over the surface of organs or bodies (see Fig. E41). The architecture of the epithelial tissues is maintained by intercellular adhesion mediated by E-cadherin molecules and a synaptogamin-like protein, Btsz (Pilot F et al 2006 Nature [Lond] 442:580). Tuba protein modulates the expression of CDC42 GEF and regulates the junctional configuration of epithelial cells (Otani T et al 2006 J Cell Biol 175:135). Mice homozygous for a missense mutation in interferon regulatory factor 6 (*Irf6*), the homolog of the gene mutated in the human congenital disorders Van der Woude syndrome and Popliteal pterygium syndrome, have a hyperproliferative epidermis that fails to undergo terminal differentiation, resulting in soft tissue fusions rather than keratinizing epithelia (Richardson RJ et al 2006 Nature Genet 38:1329). ▶[cadherin](#), ▶[synaptogamin](#), ▶[CDC42](#), ▶[GEF](#), ▶[Van der Woude syndrome](#), ▶[Popliteal pterygium syndrome](#), ▶[polycystic kidney disease](#)



Figure E41. Epithelium

Epithelioma: An autosomal dominant benign or cancerous human skin lesion, encoded in the long arm of human chromosome 9. ▶kin diseases

Epitope: The binding site on the antigen for the paratope of the antibody, the antigenic determinant. The polymorphic (private) epitopes are specific for one MHC, whereas the monomorphic (public) epitopes may be shared by more than a single MHC allele. The cryptic epitopes are usually expressed at very low levels, but they may be induced to overexpression. Immunodominant epitopes are the ones commonly binding to the antibodies. Multimeric epitopes are multivalent arrays of peptide:MHC complexes on the surface of the antigen-presenting cells (APCs). The cross-linking of MHC class II molecules and the resulting clustering of peptide:MHC/T cell receptor (TCR) greatly enhances both APC and T cell activation. Therefore, multimerized T cell epitopes increase the immunological potency of soluble peptides and can promote either antigen-specific T cell activation or tolerance through activation-induced cell death in vitro at much lower concentrations than the monomeric peptide (Piaggio E et al 2007 Proc Natl Acad Sci USA 104:9393).

The α -galactosyl epitope (Gala1-3Gal β 1-4GlcNAc-R) is expressed on the surface of most mammalian cells (except humans and Old World primates) and is the most common factor of tissue rejection. This epitope is present on several potentially pathogenic viruses, bacteria, and protozoa. Retroviral vectors also carry this epitope and it appears to be the major cause for triggering the complement cascade against them. The α -1,2-fucosyl transferase (H-transferase) may reduce the α -galactosyl residues on the viral and cellular surface and thus reduce the complement-mediated immune reaction. The elimination of the α -galactosyl epitope either by gene knockout or by increasing the H-transferase expression may facilitate xenotransplantation. ▶antibody, ▶MHC, ▶antigen, ▶paratope, ▶xenograft, ▶gene therapy, ▶complement, ▶knockout, ▶epitope tagging; <http://www.rostlab.org/services/epitome/>; epitope peptide segments: <http://140.121.196.30/remus.asp>.

Epitope Screening: If an antibody is available for a protein it can be used to screen expression libraries of the antigen with the antibody. The antigen-containing cells are plated, then transferred to nitrocellulose filter replicas, and subsequently submerged in a solution of the antibody. The epitope-containing colonies tightly bind the antibody and while incubating the filter reveal the position of the complex by a second, radiolabeled antibody that binds to the first one. This procedure is of medical significance for the development of immunological defense systems. ▶antibody,

▶antigen, ▶epitope, ▶radioactive label, ▶phage display

Epitope Spreading: An expansion of specific antigen responses to additional determinants of the same protein (intramolecular epitope spreading) or to targets present in different proteins (intermolecular epitope spreading). Epitope spreading may enhance the damage of the autoreactive immune responses. ▶immune system, ▶autoimmune diseases, ▶immune tolerance; Robinson WH et al 2003 Nature Biotechnol 21:1033.

Epitope Tagging: An immunochemical/immunocytochemical method that employs a short polynucleotide, encoding a 6 to 10 amino acid epitope, inserted into a gene, which is then transfected into a cell. This epitope already has a known antibody and when it is expressed in a transgenic cell it facilitates the tracking of the transgene tagged. It is superior as far as specificity to natural immunogens is concerned. Inserting tandem epitopes improves sensitivity. Generally, either the N or the C ends of the proteins are labeled. For identification, Western blots, immunoprecipitation, immunofluorescence, electron microscopy and other methods are used. Epitope tagging has wide applicability in basic proteomics and eventually to clinical problems. Some epitope-antibody combinations are commercially available. (See individual terms under separate entries, Jarvik JW, Telner CA 1998 Annu Rev Genet 32:601; Heintz N 2000 Hum Mol Genet 9:937; Ferrando A et al 2000 Plant J 22:553).

Epizootic: A serious disease of insects or other animals occurring occasionally, but one which spreads rapidly and involves high morbidity.

EPO: Erythroid progenitor cell regulator affecting, primarily, megakaryocyte differentiation. ▶TPO, ▶megakaryocyte, ▶erythrocyte

Eponym: The designation of a phenomenon or principle by the name of person(s) who discovered it or who was associated with it as a proband, e.g., Punnett square, centi Morgan, Hogness box, Abraham Lincoln hemoglobin, Lepore hemoglobin. (See www.whonamedit.com).

Epothilone: A water-soluble polyketide produced by myxobacteria (*Sorangium cellulosum*) in low quantity. It is a spindle fiber poison and is a potential anticancer drug, similar to taxol but more effective. The epothilone gene has been cloned and it can be produced more efficiently by transgenic other bacteria such as *Streptomyces coelicolor*. It has also been synthesized by laboratory methods. ▶taxol, ▶myxobacteria, ▶polyketide; Chen H et al 2001 Chem Biol 8:899.

Epoxide: An epoxide contains a three-membered (oxirane) ring, e.g., ethylene oxide, and they are highly reactive (see Fig. E42).

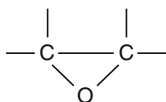


Figure E42. Epoxide ring

Epoxide Hydrolase Deficiency (1q42.1): Results in the inability to detoxify arene oxide (phenytoin/hydantoin type drugs) causing cell death, birth defects, congenital heart disease, cleft lip/palate, microcephaly, and genital/urinary, eye and limb anomalies (see Fig. E43).

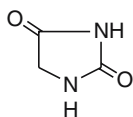


Figure E43. Hydantoin

Eppendorf: Although this company merchandises other types of laboratory tools, generally, its name is synonymous for the conical polypropylene microcentrifuge tubes of 1.5-mL capacity. Several companies market such 0.5 to 1.5-mL tubes in equal quality.

Eppin: A epididymis/testis-expressed, alternatively spliced, cysteine-rich protease inhibitor protein encoded at human chromosome 20q12-q13.2. It appears to be a promising immunocontraception agent. ▶[immunocontraceptive](#); Richardson RT et al 2001 Gene 270:93.

EPS: Exopolysaccharide.

EPS8: Transduces signals between Rac and RAS. (See Rac; RAS; signal transduction; E3B1).

Epsin (EPS): A clathrin-associated protein binding the adaptin subunit of AP2. EPS also has a ubiquitin interaction motif too. It seems to transmit signals from the endocytotic pathway to the nucleus. ▶[clathrin](#), ▶[AP1](#), ▶[adaptin](#), ▶[endocytosis](#), ▶[ENTH](#); Drake MT et al 2000 J Biol Chem 275:6479.

Epstein-Barr Virus (EBV): A 172-kbp linear DNA herpes virus with multiple direct repeats of 0.5 kb at both ends. Within the cells the EBV may make up to 100 circular, nonintegrated copies or it may integrate into the chromosomes. Some of its RNA genes are transcribed by RNA polymerase III and use upstream elements for regulation. Herpes viruses cause infectious mononucleosis, Burkitt's

lymphoma, nasopharyngeal (nose-throat) carcinoma, Marek's disease (an avian tumor), etc. About 90% of the human populations harbor EBV. EBV infects and immortalizes B lymphocytes with the aid of the EBNA1 and EBNA2 (Epstein-Barr virus nuclear antigen) genes and may be used for the (sometimes inefficient) production of monoclonal antibodies. Replication of EBV is apparently preceded by nucleosomal destabilization brought about EBNA1. EBNA2 is also a transactivator of other genes without binding to DNA. Responsive promoters are targeted through the CBF1 DNA binding transcriptional repressor protein. CBF1 binds to a consensus of GTGGGAA at a considerable distance from the EBNA2-responsive cellular promoters. EBNA2 counters transcriptional repression by CBF1. EBV is the most effective tumorigenic virus of humans and it targets the B lymphocytes and transforms them into active immunoglobulin-producing immunoblasts. More than 90% of the infections lay dormant because of the immunological surveillance of the T cells. In Hodgkin's disease and nasopharyngeal cancer cell, EBV is detectable. In case of a mutation in the cells, EBV displays the X-linked lymphoproliferative syndrome (XLP, Xq24-q25) upon infection. The syndrome includes infectious mononucleosis, acquired hypogammaglobulinemia and malignant lymphoma. The XLP/SH2D1A gene encodes a 128 amino acid protein with a single SH2 domain. The XLP/SH21A gene product appears to be the same as SAP (SLAM-associated protein). SLAM (signaling lymphocyte activation molecule, alias CDw150) is a glycosylated transmembrane protein involved in the activation of B and T cells and in the interaction between B and T cells. The EBV antigen stimulates the proliferation of CD8⁺ and CD4⁺ T lymphocytes. The CTLs keep the virus under control until its proliferation is evoked by some conditions. Within the EBV protein network 52 proteins are linked via 60 interactions and 40 EBV proteins and 112 human proteins are connected by 173 interactions as detected by the yeast two-hybrid assay (Calderwood MA et al 2007 Proc Natl Acad Sci USA 104:7606).

EBV can be used as lymphoid-tissue-specific genetic vector. This specificity depends on the presence of the CD21 complement receptor type II protein. The CD21 ligand is a gp350/220 glycoprotein. The vectors form only 2 to 4 copies in mammalian cells. They can carry 35-kb inserts and can be used as a shuttle vector. The EBV establishes latency in the target cells, making it a desirable genetic vector. The engineered EBV minireplicons need nontransforming (EBNA2-defective) helper cell line packaging. The safety of using EBV-based vectors for gene therapy may not be completely assured. ▶[Herpes](#), ▶[Burkitt's lymphoma](#), ▶[Hodgkin's disease](#), ▶[lymphocytes](#),

►CTL, ►shuttle vector, ►carcinoma, ►cancer, ►oncogene, ►CBF, ►complement, ►Duncan syndrome, ►hypogammaglobulinemia, ►lymphoma, ►mononucleosis, ►complement, ►SLAM, ►SAP, ►heterohybridoma, ►lymphoproliferative diseases; Khanna R, Burrows SR 2000 Annu Rev Microbiol 54:19; Avolio-Hunter TM et al 2001 Nucleic Acids Res 29:3520; Grinstein S et al 2002 Cancer Res 62:4876.

Epstein Syndrome: Macrothrombocytopathy. ►Alport syndrome

EQ (encephalization quotient): The comparison of brain weight relative to body weight. Although relatively larger brain weight is characteristic for humans, the brain weight alone may not reflect cognitive abilities among hominids. ►brain human

Equational Division: ►mitosis

Equational Separation of Chromosomes: The separation takes place in mitosis when the sister chromatids go to opposite poles during anaphase. Similarly, the separation of the chromosomes at anaphase I of meiosis may be equational in case of recombination or in the absence of mutation. In heterozygous autopolyploids, when crossing over takes place and the *Aa* and *aA* chromatids go to the same pole, the separation is equational. When the distance between a gene and its centromere is at least 50 map units (or more) maximal equational segregation occurs. Such a separation may permit the formation of *aa* gametes in an *AAAa* (triplex) and increases the frequency of *aa* gametes in duplex (*AAaa*) and simplex (*Aaaa*) individuals. ►mitosis, ►meiosis, ►autopolyploidy, ►reductional separation

Equatorial Plane: The middle region of a dividing cell nucleus where the chromosomes congregate before anaphase begins and where the nucleus will divide into two. Note, sometimes it is called “plate” but there is no physical plate there at that stage. ►mitosis

Equatorial Plate: ►equatorial plane

Equilibrium: A state without a net change.

Equilibrium Centrifugation: The centrifugation is continued in a density gradient until each macromolecule (subcellular organelles) reaches a position corresponding to its density. ►density gradient centrifugation, ►ultracentrifugation

Equilibrium Constant (K_{eq}): The concentrations of all reactants and products at equilibrium under specified conditions. ►dissociation constant

Equilibrium Dialysis: Known quantities of an antigen and an antibody are placed in a dialysis bag. Only those small antigens can pass the bag membrane that cannot react with the antibody. This way, the number

of specific binding sites can be determined on the basis of the antibody inside and outside the bag. ►antibody, ►antigen, ►immune reaction, ►valence, ►dialysis

Equilibrium Dissociation Constant (K_d): Expresses the strength of interaction between two molecules where (AB) is the concentration of the complex and (A) and (B) is the concentration of the separate molecules (K_a). Its reciprocal (K_d) is the equilibrium association constant.

$$K_d = \frac{(A)(B)}{(AB)} \quad K_a = \frac{(AB)}{(A)(B)}$$

Equilibrium of Heterozygotes: Both homozygotes in a random mating population are equally disadvantaged as compared to the heterozygotes and heterozygote equilibrium takes place relative to homozygotes. ►Hardy-Weinberg theorem, ►genetic equilibrium

Equilibrium of Mutations: The occurrence of a number of mutations in a random mating population has the same consequence as immigration, i.e., the frequency of the allele may increase. Unless the new mutation has substantial selective advantage, its survival (fixation) or death (extinction) is equally likely. If the mutation is frequent and random elimination (drift) is insignificant, maintenance of the mutant allele may be assured, even when it does not have a selective advantage. If a mutation from *A* to *a* is a regular event, the frequency of *a* may increase at the expense of *A*

$$qn + 1 = qn + \mu(1 - qn) \quad \{1\}$$

where q = frequency of the recessive allele, and $(1 - q)$ = frequency of the dominant allele, n = the number of generations and μ = mutation rate.

After a number of generations (n), the initial frequency of the recessive allele (q_0) may increase to q_n by the acquisition of the same mutant alleles ($A \rightarrow a$) as represented:

$$e^{-n\mu} = (1 - q_n)/(1 - q_0) \quad \{2\}$$

and hence

$$-n\mu = \ln[(1 - q_n)/(1 - q_0)] \quad \{3\}$$

If, e.g., $q_0 = 0.05$ (as we hypothesize for an example), the number of generations required to double its frequency to $q_n = 0.10$ can be computed if the value of μ (= mutation rate) is known, e.g., $\mu = 10^{-5}$. According to {3}, $\ln[(1 - 0.10)/(1 - 0.05)] = \ln[0.90/0.95] = \ln 0.94737 = 0.05407 = -n\mu$. When 0.05407 is divided by 0.00001 (the mutation rate given above, 10^{-5}), we get

5,407. This means that under the conditions specified by this hypothetical example, 5,407 generations are required to double the frequency of the recessive allele. Since this change depends not on the number of years but on the number of generations, species with many generations annually may change more rapidly than the ones with long times to sexual maturity and gestation. Therefore, it is easier to test these mathematical models with bacteria or *Drosophila* or mice than with humans or elephants.

The rate of change of allelic frequencies in a random mating population can be expressed as:

$$\Delta q_n = \mu(1 - q_n) \quad \{4\}$$

where Δ indicates change in the frequency of the recessive allele (q). Thus the rate of change {4} for the hypothetical experiment is 10^{-5} (0.90) = 0.000009 . The larger the number of alleles, which can mutate, the larger is the chance for the change. One must take into account also the fact that mutations may revert. Accordingly:

$$\Delta q = \mu p - r q \quad \{5\}$$

where μp represents the mutation $A \rightarrow a$, and/or stands for backmutation $A \leftarrow a$ (r = reversion).

At mutational equilibrium

$$\hat{q} = \mu / (\mu + r) \quad \{6\}$$

and

$$\hat{p} = r / (\mu + r) \quad \{7\}$$

where \hat{q} and \hat{p} represent the equilibrium frequencies of the recessive and dominant alleles, respectively.

It is evident if p is larger than q , a larger r is required to keep equilibrium with a smaller μ , e.g., if $p = 0.8$ and $q = 0.2$ ($p + q$ is always 1) and $\mu = 0.00001$, r must be 0.00004 to make $0.8 \times 0.00001 = 0.2 \times 0.00004$. Usually in nature the frequency μ (forward mutation) is larger because $A \rightarrow a$ change may occur by more mechanisms than base substitution alone (e.g., deletion, frame shift, etc.) whereas reversion (r) is expected to take place mainly by nucleotide replacement. Therefore, in the maintenance of allelic equilibrium, selection usually plays a major role.

► **allelic frequencies**

Equivalence Group: A group consisting of cells with equal differentiatonal potential at a particular time.

ERAB (endoplasmic reticulum associated binding protein, a putative hydroxysteroid dehydrogenase): Binds to the amyloid- β peptide and appears to cause neuronal dysfunction in Alzheimer's disease. ► **Alzheimer's disease**; He XY et al 2001 Eur J Biochem 268:4899.

ERAD: Stands for endoplasmic reticulum-associated degradation of aberrant or unneeded proteins by the proteasome. ► **proteasome**, ► **endoplasmic reticulum**; Molinari M et al 2003 Science 299:1397; Oda Y et al 2003 Science 299:1394.

ERBA: The genes present in multiple copies in both the human (chromosome 17q22-q23 or 17q11-q12) and the mouse genomes. ERBA was held responsible for the potentiation of ERBB1 and the protein is a receptor for thyroid hormones and functions in the nucleus as a transcription factor. It has the highest expression in the nervous system and, unlike other thyroid receptors, not in the liver. It is related to the avian erythroblastic leukemia virus oncogene and it is involved in leukemia and other cancers in humans, including some translocations. ► **erbB**, ► **ERBB1**, ► **oncogenes**, ► **hormones**, ► **TRE**, ► **hormone response elements**, ► **regulation of gene activity**; Andersson ML, Vennstrom B 2000 Oncogene 19:3563.

erbA: A retroviral oncogene which produces a transcription factor (member of the steroid receptor family).

erbB: An avian erythroleukemia oncogene (receptor for EGF and other cellular and viral proteins). Its overexpression may confer resistance to anticancer chemotherapy and radiation treatment. Herceptin and taxol may block erbB. Erb-specific tyrosine kinase inhibitors may also reduce its effect on chemoresistance. ErbB3 receptor-binding protein Ebp1 down-regulates the androgen receptor and may be effective against hormone-refractory prostate cancer (Zhang T et al 2005 Proc Natl Acad Sci USA 102:9890). ► **avian erythroblastoma**, ► **ERBB1**, ► **herceptin**, ► **taxol**, ► **prostate cancer**, ► **immunostimulatory DNA**; Olayioye MA et al 2000 EMBO J 19:159.

erbB1: An oncogene (human chromosome 7p12-p22, mouse chromosome 7) encodes the glycoprotein, epidermal growth factor receptor (EGFR), and a transmembrane protein tyrosine kinase. The protein has two subunits, one contains phosphotyrosine and phosphothreonine, and the other contains, in addition, phosphoserine. ERBB2 has been assigned to human chromosome 8p22-p11. The synonyms of ErbB2 are NEU and HER2. Probably ErbB2 is a normal growth factor but when its expression is enhanced it becomes a protooncogene. The amplification of its expression was detected in adenocarcinomas and gastric cancer. The ErbB2 product is present in neuroblastomas, breast and ovarian cancers. The anti-ErbB2 monoclonal antibody (trastuzumab) is recommended for metastatic tumors overexpressing ErbB2. ErbB3 is a related (mammary) oncogene in human chromosome 12q13. Regulation of ErbB2-induced mammary tumorigenesis by protein tyrosine kinase 1

occurs through the attenuation of both the MAP kinase (MAPK) and Akt pathways (Julien SG et al 2007 Nature Genet 39:338). ▶EGF, ▶oncogenes, ▶glycoprotein, ▶protein kinase, ▶proto-oncogene, ▶breast cancer, ▶neuroblastoma, ▶Heregulin, ▶Herceptin, ▶cyclin D, ▶MAPK, ▶Akt; Friedman LM et al 2005 Proc Natl Acad Sci USA 102:1915.

ERBBA: Two human genes in chromosome 19 (locus EAR2, with preferential expression in the liver) and chromosome 5 (locus EAR3) encode steroid and thyroid hormone receptors. The homologous retroviral gene is *erb*. ▶animal hormones, ▶retrovirus

ERC (extrachromosomal rDNA circle): Repeated sequences in ribosomal DNA (rDNA) may recombine and yield extrachromosomal circles. It has been suggested that accumulation of these circles may result in aging.

ERC (entorhinal cortex): The part of the central nervous system where neuritic degeneration occurs in Alzheimer's disease. (See Du AT et al 2001 J Neurol Neurosurg Psychiatry 71:441).

ERCC: ▶excision repair, ▶RAD25

ERDA1: Expanded repeat domain CAG/CTG with 50 to 90 repeats at 17q21.3. ▶trinucleotide repeats; Bowen T et al 2001 Psychiatr Genet 10:33.

Erectile Dysfunction (ED): A complex and widespread disorder causing impotence. Numerous environmental, metabolic, neurological, and disease factors may be the underlying causes. Several prescription drugs have been developed that correct the anomaly with a variable success rate for the male population. Gene therapies are under study in animal models using primarily adenoviral and plasmid vectors for the transfer of nitric oxide synthase, calcitonin gene-related peptide, brain-derived neurotrophic factor, vascular endothelial growth factor, and potassium ion channel genes. Another possibility is the transfer of genetically modified autologous cells into the corpus cavernosum of the penis. Gene therapy may eliminate the potential side effects of drugs, but it does not have yet clinically approved methodology for human use. The drug Viagra (Sildenafil citrate 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate) and other similar medications may be prescribed for alleviation of the problem. ▶gene therapy, ▶Peyronie disease; Anastasiadis AG et al 2004 In Seftel AD et al (eds) Male and Female Sexual Dysfunction Mosby, St. Louis, MO, USA, p 183.

eRF: Recognizes stop codons in mRNA and terminates translation, stimulates peptidyl-tRNA cleavage and

release. In prokaryotes there are two RFs, RF1 and RF2, and in eukaryotes there are eRF1 and eRF3. Eukaryotic eRF1 recognizes all three termination codons (UAA, UGA or UAG). In prokaryotes, RF1 recognizes UAA and UAG and RF2 recognizes UAA and UGA. In eukaryotes, eRF3 binds to the C-terminal domain of eRF1 and their cooperation realizes the release of the peptidyl tRNA bond (Alkalaeva EZ et al 2006 Cell 125:1125). eRF3 is one of the factors that controls yeast prion PSI conformation (Wilson MA et al 2005 Proc Natl Acad Sci USA 102:10244). ▶stop codon, ▶prion, ▶tRNA, ▶release factor; Ohta M et al 2001 Plant Cell 13:1959.

erg: A unit of energy or work in dyne acting through a distance of 1 cm. ▶dyne unit of force

ERG: A DNA-binding protein, oncogene, encoded in human chromosome 21q22.

Ergodic Rule: Rare events are more likely to be found when the population size is large.

Ergosterol: The most common sterol in some fungi. It is D₂ provitamin and it is used as an antirachitic drug (for prevention of certain bone deficiency problems). ▶cholesterol

Ergot: Dry sclerotia (compact dry mycelial mass) of *Claviceps purpurea* fungus on rye ears (and some other grasses) containing a large number of alkaloids and peptide alkaloids, some of which promote the contraction of the uterus (oxytocic) and are highly toxic (see Fig. E44). Lysergic acid is one of the main alkaloids of ergot which affects the nervous system, causes confusion. It has been used as a psychomimetic and was supplied to the defenders of the soviet political "conception" trials to admit to crimes they did not commit. ▶alkaloids, ▶psychomimetic; Mukherjee J, Menge M 2000 Adv Biochem Eng Biotechnol 68:1.



Figure E44. Ergot

ERK: A family of extracellular signal-regulated protein kinases. ERK5/BMK1 is required for epidermal growth factor and nerve growth factor to induce cell proliferation. ERK kinases are important for histone (H3) phosphorylation and activation of transcription. ERK activation depends on an oxysterol-binding protein (OSBP) through the cholesterol-binding scaffolding of this phosphatase (Wang P-y et al

2005 Science 3007:1472). ►signal transduction, ►SAPK, ►EGF, ►MAP kinase; Chen RH et al 1992 Mol Cell Biol 12:915; Adachi M et al 2000 J Cell Biol 148:849; Howe AK et al 2002 Current Opin Genet Dev 12:30.

ERM (ezrin-radixin-moesin): A protein cofactor complex, in its active state, of GTPase reactions. It affects the cytoskeletal system and anchors filaments to the cell surface. It may enhance metastasis in sarcomas. The ERM-like protein, merlin, appears to be a suppressor of meningiomas and schwannomas. Protein 4.1, containing ERM, is also a potential suppressor of metastasis (Wong SY et al 2007 Proc Natl Acad Sci USA 104:12784). ►cytoskeleton, ►ezrin, ►GTPase, ►merlin, ►neurofibromatosis, ►meningioma; Bretscher A 1999 Curr Opin Cell Biol 11:109.

ERP: A transcription factor of the ETS family. ►transcription factors, ►ETS

Erp1: An inhibitor of the anaphase-promoting complex. ►CSF

Erp61: An endoplasmic reticulum stress protein with functions similar to PDI. ►PDI, ►Erp72

Erp72: An endoplasmic reticulum protein with thiorodoxin- and PDI-like functions. ►thio-redoxin, ►PDI

ERR (extra radiation risk): Expresses the increased cancer or other risk compared to the unexposed population. ►risk, ►EAR

Error Catastroph: A high rate of mutation—beyond a certain threshold—that may drive a species to extinction (Eigen M 2002 Proc Natl Acad Sci USA 99:13374). Lower doses of mutagens may also accomplish viral extinction because of the replicative competition by defectors (Grande-Pérez A et al 2005 Proc Natl Acad Sci USA 102:4448). ►mitotic catastrophe

Error in Aminoacylation: Approximately 3×10^{-4} is the rate of charging a tRNA with the wrong amino acid in prokaryotes and eukaryotes, 10^{-5} in yeast to 10^{-4} and 10^{-3} in higher forms. Several aminoacyl-tRNA synthetases carry out editing functions by hydrolyzing the misactivated aminoacyl adenylates and aminoacyl-tRNAs. DNA aptamers are also involved in editing functions. Amino acids larger than the cognate amino acid are eliminated in a single step. Amino acids smaller than the critical ones are selected against a second step of screening. This is called the “double-sieve model”. ►ambiguity in translation, ►error in replication, ►aptamer, ►editing,

►aminoacyl tRNA synthetase; Parker J, Holtz B 1984 Biochem Biophys Res Commun 121:482; Mori N et al 1985 Biochemistry 24:1231; Jakubowski H, Goldman E 1992 Microbiol Rev 56:412; Nordin BE, Schimmel P 1999 J Biol Chem 274:6835.

Error in Communication: The accidental substitution of a symbol by another.

Error in Replication: Leads to base replacement and thus mutation. The rate of replicational errors of the different DNA polymerases varies but it is partly compensated for by the editing function of the 3'→5' exonuclease activity of the polymerases. The error rate of α subunit of DNA polymerase III of *E. coli* is about 10^{-5} , but it is reduced by about two orders of magnitude by exonuclease subunit ϵ . The base substitution error of the *E. coli* DNA polymerase III holoenzyme is within the range 5×10^{-6} to 4×10^{-7} . The repair polymerase, Pol I of *E. coli* also has an error rate of about 1×10^{-5} , but the 3'→5' exonuclease activity again reduces the errors by two orders of magnitude. The T7 DNA polymerase has an error rate of 10^{-3} to 10^{-4} , but the repair system lowers it to 10^{-8} to 10^{-10} . The RNA polymerases of RNA viruses do not have proofreading and editing functions and their error rate may vary within the 10^{-3} to 10^{-4} range per nucleotide. The mitochondrial DNA polymerase γ has a base substitution error of $\sim 3.8 \times 10^{-6}$ to 2.0×10^{-6} . This appears to one or two orders of magnitude higher than in the nucleus of mammals. The proofreading rate of the exonuclease depends a great deal on the availability of replacement nucleotides and therefore the difference in the final fidelity may not be so much. ►editing, ►proofreading, ►reverse transcriptases, ►DNA replication mitochondria, ►mutation rate; Kunkel TA, Bebenek K 2000 Annu Rev Genet 69:497; Johnson AA, Johnson KA 2001 J Biol Chem 276:38090; Johnson AA, Johnson KA 2001 J Biol Chem 276:38097; Pesole G et al 1999 J Mol Evol 48:427.

Error in Transcription: Error in transcription is higher (10^{-3} to 10^{-5}) than in replication because the DNA-dependent RNA polymerases do not have editing functions. The consequence of an error in RNA is not serious as relative to mutation in DNA. The yeast protein SII and the *E. coli* proteins GreA and GreB used to be credited for stimulating the cleavage of RNA with misincorporated bases. Experimental data indicate that neither of these proteins is indispensable and their proofreading value appears low. The nucleotide proximal to the 3' end of the nascent transcript stimulates the hydrolysis of the penultimate phosphodiester bond and this hydrolysis is enhanced

in case of misincorporation of a base(s). Thus, the transcript assists proofreading and assures fidelity of transcription (Zenkin N et al 2006 Science 313:518). ▶[error in replication](#), ▶[ambiguity in translation](#), ▶[RNA polymerase](#), ▶[mutation rate](#), ▶[misincorporation](#); Paolini-Giacobino A et al 2001 Hum Genet 109:40; Shaw RJ et al 2002 J Biol Chem 277:24420.

Error in Translation: ▶[ambiguity in translation](#)

Error, Systematic: A basic mistake, bias, or misunderstanding of the collection or analysis or interpretation of data.

Error Types: Type I (α), rejecting a true hypothesis; and type II (β), accepting a wrong hypothesis on the basis of statistical analysis. ▶[power of a test](#), ▶[significance level](#)

Error Variance: The variance arising from agents, conditions beyond the ability to control an experiment, and with which the apparent effect of any controlled factor must be compared to obtain meaningful evaluation. ▶[analysis of variance](#)

Error-Free Repair: ▶[DNA repair](#)

Error-Prone Repair: ▶[SOS repair](#), ▶[DNA repair](#), ▶[mutasome](#), ▶[Y-family DNA polymerases](#); Goodman MF 2002 Annu Rev Biochem 71:17.

Erucic Acid (13-eicosenoic acid): A monoethenoid acid in the seeds of *Cruciferae* (rapeseed, mustard, horseradish, etc.) and *Tropaeolaceae* plants. It may constitute 50–80% of the fatty acids in these plants. It has poor digestibility but, even worse, it accumulates in the muscles and livers of the animals (humans) and causes serious and irreversible pathological changes. In the newly developed varieties of rapeseed (canola, *Brassica napus*) the erucic acid content has been reduced to 0.3%, thus making this plant a valuable oil-seed crop, particularly in cooler climates where soybeans do not fare well. The mutation blocks the conversion of oleic acid (18:1) to eicosenoic acid (20:1) and erucic acid (22:1). ▶[fatty acids](#), ▶[canola](#); Hans J et al 2001 Plant Mol Biol 46:229.

ERV: ▶[endogenous retrovirus](#)

Erwinia: A group of gram-negative enterobacteria. It is a pathogen for a variety of plant species. *Drosophila* appears to be a vector.

Erythralgia: An autosomal dominant disease with intense burning pain in the feet and hands, redness, heat-sensation, and swelling. A susceptibility locus

was found at 2q31-q32. ▶[pigmentation defects](#); Drenth JPH et al 2001 Am J Hum Genet 68:1277.

Erythroblast: A nucleus-containing erythrocyte or, in a loose sense, immature red bloods cell.

Erythroblastoma: A tumor-type mass of nucleated red blood cells.

Erythroblastosis: The circulating blood contains immature red blood cells.

Erythroblastosis Fetalis (neonatorum): When red blood cells of the developing fetus enter the maternal blood circulation of immunogenic mothers an immunization reaction may be generated. It may be particularly intense when the mother is Rh-negative and the fetus has Rh-positive blood. The antibodies formed by the mother then may enter the fetal blood supply and cause increased bilirubin production (causing nerve damage) and agglutination, and lysis of the fetal blood resulting in intrauterine death or severe anemia unless the newborn's blood is replaced immediately after delivery. Today, monitoring, especially in the later stages of the pregnancy, for bilirubin or Rh-antibody accumulation may prevent the development of erythroblastosis. If the tests are positive, and before Rh-antibodies accumulate, the mother may be given an anti-Rh γ -globulin that can be transferred through the placenta to the fetus. This affords protection against erythroblastosis. Erythroblastosis may be caused also by infection by the avian retrovirus, AEV, and ABO blood group incompatibilities. The latter is quite common but its effects are usually mild. ▶[Rh blood type](#), ▶[SU antigen in pigs](#); Stockman JA 3rd, de Alarcon PA 2001 J Pediatr Hematol Onc 23[6]:385.

Erythrocyte (red blood cell): Erythrocytes are disk-shaped (doughnut-shape), biconcave cells (see Fig. E45). Their average numbers in human males is ~5,400,000 and in females ~4,800,000/mL of blood after puberty. The numbers may vary by as much as 15% depending on altitude or other conditions. In animals the numbers may be different; in pigeons it is ~2,400,000 in dogs it is ~6,650,000. Their red color is due to the red oxygen carrier molecules, hemoglobin they contain. The erythroblasts expel the nuclei and express phosphatidylserine on the surface and thus attract the engulfing macrophages, which destroy the nuclei (Yoshida H et al 2005 Nature [Lond] 437:754). The mature erythrocytes no longer contain nuclei or nuclear DNA. Primarily, DNaseII of the macrophages mediates the enucleation during development. ▶[blood](#), ▶[leukocyte](#), ▶[hemolytic disease](#), ▶[sickle cell anemia](#), ▶[survivin](#), ▶[TIF1- \$\gamma\$](#) ; Orkin SH, Zon LI 1997 Ann Rev Genet 31:33.



Figure E45. Erythrocyte

E

Erythroderma, Ichthyosiformis, Non-Bullous (ALOX, 17p13.1): Result of mutations in lipoxygenase. ▶ichthyosis, ▶Kid syndrome, ▶lipoxygenase; Jobard F et al 2002 Hum Mol Genet 11:107.

Erythrokeratoderma Variabilis (1p34-p35): A dominant hyperkeratosis with transient red patches, encoded by gene GJB3, responsible for connexins 31/30.3 component of gap junctions (see Fig. E46). A conditional mouse mutant that carries the human F137L mutation in the Cx31 mouse gene, which was described to act in a transdominant negative manner, is an animal model for the disease. The phenylalanine residue at position 137 is highly conserved in several human and mouse connexin genes (Schnichels M et al 2007 Hum Mol Genet 16:1216). ▶connexins, ▶Charcot-Marie-Tooth disease, ▶deafness, ▶skin diseases, ▶gap junctions



Figure E46. Erythrokeratoderma variabilis. Sharp red keratotic spots on the human back

Erythroleukemia: Erythroleukemia is based on an autosomal dominant gene causing neoplastic growth of the immature and mature red blood cells, increase in the size of liver and spleen, and acute anemia. It is considered to be a malignant disease. ▶leukemia

Erythromycin: A group of three antibiotics produced by *Streptomyces erythreus*/*Saccharopolyspora erythraea*. The sequenced circular genome of this soil bacterium comprises 8,212,805 base pairs and predicted to encode 7,264 genes (see Fig. E47). The bacterium is resistant to several antibiotics and contains 17 lactamase genes and two macrolide esterases (Olynyk M et al 2007 Nature Biotechnol 25:447). Erythromycin inhibits amino acid chain elongation on the ribosomes. ▶antibiotics. The *ery* (erythromycin resistance) gene is the most distal marker to *ap* (attachment point) in the chloroplast DNA of *Chlamydomonas reinhardtii* according to recombination tests in cytohybrids (heterozygous for

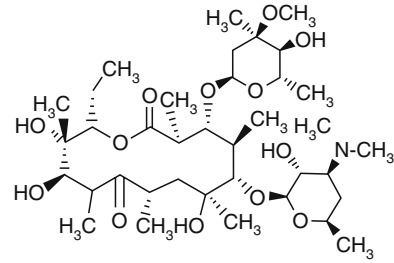


Figure E47. Erythromycin

ctDNA). Oral erythromycin therapy, when combined with the use of cytochrome-450 3A, increases the concentration of the antibiotic and may cause sudden heart failure (Ray WA et al 2004 New England J Med 351:1089). ▶chloroplast genetics, ▶chloroplast mapping, ▶nonribosomal peptide

Erythropoietin (EPO): A highly specific erythrocyte stimulating glycoprotein factor (M_r 51,000), produced mainly in the kidneys and acting in the bone marrow. It was isolated from anemic sheep but is now also produced by recombinant DNA technology. It is also used as a medication to avoid the need for blood transfusion in patients prone to anemia. The EPO receptor (EPOR) is a protein of the cytokine receptor family. It is formed as a dimer with an extracellular ligand-binding, a short, single pass transmembrane segment and a cytoplasmic domain without kinase activity. Its signaling relies on the Jak/STAT pathway. EPO/EPOR regulates caspases, which in turn control the fate of GATA-1 and apoptosis with the aid of FAS. EPO may induce tumor regression and antitumor immune response in murine myeloma. Cross talk between Janus kinase and NF- κ B signaling cascades results in neuroprotection by erythropoietin. ▶growth factors, ▶megakaryocyte, ▶hematopoiesis, ▶signal transduction, ▶FAS, ▶GATA, ▶apoptosis, ▶CIS, ▶polycythemia, ▶Jak kinases, ▶NF- κ B; Spivak JL et al 1991 Blood 77:1228; Digicaylioglu M, Lipton SA 2001 Nature [Lond] 412:641; Leist M et al 2004 Science 305:239.

ES: An embryonic stem cell; cells that can proliferate in an undifferentiated state but can give rise to differentiated cells as well and can be returned to an embryo to become part of it. These pluripotent cells are taken from blastocyst stage embryos. They are functionally similar to the meristem cells of plants. ▶totipotency, ▶pluripotency, ▶stem cell

ESA1: A histone acetylase that can activate transcription if targeted to specific promoters. ▶histones; Reid JL et al 2000 Mol Cell 6:1297.

ESAG: An expression site associated genes. ▶Trypanosoma

ESC: An embryonic stem cell. ▶ [stem cell](#), ▶ [SSC](#)

Escape Commitment: After initiation of transcription by RNA polymerase II and synthesis of four nucleotides, the polymerase proceeds to elongation with an *escape commitment* and leaving the promoter. ▶ [transcription factors](#)

Escherichia coli: ▶ [E. coli](#)

ESE (exon splicing enhancer): ca. 6–8-nucleotide sequences within exons that promote efficient splicing. They generally bind SR proteins with arginine/serine-rich tract. ▶ [NAS](#), ▶ [exon](#), ▶ [splicing](#), ▶ [SR motif](#); Woerfel G, Bindereif A 2001 Nucleic Acids Res 29:3204; Tian H, Kole R 2001 J Biol Chem 276:33833.

ESI (electrospray ionization): A source of ions in mass spectrometers for the analysis of, e.g., proteins. ▶ [electrospray](#), ▶ [MALDI/TOF/M MS/MS](#), ▶ [mass spectrometer](#); Han X 2002 Anal Biochem 302:199.

ESMP (expressed sequence marker polymorphism): ESMP is actually a SNIP marker. ▶ [SNIP](#)

Esophagus: The membrane-lined alimentary tube from the throat to the stomach. ▶ [Barrett metaplasia](#)

ESP1: A protease that cleaves the cohesin complex of the chromatids. Pds1 suppresses it. ▶ [cohesin](#), ▶ [PDS](#), ▶ [meiosis I](#)

ESS (exon splicing silencer): ▶ [ESE](#), ▶ [NAS](#), ▶ [NMD](#); Tange TO, Kjems J 2001 J Mol Biol 312:649.

Ess1: ▶ [parvulins](#)

Essential Amino Acids: Essential amino acids cannot be synthesized de novo by vertebrates and must be provided in the diet: arginine (in young), histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. The sensing of the lack of indispensable amino acids in the food/feed resides in the mammalian brain anterior piriform cortex. Uncharged transfer RNA induces phosphorylation of eukaryotic translation initiation factor eIF2 α with the aid of the GC nonrepressing 2 kinase (GCN2). This mechanism determines appropriate food selection (Hao S et al 2005 Science 307:1776). ▶ [high-lysine corn](#), ▶ [kwashiorkor](#), ▶ [amino acid metabolism](#), ▶ [transfer RNA](#), ▶ [eIF-2A](#)

Essential Athrombia: ▶ [thrombopathia](#)

Essential Fatty Acids: Essential fatty acids are required by mammals although they cannot synthesize them (linoleate [18:2 cis-D⁹, D¹²], and α -linolenate [18:3 cis-D⁹, D¹², D¹⁵]) because they are unable to introduce additional double bonds beyond the C-9. ▶ [fatty acids](#)

Essential Hypertension: ▶ [hypertension](#)

Essential Gene: An essential gene cannot be dispensed of without lethal consequences. In *Saccharomyces cerevisiae* yeast more than 80% of the genes are nonessential (Tong AHYY et al 2001 Science 294: 2364).

EST: ▶ [expressed-sequence tag](#). (See Gene Indices: <http://www.tigr.org/tldb/tgi/>).

EST1: A telomerase subunit. ▶ [telomerase](#)

EST Genome: Predicts genes on the basis of homology and aligns ESTs, cDNAs or mRNAs. ▶ [gene prediction](#), ▶ [expressed-sequence tag](#); <http://www.litbio.org>.

Established Cell Line: An established cell line of animals consists of fused cells (with one component being myeloma cancer cells) and is capable of indefinite growth without senescence. ▶ [immortalization](#), ▶ [HeLa](#)

Ester: An ester is formed when the OH end of an alcohol is combined with the COOH end of an acid leading to the removal of H₂, e.g., R–O–CO–R. Nucleotides may form ester linkages during chain elongation. ▶ [phosphodiester bond](#), ▶ [nucleotide chain growth](#)

Esterases: Esterases are enzymes involved in hydrolysis of ester bonds. Some proteolytic enzymes catalyze the reaction (see Fig. E48). In biochemical systems the esters may be phosphate-, glycerol-esters and many other molecules. Esterase A-4 (ESA4) is encoded in human chromosome 11q13-q22, ESD was located to 13q14.11; other human variants exist.

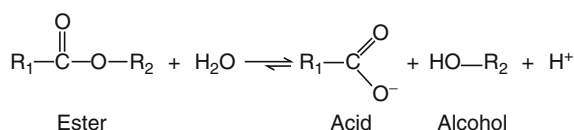


Figure E48. Esterases

Estradiol (estrogen): A steroid hormone produced by the animal (human) ovaries and placenta. It regulates secondary sexual characters and female estrus and implantation (see Fig. E49). 17 β -estradiol and raloxifene indirectly activate the estrogen-response element. The β -estradiols are carcinogenic through their metabolites (4-hydroxyesterone, 16 α -hydroxyesterone, semiquinone) by contributing to reactive oxygen and lipid compounds. Estrogen-like substances in the environment pose reproductive hazards to humans and wildlife. Estradiol (17 β) susceptibility in mice may vary by a factor of 16 or more among different strains. Although estrogen does not appear to be mutagenic in most of the standard bioassays, it generates DNA-estrogen adducts, and damages DNA

by free radicals. It produces 8-hydroxyguanine and may induce chromosomal aberrations. Estrogens may act as cancer promoters in cases where cancer cells are already present. Some estrogens or estrogen-like compounds are not steroids, e.g., diethylstilbestrol, hexestrol, the flavone and isoflavone phytoestrogens (coumestrol, genistein), mycoestrogens, and some alkylphenols, arylphenols and the nonaromatic pesticides like dieldrin, endosulfan, chlordane, some carbamates and the herbicide atrazine. Some pesticides such as DDT, methoxychlor are estrogenic pollutants. Similarly, the industrially used polychlorinated biphenyls (PCB), automobile exhaust, and Agent Orange, dioxin, etc., may be considered as endocrine disrupters and pose environmental hazards to humans and animals.

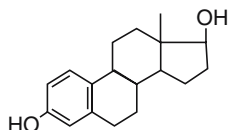


Figure E49. Estradiol

Estrogens act through the estrogen receptors and various ligands and other cooperative molecules. They may regulate + and – the transcription of many different genes (breast cancer, prolactin, dopamine, plasminogen activator, peroxidase, renin, etc.). All estrogen receptor and RNA polymerase II binding sites were mapped on a genome-wide scale, identifying the authentic *cis* binding sites and target genes, in breast cancer cells (Carroll JS et al 2006 Nature Genet 38:1289). Estrogens may have post-transcriptional and post-translational regulatory influence too. Estrogens affect the cholinergic activity in the brain and when this function diminishes by advanced age, learning and memory are impaired. Estrogens are involved in many metabolic processes. 17 β -hydroxysteroid dehydrogenase 2 and cytochrome P₄₅₀ mono-oxygenases metabolize estrogens. The latter enzymes may produce carcinogenic catechol estrogen. The anti-estrogen, tamoxifen, also appears carcinogenic to the liver and on prolonged use, to the endometrium of the uterus. Some of the estrogens appeared mutagenic in various types of assays. Several diseases (breast, endometrial, cervical prostate cancers, and thyroid diseases) increase hydroxylation of estradiol whereas osteoporosis and obesity may decrease hydroxylation. In pregnancy, the level of estrogens rises rapidly and the maintenance of an appropriate level is required for fetal development. It has been suggested that estrogens regulate the level of 5-hydroxy-tryptamine/serotonin in the brain and the lower supply of estrogens may thus be a contributing

factor to menopausal and postpartum (after-child-birth) depression. Estrogens may control glucose transport to the brain and may protect against neurodegeneration, such as is associated with aging (Alzheimer's disease). Gonadal hormones show protective effects against heart disease by contributing to the integrity of the vascular wall. Estrogens and antiestrogens modulate the immune system in various ways. A low level of estrogen is normally also present in mammalian males. Its deficiency due to mutation in the aromatase gene lowers the fertility of the male mice, but its role in the human male is less obvious although increase in estrogen may cause gynecomastia. Human males with aromatase deficiency show increased levels of estradiol. Under normal conditions, in males, the 17 β -estradiol level is higher than in postmenopausal women. ▶animal hormones, ▶estrogen response element, ▶steroid hormones, ▶antiestrogens, ▶nitric oxide, ▶androgen, ▶gynecomastia, ▶choline, ▶depression, ▶Alzheimer's disease, ▶aromatase, ▶tamoxifen, ▶raloxifene, ▶dioxine, ▶phytoestrogen, ▶targeting vector, ▶abortion spontaneous; Petterson K, Gustafsson JÅ 2001 Annu Rev Physiol 63:165; estrogen sensitive genes: <http://research.i2r.a-star.edu.sg/kberg>.

Estriol: A 16 α -hydroxylation product of estradiol. ▶estradiol

Estrogen: ▶estradiol, ▶animal hormones

Estrogen Receptor (ER): An estrogen receptor is dimeric (ER α + ER β) and to become functional, ER α is phosphorylated at Ser¹¹⁸ by a mitogen-activated protein kinase (MAPK) in the presence of an epidermal growth factor (EGF) and insulin-like growth factor (IGF). The dimeric ER associated with the proper ligands can bind to the estrogen receptor element in the chromosome and activate transcription of the estrogen receptive genes. The ERs can bind also to the AP1 transcriptional activator protein. ER α bound through the Jun and Fos oncoproteins to an AP1 site is activated by estradiol-17 β . In contrast, ER β bound estradiol-17 β inhibits transcription. The antiestrogens tamoxifen and raloxifene are transcriptional activators of ER β at the AP1 site. These pieces of information indicate that the two ERs differ in their signaling properties depending on the response element and the ligand. The practical significance of the finding is that this may provide a clue to why tamoxifen is an inhibitor of breast cancer but at the same time carcinogenic to the uterus, whereas raloxifene may be beneficial for the chemotherapy of breast cancer without a risk to the uterus. There is some recent observation that after a few years (2–5 years) raloxifene may alter the cellular machinery and promote tumorigenesis. Amplification of the

ESR1 estrogen receptor alpha gene (6q25) was detected in 20.6% of breast cancers by tissue microarray analysis of more than 2,000 clinical breast cancer samples. Ninety-nine percent of tumors with ESR1 amplification showed estrogen receptor protein overexpression, compared with 66.6% cancers without ESR1 amplification (Holst F et al 2007 Nature Genet 39:655). ▶estrogen, ▶breast cancer, ▶MAPK, ▶MAPKK, ▶EGF, ▶IGF, ▶tamoxifen, ▶raloxifene, ▶phytoestrogen; Shang Y et al 2000 Cell 103:843; Klinge CM 2001 Nucleic Acids Res 29:2905; Ciana P et al 2003 Nature Med 9:82.

Estrogen Response Elements (ERE): ERE are generally located about 200–300 bp upstream of the transcription initiation site. Despite their diversity they generally share a low homology consensus. For example, the *Xenopus* vitellogenin and the chicken ovalbumin gene carry the dyad: GGTCANNNTG^A_TCC. ▶hormone response elements, ▶regulation of gene activity, ▶animal hormones, ▶raloxifene, ▶tamoxifen; Driscoll MD et al 1998 J Biol Chem 273:29321; Shang Y, Brown M 2002 Science 295:2465.

Estrus: The recurrent sexually receptive periods of female mammals (except humans) accompanied by a sexual urge (heat); it is induced by cyclic ovarian hormonal activity (oestrus).

ET Cloning: The transformation of *E. coli* by using homologous recombination with the aid of a plasmid expressing the products of gene *RecE*, exonuclease VIII, and RecT. The gene to be transferred is flanked by about 40 nucleotides. ▶e *RecE*, ▶RecT, ▶transformation-associated recombination; Muylers JP et al 2000 Genet Eng 22:77.

Eta: ▶osteopontin

Ethanol: A common laboratory sterilizing agent used in 70–80% aqueous dilutions. Yeast synthesizes it from Glucose → Glyceraldehyde3-phosphate → 1,3-Diphosphoglycerate → Pyruvate → Acetaldehyde → Ethanol. From acetaldehyde it can make Acetate → Acetyl phosphate → Acetyl Coenzyme A and enters the Citric acid cycle. ▶alcohol, ▶alcoholism

Ethenobases: Ethenobases are metabolites of vinyl chloride through the action of the cytochrome P450 system which produces chloroethylene oxide, leading to the formation of several carcinogenic adducts. Among these are ethenobases (see Fig. E50). Ethenodeoxyguanine pairs with adenine and despite the relatively small amounts formed it is primarily responsive for the mutagenic/carcinogenic effects in the liver and brain. ▶environmental mutagens; Morinello EJ et al 2002. Cancer Res 62:5183.

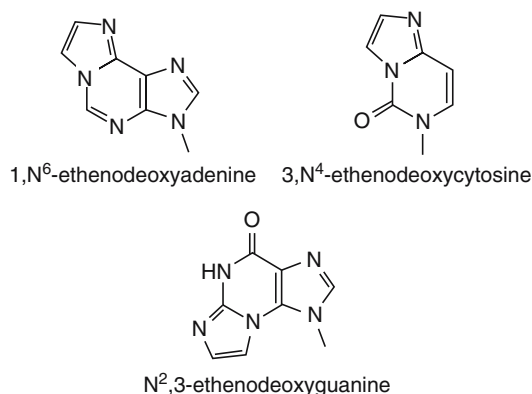


Figure E50. Ethenobases

Ethernet: The wiring and software required to share data through the Internet and local talk.

Ethics: The rules of animal and human behavior based on genetic and instinctive or social and moral traditions. The Gene Letter URL (<http://www.geneletter.org>) is a source for current problems and information on genetics (gene-related ethics). Physicians frequently face the problems of applying legal medical procedure (abortion, sedation to terminally ill, contraception to adolescents) to what they have moral or religious objections to. Among the polled 2,000 physicians, 63% believe that it is ethically permissible for doctors to explain their moral objections to patients and 86% believe that physicians are obligated to present all options to patients; 71% agree to refer them to another clinician who does not object to the requested procedure (Curlin FE et al 2007 New England J Med 356:593). The code of ethics of the American Society of Human Genetics: Boughman JA 2006 Amer J Hum Genet 79:1136). ▶behavior genetics, ▶ethology, ▶genetic privacy, ▶bioethics, ▶informed consent, ▶nuclear transplantation, ▶embryo research, ▶misconduct scientific, ▶publication ethics, ▶morality, ▶forbidden knowledge; Febr. 8 2007 comments in the New England Journal of Medicine; <http://www.ornl.gov/hgmis/elsi/elsi.html>; <http://www.nhgri.nih.gov/ELSI/>.

Ethidium Bromide (EB): A polycyclic fluorescent dye. Its fluorescence increases about 50 fold when it intercalates between DNA bases, and the sensitivity of the staining is so high that 2.5 ng DNA is detectable. It is used for revealing of DNA in agarose or polyacrylamide gels and buffers (0.5 mg/mL). The UV light absorbed by DNA at 254 nm is transferred to EB that itself has two absorption maxima at 303 and 366 nm and emits red-orange fluorescence at 590 nm maximum. DNA of more than 250 ng/mL can quantitatively be measured spectrophotometrically. The detection of

single-strand DNA or RNA is much less effective by EB. Intercalation into closed circular DNA is much less efficient than into linear DNA. Therefore, EB-stained plasmid or organellar DNA can be separated by buoyant density centrifugation from linear DNA by becoming of lesser density. EB-stained gels can be destained with water or by 1 mM MgSO₄ for 20 min. From the DNA, EB can be removed by washing several times with an equal volume of water-saturated 1-butanol or isoamylalcohol. EB is a powerful mutagen and must be handled carefully with gloves. The used solutions after dilution to no more than 0.5 mg/L require decontamination by 1 vol. 0.5 M KMnO₄ and careful mixing of 1 vol. 2.5 N HCl for several hours, followed by neutralization with 1 vol. 2.5 N NaOH. This procedure reduces mutagenicity to 3×10^{-3} of the untreated solutions.

Ethnicity: A human population related by biological features, identifiable by anthropometric, cultural, linguistic, biochemical, serological, molecular characteristics, SNPs and gene frequencies. The identification may not use all of these methods, depending on the nature of the genetic distances in the comparisons. The various ethnic groups and isolated communities provide valuable information for population genetics research. Protection of the privacy of individuals (Nature Genet 23:275), however, deserves serious consideration. The HGDP (Human Genome Diversity Project) aims to survey the world population for genetic diversity at the DNA level. The idea is to study disease susceptibility/resistance genes, evolution, population genetics, etc. Mapping by admixture linkage disequilibrium (MALD) is a potential analytical statistical method. Some analysts of the problems of ethnicity consider the study of ethnic differences to lead to racial discrimination (Duster T 2005 Science 307:1050).

Specific genetic variation among populations contributes appreciably to differences in gene expression phenotypes. Populations differ in the prevalence of many complex genetic diseases, such as diabetes and cardiovascular disease. The data collected on European, Chinese, and Japanese populations indicate allele frequency differences at regulatory polymorphisms to account for differences in prevalence of complex diseases (Spielman RS et al 2007 Nature Genet 39:226). ►genetic distance, ►Jews and genetic diseases, ►thalassemia, ►sickle cell anemia, ►Duffy blood group, ►MALD, ►SNPs, ►low-density lipoprotein, ►admixture in populations, ►myocardial infarction, ►Amish; Guglielmino CR et al 2000 Ann Hum Genet 64:145; Pastinen T et al 2001 Hum Mol Genet 10:2961; Arab genetic diseases: Teebi AS et al 2002 Hum Mut 19:615; Finnish diseases: Sipilä K, Aula P 2002 Hum Mut 19:16; ethnicity/

cancer: Wiencke JK 2004 Nature Rev Cancer 4:79; <http://gdbwww.gdb.org>; ethnic human variation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/deth.html>; Arab genetic disorders: <http://www.cags.org.ac/index.html>; Jews and genetic diseases: <http://www.mazornet.com/genetics/index.asp>.

Ethological Isolation: A type of sexual isolation. Males or females refuse to mate for some “psychological” reason(s). ►sexual isolation

Ethology: The study of behavior. ►behavior genetics, ►ethics, ►aggression, ►instinct, ►morality

Ethyl (–CH₂CH₃): An alcohol radical.

Ethylene (C₂H₄): The simplest plant hormone yet it controls a wide variety of morphogenetic and developmental processes, from stem and root growth, seed germination, to fruit ripening, senescence, and sex determination. Ethylene is synthesized as a side branch of the Yang cycle. The key enzymes in ethylene synthesis are ACC synthase and ACC oxidase. A multigene family encodes ACC synthase and it is regulated by hormonal, physical, and environmental signals. In *Arabidopsis*, a series of mutants are available that determine constitutive ethylene response and are overproducers. The ethylene insensitive mutations include a histidine kinase (*ein1*, *etr1*), *ain* is ACC-insensitive, *ctr1* is a putative serine/threonine kinase similar to the members of the MAPK. *EIN-2* has a central role in the pathway, encoding an integral membrane protein. It is a transducer of ethylene and stress responses. Gene *ERS* (ethylene response sensor) has some structural similarity to ETR (ethylene response resistance) but its role is upstream in the pathway. The order of gene action has been determined for most of the numerous mutations. Ethylene plays a key role in plant signaling and, from practical points of view, in fruit ripening and disease resistance. Several of disease and stress resistance genes and other genes controlling differentiation contain GCC box repeats that are also ethylene response elements. The ethylene insensitive *ETR1* gene of *Arabidopsis*, when transferred to yeast, conveyed ethylene binding in this fungus too. The ethylene nonresponding mutation *hookless1* seems to be a regulator of auxins. The *RTE1/GR* genes of *Arabidopsis* and of tomato, respectively, are specific repressors of insensitivity to an ethylene receptor *etr1* (Klee H 2006 Proc Natl Acad Sci USA 103:7537). ►plant hormones, ►Yang cycle, ►fruit ripening, ►SAR, ►hypersensitive reaction, ►hormone-response elements, ►MAPK, ►MAPKK; Bleecker AB, Kende H 2000 Annu Rev Cell Dev Biol 16:1; Johnson PR, Ecker JR 1998 Annu Rev Genet 32:227; Wang KL-C et al 2002

Plant Cell 14:S131; Wang K L-C et al 2004 Nature [Lond] 428:945; Alonso JM, Stepanova AN 2004 Science 306:1513; Bonaventura LM, Alonso JM 2006 Mol Biosyst 2:165.

Ethylene Oxide (C_2H_4O): A colorless, explosive gas used as a sterilizing agent for instruments, textiles, certain types of food, and soil. It is hazardous to handle; an irritant to mucous membranes and the lung and may cause pulmonary edema at higher concentrations. ▶sterilization

Ethyleneimine: ▶EI

Ethylmethanesulfonate (EMS, $CH_3SO_2OCH_2CH_3$): An alkylating mutagen and carcinogen. Its prime target for mutagenesis is the alkylation of the O⁶ position of guanine although it alkylates prefer the 7 position of guanine, but this rarely leads to base substitution. It alkylates all other nucleic acid bases too, and may cause strand scission by depurination. It is one of the most useful chemical mutagens for a wide range of organisms. ▶alkylation, ▶mutagens, ▶carcinogens, ▶depurination, ▶hydrogen pairing

Etiolated: Plants grown in the absence of light display elongation and lack of the typical leaf pigments (chlorophyll and carotenoids). The chloroplasts do not develop and the plastids only reach the etioplast stage (thylakoid membrane system incomplete). The leaves are not fully expanded. ▶photomorphogenesis, ▶phytochrome, ▶de-etiolation

Etiology: The study of cause(s) of disease and its development. Chemical etiology investigates the origin and cause(s) of the development of molecules.

Etioplast: An etioplast lacks the typical chloroplast pigments and displays a prolamellar body. The etioplast-chloroplast transition is a light-dependent process catalyzed by protochlorophyllide oxidoreductase A (PORA). ▶etiolated, ▶prolamellar body, ▶proplastid, ▶chloroplasts; Philipp K et al 2007 Proc Natl Acad Sci USA 104:678.

ETL (economic trait loci): ETL determine phenotypes that are important for practical agriculture.

ETO (eight twentyone): A translocation involving human chromosome 8q22 and 21q22.3 involved in myelogenous leukemia. ▶leukemia; Erickson P et al 1992 Blood 80:1825.

ETOPE: An evolutionary test of predictive exons (Nekrutenko A et al Nucleic Acids Res 31:3654).

Etoposide: A synthetic cytostatic compound; it inhibits topoisomerase II, cancer and nucleoside transport and CDK2. It may promote the function of nucleotidyl transferase and gene conversion in somatic mammalian cells. Etoposide may induce chromosomal

aberrations and aneuploidy. When rubbed to the skin of rats treated by chemotherapy hair loss was prevented in 50% or more of the animals. Genome-wide, 63 genetic variants were identified that contribute to etoposide-induced toxicity through their effect on gene expression. These include genes that may play a role in cancer (Huang RS et al 2007 Proc Natl Acad Sci USA 104:9758). ▶cytostatic, ▶aneuploid, ▶topoisomerases, ▶terminal deoxynucleotidyl transferase, ▶CDK, ▶camptothecin; Jacob S et al 2001 Cancer Res 61:6555.

ETS (external transcribed spacers): ETS are located between pre-tRNA gene clusters and at other genes controlling growth and development:

ETS - 5' - 18S- ITS - 5.8S - ITS - 28S) - ETS

The ETS family members usually bind to different protein monomers or dimers. ▶ITS, ▶SAP, ▶PU.1, ▶GABP, ▶spacer DNA; Borovjagin AV, Gerbi SA 2001 Mol Cell Biol 21:6210.

ETS Oncogenes: ETS-1 was located to human chromosome 11q23-q24. It is involved in acute monocytic leukemia (AMoL) when interferon β gene (IFB-1, chromosome 9p22) is translocated to it. ETS-1 and ETS-2 genes are physically contiguous in birds. The homologous two genes are coordinately expressed and the proteins are both in the cytoplasm and nucleus. In humans, ETS-2 genes are in chromosomes 21q22, 1-q22.3 and their expression is not coordinate; the ETS-1 protein is cytoplasmic whereas the ETS-2 is nuclear. ETS-1 can be phosphorylated posttranslationally in an unstructured region in multiple ways; the phosphorylation fine-tunes DNA binding, transcription and signaling (Pufall MA et al 2005 Science 309:142). Translocation t(8;21)(q22; q22) is common in patients with acute myeloid leukemia (AML-M2). The breakage point in the latter cases is not within the ETS-2 sequences. The ETS-2 gene lacks the TATA box and CAAT box, and alternative elements substitute for them. The ELK oncogenes display homology to the ETS oncogenes. This family of transcription factors has about 35 known members and regulates various aspects of growth, development, and lymphocyte pool maintenance. PEA3, a member of the ETS family of proteins, binds to the 5'-AGGAAG-3' DNA motif and suppresses the expression of the HER-2 oncogene. ETS opposes p16^{INK4a} in cooperation with Id1 during senescence. ERM, an ETS family protein, is required for the maintenance of spermatogonial stem cell niche (Chen C et al 2005 Nature [Lond] 436:1030). ▶leukemia, ▶interferon β -1, ▶oncogenes, ▶ELK, ▶SAP, ▶ERP, ▶lymphocytes, ▶HER; Blair DG, Athanasiou M 2000 Oncogene 19:6472.

Eubacteria: The majority of bacteria belong to this subkingdom of prokaryotes; the other subkingdom is *Archaeobacteria*.

Eucaryote: eukaryote; karyon [καρυον] is a Greek word and it is more appropriate to spell it with k.
►prokaryote

Euchromatic: Chromosomal regions containing euchromatin. ►euchromatin

Euchromatin: Euchromatin does not absorb the common nuclear stains during interphase and is normally transcribed into mRNA. In the human genome, the euchromatic fraction varies a great deal among the chromosomes. In chromosome 2 an almost 160 Mb sequence is less than 60% euchromatic whereas a more than 30 Mb sequence in chromosome 21 is almost entirely euchromatic. ►heterochromatin; <http://www.euchromatin.net/>; Yu A et al 2001 Nature 409:951.

EUCIB: ►European Collaborative Interspecies Backcross, a cooperative workgroup for plants.

Euclidean Distance: Calculations are used to construct dendrograms, evolutionary trees or comparisons. In the formula (see diagram) x and y represent observations in a set of multivariate data. ►dendrogram, ►evolutionary tree, ►multivariate analysis

$$d_{xy} = \sqrt{\sum_{i=1}^q (x_i - y_i)^2}$$

Eudicot: Common dicotyledonous plants.

EUG: A 65-kDa yeast protein in the endoplasmic reticulum with disulfide isomerase activity. ►PDI, ►Mpd

Eugenics: The application of genetic principles to the breeding of the human race with the purpose of improvement. *Positive eugenics* wishes to enrich the frequency of “favorable” genes whereas *negative eugenics* wants to eliminate the “undesirable” genes by selective breeding. The word eugenics was coined by Sir Francis Galton in 1883, unaware of Mendel’s discoveries, but his statistical data indicated that about 25% of the sons of eminent fathers were also eminent. From this he concluded that heredity plays a role in talent, intellect, and behavior. These fields are highly controversial because of the lack of scientific bases for the objective measurement of “desirable” and “undesirable” and the potentials of exploitation for political or unethical goals. The eugenics movements generally emerged during economic downturns in an effort to find scapegoats for the ills of societies, and the support generally

came from people without any understanding or training in genetics. By 1917, in 16 states of the USA, laws were approved for compulsory sterilization of the feeble-minded, insane, rapists, criminals and other “hereditary unfit” individuals. Actually, by 1935, about 30,000 sterilizations were carried out on the basis of these state laws. With the rise of scientific population genetics, it became obvious that this type of negative selection is ineffective. According to the Hardy–Weinberg theorem, if the frequency of the homozygous recessive “undesirable” individuals is $1/20,000$ (5×10^{-5}) then at genetic equilibrium the frequency of that gene is $\sqrt{0.00005} \cong 0.0071 = q$ and the frequency of the carriers (heterozygotes) is $2 \times p \times q = 2 \times 0.9929 \times 0.0071 \approx 0.014099$, i.e., about $1/71$. In other words, about 99.3% of this “undesirable” allele will be present in the heterozygotes of the population and about $1/71$ individual will have a 50% chance to pass it on to their children. If all the “undesirable” individuals are prevented from reproduction by sterilization the frequency of their “bad” gene (q_n) will change in 100 generations to:

$$q_n = \frac{q_0}{1 + 100q_0} = \frac{0.0071}{1 + [100 \times 0.0071]} \cong 0.004152$$

Thus, the initial gene frequency of 0.0071 will be reduced to about 0.004152 and the number of carriers by about 41% to $1/121$ in about 3,000 years. Also, behavioral traits are under the control of multiple genes, scattered in the genome, and each of them contributes partly to the phenotype. Furthermore, characters as these are under polygenic control and are greatly affected by environmental influences. Thus, the negative eugenic measures are biologically ineffective and ethically unacceptable in enlightened societies. Nevertheless, in the name of eugenics, Hitler’s regime exterminated six million Jews and millions of others of different ethnic groups, as well as sterilized more than 250,000 people. Negative eugenics, although it is quite ineffective as shown above, still may have some justification in some forms chosen by the individuals at high genetic risk of disease. The simplest humane and intellectually and ethically correct solution is refraining from reproduction. Therapeutic abortion is counterproductive because it may increase the number of carriers although the “defective” individuals (homozygotes) are eliminated.

Positive eugenics has some biological and ethical problems too because human values cannot be adequately assessed. Certain measures may, however, be acceptable and are practiced in societies without naming them as eugenics. For example, adequate scholarship to college students may facilitate their

support of a family and thus, presumably, intellectually better individuals may not be prevented from procreation because of economic hardship. Also, reproduction at a younger age may reduce chromosomal defects (see ►[Down's syndrome](#)). The Nobel-laureate geneticist H. J. Muller advocated positive eugenics throughout his career. He considered it a necessity to fight genetic load through *germinal choice*, meaning that spousal love should be separated from procreational role in marriage. He suggested the reliance of gene banks for artificial insemination of the women and recommended systematic screening of the sperm donors on the basis of health, intellect, and social consciousness. The sperm of the selected individuals were supposed to be stored frozen and used only some years after their death to make an objective and reliable assessment of their value. Although such a program may appear reasonable, problems in value judgment remain. Muller believed that in a true socialist political and social system these problems could be overcome. His own disenchantment with the Marxist society of the USSR proved, however, otherwise. Some general fears of intervention in the human system of reproduction are still not completely dissolved. Will the controlled insemination reduce the gene pool? Is it conceivable that the selection may foster the increase of some so far unforeseen genetic defects either by lack of recognition or by hitchhiking (linkage)? Is there a risk that political systems impose their selfish will upon the biologically desirable systems of reproduction? The problems of positive eugenics may not, however, be ignored. The progress in medical technologies prevents the selection against formerly inferior traits. The uses of medication, prosthetics, somatic gene therapy, etc., are devices of contraselection. Perhaps, the replacement of genes of the germline involved in clinically proven defects may offer a solution. The methodology now appears clear in principle, but the consequences are still untested. Thus, the “brave new world” is not yet at hand, primarily because our values cannot be defined in a simplistic manner. Eugenics must be separated from the racist views that discredited the field. Multiracial and multicultural societies offer unique advantages in their diversities for the betterment of life. Biologists must find the facts but the application of the principles discovered requires the democratic decisions of the ethicists and the societies. Will ethicists know enough biology? ►[gene therapy](#), ►[eutelegensis](#), ►[Hardy-Weinberg theorem](#), ►[sterilization in humans](#), ►[genetic counseling](#), ►[Galtonian inheritance](#); Kempthorne O 1997 *Genetica* 99:109; Li CC 2000 *Hum Hered* 50:22; Micklos D, Carlson E 2000 *Nature Rev Genet* 1:153; Gillham NW 2001 *Annu Rev Genet* 35:83; a historical display

on origin and flaws: <http://www.galton.org/>; <http://vector.cshl.org/>.

Euglena: A green (has chloroplast) flagellate protozoon, $n = 45$. (See Sheveleva EV et al 2002 *Nucleic Acids Res* 30:1247; <http://www.plantbiology.msu.edu/trie-mer/Euglena/Index.htm>).

Eukaryotes: Organisms with enveloped cell nucleus, mitosis, and meiosis, such as fungi, plants, and animals. The evolutionary origin of eukaryotes cannot be determined with certainty (see Fig. E51). Genomic data indicate that genes involved in transcription and translation and other processes of information are most likely descended from archaea, whereas genes involved in cellular metabolism such as synthesis of amino acids, cell envelope and lipid synthesis suggest eubacterial (proteobacteria, cyanobacteria, bacilli) origin. Conditioned reconstruction techniques used in connection with Markov-based quartet methods may overcome the problems with horizontal gene transfer and indicate that the eukaryotic genomes arose through the fusion of two different prokaryotic genomes, represented on the left and right sides of the figure. Thus, the evolution of eukaryotes indicates a ring of life, rather than the common evolutionary tree. ►[evolutionary tree](#), ►[archaea](#), ►[life form domains](#); Rivera MC, Lake JA 2004 *Nature [Lond]* 431:152; models of the origin of eukaryotic cells: de Duve C 2007 *Nature Rev Genet* 8:395; euGenes information system: <http://iubio.bio.indiana.edu/eugenet/>.

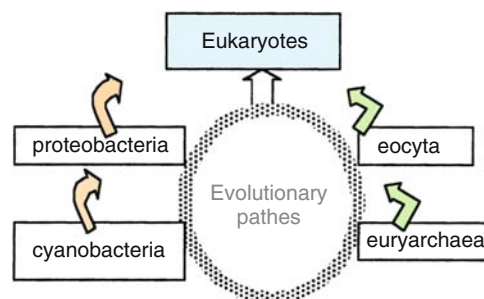


Figure E51. Eukaryotes

Eulerian Path: A mathematical solution for a DNA fragment assembly in a novel way. It is named after the mathematician L. Euler (1707–1783) who solved basic problems of sets like the Venn diagrams. ►[Venn diagram](#); Pevzener PA et al 2001 *Proc Natl Acad Sci USA* 98:9748.

Eunuch: A person whose testes have been removed by castration thereby preventing sexual functions. If this takes place early in childhood it reduces the expression of the secondary sexual characters.

E

Eunuchs were used in the Middle East and North Africa as guardians of the harems and chamberlains. The Chinese emperors employed hundreds of them in the Forbidden City as counselors. In Italy, until 1871, the “castrati” dominated the operatic stages and church choirs because these male sopranos and contraltos had high-pitched voices of a great range. The removal of the testes contributed to the increased development of the vocal folds and this combined with their greater capacities of the chest and lungs facilitated finer expression than expected from women who were banned from such roles on “moral” grounds. Medicine calls males eunuchs if their sexual function is diminished by underdevelopment of the genitalia or mutation in the sex hormone genes.

►castration

Euphenics: Corrective measures for genetically determined defects with the aid of nongenetic means (e.g., spectacles, prosthetics, insulin, etc.). ►eugenics

Euploid: Cells or organisms with one or more complete genomes, the full basic set(s) of chromosomes. ►aneuploid

Eusocial: The altruistic behavior of the sterile worker class in social insects supporting the fitness of the colony by tending to the needs of the reproductive casts. Ants, termites, bees, and wasps are eusocial insects. ►altruistic behavior, ►fitness, ►social insects; Wilson EO, Hölldobler B 2005 Proc Natl Acad Sci USA 102:13367.

Euteleogenesis: A form of positive eugenics where selected sperm sources are used for voluntary artificial insemination. The expected impact on improving IQ has been defined as: $\bar{x}_1 = p \frac{\bar{x} - M}{2} h^2 + M$ where \bar{x} = the mean IQ of the sperm donors, p = percentage of females involved, M = mean, h^2 = heritability. ►eugenics, ►heritability, ►human intelligence

Eutely: In some species of nematodes (*Caenorhabditis* and relatives) all individuals have the same cell number and all organs in all individuals show identical cell numbers. There are, however, some exceptions to this rule. ►*Caenorhabditis elegans*; Azevedo RBR, Leroi AM 2001 Proc Natl Acad Sci USA 98:5699.

Euthanasia: The method of causing “painless” death practiced on handicapped, seriously incapacitated, or fatally ill persons. Infanticide and late-term abortion are very cruel forms of euthanasia. These are morally unacceptable procedures in the majority of enlightened societies. The morality of euthanasia has been questioned even when it takes the form of a suicide although it may prevent the sufferings of terminally ill individuals. In the majority of countries, the law does not permit euthanasia, even in case of

severe illness. Euthanasia has no eugenic consequence because the objects are not expected to reproduce due to age or illness. Various scientific organizations issued guidelines for the humane and ethical principles for euthanasia of experimental animals (Demers G et al 2006 Science 312:700). In the Netherlands in 2002, after three decades of debate and research, the Euthanasia Act was passed to regulate the ending of life of people by a physician at the request of a patient who was suffering unbearably without hope of relief. A similar law was adopted in Belgium. The Oregon Death with Dignity Act legalizing physician-assisted suicide was enacted into a law in 1997. In 2005, 1.7% of all deaths in the Netherlands were the result of euthanasia, as compared with 2.6% in 2001. 0.4% of all deaths were the result of the use of lethal drugs, not at the explicit request of the patient. In 73.9% of all cases of euthanasia or assisted suicide in 2005, life was ended with the use of neuromuscular relaxants or barbiturates. Physicians also sometimes administered deep sedation when they had the explicit intention of hastening death (van der Heide A et al 2007 New England J Med 356:1957).

Eutherians: Eutherians are true placental mammals, but not the marsupials and monotrenes. ►marsupials, ►monotrene, ►X chromosome

eV: ►electron volt, ►Volt

Eva: A program that continuously and automatically analyses protein structure prediction servers “in real time”. (See <http://cubic.bioc.columbia.edu/eva/>).

Evans' Blue (direct blue): A strong oxidant and suspected carcinogen. It can be used for the isolation of intact protoplasts, which do not stain by it, whereas the damaged ones appear blue-green. ►protoplast

Eve Foremother of Molecular mtDNA: An evolutionary hypothesis attempting to trace the origin of the human race on the basis of mitochondrial DNA. Mitochondrial DNA in humans is transmitted only through the females and because of the uniparental transmission recombination cannot reshuffle the base composition of the mtDNA. Because of technical and computational difficulties, the assumption—that a single woman's descendants populate the earth—could not unequivocally be placed to Africa, and the investigators remained divided concerning the notion that all humans descended from a single female or even from a single group of females. Most likely, “Eve” represented a human population of 10,000 to 100,000 living about 150 to 200 kya (kiloyears ago). Some recent studies (based on the decline of linkage disequilibrium) indicate the possibility that paternal mitochondria may be transmitted during

fertilization and recombination may alter the maternal mtDNA sequences in larger blocks. ▶mtDNA, ▶genetic drift, ▶effective population size, ▶out-of-Africa, ▶Y chromosome, ▶F_{ST}, ▶mutation rate, ▶paternal leakage, ▶mitochondrial genetics, ▶archaeogenetics; Owens K, King M-C 1999 Science 286:451; Richards M, Macaulay V 2001 Am J Hum Genet 68:1315; Malhi RS et al 2002 Am J Hum Genet 70:905.

Eversporting: Organisms that carry unstable gene(s) and display somatic or germinal variegation. Many of the eversporting conditions are caused by the presence of transposable elements. ▶transposable elements, ▶transposons, ▶retrotransposons, ▶retroposons

Evi Oncogenes: Integration sites for retroviral insertions in human chromosome 3q24-q28, translocated to chromosome 5q34, resulting in nonlymphocytic leukemia. The Evi-1 mouse gene may cause murine leukemias. Its protein product has numerous zinc-finger domains and is presumably a transcription factor. The Evi-2A gene is in the proximal part of the long arm of human chromosome 17. The Evi-2B is in the same chromosome about 15 kb apart. Its product is apparently a transmembrane protein with surface receptor function. A homolog of these genes is associated with murine myeloid leukemia. The Evi-1 oncogene stabilizes the Emi1 inhibitor of the anaphase-promoting complex (Eldridge AG et al 2006 Cell 124:367). ▶leukemia, ▶oncogenes, ▶SMAD, ▶Evi, ▶Emi1

Evicting Plasmid: An evicting plasmid is incompatible with another type of plasmid and if selection is favoring the evicting plasmid (e.g., carries a gene for antibiotic resistance) the other plasmid can be eliminated. These operations can be used for the construction of particular genetic vectors. ▶vectors

Evidence Code: The evidence code indicates the type of evidence used for the annotation of a gene(s). ▶annotation

Evidence Viewer: An evidence viewer displays the alignments to human genome contigs of RefSeq and GenBank transcripts and ESTs supporting gene models. It points out mismatches between transcripts and genomic sequences are highlighted. It aligns transcripts exon-by-exon, including flanking genomic sequence for each exon. ▶EST, ▶exon, ▶mismatch, ▶RefSeq; <http://www.ncbi.nlm.nih.gov/Web/Newsltr/Summer03/index.html>.

Evocation: The induction of differentiation. ▶differentiation

Evo-Devo: A new term for evolutionary developmental biology. It studies the effect of development on the

direction of evolution, the relation between micro- and macroevolution, developmental genes across phylogenetic boundaries, etc. (See Arthur W 2002 Nature [Lond] 415:757).

EvoFold: A general comparative genomics method based on phylogenetic stochastic context-free grammars for identifying functional RNAs. Functional roles of RNAs are difficult to identify directly but their role can be assessed by comparative genomic surveys carried out among different genera and/or species (Pedersen JS et al 2006 PloS Comput Biol 2(4):e33). ▶AlioldZ, ▶RNAz, ▶RNA structural

Evolution: A process and theory of the biological and physical change that brings about the variety of the living world and its environment at the global and cosmic range. Biological evolution is based on changes in gene frequencies or function brought about by mutation, horizontal gene transfer, rearrangement by transposable elements, selection, migration, adaptation and fixed by reproductive isolation. The general evolutionary theory integrates all ideas about the nature, origin, and future of the universe. Evolutionary concepts can be supported by molecular, cytological, archeological, and other logical facts although the processes cannot be verified experimentally because of the lack of repeatability. Organic evolution is concerned with the origin, development, and relationship of living organisms of past and present. According to the most widely accepted current views, evolution came about in three major pathways: 1. Bacteria (including among others Proteobacteria and Cyanobacteria); 2. Eukarya (animals, fungi, plants); and 3. Archaea (Euryarchaeota, Crenarchaeota). The Proteobacteria became symbionts in Eukarya and evolved into mitochondria. The mechanism of replication, transcription, and translation of the Archaea group is more similar to those of the Eukarya than to that of the Bacteria. Cyanobacterial symbionts in plants developed into chloroplasts. Evolutionary studies are greatly facilitated by the genome-wide sequence information. The majority of protein-coding genes have homologs across widely different taxa. From nucleotide sequence data safe information on function cannot always be obtained. Comparison of gene sequences and regulatory elements reveal a great deal about the relationship of the species (Kellis M et al 2003 Nature [Lond] 423:241). In *Drosophila* some genes with substantial homology to chitinase genes actually encode imaginal disk growth factors. Genes with clear phenotypes or high level of expression are more likely conserved across phylogenetic boundaries.

A new phase occurred in evolution during the pre-Cambrian epoch when phylum and superphylum characters (*kernels* of genetic organization) emerged and subsequently conserved basic body plans of

higher organisms (such as bilateral and anterior-posterior organization). Subsequently, class and order characters determined morphological characters and size of body parts by acquiring new regulatory and metabolic systems. Different organisms share many of these regulatory networks. Through differentiation of gene batteries new functions potentiated speciation as seen in the modern living world (Davidson EH, Erwin DH 2006 *Science* 311:796).

E

Evolution is frequently contrasted with the views of creation as described in the Bible and holy books of other religions. The science of evolution is concerned with facts that can be experimentally studied with the available technological tools and has no room for faith, while the primary criterion of religion is the faith in its teaching. Thus, it is improper to compare these principles because they are not of the same nature and they are not required to support or exclude each other. The philosopher K.R. Popper defined the scientific method as “the criterion of potential satisfactoriness is thus testability, or improbability: only a highly testable or improbable theory is worth testing and is actually (and not merely potentially) satisfactory if it withstands severe tests—especially those tests to which we could point as crucial for the theory before they were ever undertaken.” At another place he says “...I refuse to accept the view that there are statements in science which we have, resignedly, to accept as true merely because it does not seem possible, for logical reasons, to test them.” Thus, testability and refutability are the most basic cornerstones of evolution. Evolution is using the methods of cytogenetics, population genetics, molecular biology and geological fossil records of the past to establish the relationship, origin and variation in the living world. Ideas about evolution that are not supported by the methods referred to above are just ideas but not science. With the progress of sequencing DNAs, RNAs and proteins, evolutionary studies are shedding light on mechanisms common to a wide range of organisms and assist in the solution of problems in health-related areas as well as improving the productivity of economically important organisms. Evolution is generally believed to be a *stochastic* (random) process in finite (small) populations and drift plays out the differences. In case the population is infinitely large, evolution may be *deterministic* (predictable on the basis of selective values) and selection has major importance. ▶Hardy-Weinberg theorem, ▶duplication, ▶reductive evolution, ▶orthologous loci, ▶paralogous loci, ▶genomics, ▶gene evolution, ▶genome evolution, ▶genome projects, ▶mutation, ▶migration, ▶selection, ▶speciation, ▶microevolution, ▶macroevolution, ▶phylogeny, ▶fossil records, ▶population genetics, ▶evolutionary trees, ▶evolutionary distance,

▶eukaryotes, ▶PAUP, ▶unified genetic map, ▶Eve foremother, ▶Y chromosome, ▶human evolution, ▶microsporidia, ▶covarion, ▶hovergen, ▶creationism, ▶acquired characters inheritance of, ▶horizontal gene transfer, ▶molecular evolution, ▶indel, ▶SNP, ▶mobile genetic elements; Rouzine IM et al 2001 *Microbiol Mol Biol Rev* 65:151; Cronk QCB 2001 *Nature Rev Genet* 2:607; Medina M et al 2001 *Proc Natl Acad Sci USA* 98:9707; Joyce EA et al 2002 *Nature Rev Genet* 3:462, evolution of the eye: Fernald RD 2006 *Science* 313:1914; adaptive evolution of plants and animals: <http://www.bioinfo.no/tools/TAED>.

Evolution and Base Substitutions: Base substitutions are generally estimated on the basis of number of changes per site per 10^9 years. Accordingly, the rates in various genomes are: mammalian nuclear 2–8, angiosperm nuclear 5.4, mammalian mitochondrial 20–50, angiosperm mitochondrial 0.5, angiosperm cpDNA single copy regions 1.5, angiosperm cpDNA inverted repeats 0.3. The high mutation rate of mammalian mtDNA may be the result of the deficiency in excision, photoreactivation and recombinational repair, as well as the low level of selection, and the ability of mtDNA's tRNAs to recognize all four synonymous codons within a family of amino acids. Base substitution rates in fungi as well as in plant mtDNAs are much smaller than in mammalian mtDNAs. Molecular evolution is generally interpreted on the basis of common descent of the nucleotide sequences. The orthogonal theories must accommodate the apparent facts of horizontal transfer by way of symbiosis and infections in both prokaryotes and eukaryotes. ▶base substitutions, ▶diversity, ▶evolution, ▶evolutionary distance, ▶nongenic DNA sequences, ▶Jukes-Cantor estimate, ▶parallel substitution, ▶orthologous loci, ▶plasmids, ▶retroviruses, ▶retrotransposons, ▶retrotransposons; Salse J et al 2002 *Nucleic Acids Res* 30:2316.

Evolutions and Duplications: Molecular evidence indicates that duplications have played important roles in evolution (see Fig. E52). Duplication may arise by unequal crossing over between similar genes and may occur repeatedly. The example in the diagram shows the molecular consequences of an unequal crossing over in the DNA at the level of the protein products. Human haptoglobins have two α and two β chains and when an unequal crossing over takes place, duplication is also detectable in the protein product. Genes encoding multiple protein subunits or members of complex genomes are less likely to be maintained by evolution (Yang J et al 2003 *Proc Natl Acad Sci USA* 100:15661). ▶unequal crossing over, ▶cluster homology region, ▶duplication, ▶deletion, ▶polyploidy in evolution; Ohno S 1970 *Evolution by Gene*

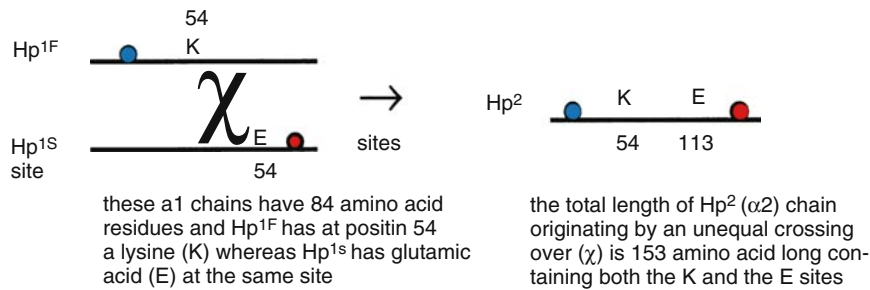


Figure E52. Evolution of duplication

Duplication. Springer, New York; Ku H-M et al 2000 Proc Natl Acad Sci USA 97:9121; *ibid.* p 4168; Vallente S R, Eichler EE 2002 Nature Rev Genet 3:65.

Evolution, Convergent: Homologous changes occur among distantly related organisms. ►[evolution parallel](#)

Evolution, Cost of: Evolution proceeds by replacing old alleles with new ones and the replacement may also sacrifice some individuals. This is the way the cost is paid. ►[genetic load](#)

Evolution, Directed: Directed evolution involves in vitro synthesis of proteins or polynucleotides with new functions. ►[mutation directed](#); Xia G et al 2002 Proc Natl Acad Sci USA 99:6597.

Evolution in vitro: Mutations in RNA molecules can occur in vitro during cell-free replication and may improve their catalytic and amplification rate. evolution, prebiotic.

Evolution, Non-Darwinian: Non-Darwinian evolution is supposed to take place by the fixation of neutral mutations in contrast to Darwinian evolution that postulates evolution by survival of the fittest. Because of the degeneracy of the genetic code, many mutations will leave the phenotype or function unaltered. There is no reason why these neutral mutations would not be fixed. Although it must be remembered that the codon usage in different genes and/or organisms is not identical, and the codon selection may have an adaptive nature. Also, there is no reason to doubt that certain amino acid substitutions have no effect on protein structure and function and thus appear without selective effect. Rapid evolution is favored by the fixation of neutral changes. If neutral mutations are fixed, there is no need for concomitant elimination of the old genotypes. Random genetic drift may also lead to changes in gene frequencies and possibly to evolution. ►[neutral mutation](#), ►[beneficial mutation](#), ►[drift](#)

[genetic](#); Matsuda H, Ishii K 2001 Genes Genet Syst 76[3]:149; King JL, Jukes TH 1969 Science 164:788.

Evolution of Amounts of DNA: There is tendency toward increased amounts of genetic material in the more highly evolved organisms. Viruses have generally less DNA than bacteria and microorganisms have smaller genomes than higher eukaryotes ►[genome](#). It is not entirely clear, however, why the total size of the genome varies by orders of magnitude among higher eukaryotes and, e.g., amphibians and several plants have much more DNA than humans. This is frequently called the C value paradox. ►[C amount of DNA](#), ►[C value paradox](#), ►[genome](#), ►[duplication](#), ►[deletion](#)

Evolution of Biological Information: Binding sites on nucleotide sequences. (See <http://www.lecb.ncifcrf.gov/~toms/paper/ev/>).

Evolution of Chemicals: ►[evolution](#), ►[prebiotic](#)

Evolution of Metabolism: <http://compbio.mcs.anl.gov/puma2/>.

Evolution of Organelles: The cytoplasmic organelles of eukaryotes, mitochondria, and plastids contain DNA but the base composition of this DNA displays very little similarity to that of the nucleus. The organellar DNA is usually circular versus the nuclear that is linear. The ribosomes in the organelles bear more similarities to prokaryotic ribosomes, being also 70S, in contrast to the ribosomes in the cytosol that are 80S. Several mitochondrial codons do not conform to the universal code words (►[mtDNA](#)) and no organisms are known that would have the same nuclear codon dictionary. Plastids use the universal codons. The mitochondrial genome probably has polyphyletic origins with major similarity to purple non-sulphur photosynthetic bacteria. The plastid genome may have derived from non-cyanobacterial oxygenic bacteria and it may be closest to *Prochloron*. The plastid genome is also most likely descended from more than a single species. It is assumed that

these organelles were captured by means of endocytosis of some lower organisms, perhaps repeatedly during evolution. The double membranes wrapping the cytoplasmic organelles may have their origin part from the ancestral donor part from the plasmalemma of the recipient cells. In the Euglenoids the plastids have triple membranes, suggesting that this is the relic of double endocytotic events. The size of the mitochondrial genome is very variable among the various organisms. In mammals, it is about 16 kbp but in the muskmelon it may be up to 2,400 kbp and in the majority of other plants varying generally between 200 and 500 kbp and thus exceeding those of the plastids, which are rather conservatively between 120 and 270 kbp. The amount of intergenic nuclear DNA in vertebrates is 0.65, in invertebrates 0.64 and in plants 0.68%. In the mitochondria of animals it is only 0.05 to 0.10, whereas in plant mitochondria the intergenic DNA fraction is ~ 0.72 . The mitochondrial mutation rate in animals is about 9–25 times higher than in the nuclei; in plant mitochondria the rate is however only 0.05 times higher than in the nuclei. In unicellular eukaryotes the mutation rates are about the same in the nuclei and mitochondria. The high level of free oxygen radical, the high rate of replication, and the loss of nucleotide excision repair and reduced mismatch repair cause the high mutation frequency in animal mitochondria. There is no general explanation for the differences in mutation rates of plant mitochondria (Lynch M et al 2006 Science 311:1727).

The transcriptional machinery in plastids and mitochondria resembles that of prokaryotes. Some of the chloroplast genes have upstream elements similar to the promoter sequences of bacteria. The plastid RNA polymerase is not inhibited by rifampicin whereas this antibiotic blocks transcription in prokaryotes. Both plastids and mitochondria have genes for rRNAs and tRNAs and these also resemble more the prokaryotic ones than that of eukaryotes in the cytosol. More than a dozen of the plastid genes and about three of the mitochondrial genes have introns, an uncommon feature of prokaryotes. Less than one third of the ribosomal proteins in the plastids are coded within this organelle, the rest is of cytosolic origin. This and other facts indicate that the acquisition of the organelles was followed by loss of some functions that could be taken care of by genes in the nucleus. There is also a regular import of proteins into the organelles from the cytosol, aided by the transit peptides of the nuclear-coded proteins. Nuclear genes encode the photosynthetic rubisco protein small subunits whereas the large subunits are transcribed and translated of plastid DNA. Also, organellar gene functions, including mutability, are regulated by nuclear genes. It appears that some DNA

sequences have homologs among the nucleus, plastids and mitochondria, indicating the availability of some DNA transfer mechanism(s). ▶mitochondria, ▶mtDNA, ▶chloroplast, ▶chloroplast genetics, ▶organelles, ▶ribulose1, ▶6-bisphosphate carboxylase-oxidase, ▶organelle sequence transfers, ▶*Rickettsia prowazekii*; Margulis L, Bermudes D 1985 Symbiosis 1:101; Delihans N, Fox GE 1987 Ann NY Acad Sci 503:92; Takemura M 2001 J Mol Evol 52:419; Sato N 2001 Trends Plant Sci 6:151; Selosse M et al 2001 Trends Ecol Evol 16:135; Wallace DC. 2007 Annu Rev Biochem 76:781.

Evolution of Proteins: The amino acid sequence in the proteins reflects the coding sequences in the DNA or RNA genetic material. Although the genetic code has synonymous codons, the primary, secondary, tertiary and quaternary structure reveals important information how proteins function. Adaptive evolution relies primarily on the expression of genes rather than on their structure, although the latter is important for tracing the path of this evolution. Certain proteins such as cytochrome c (coded by the nucleus but present in the mitochondria) reveals similarities and differences in the amino acid sequence in the widest range of eukaryotes and displays similarities even to bacterial cytochrome c2. Such analyses carried out two to three decades ago have shown that similar functions require similar structures. Furthermore, the similarities within apparently related groups are greater than among those that are more distant by any type of classification. Protein domains, which are essential for functions evolve at a restricted rate and are rather well conserved by physiological necessity and alterations are subject to negative selection. About 50,000 different protein family domains could be recognized in 2005 on the basis of three-dimensional structures (Lee D et al 2005 Proteins 59:603).

These studies brought recognition to the fact that some gene loci are *orthologous*, i.e., they seem to be directly connected by descent across phylogenetic groups whereas other genes, arising by duplication, (*paralogous loci*) may show greater difference in the primary structure because the ancestral copy of the gene could continue providing the needed function while the duplication was more free for (adaptive) evolutionary experimentation. Proteins may evolve by recruitment of new domains or by rearrangement of domain organization. New catalytic properties can now be created on existing protein scaffolds in the laboratory using biochemical techniques. Proteins encoded by linked genes appear to evolve at similar rates due apparently to the force of stabilizing selection. It is not entirely certain that organic evolution proceeds through the same path yet the

new enzymes are functional and technology provides means for the generation of enzymes not found in nature but which may have the advantage for biotechnology. It appears that indispensability (i.e., importance of presence for survival) and the level of expression affect evolution although their effects are independent from each other (Wall DP et al 2005 *Proc Natl Acad Sci USA* 102:5483). Highly expressed proteins, involved with networks evolve slowly, and a high level of expression is better correlated with their evolutionary rate than their function (Drummond DA et al 2005 *Proc Natl Acad Sci USA* 102:14338). ►homology, ►ribozymes, ►protein families, ►proteome, ►PRINTS; Altamirano MM et al 2000 *Nature [Lond]* 403:617; Williams EJ, Hurst LD 2000 *Nature [Lond]* 407:900; Gerlt JA, Babbitt PC 2001 *Annu Rev Biochem* 70:209; Aravind L et al 2002 *Current Opin Struct Biol* 12:392; Kinch LN, Grishin NV 2002 *Curr Opin Struct Biol* 12:400; Davis BK 2002 *Progr Biophys Mol Biol* 79:77; Fay JC 2003 *Annu Rev Genomics Hum Genet* 4:213; Orengo CA, Thornton JM 2005 *Annu Rev Biochem* 74:867; Pál C et al 2006 *Nature Rev Genet* 7:337; <http://www.ebi.ac.uk/goldman-srv/pandit/>, distant similarity search; <http://crick.mbu.iisc.ernet.in/~CASCADE/CascadeBlast.html>; software: <http://www.pantherdb.org/>, analysis of evolution of non-conventional structure and protein fold: <http://sisyphus.mrc-cpe.cam.ac.uk>; prokaryotic protein family definitions built to aid in high-throughput annotation of specific protein functions: <http://www.tigr.org/TIGRFAMs>.

Evolution of Recombination: The evolution of recombination is influenced by the physiological needs of the organisms such as improvement of genetic repair, chromosome distribution in mitosis and meiosis, etc. Alternatively, the breakage of linkage to disadvantageous genes may have adaptive value. The evolution of sexual reproduction aids both of these mechanisms. Under conditions of high (deleterious) mutations the increase in recombination frequency may be beneficial, and the reduction of linkage disequilibrium is expected. ►linkage disequilibrium

Evolution of Sexual Reproduction: In an asexually reproducing strain, two advantageous mutations must occur sequentially to be maintained by evolution. In a sexual population the advantageous mutations can occur in independent lineages because recombination can permit their incorporation. Also, sexual reproduction has an advantage in facile elimination of deleterious mutations. (See Felsenstein J 1974 *Genetics* 78:737; J Arjan GM et al 2007 *Nature Rev Genet* 8:139).

Evolution of the Genetic Code: The genetic code is practically universal with the exception of a few mitochondrial codons. Furthermore, the structures of tRNAs reveal much greater similarities than expectable on the basis of random assembly of the nucleotides. The most plausible interpretation of these facts is that these nucleotide sequences developed by an evolutionary process from common ancestral sequences and also indicate a relation of descent of eukaryotes from prokaryotes. It seems that the most archaic genetic code existed in RNA in the RNA world. The ancestral triplets probably escaped from the amino acid-binding sites and acquired new functions as codons and anticodons (escaped triplet theory, Yarus M et al 2005 *Annu Rev Biochem* 74:179). The original sequences were probably relatively short although they probably contained meaningless tracts mixed with useful ones. For the development of well-organized nucleotide sequences specifying an ancestral gene, mechanisms were required for the recognition and correction of errors. This ability probably evolved when the first DNA sequences appeared. Modern DNA polymerases are generally endowed with synthetic, proofreading and editing (endonuclease) functions. This was indispensable for the development of larger and conservative genetic molecules. The first codon probably specified those amino acids, which were most abundant among the molecules formed under abiotic conditions. It was suggested that the earliest codons were of the GNC type (where N is any base). This idea is supported by the fact that G=C base pairs having three hydrogen bonds are more stable than the A = T pairs and under simulated prebiotic conditions, glycine (GGC), alanine (GCC), aspartic acid (GAC) and valine (GUC) are produced in relative abundance. It is conceivable that these four amino acids formed the first protein involved in replication. The next three amino acids might have been glutamic acid, serine, and phenylalanine. These seven early amino acids could later have served as precursors of others, first through abiotic pathways; later the synthesis might have been facilitated by enzymes. The earliest codons might have been somewhat ambiguous aggregates of nucleotides. Later, each amino acid probably shared its codon with its daughter amino acid(s). The successive subdivision of codon domains is still reflected in the similarities of the codons among structurally related amino acids. Apparently, the expansion of the amino acid repertoire took place in parallel with the evolution of the code. Eventually, the assignment of all 64 codons was completed.

In the primordial dictionary, probably only the first two bases were required for the specification of an amino acid. Today, in most of the degenerate codon

domains, still, the first two positions are identical. Codons beginning with C specify amino acids derived from α -ketoglutarate; those starting with A encode amino acids of oxaloacetate metabolic origin; and those starting with U encode amino acids synthesized from pyruvate. Codons starting with G encode amino acids (glycine, alanine, aspartate, glutamate) formed by direct reductive amination of α -keto acid. Codons with U at the 2nd position specify the most hydrophobic amino acids and those codons, which have A at the 2nd place, encode the most hydrophilic amino acids. Simple amino acids might have been synthesized in covalent linkages with dinucleotides and the phosphates of the dinucleotides might have enhanced synthetic reactions (Copley SD et al 2005 Proc Natl Acad Sci USA 102:4442).

With the acquisition of new amino acids and new codons, the stability, specificity and efficiency of the primordial proteins adaptively changed. The archaic, ambiguous codons with lesser precision must have been then eliminated, culminating in the development of a codon dictionary common to prokaryotes and eukaryotes, as we know it today. Through functionally improved enzymes, faster and more reliable replicational processes emerged. As the efficient and precise replication, transcription and translation began, the prebiotic synthesis was no longer needed in this era, about 3 billion years ago. Some investigators have doubted the idea that high G + C content was required for origin of the code under high temperature. Also, it was suggested—on the basis of evolutionary calculations on ribosomal RNA—that life may not necessarily have arisen in a hot environment, but the high G + C content of thermophilic microbes might have been due to adaptive evolution.

Universality of the genetic code has been recently attributed to communal evolution permitting to share genetic information by horizontal gene transfer at the early stages. This processes led to the emergence of innovation-sharing protocols. In a following phase individual (Darwinian) evolution could proceed in a vertical manner. Thus, collective evolution was facilitated by utility of the mechanisms of translation in a Lamarckian sense (Vetsigian K et al 2006 Proc Natl Acad Sci USA 103:10696).

►spontaneous generation, ►origin of life, ►genetic code, ►code genetic, ►transcription, ►translation, ►prebiotic, ►operational RNA code; Rodin SN, Ohno S 1997 Proc Natl Acad Sci USA 94:5183;

Wakasugi K et al 1998 EMBO J 17:297; Davis BK 1999 Progr Biophys Mol Biol 72:157; Szathmáry E 1999 Trends Genet 15:223; Knight RD et al 2001 Nature Rev Genet 2:49; Sella G, Ardell DH 2002 J Mol Evol 54:638; Szathmáry E 2003 Nature Rev Genet 4:995; Yang X-L et al 2003 Proc Natl Acad Sci USA 100:15376.

Evolution of the Karyotype: The chromosome number is a rather good characteristic of related species. Cytotaxonomists define homologies among taxonomic groups on the basis of the karyotype, the morphology of the chromosomes at (generally) metaphase. Some important landmarks of the chromosomes (chromomeres, band, knobs) can be better visualized at prophase (pachytene). Some chromosomal aberrations (inversions) are identified also at anaphase. Salivary gland (polytenic) chromosomes reveal a great deal of morphological information on the chromosomes. With the introduction of the “banding techniques” (Giemsa, C-banding) various taxonomic groups can be rather well defined. Various chromosomes or chromosomal segments can be identified by in situ hybridization with DNA probes “painted” with fluorochromes of various colors (such as fluorescein isothiocyanate [FITC, green], Spectrum Orange [red], 4',6'-diamidino-2-phenyl indole [DAPI, blue fluorescence in UV], biotin derivatives, etc.), and the genomes in amphiploids can be distinguished. Although the number of chromosomes may vary even in closely related taxonomic groups because of centromeric fusion or fission of telochromosomes and bi-armed inversions, by analysis of the natural banding pattern of salivary gland chromosomes, inversions could be traced among related species (see Fig. E53).

By analysis of the natural banding pattern of salivary gland chromosomes, inversions could be traced among related species. Acrocentric chromosomes may undergo Robertsonian translocation changes in chromosome numbers by making from two acrocentrics one bi-armed chromosome (quite common in mice).

If, for e.g., chromosome arms A and B as well as A and D, and similarly, D and C as well as C and B are fused in diploid cells, at meiotic metaphase I, the configuration (see Fig. E54) is displayed.

Such a situation may lead to sterility, reproductive isolation, and eventually speciation. Although inversion heterozygosity may lead to sterility depending on the frequency of crossing over in the inverted

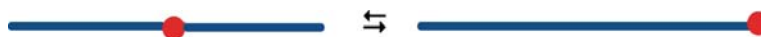


Figure E53. Conversion of metacentric chromosome into telochromosome

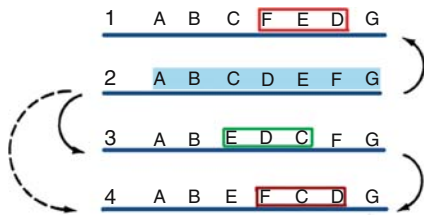


Figure E54. Tracing the origin of chromosomal inversions

segment, many wild populations contain various types of inversions. Paracentric inversions do not affect the fertility of the females (either in plants or animals) because the inversion bridge prevents the incorporation of the crossover chromosomes into the eggs (►inversions paracentric). Chromosomal inversions can frequently be traced in the polytenic chromosomes. Inversions may occur repeatedly and may partially involve the same chromosomal segment each time (see Fig. E55).

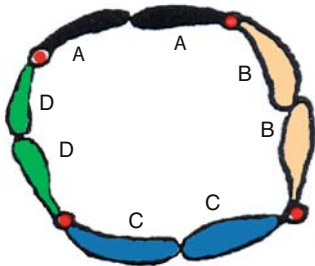


Figure E55. Robertsonian translocation ring

The serial origin of such inversions can be detected. Molecular analysis of *Drosophila* chromosomes confirms the cytological evidence that extensive reshuffling has taken place during evolution. ►inversions, ►chromosome painting, ►comparative chromosome painting, ►comparative genomic hybridization, ►chromosome banding, ►telochromosome, ►microinversions, ►Robertsonian translocation, ►acrocentric, ►reproductive isolation, ►polyteny, ►duplication, ►deletion, ►karyotype, ►karyotype evolution; Ranz JM et al 2001 Genome Res 11:230; Nurminsky D et al 2001 Science 291:128; Gonzalez J et al 2002 Genetics 161:1137; Posada D et al 2002 Annu Rev Genet 36:75; mammalian chromosome evolution—comparative maps: Murphy WJ et al 2005 Science 309:613.

Evolution, Parallel: Parallel evolution involves homologous features among closely related organisms. ►evolution convergent

Evolution, Prebiotic: Before living cells appeared on earth, organic molecules must have been formed. In

1953, Stanley Miller and Harold Urey showed that when mixtures of ammonia, methane, hydrogen, and water were exposed to electric sparks (simulating stormy conditions of the early atmosphere), carbon monoxide, carbon dioxide, amino acids, aldehydes and hydrogen cyanide were generated during the experiments lasting for several weeks. Later, more extensive experiments revealed hundreds of organic molecules under such simulated abiotic conditions. It was of particular significance that more than ten different amino acids, various carboxylic acids, fatty acids, adenine, sugars, etc., could be obtained in abiotic experiments with increased sophistication. HCN and heavy metal ions present in the early earth environment and in laboratory simulation could promote polymerization. Carbonyl sulfide ($O=C=S$, a volcanic, inflammable gas with potential health hazards) forms peptides from amino acids under mild conditions, at room temperature with high efficiency (Leman L et al 2004 Science 306:283). Thus the conclusion appeared logical that primitive macromolecules could be formed de novo and the macromolecules required for life could eventually evolve. Amino acids, under anaerobic aqueous conditions at 100°C and pH 7 to 10—in the presence of NiS, FeS and CO, and H₂S or CH₃SH as catalysts—coprecipitate and form peptides. ►origin of life, ►spontaneous generation unique and repeated, ►abiogenesis, ►evolution in vitro, ►evolution of proteins, ►evolution of the genetic code; Brack A 1999 Adv Space Res 24:417.

Evolution, Retrograde: ►retrograde evolution

Evolutionary Clock (molecular clock): The evolutionary clock measures the time required for 1% amino acid replacement in a protein in a million years (MY). It is based on the assumption that mutations are neutral and occur at random and the amino acid changes reflect the time elapsed since a particular event. The molecular clocks may be biased because of selection. A better procedure is to determine the rate of nucleotide substitution in homologous genes because mutation in synonymous codons does not lead to amino acid replacement. The rate of protein evolution is frequently expressed as the accepted number of point mutations per 100 residues in the protein. This parameter is generally symbolized with the acronym PAM. The rate of amino acid substitution per site per year was estimated to be, on average, 10^{-9} , which is frequently referred to as the “pauling” unit of molecular evolution (named after the Nobel-Laureate chemist, Linus Pauling). Individual proteins evolve at very different rates (see Table E1). Perhaps better comparisons can be made if enzymes rather than other proteins are used. There are differences in

Table E1. Amino acid substitution rates

| Proteins | Amino acid substitutions per residues per million years |
|-------------------------|---|
| Fibrinopeptides | 90 |
| Pancreatic ribonuclease | 33 |
| Hemoglobins | 14 |
| Cytochrome C | 3 |
| Histone 4 | 0.06 |

substitution rates among different organisms. Mitochondrial base substitutions involve similar differences. The data may be biased if orthologous and paralogous loci cannot be safely distinguished. From the comparison of enzymes it appears that eukaryotes and eubacteria shared common ancestors about 2 billion years ago. The divergence of plants and animals took place about 1 billion years ago. The similarity of fungi to animals is somewhat better than to plants. The molecular evolutionary clocks cannot adequately estimate evolution because of the highly different rates of amino acid or base substitutions in individual proteins and genes, respectively. Recently, multiprotein sequences have also been used with promise for improved estimates. In addition, there is no comforting proof that the molecular clocks ticked uniformly through the ages. Another problem is the not infrequent discrepancy between the molecular and the paleontological estimates. It appears that the molecular clock (mutation) depends on the metabolic rate of the organisms and also on the prevailing temperature and these factors should be considered in the estimations (Gilloly JF et al 2005 Proc Natl Acad Sci USA 102:140). The rate of evolution of the molecular clock is in decreasing order: human > chimpanzees > gorillas > orangutans (Elengo N et al 2006 Proc Natl Acad Sci USA 103:1370). Unfortunately, the evolutionists do not have many choices.

In a somewhat similar manner the progression of a cancerous tumor can be reconstructed. Colorectal tumors may be caused by the loss of genes controlling mismatch repair (MMR). The loss of MMR also involves the expansion of microsatellite sequences. Microsatellites are expanded during cell divisions and thus the expansion—relative to the noncancerous or nonexpanded state—indicates the number of cell divisions since the loss of MMR. The mass spectrometric method of deamidation of glutaminy and asparaginy residues in peptides has also been developed as molecular timers. ▶racemate, ▶orthologous, ▶paralogous, ▶Eve foremother, ▶Y chromosome, ▶microsatellite, ▶colorectal cancer,

▶radiocarbon dating; Robinson NE, Robinson AB2001 Proc Natl Acad Sci USA 98:944; Nei M et al 2001 Proc Natl Acad Sci USA 98:2497; Bromham L, Penn D 2003 Nature Rev Genet 4:216; history of development of concepts: Kumar S 2005 Nature Rev Genet 2005 6:654.

Evolutionary Distance: Evolutionary distance can be numerically estimated on the basis of allelic differences (amino acid differences in proteins, RFLPs, nucleic acid base sequences, etc.). It must be remembered that evolution may proceed either by divergence or convergence of whatever criteria are used (see Table E2). When larger number of loci is used the greater the accuracy of the estimate. There are several procedures in the literature. Here the method of Nei (Molecular Population Genetics, Elsevier/North Holland, 1975) will be illustrated. The normalized identity of alleles in populations is determined by dividing the arithmetic means of the products of allelic frequencies by the geometric means of the sum of squares of the homozygote frequencies in each population to be compared.

$$I = \frac{\{[p1 \times p2] + [q1 \times q2]\}/L}{\sqrt{\{[p1^2 + q1^2] \times [p2^2 + q2^2]\}/L^2}}$$

where *I* is the index of identity, *p* and *q* are allelic frequencies in the two populations and *L* is the number of loci studied (including even those with single allele representation). The evolutionary (genetic) distance is then calculated from the natural logarithm of *I*, i.e., *D* = -log_e*I*. This type of calculation is meaningful and reliable if a minimum of 25 loci is compared. It can be used with any type of alleles, including even proteins of different electrophoretic mobilities. An example for the procedure is given in table. By using the procedure outlined, the human racial distance and the number of years of divergence have been estimated (after M Nei, AK Roychoudhury 1974 Amer J Hum Genet 26:421) and it turned out to be minimal:

The evolutionary distance can be estimated more precisely on the basis of nucleotide sequence and replacements (Kimura M 1980 J Mol Evol 16:111): The pyrimidine ⇌ pyrimidine and the purine ⇌ purine substitutions are designated as *P* and the pyrimidine ⇌ purine or purine ⇌ pyrimidine transversions are represented by *Q*. The evolutionary distance *K* is

$$K = -(0.5)\log_e[(1 - 2P - Q)\sqrt{1 - 2Q}]$$

The standard error of *K*:

$$s_k = \frac{1}{\sqrt{n}} \{ \sqrt{[a^2P + b^2Q] - [aP + bQ]} \}$$

Table E2. Evolutionary distance

| Human races | Genetic distance | Years of divergence |
|--------------------------------------|------------------|---------------------|
| Caucasoid - African Negroid | 0.023 | 115,000 |
| Caucasoid - Oriental Mongoloid | 0.011 | 55,000 |
| African Negroid - Oriental Mongoloid | 0.024 | 120,000 |

where $a = \frac{1}{1-2P-Q}$ and $b = 0.5 \left[\frac{1}{1-2P-Q} + \frac{1}{1-2Q} \right]$

In a sequencing study of the 438 nucleotide β -globin genes of chicken and rabbit the P value was $58/438 = 0.132$ and $Q = 63/438 = 0.144$, and after the appropriate substitutions the evolutionary distance thus appeared to be 0.347 ± 0.0329 .

The time of divergence (in million years) varies according to the specific gene and taxonomic category considered, e.g., in Echinodermata–Chordata, Annelida–Chordata for ATPase: 786 and 1059, for cytochrome: 883 and 1078, for cytochrome oxidase I: 1160 and 1465, for cytochrome oxidase II 608 and 773, for 18S RNA: 1288 and 1214, respectively. ▶DNA sequencing, ▶array hybridization, ▶amino acid sequencing, ▶evolutionary tree, ▶genetic distance, ▶minimum evolution method, ▶four-cluster analysis, ▶neighbor joining method, ▶evolutionary tree, ▶least square methods, ▶transformed distance, ▶Fitch–Margoliash test, ▶DNA likelihood method, ▶protein-likelihood method, ▶nucleotide diversity, ▶ F_{ST} , ▶ $[\delta\mu]^2$; Tamura K, Nei M 1993 Mol Biol Evol 10:512, <http://warta.bio.psu.edu/DED/>.

Evolutionary Substitution Rate: Estimates the number of mutations leading to an evolutionary divergence in a million years: $\sum \frac{(d_{ij}-2d_{ik})}{n_i n_j} \times \frac{1}{t_j}$ where d_{ij} and d_{ik} are the number of the DNA base substitutions per number of sites in genotypes i and j and between genotype i and evolutionary tree node k , respectively; $n_i n_j$ are the number of pairwise comparisons, t is the time in million years when the i genotype was deposited in the rock stratum and the k is the node furthest from the common root. ▶evolutionary tree, ▶evolutionary distance, ▶PAUP

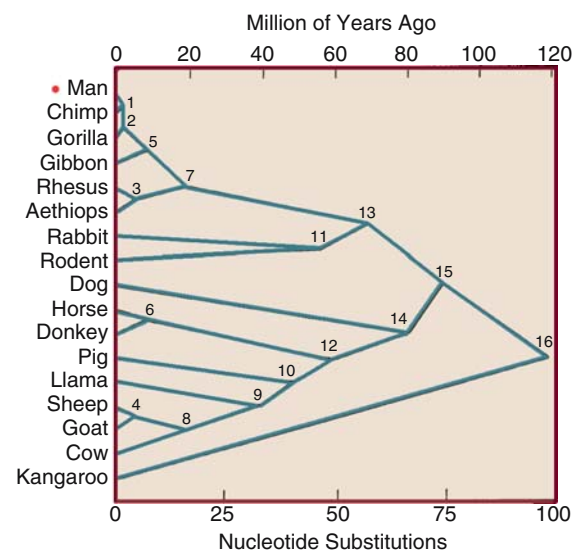
Evolutionary Tree: Displays the descent of organisms from one another. Initially trees were constructed on the bases of morphological traits, and later on the basis of chromosome numbers and pairing affinities in hybrids and chiasma frequencies. The former criteria are not well quantifiable; the latter features are applicable to only relatively closely related forms because of the sexual isolation among distant species.

The numbers of substitutions at large or all comparable sites of macromolecules provide the most accurate information.

Evolutionary trees based on nucleotide sequences are more reliable than those based on proteins because silent genes are not included in the proteins. Since DNA sequences are available in several organisms, nucleotide sequence alignment and percentage of homologies are frequently used. Caution may be necessary to interpret evolutionary trends because the similarities or differences can be brought about either by convergence or divergence or lateral transfer. In prokaryotes lateral gene transfer—based on >220,000 proteins in 144 organisms—can obscure the line of descent in some instances (Beiko RG et al 2005 Proc Natl Acad Sci USA 102:14332). From the nucleotide sequences in the DNA, the amino acid sequence in the protein can be relatively easily inferred on the basis of the genetic code with some caution. Before nucleotide sequencing became practical in the late 1970s, amino acid sequencing was available and many of the evolutionary trees constructed were based on protein primary structure.

An evolutionary tree of mammals has been constructed on the basis of molecular clocks of seven proteins (see Fig. E56). The right end of the tree was fixed by paleontological information on marsupial divergence from the placental mammals, an estimated 120 million years ago. The nodes of divergence are based on the putative nucleotide substitutions in the seven coding genes. (After Fitch WM, Langley CH 1976 Fed Proc 35:2092).

From 300,000 protein sequences, the *Tree of Life* has been constructed for the evolution of all


Figure E56. Evolutionary tree

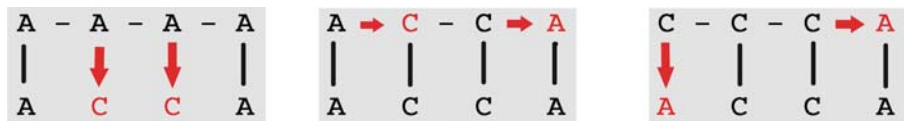


Figure E57. Possible amino acid substitutions

E

organisms although large gaps still remain because not enough data is available in the databases (Driskell AC et al 2004 Science 306:1172).

Since amino acids have up to six synonymous codons, there is no simple way from the amino acid positions in the protein to determine the nucleotide sequence in the gene. Furthermore, as evolutionists rely on the principle of *maximal parsimony*, i.e., they suppose that the actual evolution took place in the simplest possible way (what may not be true). Let us assume that the nucleotide sequence A C C A is the result of evolution (see Fig. E57). Through two mutational events (indicated by →) the original sequence may have changed the following ways:

Let us assume that in three different taxa (or orthologous loci) at a particular site, valine, leucine and serine are found (see Fig. E58). Valine has four code words (GTT, GTC, GTA, GTG), leucine has six (TTA, TTG, CTT, CTC, CTA, CTG), and serine has six as well (TCT, TCC, TCA, TCG, AGT, AGC). A single mutation may replace the first G of the valine codon by T and a second mutation may lead to a T→C change at the second nucleotide and thus in place of a valine residue serine may occur. From the four valine triplets only two may result in serine codons via two mutational events.

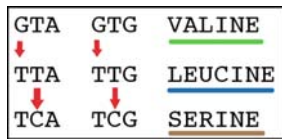


Figure E58. Possible routes from valine to serine

There are many ways to construct evolutionary trees and each has advantages and disadvantages under a particular condition (see Fig. E59). Evolutionary trees of genes may not be the same as phylogenetic trees because individual genes evolve at different rates. The evolutionary trees constructed by different methods appear different depending on type and number of markers used (Kolaczowski B, Thornton JW 2004 Nature [Lond] 431:980). A ring of life may best represent the evolution of eukaryotes. (<http://www.astrobio.net/cgi-bin/h2p.cgi?sid=1191&ext=.pdf>). ▶evolutionary distance, ▶phylogenetic tree, ▶gene tree, ▶microarray hybridization, ▶population tree, ▶indel, ▶rooted evolutionary tree, ▶unrooted evolutionary tree, ▶eukaryotes, ▶DNA sequencing, ▶lateral transmission, ▶amino acid sequencing, ▶METREE, ▶patristic distance, ▶PAUP, ▶heuristic search, ▶exhaustive search, ▶four-cluster analysis, ▶least square methods, ▶Euclidean distance, ▶transformed distance, ▶branch length, ▶Fitch–Margoliash test, ▶DNA likelihood method, ▶protein likelihood method, ▶neighbor joining method, ▶UPGMA, ▶bootstrap, ▶homoplasy, ▶lateral transfer; Miyamoto MM, Ctacraft J 1992 Phylogenetic Analysis of DNA Sequences, Oxford Univ. Press for detailed discussions, Holder M, Lewis PO 2003 Nature Rev Genet 4:275; Seao T-K et al 2005 Proc NatlAcad Sci USA 102:4436; software: <http://evolution.genetics.washington.edu/phyip/software.html>.

Evolvability: The ability to evolve. Evolvability in viruses is generally considered an adaptive response to natural selection. In RNA virus φ6 the experimental

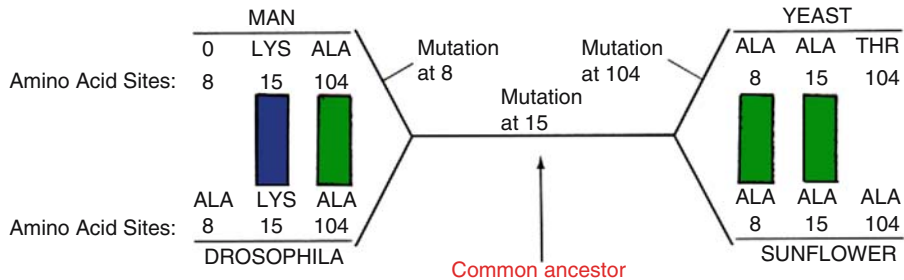


Figure E59. An over-simplified example for construction of a protein evolutionary tree. Mutation at site 15 separates the left from the right. Mutation at site 8 distinguishes man from *Drosophila* and site 104 yeast from sunflower. (Constructed after Dayhoff, M et al. 1972 Atlas of Protein Sequence and Structure Vol.5 Natl. Biomed. Res. Found. Washington, DC)

data indicate that advantageous genes favor the accumulation of advantageous mutations in their vicinity. Pigliucci, M 2008 *Nature Rev. Genet.* 9:75, ► [hitchhiking](#)

Evoprinter: A software for the detection of evolutionarily conserved DNA sequences in a species (Odenwald WF et al 2005 *Proc Natl Acad Sci USA* 102:147000).

Ewing Sarcoma: ► [EWS](#), ► [sarcoma](#), ► [neuroepithelioma](#)

EWS: Ewing sarcoma oncogene; a binding protein, encoded at human chromosome 22q12. In Ewing sarcoma translocations t(11;22)(q24;q12) are common but several other types also occur. ► [FLI](#), ► [gene fusion](#)

Ex Vivo: An operation carried out outside the body, but the manipulated organ or gene is returned to the body. For example, genetically engineered cells are introduced into a specific tissue as a means of gene therapy. ► [in vivo](#), ► [in vitro](#), ► [gene therapy](#)

Exact Test: ► [Fisher's exact test](#), ► [association test](#), ► [G test](#)

Exaggeration: A recessive mutation in one chromosome and a deficiency for the same site in the homologous chromosome results in a more extreme mutant phenotype than homozygosity for the same recessive mutation. (Mohr OL 1923 *Indukt Abstamm-Vererb-Lehre* 30:279).

Exaptation: When an adapted function is modified to become useful for a different biological function. An originally nonadaptive feature may become adaptive during evolution. A short interspersed repeat (SINE) of a 410-million-years-old coelacanth evolved into an enhancer of mammals; a 200-bp ultraconserved region is practically identical in an exon of the messenger RNA processing genes PCBP2 of modern day mammals and the “living fossil” Indonesian coelacanth *Latimeria menadoensis* (Bejerano G et al 2006 *Nature [Lond]* 441:87). ► [coelacanth](#)

Exchange Pairing: Chromosomes that have paired and recombined in meiosis are distributed normally to the pole. ► [distributive pairing](#), ► [chromosome pairing](#)

Exchange Promoting Protein (EP): Increases the separation of GDP from the bound form (E.GDP) in signal transduction. ► [GDP](#), ► [E.GDP](#)

Excimer (excited dimer): Excitation by light can raise the energy levels and two molecules can occupy, as a dimer, the same level of molecular orbital. Vertical base stacking, and not base pairing, determines the fate of singlet electronic states. In ultraviolet irradiated A≈T DNA in B form double helix excimers

are limited to one of the strands and enable repairing the damage by using the undamaged strand as a template (Crespo-Hernández CE et al 2005 *Nature [Lond]* 436:1141). ► [base stacking](#), ► [pyrene](#), ► [platelet-derived growth factor](#)

Excinucleases: ► [DNA repair](#)

Excipient: A molecule added to proteins for protection from degradation during storage.

Excision: The release of a phage, insertion element, episome or any other element or DNA sequence from a nucleic acid chain. In *precise excision*, for the affected or involved sequence, the “wild type” DNA is copied from the homologous DNA strands and thus substituted for the stretch. Any interruption of this repair copying may result in retaining some parts of the inserted piece and thus resulting in *imprecise excision*. ► [transposable elements](#), ► [transposons](#), ► [T-DNA](#), ► [insertion elements](#), ► [episome](#)

Excision Repair (dark repair, NER, BER): The removal of damaged DNA segments followed by localized replacement (unscheduled DNA synthesis). In excision repair, a DNA glycosylase excises the damaged base and then the abasic deoxyribose is removed by AP endonucleases. In nucleotide excision repair, an enzyme system hydrolyzes the phosphodiester bonds on both sides of the damaged single-strand tract and the sequence including the defect (12–13 nucleotides in prokaryotes, and 27–29 nucleotides in eukaryotes) is removed by excinucleases. Subsequently, the gap is refilled by repair polymerase and the ends are religated. The gap filling process by DNA polymerases δ and ϵ is highly accurate involving $\sim 10^{-5}$ errors. These enzymes correct incorporation errors by 3'→5'-exonuclease function. The first 15 nucleotides are added by pol α and β but they, by lacking exonuclease function, start the replication much less faithfully. DNA pol β by repairing single-nucleotide gaps makes errors in the range of $3-5 \times 10^{-3}$. Fortunately, DNA ligase III refuses to join mismatched ends and a mammalian exonuclease (homolog of the bacterial Pol III subunit encoded by DnaQ) then may correct the wrong base. Similarly, in prokaryotes Pol III is endowed by both 3'→5' and 5'→3' editing functions. Another solution to avoid the DNA damage without excision is provided by the yeast DNA polymerase ζ (and its homolog in humans) that can bypass pyrimidine dimers and other adducts and may incorporate in their place the correct nucleotides. The Rev1 (human hREV1) protein encodes a template-dependent deoxycytidylic acid transferase that can mediate translesion and insertion of a base opposite to a gap. The DNA polymerase η

can insert two adenylic residues opposite to a thymine dimer and thus saves the otherwise damaging situation. Excision repair genes have been identified in many organisms, including mammals. XPA (human single-strand binding protein [HSSB]) and its homologs (Rpa in yeast) are essential binding proteins for nucleotide exchange repair. The damage-binding proteins (DDB or UV-DDB) generally recognize defective areas caused by photo-adducts. These proteins may recruit others such as XPC (human) and some similar proteins of yeast (Rad4 and Rad23). The transcription complex TFIIH is composed of several subunits required for repair (XPB and XPD in humans) and in yeast (Ss12 and Rad3). TFIIH contains also kinases (CDK2). The human excision repair genes were identified by genetic transformation of UV-sensitive Chinese hamster cells with human DNA (excision repair cross-complementing genes, ERCC). Gene ERCC3 (human chromosome 2q21) appears to be at the locus responsible for xeroderma pigmentosum type II (B) and it controls an early step of excision repair involving a DNA helicase function; it is also associated with the basal transcription factor TFIIH. ERCC1/XPF (*RAD10*) endonuclease appears to be in human chromosome 3 and it is involved with xeroderma pigmentosum F. ERCC2 is in human chromosome 19, ERCC4 in chromosome 16, and ERCC5 (rad2) in chromosome 13q22. Excision repair gene UV-135 (ERCC2) appears to be in human chromosome 13 and UV-24 in chromosome 2. Transcription factor TFIIH is also involved in nucleotide excision repair in transcriptionally not active DNA, in cooperation with Rad 2 and Rad4. Pol δ and pol ϵ in cooperation with PCNA (proliferating cell nuclear antigen) and RFC (replication factor) auxiliary proteins may carry out repair synthesis.

►DNA repair, ►oxidative DNA damage, ►mismatch repair, ►AP endonucleases, ►ABC excinucleases, ►excision repair bioassays, ►X-ray repair, ►UVRBC, ►ultraviolet light, ►pyrimidine dimer, ►glycosylases, ►photolyase, ►phosphodiester bond, ►DNA ligase, ►DNA polymerases, ►DNA ligase, ►cyclobutane dimer, ►adducts, ►xeroderma pigmentosum, ►Cockayne syndrome, ►Bloom's syndrome, ►trichothiodystrophy, ►light-sensitivity diseases, ►transcription factors, ►translesion; Sancar A 1996 Annu Rev Biochem 65:43; de Laat WL et al 1999 Genes & Development 13:768; Mol CD et al 1999 Annu Rev Biophys Biomol Struct 28:101; BER workshop papers: Moldave K ed 2001 Progr Nucleic Acid Res Mol Biol 68.

Excision Repair Bioassays: Excision repair bioassays are essentially biochemical procedures. The mutagen may cause the formation of cyclobutane rings, alkylation

of bases, formation of covalent adducts between bases and the reactive chemical, depurination of the DNA, interstrand cross-links in the DNA, cross-links between DNA and protein, breakage of the phosphodiester bonds, intercalation of the mutagen between DNA bases, etc. The defects are detected in the extracted DNA cleaved by acids (formic acid or trifluoroacetic acid). The acid hydrolysis does not give as reliable results as the use of DNase or phosphodiesterase enzymes. The free bases and the pyrimidine dimers are analyzed by one-dimensional or two-dimensional paper or thin-layer or column or Sephadex or Dowex chromatography. By similar procedures the alkylated bases can be identified. Identification of adducts has been attempted by using radiolabeled mutagens and detecting the sites of the adduct formation. This procedure, however, is not completely reliable. The use of single-strand specific nucleases may detect the consequences of strand breakage resulting in strand separation liable to digestion by these nucleases. DNA breakage has also been evaluated by centrifugation of the extracted DNA in 5–20% alkaline sucrose-gradients where the intact DNA peaks closer to the bottom of the centrifuge tube while the damaged one floats at the lower sucrose concentration areas. A different type of approach is to provide radioactively labeled bases after the mutagenic treatment and monitor the extent of repair replication that is supposed to be increased if the mutagen damages the DNA. The extent of repair is reflected by the increase in radioactivity in the DNA. Adding bromodeoxyuridine (BrDU) to the mutagen-treated DNA can assess extensive repair replication. Incorporation of BrDU increases the buoyant density of the DNA and that is detectable upon separation by ultracentrifugation. Another variation is the exposure of BrDU containing DNA tracts to irradiation by 313 nm UV-B. The patches containing the analog are cleaved by this and thus reveal, by photolysis, the original sites of damage. ►unscheduled DNA synthesis, ►ultracentrifuge, ►ultraviolet light, ►buoyant density, ►bioassays in genetic toxicology, ►mutation detection, ►site-specific mutation; Rédei GP et al 1984 In Chu EHY, Generoso WM (Eds.), Mutation Cancer and Malformation, Plenum, New York p 689; Pavlov YI et al 2006 Int Rev Cytol 255:41.

Excision Vector: An excision vector carries the prokaryotic *Cre* gene (see Fig. E60). If a mouse is transformed by *Cre* and its mate carries a gene closely flanked by loxP, then their F₁ offspring (or any heterozygote) may evict the targeted gene as shown on the diagram. ►*Cre*, ►targeting genes, ►homologous recombination

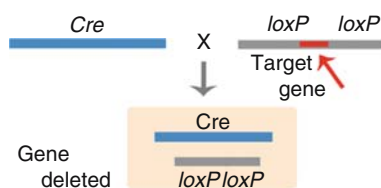


Figure E60. Excision vector

Excitation: Illumination with ultraviolet light may raise transiently the orbital electrons of an atom to a higher level of energy. Such excitation may lead to electron loss and may be sufficient to cause mutation although the level of energy may drop back to ground level. ▶ultraviolet light, ▶electron

Excitatory Neurotransmitters: Excitatory neurotransmitters open cation channels and facilitate the influx of Na^+ to depolarize postsynaptic membranes. ▶acetylcholine, ▶glutamate, ▶serotonin, ▶neurotransmitter

Excited State: An energy rich atom or molecule after the absorption of light energy.

Excitotoxicity: Natural and man-made compounds with glutamic acid resemblance may excite the central nervous system and cause excessive Ca^{2+} influx across the postsynaptic membrane resulting in neural death by mitochondrial permeability transition. Excitation of the neurons is essential for brain activity but its excess is toxic and must be protected against. The cannabinoid receptor (CB1) provides a homeostatic mechanism. Kainic acid and several other compounds have the opposite effect. ▶cannabinoids, ▶synapse, ▶kainate; Marsicano G et al 2003 Science 302:84.

Exclusion Mapping: Exclusion mapping can be used to eliminate a certain DNA tract from being linked to a particular gene. (See <http://www.wardsystems.com/products.asp?p=genehunter>).

Exconjugant: Ciliates (*Paramecia*) may pair (conjugate) and the paired cells mutually fertilize each other followed by separation of the two, now diploid cells, the exconjugants. ▶*Paramecium*

Exencephaly: An overgrowth of mid-brain neural tissue (the brain may be outside the cranium) caused by a defect in protein p53. ▶p53, ▶neural-tube defects, ▶Gadd45

Exergonic Reaction: An exergonic reaction releases free energy.

Exflagellation: The transformation of the nonmotile *Plasmodium* male gametocyte into the very motile male gamete in the mosquito, triggered by xanthurenic acid, a derivative of tryptophan. ▶malaria, ▶*Plasmodium*

Exhaustive Search: A procedure of constructing an evolutionary tree by analyzing several individuals to calculate the length of the branches of evolutionary trees. ▶heuristic search, ▶PAUP, ▶evolutionary tree

Exine: The outer layer (of pollen grains).

Exobiology: Exobiology inquires about the possibilities of extraterrestrial life forms. So far no firm evidence exists in spite of several claims. Biogenic hexa and octahedral magnetite crystals in Martial meteorites is one recent suggestive indication. ▶astrobiology, ▶extraterrestrial; Thomas-Keprta KL et al 2001 Proc Natl Acad Sci USA 98:2164; Friedmann EI et al 2001 *ibid.* 2176; Cohen J, Stewart I 2001 Nature [Lond] 409:1119.

Exocarp: The outer layer of the fruit wall, the peel of citrus fruits, the skin of peaches.

Exocrine: The secretory glands that release substances (enzymes, hormones, etc.) through ducts in an outward direction. ▶endocrine

Exocyst: A protein complex that marks the docking position of transporting vesicles on the surface of the plasma membrane. Also involved in the control of cell separation during cytokinesis. ▶cytokinesis; Kee Y et al 1997 Proc Natl Acad Sci USA 94:14438, tethering complexes: Koumandou VL et al 2007 BMC Evol Biol 7(1):29.

Exocytosis: The secretion of molecules from the cell into the medium or transfer of molecules into membrane-enclosed storage compartments in the cell. Exocytosis is one the mechanisms by which cytotoxic T lymphocytes (CTL) release, in a Ca^{2+} -dependent process, perforin and granzymes to lyse the target cells. An antibody to host antigens can activate human endothelial cell exocytosis and leukocyte trafficking. By triggering vascular inflammation, antibody activation of exocytosis may play a role in transplant rejection (Yamakuchi M et al 2007 Proc Natl Acad Sci USA 104:1301). ▶exocytotic vesicles, ▶perforin, ▶granzymes, ▶apoptosis, ▶SNARE, ▶syntaxin; Lin RC, Scheller RH 2000 Annu Rev Cell Dev Biol 16:19.

Exocytotic Vesicles: Exocytotic vesicles serve as vehicles for transport by exocytosis. ▶exocytosis

Exogamy: Exogamy is cross-fertilization.

Exogenic heredity: Exogenic heredity is based not on biological inheritance but on cultural transmission of traditions, scientific information, laws, ethics, values, etc.

Exogenote: When the bacterial genetic material recombines, the recipient genome is called endogenote and

the corresponding segment of the donor genome is an exogene. ► [conjugation bacterial](#)

Exogenous: The influences which come from outside.

Exogenous Evolution: The evolution of cells of higher organisms by inclusion of prokaryotic cells such as plastids and mitochondria. ► [autogenous evolution](#)

E

Exon: Segments of eukaryotic mosaic genes that are represented in the mature mRNA and are translated into a protein. The exon intron boundaries are usually conserved, e.g.:

5'-ACTGCAGtaagg...tttcctctctctagTGGGCG-3' DNA
 exon intron exon

All coding genes have exons but introns are exceptional in prokaryotes, and yet they occur in the plastid and mitochondrial genes. The parts of the RNA genes that are retained in the mature transcripts are also called exons. The length of individual exons is usually short, 10 to 300 nucleotides. The total average exon size per genes in mouse is about 2,300 and in humans ca. 3,400, although large differences exist among the different genes. Generally, the human genes display many short exons (average 50 codons) and are separated by long introns up to 10 kbp larger. The splice sites of exons may vary. In humans, more than 1/3 of the exons may not be translated. The largest exon number, 234, was found in the human *titin* mRNA, whereas the average is about 7–9. In human chromosome 11 there are 296 single-exon genes whereas 80.53% of the genes have an average of 9.39 exons (Taylor TD et al 2006 Nature [Lond] 440:497). Exons comprise approximately 1% of the human genome. The exons can be *constitutive* if they are always spliced and included into the mRNA. Some exons, the *cassette exons*, are included in a facultative manner, i.e., they are regulated. The size of particular exons may vary because both the 5' and 3' splice sites may vary as alternative promoters, and alternative polyadenylation sites are used with alternative splice sites. Splicing of the primary transcript is mediated by small ribonuclear proteins (snRNP) located at the exon-intron boundaries, but the DNA-dependent RNA polymerase II is tethered to the transcript and to the spliced exons to protect the continuity of the message (Dye MJ et al 2006 Mol Cell 21:849). Exons are apparently evolving from introns and thus contribute to gene evolution (Zhang XH-F et al 2006 Proc Natl Acad Sci USA 103:13427). ► [introns](#), ► [spliceosome](#), ► [alternative splicing](#), ► [branch-point sequence](#), ► [mosaic genes](#), ► [titin](#), ► [gene](#), ► [exon junction complex](#), GeneAlign exon prediction: <http://genealign.hccvs.hc.edu.tw/>.

Exon Connection: A method for isolating genes by following the steps: 1. Isolate RNA from a cell line;

2. Obtain cDNA; 3. Use PCR with primers of suspected adjacent exons; 4. Clone the product of PCR; 5. Sequence is tested for connection of exons; 6. Southern blot is performed with the probe generated; 7. Identify and isolate the whole gene. ► [exon](#), ► [cDNA](#), ► [PCR](#), ► [DNA sequencing](#), ► [gene isolation](#), ► [introns](#); Bardos J et al 1997 Int J Cancer 73:137.

Exon Definition: In pre-mRNAs with large introns the splicing machinery searches for closely spaced splice sites in a polar fashion. When such a pair is found U1 and U2 snRNPs and other splicing proteins, 3'-factors (U2AF, SC35) and 5'-recognizing factors (ASF, SF2) bind to the transcript. This definition is then followed by exon juxtaposition into an orderly fashion rather than random scrambling and joining of U4/U5/U6 snRNPs (Berget SM 1995 J Biol Chem 270:2411). ► [spliceosome](#), ► [intron](#), ► [exonscrambling](#), ► [exon skipping](#)

Exon Junction Complex (EJC): A 335-kDa protein complex (approx.) deposited 20–24 nucleotides upstream of the splice junction (see Fig. E61). DEXH/D proteins are instrumental in separating the RNA from the EJC protein complex. The complex includes SRm160 and RNPS1 coactivators of splicing and SRm160 enhances the processing of the 3'-end. RNPS1 and Y14 are also implicated in nonsense-mediated decay. Protein Aly/REF is supposed to mediate the nuclear export of the mRNA. MAGOH (post-splicing processing factor) facilitates sub-cytoplasmic localization of the mRNA. The stable core complex of EJC includes four proteins (eIF4AIII [a DEAD-box protein], Barents [Btz]/MLN51 localization factor, Mago and Y14 [RNA localization factors]), mRNA and ATP (Bono F et al 2006 Cell 126:713). ► [exon](#), ► [intron](#), ► [spliceosome](#),

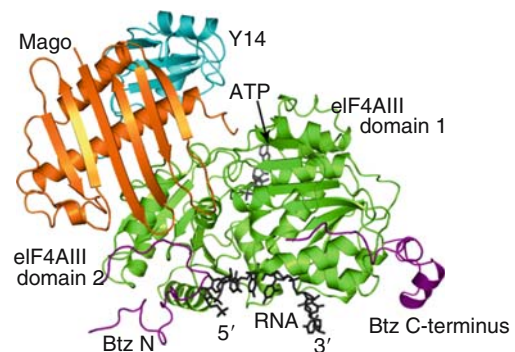


Figure E61. Structure of the exon junction complex. Btz (magenta) stretches around eIF4AIII helicase (green). These two proteins interact with RNA (black). ATP (gray) is at the interface of the helicase domains. Mago (rust) and Y14 (turquoise) bind mainly to domain 2 of the helicase. Courtesy of Fulvia Bono and Elena Conti.

►NAS, ►nonsense-mediated decay, ►DEXH/D; Wiegand HL et al 2003 Proc Natl Acad Sci USA 100:11327; Wilkinson MF 2005 Trends Genet 21:143, exon junction core complex: Andersen CB et al 2006 Science 313:1968.

Exon Parsing: Determining the exact boundaries of exons or genes.

Exon Scanning: Molecular testing the gene for mutation. ►single strand conformation polymorphism, ►denaturing gradient gel electrophoresis, ►DNA sequencing

Exon Scrambling: In eukaryotes the exons may be spliced correctly but in a different order from that in the genomic DNA. This scrambling is believed to be mediated by loops in the pre-mRNA and makes possible the alternative processing of the transcripts. These exons are not polyadenylated. ►exons, ►exon definition, ►introns; Caldas C et al 1998 Gene 208(2):167.

Exon Shuffling: Exons of the same gene may be processed and thus expressed in more than one pattern and may be recruited for the synthesis of more than one protein. It has been suggested that the role of introns in the earliest cells during evolution was to facilitate the assembly of new genes by exon shuffling. Exon shuffling is most common in vertebrates but it has also been detected in the cytosolic glyceraldehyde-3-phosphate dehydrogenase gene of plants. The ubiquitous retrotransposons of eukaryotic cells may move exons and promoters into other genes and thus generate new composite genes with different function(s). The L1 retrotransposons may be copied into the genes. They can also mobilize the L1 flanking 3' sequences into the genes. The combination of different exons by recombination or genetic engineering may produce enzymes with potential advantage. Protein domains bordering the encoding exons are more numerous and widely distributed in the genomes indicating that these domains were amplified and interchanged more often than other domains during evolution (Liu M et al 2005 Nucleic Acids Res 33:95). ►exon, ►intron, ►retrotransposon, ►LINE, ►3' transduction; Pathy L 1996 Matrix Biol 15:301; Kolkman JA, Stemmer WPC 2001 Nature Biotechnol 19:423.

Exon Skipping: The out-splicing of an exon, i.e., skipping the inclusion into the mRNA. Exonic splicing enhancers can suppress exon skipping (Ibrahim EC et al 2005 Proc Natl Acad Sci USA 102:5002). Exon skipping causes several human diseases. Exon-specific activators of the serine/arginine rich (SR) type may correct disease-associated skipping (Cartegni L, Krainer AR 2003 Nature Struct Biol 10:120). In certain instances exon

skipping may alleviate the disease symptoms by the elimination of a defective exon—resulting from mutation—as long as the deletion does not affect the proper in-frame sequence of the truncated mRNA (see Fig. E62). Exon skipping may be induced by antisense RNA technology. ►splicing, ►alternative splicing, ►exonic splicing enhancer, ►antisense RNA, ►antisense technologies; Harper SQ et al 2002 Nature Med 8:253; Sherratt TG et al 1993 Am J Hum Genet 53:1007.

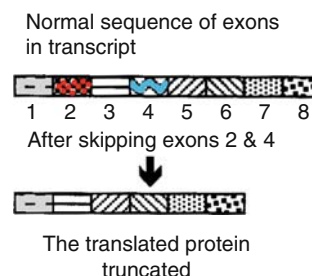


Figure E62. Exon skipping

Exon Theory: The exon theory has suggested that split genes arose by aggregation of exons during prebiotic or early evolution. Convincing experimental evidence is still lacking.

Exon Trapping: In physical mapping identifies “candidate genes” in transcribed sequences. By the use of an appropriate (commercially available) vector and a transfection technique an exon is inserted into an intron adjacent to the exon targeted. The transcript then appears longer and can be identified by Northern blot. ►candidate gene, ►physical mapping, ►Northern blotting, ►exon, ►trapping promoters; Wapenaar MC, Den Dunnen JT 2001 Methods Mol Biol 175:201.

Exonic Splicing Enhancer: The binding site for serine/arginine-rich splicing proteins and which facilitates the assembly of the pre-spliceosome (Shen H et al 2004 Mol Cell 13:302). ►spliceosome

Exonization: ►Alu family

Exonuclease: An enzyme that digests a polynucleotide chain beginning at either the 5' (RecJ) or the 3' terminus (Exo I, VI, X) or from both ends (ExoVII). Among these only ExoX degrades double-strand DNA. Exonucleases may degrade misaligned tandem repeats and thus favor DNA stability (Feschenko VV et al 2003 Proc Natl Acad Sci USA 100:1134). ►Ball, ►recombination mechanisms, ►endonuclease, ►restriction enzymes, ►mismatch repair, ►RecA-independent recombination; Grunberg-Manago M 1999 Annu Rev Genet 33:193; Shevelev IV, Hübscher U 2002 Nature Rev Mol Cell Biol 3:364.

Exonuclease I: Degrades DNA single-strands 3'→5'.

Exonuclease III: A multifunctional enzyme; in *E. coli* it works as a DNA-repair endonuclease, as an exonuclease 3'→5', phosphomonoesterase, and ribonuclease. ▶endonuclease, ▶exonuclease, ▶phosphomonoesterase, ▶ribonuclease

Exonuclease V: Digests double-stranded DNA and displays DNA-dependent ATPase activity; it is encoded by the *recBCD* complex of *E. coli*.

Exonuclease VII: A heterodimer; cuts single-stranded DNA from both 3' and 5' ends without requirement for Mg²⁺.

Exonuclease λ: Encoded by phage λ, binds to the free end of a DNA duplex, and degrades one strand in 5'→3' direction releasing about 3,000 5'-mononucleotides at a rate of about 12/sec. The 3' overhangs participate in genetic recombination with the assistance of the bacterial RecA protein. Alternatively, two homologous single-strands may anneal without Rec and form double-stranded recombinants. ▶recombination mechanisms, ▶lambda phage

Exoribonucleases: Exoribonucleases are enzymes which digest RNA from the terminus. They belong to six superfamilies and occur in all organisms. In *E. coli* 3'→5' the exoribonucleases are polynucleotide phosphorylase, RNase II, RNase D, RNase BN, RNase T, RNase PH, RNase R and oligoribonuclease. Eukaryotes also have similar enzymes. All eukaryotes also have 5'→3' exoribonucleases apparently absent from *E. coli*. ▶exosome; Deutscher MP, Li Z. 2000 *Progr Nucleic Acids Res Mol Biol* 66:67; Zuo Y, Deutscher MP. 2001 *Nucleic Acids Res* 29:1017; Gagliardi D et al 2001 *J Biol Chem* 276:43541.

Exoskeleton: The hard shell of the body (insects, crustaceans, etc.) including the vertebrate nails, hoofs, hair and other epidermal structures are considered as exoskeleton. ▶chitin

Exosite: An anion-binding site on the surface of a protein molecule. ▶anticoagulation

Exosome: A putative segment of DNA associated with, but not integrated into, the chromosome, yet it can express its genetic information. Exosomes may play a role in the quality control of mRNA. Either the hypopolyadenylated or hyperpolyadenylated molecules are permitted to exit from the nucleus and may be translated in case the nucleolytic complex of the exosome is defective. ▶episome, ▶RNA surveillance, ▶nonstop decay, ▶microRNA; Fox AS et al 1971 *Proc Natl Acad Sci USA* 68:342; Hilleren P et al 2001 *Nature [Lond]* 413:538.

Exosome: A complex of exoribonucleases, RNA-binding proteins and helicases in prokaryotes and

eukaryotes degrading RNA in the 3'→5' (or 5'→3') direction. In yeast, each of the 11 components is essential for viability. The complex—present in the cytoplasm and in the nucleus—trims rRNA primary transcripts and mRNA and degrades some other RNAs. Other eukaryotes may have somewhat different types of exosomes. The function(s) of exosomes is/are not fully understood and the views of the various investigators are not unanimous. According to some the exosomes are transporters of infectious agents such as prions or HIV virus. Some believe they reinforce/bolster the immune system, while others find it hard to confirm these ideas. ▶RNA processing, ▶mRNA degradation, ▶exoribonuclease; Suzuki N et al 2001 *Genetics* 158:613; Estavez AM et al 2001 *EMBO J* 20:3831; Brouwer R et al 2001 *Arthritis Res* 3:102; Koonin EV et al 2001 *Genome Res* 11:240; structure of the 9-subunit eukaryotic exosome: Liu Q et al 2006 *Cell* 127:1223.

Exosomes: Dendritic cells constitutively secrete 50–90 nm diameter vesicles that present antigens. They may stimulate antitumor responses by the ca. two dozen proteins. Exosomes may fuse with the membranes of other cells and thus serve as transfer vehicles for different proteins. Exosomes uptake may be followed by endocytosis. Exosomes and proteasomes have similar degradative functions although their composition and substrates are different (Lorentzen E, Conti E 2006 *Cell* 125:651). ▶endocytosis, ▶proteasome; Thery C et al 2001 *J Immunol* 166:7309; Denzer K et al 2000 *J Cell Sci* 113:3365.

Exostosis (EXT, diaphyseal aclasis): Autosomal dominant (EXT1, human chromosome 8q24.1-p13, EXT2 in 11p11.1, EXT3 in 19p) phenotypes involving growth of extra cartilage or bony projections at the end of bones (mainly on hands and fingers but rarely on the head, except the ear). EXT1 in chromosome 8 encodes a transmembrane glycoprotein and affects the cell surface of heparan sulfate glycosaminoglycans (see Fig. E63). Exostosis is generally accompanied by short stature. EXT2 encodes α-1,4-*N*-acetyl hexosaminyltransferase. The incidence of such defects in Western populations is about 1–2 × 10⁻⁵ and the estimated rate of mutations is 6–9 × 10⁻⁶. Their chance for bone cancer is increased to 0.5–2% of the cases. A deletion at 11p11.2 causes oval defects of a nerve/vein opening in the parietal bones (of the head) called Potocki-Shaffer syndrome. The highly homologous EXTL (EXT-like, EXTL1, 1p36.1, EXTL2, 1p12-p11) genes encode α1,4-*N*-acetyl glucosaminyl transferase involved in the biosynthesis of heparan sulfate and heparin. ▶stature in humans, ▶limb defects in humans, ▶Langer-Giedion syndrome, ▶Ehlers-Danlos syndrome, ▶fibrodysplasia, ▶metachondromatosis, ▶cancer, ▶heparan sulfate,



Figure E63. Exostosis, horse leg

► [glycosaminoglycan](#); Cheung PK et al 2001 Am J Hum Genet 69:55.

Exophthalmus (exophthalmos): A protrusion of the eyeball; it is frequent in goiter.

Exothermic Reaction: An exothermic reaction releases heat.

Exotoxin: Toxins secreted outside the cells (body) such as the protein toxins of several bacteria, e.g., *Clostridium botulinum* nerve toxin, etc. The diphtheria, pertussis, cholera and other toxins target either the α -subunit of the heterotrimeric G proteins, actin, Rho/Rac and eEF2. The ADP-ribosylating toxins share a common structural core containing the NAD⁺ binding site. The eEF2 elongation factor contains a single diphthamide residue (a modified histidine at site 699); diphthamide occurs only in this protein. Exotoxin A and diphtheria toxin inactivate eEF2 and interfere with protein synthesis (Jørgensen R et al 2005 Nature [Lond] 436:979). ► [toxins](#)

Expanded DNA: ► [xDNA](#)

Expansins: Plant cell wall proteins (ca. 26-K molecular mass) that facilitate the elastic growth of cell walls, loosening the stigmatic surface to aid penetration of the grass pollen tube, and fruit ripening. They may have a role as allergens. (See Shie MW, Cosgrove DJ 1998 J Plant Res 111:149; Pien S et al 2001 Proc Natl Acad Sci USA 98:11812).

Expansion Card: A circuit board that can be inserted into some computers and permits the user to perform some special, additional functions.

ExPaSy (Expert Protein Analysis System): Links to the Glaxo Institute of Molecular Biology, Geneva, 2-dimensional electrophoretic database to the SWISS-PROT protein sequence database. ► [laser desorption MS](#), ► [electrospray MS](#), ► [MELANIE II](#), ► [SWISS-PROT](#), ► [databases](#)

Expectation-Maximization Algorithm: Frequently used for studying the association of a certain haplotype with predisposition to disease. In population studies it may be necessary to estimate the linkage phase, the haplotype frequency and the role of a number of factors such as sampling error, sample size, allelic frequencies, deviations from the Hardy-Weinberg equilibrium, etc. ► [haplotype](#), ► [association test](#), ► [Hardy-Weinberg equilibrium](#); Fallin D, Schork NJ 2000 Am J Hum Genet 67:947; Epstein MP, Satten GA. 2003 Am J Hum Genet 73:1316.

Expected Phenotypic Superiority: Expected phenotypic superiority is $i_p \sigma p_1$ where i is the selection intensity when fraction p is selected in a breeding program. ► [selection intensity](#)

Experiments: Experiments are conducted to test a hypothesis (deductive method) or to generalize from empirical data (inductive method). In either case the work has clearly defined objective(s). Genetics is basically an experimental science. The results of medical research are investigated by clinical trials. 28 Phase III trials conducted by the US National Institute of Health cost \$335 million. As a result the projected net gain to society during a period of 10 years was estimated to be \$15.2 billion. Six trials (21%) generated measurable improvement in health and four (14%) resulted in cost savings for society. In addition to saving, the trials adjusted 470,000 life years for the patients during a period of 10 years (Johnston S et al 2006 Lancet 367:1319). The experimental cost does include the annual investment of basic and applied health research in the USA. ► [science](#), ► [genetics](#), ► [clinical trial phases](#)

Explant: A cutout piece of (plant/animal) tissue, used for in vitro culture. ► [tissue culture](#)

Exponential Distribution: May represent the amount of time until the first of a series of events occurs and the distribution of time between occurrences of the subsequent events in case the events occur according to a Poisson process of independent events (see Fig. E64). ► [distributions](#), ► [Poisson distribution](#)

$$P(r \text{ occurrences in } T \text{ units} | \lambda = \frac{e^{-\lambda T} (\lambda T)^r}{r!} \text{ where } \lambda = \text{the intensity per time units } t \text{ and } T = \text{the number of units of } t; \lambda T = \text{intensity}/T \text{ units}$$

Figure E64. Exponential distribution

Exponential Growth: Takes place when nutrients and other factors required for growth are optimal. The multiplication of the cells is determined by the exponent of 2. For example, after 10 divisions of a cell the number of cells becomes $2^{10} = 1,024$ and if

the number of initial cells were 8, then after 10 divisions the number of cells becomes $2^{10} \times 8 = 8,192$. This type of growth is also called logarithmic growth because $\log_2[1024] = 10$. The conversion to \log_2 from \log_{10} is carried out as follows:

$$\begin{aligned}\log_2[1024] &= \log_{10}[1024](1/\log_{10}[2]) \\ &= 3.010299957 \times \log_{10}(1/0.301029995) \\ &= 3.010299957 \times 3.321928095 \approx 10\end{aligned}$$

►growth curve

Export Adaptor: Export adaptors are proteins which attach to proteins of RNAs and assist their export or import, respectively, between nucleus and cytoplasm. Leucine-rich nuclear export signals (NES) move, e.g., the 5S rRNA to the cytoplasm through the nuclear pore complex. The members of the hnRNP family (~20 proteins) are involved in the transport of mRNA. ►RRE, ►nuclear pore, ►nuclear localization sequence, ►Gle1, ►Mex67, ►RNA export, ►RNA transport, ►transportin, ►Ran, ►CBC, ►snRNA; Segref A et al 2001 RNA 7(3):351.

Export Signals: Export signals can be RNA-binding proteins specific for RNA classes (mRNA, tRNA, rRNA, etc.) and mediate the interaction with export receptor molecules. The recognition of U snRNAs depends on their monomethylguanosine caps, the cap and tail structures, the HIV-1 Rev-responsive element, and 5S RNA binding sites for TFIIIA. Or, they may bind to proteins with leucine-rich nuclear localization signals. ►U RNA, ►hnRNA, ►acquired immune deficiency syndrome, ►ribosomes, ►transcription factors, ►nuclear localization sequences, ►Cap, ►export adaptor; Rashevsky-Finkel A et al 2001 J Biol Chem 276:44963.

Exportin: ►chromosome maintenance region, ►nuclear pore

Expressed Protein Ligation: Links together natural or synthetic peptide blocks into a final, functional protein. The ends of the components are engineered to become sticky and peptides with several unnatural amino acids can be consolidated. This approach permits modification of only a single domain within a multidomain protein. ►semisynthesis of proteins; Muir TW 2003 Annu Rev Biochem 72:249.

Expressed-Sequence Tag (EST): A probe of short nucleotide sequences for genes that are expressed in a particular tissue, although no information may be provided regarding their function or role. The use of ESTs greatly facilitated the analysis of the functional fraction of the eukaryotic genomes. The use of ESTs was important for the progress of the genome projects by being usually single-pass tracts although they may involve various artifacts. Patents for them were

sought; the ethical justification for their patenting has been criticized. ►EST, ►physical mapping, ►gene discovery, ►UniGene, ►patent, ►ORESTES, ►dbEST, ►gene indexing; Adams MD et al 1991 Science 252:1651; Gemünd C et al 2001 Nucleic Acids Res 29:1272; UniGene, Genomic Survey, <http://www.ncbi.nlm.nih.gov/dbEST/index.html>; barley, pea, potato, wheat, tobacco EST: <http://pgrc.ipk-gatersleben.de/cr-est/index.php>; <http://www.ncbi.nlm.nih.gov/ncic-gap/>, human EST: <http://genecards.weizmann.ac.il/genetide>; Gene Indices: <http://www.tigr.org/tdb/tgi/>; human EST DNA segment sequences alignment tool: <http://egassembler.hgc.jp/>; new marker tool across legume and grass species: <http://cgi-www.daimi.au.dk/cgi-chili/GeMprospector/main>; EST of 49 diverse organisms: <http://tbestdb.bcm.umontreal.ca/>; EST characterization: <http://www.conifergdb.org/software/wtm1.2/>; EST annotation: <http://estexplorer.biolinfo.org>, cleansing and annotating EST: <http://estpass.kobic.re.kr/>.

Expression: In genetics means phenotype; the phenotype may be any morphological trait or a (protein) product of a gene. ►phenotype, ►genotype

Expression Cassette: Contains all the sequences required for the expression of a gene and can be inserted into various expression vectors for transcription. Also, the structural gene may be replaced by another structural gene. ►expression vector, ►structural gene

Expression Cloning (reverse biochemistry): Cloned cDNA is expressed in a cellular or cell-free translation system in order to study the pure product of a gene. ►molecular cloning, ►cDNA, ►FL-REX, ►rabbit reticulocyte in vitro translation system, ►wheat germ in vitro translation system

Expression Library: Includes cDNAs in expression vectors permitting their ready use for transformation and expression in several hosts. ►expression vector

Expression Matrix: An expression matrix may be used to study genetic data obtained by microarray hybridization. These are tables where rows designate genes, columns represent the various samples of tissues or conditions of expression, and within each cell of the grid the level of gene expression is shown. ►microarray hybridization; Brazma A, Vilo J 2000 FEBS Lett 480:17.

Expression Profile: The collection of mRNAs transcribed (expressed) from genomic DNA thus determining the cellular phenotype. It reveals developmental and extended, interacting metabolic pathways. It may represent, also, the expression pattern of a single gene over time or during development. ►transcriptome, ►microarray hybridization, ►DNA chips; Miki R et al 2001 Proc Natl Acad Sci USA 98:2199, tools for clustering,

gene expression, pattern discovery, gene ontology, regulatory sequences, protein interactions: <http://ep.ebi.ac.uk/EP/>.

Expression Trapping: The survey of embryonic stem cells containing gene-trap integrations in genes responding to specific agents. ▶trapping promoters, ▶stem cells

Expression Vector: An expression vector carries to the target cell by transformation the structural gene and all the regulatory signals required for expression. ▶vectors

Expression-Linked Copy: In the *Trypanosomes*, for the expression of a different type of antigen, gene transposition is required. ▶*Trypanosoma brucei*

Expression-Verified Genes (EVGs): Coregulated exons as detected by microarray hybridization. ▶microarray hybridization, ▶exon

Expressivity: The degree of expression of a gene. ▶penetrance, ▶microarray hybridization; Oleksiak MF et al 2002 Nature Genet 32:261.

EXProt: A database of proteins with experimentally verified function. (See <http://www.cmbi.kun.nl/EXProt/>; ▶metabolism).

Exstrophy: A rare congenital developmental anomaly of turning an organ inside out, involving the bladder or in the pubic area.

Extein: Flanking protein sequences remaining after the removal of inteins. ▶intein

Extensible Markup Language: The structural format for documents on the WEB. (See <http://www.w3.org/XML/>).

Extensins: Plant cell wall glycoproteins. (See Yoshida Y et al 2001 DNA Res 8:115).

External Guide Sequences (EGS): RNA oligonucleotides that can bind to specific RNA sites in an RNA molecule and guide to this location ribonuclease P that cleaves at specific sites. ▶Ribonuclease P, ▶antisense technology; McKinney J et al 2001 Proc Natl Acad Sci USA 98:6605).

External Transcribed Spacers: ▶ETS

Extinction: The loss of a genotype (phenotype) from a population; disappearance of a conditioned response; suppression of cell-type-specific function in fused somatic cells. During the Permian period (250–225 million years ago) atmospheric oxygen levels decreased and the warming climate caused extinction due to hypoxia of many species (fishes, amphibians, etc) that evolved in the preceding epochs before birds and mammals emerged (Huey RB et al 2005 Science 308:398). The causes of extinction are multiple, but

in larger mammals the increased body is a significant disadvantage for survival (Cardillo M et al 2005 Science 309:1239). (See ▶species extant, ▶equilibrium of mutations, ▶geological-evolutionary time periods) In spectrophotometry it means the intensity of the absorption (ϵ_{\max}) at the absorption peak (λ_{\max}). ▶O.D

Extirpation: The complete removal of an organ, a type of cell(s) or tissues. ▶ablation

Extracellular DNA: Extracellular DNA is cell-free, naked DNA that may be a waste of laboratory operations and may persist in the environment as a polymer and a potential hazard. In soil or other aqueous environments the polymer rapidly decays. Plasmid or other supercoiled DNA may be less prone to degradation. Antibiotic resistance DNA may not pose serious hazards unless selective conditions exist. (See Doblehoff-Dier O et al 2000 Trends Biotechnol 18:141).

Extracellular Matrix (ECM): A complex of polysaccharides and proteins, secreted by cells. Its role in the tissues is structural and physiological. ECM includes collagens, a variety of fibrous proteins of triple-helical coiled coil structure, glycoproteins (laminin, fibronectin), proteoglycans, etc. ECM is linked to the intracellular cytoskeleton by integrins. Without anchorage, most cells succumb to apoptosis. Matrix metalloproteinase modifies the extracellular matrix of cancer cells and allows changes in the shape of the cell and the cytoskeletal organization and thus facilitates the proliferation of cancer cells. Cell surface architecture and ECM organization attracted much interest recently because of the potentials of engineering natural and synthetic cell surfaces that can effect growth, tissue regeneration, cell migration, differentiation and novel application of medical implants (Stevens MM, George JH 2005 Science 310:1135). A FRET technique can be used to quantify the number of bonds formed between cellular receptors and synthetic adhesion oligopeptides coupled to an artificial extracellular matrix. Similar quantitative relations were found between bond number and the proliferation and differentiation of some preosteoblasts and myoblasts, although the relation was distinct for each cell type. This approach to understanding 3-dimensional cell-extracellular matrix interactions will allow one to both predict cell behaviors and to use bond numbers as a fundamental design criteria for synthetic extracellular matrices (Kong HJ et al 2006 Proc Natl Acad Sci USA 103:18534). ▶fibronectin, ▶collagen, ▶laminin, ▶proteoglycans, ▶basement membrane, ▶metalloproteinase, ▶integrin, ▶ICAM, ▶elastin, ▶fibronectin, ▶Kindler syndrome, ▶nanotechnology, ▶FRET

Extrachromosomal Inheritance: Extrachromosomal inheritance is determined by nonnuclear elements. ▶mtDNA, ▶mitochondrial genetics, ▶chloroplast genetics, ▶plasmids

Extragenic: The genetic factor is outside the boundary of the gene that it affects, e.g., suppressor tRNA. ▶suppressor tRNA, ▶suppressor gene

E

Extranuclear Genes: Extranuclear genes are in the cellular organelles (mitochondria, plastids), except the cell nucleus.

Extranuclear inheritance: Extranuclear inheritance is determined by genes in cellular organelles and not by those in the nucleus. ▶ctDNA, ▶mtDNA, ▶symbionts hereditary

Extrapolation: To calculate values beyond an interval on the basis of the knowledge of values known within the interval. This is usually done with the assistance of the linear regression equation, $Y = a + bx$. Extrapolation may involve some risks of error if the value of x is increasing beyond the range known and, even more seriously, if the linear regression equation (Y) values do not represent the values properly, but in effect may be a curved line beyond the interval. ▶correlation, ▶interpolation linear

Extrasensory Perception: Goes beyond the recognition of facts by rationally explainable means. ▶paranormal

Extraterrestrial Life: Living creatures outside the earth have been claimed on the basis of various observations but so far no unchallenged evidence has been available. (See Wilson TL 2001 Nature [Lond] 409:1110).

Extravasation: Passing cells from the blood into tissues. Such events occur during metastasis. ▶diapedesis, ▶metastasis, ▶intravasation

Extreme-Value Distribution Theory: If from a population many values are chosen but only the maximal values are reproduced repeatedly the distribution approaches the extreme-value condition. Also, the probability of an alignment score is caused by chance in the physical mapping of DNA. This principle is also applicable for search of microarray dataset-based gene selection (Li W et al 2004 J Comput Biol 11:215). ▶physical mapping, ▶microarray hybridization; Pagni M, Jongeneel CV 2001 Brief Bioinform 2(1):5; Dudbridge F, Koeleman BP 2004 Am J Hum Genet 75:424.

Extremities: Body appendages such as the limbs.

Extrinsic: Outside (factor); an adjective, defining that an effect is not intrinsic (essential feature) of the phenomenon. ▶intrinsic

Exudative, Vitreoretinopathy, Familial (11q13-q23): Dominant/recessive retinal detachment and vitreous hemorrhages. The symptoms are similar to vitelliform macular dystrophy. ▶macular dystrophy, ▶retinal dystrophy

Exules: Successive generations of insects (aphids).

Eye Color: Eye color in humans is a polygenically controlled trait. It is frequently assumed that one gene locus (BEY, 15q11-q15) is responsible for brown/blue color and another for green/blue (GEY, 19p13.1-q13.11) color. Genome-wide linkage scan for eye color suggested that 74% of variation in eye color in Europeans could be attributed to a QTL linked to the *OCA2* region of chromosome 15q (Duffy DL et al 2007 Am J Hum Genet 80:241). Brown (dark) tends to be dominant over blue, and green over blue. It is not too uncommon that blue-eyed parents have both blue-eyed and brown-eyed offspring. This is no basis for suspecting illegitimacy. Brown sectors in blue eyes (sometimes almost invisibly small) are attributed to somatic mutation. Such individuals are more likely to have brown-eyed children even if their spouses have blue eyes. Pigmentation of the retinal layer of the iris and the nature of the semi-opaque layers in front of the iris determine the eye color. A blue layer may be present in all individuals but it may be masked by another layer of melanin in the front part of the iris. Therefore, blue-eyed babies may develop brown eyes when melanin is accumulating in the front part of the iris at later stages. Green and hazel eyes indicate that melanin partially masks the reflections from the deeper layers of the iris. Gray eyes are variants of the blue color. Black eyes indicate very deep brown melanin layer. When all pigments are absent in albinos, the eyes appear pink or very pale blue because of the reflections of the blood vessels. Some eye diseases involving coloboma may change eye color. Phenylketonurics may display light eye color because of the defect in pigment synthesis. It is not too uncommon that the color of the two eyes of a person does not match (heterochromia iridis, Morrison DA et al 2000 Arch Ophthalmol 118:1590) due to a developmental anomaly. Heterochromia iridis may occur in individuals affected by Waardenburg syndrome II. It is also conceivable that somatic mutation to ocular albinism may result in white sectors in the otherwise normal eye (Hegde M et al 2002 Genet Test 6:7). In insects the bright red color is derived from pteridines and the brown from ommochromes. The intermediate shades develop from the presence of both pteridines and ommochromes. ▶albino, ▶Hermansky-Pudlak syndrome, ▶incontinentia pigmenti, ▶Waardenburg syndrome, ▶pigmentation in animals, ▶eye

diseases, ►coloboma, ►phenylketonuria, ►QTL; Sturm RR et al 2001 *Gene* 277:49; Frudakis T et al 2003 *Genetics* 165:2071.

Eye Diseases (ophthalmologic diseases): Eye diseases are concerned with anatomical and pathological conditions related to vision. More than 0.5% of the population of the USA is afflicted with some serious eye problems and almost 0.02% is legally blind. In other parts of the world, eye-related diseases may be even more prevalent. The genetic component of these ailments is variable and it is usually part of complex syndromes affecting anatomical and physiological disorders. Clouding of the cornea occurs in the Hurler, Marquio, Maroteaux-Lamy syndromes, and Fabry's disease. Cataracts may be present in Wilms tumors, Lowe syndrome, galactosemia, Werner syndrome, and myotonic dystrophy. A cherry-red spot may appear on the retina in sphingolipidoses, gangliosidoses, and mucopolidoses. Reduced vision occurs in neuroaminidase deficiency. Retinitis pigmentosa (most commonly clumped pigments and atrophy of the retina, contraction of the field of vision), Usher, Laurence-Moon, Bardet-Biedl syndromes, Refsum disease may involve eye pigment disorders. Amaurosis congenita, retinoschisis are malformations or deficiency of the retina. Loss of eye pigments and reduced vision in albinism, Blue sclera (the normally white outer surface of the eye) in osteogenesis imperfecta are characteristic. Variegation of the eye color (iris) is found in the Waardenburg syndrome. Retinal neoplasia is the most critical feature of Norrie disease. Hypoplasia of the iris occurs in Rieger syndrome and reduction in eye size is caused by microphthalmos. Myopia is common in the Stickler syndrome, Marfan syndrome, Kniest dysplasia. Tumors of the eye tissues develop in retinoblastoma and von Hippel-Lindau syndrome. Tumorous eyes are also found in the Crouzon syndrome. In human trisomy 21 (Down syndrome) slanted eyelids and white spots around the iris appear. Autoimmune eye disease may involve ocular cicatricial (scar-like) pemphigoid. Approximately 100 mapped genes are responsible for blindness. (See under separate entries the named conditions; ►mitochondrial diseases in humans, ►color blindness, ►night blindness, ►Oguchi disease, ►S-cone syndrome, ►ophthalmoplegia, ►oculodentodigital dysplasia, ►Michel syndrome, ►focal dermal hypoplasia, ►Hirschsprung disease, ►glaucoma, ►strabismus, ►Duane retraction syndrome, ►nystagmus, ►coloboma, ►aspartoacylase deficiency, ►cat eye syndrome, ►galactosemia, ►myopia, ►Rothmund-Thompson syndrome, ►Rieger syndrome, ►Cohen syndrome, ►Zellweger syndrome, ►cataracts, ►ferritin, ►foveal dystrophy, ►macular

dystrophy, ►macular degeneration, ►retinal dystrophy, ►Stargardt disease, ►cornea plana, ►anophthalmos, ►anophthalmia, ►microphthalmos, ►pemphigus, ►retinitis pigmentosa, ►choroidoretinal degeneration, ►choroidal osteoma, ►Aphakia, ►GDLD mitochondrial diseases of humans, ►Leber optical atrophy, ►choroideremia; <http://mutview.dmb.med.keio.ac.jp/>; www.eyepathologist.com; <http://eye.site.cryst.bbk.ac.uk/>.

Eyelashes, Long (trichomegaly): May be an autosomal dominant anomaly associated with cataract and spherocytosis and other ailments. An autosomal recessive form was also studied, and the latter involved mental retardation, retinal degeneration and a number of other symptoms with unclear relevance to the formation of the eyelashes. Multiple rows of eyelashes were also observed to apparently follow either recessive or dominant inheritance, or being only a nongenetic anomaly. ►spherocytosis, ►emphedema-distichiasis

eyeless: A *Drosophila* mutation controlling eye differentiation but not the ocelli. The *Small eye* (*Sey/Pax-6*) of mice and the human Aniridia genes are homologous. Several other genes also affect eye development in *Drosophila*. The gene *Eyes absent* encodes a transcription factor with a function of a protein tyrosine phosphatase (Rayapureddi JP et al 2003 *Nature [Lond]* 426:295; TootleTL et al *ibid* 299). ►aniridia, ►anophthalmia, ►microphthalmos

Eye piece: A microscope lens through which the eye directly views the object through the tube. The eye piece only enlarges the image but does not afford better resolution unlike the lens of the objective. ►microscopy, ►objective

Eyespot: A complex light-perception structure in algae involved also in the movement of the flagella (singular flagellum). By the light microscope in *Chlamydomonas reinhardtii* it appears as an orange spot in the chloroplast stroma. It is also involved with a Ca²⁺ channel. The eyespot is controlled by several genes. ►*Chlamydomonas*

Eyk: A receptor tyrosine kinase encoded by a chicken protooncogene. ►protooncogene, ►tyrosine kinase

Ezetimibe: A potent inhibitor of cholesterol and phytosterol uptake. It lowers circulating cholesterol levels by 15–20%, especially when it is administered with statins. It is a drug used for treatment of hypercholesterolemia (Knopp RH et al 2003 *Eur Heart J* 24:729). Ezetimibe targets the Neumann-Pick C1-like protein (see Fig. E65). ►cholesterol, ►phytosterol, ►familial hypercholesterolemia, ►Niemann-Pick disease; Garcia-Calvo M et al 2005 *Proc Natl Acad Sci USA* 102:8132.

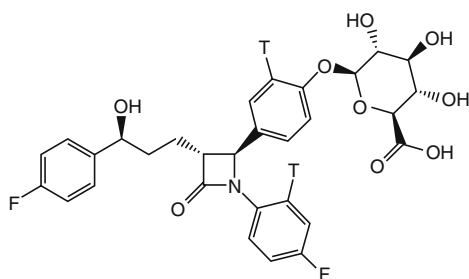


Figure E65. Ezetimibe glucuronide

Ezrin: A cytoskeletal protein. ▶ICAM, ▶T cell receptor, ▶caveolae, ▶ERM, ▶*Listeria*; Ng T et al 2001 EMBO J 20:2723; Saotome I et al 2004 Dev Cell 6:855.

Historical vignette

Bacteriophages were discovered by FW Twort (1915, *Lancet* ††:1241). In 1925 F D'Herelle (then Directeur du Service Bacteriologique du Conseil Sanitaire, Maritime et Quarantenaire d'Egypte) wrote a remarkable book of 629 pages about this agent, which he named bacteriophage because it could eat bacteria. The preface of the book emphasizes the practical significance of bacteriophages:

“Although up to the present time but few authors have undertaken the study of the behavior of the bacteriophage within the organism there are a relatively large number who have carried out investigations on what might be termed the other side, that is to say, on the application of the bacteriophage to the therapy of various infectious diseases. Of particular interest are the contributions of Hauduroy, who has applied this mode of treatment in colon bacillus infections, of Gratia, who has conclusively demonstrated a therapeutic effect in staphylococcus infections, and of da Costa Cruz who, after having confirmed my first studies on the specific treatment of the bacillary dysenteries, has undertaken a large scale demonstration of this mode of therapy with such results that all other modes of treatment have today been abandoned in Brazil.”

Today bacteriophages are not used as therapeutic agents, but their application as a tool for biological research led to the development of molecular biology, which in turn is making a great impact on medicine.

At the 16th Cold Spring Harbor Symposium (p. 436) J Lederberg et al., discussing bacterial recombination, say: “The exposure of sensitive cells to suspensions of the free phage, which we named “λ,” by analogy to a killer factor in *Paramecium*, results in the lysis of a variable proportion of the cells. ... The speculation that λ might be involved in genetic recombination needs no further mention.”

F

F: The coefficient of inbreeding expresses the probability for homozygosity of alleles, identical by descent, at a locus. It can simply be determined from the pedigree of an individual in a family (see Fig. F1).

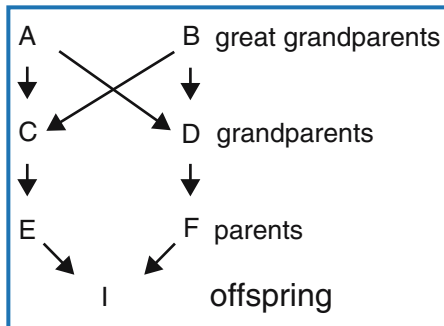


Figure F1. F

Each gamete has a 0.5 chance to transmit a particular allele through the paths available. Thus, in the progeny of a half-brother and half-sister mating, with three relevant ancestors involved, the coefficient of inbreeding, $F = 0.5^3$. Similarly, the value of F for the offspring of first cousins is $1/16$ because through two loops, represented by E-C-B-D-F and F-D-A-C-E, the same allele can be transmitted from the great grandparental gametes to the offspring I. F, therefore, is: $0.5^5 + 0.5^5 = 0.03225 + 0.03125 = 0.0625 = 1/16$. Note that the looping is done backwards from the I offspring. F_{IS} is the coefficient of inbreeding of an individual relative to the sub-population it lives in. Its value is determined by analysis of its descent (pedigree). F_{ST} is the index of fixation. F_{IT} is the coefficient of inbreeding of an individual (I) relative to the (T) total population. Employing F_{IS} , F_{ST} , and F_{IT} is called F-statistics. ▶ [coefficient of coancestry](#), ▶ [relatedness](#), ▶ [fixation index](#), ▶ [metapopulation](#); Wang J 1997 Genetics 146:1453, 1465.

F' (F prime): The fertility factor that carries regularly bacterial chromosomal gene(s). (See Clark AJ, Adelberg EA 1962 Annu Rev Microbiol 16:289).

F⁺: Bacterium carrying a sex element (F, fertility factor). ▶ [F plasmid](#)

F₁, F₂, F_n: Subsequent filial generations; the parents of the F₁ are homozygous for different alleles of the corresponding gene(s).

F Duction: In F duction, a gene is transferred to the F⁻ bacterial cell by an F plasmid, called F'; the process is the same as that of sexduction. ▶ [sexduction](#), ▶ [F plasmid](#)

F Element: The “dot-sized” smallest chromosomes, common to all *Drosophila* species.

F Elements: See non-viral retrotransposable elements. ▶ [hybrid dysgenesis](#), ▶ [I – R](#), ▶ [FB](#), ▶ [F factor](#)

F Factor: The bacterial fertility element (F plasmid, sex plasmid). ▶ [Hfr](#), ▶ [episome](#), ▶ [F plasmid](#); Bernstein HL 1958 Symp Soc Exp Biol 12:93.

F₂ Linkage Estimation: In some species where controlled mating or crossing is difficult, linkage intensities (recombination frequencies) can be estimated in the selfed progeny of F₁ or in the offspring of brother–sister matings. In testcrosses, the recombination frequencies can be determined in a straightforward manner by dividing the number of recombinants by the sums of the parental and recombinant individuals in the progeny. In F₂, the computations rely on indirect means, using statistical tables (see Table F1). The product ratio tables were constructed on the basis of the formula:

$\frac{ad}{bc} = \frac{T(2+T)}{(1-T)^2}$ where the meaning of a, b, c, d is given, and $T = (1 - p)^2$ for coupling, and $T = (p)^2$ for repulsion data; p is recombination frequency. The procedure can be best described by an example. Let us consider a hypothetical F₂ population with four phenotypic classes (a, b, c, d):

| AB (a) | Ab (b) | aB (c) | ab (d) | Total |
|--------|--------|--------|--------|-------|
| 660 | 38 | 40 | 183 | 921 |

Linkage is obvious, because the frequency of the double homozygous recessive class (ab or briefly d) exceeds that of the single heterozygotes (Ab and aB, classes b and c), the linkage phase is *coupling* in the two parents (AB and ab).

We can use the product ratio method (formula R for repulsion) and formula C in coupling:

$$\frac{a \times d}{b \times c} = R, \text{ and } \frac{b \times c}{a \times d} = C.$$

$(b \times c)/(a \times d) = (38 \times 40)/(660 \times 183) \cong 0.012584865 = C$. In the table, this exact fraction is not found; therefore, interpolation is necessary to find the right value (see Table F2). Interpolation is expected to provide a more accurate estimate than values in the product ratio table, where the recombination fraction is shown in increments of 0.005.

Table F1. F₂ Linkage Estimation. Recombination fractions determined by the product ratio method using F₂ data. Modified after F. R. Immer, *Genetics* 15:81. Recombination fraction = y , product ratio in repulsion: R , product ratio coupling: C factor to be divided by \sqrt{N} , to obtain standard error of y , for repulsion SeR and for coupling SeC . N = total number of individuals in F₂. When the value of the product ratio does not correspond to a close-enough value of y , interpolation is required. More precise estimates can be obtained by the table of W. L. Stevens (*J. Genetics* 39:171), using 5 decimals, rather than 3, as in this table. Since recombination fractions are generally variable, for most purposes this accuracy may be entirely satisfactory. For the method of use of this table, see text on preceding page and next page.

| y | R | C | SeR | SeC |
|-------|------------|------------|--------|--------|
| 0.005 | 0.00005000 | 0.00003361 | 1.0000 | 0.0707 |
| 0.010 | 0.00020005 | 0.0001356 | 0.9999 | 0.1001 |
| 0.015 | 0.0004503 | 0.0003076 | 0.9997 | 0.1226 |
| 0.020 | 0.0008008 | 0.000516 | 0.9996 | 0.1411 |
| 0.025 | 0.001252 | 0.0008692 | 0.9993 | 0.1585 |
| 0.030 | 0.001804 | 0.001262 | 0.9988 | 0.1736 |
| 0.035 | 0.002458 | 0.002733 | 0.9985 | 0.1877 |
| 0.040 | 0.003213 | 0.002283 | 0.9979 | 0.2007 |
| 0.045 | 0.004070 | 0.002914 | 0.9975 | 0.2129 |
| 0.050 | 0.005031 | 0.003629 | 0.9969 | 0.2246 |
| 0.055 | 0.006096 | 0.004429 | 0.9962 | 0.2357 |
| 0.060 | 0.007265 | 0.005318 | 0.9956 | 0.2463 |
| 0.065 | 0.008540 | 0.006296 | 0.9947 | 0.2565 |
| 0.070 | 0.009921 | 0.007366 | 0.9939 | 0.2663 |
| 0.075 | 0.01141 | 0.008531 | 0.9930 | 0.2758 |
| 0.080 | 0.01301 | 0.009793 | 0.9920 | 0.2850 |
| 0.085 | 0.01471 | 0.01116 | 0.9910 | 0.2339 |
| 0.090 | 0.01663 | 0.01262 | 0.9899 | 0.3025 |
| 0.095 | 0.01846 | 0.01419 | 0.9889 | 0.3109 |
| 0.100 | 0.02051 | 0.01586 | 0.9977 | 0.1392 |
| 0.105 | 0.02267 | 0.01765 | 0.9864 | 0.3272 |
| 0.110 | 0.02495 | 0.01954 | 0.9850 | 0.3351 |
| 0.115 | 0.02734 | 0.02156 | 0.9837 | 0.3428 |
| 0.120 | 0.02986 | 0.02369 | 0.9822 | 0.3503 |
| 0.125 | 0.03250 | 0.02594 | 0.9809 | 0.3578 |
| 0.130 | 0.03527 | 0.02832 | 0.9793 | 0.3652 |
| 0.135 | 0.03816 | 0.03083 | 0.9776 | 0.3723 |
| 0.140 | 0.04118 | 0.03347 | 0.9760 | 0.3792 |
| 0.145 | 0.04434 | 0.03624 | 0.9744 | 0.3862 |
| 0.150 | 0.04763 | 0.03915 | 0.9726 | 0.3930 |

Table F1. Continued

| y | R | C | SeR | SeC |
|-------|---------|---------|--------|--------|
| 0.155 | 0.05105 | 0.04220 | 0.9708 | 0.3999 |
| 0.160 | 0.05462 | 0.04540 | 0.9689 | 0.4064 |
| 0.165 | 0.05832 | 0.04875 | 0.9670 | 0.4129 |
| 0.170 | 0.06218 | 0.05225 | 0.9650 | 0.4194 |
| 0.175 | 0.06618 | 0.05591 | 0.9629 | 0.4258 |
| 0.180 | 0.07043 | 0.05973 | 0.9610 | 0.4320 |
| 0.185 | 0.07464 | 0.06371 | 0.9588 | 0.4383 |
| 0.190 | 0.07911 | 0.06787 | 0.9567 | 0.4445 |
| 0.195 | 0.08374 | 0.07220 | 0.9545 | 0.4506 |
| 0.200 | 0.08854 | 0.07671 | 0.9521 | 0.4565 |
| 0.205 | 0.09351 | 0.08140 | 0.9499 | 0.4624 |
| 0.210 | 0.09865 | 0.08628 | 0.9475 | 0.4683 |
| 0.215 | 0.1040 | 0.09136 | 0.9452 | 0.4741 |
| 0.220 | 0.1095 | 0.09663 | 0.9426 | 0.4799 |
| 0.225 | 0.1152 | 0.1021 | 0.9401 | 0.4857 |
| 0.230 | 0.1211 | 0.1078 | 0.9376 | 0.4913 |
| 0.235 | 0.1272 | 0.1137 | 0.9351 | 0.4970 |
| 0.240 | 0.2334 | 0.1198 | 0.9324 | 0.5026 |
| 0.245 | 0.1400 | 0.1262 | 0.9297 | 0.5081 |
| 0.250 | 0.1467 | 0.1328 | 0.9271 | 0.5136 |
| 0.255 | 0.1536 | 0.1396 | 0.9243 | 0.5191 |
| 0.260 | 0.1608 | 0.1467 | 0.9214 | 0.5244 |
| 0.265 | 0.1682 | 0.1540 | 0.9186 | 0.5297 |
| 0.270 | 0.1759 | 0.1616 | 0.9158 | 0.5351 |
| 0.275 | 0.1837 | 0.1695 | 0.9128 | 0.5404 |
| 0.280 | 0.1919 | 0.1717 | 0.9099 | 0.5456 |
| 0.285 | 0.2003 | 0.1861 | 0.9069 | 0.5509 |
| 0.290 | 0.2089 | 0.1948 | 0.9039 | 0.5560 |
| 0.295 | 0.2179 | 0.2038 | 0.9008 | 0.5612 |
| 0.300 | 0.2271 | 0.2132 | 0.8977 | 0.5663 |
| 0.305 | 0.2367 | 0.2228 | 0.8946 | 0.5714 |
| 0.310 | 0.2465 | 0.2328 | 0.8913 | 0.5764 |
| 0.315 | 0.2567 | 0.2432 | 0.8882 | 0.5815 |
| 0.320 | 0.2672 | 0.2538 | 0.8850 | 0.5864 |
| 0.325 | 0.2780 | 0.2649 | 0.8817 | 0.5914 |

Table F1. Continued

| y | R | C | SeR | SeC |
|-------|--------|--------|--------|--------|
| 0.330 | 0.2892 | 0.2763 | 0.8784 | 0.5963 |
| 0.335 | 0.3008 | 0.2881 | 0.8750 | 0.6012 |
| 0.340 | 0.3127 | 0.3003 | 0.8716 | 0.6061 |
| 0.345 | 0.3250 | 0.3128 | 0.8684 | 0.6110 |
| 0.350 | 0.3377 | 0.3259 | 0.8648 | 0.6157 |
| 0.355 | 0.3508 | 0.3393 | 0.8614 | 0.6205 |
| 0.360 | 0.3643 | 0.3532 | 0.8580 | 0.6254 |
| 0.365 | 0.3783 | 0.3675 | 0.8544 | 0.6301 |
| 0.370 | 0.3927 | 0.3823 | 0.8509 | 0.6347 |
| 0.375 | 0.4076 | 0.3977 | 0.8473 | 0.6395 |
| 0.380 | 0.4230 | 0.4135 | 0.8437 | 0.6442 |
| 0.385 | 0.4389 | 0.4298 | 0.8400 | 0.6488 |
| 0.390 | 0.4553 | 0.4467 | 0.8353 | 0.6534 |
| 0.395 | 0.4723 | 0.4641 | 0.8328 | 0.6580 |
| 0.400 | 0.4898 | 0.4821 | 0.8291 | 0.6626 |
| 0.405 | 0.5079 | 0.5007 | 0.8252 | 0.6672 |
| 0.410 | 0.5266 | 0.5199 | 0.8215 | 0.6718 |
| 0.415 | 0.5460 | 0.5398 | 0.8178 | 0.6762 |
| 0.420 | 0.5660 | 0.5603 | 0.8139 | 0.6808 |
| 0.425 | 0.5867 | 0.5815 | 0.8101 | 0.6853 |
| 0.430 | 0.6081 | 0.6034 | 0.8062 | 0.6997 |
| 0.435 | 0.6302 | 0.6260 | 0.8024 | 0.6941 |
| 0.440 | 0.6531 | 0.6494 | 0.7985 | 0.6986 |
| 0.445 | 0.6768 | 0.6735 | 0.7945 | 0.7029 |
| 0.450 | 0.7013 | 0.6985 | 0.7907 | 0.7073 |
| 0.455 | 0.7766 | 0.7243 | 0.7867 | 0.7116 |
| 0.460 | 0.7529 | 0.7510 | 0.7827 | 0.7159 |
| 0.465 | 0.7801 | 0.7786 | 0.7787 | 0.7204 |
| 0.470 | 0.8082 | 0.8071 | 0.7747 | 0.7247 |
| 0.475 | 0.8374 | 0.8366 | 0.7705 | 0.7288 |
| 0.480 | 0.8676 | 0.8671 | 0.7665 | 0.7331 |
| 0.485 | 0.8990 | 0.8986 | 0.7623 | 0.7374 |
| 0.490 | 0.9814 | 0.9318 | 0.7583 | 0.7416 |
| 0.495 | 0.9651 | 0.9651 | 0.7542 | 0.7459 |
| 0.500 | 1.0000 | 1.0000 | 0.7500 | 0.7500 |

F

Corresponding to $y = 0.085$ and 0.090 in the C column, the table shows 0.01116 and 0.01262 . The procedure of **linear interpolation** is illustrated.

Table F2. F_2 Linkage Estimation

| | 1 | 2 | 3 |
|----------|---------|-------------|---------|
| C values | 0.01116 | 0.012584865 | 0.01262 |
| y values | 0.085 | ? | 0.090 |

Calculation: $\frac{C_2 - C_1}{C_3 - C_1} = \frac{0.012584865 - 0.01116}{0.01262 - 0.01116} = \frac{0.001424865}{0.00146} = 0.975934931 = \alpha$ and $1 - \alpha = 0.024065068$; **y2** (the recombination fraction sought) $= (y_1)(1 - \alpha) + (y_3)(\alpha) = 0.085(0.024065068) + 0.090(0.975934931) = 0.087834143$ or \approx **0.08783**

The interpolated SeC value is obtained as: $0.2339(0.024065068) + 0.3025(0.975934931) = 0.300849136$

The standard error of the y_2 is calculated by $0.300849136 / \sqrt{921} = 0.009913316$. Thus the interpolated recombination fraction, $(y_2) = \mathbf{0.08783 \pm 0.00991}$.

The efficiency of the product ratio method in F_2 coupling phase equals that of the testcrosses when the recombination frequency is low (below 8%) but approaching independent segregation the efficiency decreases. Maximally in F_2 , 2.5 times larger populations may be required to obtain equally dependable results. In repulsion, especially at close linkage, (below 8% recombination) the F_2 and product ratio procedures are very inefficient. The product ratio method is very useful when both recessive alleles reduce gametic or zygotic viability but not so when only one of the alleles is causing differential mortality. Generally, the product ratio method is equal in efficiency to the maximum likelihood procedure. The dependability of the results is determined primarily by the data collected and not by the statistical procedures. [►recombination](#), [►coupling](#), [►repulsion](#), [►maximum likelihood method applied to recombination frequencies](#), [►mapping functions](#), [►mapping genetic](#), [►table above](#), Table F1, Stevens WL 1939 J Genet 39:171.

F₃ Linkage Estimation: This process may be used both in repulsion and with coupling phases. In repulsion, the information is not very trustworthy unless the recombination frequency is about 0.1 or less. Recombination can be estimated by combining F_2 and F_3 data as follows: $x = \frac{a/aB/b}{n}$ = $\frac{\text{Number of segregating lines}}{\text{Number of } a/a \text{ lines}}$ then p (recombination fraction) =

$$\frac{x}{2-x} \text{ and the standard error of } p, s_p = \frac{2\sqrt{x(1-x)}}{[2-x]^2\sqrt{n}}$$

F⁻ Phenocopy: A bacterial cell that has no F pilus. Although it carries an F element, it is not in a conjugative state. [►bacterial conjugation](#), [►conjugation mapping](#)

F Plasmid: Also known as the F factor or fertility plasmid of *E. coli*; it is about 100 kb and has four major regions (see Fig. F2). The (1) *inc* and *rep* tracts control its vegetative replication. When only this is retained it is called a *miniplasmid*. The (2) *IS* sequences are insertion elements and *Tn1000* is a transposon (called also $\gamma\delta$) is similar to *Tn3*. In the (3) *silent region* few functions are known. The (4) *tra* sites control transmission of the plasmid, which originates at the *oriT* site. The *tra* region includes more than two-dozen genes. The *tra M* is regulated by the *traJ* gene, which in turn is negatively regulated by *fin* (fertility inhibition) gene products. The *tra* operon also includes genes for the formation of the sex pilus through which plasmid and/or chromosomal DNA is transferred to the recipient cells. The total number of genes in this plasmid is about 30. The plasmid may be present in one or two copies per F^+ bacterial cells. It is an episome and can integrate clockwise or counterclockwise at various sites into the bacterial chromosome. When excised it may become an F' plasmid. [►episome](#), [►conjugation](#), [►pilus](#), [►mapping](#), [►transposon](#), [►episome](#), [►F' plasmid](#), [►Hfr](#); Cavalli LL et al 1953 J Gen Microbiol 8:89.

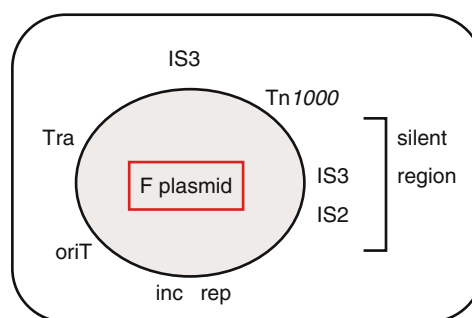


Figure F2. F plasmid

F Statistics: F statistics estimates the significance of the difference between means by the use of analysis of variance (ANOVA); it was named after R.A. Fisher who developed it. [►analysis of variance](#), [►F-distribution](#)

F₂ Segregation: [►Mendelian segregation](#)

φValue: A biophysical characteristic of a macromolecule. It is obtained by dividing the change in transition-state free energy accompanying a side-chain truncation by the change in native-state free energy. [►transition state](#)

FAA: A histological fixative containing formalin, acetic acid, ethanol. [►fixatives](#)

Fab Domain: The fab domain of the antibody includes a whole light chain and a part of the heavy chain (can be split off by digestion with papain), including the paratope (the antigen recognition site). ►antibody, ►epitope

FABPs: FABPs are fatty acid binding proteins facilitating lipid utilization and fat homeostasis. ►obesity; Maeda K et al 2005 Cell Metabolism 1:107.

Fabry Disease: An Xq22 chromosome disorder caused by a deficiency of α -glycosidase (α -galactosidase A) enzyme. Vascular NO dysregulation, increased nitrotyrosine staining, and accelerated atherosclerosis were confirmed in the murine model. The hemizygous males have skin lesions, opacity of the eye, periodic fevers, burning sensation in the extremities, and edema (fluid accumulation) due to kidney malfunction. The heterozygous females have much milder symptoms yet they also develop opacity of the eyes. The afflicted individuals survive to adulthood when death is caused by heart, kidney, and brain problems. The heterozygotes can be identified and the condition is detectable by amniocentesis; thus, genetic counseling is effective. Galactosylgalactosyl-glucosyl ceramide accumulates in the endothelium (the tissue lining the heart, blood and lymph vessels, and other cavities), in the nerve system, the epithelium (surface cell layers) of the kidney and cornea (the transparent outer coat in front of the eyes). Attempts have been made to correct the condition by retroviral vectors with α -glycosidase A (α -galactosidase A) expression. ►galactosidases, ►sphingolipidoses, ►sphingolipids, ►viral vectors, ►gene therapy, ►enzyme replacement therapy; Ioannou Y et al 2001 Am J Hum Genet 68:14; Blom D et al 2003 Am J Hum Genet 72:23.

FAC: ►Fanconi's anemia

Face/Heart Defects: ►Alagille syndrome, ►Williams syndrome, ►Noonan syndrome, ►Ellis-van Creveld syndrome, ►DiGeorge syndrome, ►velo-cardiofacial syndrome

Facet: The small flat surface on a structure or component of the insect eye. ►ommatidium, ►compound eye

Facilitation: In facilitation by repeated impulses to the nerve cells, the amount of neurotransmitter is increased but eventually this process may lead to exhaustion of the neurotransmitter supply.

Faciogenital Dysplasia (FGD1, Xp11.21): Faciogenital dysplasia involves hypertelorism (increased distance between parts of the face), cryptorchidism (hidden testes), bone deformation, cup-shape ear-lobes, etc., caused by defects in a guanine nucleotide exchange factor that activates Cdc42. ►Aarskog syndrome, ►guanine nucleotide exchange factor, ►CDC42, ►GEF; Estrada L et al 2001 Hum Mol Genet 10:485.

FACS (fluorescence-activated cell sorting): cell sorter, flow cytometry.

FACT (complex of p140 and p80): A histone chaperone, which in cooperation with other proteins, facilitates transcription through nucleosomes by chromatin remodeling and transcript elongation by RNA polymerase II. ►chromatin remodeling; Orphanides G et al 1998 Cell 92:105; Pavri R et al 2006 Cell 2006 125:703.

Factor: A genetic unit such as a gene.

Factor D: Synonymous with TIF-1B.

Factorial: $1 \times 2 \times 3 \dots \times (n - 1) \times n = n!$, the products of integers from 1 to n , the factorial of n numbers. Note: $0! = 1$.

Factorial Experiment: A factorial experiment analyzes simultaneously the effects of several factors, e.g., a_1b_1 , a_2b_1 , a_1b_2 , a_2b_2 . The comparison $a_2b_2 - a_1b_2$ assesses the "main effect" of A when B remains constant and $a_2b_1 - a_1b_1$ determines the B "main effect" when A is constant. Such experiments are very economical for testing simultaneously the consequences of several factors and their interactions (AB), and are frequently used to determine dose responses by using different levels of the individual elements such as a_1 and a_2 . ►Graeco-Latin square, ►principal component analysis; Fisher RA 1937 The design of experiments, Oliver & Boyd, Edinburgh, UK.

Facultative: A facultative has no absolute single determination; it may show alternative forms or functions.

Facultative Heterochromatin: Facultative heterochromatin behaves as a heterochromatin only under certain conditions, like in the mammalian X-chromosome when present in more than a single copy. ►heterochromatin

FAD: Flavin adenine dinucleotide, a riboflavin containing coenzyme in some oxidative-reductive processes; also an acronym of familial Alzheimer disease. ►Alzheimer disease

FADD/MORT-1 (FAS-associated death domain, 26-kDa): The FLIP proteins interact with FADD in the presence of FLICE and inhibit apoptosis. FADD interacting with Fas permits the recruitment of caspase-8 (FLICE/MACH) and that activates the protease cascade of apoptosis. FADD also signals to TNFR associated death domain (TRADD) and to developmental pathways. FADD also regulates the pre-T cell receptor and may act as a tumor suppressor. FADD^{-/-} cells are more susceptible to RNA virus infection (Balachandran S et al 2004 Nature [Lond] 432:401). ►FAS, ►FLICE, ►death domain, ►apoptosis, ►TNFR; Zhang J, Winoto A 1996 Mol Cell

Biol 16:2756; Gómez-Angelats M, Cidlowski JA 2001 J Biol Chem 276:44944; Werner MH 2006 Cell Cycle 5:2332; CD95 in apoptosis: Peter ME et al 2007 Cell 129:447.

FAHR Disease (14q): Idiopathic basal ganglia calcification, a neurobehavioral and cognitive disorder.

FAIRE (formaldehyde-assisted isolation of regulatory elements): A method to assay open chromatin using formaldehyde crosslinking followed by detection of the products using a genomic tiling array. It has utility as a positive selection for genomic regions associated with regulatory activity, including regions traditionally detected by nuclease hypersensitivity assays (Giresi PG et al 2007 Genome Res 17:877). ▶tiling, ▶nuclease-sensitive sites

FAK (focal adhesion tyrosine kinase): A protein tyrosine kinase occurring at high level in SRC transformed cells. Its role is in mediating cell adhesion and migration. FAK is localized at the cell membrane integrin receptors. Association of integrin with fibronectin results in binding of the Grb2 adaptor to SRC and FAK protein tyrosine kinases and in the activation of MAPK (mitogen-activated protein kinase) in the signal transduction pathway. FAK interacts with phospholipase C- γ -1. ▶CAM, ▶Grb, ▶SRC, ▶MAPK, ▶signal transduction, ▶PTEN, ▶integrin, ▶cell migration, ▶phospholipase, ▶FLT; Xie B et al 2001 J Biol Chem 276:19512; structural

and functional domains: Dixon RDS et al 2004 Structure 12:2161.

Fallopian Tube (uterine tube, oviduct): The fallopian tube connects the mammalian ovary to the uterus. Upon maturation, the egg is released into the Fallopian tube and fertilization may take place after the sperm injected into the vagina travels to the egg through the cervical canal. ▶fertilization, ▶gonads, ▶uterus, ▶ovary

Fallot's Tetralogy (TOF): Pulmonary stenosis, atrial septal defect, and right ventricular hypertrophy constitute the *trilogy*. The *tetralogy* = trilogy + the right shifting of the aorta overriding the interventricular septum and thus receiving both arterial and venous blood, the *pentalogy* = the tetralogy + open foramen oval or atrial septal defect. Mutations at JAG1 (20p12) ligand of NOTCH may cause TOF. Its prevalence is ~1/3,000 live birth. (See meaning of these terms under separate entries, ▶heart disease, ▶Alagille syndrome; Eldadah ZA et al 2001 Hum Mol Genet 10:163).

Fallout: The radiation emitted by isotopes released into the atmosphere by applying or testing nuclear weapons, by nuclear explosions and atomic power plants. ▶atomic radiations

False Allelism: A series of overlapping deficiencies may mimic an allelic series at a gene locus (see Fig. F3).

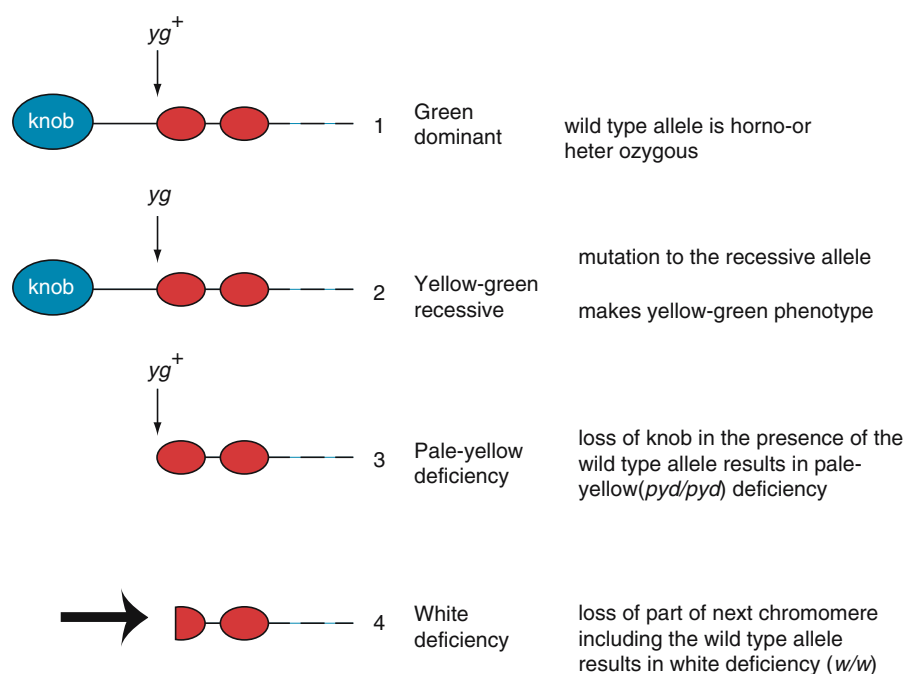


Figure F3. False allelism due to deficiencies

For an illustration, see the consequences of overlapping deficiencies observed at the tip of the short arm of chromosome 9 of maize. Note particularly that the *yg/pyd* heterozygotes are normal green demonstrating that in the *pyd* deficiency the wild type allele is present despite the phenotype of the homozygotes, and the allelism is only apparent. ► [allelism](#), ► [position effect](#)

False Discovery: Statistical procedures are available for the estimation of false negative and false positive information in scientific studies. (See Wakefield J 2007 *Amer J Hum Genet* 81:208).

F

False Negative: A result is a false negative when the test performed indicates the absence of a condition but in fact it is an incorrect observation. ► [false positive](#)

False Positive: A result is a false positive when it indicates the presence of a particular condition but the observation is incorrect. The determination of the rate depends on the prevalence of the condition. Example: on the basis of existing evidence the incidence of a disease in a particular population is 3/10,000 but the clinical test has an error rate of 6%. In this case, the probability that a person who is diagnosed positive actually has the condition is: $(3/10,000)/0.06 = 0.005$, i.e., 0.5% and that he/she represents a false positive case is $1 - 0.005 = 0.995$ or 99.5%. Hoffrage U et al 2000 (*Science* 290:2261) use the following illuminating example. Assume that 0.003 fraction (0.3%) of the population may be afflicted by colorectal cancer. The clinical laboratory test (blood in the feces) has a sensitivity of only 50% and the false positive rate is 3%. What then is the probability that a positive test is actually correct? According to the rate of incidence stated above (0.3%), out of 10,000 individuals 30 ($10,000 \times 0.003$) have colorectal cancer but because of the efficiency of the test (50% sensitivity) only 15 will be diagnosed as positive. Actually, of the 9970 ($10,000 - 30$), 300 individuals will test positive (3% of $10,000 = 300$). Thus the frequency of those actually afflicted among the positives is $15 / (15 + 300) \leq 0.047$. The correct estimation of the rate of false positives/negatives may be a question of life or death in medical or in forensic cases. ► [false negative](#), ► [sensitivity](#), ► [estimation of false positive](#), false negative and true discovery rates: Norris AW, Kahn CR et al 2006 *Proc Natl Acad Sci USA* 103:649.

Familial Adenomatous Polyposis: ► [FAP](#), ► [Gardner syndrome](#)

Familial Aggregation: A certain trait is more common in some families although the precise genetic control may not be known.

Familial Hypercholesterolemia (FHC, 19p13.2): FHC involves increase in low-density lipoprotein (LDL) bound cholesterol, as a consequence of which, at birth the homozygotes develop surface tumors filled with lipids (xanthomas) between the first two digits. Later on these plasias appear at the tendons, the cornea of the eye may also display gray lipid-containing little sacks, and by adulthood coronary heart disease is expected. The basic defect affects the cell membrane or its receptor of LDL. Under normal conditions, the LDL passes into the lysosomes where upon degradation, the liberated cholesterol feedback represses hydroxy-methylglutaryl Coenzyme A reductase (HMGR), an enzyme responsible for cholesterol biosynthesis. The fungal products lovastatin and compactin are inhibitors of this enzyme and may be considered for treatment of FHC. The LDL receptor with 18 exons codes for 13 polypeptides with homologies to different proteins of a large superfamily. The dominant gene located to human chromosome 19p13.2-p13.11 has various base substitutions, frameshift, and deletion mutations. Some of the deletions are apparently caused by unequal recombination in the Alu sequences of introns 4 and 5 or others and missplicing. The heterozygotes may show the same symptoms but less evidently. The serum cholesterol and low-density lipoprotein levels in the homozygotes may exceed up to twice or more than that of the normal (75–175 mg/100 mL). About 5% of the myocardial infarction patients are heterozygous for this condition. The prevalence of FHC homozygotes is in the 10^{-6} range and that of the heterozygotes is higher than 0.002. A cholesterol-lowering gene has been assigned to 13q. Animals transplanted with autologous but genetically engineered hepatocytes developed a persisting 30–50% decrease of serum cholesterol levels. FHC may be identified at birth. This condition may not result in obesity, high blood pressure, or some other common indicators of susceptibility to heart ailments. Using retroviral vectors carrying the LDL receptor gene, gene therapy has shown itself to be promising, although, improvement of the efficiency of the transformation technology is still desirable. FHC may involve haplo-insufficiency. Recessive mutations at 15q25-q26, 1p34-p32, and at 2p24 are also factors in FHC. An autosomal dominant hypercholesterolemia (HCHOLA3 or FH3) also at 1p34.1-p32 encodes also a subtilase family protein (PCSK9), which is related to the subtilisin kexin isoenzyme protease, controlling cholesterol homeostasis through sterol-regulatory element-binding proteins (Abifadel M et al 2003 *Nature Genet* 34:154). Other genetic factors may also contribute to the disease. ► [coronary heart disease](#), ► [lipoprotein](#), ► [LDL](#), ► [VLDL](#),

►HDL, ►lipids, ►cholesterols, ►statins, ►lovastatin, ►sphingolipidoses, ►unequal crossing over, ►Alu, ►genetic screening, ►missplicing, ►gene therapy, ►hypertension, ►haplo-insufficient, ►sitos-terolemia, ►Ezetimibe; Eden ER et al 2001 Am J Hum Genet 68:653.

Familial Hypertriglyceridemia: An autosomal dominant hyperlipoproteinemia leading to coronary heart disease. ►coronary heart disease, ►hyperlipoproteinemia

Familial Medullary Thyroid Carcinoma (FMTc): ►RET oncogene

Familial Trait: A familial trait appears in certain families; its cause may be hereditary or otherwise, e.g., deafness may result from about two dozen genetic conditions, but ear infection, diabetes of the mother, birth injury, or senescence may be responsible for it. ►congenital trait

Family: Offspring descended from a common mother (and father). In taxonomy it means a group of genera. ►nuclear family, ►gene family, ►protein families

Family Box: A group of RNA nucleotide triplets with identical nucleotides near the 5'-end but different at the 3'-end yet coding for the same amino acid. ►code genetic

Family History: The family history is an essential source for genetic counselors to determine recurrence risks. ►risk, ►genetic risk, ►recurrence risk, ►empirical risk, ►genetic counseling, ►pedigree analysis

Family of Genes: A similar set of genes (coding for basically similar polypeptides); they probably arose during evolution by successive duplications and modifications. ►duplication; detection of genes families arisen by duplication: <http://fgf.genomics.org.cn/>.

Family Planning: Family planning includes a variety of resources and considerations in determining family size, use of contraceptives, decisions regarding the genetic constitution, knowledge of genotypes, and family history. ►genetic counseling, ►ART, ►contraceptives, ►abortion medical

Family-Based Association Test (FBAT): A variation of the association mapping procedure, where case and control are selected within families rather than in the general population. ►association mapping, ►linkage disequilibrium; <http://www.biostat.harvard.edu/~fbat/default.html>.

FAN: A WD-repeat protein signaling to neutral sphingomyelinase activation. ►WD-40, ►sphingolipids

Fanconi Anemia (FA, aplastic anemia, Fanconi's syndrome, Fanconi's disease, Fanconi pancytopenia): A recessive genetic disorder assigned to nine complementation groups. The A complementation group (FANC-A/H) was localized to human chromosome 16q24.3, the FANC-C group to 9q22.3, the FANC-D to 3p25.3, FANCE (6p21-p22), FANCF (11p15), the FANC-G to 9p13, the same as XRCC9. The FANC-L complementation group (chromosome 2) encodes E3 ubiquitin ligase activity (PHF9) and it is essential for FANC-D2 (Meetei AR et al 2003 Nature Genet 35:165). FANCD1 is also called BRCA2. FANCF is a DNA helicase (BRIP1/BACH1) is a binding partner of the breast cancer suppressor gene BRCA1 (Levan O et al 2005 Nature Genet 37:931). The earlier assignment to chromosome 20q could not be confirmed by newer data. FA shows a wide range of symptoms: leukopenia (less than 5,000 leukocytes/mL blood), thrombocytopenia (reduced platelet count), pigmentation of the skin, and various malformations at different degrees of expression. The homozygous cells suffer high frequency chromosome defects. Both red and white blood cells appear normal. Generally, it is fatal by the teen years. The genetic basis is chromosomal instability and associated leukemia and other malignancies. FA is accompanied by genito-urinary anomalies, cystinuria, heart disease, dwarfism, skeletal problems, microcephaly (small head), deafness, etc. The genetic repair system appears to be defective in the complementation group C (FANC-C) protein (163-kDa), which seems to possess a nuclear localization signal. FancD2 after monoubiquitination—in association with other proteins—is involved in DNA repair (Matsushita N et al 2005 Mol Cell 19:841). Fanconi cells are hypersensitive to DNA cross-linking agents (mitomycin C, diepoxybutane) because of defects in DNA helicases involved in direct DNA repair or in bypassing the defect at replication (Niedemhofer LJ et al 2005 Cell 123:1191). The A complementation group-coded protein is cytoplasmic and its precise function is unclear, however, a general regulatory role is suspected. Because of apparent reverse mutations, there is evidence for somatic mosaicism. Gene therapy for the C protein appears promising, although does not remedy all the disease. The FANC-F (11p15) encodes a 347-amino acid protein, which is homologous to the prokaryotic RNA-binding protein, ROM. FA cells are very sensitive to bifunctional alkylating agents such as mitomycin C and diepoxybutane. FA involves a roughly three-fold increase in telomere defects and

a substantial increase in extra-telomeric and intra-chromosomal TTAGGG signals characteristic for telomeres.

PALB2 (partner and localizer of BRCA2) is a protein that interacts with BRCA2 and is important in determining the localization and stability of BRCA2 in the nucleus. If in HeLa cells RNAi reduces PALB2 expression, an increased sensitivity to mitomycin C (MMC) appears; FA is very sensitive to MMC (Xia B et al 2007 *Nature Genet* 39:159). Biallelic *PALB2* mutations cause a new subtype of Fanconi anemia, FA-N, and, similarly as biallelic *BRCA2* mutations, confer a high risk of childhood cancer (Reid S et al 2007 *Nature Genet* 39:162; Rahman N et al 2007 *Nature Genet* 39:165).
 ▶hemostasis, ▶platelet anomalies, ▶DNA repair, ▶stature in humans, ▶limb anomalies, ▶light-sensitivity diseases, ▶cancer, ▶Dubowitz syndrome, ▶Bloom syndrome, ▶breast cancer, ▶gene therapy, ▶XRCC, ▶ROM, ▶functionality of mutagens, ▶mitomycin C, ▶DEB, ▶PGD; de Winter JP et al 2000 *Am J Hum Genet* 67:1306; Medhurst AL et al 2001 *Hum Mol Genet* 10:423; Joenje H, Patel KJ 2001 *Nature Rev Genet* 2:446; Callén E et al 2002 *Hum Mol Genet* 11:439; D'Andrea AD, Grompe M 2003 *Nature Rev Cancer* 3:23; Meetei AR et al 2005 *Nature Genet* 37:958.

Fanconi-Bickel Syndrome: ▶glucose transporter (GLUT2)

Fanconi Renotubular Syndrome (15q15.3): An autosomal dominant, late onset kidney disease resulting in aminoaciduria and glycosuria; sometimes associated with bone problems. There are types with and without cystinosis. ▶aminoacidurias, ▶cystinosis, ▶glycosuria

FANCY (functional analysis by co-responses in yeast): An analytical method for the expression of genes with minimal effect, based on metabolite concentrations rather than metabolic flux. (See Raamsdonk L et al 2001 *Nature Biotechnol* 19:45).

FANTOM (functional annotation of microarrays): In 2005 the transcriptional landscape (control signals + transcripts) of the mouse genome included 181,047 transcriptional units (TU) with 1.32 start sites (5') for each 3' end. There were 7.3 TUs per transcriptional framework (TK) in the mouse genome. Overlapping transcription occurred on both strands of the DNA and separated by deserts without transcription. Since then, with FANTOM3, the coverage has increased. The mouse genome's ~22,000 genes seems to have more transcripts by an order of magnitude. The transcriptional forests include genomic regions transcribed by either strand without gaps. ▶microarray hybridization, ▶annotation, ▶gene expression,

▶interaction of gene products; FANTOM Consortium and RIKEN 2005 *Science* 309:1559; <http://fantom.gsc.riken.go.jp>.

FAO: Food and Agricultural Organization of the United Nations, Rome, Italy.

FAP: Familial adenomatous polyposis. The genetically controlled polyps in the colon may develop into colorectal cancer after additional somatic mutations.
 ▶polyp, ▶Gardner syndrome

FAP-1: A protein tyrosine phosphatase regulating the activity of the Fas cell surface receptor. ▶Fas

FAPY (formamidopyrimidine): A DNA base analog. It is removed from the DNA by the Fpg (a corresponding glycosylase). The lesion is repairable. ▶glycosylases; Ide H 2001 *Progr Nucleic Acid Res Mol Biol* 68:207.

FAR: A protein required for pheromone-induced cell cycle arrest at G1. ▶CKI, ▶cell cycle

Farber's Disease (8p22-p21.3): Farber's disease is concerned with a defect of the enzyme ceramidase. It manifests in early infancy as irritability, swelling of the joints, motor abnormalities, mental retardation, and early death. ▶sphingolipids, ▶ceramide

Farnesoid X Receptor (FXR): FXR is involved in the regulation of the bile acid metabolism. Chenodeoxycholic acid binds to FXR and subsequently, cholesterol 7 α -hydroxylase is down-regulated and bile acids are transported from the gut to the liver. Chenodeoxycholic acid indirectly regulates both its own proportion and that of bile acid. Other proteins playing key role in the synthesis of cholic acids from cholesterol are PPAR and LXR α . Oxysterol is the ligand for the latter in the liver. FXR and RXR (retinoid X receptor) jointly regulate cholesterol transport and bile acid synthesis. ▶PPAR, ▶cholesterol, ▶cholic acid, ▶sterol, ▶hepatocyte, ▶cholestasis; Kast HR et al 2001 *Mol Endocrinol* 15:1720; Zhang Y et al 2003 *J Biol Chem* 278:104.

Farnesyl Pyrophosphate: An intermediate in the synthesis of cholesterol. It plays a role in mediating binding of proteins to membranes. ▶prenylation

Farnesylation: ▶prenylation

Farsighted (hyperopia): In hyperopia, distant objects can be seen better than those nearer. ▶myopia

Far-Western Hybridization: A method for isolating genes, which encode interacting proteins. ▶Western blot, ▶two-hybrid method; Blanas MA, Rutter WJ 1992 *Science* 256:1014.

FAS (fatty acid synthase): A homodimeric enzyme with seven catalytic domains. This explains its multifunctional nature in fatty acid synthesis. FAS activity is

indispensable for embryo development and FAS^{+/-} progeny has reduced embryo viability. ▶ [fatty acids](#); Chirala SS et al 2003 Proc Natl Acad Sci USA 100:6358; mammalian fatty acid synthase structure: Maier T et al 2006 Science 311:1258; fungal fatty acid synthase structure: Jenni S et al 2006 Science 311:1263; yeast FAS crystal structure: Lomakin IB et al 2007 Cell 129:319.

Fas (fibroblast associated surface antigen, CD95, APO-1, 10q24.1): A member of the tumor necrosis factor and nerve growth factor receptor protein family that also includes Cd40, CD27, CD30, OX40, and SFV-2. FasL or the Fas ligand is encoded in human chromosome 1q23. FasL expression is induced by PMA. Fas plays a key role also in apoptosis and autoimmune disease by binding the FasL, a TNF protein. PMA and protein tyrosine kinase inhibitors (herbimycin, genistein) can rapidly induce FasL and cyclosporin inhibits its induction. The antibody to FasL is an immunoglobulin M (IgM), whereas the antibody to APO-1 is IgG3. Human Fas is a trans-membrane protein containing 325 amino acids. Fas is up-regulated by interferon- γ and tumor necrosis factor- α in human B and T cells. Fas signaling leads to apoptosis and it is triggered by cross-linking of Fas with Fas antibodies, and by cells expressing FasL. Fas-induced apoptosis is faster than that induced by TNF-receptor. Fas and TNF induce apoptosis in the cells of the immune system. Therefore, in cancer gene immunotherapy the Fas-L may be considered an appropriate target. Fas mediates two apoptotic pathways; one involves the FADD adaptor protein and pro-caspase-8. The other path is mediated by Daxx (death associated protein, human chromosome 6q21.3) and the activation of the JNK - MAPKKK through ASK1 (apoptosis signal-regulating kinase 1). FAS-FasL expression, however, does not lead to apoptosis under all circumstances. The DcR3 (decoy receptor, human chromosome 20q) may associate with the FasL and inactivate the apoptotic pathway in lung and colon cancer cells. Apo-3 is a CD120A homologous TNF/NGF receptor encoded at 1p36.3. ▶ [apoptosis](#), ▶ [caspase](#), ▶ [TNF](#), ▶ [autoimmune disease](#), ▶ [FADD](#), ▶ [FAP-1](#), ▶ [PMA](#), ▶ [cyclosporin](#), ▶ [immune system](#), ▶ [signal transduction](#), ▶ [JNK](#), ▶ [Lyell syndrome](#), ▶ [CD120](#), ▶ [NGF](#), ▶ [Canal-Smith syndrome](#), ▶ [survival factors](#), ▶ [TACE](#); Nagata S 1999 Annu Rev Genet 33:29.

Fasciation: An abnormal development resulting in a flat stem and club-shaped fruit with four rows of seeds rather than two in *Arabidopsis*. In zoology, it designates sheets of tissues. ▶ [CAF](#); Kaya H et al 2001 Cell 104:131, see Fig. F4.



Figure F4. Fasciation

Fascicle (fasciculus): A bundle of (nerve, muscle, etc.) fibers.

Fasciclins: Cell adhesion molecules of the immunoglobulin superfamily that are expressed in motor neurons. It acts with semaphorin and connectin/titin. ▶ [titin](#), ▶ [semaphorin](#); Cheng Y et al 2001 Cell 105:757; Wright JW, Copenhaver PF 2001 Dev Biol 234:24.

FasL: ▶ [FAS](#)

FAST (fiber-optic array scanning technology): FAT cytometry combined with laser-printing optics can excite 300,000 cells per sec and the emission collected on a wide field of view is 500 times faster than ADM with comparable sensitivity and specificity for the early detection of rare metastatic cells in blood. ▶ [ADM](#), ▶ [metastasis](#); Krivacic RT et al 2004 Proc Natl Acad Sci USA 101:10501.

Fast Blue: A fluorescent (neuronal) tracer dye.

Fast Component: The fast component of the nucleic acid reassociation reaction represents the repetitive sequences. ▶ [c₀t curve](#), ▶ [c₀t value](#)

Fast Green: A histochemical stain for basic proteins; it is generally used in combination with other stains, e.g., safranin or pyronin.

Fastlink: A computer program for genetic linkage analysis.

Fast Neutrons: Fast neutrons are particulate, ionizing radiations released at atomic nuclear fission. They are highly effective mutagens. ▶ [radiation](#), ▶ [physical mutagens](#); Hacker-Klom UB et al 2000 Radiat Res 154:667.

FASTA: A program used for sequence comparisons in DNA, RNA and proteins (Pearson WR 1991 Genomics 11:635). E-mail address ►fasta@ebi.ac.uk. (See BLAST; BLOSUM; FASTA programs: <http://www.ebi.ac.uk/fasta/>).

Fat: Fatty acid–glycerol ester. Its caloric value (9.3 kcal/g) is approximately 2.3 times that of carbohydrates and proteins. Oxidation of fats (rancidity) may result in the formation of mutagenic compounds in natural products. ►[fatty acids](#), ►[cholesterol](#), ►[triacylglycerols](#), ►[atherosclerosis](#)

F

Fat Body: An insect organ comparable to the liver of higher animals. It secretes antimicrobial peptides and its role is similar to that of the immune system of higher animals. Fat cells in the *Drosophila* head are the sites of expression of several male and female-specific genes (Fujii S, Amrein H 2002 EMBO J 21:53). These genes appear to modulate sex-specific neuronal activity in the brain. ►[sex determination](#), ►[oenocyte](#); Khush RS, Lemaitre B 2000 Trends Genet 16:442.

Fatal Familial Insomnia (insomnia-dysautonomia thalamic syndrome, FFI): An autosomal dominant degenerative disease of the thalamic nuclei (the basal; part of the brain involved in transmission of sensory impulses). It is a progressive insomnia that involves defects in the autonomous nervous system, speech defect, tremors, and seizures, and may eventually lead to death. The pathological symptoms may resemble those of the Creutzfeldt-Jakob disease (CJD) with the difference that the spongy transformation of the cells here is limited to the thalamus. In CJD, the mutation at amino acid position 129 results in a valine replacement, whereas in FFI there is a methionine at 129. In mice devoid of prion protein (PrP^C) because of mutation, the circadian activity rhythm, including the sleeping pattern is altered. Sporadic fatal insomnia also occurs because of somatic mutation. ►[prion](#), ►[encephalopathies](#), ►[Creutzfeldt-Jakob syndrome](#); Collins S et al 2001 J Clin Neurosci 8(5):387; Montagna P 2005 Sleep Med Rev 9:339.

Fate Map, Morphogenetic: The morphogenetic fate map indicates the positions in the blastoderm from which adult structures (legs, eyes, nerves, etc.) develop. In terms of basic principles, it has some resemblance to the genetic mapping of genes to chromosomes (both ideas were developed by A. Sturtevant). The procedure is generally as follows. The investigator constructs a diploid individual with an unstable chromosome with the wild type allele and the homologous chromosome carries the recessive gene whose expression is to be traced to developmental origin or control center. When the unstable chromosome is

lost, the critical recessive allele can display pseudodominance in the sector, which no longer carries the wild type allele. Most commonly the defective chromosome in *Drosophila* is an X-chromosome. Thus its loss generates a gynandromorphic sector as well. The association between the gynander sector and critical gene expression can be classified and the developmental origin of the function determined. The developmental distances calculated from fate mapping are expressed in *sturt* units; 1 *sturt* is the fate mapping quotient multiplied by 100. In other words, 1 *sturt* means that two cell clusters are different in 1% of the mosaics.

The results of a fate mapping experiment using an unstable ring X-chromosome and the *drop dead* mutation of *Drosophila* are shown here (see Table F3).

Table F3. Fate map morphogenetic

| Behavior ↓ | Number of individuals with the constitution indicated in the head cuticle and in the abdominal cuticle | | | |
|------------------|--|----|---------|----|
| | Head | | Abdomen | |
| | XX | XO | XX | XO |
| Normal | 91 | 8 | 54 | 28 |
| <i>drop-dead</i> | 6 | 72 | 23 | 51 |
| Total | 97 | 80 | 77 | 79 |

The homo- and hemizygous individuals walk in an uncoordinated manner and suddenly die about ten days after eclosion. (Abridged from Hotta Y, Benzer S Nature [Lond] 240:527).

The frequency of *drop-dead* gynander and non-gynander (normal) heads and abdomens can be calculated similarly to recombination frequencies.

Thus,

| HEAD | ABDOMEN |
|---------------------------------|-----------------------------------|
| $\frac{6 + 8}{97 + 80} = 0.079$ | $\frac{23 + 28}{77 + 79} = 0.327$ |

The fractions above indicate that the *drop-dead* phenotype is more closely associated with the head cuticle gynandromorphy than with that of the abdomen. It shows that this behavior is determined by the development of the head. Anatomical studies have shown perforations in the brain of the flies, confirming the conclusions of the fate-mapping experiments. Fate maps can be constructed also on the basis of the distribution of molecules in the developing embryo. According to the suggestion of

Sydney Brenner, the fate of individual cells may follow the “European plan,” i.e., the ancestry of a cell determines its developmental fate or according to the “American plan,” when interaction with neighboring cells is the most critical for its fate. The distinction between these alternatives may not always be possible. In a more complex organisms such as mice, fate mapping may be possible by injecting cells equipped with a site-directed recombination or mutation system. ►[gynandromorphs](#), ►[deletion mapping](#), ►[mapping](#), ►[physical mapping](#), ►[cell lineages](#), ►[site-directed mutation](#), ►[site-directed recombination](#); Inoue T et al 2000 Dev Biol 219:373.

Fatty Acids: Aliphatic carboxylic acids of long chain structure, parts of the membrane phospho- and glycolipids, cholesterol, and fats and oils (see Fig. F5). Saturated fatty acids are formic (1:0), acetic (2:0), propionic (3:0), butyric (4:0), lauric (12:0), myristic (14:0), palmitic (16:0), stearic (18:0), arachidic (20:0), behenic (22:0), and lignoseric (24:0) acids (Indicated within the parenthesis is the number of carbon atoms in the chain and after the colon the number of double bonds.). Unsaturated fatty acids are crotonic acid (4:12), palmitoleic (16:1), oleic (18:1), vaccenic (18:1), linoleic (18:2), linolenic (13:3), and arachidonic (20:4) acids. Triacylglycerides (glycerol esters with three fatty acids) are one of the major sources of energy in mammals, particularly during hibernation (when nearly all the energy comes from these compounds). Linoleate and linolenate are essential fatty acids for mammals. Lipids are complexes of fatty acids with phosphates, sterols, or sugars and have indispensable functions in the cellular membranes. Lipids associated with proteins have the role of transporting fatty acids.

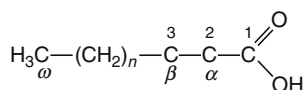


Figure F5. General nomenclature of fatty acids

When fatty acid nodules are deposited on the inner walls of the blood vessels, it results in atherosclerosis, a major cause of heart disease. Fatty acid biosynthesis is important, not just from the viewpoint of human disease, but its knowledge may help in developing plant varieties for human consumption and also for the production of special raw material for industrial

purposes. FAS (fatty acid synthase) is a primary enzyme in fatty acid synthesis (see Fig. F6). Inhibition of FAS has antitumor effect. Fatty acids regulate in a positive and negative way the transcription of some genes (Duplus E et al 2000 J Biol Chem 275:30749). ►apolipoproteins, ►fat, ►triaglycerols, ►lipids, ►lipidoses, ►sphingolipids, ►sphingolipidoses, ►glucose, ►atherosclerosis, ►omega-3-fatty acids, ►FAS, ►acetyl-coenzyme A carboxylase; Black PN, DiRusso CC 2003 Microbiol Mol Biol Rev 67:454; White SW et al 2005 Annu Rev Biochem 74:791.

Favism: A hemolytic anemia caused by eating even extremely small quantities of *Vicia faba* (broad bean) or by inhaling its pollen. The initial reaction (headache, dizziness, nausea, chills, etc.) may occur within seconds and may be followed within a day by jaundice and blood in the urine. People who are deficient in glucose-6-phosphate dehydrogenase are susceptible to this condition. The light sensitivity of the skin after eating the seeds of *Fagopyrum vulgare* (buckwheat) is different; a photodynamic substance causes the latter. ►glucose-6-phosphate dehydrogenase deficiency, ►broad bean, ►buckwheat, ►vicine; Burbano C et al 1995 Plant Foods Hum Nutr 47 (3):265.

FB: ► hybrid dysgenesis

FBI Site (fold back inhibition): The transcript of *Tn10* transposase folds back a region (UGGUC) complementary to the modified Shine-Dalgarno sequence (AUCAG) and prevents ribosome binding and thus reduces transposition. ▶ *Tn10*

F-BOX: A cyclin F interacting protein domain recruiting various proteins for proteolytic degradation (ubiquitination). F-box proteins are involved with the cell cycle, developmental processes, the immune reactions, etc. ►SCF, ►ubiquitin, ►cyclin F, ►IκB, ►proteasome, ►glucose induction, ►dominance reversal, ►protein degradation; Strohmaier H et al 2001 Nature [Lond] 413:316.

FBS: Fetal bovine serum.

Fc: A crystallizable fragment of immunoglobulin containing the C end of the heavy chains. The Fc receptors are expressed in monocytes and macrophages and some other cells of the immune system.
▶antibody, ▶immune system, ▶FcRn

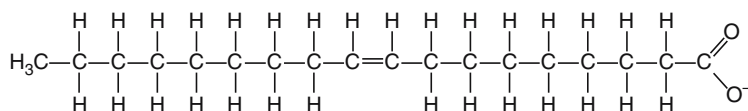


Figure F6. Oleate

FcγR: Receptors (I, II, III) of the immunoglobulin G antibody crystalline fragments. ►antibody, ►ITIM

FcεRI: Immunoglobulin IgE (Igε) crystallizable fragment high-affinity receptor on lymphocytes. It controls IgE-mediated antigen presentation and participates in several signaling pathways of the allergic responses. ►immunoglobulins, ►antibody, ►antigen presentation, ►allergy, ►asthma

FCP: ►transcription complex

F

FcRn: The crystallizable fragment receptor of the neonatal antibody. It transfers antibodies from the placenta to the fetus and secures the newborns' immunity right after birth. ►antibody, ►Fc

FCS (fluorescence correlation spectroscopy): FCS facilitates measuring diffusion constants of various proteins, the ratios of free and bound proteins, and protein-protein connections within the cell by microscopic examinations. ►FRAP, ►FRET

F-Distribution: This process is used for testing the significance of the difference between variances. The *F-test* is based on $F = (s_1)^2/(s_2)^2$ [s = standard deviation] that are computed from two different populations or samples. In this procedure, the null hypothesis is that the two samples are identical. However, if the variance ratio exceeds the values at the appropriate degrees of freedom, in the body of the table the differences are significant. (The name *F* is in honor of R.A. Fisher). (See Table F4).

fdNA (fossil DNA): DNA extracted from ancient bones or other relics. ►ancient DNA

F-Duction: Transfer of genes from donor to the recipient bacteria with the aid of an *F'* plasmid. (See Hanson RL, Rose C 1979 J Bacteriol 138:783).

Fear (Cdc fourteen, early anaphase release): FEAR regulates the mitotic exit network (MEN) with the joint action of the polo kinase Cdc5, the separase Esp1, kinetochore-associated protein Slk19, and Spo. ►Cdc14, ►MEN, ►polo, ►separins, ►kinetochore, ►SPO; Stegmeier F et al. 2002 Cell 108:207.

Feature: DNA chips.

Fechtner Syndrome: ►May-Hegglin anomaly, ►Alport disease

Fecundity: Reproductive ability determined by the quantity of gametes produced per time units. ►fertility, ►parity

Feedback Control: A late metabolite of a synthetic pathway regulates synthesis at earlier step(s). It can be negative or positive. Two specific sites on an early enzyme in the biosynthetic pathway mediate the

feedback control. One site serves for recognition of the substrate, the other site recognizes a later product in the biosynthetic path. When this late product (end product) accumulates because it is not utilized in proportion to its synthesis, it may combine with the early enzyme's feedback recognition site, resulting in a reversible conformational change and cessation or lowering the activity of this enzyme.

The feedback is an economy device of the cell; the production of a metabolite is slowed down in the absence of a need. Feedback systems may operate in a number of self-explanatory ways (see Fig. F7); for the compensating feedback a note is needed. E inhibits the path between C and D, but product F may alleviate the inhibition by reducing the activity of enzyme A. Thus, E never accumulates excessively.

If feedback-sensitivity is eliminated through mutation, the system may be overproducing the end product and this, in industrial or agronomic organisms, may be beneficial from the economic point of view.

These are the most common regulatory mechanisms in eukaryotes. In living cells, feedback systems of metabolic processes are interlinked (Brandsman O et al 2005 Science 310:496). ►regulation of enzyme activity, ►inhibition, ►repression, ►attenuation negative control, ►positive control, ►genetic networks; Savageau MA 1972 Curr Top Cell Reg 6:6.

Feeder Cell Layer: The feeder cell layer provides soluble nutrients to the cells layered above in animal and plant cell cultures.

Feed-Forward: A mechanism of interacting networks. Such a system operates in the brain where the effect of individual inputs is much increased by activation of additional neurons (see Fig. F8). From very simple processing units, extremely complex tasks can be performed. The essential requirement is that the first signal received must exceed a certain threshold level. Similar networking occurs in other biological systems too. ►genetic networks, ►feedback control, ►cascade; Penn BH et al 2004 Genes and Development 18:2348.

Feingold Syndrome (OED, MOED, MMT, 2p23-p24): A complex dominant anomaly including defects of the esophagus (food tube leading from the throat to stomach), eyes, digits, duodenum (small intestine), microcephaly, mental retardation, etc.). The basic defect is in the MYCN protooncogene, and most commonly is the truncation of the 3rd exon. ►MYC; van Bokhoven H et al 2005 Nature Genet 37:465.

Feline: Pertaining to cat or cats.

Table F4. F-Distribution at 5% and 1% probability levels. At significance the F value computed must exceed the numbers in the table at the intersection of the degrees of freedom (df_1 and df_2). (Condensed by permission from S. Koller, *Biochemisches Taschenbuck*, H. M. Rauen, ed. Springer-Verlag, Berlin.)

| Df ₂ for Denominator | Degrees of Freedom for Numerator Df ₁ | | | | | | | | | | | | |
|---------------------------------|--|------|------|------|------|------|------|------|------|------|------|------|------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 15 | 20 | 30 | 50 | ∞ |
| 5% | | | | | | | | | | | | | |
| 1 | 161 | 200 | 218 | 225 | 230 | 234 | 239 | 242 | 246 | 248 | 250 | 252 | 254 |
| 2 | 19 | 18 | 19 | 19 | 19 | 18 | 19 | 19 | 9 | 9 | 20 | 20 | 20 |
| 3 | 10.1 | 9.6 | 9.3 | 9.1 | 9.0 | 8.9 | 8.8 | 8.6 | 8.7 | 8.7 | 8.5 | 8.6 | 8.5 |
| 4 | 7.7 | 6.9 | 6.6 | 6.4 | 6.8 | 8.2 | 6.0 | 6.0 | 5.9 | 5.8 | 5.8 | 5.7 | 5.6 |
| 5 | 6.6 | 5.8 | 5.4 | 5.2 | 5.1 | 5.0 | 4.8 | 4.7 | 4.6 | 4.6 | 4.5 | 4.4 | 4.4 |
| 6 | 6.0 | 5.1 | 4.8 | 4.5 | 4.4 | 4.3 | 4.2 | 4.1 | 3.9 | 3.9 | 3.8 | 3.8 | 3.7 |
| 7 | 5.6 | 4.7 | 4.4 | 4.1 | 4.0 | 3.9 | 3.7 | 3.6 | 3.5 | 3.4 | 3.4 | 3.3 | 3.2 |
| 8 | 5.3 | 4.5 | 4.1 | 3.8 | 3.7 | 3.6 | 3.4 | 3.4 | 3.2 | 3.2 | 3.1 | 3.0 | 2.9 |
| 9 | 5.1 | 4.3 | 3.9 | 3.8 | 3.5 | 3.4 | 3.2 | 3.1 | 3.0 | 2.9 | 2.9 | 2.8 | 2.7 |
| 10 | 5.0 | 4.1 | 3.7 | 3.5 | 3.3 | 3.2 | 3.1 | 3.0 | 2.9 | 2.8 | 2.7 | 2.6 | 2.5 |
| 12 | 4.3 | 3.9 | 3.5 | 3.3 | 3.1 | 3.0 | 2.9 | 2.8 | 2.6 | 2.5 | 2.5 | 2.4 | 2.3 |
| 14 | 4.6 | 3.7 | 3.3 | 3.1 | 3.0 | 2.9 | 2.7 | 2.6 | 2.5 | 2.4 | 2.3 | 2.2 | 2.1 |
| 16 | 4.5 | 3.6 | 3.2 | 3.0 | 2.9 | 2.7 | 2.6 | 2.5 | 2.4 | 2.3 | 2.2 | 2.1 | 2.0 |
| 18 | 4.4 | 3.6 | 3.2 | 2.9 | 2.8 | 2.7 | 2.5 | 2.4 | 2.3 | 2.2 | 2.1 | 2.0 | 1.9 |
| 20 | 4.4 | 3.5 | 3.1 | 2.9 | 2.7 | 2.6 | 2.5 | 2.4 | 2.2 | 2.1 | 2.0 | 2.0 | 1.8 |
| 25 | 4.2 | 3.4 | 3.0 | 2.8 | 2.6 | 2.5 | 2.3 | 2.2 | 2.1 | 2.0 | 1.9 | 1.8 | 1.7 |
| 30 | 4.2 | 3.3 | 2.9 | 2.7 | 2.5 | 2.4 | 2.3 | 2.2 | 2.0 | 1.9 | 1.8 | 1.8 | 1.6 |
| 40 | 4.1 | 3.2 | 2.8 | 2.6 | 2.5 | 2.3 | 2.2 | 2.1 | 1.9 | 1.8 | 1.7 | 1.7 | 1.5 |
| 50 | 4.0 | 3.2 | 2.8 | 2.6 | 2.4 | 2.3 | 2.1 | 2.0 | 1.9 | 1.8 | 1.7 | 1.6 | 1.4 |
| 60 | 4.0 | 3.2 | 2.8 | 2.5 | 2.4 | 2.3 | 2.1 | 2.0 | 1.8 | 1.8 | 1.7 | 1.6 | 1.4 |
| 80 | 4.0 | 3.1 | 2.7 | 2.5 | 2.3 | 2.2 | 2.1 | 2.0 | 1.8 | 1.7 | 1.6 | 1.5 | 1.3 |
| 100 | 3.9 | 3.1 | 2.7 | 2.5 | 2.3 | 2.2 | 2.0 | 1.9 | 1.8 | 1.7 | 1.6 | 1.5 | 1.3 |
| ∞ | 3.84 | 3.00 | 2.60 | 2.37 | 2.21 | 2.10 | 1.94 | 1.83 | 1.57 | 1.57 | 1.46 | 1.35 | 1.00 |
| 1% | | | | | | | | | | | | | |
| 1 | 4100 | 5000 | 5400 | 5600 | 5800 | 5900 | 6000 | 6000 | 6200 | 6200 | 6200 | 6300 | 6400 |
| 2 | 98 | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 99 | 100 | 100 |
| 3 | 34 | 31 | 29 | 28 | 28 | 28 | 27 | 27 | 27 | 27 | 27 | 26 | 26 |
| 4 | 21 | 18 | 16 | 16 | 16 | 15 | 15 | 15 | 14 | 14 | 14 | 14 | 13 |
| 5 | 16 | 13 | 11 | 11 | 11 | 11 | 10 | 10 | 9.7 | 9.6 | 9.4 | 9.2 | 9.0 |
| 6 | 14 | 11 | 8.8 | 9.2 | 8.8 | 8.5 | 8.1 | 7.8 | 7.6 | 7.4 | 7.2 | 7.1 | 6.9 |
| 7 | 12 | 9.6 | 8.5 | 7.8 | 7.5 | 7.2 | 8.8 | 6.6 | 6.3 | 6.2 | 6.0 | 5.9 | 5.7 |
| 8 | 11 | 8.7 | 7.6 | 7.0 | 6.6 | 6.4 | 6.0 | 5.8 | 5.5 | 5.4 | 5.2 | 5.1 | 4.9 |
| 9 | 11 | 8.0 | 7.0 | 6.4 | 6.1 | 5.8 | 5.5 | 5.3 | 5.0 | 4.8 | 4.7 | 4.5 | 4.3 |

Table F4. Continued

| Df ₂ for Denominator | Degrees of Freedom for Numerator Df ₁ | | | | | | | | | | | | |
|---------------------------------|--|------|------|------|------|------|------|------|------|------|------|------|------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 15 | 20 | 30 | 50 | ∞ |
| 10 | 10 | 7.6 | 6.6 | 6.0 | 5.6 | 5.4 | 5.1 | 4.9 | 4.7 | 4.4 | 4.3 | 4.1 | 3.9 |
| 12 | 8.3 | 6.9 | 6.0 | 5.4 | 5.1 | 4.8 | 4.5 | 4.3 | 4.0 | 3.9 | 3.7 | 3.6 | 3.4 |
| 14 | 8.9 | 6.5 | 5.6 | 5.0 | 4.7 | 4.5 | 4.1 | 3.9 | 3.7 | 3.5 | 3.4 | 3.2 | 3.0 |
| 16 | 8.5 | 6.2 | 5.3 | 4.8 | 4.4 | 4.2 | 3.9 | 3.7 | 3.4 | 3.3 | 3.1 | 3.0 | 2.8 |
| 18 | 8.3 | 6.0 | 5.1 | 4.6 | 4.3 | 4.0 | 3.7 | 3.5 | 3.2 | 3.1 | 2.9 | 2.8 | 2.6 |
| 20 | 8.1 | 5.9 | 4.9 | 4.4 | 4.1 | 3.9 | 3.6 | 3.4 | 3.1 | 2.9 | 2.8 | 2.6 | 2.4 |
| 25 | 7.8 | 5.6 | 4.7 | 4.2 | 3.9 | 3.6 | 3.3 | 3.1 | 2.9 | 2.7 | 2.5 | 2.4 | 2.2 |
| 30 | 7.8 | 5.4 | 4.8 | 4.0 | 3.7 | 3.5 | 3.2 | 3.0 | 2.7 | 2.6 | 2.4 | 2.3 | 2.0 |
| 40 | 7.3 | 5.2 | 4.3 | 3.8 | 3.5 | 3.3 | 3.0 | 2.8 | 2.5 | 2.4 | 2.2 | 2.1 | 1.8 |
| 50 | 7.2 | 5.1 | 4.2 | 3.7 | 3.4 | 3.2 | 2.9 | 2.7 | 2.4 | 2.3 | 2.1 | 2.0 | 1.7 |
| 60 | 7.1 | 5.0 | 4.1 | 3.7 | 3.3 | 3.1 | 2.8 | 2.6 | 2.4 | 2.2 | 2.0 | 1.9 | 1.6 |
| 80 | 7.0 | 4.9 | 4.0 | 3.6 | 3.3 | 3.0 | 2.7 | 2.6 | 2.3 | 2.1 | 1.9 | 1.8 | 1.5 |
| 100 | 6.9 | 4.8 | 4.0 | 3.5 | 3.2 | 3.0 | 2.7 | 2.5 | 2.2 | 2.1 | 1.9 | 1.7 | 1.4 |
| ∞ | 6.64 | 4.60 | 3.78 | 3.32 | 3.02 | 2.80 | 2.51 | 2.32 | 2.04 | 1.88 | 1.70 | 1.52 | 1.00 |

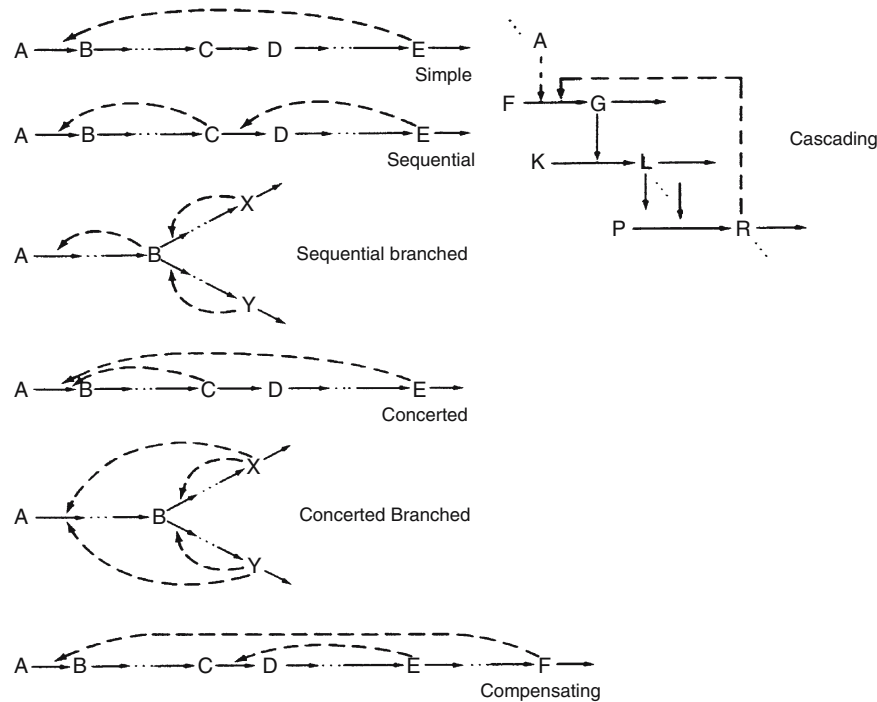


Figure F7. Feedback Control. The dashed lines indicate feedback loops. The solid lines stand for biosynthetic pathways. Redrawn after Savageau MA 1972 Curr. Top. Cell. Reg. 6:63

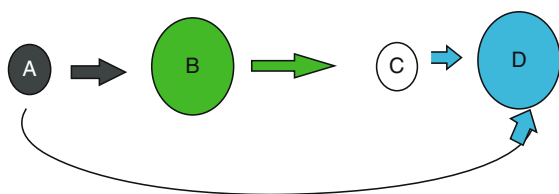


Figure F8. Feed forward

Female: The individual producing the larger usually non-motile gamete (egg). Its symbol is the “Venus mirror” or in pedigree charts, a circle (see Fig. F9). This is the most ancient symbol of genetics, used as far back as three thousand years ago on stone tablets in Asia Minor. ▶pedigree analysis, ▶Mars shield

Female Gametophyte: ▶gametophyte; <http://biocomp.cnb.uam.es/FEMME/>: database storing topological and geometrical features of medium resolution data solved by three-dimensional electronmicroscopy or high-resolution data simulated from atomic coordinates regardless of the resolution.

Femto-: 10^{-15} , e.g., femtomole.

FEN: ▶Rad27

Fenton Reaction: The Fenton reaction in the presence of (Fe^{2+}) iron and copper (Cu^{2+}) catalyzes the formation of $\text{OH}^\bullet + \text{H}_2\text{O}$ from H_2O_2 . ▶OH $^\bullet$, ▶ROS; Dikalova AE et al 2001 Proc Natl Acad Sci USA 98:13549.

FEO (familial expansile osteolysis): ▶Paget disease

Feral Population: Feral animals inhabit natural surroundings rather than living under laboratory or domesticated conditions (e.g., feral mice, feral *Drosophila*, feral pigs, etc.).

Fermentation: The energy-producing anaerobic degradation of carbohydrates to lactate or ethanol. Engineered mutations in the transcription factor TFIID, affecting TATA-binding protein of yeast (SPT15), and the TATA-binding protein associated factor (TAF25) substantially increase the fermentation capability and improve the efficiency of ethanol production (Alper H et al 2006 Science 314:1565).
▶transcription factors, ▶TAF

Fermentors: Precisely controlled mass culture vessels that may be used for industrial manufacturing of biological products (such as alcohol, antibiotics, proteins, etc.) by bacterial, fungal, animal or plant cells.

Ferns: Lower plants of the *Pterophyta* taxonomic group. They exist in two generations: sporophyte and gametophyte. The sporophytes develop roots, rhizomes, and leaves (see Fig. F10). These diploid plants form generally one type of sporangium on the lower surface of the leaves in aggregates called sori. Meiosis takes place within the sporangia and the released haploid products develop into generally heart-shaped gametophytes that (unlike in higher plants) form an independent organism on soil (thallus). When mature, on the lower surface of the gametophyte, eggs develop within the female archegonia and sperms in the male antheridia (6–10 cells). After a swimming spore fertilizes an egg, the diploid zygote grows on the gametophyte until the young sporophyte becomes ready (rooted) for independent existence. The gametophytes then die and the life cycles are repeated through the sporophytes. Ferns have a wide range of chromosome numbers of relatively large sizes, and many species are well suited for cytological analyses also because of the long haploid phase.

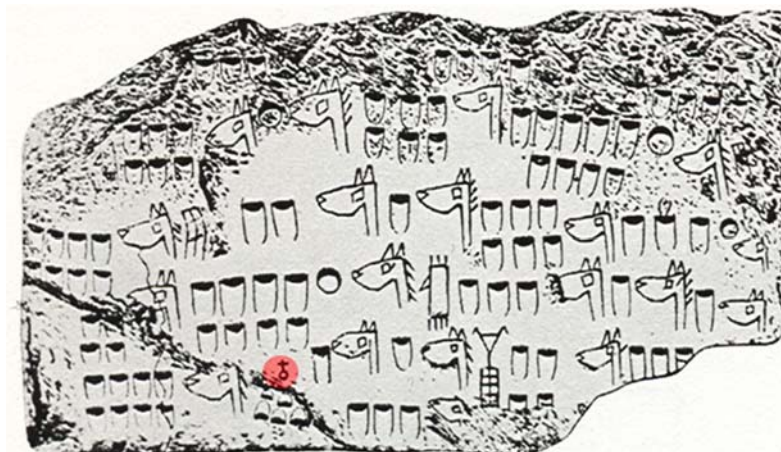


Figure F9. Female. Probably the earliest (~5000 years old) pedigree chart excavated in East Ur of Mesopotamia (From Amschler W 1935 J Hered 26:223)

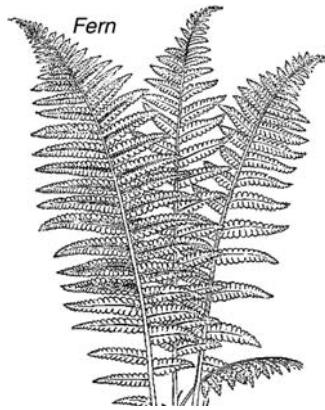


Figure F10. Fern

F

Ferredoxin: An iron-containing protein involved in electron transport.

Ferritin: An ubiquitous, iron-storing cellular protein, and thus protects the cells from the toxic effects of this heavy metal. Also, it transports iron to the sites of need. Ferritin consists of 24 subunits around an iron core that are encoded in human chromosomes at 11q13 and 19q13.1. An intronless 242 precursor of a ferritin-like protein, encoded at 5q23.1, is targeted to the mitochondria. An iron-regulatory protein (IRP) and an iron-responsive element (IRE) CAGUGU determine the synthesis. Small molecules such as yohimbine, which blocks oxidation in the three-dimensional loop of guanines in the IRE in the mRNA, selectively inhibit the binding of the iron-regulatory protein (IRP) and increase ferritin synthesis in a cell-free system by ~40% (Tibodeau JD et al 2006 Proc Natl Acad Sci USA 103:253). Mutation in IRE results in dominant hyperferritinemia that may cause cataracts. Neuroferritinopathy (19q13.3) is a dominant disease of the basal ganglia caused by mutation in the gene encoding the light polypeptide of ferritin. In Alzheimer disease and Parkinson disease, ferritin increases as iron accumulates in the brain. ▶aconitase, ▶apoferritin, ▶eye diseases, ▶hyperferritinemia, ▶MYC, ▶ganglion, ▶Alzheimer disease, ▶Parkinson disease, ▶Hallervorden-Spatz syndrome, ▶yohimbine; Levi S et al 2001 J Biol Chem 276:24437; Curtis ARJ et al 2001 Nature Genet 28:350.

Ferroportin: An iron exporting protein regulated by hepcidin, a liver-secreted hormone (see Fig. F11). Decreased hepcidin causes iron overload in the tissues. Hepcidin overproduction causes hypoferrremia and anemia. Ferroportin-deficient mouse accumulates iron in macrophages, enterocytes, and hepatocytes. Human hemochromatosis may be

related to ferroportin malfunction (Donovan A et al 2005 Cell Metabolism 1:191). ▶ferritin, ▶ferroportin, ▶hemochromatosis, ▶IRE, ▶transferrin; Nemeth E et al 2004 Science 306:2090.



Figure F11. Mouse intestinal cells. Left: normal, Right: accumulated iron at periphery. (Redrawn after Donovan, A. et al.)

Fertilin: A sperm cell surface protein mediating membrane adhesion and sperm-egg fusion, migration from the uterus to the oviduct and binding to the zona pellucida. Fertilins belong to the ADAM family of proteins. The disintegrin domain binds to an integrin receptor of the egg plasma membrane during fertilization. ▶fertilization, ▶acrosomal process, ▶ADAM, ▶integrin, ▶CD9; Evans JP 2001 Bioessays 23:628.

Fertility: The production of viable offspring (gamete) per individual during the reproductive period. *Effective fertility* denotes the reproductive rate of individuals afflicted by a disease compared to that of normal, healthy individuals. The ability to form fertile hybrids has been generally used to define species. Different species are not expected to produce fertile hybrid progeny. This distinction has some problems because, e.g., the female hybrids of *Drosophila melanogaster* female and *D. simulans* male are viable and fertile, whereas the males of the same cross die at the larval/pupal stage of development. In the reciprocal crosses, *D. simulans* female x *D. melanogaster* male, most of the females also die as embryos, and only a few escape death. Human susceptibility to conception is about six days prior and including the day of ovulation. The raise in hormone level, particularly by the raised level of luteinizing hormone (LH), can clinically monitor ovulation. ▶fecundity, ▶fitness, ▶ovulation, ▶reproductive isolation, ▶species, ▶speciation, ▶infertility, ▶spermiogenesis, ▶transmission, ▶animal hormones, ▶parity

Fertility Factor: ▶F factor, ▶F plasmid

Fertility Inhibition: In fertility inhibition, the conjugal function of the bacterial cell is prevented by an inhibitory plasmid. ▶bacterial conjugation

Fertility Restorer Genes: Fertility restorer genes may assist to overcome cytoplasmically determined male sterility. Their ability to function also depends on the nature of the cytoplasm. In the S cytoplasm of maize, the restoration of fertility by *Rf3* is gametophytic, i.e., only 50% of the pollen is fertile in the heterozygous plants. In the T cytoplasm, the restoration of fertility is under sporophytic control and the heterozygotes for the two complementary fertility genes *Rf1* and *Rf2* produce nearly 100% viable pollen. The *Rf4* gene is a sporophytically expressed restorer in the C cytoplasm. Fertility restoration may also involve some additional minor factors. The cytoplasmic male sterility in these cytoplasms is controlled by mitochondrial plasmid genes. The fertility restorer genes have applied significance in the commercial production of hybrids. T (Texas) cytoplasmic male sterility is associated with susceptibility to *Helminthosporium* blight. However, the fertility restorer genes do not alleviate the symptoms of the disease, indicating that the latter is controlled by other means than the fertility. Cytoplasmic male sterility occurs in several plant species. ▶cytoplasmic male sterility, ▶pollen sterility, ▶mtDNA; Duvick DN 1965 *Advances Genet* 13:1; Liu F et al 2001 *Plant Cell* 13:1063; When L, Chase CD 1999 *Curr Genet* 35:521.

Fertilization: Fertilization involves the fusion of gametes of opposite sexuality (see Fig. F12). It may take place in different forms in hermaphroditic organisms such as the majority of plants and some of the animals: self-fertilization (autogamy), cross-fertilization (allogamy) or a mixture of the two. Only cross-fertilization can take place in the dioecious species of the majority of animals and a few plants. Fertilization results in the formation of zygotes and the restoration of the chromosome number to the 2n level. In many plant species, double fertilization takes place: the generative sperm fertilizes the egg and the vegetative sperm unites with the fused polar nuclei and as a result the triploid endosperm mother cell is generated. In some plant species, the sperm egg

nuclei fail to fuse and each contributes independently to the development of the embryo: *semigamy*. In some plants, the generative sperm and the vegetative sperm may come from a different pollen grain and thus *heterofertilization* results. If the genetic constitution of these two sperms is not identical, there is discordance (non-correspondence) between the genetic constitution of the embryo and the endosperm. Embryo development without fertilization is called *apomixis* in plants, and *parthenogenesis* in animals. In the majority of plants and animals, only the nucleus of the sperm enters the embryosac and egg, respectively, and the cytoplasmic genes are transmitted only through the female in these cases. Some plants also transmit cytoplasmic elements via the sperm during fertilization, resulting in complete biparental inheritance. In plants, only a limited number of pollen tubes grow down the pistil. In animals, more than a thousand sperms may attach to the surface of the egg but only one succeeds in fertilization, although normal ejaculates may contain 20 million sperms. In autogamous plants, the pollen count is much more limited than in the allogamous species. A large quantity of sperm is essential for normal fertilization of plants and animals. Human males with spermatozoa counts per ejaculate below 20,000 are generally sterile. The number of eggs per ovule in plants or number of ova released during ovulation in animals may also be only one or a few. *Drosophila* females can, for a prolonged period, store about 700 sperms (spermatozoa) from a single injection by the males and fertilization may take place gradually. After a second mating within a period of two weeks, the leftover sperms may be destroyed. Usually, fertilization takes place within the female body, in other cases fertilization is an external process or the eggs may be deposited in a pouch of the female where fertilization and further development follow. Even in cases of internal fertilization, a variable amount of time may elapse between pollination or copulation and the actual penetration and fusion of the sperm and egg nuclei.

During spermatogenesis the paternal genome is condensed about 6-fold and (98% in the mouse and ~85% in humans) histones are replaced by protamines. After penetration in the male pronucleus, the protamines are replaced by histones. In humans, it takes about an hour for the spermatozoa (~250/24 million) to travel the 6–7 inch route to the ovum. Within 24–48 hours after copulation, generally a single spermatozoon fertilizes the human ovum. In mammalian fertilization, the first step after the sperm reaches the follicular cells is the binding to the egg membrane. The sperm is “capacitated” to this task by changes in the sperm plasma membrane through the secreted products of the female (Wu C et al 2001 *J Biol Chem* 276:26962). The sperm then

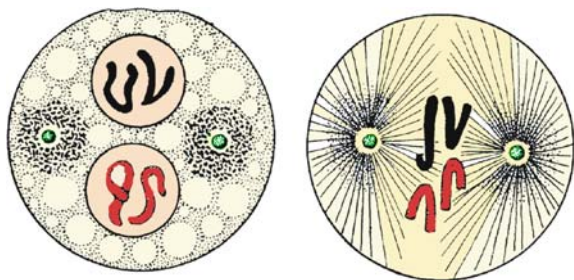


Figure F12. Fertilization. The paternal and maternal pronuclei within an ascaris egg (left), The pronuclei have fused into a zygote nucleus, Ready for mitosis (right)

binds to the zona pellucida membrane. This membrane is made up of cross-linked network of glycoproteins ZP1, ZP2, ZP3. The latter are *sperm-receptors*. In mouse, the sp56 spermatid-specific protein recognizes ZP3. After this step, the protease and hyaluronidase content of the acrosome is released (*acrosomal reaction*), facilitating the penetration and passing through the zona pellucida. On the egg membrane, CD9 was essential and on the sperm Izumo globulin was required even after the penetration of the zona pellucida for fusion with the egg (Inoue N et al 2005 Nature [Lond] 434:235). After one sperm has fused with the egg plasma membrane, the so-called cortical reaction blocks the entry of other sperms as the zona hardens. For the prevention of polyspermy, the fertilized sea urchin egg releases hydrogen peroxide through the action of a protein encoded by gene *Udx1*. This peroxidase has a dual function, it converts oxygen into peroxide and later it breaks down the peroxide so the toxic substance would not hurt the zygote (Wong JL et al 2004 Dev Cell 7:801). The mitochondria of the fertilizing sperm are generally destroyed by ubiquitination and other components, not required for the following events, are also degraded.

The *cortical reaction* is mediated by an increase in cytosolic calcium through an inositol-phospholipid signaling pathway. On the surface of the egg coat, microvilli develop in such a manner that they firmly hold the sperm. After fertilization, the egg becomes a zygote and the process is completed when the male and female pronuclei fuse into a *zygote nucleus*. The sperm donates to the egg not just the male pronucleus, containing a complete haploid set of chromosomes, but also the *centriole* that is not available in the egg. The centrioles are then associated with the female *centrosome* and a *mitotic organizing center* is initiated. Transcription factors such as STAT4, perinuclear theca protein (PT32), and phospholipase C ζ are released. Paternally derived proteins, mRNAs, and microRNAs also seem to be transferred to the ovum. Mitotic divisions and embryogenesis follow these events. The mammalian zygote is formed through the fusion of the highly compacted nucleoprotamine-containing sperm chromatin, and the metaphase II-arrested chromosomes of the oocyte. Remodeling of the chromatin of the two gametic chromosome sets into a diploid genome takes place following fertilization. The sperm genome is much more highly methylated than that of the egg. Within 7–8 hours after fertilization, the paternal genome is significantly de-methylated. Demethylation of the maternal genome follows after the second division of the zygote. The global demethylation however, exempts the imprinted genes. ▶*apomixis*, ▶*androgenesis*, ▶*gametogenesis*, ▶*embryogenesis*, ▶*selective*

fertilization, ▶*polyspermic fertilization*, ▶*pollen tubes*, ▶*synergids*, ▶*certation*, ▶*megaspore competition*, ▶*sperm*, ▶*IVF*, ▶*artificial insemination*, ▶*RPTK*, ▶*centrosome*, ▶*acrosomal process*, ▶*bindin*, ▶*fertilin*, ▶*cyritestin Cd9*, ▶*sex hormones*, ▶*hormone receptors*, ▶*fertility*, ▶*imprinting*, ▶*methylation of DNA*; Primakoff P, Myles DG 2002 Science 296:2183; plants: Lord EM, Russell SD 2002 Annu Rev Cell Dev Biol 18:81; Krawetz SA 2005 Nature Rev Genet 6:633; <http://www.nature.com/fertility>.

FES: Feline fibrosarcoma viral oncogene (*fes*). It is in the long arm of human chromosome 15, and in most cancer cells it is translocated to chromosome 17, causing leukemia. Its protein product is a protein tyrosine kinase. ▶*ABL*, ▶*ERBA*, ▶*PTK*

FET: Genes involved in iron uptake and metabolism

Fetal Alcohol Syndrome: ▶*alcoholism*

Fetal Hydantoin Syndrome: ▶*epoxide hydrolase 1*

Fetal Tissue Research: ▶*embryo research*, ▶*stem cells*

Fetoprotein- α (AFP): AFP is expressed in the embryonic yolk and liver of mammals. Serum albumin and α -fetoprotein genes are linked at about 15 kb apart, and each encodes approximately 580 amino acids. The two proteins are immunologically cross-reactive and display about 35% homology. The rate of transcription of AFP drops four orders of magnitude after birth in the majority of mouse strains. BALB/cJ is an exception because in these animals the adult serum contains 5–20-fold higher levels of AFP. This anomaly was caused by a recessive transcription factor mutation, *Afr1^b*, unlinked to the AFP coding gene. *Afr1^a*, the wild type allele, is a suppressor of *Afp* and its 1st intron encodes—in chromosome 15—a putative zinc finger homeobox protein (ZHX), derived from a murine endogenous retrovirus. This repressor affects also gene *H19* involved in imprinting (Perincheri S et al 2005 Proc Natl Acad Sci USA 102:396).

Regulatory sequences are positioned within 150 bp 5' and there are also enhancers 6.5, 5, and 2.5 kbp upstream from the transcription initiation site. The gene (human chromosome 4q11-q22) is a classical example for tissue-specific and developmental regulation. ▶*MSAFP*, ▶*imprinting*; Mizejewski GJ 2001 Exp Biol Med 226:377.

Fetoscopy: The viewing (or possibly sampling of tissues) of the fetus within the womb to detect probable developmental or biochemical anomalies in case there is a good indication for them. Fetoscopy may involve up to 10% risk to the fetus, and if other less invasive (e.g., sonography) methods are available, it should be avoided. It is also used for the

detection of fetal heartbeat. ►[prenatal diagnosis](#), ►[amniocentesis](#), ►[sonography](#), ►[echocardiography](#)

Fetus (foetus): The unborn child of viviparous animals at the stages following the embryonal state after substantial differentiation has been completed. In humans, the fetal period is from nine weeks after conception to birth. ►[vivipary](#), ►[embryo](#), ►[embryo research](#)

Feulgen: A microtechnical staining method detecting deoxyribose and thus, DNA, in warm acid-hydrolyzed tissue followed by staining with leucobasic fuchsin. ►[stains](#)

FeV (feline leukemia virus): A retrovirus causing immunodeficiency in cats. Its receptor is CD134 (in contrast to HIV, which requires CD4). Productive infection also requires CXCR4. ►[acquired immunodeficiency syndrome](#), ►[CD4](#), ►[CD134](#), ►[CXCR](#); Shimojima M et al 2004 Science 303:1192.

Fever, Periodic: A periodic fever is observed in different diseases. The familial Mediterranean fever appears recessive (16p13) and may be associated with amyloidosis. The dominant form (12p13.2) is based on a defect in the tumor necrosis factor receptor. The recessive Dutch type (12q24) is a mevalonate kinase deficiency. ►[Fabry disease](#), ►[hyperimmunoglobulinemia D](#), ►[amyloidosis](#), ►[fibroblast growth factor](#); Aksentijevich I et al 2001 Am J Hum Genet 69:301.

Feverfew (*Chrysanthemum parthenium*/*Tenacetum parthenium*): An old herbal medicinal plant used against headache (see Fig. [F13](#)). It contains a sesquiterpene lactone parthenolide (C₁₅H₂₀O₃),



Figure F13. Feverfew

which effectively and selectively induces apoptosis in myelogenous and chronic leukemia stem cells. The molecular basis of action is the inhibition of NF-κB, the pro-apoptotic activation of p53 tumor suppressor, and the increase in reactive oxygen species (ROS). It inhibits thromboxanes and leukotrienes. ►[leukemia](#), ►[NF-κB](#), ►[p53](#), ►[ROS](#), ►[leukotrienes](#), ►[thromboxanes](#); Guzman ML, Jordan CT 2005 Expert Opin Biol Ther 5:1147.

FFA (focus forming activity): A 170-kDa protein (a RecQ helicase) is required for the association of replication protein A (RPA) with the focus forming units of replication (the 100 to 1000 DNA loops [replication bubbles], centers of replication along the euchromatic chromosome). (See Chen C-Y et al 2001 J Cell Biol 152:985; ►[replication bubble](#), ►[replication protein A](#), ►[Werner syndrome](#))

Ffh: A GTPase of the signal recognition particle of bacteria. ►[FtsY](#), ►[SRP](#)

FGENE: A program based on linear discriminant function for the identification of splice sites, 5'[-coding, internal exons, and 3'-coding sequences with high accuracy. ►[GENESCAN](#), ►[Genie](#), ►[MZEF](#); Solovyev VV et al 1995 Proc Int Conf Intell Syst Mol Biol 3:367.

FGF (fibroblast growth factor, 22 human genes): FGF is also an FGF-related oncogene (see Fig. [F14](#)). FGF-B (the bovine form, FGF2) was assigned to human chromosome 4q25. FGF-6 and FGF-4 (human chromosome 2q13) bear similarity to the NT2 oncogene. FGF may also have a critical role in organ differentiation. The fibroblast growth factor receptor (FGFR) has a cytoplasmic tyrosine kinase domain. Mutations in FGFR1 and FGFR2 have been associated with the Crouzon, Jackson-Weiss, Pfeiffer, and Beare-Stevenson syndromes. FGFR3 is involved in hypochondroplasia. Defects in FGFR1c may lead to diabetes type II. FGF1 (in human chromosome 5q31) is implicated in angiogenesis. FGF3 (11q13) is homologous to a mouse mammary carcinoma gene, FGF5 (4q21). FGF7 is a keratocyte growth factor. FGF8 is an androgen-induced growth factor and it mediates heart development (Ilagan R et al 2006 Development 133:2435). FGF9 is the glia-activating factor. FGF10 is essential for limb and lung development in mice. The activation of FGF requires appropriate transmembrane receptors that are activated by oligomerization in the presence of heparin-like molecules. The human genome contains 30, and *Drosophila* and *Caenorhabditis*, each show two FGFs. ►[growth factors](#), ►[signal transduction](#), ►[HST oncogene](#), ►[INT oncogene](#), ►[organizer](#), ►[tyrosine kinase](#), ►[achondroplasia](#), ►[hypochondroplasia](#), ►[thanatophoric dysplasia](#), ►[Jackson-Weiss](#)

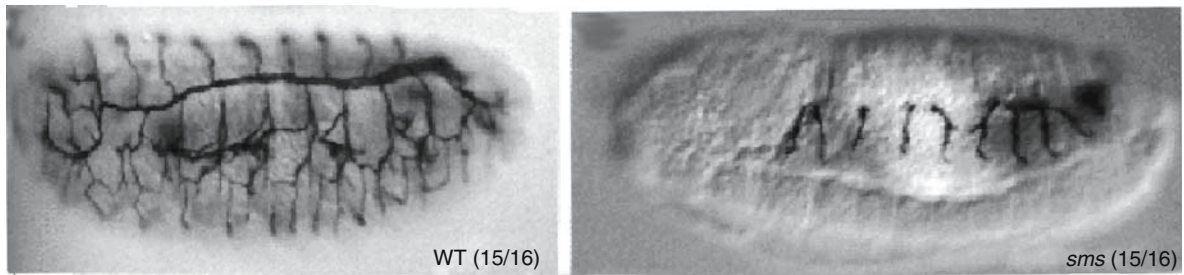


Figure F14. FGF. In *Drosophila*, the *stumps* gene is required for the FGF-dependent migration of the tracheal and mesodermal migration in the embryo. The tracheal phenotype of the wild type (Left) and the *sms* mutant (Right) is shown at stage 15/16. (Courtesy M. A. Krasnow, see Genetics 152:307)

F

syndrome, ▶Pfeiffer syndrome, ▶Apert syndrome, ▶Crouzon syndrome, ▶Beare-Stevenson syndrome, ▶hypochondroplasia, ▶craniosynostosis, ▶angiogenesis, ▶glial cell, ▶keratosis, ▶heparin, ▶embryogenesis, ▶diabetes, ▶sex reversal, ▶LADD syndrome; Dubrulle J et al 2001 Cell 106:219; Vasiliauskas D, Stern CD 2001 Cell 106:133; Ahmad SM, Baker BS 2002 Cell 109:651; Sun X et al 2002 Nature [Lond] 418:801.

FGFR (fibroblast growth factor receptor): ▶FGF

FGR Oncogene: The FGR oncogene located to human chromosome 1p36.2-p36.1 encodes an actin-like sequence and a tyrosine kinase sequence that is homologous to the viral gene *fgr*. Mouse involved with reduced FGR1c receptor is prone to inflammatory response upon aging (Aoshiba K, Nagai A 2007 FEBS Lett 581:3512).

FHA (forkhead-associated domain): FHA interacts with phosphorylated molecules. It has a role in DNA damage signaling and CHK2-dependent tumor suppression and various developmental processes. ▶CHK2; Durocher D et al 2000 Mol Cell 6:1169.

FHIT: ▶renal cell carcinoma

fi Plasmid: The fi plasmid inhibits the fertility factor of bacteria. ▶F element, ▶F plasmid

Fialouridine (FIAU, [1-(2-deoxy-2-fluoro-D-arabinofuranosyl)-5-iodouracil]): An inhibitor of DNA polymerase γ , responsible for the synthesis of mtDNA. ▶DNA polymerases, ▶mtDNA

Fibonacci Series: In the Fibonacci series, the denominator doubles in each subsequent term while the numerator becomes the sum of its two preceding numerators, e.g., 1, 1/2, 2/4, 3/8, 5/16, 8/32, 13/64, and so on. This has applications in predicting the proportion of heterozygotes in an interbreeding population at each loci that were heterozygous initially ($H = 0.5$). Thus six generations of sib mating leave 13/64, i.e., ~20.31% heterozygous for each

originally heterozygous loci, and its complement ($100 - 20.31$) 79.69% will be expected to become homozygous. The phyllotaxis of plant leaves may follow Fibonacci series. Various developmental patterns may represent Fibonacci patterns. ▶phyllotaxis; Li C et al 2005 Science 309:909.

Fibrillarin: A fibrillar protein present in many snRNPs within the nucleolus; it is also an autoantigen. ▶snRNP, ▶autoantigen, ▶snoRNA; Snaar S et al 2000 J Cell Biol 151:653.

Fibrillin: A large cystein-rich glycoprotein molecule involved in the formation of microfibrils along with elastin. The fibrillin microfibrils are encoded by two genes in human chromosomes 15q-21.1 (FBN1) and 5q23-q31 (FBN2), respectively. Mutation of *Fbn-2* in mouse may cause syndactyly. ▶Marfan syndrome, ▶Marfanoid syndrome, ▶aneurysm aortic, ▶arachnodactyly, ▶syndactyly; Chaudhry SS et al 2001 Hum Mol Genet 10:835.

Fibrin: An insoluble protein formed during blood clotting from fibrinogen (4q28) by the action of thrombin. ▶thrombin, ▶fibrinogen, ▶fibrin-stabilizing factor deficiency

Fibrin-Stabilizing Factor Deficiency: The fibrin-stabilizing factor deficiency is controlled by X-chromosomal recessive factors causing a deficiency of blood coagulation factor XIII that normally stabilizes clot formation by cross-linking fibrin. Wounds heal more slowly, the umbilicus bleeds days after birth, bleeding may occur inside the joints (hemarthrosis), in the genito-urinary tract (hematuria), abortion with bleeding, intracranial bleeding (generally lethal) may occur. Apparently, the condition is caused not by the lack of factor XIII, but rather by the formation of defective molecules. ▶afibrinogenemia, ▶defibrinogenemia, ▶antihemophilic factors, ▶hemophilia, ▶von Willebrand disease

Fibrinogen: ▶fibrin

Fibrinolysin: A serine endopeptidase. ▶plasmin

Fibroblast: The elongated connective tissue cells (give rise to tendons and other supportive structures), which may produce collagen; they are relatively easy to culture in vitro (see Fig. F15). ►collagen



Figure F15. A fibroblast cell. They may occur in many shapes

Fibroblast Growth Factors (FGF): Stimulates blood vessel growth. Genes were located in several human chromosomes: FGF1 at 5q31, FGF2, 4q25-q27, FGF3 at 11q13, FGF4 at 11q13, FGF6 at 12p13, FGF7 at 15q15-q21.1, FGF9 at 13q11-q12, FGF10 at 5p13-p12, FGF11 at 17q21, FGF12 at 3q28, FGF13 at Xq26.3, FGF14 at 13q34, and FGF23 at 12p13.3. The *FGF receptors* (FGFR) proteins have an extracellular immunoglobulin-like domain and the cytoplasmic domains are tyrosine kinases. FGFR1 in chromosome 8p112-p11.1 co-segregates with the Pfeiffer syndrome. FGFR2 in chromosome 10q26 seems to be associated with the Crouzon syndrome (identical with the Jackson-Weiss syndrome). FGFR3 (4p16.3) deficiency accounts for achondroplasia, hypochondroplasia, and thanatophoric dysplasia. ►signal transduction, ►angiogenesis, ►achondroplasia, ►Crouzon syndrome, ►Pfeiffer syndrome, ►achondroplasia, ►hypochondroplasia, ►thanatophoric dysplasia, ►RTK, ►craniosynostosis

Fibrochondrogenesis: A rare autosomal lethal recessive malformation of the hip cartilage (rhizomelic chondrodysplasia).

Fibrodysplasia Ossificans Progressiva (FOP): A rare autosomal (4q27-q31) dominant progressive ectopic (malplaced) bone formation. The basic defect appears to be the inappropriate production of bone morphogenetic protein (BMP-4) by the lymphocytes. Sometimes FOP is accompanied by short fingers, anomalous vertebrae, deafness, baldness, and mental retardation. The activin A type I receptor of the bone morphogenetic protein, which causes FOP, has been mapped to 2q23-q24 (Shore EM et al 2006 *Nature Genet* 38:525). ►exostosis, ►metachondromatosis, ►bone morphogenetic protein, ►activin

Fibromatosis, Juvenile Hyaline (JHF, 4q21): and infantile systemic hyalinosis (ISH) are apparently allelic recessive conditions caused mutations in the capillary morphogenesis protein 2. The basic defect appears in the assembly of the basement membrane. Subcutaneous skin nodules, gingival hypertrophy, joint contractures, and hyaline deposition appear during the first few years of life. The symptoms in ISH appear usually at birth and the condition may

improve later. ►hyaline, ►basement membrane; Hanks S et al 2003 *Am J Hum Genet* 73:791.

Fibromyalgia: An apparently non-hereditary, non-progressive, not life-threatening condition of general tiredness and pain in muscles, tendons, and ligaments. Its cause of it is not entirely clear and no sure medication is available. Improving sleeping habits and exercise may help.

Fibroin: Silk protein. ►silk fibroin, ►silk worm; Hayashi CY, Lewis RV 2001 *Bioessays* 23:750.

Fibronectin: Dimeric (~220-kDa monomers, 2q24) extracellular matrix glycoprotein involved in development, morphogenesis, wound healing, anti-tumorigenesis (anti-metastasis), and suppressing angiogenesis. Fibronectin is required, however, for the metastasis of melanoma. Fibronectin binds to the Fc fragment of immunoglobulins, particularly to IgG. It may play a role in autoimmune diseases, pulmonary fibrosis (formation of fibrous tissues), and glomerulonephritis. Fibronectin deficiency is characteristic for type X Ehlers-Danlos syndrome. ►integrin, ►L1, ►RGD, ►immunoglobulins, ►autoimmune disease, ►glomerulonephritis, ►CAM, ►metastasis, ►angiogenesis, ►melanoma, ►Ehlers-Danlos syndrome; Yi M, Ruoslahti E 2001 *Proc Natl Acad Sci USA* 98:620; Sakai T et al 2003 *Nature [Lond]* 423:866.

Fibulin-5 (DANCE): An integrin ligand required for tissue elasticity. Fibulin-1, component of the extracellular matrix, rescues gonad morphogenesis in *Caenorhabditis* in the absence of two secreted metalloproteases (Hesselson D et al 2004 *Current Biol* 14:2005). ►integrin; Nakamura T et al 2002 *Nature [Lond]* 415:171.

Ficoll: A synthetic polymer of sucrose. It is used in the Denhardt reagent and in gel-loading buffers to increase the density of the sample applied to the wells in the agarose gel. ►gel electrophoresis, ►Denhardt reagent

Fidelity in Gene Conversion: The converted allele is identical to the converter. ►gene conversion

Fidelity of Replication: ►error in replication

Fidelity of Transcription: The fidelity of transcription may be mediated by the very low level 3'→5' ribonuclease activity of eukaryotic RNA polymerase II. ►RNA polymerase, ►error in transcription

Fidelity of translation: In the fidelity of translation, errors occur approximately in the 10⁻⁴ range. ►ambiguity in translation

Fidelity Paradox: *E. coli* DNA polymerase II makes 3–5-fold more incorporation errors at the AT-rich sequences than at the GC-rich sequences. The

polymerization activity of the same enzyme is 2–6-fold higher at the AT sequences. Normally, one would expect higher proof-reading by the 3'-exonuclease function in the less stable AT-rich tracts. It seems that the increased polymerization activity prevents proof-reading efficiency. ►[proofreading](#); Wang Z et al 2002 J Biol Chem 277:4446.

Fiducial Limits: Synonymous with confidence limits and confidence intervals. ►[confidence intervals](#)

F

Field-Flow Fractionation (FFF): A size-based fractionation of large molecules through thin channels. From its retention time hydrodynamic properties are estimated.

Field-Inversion Gel Electrophoresis: ►[FIGE](#)

FIG (*Ficus carica*): The genus includes about 2,000 species with $x = 13$, and the majority of them are diploid ($2n = 26$), although triploid and tetraploid forms are also known. It is a freeze-sensitive fruit tree with the amount of Ca^{2+} in the fruits about three times higher than those in fruits in other plant species.

FIGE: Field-inversion (10–0.02 Hertz) gel electrophoresis; it has been used to separate DNAs in the range of 15–700 kb, similar in size to the genetic material in the chromosomes of lower eukaryotes. Its advantage over pulsed-field gels is that the runs are straight. ►[pulsed field electrophoresis](#), ►[Hertz](#)

Figure 8: The configuration of cointegration of two ring DNAs before completion of the process (see Fig. F16). ►[cointegration](#)



Figure F16. Figure 8

Filaggrin: A protein controlling terminal differentiation of the epidermis. ►[eczema](#), ►[ichthyosis](#)

Filament: Myosin and actin fibers in animal tissue. The microfilaments (6 nanometers in diameter), the intermediate filaments (10 nm), and the microtubules (23 nm) form the structural mesh of the cytoplasm. The intermediate filaments (IF) carry out a variety of functions, depending on the ca. 50 genes that encode them in human cells. Defects or deficiency of the IF may lead to genetic lesions of the epidermal keratin and thus, blistering. Defects in the neurofilaments may account for some cases of amyotrophic lateral sclerosis, muscular atrophy, and sensory neuropathy. ►[intermediate filaments](#), ►[cytoskeleton](#), ►[keratosis](#), ►[epidermolysis](#), ►[amyotrophic lateral sclerosis](#), ►[neuropathy](#), ►[corneal dystrophy](#), ►[monilethrix](#), ►[desmosome](#), ►[plakin](#), ►[pachyonychia](#), ►[stamen](#)

Filamentation: Bacteria may grow as long filaments during SOS repair. ►[SOS repair](#)

Filamentous Growth: ►[pseudohypha](#)

Filamentous Phages: Filamentous phages frequently used as cloning vectors in genetic engineering are M13 (6408 b), f1 and fd (6408 b) single-stranded DNA phages. The f1 phage is $8,500 \text{ \AA} \times 60\text{--}70 \text{ \AA}$ in size. They have many advantages; among others they are easy to purify, have little constraint on packaging, and accept relatively large inserts (up 5 times their original DNA). M13 and its derivatives are generally used in DNA sequencing by the Sanger method. They contain multiple cloning sites within a truncated *E. coli lacZ gene*. The vectors containing a successful insertion produce white plaques, whereas the plaques of the phage without the insertion are blue on X-gal medium because *LacZ* is not interrupted and thus expressed. The f1 phage—unlike the lytic ones—does not destroy the host bacterium in order to exit. The phage encodes and excretes protein pIV that is used to create a tightly gated channel in the bacterial cell membrane. Through this gate, the single-stranded phage genome emerges dressed in the coat protein and fully formed without disruption of the bacterial host. ►[bacteriophages](#), ►[phagemids](#), ►[DNA sequencing Sanger](#), ►[cloning vector](#), ►[cloning site](#), ►[Xgal](#), ►[lysis](#), ►[pUC vectors](#), ►[phage display](#); Horiuchi K 1997 Genes Cells 2(7):425; Marvin DA 1998 Curr Opin Struct Biol 8(2):150; Cabilly S 1998 Methods Mol Biol 87:129; Larocca D et al 1999 FASEB J 13 [6]:727.

Filamins: Diverse extended dimeric proteins that cross-link actins involved in membrane receptors and signaling molecules. Filamin-A is a 280-kDa protein encoded at Xq28 and its defect is responsible for heterotopia. Filamin-B (encoded at 3p14.3) is similar in size to Filamin-A and it is bound to it. Filamin-C is encoded at 7q32-q35. The filamin defects may be the cause of several human maladies such as Alzheimer disease, Graves disease, platelet abnormalities, von Willebrand disease, epilepsy, malformations, etc. (See terms at separate entries; Stossel TP et al 2001 Nature Rev Mol Cell Biol 2:138; Robertson SP et al 2003 Nature Genet 33:487).

File: A unit of related records in the computer.

File Server: A file server permits additional users to share files and application programs on a computer.

Filial: Filial refers to offspring (generation). ►[F₁](#)

Filler DNA: Nucleotides inserted at the junctions and excision sites of transposable elements and genetic vector-carried sequences or at sites of non-homologous end-joining. ►[transposable elements](#), ►[insertion elements](#), ►[NHEJ](#)

Filopodium: A slender amoeba-like cell structure involved in movement and/or growth. Also, the spikes on the growth cones or on cell surface (see Figs. F17 and F18). Myo10 myosin motor protein, localized to the tip of cell-surface filopodia, appears to be responsible for their formation (Bohil AB et al 2006 Proc Natl Acad Sci USA 103:12411). ▶[growth cone](#), ▶[lamellipodium](#); Wood W, Martin P 2002 Int J Biochem & Cell Biol 34:726.



Figure F17. Filopodium

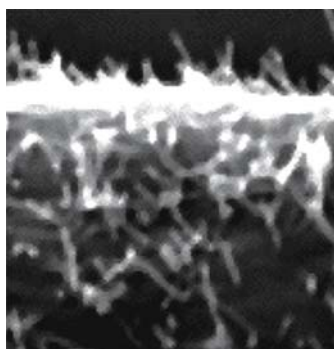


Figure F18. Cell surface filopodia

Filter Enrichment: ▶[filtration enrichment](#)

Filter Hybridization: In this process, one of the nucleic acid components is immobilized on a (nitrocellulose) filter and the other labeled, liquid component is allowed to anneal with it. ▶[DNA hybridization](#)

Filter Mating: In filter mating, the bacterial cells at high density conjugate on the surface of a filter.

Filter Sterilization: The removal of microbes from liquids without heating by the use of 0.45 or 0.2 μm pore size membranes. ▶[sterilization](#), ▶[autoclaving](#)

Filterable Agent: Filterable agent was the name of tobacco mosaic virus, and other viruses, before their nature was revealed. The name comes from the fact that they passed through bacterial filters and retained their biological activity. ▶[TMV](#)

Filtering Data: Filtering data extracts subgraphs of representative links in a complex dataset such as encountered in protein networks, metabolic correlations, etc.

Filtering Nucleotide and Protein Sequences: The removal of low-complexity (repetitive) sequences

that might inflate the homology between/among macromolecules and would introduce errors in conclusions concerning common ancestry. Some of the BLAST search programs automatically filter the data. ▶[BLAST](#)

Filtration Enrichment: A method of selective isolation of all types of nutritional mutants used primarily in fungi. The wild type mycelia grow on minimal media but cells that have any type of special nutritional requirement most likely will not. A filter will retain the wild type mycelia while the non-growing spores pass through and are thus separated from the bulk. This mutant-enriched filtrate can then be analyzed for the specific nutritional requirement. ▶[mutant isolation](#), ▶[mutation detection](#); Fries N 1947 Nature [Lond]:159:199; Woodward VW et al 1954 Proc Natl Acad Sci USA 55:872.

Fimbriae: Flagellum-like appendages in the surface of bacteria that help, e.g., *Salmonella* in adhering to and infecting intestinal epithelia. ▶[pilus](#), ▶[E. coli](#); Shembri MA, Klemm P 2001 EMBO J 20:3074; Vetsch M et al 2004 Nature [Lond] 431:329.

Fimbrin: An actin filament bundling protein, encoded by gene *SAC6* in yeast. Its overproduction may be lethal. ▶[actin](#), ▶[ankyrin](#), ▶[spectrin](#); Klein MG et al 2004 Structure 12:999.

Finches (Galapagos finches, Darwin's finches): 14 species of small birds of South America, showing substantial variations primarily in the shape and size of the beak depending on their terrestrial or tree habitat and life style, yet Darwin correctly recognized their common descent (see Fig. F19). A calmodulin-dependent pathway regulates the elongated beak morphology (Abzhanov A et al 2006 Nature [Lond] 442:563), whereas bone morphogenetic protein has major role in the development of sturdy beaks. ▶[calmodulin](#); more about Darwin's finches: Grant PR, Grant R 2005 Current Biol 15(16):R614.

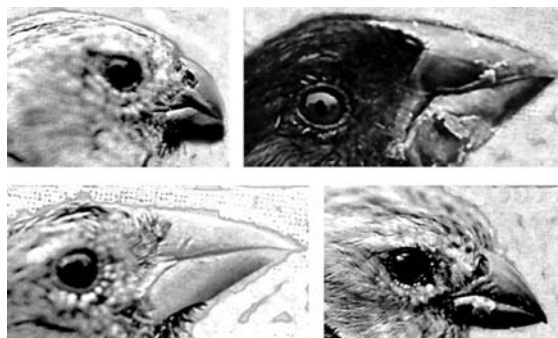


Figure F19. Finches

Fine Structure Mapping: Genetic mapping of the position of mutations (alleles) within a gene locus.

►allele, ►locus

Fine Structure of Genes: Initially, the fine structure of genes meant recombinational analysis at high resolution in large populations, frequently based on selective identification of the recombinants that permitted mapping of the sites of different alleles within the locus. The ultimate fine structure analysis uses DNA (RNA) sequencing of cloned genes.

►mapping genetic, ►physical mapping, ►deletion mapping

F

Finger: ►Zinc finger, ►Ring finger

Fingerprint Clone Contig: Clones are arranged in contigs on the basis of fingerprints generated by restriction enzyme-digests. (See Barillot E et al 1991 Proc Natl Acad Sci USA 88:3917).

Fingerprinting of Macromolecules: Two-dimensional separation (by chromatography and/or electrophoresis) of digests of proteins or electrophoretic separation pattern of restriction enzyme digests of DNA for the purpose of characterization. ►chromatography, ►electrophoresis, ►RNA fingerprinting, ►DNA fingerprinting, ►motifs; Ingram VM 1956 Nature [Lond] 178:792; Baglioni C 1961 Biochim Biophys Acta 48:392; Tao Q et al 2001 Genetics 158:1711, <http://www.bioinf.man.ac.uk/dbbrowser/PRINTS/printsman.html>.

Fingerprints: Fingerprints are analyzed by forensic and police investigations to determine personal identity through dactyloscopy, a branch of dermatoglyphics. Ink is applied to the fingertips and impressions are made on paper. There may be a slight difference between the fingerprint pattern of the corresponding left and right hand fingers yet the overall pattern is characteristic for an individual. Fingerprints are determined by a relatively small number of genes, yet each person has a unique fingerprint pattern. There is about 0.43 correlation between paternal and offspring fingerprints. The pattern is determined by the end of the third month of the fetus. The forensic value of fingerprints depends on quality of the prints collected.

Environmental effects have very little influence upon fingerprints. Even if the epidermis is destroyed, regrowth reestablishes the original pattern. Toe and palm prints may provide additional confirmatory evidence for identity. There are three major types of fingerprint *loops*, *whorls*, and *arches* with 65, 30, and 5% of the fingerprints falling into these broad categories (see Figs. F20 and F21). Autosomal dominant genes are known that either eliminate the

dermal ridges or alter their pattern. There are elaborate systems for their classification into up to a million subgroups within which, individual differences are still detectable. The uniqueness of the fingerprints became known by the second half of the sixteenth century at about the same time as the anatomist, Nehemiah Grew, identified sexuality of plants. Francis Galton, the founder of quantitative genetics, had already used it for forensic purposes in the nineteenth century. The forensic value of fingerprints may not be always perfect because the analysis may be subject to personal errors.

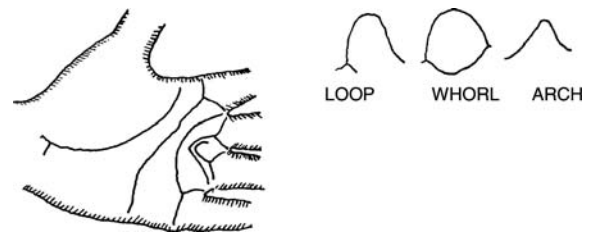


Figure F20. Fingerprints and palmprint patterns. The main types of the fingerprints are “loop”, “whorl” and “arch” as shown but the additional dermal ridges within and outside are omitted here. The average number of ridges for women is about 127 and for men about 144. The far-left palmprint illustrates the main angles of the palmar triradial ridges. These are separate from the palmar creases affected in certain hereditary anomalies. (See Down’s syndrome)



Figure F21. Whorl type fingerprint.

Fingerprinting is used also in visa applications of foreigners (some countries are exempt) and at entry points to the USA for screening undesirable individuals. Prints are generally taken of both index fingers. The pattern is checked against a watchlist maintained in a database by the National Institute of Standards and Technology. The currently used system has a detection probability of 0.526 to 0.733 (using 10 fingers the probability increases to 0.949) and the probability of false positives is 3.1×10^{-3} in a list of

6 million people. In case the quality of the fingerprints is low because of surgery or deliberate erasure of the dermal ridges by sand paper or by other means, the identification probability is lower (Wein LM, Baveja M 2005 Proc Natl Acad Sci USA 102:7772).

Although lip prints have not been used for the same purpose as fingerprints, they also may permit individual identification. ▶ectodermal dysplasia, ▶dyskeratosis, ▶DNA fingerprinting, ▶iris pattern, ▶lip-prints, ▶forensic genetics; Alter M 1966 Medicine 46:35; Williams G et al 2001 J Forensic Sci 46:1085.

Finishing: A DNA sequencing step that eliminates most of the errors and gaps in the genomic sequence and leads to a nearly complete sequence from the first draft. The finished DNA sequence originally was not expected to have a higher error rate than 1×10^{-4} ; the 2004 finished euchromatic sequence of the human genome has an error rate of only 1×10^{-5} . ▶first-draft sequence, ▶gaps; Deloukas P et al 2001 Nature [Lond] 414:865; Nature [Lond] 431:931 (2004).

Finlay-Marks Syndrome: Autosomal dominant scalp lesions, anomalous ears, reduced or absent nipples in females, and syndactily.

FIR (*Abies* spp.): Timber trees, $2n = 24$.

Fire: The intragenic (negative) regulatory element in the c-fos proto-oncogene and it must be relieved before Fos can be expressed. ▶FOS

Firmicutes: A phylum of low GC content Gram-positive bacteria.

First Division Segregation: ▶tetrad analysis

First-Male Sperm Precedence: A method of sperm competition in case of multiple mating during a period of receptivity of the same female. In the newt, the process is controlled by the female in contrast to other animals, and last-male precedence may occur. ▶certation; Jones AG et al 2002 Proc Natl Acad Sci USA 99:2078.

First Messenger: Peptide hormones. ▶animal hormones

First Strand DNA: The immediate product of reverse transcription. ▶reverse transcription, ▶cDNA

First-Draft Sequence: Before entirely completing a genome project, a nearly contiguous sequence may still have an error rate of 10^{-3} . ▶high-quality sequence, ▶genome projects

FirstEF: A computational program based on discriminant function that detects promoters and first exons with over 80% accuracy. ▶discriminant function; Davuluri RV et al 2001 Nature Genet 29:412.

FIS (factor for inversion stimulation): A protein involved in the movement of inversion and transposable elements. This element (11.2-kDa) may activate rRNA transcription (7x) after binding upstream promoter sites at -71, -102, and -143. In *E. coli* and *Salmonella typhimurium*, Fis affects also recombination, replication and other functions. ▶invertases, ▶insertion elements, ▶transposable elements, ▶promoter, ▶rm; Pan CQ et al 1996 J Mol Biol 264:675.

Fish: ▶zebrafish, ▶medaka, ▶pufferfish, ▶salmon, <http://www.fishbase.org/search.cfm>, fish biology: <http://www.larvalbase.org>.

FISH (fluorescence in situ hybridization): FISH detects eukaryotic chromosomal sites by the use of non-radioactive, fluorescence-labeled probes (see Fig. F22). In human chromosomes it permits the resolution of about 0.05–10 million base pairs as a band. The multiplex FISH technique using several fluorochromes simultaneously permits the identification of rather complex chromosomal rearrangements in amazing colors. Using DNA fibers, cloned probes can be mapped with a resolution down to 1 kb. The effectiveness of the FISH approach has been greatly increased by the use of epifluorescent filters and computer evaluation, permitting the simultaneous identification of 27 different DNA probes. This *multiplex FISH* (M-FISH) has been described by Speicher R et al 1996 Nature Genet 12:368; Henegariu O et al 1999 Nature Genet 23:263. In recent years, special probes for different chromosomal locations (centromere, telomere and various insertions) have become available (▶ENCODE; <http://genome.cse.ucsc.edu/>). *Fibre FISH* deals with chromosome fibers that were subjected to histone removal and it has a resolution of 1–500 kb. *RNA FISH* uses a fluorescently labeled nucleic acid probe to detect cellular transcripts in situ. Probes that are complementary to intronic sequences will hybridize at the site of nuclear transcription. ▶chromosome painting, ▶spectral karyotyping, ▶non-radioactive labels, ▶fluorochromes, ▶GISH, ▶in situ hybridization, ▶probe, ▶WCPP, ▶telomeric probes, ▶stretching chromosomes, ▶Chip, ▶FRET, ▶DIRVISH, ▶MFISH, ▶COBRA, ▶combinatorial labeling, ▶ratio labeling, ▶IRS-PCR, ▶chromosome territories; Azofeifa J et al 2000 Am J Hum Genet 66:1684; Lee C et al 2001 Am J Hum Genet 68:1043; Speicher MR, Carter NP 2005 Nature Rev Genet 6:782.

FISH: low sequence homology search: <http://babel.ucmp.umu.se/fish/>.

Fish Orthologous Genes: <http://www.evolutionsbiologie.uni-konstanz.de/Wanda>.

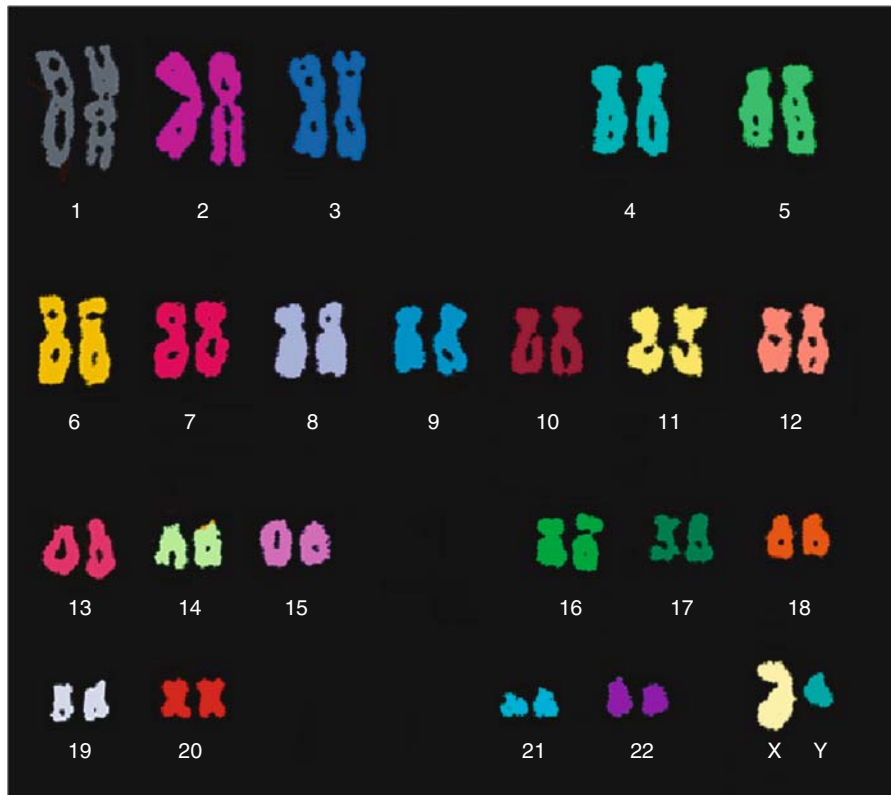


Figure F22. Fish. Human male metaphase chromosomes. In situ multiplex-fluorescence hybridization identified each chromosome pair in different color. (Courtesy of Dr. Michael Speicher, Institut für Anthropologie und Human Genetik, LMU, München, Germany)

Fisher's Exact Test: is an exact probability test for independence that can be used similarly to a goodness of fit and contingency tests. The probabilities are determined with the aid of hypergeometric distribution tables and if the populations are large the binomial distribution may satisfactorily approximate the hypergeometric distribution. (See for details Sokal RR, Rohlf FJ Biometry, Freeman, Everitt, B.S., ed. 2002 Cambridge Dictionary of Statistics. Cambridge University Press, Cambridge, UK, also ►association test, ►chi square, ►G test, ►hypergeometric distribution)

Fisher-Muller Hypothesis: As per the Fisher-Muller hypothesis, the advantage of sex is that beneficial mutations occurring in two different individuals can be combined in one.

Fish-Eye Disease: Cholesterol acyltransferase deficiency. ►lecithine

Fission: A mode of asexual reproduction involving the division of a single cells or organelles by cleaving into two (generally) equal progeny (daughter) cells or organelles (see Fig. F23). ►alternation of generations, ►life cycles, ►contractile ring



Figure F23. Fission

Fission Yeast: ►*Schizosaccharomyces*

FITC: A fluorochrome, a conjugate of fluorescein with isothiocyanate, used for cellular, chromosomal labeling. ►chromosome morphology, ►fluorochromes, ►chromosome painting, ►FISH

Fitch-Margoliash Method for TD: In the Fitch-Margoliash method, using n number of species, an evolutionary distance is computed by minimization of the branches of the evolutionary tree:

$$S_{\text{Fitch-Margoliash}} = \left[\frac{2 \sum_{i < j} \{ (d_{ij} - e_{ij}) / d_{ij} \}^2 }{n(n-1)} \right]^{1/2} \times 100 \quad \text{where}$$

d_{ij} is the observed distance between species i and j and e_{ij} is the patristic distance. ►evolutionary tree, ►evolutionary distance, ►patristic distance, ►transformed distance

Fitness: The reproductive value in a population under specified conditions, determined by a genotype (see Table F5). High fecundity and fertility do not necessarily increase fitness of a population if the offspring does not reach or proceed beyond reproductive age. In monogamous societies, primarily the females determine the reproductive success. For the method of calculation of fitness see table. In natural populations when hybrids have superior fitness, it can be estimated by the following equation: $w_{F1} = [(1 - p_1)p_3]/[p_1(1 - p_3)]$ where p_1 and p_3 are the frequencies of hybrids at the beginning and at the end of the study (Ebert D et al 2002 Science 295:485).

In pre-industrial American populations, increasing number of offspring and rates of reproduction were associated with reduced parental survivorship, especially more for mothers than fathers. Parental mortality resulted in reduced survival and reproduction of offspring, and the mothers' mortality was more detrimental to offspring than the fathers'. Increasing family size was associated with lower offspring survival, primarily for later-born children, indicating a tradeoff between offspring quantity versus quality. Thus maximal reproduction imposed fitness costs (Penn DJ, Smith KR 2007 Proc Natl Acad Sci USA 1004:553).

►selection coefficient, ►hybrid vigor, ►mutation rate in fitness, ►inclusive fitness, ►fecundity, ►fertility, ►parity, ►cultural transmission of fitness; Loeske EB et al 2000 Proc Natl Acad Sci USA 97:698; Wloch DM et al 2001 Genetics 159:441; Rozen DE et al 2002 Current Biol 12:1040.

Fitness-Associated Recombination: Breaking linkage with deleterious genes or generating new linkage relations in a changing environment may increase the fitness of an evolving population. ►genetic load,

►recombinational load, ►fitness; Hadany L, Beker T 2003 Genetics 165:2167.

Fitness Density: The proportion of amino acids in a protein that affect fitness during evolution.

Fitness, Standardized: ►selection coefficient

Fitness Valley: In graphical representation of fitness, individual mutations reduce fitness whereas joint effects of mutations increase fitness.

fix: ►nitrogen fixation

Fixation: The allele becomes homozygous in every individual of the population.

Fixation Index: The fixation index is the average coefficient of inbreeding in a population. In case of random mating, the probability that an offspring would have exactly the same two ancestral alleles at a locus is $(1/2)N$, where N is the number of diploid individuals in the population. The probability of having two different alleles at the same locus is $1 - (1/2)N$. The coefficient of inbreeding of the first generation of this population is also $(1/2)N$ by definition of inbreeding. In each succeeding generation, the non-inbred part of the population will have a chance to produce offspring with an allele pair identical by descent. Therefore, the coefficient of inbreeding in the next generations will be $(1/2)N + [(1 - (1/2)N) \times F]$, where F is the inbreeding coefficient of the preceding generation. After the g th generation the coefficient of inbreeding of this population will be: $F_g = (1/2)N + [1 - (1/2)N]F_{g-1}$ and this is called the *index of fixation*. Its complement is the *panmictic index* (P_g) that represents the average non-inbred fraction of the population:

$$P_g = 1 - F_g$$

Table F5. Estimation of fitness and equilibrium frequencies of the alleles at heterozygote advantage in a hypothetical population

| | | | |
|---|---|-----------------------------------|---|
| Observed (N = 2000): | AA = 900, | Aa = 1000, | aa = 100 |
| Representation of alleles ($\Sigma = 4000$): | A: $(2 \times 900) + 1000 = 2800$, | a: $(2 \times 100) + 1000 = 1200$ | |
| Allelic frequencies: | A: $2800/4000 = 0.7 = p$, | a: $1200/4000 = 0.3 = q$ | |
| Expected no. of genotypes N | AA: 0.49×2000 , | Aa: 0.42×2000 , | aa: 0.9×2000 |
| ($p^2 + 2pq + q^2$) | AA: 980 | Aa: 840 | aa: 180 |
| Fitness <small>$\frac{\text{observed number of genotypes}}{\text{expected number of genotypes}}$</small> | AA: $\frac{900}{980} = 0.92$ | Aa: $\frac{1000}{840} = 1.19$ | aa: $\frac{1000}{180} = 0.56$ |
| Standardized fitness (rel. to w_2) | AA: $\frac{0.92}{1.19} = 0.77$ | Aa: $\frac{1.19}{1.19} = 1.00$ | aa: $\frac{0.56}{1.19} = 0.47$ |
| Selection coefficients | $s = 1 - 0.77 = 0.23$ | | $t = 1 - 0.47 = 0.53$ |
| Allelic frequencies at equilibrium | A: $\frac{t}{s+t} = \frac{0.53}{0.23+0.53} = 0.7$, | | a: $\frac{s}{s+t} = \frac{0.23}{0.23+0.53} = 0.3$ |

The probability for the offspring to have two identical *A* or *a* alleles is $F_{p_{AA}}$ and $F_{q_{aa}}$, respectively. Also, the probability of two alleles of a locus being non-identical by descent is $1-F$, and the proportions of *AA*, *Aa*, and *aa* are p^2 , $2pq$, and q^2 (according to the Hardy-Weinberg theorem). Because the population will have both inbred and non-inbred components, its genetic structure will be:

$$(p_{AA} + q_{aa}) \text{ and } (1-F)(p^2AA + 2pqAa + q^2aa)$$

F

When a population is completely inbred, only homozygotes are found. There may be a change in genotypes but may not be a change in allelic frequencies if both alleles have equal fitness. The change may actually be from $AA + 2Aa + aa \rightarrow AA + AA + aa + aa$, i.e., mathematically it is the same. The ultimate probability of fixation $P_f = \frac{1-e^{-N_e s p}}{1-e^{-N_e s}}$ may be estimated also on the basis of the *initial frequency of the gene* ($= p$), the *selection advantage* ($= s$) and the *effective population size* (N_e). [The base of the natural logarithm $= e \approx 2.718$]. ▶inbreeding, ▶panmixis, ▶inbreeding rate, ▶Hardy-Weinberg theorem, ▶mutation neutral, ▶mutation beneficial, ▶hybrid vigor; Whitlock MC 2003 Genetics 164:767.

Fixative: An agent(s) required to treat biological materials before a stain is applied for microscopic examination (see Table F6). The fixative rapidly kills the cells, immobilizes the structures, and assures better staining. Many different types of fixatives have been developed since the introduction of microscopic techniques. Some of the most widely used (especially for cytology) with composition in parts (volume) are given.

Newer fixatives may contain formalin 5%, glacial acetic acid 5%, 90% or 70% ethanol, glutaraldehyde (4% in 0.025 M phosphate buffer pH 6.8), etc. Detergents (Tween 20) may be added for facilitating penetration or aspiration is applied for a few minutes. Fixation time is a day or two. The fixed material can be stored for months in 70% ethanol in a refrigerator. For electron microscopy, different fixatives are required. The fixatives used in photographic processing are completely different. ▶light microscopy, ▶electron microscopy, ▶stains

FixL: *Rhizobium* kinase regulating N₂ fixation by FixJ. ▶nitrogen fixation

FFU (focus forming unit): The measure of focus formation in transformed (cancer) cells.

FK506 (Tacrolimus): An immunosuppressive protein, in combination with rapamycin, binds to cellular proteins FKB12/FKBP13. FK506 intercepts the signal of the T lymphocyte receptor while rapamycin interferes with the signal of cytokines and growth factors. The FKBP12 - FK506 complex inhibits the serine-threonine phosphatase, calcineurin. The FK506 family protein FPR3 helps to maintain meiotic checkpoint to facilitate recombination through controlling protein phosphatase 1. Thus the chromatid breakpoints remain open until strand exchange is completed by delaying the premature progression of meiosis (Hochwagen A et al 2005 Cell 122:861). The rapamycin-FKBP12 complex binds to FRAP and regulates p70 ribosomal protein S6 kinase that is required for the progression from G₁ phase of the cell cycle. Fkbp6 is essential for normal chromosome pairing in male mouse meiosis and fertility (Crackower MA et al 2003 Science 300:12191). Mutant Fkbp does not seem to affect female meiosis and fertility. (Also called TOR, RAFT, FRAP. Members of this protein family are common in animals (FKBP25, FKBP12, FKBP51, etc.) and occur also in fungi (Npi46) and plants (FKBP73). ▶immunosuppression, ▶cell cycle, ▶calcineurin, ▶immunophilins, ▶ataxia telangiectasia, ▶signaling to translation, ▶checkpoint, ▶cell cycle, ▶meiosis, ▶PPI, ▶NF-AT, ▶FkpA, ▶peptidyl-prolyl isomerases, ▶recombination molecular mechanism of, ▶checkpoint, ▶cardiomyopathy hypertrophic familial, ▶cyclosporine, ▶immunophilins, ▶plasmacytoma, ▶amyloids, ▶histone tails; Glynne R et al 2000 Nature [Lond] 403:672; Aghdasi B et al 2001 Proc Natl Acad Sci USA 98:2425.

FK1012: A lipid-soluble ligand; a dimeric form of FK506. It directs the interaction between proteins linked to the FKBP12 receptor. ▶FK506

FKB12/FKBP13: The enzyme complex involved in the catalysis of peptidyl-prolyl cis-trans isomerization of

Table F6. Fixatives

| Designation | Ethanol | Propionic Acid | Acetic Acid | Chloroform |
|-----------------|---------|----------------|-------------|------------|
| Farmer's | 3 | 0 | 1 | 0 |
| Farmer's modif. | 3 | 1 | 0 | 0 |
| Carnoy A* | 6 | 0 | 1 | 3 |
| Carnoy B* | 6 | 0 | 3 | 1 |

*fresh

*fresh

proteins. The FKBP12 molecules may be complexed with hormones or other proteins and facilitate the export of molecules from the endoplasmic reticulum. ►FK506, ►COP, ►Ire; Marx SO et al 2000 Cell 101:365; Gaburjakova M et al 2001 J Biol Chem 276:16931.

FKH (forkhead): The embryonic lethal *Drosophila* gene at 3–95. A human homologue (13q14) is a DNA-binding protein; the human gene (FKHL7) at 6p25 encodes a transcription factor responsible for a dominant glaucoma. It seems that that FKH1 and FKH2 of yeast are general transcription factors regulating the elongation of the RNA polymerase II transcripts (Morillon A et al 2003 Science 300:492). Translocations to 2q35 (PAX) may result in rhabdomyosarcoma (epithelial tumor). The forkhead homolog of *Caenorhabditis* (DAF-16) controls longevity of the worms and in humans it indirectly mediates apoptosis and the cell cycle. The protein Chfr (checkpoint with FHA and ring finger) seems to control in the cell cycle the entry into metaphase. The human homolog, FoC1 at 6p25 is a glaucoma gene. FOXC2 defect involves lymphedema distichiasis. FOXC1 and FOXL2 genes are also involved in several other human diseases. Foxa2 regulates lipid metabolism and ketogenesis in liver during fasting and in insulin-deficient diabetes (Wolfrum C et al 2004 Nature [Lond] 432:1027). FOXP3 deficiency leads to autoimmune disease (IPEX). FOXP3 controls ~700 genes that are key modulators of T_R cell activation (Marson A et al 2007 Nature [Lond] 445:931; Zheng Y et al Nature [Lond] 445:936). ►PAX, ►glaucoma, ►lymphedema distichiasis, ►Axenfeld-Rieger anomaly, ►blepharophthalmosis, ►Akt, ►checkpoint, ►FHA, ►ketogenesis, ►diabetes, ►dyspraxia, ►hepatocyte, ►T cell regulatory; mitotic program: Alvarez B et al 2001 Nature [Lond] 413:744; Tran H et al 2002 Science 296:530; fox gene classifications for various organisms: <http://www.biology.pomona.edu/foxbyclass.html>.

FkpA: A periplasmic FK506-binding protein. ►FK506, ►periplasma

Flag: The eukaryotic translation initiation factor (eIF-4G2, encoded in humans at 11p15) and provides support for the capping protein eIF-4F by binding to eIF-4A. FLAGGED proteins are usually repressed. ►eIF-4G, ►eIF-4A, ►eIF-4F, ►cap, ►capping enzymes

Flag Tag: An 8-amino acid (Asp-Lys-Tyr-Lys-Asp-Asp-Lys) fusion tag is used for immunoaffinity chromatographic purification of proteins (Einhauer A, Jungbauer A 2001 J Biochem Biophys Methods 49:455).

Flagellar Antigen: Flagellar antigen of *Salmonella* is encoded by the *H1* and *H2* genes. At a particular time, only one of the two flagellins is expressed. The expression is controlled by “phase variation”, i.e., a transposition (inversion) of the 970 bp long DNA segment. In one of the positions, the *rh1* regulatory element represses the *H1*, and after the inversion of the other, *H2* is expressed. ►phase variation, ►flagellin, ►Trypanosoma, ►mating type determination in yeast; Masten BJ, Joys TM 1993 J Bacteriol 175:5359.

Flagellin: The protein material of the (bacterial) flagellum. Perception of flagellin is an early step of bacterial resistance in *Arabidopsis* (Zipfel C et al 2004 Nature [Lond] 428:764). Flagellin induces non-host innate immunity against bacteria, but *Pseudomonas syringae* suppresses the effector in *Arabidopsis* (Li X et al 2005 Proc Natl Acad Sci USA 102:12990). ►flagellum, ►phase variation, ►host-pathogen relation, ►EF-Tu; Samatey FA et al 2001 Nature [Lond] 410:331.

Flagellum (plural flagella): A cell appendage used for back and forth movement of microbial cells; in bacteria it is controlled by about 50 genes (see Fig. F24). The core components of the bacterial flagellum originated through the successive duplication and modifications of a few, or perhaps even a single, precursor gene (Liu R, Ochman H 2007 Proc Natl Acad Sci USA 104:7116). ►flagellin, ►cilia; Yonekura K et al 2003 Nature [Lond] 424:643; molecular structure: Samatey FA et al 2004 Nature [Lond] 431:1062.



Figure F24. Flagellum

Flame: ►FLICE, ►apoptosis

Flanking DNA (flanking gene): Nucleotide sequences adjacent to a gene, or adjacent genes.

Flap: A binding or attaching/overlapping site of an enzyme/protein.

Flap Nuclease: The flap nuclease has both endo- and exonuclease activity. ►RAD27/FEN1; Debrauwere H et al 2001 Proc Natl Acad Sci USA 98:8263; Dervan JJ et al 2002 ibid. 99:8542.

Flash (FLICE-associated huge protein): A caspase-regulatory protein in apoptosis, it interacts with FAS/CD95. ►apoptosis, ►Fas, ►caspase, ►FLICE, ►DISC; Choi Y-H et al 2001 J Biol Chem 276:25073.

Flat File: A non-machine-readable, non-standardized file that can be used for information exchange in databases. ▶[databases](#)

Flatworm (*Planaria torva*): $2n = 16$ (see Fig. F25).
▶[Planarians](#)

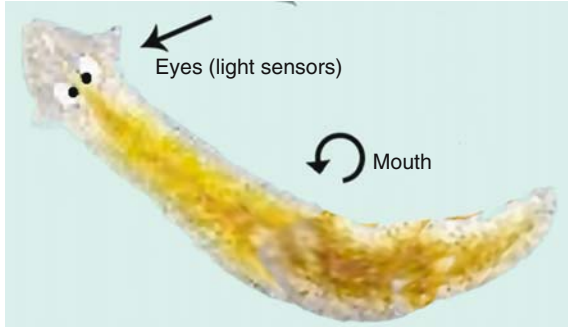


Figure F25. Planaria

Flax (*Linum usitatissimum* ($2n = 30, 32$)): Flax includes the fiber crop and the seed crop, linseed, altogether with about 200 species. In the highly variable *Linum* genus, the basic chromosome numbers vary: $x = 8, 9, 12, 14, 15, 16$ but the most common $2n$ numbers are 18 and 30. Some strains also show non-nuclear inheritance.

Flavin Nucleotides: Riboflavin-containing coenzymes.
▶[FMN](#) and ▶[FAD](#)

Flavone: Along with, flavonones, flavonols are plant pigments derived from chalcones. ▶[anthocyanidins](#) and ▶[chalcone](#)

Flavonoids: Pigments with trimeric heterocyclic nucleus, and are frequently glycosylated. The synthetic enzymes may assemble as macromolecular complexes. Flavonoids may act as antioxidants and their presence in dark chocolate or red wine may be advantageous for the cardiovascular system. ▶[flavone](#); Serafini M et al 2003 Nature [Lond] 424:1013.

Flavoproteins: Flavoproteins are tightly bound with a flavin nucleotide prosthetic group. ▶[flavin nucleotides](#)

flea: ▶[copia](#)

FL-cDNA (full-length cDNA): Genuine fl-cDNAs include the 5' ATG initiating codon, which is frequently missing in cDNA libraries. ▶[cDNA](#); Draper MP et al 2002 Genomics 79:603.

Fletcher Factor: Fletcher factor causes a usually asymptomatic hereditary anomaly involved in the early regulation of the intrinsic blood-clotting pathway. ▶[blood clotting pathways](#), ▶[anti-hemophilic](#)

[factors](#), ▶[kallikrein](#), ▶[hemostasis](#); Weiss AS et al 1974 J Clin Invest 53:622.

Flexer: A protein that determines DNA folding and bending, as do the chaperones of proteins. ▶[chaperone](#), ▶[DNA bending](#), ▶[folding](#); Lavoie BD et al 1996 Cell 85:761.

FLI: One of the consistent translocation breakpoints (22q12) in Ewing sarcoma.

FLICE (I-FLICE/caspase 10, human chromosome 2q33): An inhibitory participant in apoptosis; it is a member of the ICE family proteases, and is apparently the same as MACH (mort-associated Ced-3 homolog). Other apparent synonyms are FLIP, Casper, FLAME, CASH. ▶[ICE](#), ▶[apoptosis](#), ▶[FLASH](#), ▶[caspases](#); Poulaki V et al 2001 Cancer Res 61:4864.

FlIG, FlIM, FlIN: Bacterial switch proteins controlling flagella rotation. ▶[phase variation](#); Lux R et al 2000 J Mol Biol 298:577.

FLIP (fluorescence loss in photobleaching): Occurs in living cells, which were repeatedly spot-bleached by laser beam. The loss of fluorescence indicates the dissociation of e.g., green fluorescent protein from a particular compartment and reveals the protein traffic within the cell nucleus. ▶[aequorin](#)

FLIP (FLICE inhibitory protein, Casper): ▶[FLICE](#), ▶[FLP/FRT](#); Pkada Y et al 2001 Cytokine 15(2):66.

Flipase/Flippase: Aminophospholipid translocase. ▶[phospholipid](#), ▶[annexins](#); McIntire JA 2003 Am J Reprod Immunol 49:221; Smriti et al 2007 Biochemistry 46:2249.

Flip-Flop Recombination: Occurs between two inverted repeats (in organelle genomes) and produces equal mixtures of two isomeric forms. ▶[mtDNA](#), ▶[chloroplast genetics](#), Hudspeth ME et al 1983 Proc Natl Acad Sci USA 80:142.

Flip-Flop Transcription: A single locus-control region may move back and forth by looping in between members of a large complex gene cluster, thus permitting the transcription of different members of the complex. ▶[locus control region](#), ▶[gene cluster](#); Kano M et al 1998 Biochem Biophys Res Commun 248:806.

Flk-1: A receptor tyrosine kinase with supposed role in endothelial and B lymphocyte differentiation, angiogenesis, and formation of solid tumors. Its ligand is VEGF (vascular endothelial growth factor). ▶[vascular endothelial growth factor](#), ▶[Flt-1](#), ▶[Tie-1](#), ▶[Tie-2](#), ▶[KIT](#), ▶[FLT](#); Matsumoto K et al 2001 Science 294:559.

Flood Factor: A blood protein resembling blood factor VII; it shortens the slightly long prothrombin action time in asymptomatic individuals. ►[antihemophilic factors](#), ►[blood clotting pathways](#), ►[hemostasis](#)

Floor Plate: The organizer center in the ventral midline of the neural tube directing the development of the central nervous system of vertebrates. ►[organizer](#), ►[neural tube](#), ►[roof plate](#)

Floppy Disk: ►[disk](#)

Flora: A description of higher plant communities growing in a particular area or the vegetation present in an area.

Floral Dip: A simple method of transformation of *Arabidopsis* plants by agrobacterial vectors. The inflorescence is dipped into a bacterial suspension containing 5 g sucrose and 500 μ L Silwet L-77 surfactant. No in vitro tissue culture is required. ►[transformation genetic/plants](#); Clough SJ, Bent AF 1998 Plant J 16:735.

Floral Evocation: The process of commitment to flower differentiation of plants. ►[commitment](#), ►[determination](#); Nelson DC et al 2000 Cell 101:331.

Floral Induction: The internal and external factors bringing about floral evocation. Induction of flowering is a complex process and may require low temperature (vernalization), long- or short-day photoperiodic regimes, respectively (see Fig. F26). Recessive mutations of single genes of *Arabidopsis* at several unlinked loci may dramatically affect the flowering response. The flowering response is under the negative control of *FLC* (*FLOWERING LOCUS C*), which is regulated by vernalization and methylation (Sheldon CC et al 1999 Plant Cell 11:949).

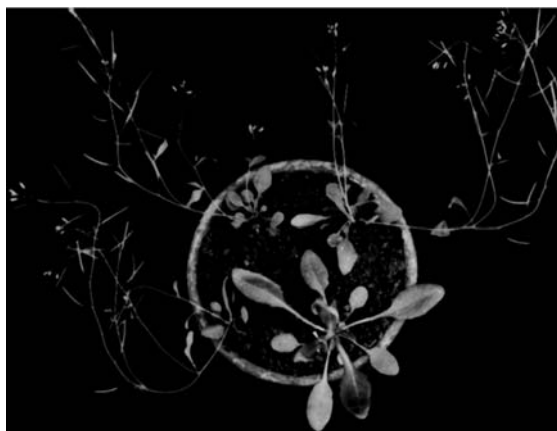


Figure F26. Floral induction. Segregation of the *gr²* Mutant with wild type sibs (From Rédei GP 1962 Genetics 47:443)

Two small RNAs (30 and 24 nucleotides) corresponding to the reverse strand 3' to the canonical poly(A) site of *FLC*, an *Arabidopsis* gene encode a repressor of flowering. These RNAs originate from a genomic region of *FLC* lacking repeats. The 24-nt small RNA, which is most abundant in developing fruits, is absent in mutants defective in RNA polymerase IVa, RNA-dependent RNA polymerase 2, and DICER-LIKE 3, components required for RNAi-mediated chromatin silencing. The corresponding genomic region shows histone 3 lysine 9 dimethylation (Swiezewski S et al 2007 Proc Natl Acad Sci USA 104:3633).

It seems that siRNAs control methylation of specific loci involved in the onset of flowering (Chan SW-L et al 2004 Science 303:1336). *FLC* is apparently repressed by FVE, a retinoblastoma-associated protein that deacetylates histones (Ausin I et al 2004 Nature Genet 36:162). The role of negative regulators of flowering in mutants of *Arabidopsis* has been shown as early as 1966 (Rédei GP et al 1974 Stadler Symp 6:135). Nitric oxide (NO) appears to be a repressor of floral initiation of the *co* and *gi* mutants but was found to enhance the expression of *FLC* (He Y et al 2004 Science 305:1968). ►[flower differentiation](#), ►[florigen](#), ►[photoperiodism](#), ►[vernalization](#), ►[shade-avoidance syndrome](#), ►[RNAi](#), ►[histones](#), ►[RNA polymerases](#); Rédei GP 1962 Genetics 47:443; Suárez-Lopez P et al 2001 Nature [Lond] 410:1116; Simpson GG, Dean C 2002 Science 296:285; Mouradov A et al 2002 Plant Cell 14:S111; Blázquez MA et al 2003 Nature Genet 33:168; He Y et al 2003 Science 302:1751.

Floret: An individual small flower that is a part of an inflorescence.

Florigen: A term coined in the mid 1930s by Mikhail Chailakhyan, a Russian plant physiologist, for a hypothetical mobile flowering hormone under the control of photoperiodism. During the decades, its chemical definition has defied all efforts of description. Although gibberellins have been attributed with its property, this suggestion has been incorrect. Research in 2005 credited the *Arabidopsis FT* mRNA or the encoded protein with florigen properties, i.e., synthesized in the leaves and moving to the shoot apex and promoting flower evocation (Huang T et al 2005 Science 309:1694; this paper has been retracted: Böhlenius H et al 2007 Science 316:367). More recently, the mRNA nature of the flowering substance has been questioned and evidence has supported its protein-like nature (Corbesier L et al 2007 Science 316:1030). The rice homolog of FT, Hd3a has been identified also as a florigen protein (Tamaki S et al 2007 Science 316:1033). ►[photoperiodism](#), ►[flower differentiation](#), ►[flower induction](#), ►[gibberellins](#)

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Flor's Model: The Flor's model developed by the plant pathologist, H.H. Flor in the 1950s, claims that for each virulence gene of the pathogen, a gene exists in the host and thus, corresponding gene pairs (GCP) exist. These can be expressed in four different categories. Actually, the models were further elaborated and only pathogenicity and host reaction alleles were recognized, while the terms virulence and resistance were deemed unnecessary. Thus, the expression of the disease symptoms (aegricorpus), dependent also on environmental factors, required an inter-organismal genetic system. This rather complicated, interacting system was considered a great idea to explain the genetic control of host–pathogen relationships by many plant pathologists. But many geneticists dismissed it as commonplace. They argued that in all organisms, all functions are genetically controlled and it is the interaction of gene products that determines the phenotypes within organisms and also between organisms, and disease is no exception. Thus, the model—they argued—in the absence of biochemical or molecular facts, is not helpful. Since several plant genes have now been cloned, there will be new opportunities to study host–pathogen relationships in physico-chemical terms. The resistance of maize against *Cochliobolus carbonum* (*Helminthosporium*) seems to support the latter argument inasmuch as a plant enzyme degrades the fungal toxin. The discoveries that some resistance genes encode elicitors of the signal transduction pathways in one way or another still do not invalidate the simplest interpretation. Recent experiments using the yeast two-hybrid system with the *Lac* reporter indicate that the *AvrPto* bacterial virulence gene interacts with the tomato resistance gene *Pto*. This reaction was evident only in this genic combination. Analysis of the *Pto* protein also revealed that a 95 amino acid stretch (129 to 224) of the protein was alone responsible for the specific interaction between the pathogen and the host. The plant resistance proteins (R) contain nucleotide-binding sites (NBS) and leucine-rich repeat (LRR) domains for the recognition of pathogens. The pathogens generally contain avirulence (*Avr*) proteins that are effectors of infection. These two groups of proteins co-evolved competitively to assure infection by the pathogen and resistance in the host, respectively. The plant *Arabidopsis* synthesizes RPM1, RPS2, and RPS5 nucleotide-recognition and leucine-rich repeat proteins. These proteins are modified by the effector function of the pathogenic *Pseudomonas syringae* *Avr* proteins made by virulent strains. During evolution, a balance must have evolved between these two sets of genes in order to maintain the status quo despite mutations. In flax plants, there is a polymorphic L locus, which encodes NBS-LRR

proteins that recognize different variants of *Avr* of the fungus *Melampsora lini*. The *AvrL567* rust locus encodes 150 amino acid proteins, which are presumably cleaved and release a 127 amino acid polypeptide. The flax proteins L5, L6 and L7 R recognize the signals of the pathogen. During evolution, the many variants existing in the different strains fungi and plants are apparently in a continuous arms race (Dodds PN et al 2006 Proc Natl Acad Sci USA 103:8888). ▶aegricorpus, ▶host-pathogen relations, ▶immune response, ▶quadratic check, ▶two-hybrid system; Flor HH 1971 Annu Rev Phytopath 2:131; Ellis J et al 2000 Curr Opin Plant Biol 3:278; Bergelson J et al 2001 Science 292:2281.

Flotillin: A protein of the caveolae. ▶caveolae; Garin J et al 2001 J Cell Biol 152:165.

floury (fl-2): The *fl-2* gene of the maize improves the nutritional value of the kernels by reducing the contents of prolamine and zein, resulting in an increase in lysine, tryptophan, and methionine. ▶opaque, ▶kwashiorkor

Flow Cytogenetics (flow karyotyping): The analysis of chromosomes by flow cytometry. (See Davies DC et al 2000 Flow Cytometry, see below).

Flow Cytometry: In the flow cytometer, suspended particles (cells, chromosome, etc.) are stained with fluorochromes and a laser beam excites the dyes. The particles are then sorted with the aid of a computer according to their special properties. The procedure directly estimates cell (rather than population) characteristics such as nucleic acid content, enzyme activity, membrane potential, calcium flux, cell surface receptors, cytoplasmic constituents, etc. It requires sophisticated instrumentation. ▶bivariate flow cytometry; Ormerod MG ed. 2000 Flow Cytometry, Oxford University Press, Oxford, UK; Gygi MP et al 2002 Nucleic Acids Res 30:2790.

Flowchart: The graphical display of procedures of analyses for the solution of a particular problem or subset of that problem or an experimental protocol.

Flower Differentiation: Flower differentiation is under very strict genetic control. Numerous genes have been identified which change the basic pattern of the morphogenesis. An idealized wild type dicot flower and the most common three types of homeotic conversions are indicated in the diagram. The homeotic transformations may not be complete and thus, e.g., carpelloid sepals, stamoid petals, or petaloid stamens, etc. were identified. Usually, an entire whorl of the flowers ([1] sepals, [2] petals, [3] stamens, [4] and carpels) is affected. The conversions generally involve adjacent whorls and simultaneously more than two whorls may be affected. On the basis of mutational evidence, it has been

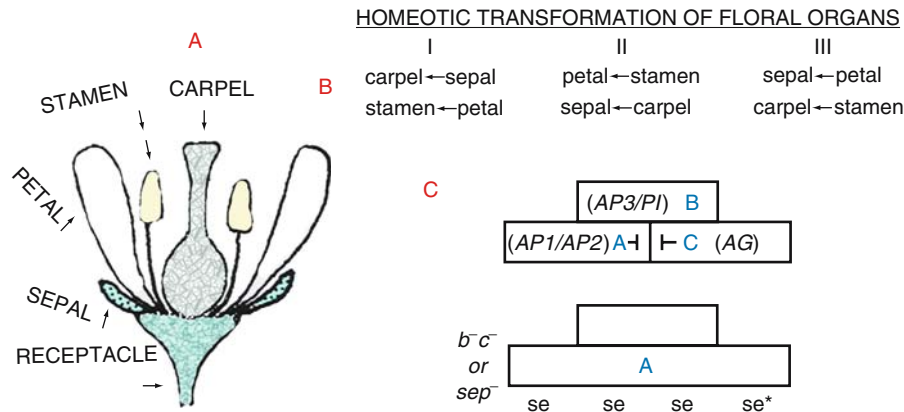


Figure F27. Homeotic transformation of floral organs. Genetic determination of flower organs (shown at A). Homeotic transformation affects neighboring whorls (B). The Meyerowitz-Coen-Yanofsky model of flower organ identity (C). This is also called the ABC model represented by the blue letters in the three boxes (at top) and including the symbols of the genes (in italics) responsible for the control of differentiation of these organs. Box **A** Alone specifies sepals, **C** Alone controls carpels and **A** and **B** are responsible for petals whereas **B** and **C** for stamens. **A** counteracts the activity of **C** and **C** is antagonistic to **A**. If **c** is not active an indeterminate number of floral whorls appear. The lower two boxes illustrate the floral development in double mutants when both **B** and **C** genes mutate ($b^- c^-$) or when mutation occurs at the *sepallata* (formerly denoted as *agamous-like* AGL) sites. When all three (*sep1*, *sep2*, *sep3*) are mutant only **A** activity is displayed, i.e., in all three whorls sepals appear

suggested that the four whorls belong to A (1 + 2), B (2 + 3), and C (3 + 4) identity groups in the floral meristem (see Fig. F27, Fig. F28).

The identity groups affected by the mutation(s) determine the actual phenotype of the mutants. e.g., a type II change is the result of interaction between domain A (*Apetala 1* [*AP1*] and 2 [*AP2*] genes) and domain B (*Apetala 3* [*AP3*] and *Pistillata* [*PI*] genes). Mutations in the C and B domains result in the *agamous* (*AG*) in *Arabidopsis* and in the *plena*, *pleniforma* or *petaloida* alterations in *Antirrhinum*. *AP1*, *AP3*, *PI*, and *AG* proteins all contain a MADS box, but *AP2* represents another DNA binding protein. microRNA 177 appears to be a translational suppressor of *AP2* (Chen X 2004 Science 303:2022). In *Antirrhinum*, phenotypically similar mutations *blind* (*bl*) and *fistula* (*fis*) control microRNA genes located in the center of the flower although they are expressed also during early floral development (Cartolano M et al 2007 Nature Genet 39:901; for *fis* phenotype ► [mutation spectrum](#)).

The plant MADS box proteins contain another conserved element, the K box that may form amphipathic α helices. *AG* binds also to another consensus ([CC(A/T)₆GG], the CA₂G-box).

These proteins interact with each other and may form *AP1/AP1*, *AP3/PI*, and *AG/AG* dimers including the truncated *AG/PI* heterodimer. The association of these proteins is mediated to a large degree by the so called L (linker) region that involves amino acids 31–35 situated between the MADS box and the K (keratin homology) box:



Figure F28. Some mutants of *Arabidopsis* violate the normal path of development of the flower whorls. Here we see 7 petals and 12 stamens and a somewhat complex stigma and carpels but the sepals are absent. (G.P. Rédei, unpublished)

N — terminus < MADS DOMAIN >
< L REGION > < K BOX > C terminus

The MADS box appears to represent a large family of genes with critical functions in plant development.

Flower differentiation seems to be controlled at the level of transcription and the specific RNA transcripts

appear in regions of the flower primordia, which are affected by the specific genes (see Fig. F29). These genes are studied under the control of different promoters introduced by transformation. Recent studies also indicate that at least some of the genes are regulated post-transcriptionally.

Cell fate signaling in the apex of *Arabidopsis* is mediated by a receptor encoded by the *CLAVATA1* trans-membrane protein kinase gene and it is activated by the ligand encoded by *CLAVATA3*, regulating the balance between growth and differentiation. The *WUSCHEL* gene interferes with the activity of *CLAVATA* and maintains the undifferentiated status of the meristem. In *Arabidopsis*, the *LEAFY* and *SPLAYED* genes appear to be activators of the floral homeotic genes such as *APETALA1* and *AGAMOUS*. The quartet theory of floral differentiation has been proposed by Honma T, Goto K 2001 (Nature 409:525). According to this model, four MADS box proteins in four different combinations determine primarily the identity of floral parts in *Arabidopsis*. Petals are under the control of genes *API*, *AP3*, *PI* and *SEP*, carpels under (*AG*, *SEP*)₂, stamens under *PI*, *SEP*, *AP3*, and *AG* and sepals under *API* and two as yet unidentified proteins.

Constans (*CO*) mutants of *Arabidopsis* mediate photoperiodic induction. *FLOWERING LOCUS T* (*FT*), expressed in the vasculature of the cotyledons and in the shoot apex, is a promoter of flowering and regulates *CO*. *FD*, a basic leucine zipper transcription factor expressed in the shoot apex, supports *FT* and they cooperatively mediate initiation of flower development through transcriptional activation of *APETALA 1*, which a floral meristem identity gene

(Abe M et al 2005 Science 309:1052; Wigge PA et al 2005 Science 309:1056).

LEAFY and *APETALA1* promote the establishment of floral identity by positive regulation of other flowering genes. *AGAMOUS-LIKE24* is a central regulator of the floral meristem, and *LEAFY* and *APETALA1* negatively control *AGL24*. Without their activity the floral primordium develops inflorescence characteristics (Yu H et al 2004 Nature Genet. 36:157; this paper summarizes the intricate control of flower differentiation up to 2004).

Normally, *Arabidopsis* develops flowers following the development of a whorl of leaves in the vegetative rosette. The *EMBRYONIC FLOWER* (*EMF*) eliminates the rosette stage and promotes the development of a flower at the apical meristem of each shoot. Other MADS box genes (*SHP1*, *SHP2* and *STK*) mediate the development of the carpels and the ovules.

►MADS box, ►florigen, ►morphogenesis, ►peloric, ►petals, ►homeotic genes, ►auxin; Ma H 1998 Trends Genet 14:26; Fletcher JC et al 1999 Science 283:1911; Busch MA et al 1999 Science 285:585; Ma H, dePamphilis C 2000 Cell 101:5; Pelaz S et al 2000 Nature 405:200; Lohmann JU et al 2001 Cell 105:793; Aubert D et al 2001 Plant Cell 13:1865; Wagner D, Meyerowitz EM 2002 Curr Biol 12:85; Lohmann JU, Weigel D 2002 Developmental Cell 2:135; Pinyopich A et al 2003 Nature [Lond] 424:85; Durfee T et al 2003 Proc Natl Acad Sci USA 100:8571; comprehensive survey of flowering genes and molecules: Krizek BA, Fletcher JC 2005 Nature Rev Genet 6:688.

Flower Dip: ►floral dip

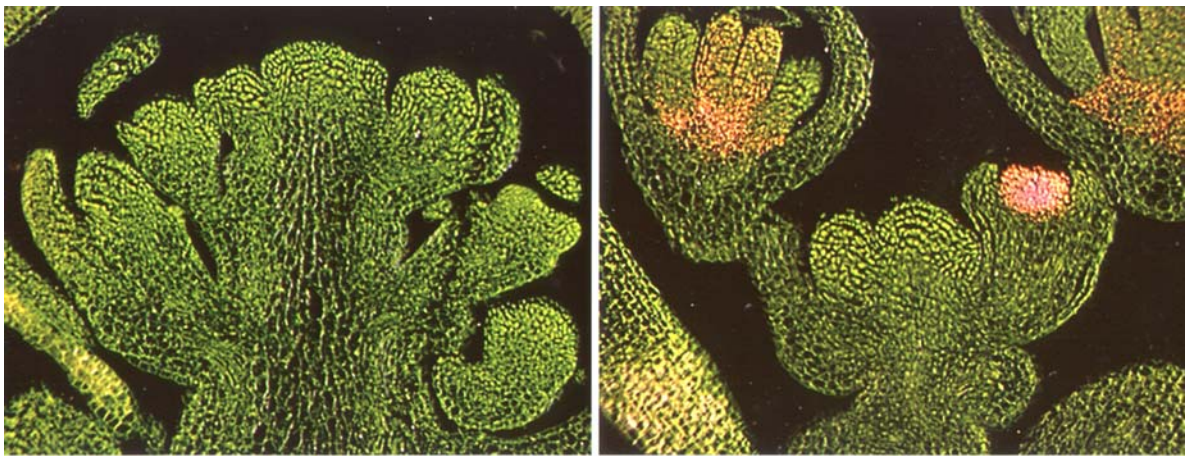


Figure F29. Apical meristem of *Arabidopsis*. At left the *lfy* (*leafy*) mutant, at right the wild type transgenic for the GUS reporter under the control of the *ag* regulatory sequences. *Leafy* encodes a transcription factor, which determines whether the apical meristem will produce flowers instead of leaves or shoots. The original picture was taken by darkfield microscopy and in color. The expression of the transgene in orange color. (Courtesy of Dr. Detlef Weigel)

Flower Evocation: The determination of the flowering process. ► [floral induction](#)

Flower Pigments: ► [anthocyanin](#), ► [flavone](#), ► [chalcones](#)

Floxing: ► [targeting genes](#)

FLP/FRT: A *Saccharomyces* recombinase system that can be expressed also in *Drosophila*. FLP is a recombinase and FRT defines target sites of transposable elements (see Fig. F30). The system is very similar to the Cre-loxP of bacteriophage P1. The 43-kDa “flip” (FLP) is encoded by the 2μ circular yeast plasmid. Recombination (X) takes place within the core sequence and between FLP binding sites.

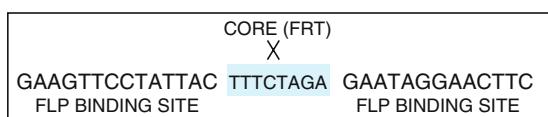


Figure F30. FLP/FRT

This, as well as the *Cre/loxP* system, can be used for site-specific integration of transgenes and also for engineering chromosomal rearrangements in higher eukaryotes. ► [recombinase](#), ► [Cre/loxP](#), ► [targeting genes](#), ► [transposable elements](#), ► [chromosomal rearrangements](#), ► [homing endonuclease](#); Buchholz F et al 1998 Nat Biotechnol 16:857.

Flpter: The fractional length from the hybridization signal to the terminus of the short arm of the chromosome. It is used for the localization of FISH labels on the chromosome. ► [FISH](#)

FL-Rex (fluorescence localization based retrovirus-mediated expression cloning): In FL-Rex cloning, mRNA is isolated and reverse-transcribed into cDNA. Then the cDNA (about 1000 bp) is inserted into a multiple cloning site of a green fluorescent protein (GFP) gene within a retroviral vector (see Fig. F31). With the aid of the vector, packaging cells are transfected and the isolated retroviruses used to infect cultured mammalian cells. The GFP fusion permits the screening of the infected cells and subcloning individual cell lineages for a variety of different proteins with subcellular expression. Also the different DNAs can be amplified by PCR and sequenced. In a similar manner, GFP fusion proteins can be localized within the cytoplasm of plants with the aid of agrobacterial vectors. ► [expression cloning](#), ► [subcellular](#), ► [subcloning](#), ► [aequorin](#), ► [reverse transcription](#), ► [polymerase chain reaction](#), ► [DNA sequencing](#), ► [lipofection](#), ► [packaging cell lines](#), ► [ψ](#); Misawa K et al 2000 Proc Natl Acad Sci USA 97:3062.

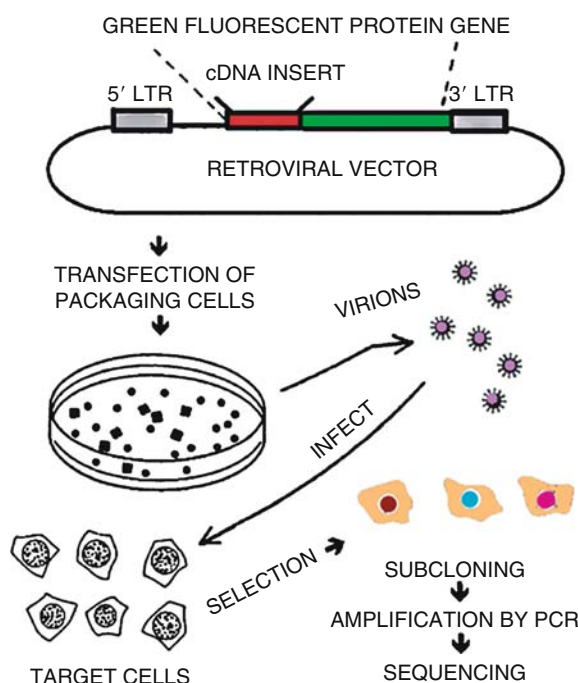


Figure F31. The FL-Rex test

FLRTED Transmissible variations generated by Flp/FRT system of site-specific recombination. ► [Flp/FRT](#)

FLT Oncogene: FLT oncogene is located in human chromosome 13q12 and it encodes a protein tyrosine kinase. It shows homology to FMS and ROS. Flt-1 is essential for animal embryonal vasculature but not for endothelial differentiation. The FLT3/FLK2 receptor tyrosine kinase is closely related to KIT and FMS. Flt-4 is a receptor of VEGF-C and promotes angiogenesis and their activity correlates with cancer metastasis (Su J-L et al 2006 Cancer Cell 9:209). ► [vascular endothelial growth factor](#), ► [Flk-1](#), ► [KIT](#), ► [FAK](#), ► [oncogenes](#), ► [Tie-1](#), ► [Tie-2](#), ► [receptor tyrosine kinase](#), ► [FMS](#), ► [ROS](#), ► [eclampsia](#), ► [VEGF](#); Maru Y et al 2001 Biochim Biophys Acta 1540:147.

Fluctuation Test: The fluctuation test was designed originally to determine whether the mutations observed were induced by a particular treatment or the treatment merely was a means of screening for that particular class of mutations that preexisted in the cultures. The design of the fluctuation test by Luria and Delbrück in 1943 initiated experimental bacterial genetics. It can be used also in other microorganisms and in animal and plant cell cultures; and the principles can be adapted to most types of mutation experiments. The principle is as follows: from the same original culture two series are generated. In series I the culture

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is continued until a particular cell density is reached. In series II, small inocula are placed in say 10 (or more) vessels and the culture is continued until the same cell density is reached in all vessels of series I and II. Then plating is made in say 10 Petri plates from the single vessel culture I, and one Petri plate from each of the 10 test tubes of series II. After incubation for a period the number of mutations are scored separately on each of the 20 Petri plates. The abridged data of an experiment by M. Demerec (J Bacteriol 56:63) are tabulated. The averages (\bar{x}) and the variances ($(\sum x^2 - n\bar{x}^2)/n - 1$) are determined. If it appears that the average number of mutational events in both series I and II are practically the same but the variance in series II significantly exceeds that of series I, the conclusion is that the treatment was not the cause of the mutations. A fluctuation test of bacterial mutation for streptomycin resistance series I showed an average of 127.6 mutations, and the variance was 145.4. In series II, the average was almost the same at 123.3, but the variance was 4,392.0. Thus, streptomycin only revealed the presence of preexisting mutations for streptomycin resistance. The logic of this argument is that in the single vessel #I the preexisting mutants were distributed uniformly and therefore upon plating the variance was low. In the 10 vessels of series #II, mutations occurred or did not before plating. If mutations occurred early, many mutants appeared on that Petri plate, if mutation occurred late in the test tube,

few mutations were detectable after plating and if no mutations occurred in a particular test tube, the Petri plate failed to display any. The propagation of the pre-existing mutations caused the presence of a large number of the mutant colonies on some plates and when there were no mutations prior to the treatment, no such colonies appeared after plating in series II. In series I in the single batch the pre-existing mutations were uniformly dispersed without fluctuation in the variation. Thus the different fluctuations on the identical series of Petri plates presented the critical argument for the conclusion that the treatment was ineffective (see Table F7). Interestingly the classical publication of Luria & Delbrück contains computational error yet the basic principle contributed significantly to the development of bacterial and cell genetics. ►mean, ►variance, ►statistics; Luria SE, Delbrück M 1943 Genetics 28:491.

Fluid genome Paradigm: ►constant genome paradigm

Fluidity: Lipids can move within membranes. ►cell membranes

Fluorescein: A fluorochrome with excitation at 490-nm wavelength of light and emission at 525-nm (see Fig. F32). Generally used in conjugates with avidin, isothiocyanate or antibodies.

Table F7. Fluctuation test

| Series I | | | Series II | | |
|-------------------|---------------------|----------------|-------------------|---------------------|----------------|
| Culture No. | Resistant Cells (X) | X ² | Culture No. | Resistant Cells (X) | X ² |
| 1 | 146 | 21,316 | 1 | 67 | 4,489 |
| 2 | 141 | 19,881 | 2 | 159 | 25,281 |
| 3 | 137 | 18,669 | 3 | 135 | 18,225 |
| 4 | 128 | 18,384 | 4 | 291 | 84,681 |
| 5 | 121 | 14,641 | 5 | 75 | 5,625 |
| 6 | 110 | 12,100 | 6 | 117 | 13,689 |
| 7 | 125 | 15,625 | 7 | 73 | 5,329 |
| 8 | 135 | 18,225 | 8 | 129 | 16,641 |
| 9 | 121 | 14,641 | 9 | 86 | 7,396 |
| 10 | 112 | 12,544 | 10 | 101 | 10,201 |
| SUMS | 1,279 | 164,126 | SUMS | 1,233 | 191,557 |
| Average \bar{X} | 127.6 | | Average \bar{X} | 123.3 | |
| Variance | 154 | | Variance | 4,392.0 | |

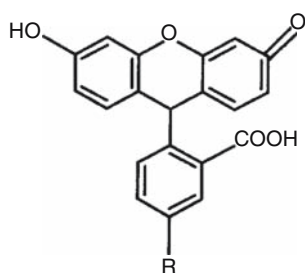


Figure F32. Fluorescein → R = radix of different types

Fluorescein Diacetate: A vital stain for protoplasts.

Fluorescence: The property of chemical compounds to emit radiation (light) upon absorption of radiation from another source. Fluorescent radiation generally has longer wavelength than the wavelength absorbed, e.g., nucleotides irradiated by 260 nm UV light display a visible purple color. The fluorescence lasts only as long as the exposure to the irradiation. ▶UV

Fluorescence Microscopy: This technique uses a microscope with an illuminator equipped with a light filter that assures that the stage receives only that narrow spectral band of light that is required for the excitation of the fluorochrome used for staining the specimen. In front of the ocular, there is another filter that transmits only the fluorescence emitted but shuts out the exciting wavelength light. By staining with more than one dye and changing filters, in the same specimen different structures (molecules) may be distinguished by different bright colors. Some of the fluorochromes permit viewing also living cells. ▶fluorochromes, ▶chromosome painting, ▶FISH, ▶microscopy; Lippincott-Schwartz J, Patterson GH 2003 Science 300:87; Hadjantonakis A-K et al 2003 Nature Rev Genet 4:613.

Fluorescent Dyes: ▶fluorochromes

Fluorescent in Situ Hybridization: ▶FISH

Fluorescent-Focus Assay: The fluorescent-focus assay is used to determine titers of non-killer viruses. Permeabilized (by acetone, methanol) cells are incubated with antibody against the virus. Then another antibody that recognizes the first, and is conjugated with a fluorescent dye is added. The fluorescing cells are counted by UV light microscopy. (See Yang DP et al 1998 Clin Diagn Lab Immunol 5:790).

Fluorescent Speckle Microscopy (FSM): FSM permits the analysis of the dynamics of the cytoskeleton in living cells. ▶cytoskeleton; Waterman-Storer CM, Danuser G 2002 Current Biol 12:R633.

Fluorochromes: Non-radioactive labels such as DAPI, fluorescein, rhodamine B, FITC, Texas Red, R-Phycoerythrin, RED613, RED670, allophycocyanin, isothiocyanate, aequorin, Cy3 (green), Cy5 (red), etc. The dipyrrometheneboron difluoride dyes may have special advantages for automatic sequencing of DNA. The fluorescent amino acid 2-amino-3-[5-(dimethylamino)naphthalene-1-sulfonamide]propanoic acid (dansylalanine) can be genetically encoded in *Saccharomyces cerevisiae* by using the amber codon (UAG) and the appropriate tRNA/aminoacyl-tRNA synthetase pair (see Fig. F33). This procedure thus forgoes the use of fluorochrome complexes for the study of protein structure, folding and localization (Summerer D et al 2006 Proc Natl Acad Sci USA 103:9785). See under individual names, ▶fluorescent microscopy, ▶biotinylation, ▶FRET, ▶FISH, ▶aequorin, ▶unnatural amino acids; Han M et al 2001 Nature Biotechnol 19:631; Giepmans BNB et al 2006 Science 312:216.

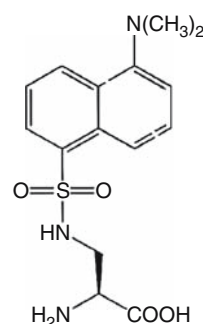


Figure F33. Dansylalanine

Fluorography: A method used to enhance the sensitivity of autoradiographic detection by adding to the sample scintillants such as 2,5-diphenyloxazole (PPO) or sodium salicylate. ▶autoradiography, ▶scintillation counters

Fluorophore: A pigment that upon activation brings forth color. Numerous different fluorophores are used for labeling of macromolecules. ▶fluorochrome

Fluoroscope: A medical apparatus for X-ray examination of deep-seated tissues. The image is seen on a fluorescent screen coated with calcium tungstate or zinc cadmium sulfide and other materials. It was favored in the past because it could also detect motions. It has become of lesser significance with introduction of television cameras. It uses about ten fold higher doses of radiation than diagnostic X-ray machines, because of which it poses radiation hazards to both operator and patient. ▶X-rays, ▶tomography, ▶sonography

5' Fluorouracil (FU): A uracil analog that is incorporated into RNA. It is metabolized into deoxyfluorouridine monophosphate and triphosphate, and can get incorporated into the DNA (see Fig. F34). It is a potent antineoplastic agent, although resistance can develop. ▶neoplasia

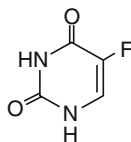


Figure F34. FU

Flush-Crash Cycles: In flush-crash cycles, the size of a natural population fluctuates greatly.

Flush End: ▶blunt end (of DNA)

Flux: The spread of a label from a metabolic precursor to other molecules in the cell.

Flux, Genetic: Alterations in the cell in response to internal and external stimuli.

Flux, Metabolic: The production or decrease of metabolite(s) in an organ or individual within a period of time; it may be expressed as mole/kg/hr.

Fluxome: The complete set of metabolic fluxes within a cell. (See Almaas E et al 2004 Nature [Lond] 427:839).

FlyAtlas: Provides information on gene of interest expressed/enriched in the adult *Drosophila*. mRNA signal is provided for each gene and tissue. The homologs of many human genetic disease loci show selective expression in the *Drosophila* tissues analogous to the affected human tissues, providing a useful filter for potential candidate genes (Chintapalli VR et al 2007 Nature Genet 39:715) (<http://flyatlas.org>).

Flybase: *Drosophila* database (<http://flybase.bio.indiana.edu>).

fMet: Formylmethionine is generally the first (modified) amino acid in the translation on the ribosome of prokaryotes mediated by tRNA^{fMet-i} (i for initiator). At internal peptide sites even at prokaryotes, the tRNA^{Met-e} (e for elongation) is functional. The formylation is the duty of the methionyl-tRNA^{Met} formyltransferase. This enzyme recognizes the tRNA as the initiator by a CA mismatch at position 1–72. The eukaryotic (and Archea) initiator carries the A1–T72 base pair at the comparable site. In the mitochondria, there may be only a single type of tRNA^{Met} and that resembles the initiator type or it

may have the C1–A72 mismatch. Trypanosomal mitochondria lost their tRNA genes and imports from the cytosol all the tRNAs. Further, the mitochondria formylate some of the imported elongation tRNAs with the aid of an enzyme that is similar to formyltransferases, but has twice the mass of that of the prokaryotic enzyme. ▶formylmethionine; ▶protein synthesis; Tan THP et al 2002 Proc Natl Acad Sci USA 99:1152.

FMN: Flavin mononucleotide composed of flavin (riboflavin) phosphate and dimethylisoalloxazine base (yellow enzyme); it is a coenzyme for oxidation-reduction mediating proteins.

FMR (fragile X mental retardation): ▶fragile X chromosome

FMR1: ▶trinucleotide repeats, ▶fragile, ▶sites, ▶KH module

FMRI (functional magnetic resonance imaging): ▶MRI

FMR1 Mutation: FMR1 mutation involves the expansion of the CGG trinucleotides, which are frequently methylated on C and thus silenced. Hypermethylation of FMR1 is called *full mutation*, whereas the *premutation* is an intermediate range of expansion (50–200) of these repeats. ▶fragile sites, ▶trinucleotide repeats, ▶human intelligence, ▶KH module; Crawford DC et al 2001 Genet Med 3(5):359.

FMRFamides: Neuropeptides. (See Parker SL, Parker MS 2000 Can J Physiol Pharmacol 78[2]:150).

FMS: Feline sarcoma virus protooncogene is a receptor of colony-stimulating factor-1 [CSF] and macrophage colony stimulating factor. This gene is located in human chromosome 5q33.2–q33.3. It is involved in different types of leukemias. Its sequence is homologous to oncogene FLT, a tyrosine kinase. ▶leukemias, ▶colony stimulating factor, ▶FGR, ▶FLT, ▶protooncogene

FNR: A ferrous/ferric binding bacterial aerobic/anaerobic regulator protein with some similarity to the catabolite repressor protein. ▶catabolite repression; Moore LJ, Kiley PJ 2001 J Biol Chem 276:45744.

Foam Cells (xanthoma cells): Lipid streaks develop into foam cells, which can develop into atherosclerotic plaques and restrict the lumen of arteries, and can lead to thrombosis and myocardial infarction. ▶atherosclerosis, ▶thrombosis, ▶myocardial infarction, ▶angina pectoris

Foamy Viral Vectors: Foamy viral vectors are derived from Spuma retroviruses that may not be pathogenic for humans, although they infect many cell types in several hosts. Their carrying capacity is ~12 kb, somewhat larger than that of the murine leukemia

virus (MLV) which accepts 9–10 kb. In addition, they transduce non-dividing cells somewhat more efficiently than the MLV vectors. ►retroviral vectors; Vassilopoulos G et al 2001 Blood 98:604.

Focal Contact: An adhesion plaque on the surface of a cell that is attached to the extracellular matrix by transmembrane proteins (integrin).

Focal Dermal Hypoplasia (Goltz syndrome, FDOF): X-linked dominant lethal in males, involving atrophy, skin pigmentation in a linear pattern, papillomas (epithelial neo-plasms), polydactyly, underdevelopment of teeth, small defective eyes, mental retardation, etc. Apparently, deficiency of a putative O-acetyltransferase, regulator of Wnt signaling, is involved (Grezschik K-H et al 2007 Nature Genet 38:833; Wang X et al 2007 *ibid.* 38:836). ►skin diseases, ►cancer, ►pigmentation defects, ►polydactyly, ►eye diseases, ►mental retardation

Focus Formation: In focus formation, neoplastic (cancerous) cells grow up in dense clusters. ►cancer

Focus Forming Unit: ►FFU

Fodrin (spectrin): α -fodrin is a non-erythroid α -spectrin (a cytoskeletal protein) with the critical amino terminus of RQKLEDSY RFQFFQRDAEEL. β II-spectrins (2p21, 11q13, 15q21) are schwannomin- and other membrane-binding proteins. ►spectrin, ►Sjögren syndrome, ►schwannoma, ►neurofibromatosis; Takahashi K et al 2001 Eur J Pediatr 160:520.

Foetus: ►fetus

FOG (Friend of GATA): A multitype zinc finger protein cofactor of the GATA transcription factors. FOG facilitates the access of GATA to the transcription site. ►GATA; Tsang AP et al 1997 Cell 90:109; Pal S et al 2004 Proc Natl Acad Sci USA 101:980.

FokI: The FokI endonuclease recognizes the 5'-GGATG-3' sequence and cleaves away DNA 9 and 13 bases.

Folate: Salt of folic acid. ►folic acid

Folate Malabsorption: A defect in the transport of folate through the blood-brain barrier, resulting in anemia, movement problems, mental defects, seizures, etc.

Folate-Sensitive Fragile Site: In cultured cells in folate or thymine deficiency, the chromatin fails to condense normally.

Fold Recognition (prediction): A program that detects tertiary structure of proteins from the primary structure. ►folding, <http://bioinf.cs.ucl.ac.uk/psipred/index.html>.

Fold-Back DNA: Palindromic (inverted repeat sequences) sequences in a single strand of polynucleotides pair within the same strand (see Fig. F35).



Figure F35. DNA fold-back

Fold-Back Inhibition Site: ►FBI site

Fold-Back Transposon (FB): FBs transpose through DNA-intermediate carrying imperfect inverted repeats ranging from 300-bp to several kbp. They may or may not contain open reading frames. ►transposon, ►repeat, ►inverted, ►open, ►reading, ►frame

Folded Leaf: Protein α -helices wrapped around a hydrophobic core. ►hydrophobic, ► α -helix

Folding: A thermodynamically reversible process involving macromolecules (proteins), resulting in a functional conformational state. The folding may follow different pathways from simple two-state to sequential complex ones. Thiol (SH) \rightleftharpoons disulfide (-S-S-) conversions are generally involved. During the process of folding, the foldons assemble in a step-wise manner (Maity H et al 2005 Proc Natl Acad Sci USA 102:4741). Duplications followed by truncation and rearrangements may lead to new proteins with sufficient fitness (Peisajovich SG et al 2006 Nature Genet 38:168). ►conformation, ►chaperone, ►protein folding, ►ITCHY; Thomas PJ et al 1995 Trends Biochem Sci 20:456; Baker D, Agard DA 1994 Biochemistry 33:7505; Frydman J 2001 Annu Rev Biochem 70:603; Mirny L, Shakhnovich E 2001 Annu Rev Biophys Biomol Struct 30:361, <http://www.ebi.ac.uk/dali/>.

Foldon: The protein domain involved in folding.

Folic Acid (pteroyl glutamic acid): A water-soluble vitamin; it is required for *de novo* nucleotide synthesis and amino acid conversions. As a derivative of pteridines, it is involved in many oxidation reactions, in mediating animal coloring, and in various light reactions (see Fig. F36). Tetrahydrofolic acid is an important coenzyme. Folic acid deficiency during pregnancy may lead to congenital malformations. Experimental data indicate that the folic acid-binding FOLR1 receptor may be insufficient. Folic acid deficiency may increase single-strand and double-strand chromosome breakage (~4 million/cell) because of uracil incorporation into the DNA in place of thymine. Leukemia (ALL but not AML) and colon cancer risk may also increase, especially when at site 677 of methylenetetrahydrofolate, reductase C is replaced by T. The same genetic alteration may increase the risks of Down syndrome and various types of cancer. Diets high in fruits and vegetables

(and thus folic acid) and micronutrients such as vitamins B12, B6, niacin, C, E, and iron and zinc may be beneficial. ►fragile sites FMR1, ►methotrexate, ►aminopterin, ►phosphoribosylglycineamide formyltransferase, ►formiminotransferase deficiency, ►5,10-methylenetetra-hydrofolate dehydrogenase, ►formyltetrahydrofolate synthetase, ►homocystinuria, ►nondisjunction, ►spina bifida, ►vitamins; Ames BN 1999 Proc Natl Acad Sci USA 96:12216; Hobbs CA et al 2000 Am J Hum Genet 67:623.

F

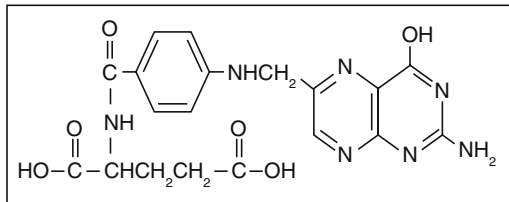


Figure F36. Folic acid

Folksonomy: A communication system (a language) for Internet-based information retrieval by collaboratively generated labels (tags) that identify web pages and other web links. ►WEB, ►collaborative tagging. See <http://del.icio.us/>; for references: <http://www.conno-tea.org/>; find photos: <http://www.flickr.com/>.

Follicle: A small secretory sac or gland. Examples are the cell layer covering the ovary, and in botany a simple dry fruit, dehiscing along one suture and formed of a single carpel. ►ovary, ►carpel

Follicle Stimulating Hormone: ►FSH

Fölling Disease: ►phenylketonuria

Follistatin: A maternally expressed protein that by binding activin may interfere with activin-induced mesoderm formation. Follistatin-deficient mice die within hours after birth because of multiple defects indicating its requirement for several proteins of the transforming growth factor family. Follistatin regulates tooth enamel formation in balance with bone morphogenetic protein (Wang X-P et al 2004 7:719). ►activin, ►mesoderm, ►organizer, ►bone morphogenetic protein; Michel U et al 1993 Mol Cell Endocrinol 91:1; DePaolo LV 1997 Proc Soc Exp Biol Med 214:328.

Fomivirsen (Isis 2922): An antisense DNA phosphorothioate (5'-dGCGTTGCTCTTCTTC TTGCG-3') "drug" against the 55-kDa protein of the cytomegalovirus, causing RNase H degradation of the mRNA, and inhibition of human CMV replication. In addition, it may interfere with viral adsorption.

►cytomegalovirus, ►antisense technologies; Perry CM, Balfour JA 1999 Drugs 57(3):375.

Fonts: The various styles of characters and scripts that the computer can use.

Footprinting: In footprinting, fragments of 5'-labeled double-stranded DNA are partially degraded by a DNase in the presence and also in the absence of a protein that is expected to bind to certain sequences in the DNA. Subsequently, both samples (with and without the binding protein) are sequenced (Maxam and Gilbert method) and a comparison reveals the nucleotide sequences protected from DNase by the binding protein. Thus, from the path (footprints) of the DNase, the position of the binding protein is revealed. These sites may have importance for transcription initiation. In vitro *footprinting* is basically very similar to the methylation interference technique but it is performed in living cells and is followed by DNA extraction and electrophoresis. Footprinting may be used, with the aid of PCR, to identify the position of transposable elements in the genome when the PCRs are compared with the transposon-free and transposon-containing genomic tracts. ►regulation of gene activity, ►methylation interference assay, ►PCR; Fox KR, Waring MJ 2001 Methods Enzymol 340:412; Metzger W, Heumann H 2001 Methods Mol Biol 148:39; phylogenetic footprinting of prokaryotes: <http://bio.cs.washington.edu/software.html>; footprinting across phylogeny server: <http://genome.cs.mcgill.ca/cgi-bin/FootPrinter3.0/FootPrinterInput2.pl>.

Footprinting, Genetic: The role of sequenced genes without known function can be determined by inserting transposable elements (Ty) in a sequential manner and then determining the genetic consequences of the disruption. This process can screen yeast cell populations in 10^{11} range and detects a wide range of mutations of variable severity or fitness. ►Ty, ►transposon footprint, ►mutation detection

Footprinting, Evolutionary: The analysis of cis- and trans-acting regulatory elements in different species (Gumucio D et al 1996 Mol Phylogenet Evol 8:18). ►footprinting

Footprints, Transposable Element: After a mobile genetic element (insertion- or transposable element) moves, it usually leaves behind some nucleotides (as a footprint) at the original target site. ►insertional mutation, ►transposon mutagenesis, ►transposon footprint; van Houwelingen A et al 1999 Plant Cell 11:1319.

Foramen: A natural, anatomical opening or passageway.

Forbes Disease: A defect or deficiency of amylo-1,6-glucosidase and/or oligo-1,4-1,4-glucantransferase. (See under alternative name of glycogen storage disease III).

Forbidden Knowledge: A controversial concept regarding areas that we ought not to know, and research in which should be restricted. The problem lies generally not in the scientific goals but rather in the means of the inquiries. Human experimentation should be forbidden to avoid torture, exposing people to unnecessary risks, and violating human dignity or religious beliefs. In these instances, alternative but not offensive means must be adopted to arrive at the same goals. Medical procedures can be tested on animal models or in cell cultures or by in vitro molecular means. Some concepts of forbidden inquiry also have cultural or historical context, such as studies of evolution, the physical nature and origin of the universe, sexuality, and genetic engineering. Knowledge itself is not unethical or immoral, but some of the methods used or their applications in obtaining knowledge may be contrary to enlightened human standards. (See discussion in Science 308:1549 2005, ethics).

Fore Tribe: The fore tribe of New Guinea is most affected by the kuru disease because of the behavioral tradition of cannibalizing dead relatives. ► [kuru](#)

Forelock, White: A dominant autosomal human trait (a lock of white hairs in the front part of the scalp) (see Fig. F37). ► [Waardenburg syndrome](#)

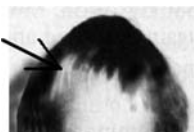


Figure F37. White forelock

Forensic Genetics: Genetic studies used for legal purposes or in the judiciary courts, relying on fingerprints, blood groups, other antigens, isozymes, VNTR (variable number tandem repeats of DNA), by employing RFLP (restriction fragment length polymorphism), PCR, mitochondrial DNA, or other heritable criteria to identify biological relationship, paternity, or criminals, etc. Admitting or compelling genetic tests to the court is somewhat controversial in cases of diseases such as schizophrenia or other mental conditions, but fragile X syndrome or complex genetic traits and environmental impacts on the condition are generally more acceptable to judges (Hoffmann DE, Rothenberg KH 2005 Science 310:241). Evidence from nuclear DNA is the most

reliable. Mitochondrial DNA is important when nuclear samples are not available because of decay of soft tissues, but bone mitochondria can be extracted. The usefulness of mtDNA is more limited yet by proper analysis the information obtained may be very critical. Most of the chemical analyses require small samples of blood (60 μ L), semen (5 μ L), hair roots, saliva, or teeth. For some of the tests, dried blood or semen spots may be useful even if they are weeks, months, or years old. On the basis of polymorphic proteins, identity can be defined to higher than 99% probability and the exclusion of an individual requires much less effort. Generally, the spectrum of the protein components (separated by electrophoresis) in the sample obtained from the person to be identified is compared with the spectrum of the same protein components within the same (ethnic) population. The product of the frequencies expected by chance is compared with the actually observed data. The first test is generally for the ABO blood group but this alone rarely suffices because of the limited variations and its failure to identify all heterozygotes. Other proteins assayed for polymorphism are adenylate kinase (AK), adenylate deaminase (ADA, must be examined within six months), carbonic anhydrase (CA-II, within a week), erythrocyte acid phosphatase (EAP, within six months), esterase (EsD, within one month), glyoxylase (GLO), hemoglobin (Hb), peptidase A (pepA), phosphoglucomutase (PGM, within six months), gammaglobulin (Gm, displays about a dozen antigens determined by very closely linked genes and the clusters have different frequencies in different ethnic groups), Lewis antigens (Lea, Leb), and the rhesus antigens (47 Rh determinants, within six months). In semen samples, generally ABO, GLO, Pep A, PGM, and Le are used. If in a case of rape, the semen sample is obtained by vaginal swabs it may be contaminated by vaginal fluids (may obscure semen fluids), proteolytic enzymes (that may degrade the proteins), or the presence of bacteria may interfere with blood typing. Actually, female cells may be separated from sperm by digestion with sodium dodecylsulfate/proteinase K that does not destroy sperm. Later the sperm can also be digested in the same reaction mixture with (dithiothreitol) DTT added. The greatest specificity of identification can be obtained by analysis of the DNA in body fluids or skin or other tissue samples. The interpretation of the evidence must be carefully weighted as Bruce Weir pointed out. When it seems, on the basis of DNA evidence, that there is only one chance in a million that someone else than the defendant left the critical evidence at the scene of the crime, it should rather be said that if the defendant did not leave behind a sample there is only 1/1,000,000 chance that the observed match would be

with his DNA. The DNA profile also depends on the population concerned.

By June 1998, the Forensic Science Service in the United Kingdom had collected 320,000 DNA samples and removed from the databank 51,000 of them after the suspects were exonerated. The establishment and maintenance of such national databases—although very useful—may be quite demanding because about 30% of the male population under age 30 may have at least one felony conviction. Forensic technologies are all loaded with some degrees of error, inherent in the methods or due to the experience of the technicians. DNA evidence is the most reliable and in dermal fingerprints there may be an average of 4–6% examiner's errors. The old types of forensic technologies generally involved higher errors (Saks MJ, Koehler JJ 2005 Science 309:892). DNA fingerprints may facilitate personal identification also by comparing the databases of relatives if law permits (Bieber FR et al 2006 Science 312:1315). ►fingerprinting, ►lip-print, ►DNA fingerprinting, ►mitochondrial DNA, ►VNTR, ►RFLP, ►SNIPs, ►blood groups, ►ADA, ►PGM, ►hemoglobin, ►gammaglobulin, ►sodium dodecyl sulfate, ►Frye test, ►forensic index, ►CODIS, ►phylogenetic analysis, ►admissibility criteria; National Research Council Technology in Forensic Science by Natl Acad Sci USA, Washington, DC; Budowle B et al 2000 DNA Typing Protocols: Molecular Biology and Forensic Analysis. BioTechniques Press/Eaton Publishing Co., Westborough, Massachusetts; Masters JR et al 2001 Proc Natl Acad Sci USA 98:8012; Benecke M 2002 EMBO Rep 3:498; mt DNA: Wilson MR et al 1995 Int J Legal Med 108(2):68; population specificities: Budowle B et al 1995 J Forensic Sci 40:45; Lee HC, Tirnady F 2003 blood evidence: How DNA is Revolutionizing the Way We Solve Crime. Basic Books, New York; Budowle B et al 2003 Annu Rev Genomics Hum Genet 4:119; ethical issues in population identification: Shriver M et al 2005 Nature Genet 37:449; Cho MK, Sankar P 2005 Nature Genet 37:450; genetic identification: <http://www.fbi.gov/hq/lab/fsc/backissu/oct2002/index.htm>; <http://www.merck.com/mrkshared/mmanual/section21/chapter286/286i.jsp>.

Forensic Index: The forensic index provides statistical information regarding the probability that the evidence (E) collected at a crime scene or from other potentially incriminating object would belong to the perpetrator (P) or to a suspect (S). Let us assume that the perpetrator and the suspect have DNA (VNTR or STR) or protein profile (blood group or enzymes) A and we must find the probability for the suspect being liable for that event or fact (C). Or, we can assume the suspect and the perpetrator are different individuals

(event C'). These conditional probabilities are called L (forensic index) $\rightarrow L = \frac{\Pr(E|C)}{\Pr(E|C')} = \frac{\Pr(S=A|P=A,C)}{\Pr(S=A|P=A,C')}$

S = A indicates that the profile of S is A, i.e., the match is L times more probable if S and P are the same persons. Actually, the decisions are more complex because in the match, the relatedness within the population (population structure) must be considered. ►inbreeding coefficient, ►inbreeding and population size, ►fixation index, ►Bayes theorem, ►conditional probability, ►DNA fingerprinting, ►VNTR, ►STR, ►paternity index

Forespore: In the division of some bacteria two unequal-size products are generated: the larger mother cell and the smaller forespore. The mother cell eventually engulfs the forespore and the endospore results. After a process of maturation controlled by factors in these two components, the mother cell releases the endospore and undergoes apoptosis, whereas the endospore becomes the vegetative cell and assures its continuity by the process outlined here. ►endospore; Stragier P, Losick R 1996 Annu Rev Genet 30:297; forespore engulfment: Broder DH, Pogliano K 2006 Cell 126:917.

Forest Trees: <http://foresttree.org/fldb>.

Forestomach: The forestomach is found in mice, rats, and hamsters between the esophagus (the channel of food from the throat to the stomach) and the glandular stomach. Humans do not have it. The forestomach is a common target of chemical carcinogens.

FORKED (*f*, 1–56.7): *Drosophila* gene affecting the ends of micro-, macrochaete, and trichomes. This phenotype may be suppressed by *suppressor of forked*, *su(f)* (1–65.9) and *suppressor of Hairy wing*, *su(Hw)* (3–54.8) in an allele-specific manner. ►chaeta, ►trichome, ►cleavage stimulation factor

Forked Tongue: The forked tongue enables snakes to assess different signals (pheromones) simultaneously.

Forkhead: A family of transcription factors. ►FKH

Forma specialis: A genetically distinguishable 'race' of a pathogen that can infect primarily a particular host or a host of a defined genotype/phenotype.

Formal Genetics: ►classical genetics

Formiminotransferase Deficiency: An autosomal recessive physical retardation without mental retardation, anemia, etc., caused by oversupply of folate. ►folic acid

Formin: A large family of morphoregulatory proteins involved in the polymerization of actin cables controlling cytokinesis, cell (oocyte) polarization, limb development, etc. Formins have basically

similar features in different organisms. Profilins accelerate filament elongation by formin without the requirement of ATP hydrolysis for processivity (Kovar DR et al 2006 Cell 124:423). ▶[actin](#), ▶[profilin](#), ▶[cytokinesis](#); Leader B et al 2002 Nature Cell Biol 4:92; Kobiela A et al 2004 Nature Cell Biol 6:211; Goode BL, Eck MJ 2007 Annu Rev Biochem 76:593.

Formylmethionine: The translation initiation amino acid in prokaryotes and cytoplasmic organelles (plastids and mitochondria) of eukaryotes, but not used in the cytosol of eukaryotes. It is carried to the 70S ribosomes by a formylmethionine tRNA (tRNA^{fMet} or tRNA^{fMet}) that is distinct from the regular tRNA^{Met}. ▶[protein synthesis](#); Takeuchi N et al 2001 J Biol Chem 276:20064.

10-Formyltetrahydrofolate Synthetase: A key enzyme of folic acid metabolism. ▶[folic acid](#)

Forskolin: A diterpene isolated from the plant *Coleus forskohlii*. It is an activator of adenylate cyclase and some other mechanisms that depend on cAMP. ▶[signal transduction](#), ▶[adenylate cyclase](#), ▶[cAMP](#)

Forssman Antigen: A glycopospholipid, a ceramide pentasaccharide; it is frequently used for the identification of anti-sheep hemolysin in various animals. It has been used also to react with stage-specific and mouse embryonal carcinoma cells. ▶[hemolysis](#)

FORTAN (formula translating system): Computer languages with specific problem orientations.

Forward Chemical Genetics: Forward chemical genetics attempts the identification of new regulators of metabolic pathways and biochemical reactions and seeks molecular targets for therapeutic interventions.

Forward Mutation: Mutation from wild type to mutant allele. ▶[reversion](#)

fos: Murine osteosarcoma (chondrosarcoma) proto-oncogene, general transcription factor (AP1). The fos—jun heterodimers bind to the 5'-TGAGTCAA-3' sequence. Fos also controls complex behavioral traits such as nurturing and the development of the dorsal closure during embryogenesis in cooperation with *jun* in *Drosophila*. ▶[proto-oncogene](#), ▶[AP1](#), ▶[sarcoma](#), ▶[jun](#), ▶[apoptosis](#), ▶[FOS oncogene](#), ▶[apoptosis](#), ▶[JUN](#), ▶[transcription factors](#)

FOS Oncogene: The FOS oncogene in human chromosome 14q21–31 is homologous to the v-oncogene *fos*. The c-FOS protein is a transcription factor of the Jun family. The human FOS has a normal expression in fetal membranes almost as high as that is detectable in osteosarcomas of mouse. Products of FOS and Jun

contribute to the formation of the AP1 transcription factor and participate in multiple ways in tissue differentiation. Ca²⁺/CRE, SRE, SIE elements in the upstream regions of the gene regulate the c-FOS oncogene. These elements are under the control of neurotransmitters, neurotrophins, and cytokines, respectively. Recent studies indicate that Fos knock-outs in mice fail to nurse their pups. ▶[JUN](#), ▶[AP1](#), ▶[oncogenes knock-out](#), ▶[behavior genetics](#), ▶[apoptosis](#), ▶[CRE](#), ▶[SRE](#), ▶[SIE](#), ▶[neurotransmitters](#), ▶[neurotrophins](#), ▶[cytokines](#), ▶[signal transduction](#); Takeuchi K et al 2001 J Biol Chem 276:26077.

Fosmids: Very low, single copy number *E. coli* F replicon-based stable vectors, which are particularly useful for cloning large eukaryotic genes. ▶[F plasmid](#), ▶[vectors](#)

Fossil: Petrified remains or impression of an organism of past geological ages, preserved in the earth or rocky layers. ▶[fossil record](#), ▶[taphonomy](#)

Fossil Record: A fossil record is used to reveal the pattern of macroevolution (evolution of taxonomic categories above the species level) at the geological scale. Macroevolution was traditionally inferred from the paleontological data, the appearance of petrified taxa in the successive geological strata. The age of the remains is estimated by *radioisotope dating*. If the fossils are less than 40 thousand years old, their age is inferred from the amount of carbon-14 (¹⁴C) contained. This isotope is produced at a relatively constant rate from nitrogen-14 (¹⁴N) under the bombardment of cosmic radiation through the ages. This ¹⁴C is utilized by the organisms the same way as the more common ¹²C. The former is unstable, however, and it decays to half in each 5,730-year cycle. The amount of ¹⁴C in the organic material serves as a clock with an accuracy of ±1 to 2%. The age of fossils over 40,000 years is inferred from the age of the sedimentary rocks where the organism died (if that is the site of the fossil and it was not moved by geological changes in the strata). The age of the rocks is estimated by the decay of other isotopes. Uranium-238, e.g., decays into lead-206 with a half-life of 4.51 × 10⁹ years. Therefore, the proportion of these two elements in the rocks indicates their geological age. The evolutionary relation of the fossils can be better defined if protein and DNA analyses are also feasible. ▶[half-life](#), ▶[isotope](#)

Fossils, Genomic: Genomic fossils are inactive retroviral elements that are relics of past infections that occurred during evolution.

Foulbrood: A disease of the honeybee caused by *Bacillus alvei*. Resistance against it is based on homozygosity of two non-allelic recessive genes

determining behavior. One gene is responsible for uncapping the honeycombs when the larvae die, the other gene is responsible for the removal of the dead.
 ▶ [behavior genetics](#), ▶ [honeybee](#)

Foundation Stock: The foundation stock in rodents consists of 10–20 monogamous brother × sister pairs. This breeding/maintenance regime is necessitated so that the new, spontaneous, recessive mutations could be readily detected before they would spread through the multiplication stocks. In mice (i) breeding tests, (ii) skin grafts (immunological reaction), and (iii) biochemical tests (electrophoresis) can monitor authenticity/identity of the strain designation. In plant breeding, the elite seed from authentic registered varieties are multiplied. ▶ [multiplication stock](#)

Founder Cells: Early embryonic cells that contribute to the different cell lineages during differentiation and development. In *Caenorhabditis elegans*, five founder cells are generated during first cleavages of the embryo. The first of these cells (AB) gives rise to 389 of the total 558 nuclei present at hatching. The AB cell lineage is specified by at least five inductions before gastrulation. The inductions do not actually specify the final tissues but eight blastomeres, which contribute to the final body plan. The specification usually requires binary (0 or 1) switches. In the mature seed of *Arabidopsis*, there are 12–16 founder cells. ▶ [morphogenesis](#), ▶ [blastomere](#), ▶ [cell lineage](#), ▶ [fate map](#), ▶ [gastrula](#)

Founder Effect: Same as founder principle.

Founder Mouse: A chimeric animal obtained after transformation that may or may not involve the germline. ▶ [chimera](#), ▶ [germline](#), ▶ [microinjection](#)

Founder Principle: A new population descends from a limited number of immigrants (because of sampling error), resulting in genetic drift. It is called also founder effect. ▶ [effective population size](#), ▶ [drift genetic](#), ▶ [porphyria variegata](#)

Four-Cluster Analysis: A procedure for determining the evolutionary relationships among four large groups of organisms such as animals, plants, fungi, and protists without considering variations within each of

these groups. If we designate the four monophyletic groups as A, B, C, and D, three unrooted evolutionary trees can be generated. These are $T_1 = [(AB)(CD)]$, $T_2 = [(AC)(BD)]$, and $T_3 = [(AD)(BC)]$ from which one is expected to be correct on the basis that the correct construct would have the shortest sum of tree branch length. The three sums of branch lengths may be designated as S1, S2, and S3. An appropriate algorithm determines the differences S1-S2, S1-S3, and S2-S3. ▶ [evolutionary distance](#), ▶ [evolutionary tree](#), ▶ [least square methods](#), ▶ [neighbor joining method](#), ▶ [unrooted evolutionary trees](#); Rzhetsky A et al 1995 Mol Biol Evol 12:163.

Four-Gamete Test: The four-gamete test reveals in biallelic, linked two loci populations whether recombination occurred and all possible four products *AB*, *Ab*, *aB*, and *ab* are present. The proportions may be biased by differences in selective values, random drift, and possibly even by mutation. ▶ [recombination](#), ▶ [linkage](#), ▶ [disequilibrium](#)

Four-Hybrid System: A construct suitable for the activation of specific genes such as *HIS* or *lacZ* (see Fig. F38). The Cyclin, CDK, and MAT1 stable system is part of the general transcription factor TFIID or the cell cycle and the interaction turns on genes in the presence of the target protein X and the VP16 activator. ▶ [MAT1](#), ▶ [transcription factors](#), ▶ [VP16](#), ▶ [LexA](#), ▶ [two-hybrid system](#); Sandrock B, Egly J-M 2001 J Biol Chem 276:35328.

Fourier Method: ▶ [FT-IR](#)

Four-O'clock: ▶ [Mirabilis jalapa](#)

Foveal Dystrophy: An autosomal dominant lesion of the macula in the eye fundus that occurs along with aminoaciduria. ▶ [macula](#), ▶ [eye diseases](#)

Fox: These canid species are quite variable genetically and by chromosome number (see Figs. F39 and F40). *Vulpes velox* (kit fox) 2n = 50; *Vulpes vulpes* (red fox) 2n = 36; *Vulpes fulva* (American red fox) 2n = 34; *Urocyon cinereoargenteus* (gray fox) 2n = 66; *Otocyon megalotis* (bat-eared fox) 2n = 72; *Lyalopex vetulus* (hoary fox) 2n = 74; *Cerdocyon thous* (crab-eating fox) 2n = 74. The fur color varies from red to

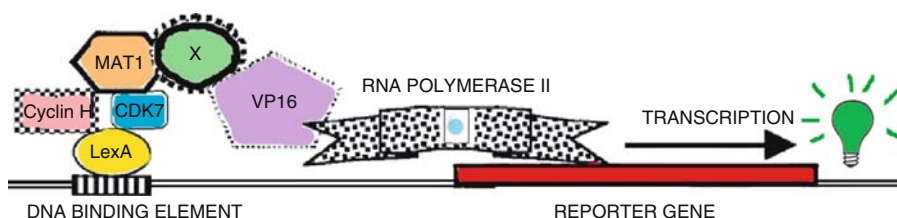


Figure F38. Four-hybrid system

gray or grizzled. The Arctic fox is gray in the summer and white during winter. The ear size varies according to the ecological home of the species. The Arctic fox (*Alopex lagopus*) has shorter ears than the red fox, while the African fox (*Otocyon megalotis*) has much bigger ears. ▶wolf, ▶FKH

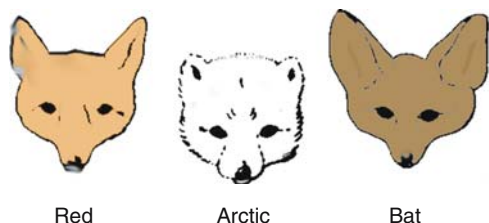


Figure F39. Fox



Figure F40. Red Fox

Fox (human homolog of forkhead): This family of transcription factors regulates the immune response, metabolism, and cell proliferation. Mutant Foxj1 is involved in systemic autoimmune inflammation. Foxo activation may lead to muscular atrophy. Acetylation of Foxo 1 by CREB-binding protein and NAD-dependent histone deacetylase silent information regulator 2 attenuates its ability to bind to DNA and sensitivity to phosphorylation (Matsuzaki H et al 2005 Proc Natl Acad Sci USA 102:11278). MST1/CST-1 and FOXO transcription factors can mediate oxidative stress and longevity (Lehtinen MK et al 2006 Cell 125:987). ▶autoimmune, ▶immune system, ▶Langerhans islets, ▶CREB, ▶histone deacetylase, ▶ecdysone, ▶longevity, ▶oxidative stress, ▶FKH, ▶transcription factors; Lin L et al 2004 Science 303:1017; Accili D, Arden KC 2004 Cell 117:421.

FPC: Finger-printed clone.

F-Pili (or F-pilus or sex pilus): The bacterial cell appendage that forms the conjugation tube through which the F element, conjugative plasmids, and the

Hfr bacterial chromosome is mobilized into the F⁻ cells. ▶F factor, ▶sex factor, ▶Hfr, ▶conjugation; Anthony KG et al 1999 J Bacteriol 181:5149.

FPR (FKB): ▶peptidyl-prolyl isomerase, ▶FK506

FPS (fixed pairing segment): A hypothesis that in eukaryotes, recombination is not entirely random but occurs in tracts which are either fixed at both, or one end, or in the middle. During a single meiosis, only a fraction of these segments pair and there is positive interference in their vicinities. ▶interference

fps: Chicken sarcoma oncogene. ▶sarcoma

FRA: FRA forms active heterodimer with Jun in the AP activator protein. ▶AP1

Fractals: Fractal geometry is considered to describe chaotic systems such as the complexities of many biological phenomena. Fractals emerge from interaction of self-similar entities. The two-dimensional squares can be resolved into many squares and the three-dimensional cubes into many smaller identical-looking cubes. Irregular shape objects also have self-similar fractions but they cannot be adequately described like the square or cube in two or three dimensions, but their characterization requires fractals—such as e.g., 2.2—rather than integers. ▶chaos, ▶networks; Song C et al 2005 Nature [Lond] 433:392.

Fractalkine: A CX3C type chemokine. ▶chemokines, ▶acquired immunodeficiency

Fraction 1 Protein: The old name of ribulose biphosphate carboxylase/oxygenase enzyme that is the largest single protein encoded by the plastid and forms about 50% of the proteins in the chloroplasts. ▶rubisco

Fractional Mutation: Fractional mutation displays mosaicism (variegation) in the tissues of the body. If the mutation was induced in the germ cells, it indicates that the mutagenic agent was associated with only one strand of the DNA and therefore mutant and non-mutant sectors arose and DNA repair occurred during the post-fertilization stage. Fractionals may also be due to unstable genes, mitotic recombination, nondisjunction, transposable elements, etc. ▶unstable genes, ▶mitotic recombination, ▶gene conversion, ▶nondisjunction, ▶transposable elements; Altenburg E, Browning LS 1961 Genetics 46:203.

Fractionated Dose: Irradiation is provided not in a chronic manner but with interruptions between each exposure although the doses are summed up. ▶chronic radiation

Fragile Sites: FRA occur in several human chromosomes (see Fig. F41). The overall frequency of autosomal fragile sites is about 2×10^{-3} .



Figure F41. Fragile site

F

Generally three types are distinguished: (i) folate sensitive [shows up if the cell culture medium is deficient in folate], (ii) elevated pH triggers their appearance and (iii) 5-bromodeoxyuridine (BdUR) is required for expression. The best studied is the fragile X syndrome. Fragile sites have been identified also at 2q11, 3p14.2, 6p23, 9p21, 9q32, 10q23 (folic acid sensitive), 10q 25 (BdUR sensitive), 11q23, 12q13, 16 p12, 16q22 (appeared only in the presence of Epstein-Barr virus [EBV] antigen), 17p12, and 20p11. Idiopathic (17q21.31) or fragile site (Xq27.3) mental retardation is known. The fragile sites are generally dominant and involve overlapping syndromes such as mental retardation, cancer susceptibility, and other symptoms. In the fragile X syndrome, the number of CGG repeats may run into hundreds whereas under normal conditions only about 30 repeats are found. In Friedreich's ataxia, GAA repeats are found in the introns of the frataxin gene. Five neurological disorders, spinal and bulbar muscular atrophy (Kennedy disease), spinocerebellar ataxia (olivopontocerebellar atrophy) Type 1, Huntington's chorea, dentatorubral-pallidoluysian atrophy, and Machado Joseph disease display poly CAG sequences within their genes and encode polyglutamine. Myotonic dystrophy is accompanied by CTG repeats in the untranslated last exon of a protein kinase gene. The recessive myoclonous epilepsy (human chromosome 21) contains multiple repeats at the 5' and 3' area of the promoter of the cystatin B gene. Fragile sites may occur upon incorporation of double minutes into the chromosome. Hypoxia favors the formation of fragile sites. Fragile sites seem to promote gene amplification and remodeling of the genome. In cancer, the most commonly amplified sites involve oncogenes ERBB, RAS, KRAS, MYC, and genes controlling the cell cycle. Fragile sites in humans and mice show rather high homology and conservation. In yeast, a pair of Ty elements are the preferred sites for double-strand breaks when DNA replication is compromised (Lemoine FJ et al 2005 Cell 120:587). When replication is inhibited by aphidicolin or condensation of the chromosome is promoted by calyculin (an inhibitor of phosphatases 1 and 2A), breaks may occur as a consequence of tension that may be

the source of cancer (Achkar EE et al 2005 Proc Natl Acad Sci USA 102:18069) (see Fig. F42).
 ▶X chromosome, ▶Kennedy disease, ▶glutamine-repeat diseases, ▶anticipation, ▶Huntington's chorea, ▶ataxia, ▶Machado-Joseph disease, ▶dentatorubral-pallidoluysian atrophy, ▶FMR1 mutation, ▶Myoclonous epilepsy, ▶human intelligence, ▶mental retardation, ▶trinucleotide repeats, ▶pre-mutation, ▶smoking, ▶double minutes, ▶hypoxia, ▶aphidicolin; Jin P, Warren ST 2000 Hum Mol Genet 9:901; Richards RI 2001 Trends Genet 17:339.

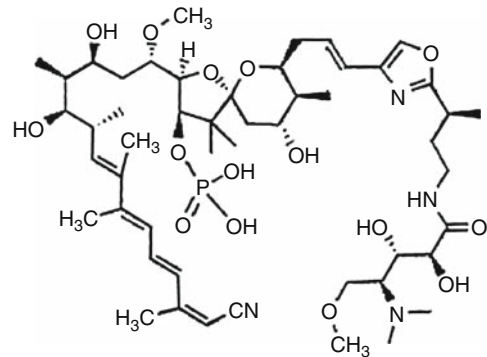


Figure F42. Calyculin

Fragile X Chromosome (FRAXA): FRAXA displays poorly stainable sites under the light microscope. These sites are liable to breakage and may result in mental retardation and cancer. The affected individuals have also shown macrocephaly (large head), prominent jaws, macroorchidism (enlarged testes), and a high-pitched funny voice. The condition is caused by folate deficiency leading to low levels of thymidylate. It involves amplification (up to >200) of a CGG repeat in the FMR-1 (fragile site mental retardation) gene (at Xq27.3, Martin-Bell syndrome) that occurs in human populations at a frequency of ~1/1,250–4,000 in males and 1/2,500–6,000 in females. Under normal conditions, there are 6–50 of the repeats and in fully expressed FRAXA the number of repeats exceeds 200, which may become methylated later. When the number of repeats is between 50 and 200 (unmethylated, pre-mutation), there is ~50% risk for full expression in the progeny of females but not in the immediate offspring of males. The CGG tracts, usually after 8–12 repeats, are interrupted by AGGs, generally by two but sometimes by three. The AGG interruptions are key elements in the instability of the CGG sequences. These sequences stall the translation of the FMR mRNA and this seems to be the major cause of mental retardation (Napierala M et al 2005 Nucleic Acids Res 33:451). The FMR protein complex apparently

modulates actin dynamics, which is a key process in the morphogenesis of dendritic spines and synaptic structures in the brain (Castets M et al 2005 Hum Mol Genet 14:835). The pre-mutational condition is not always revealed by the phenotype but can be detected by Southern blotting or by PCR. Pre-mutational individuals may display cognitive and/or behavioral deficits and other neurodegenerative disorders of adult carriers as well as premature ovarian failure (Hagerman PJ, Hagerman RJ 2004 Am J Hum Genet 74:805). Pre-mutational transcripts, which are not translated into protein, and are expressed in the neurons, can cause RNA-induced degeneration (Zarnescu JP et al 2003 Neuron 39:739). Methylation and deacetylation of histones H3 and H4 and gene silencing follow the amplification. Treatment of the fragile X cells with 5-aza-2'deoxyctidine restores transcription. In a *Drosophila* model, the fragile X syndrome was treated with metabotropic glutamate receptor antagonists or lithium and the cognitive defects and courtship behavior were restored (McBride SMJ et al 2005 Neuron 45:753). Fragile X syndrome results in the absence of the RNA-binding FMR protein. The fragile X mental retardation seems to be physiologically linked to the RNA-induced silencing complex of RNAi (Gaudy AA et al 2002 Genes Dev 16:2491). The FRAXA protein (FMRP) defects appear to interfere with the translation template and thus with translation. FMRP binds intramolecular G quartets and this may result in dysregulation of the mRNA. FMR1 promoter is not active in FMR1 mental retardation and histone organization is also affected (Gheldof N et al 2006 Proc Natl Acad Sci USA 103:12463).

Trichostatin restores acetylation of H4 but that of H3 only minimally, and would not result in transcription. The males are predominantly affected (80%); about 1/3 of the carrier females are also mentally retarded. Usually, 20% of the males with this X-chromosome are phenotypically normal and their daughters are also normal but their grandsons display the chromosome and the phenotype. Prenatal diagnosis is feasible. On folate-deficient cell culture media, the critical X-chromosome displays a constriction at the Xq27-p28 site. Other fragile sites may account for some of the less common forms of the disease. Fragile X knockout mice could be normalized to some extent by enriched environment and the treatment increased the AMPA receptor too (Restivo L et al 2005 Proc Natl Acad Sci USA 102:11557). Fragile X Tremor/Ataxia syndrome (FXTAS) is a disease with the occurrence of progressive tremors and a decline in cognitive functions. It seems to be caused by increasing level of CGG repeats in the FMR mRNA, a premutation. The age of onset of the disease is about 50 years. Initially, the patients are

diagnosed with Parkinson disease. It afflicts men more frequently than women. Mothers of fragile-X males are generally the carriers of FXTAS. The incidence in the general population is about 1/3,000 men. Postmortem studies indicate protein inclusions in the neurons and in astrocytes of the diseased individuals.

►fragile sites, ►mental retardation, ►Jacobsen syndrome, ►trinucleotide repeats, ►head/face/brain defects, ►histones, ►azacytidine, ►trichostatin, ►histone deacetylase, ►Southern blot, ►PCR, ►G quartet, ►AMPA, ►astrocyte; Tassone F et al 2000 Am J Hum Genet 66:6; Toledano-Alhadeff H et al 2001 Am J Hum Genet 69:351; Li Z et al 2001 Nucleic Acids Res 29:2276; Brown V et al 2001 Cell 107:477; Darnell JC et al 2001 Cell 107:489; Dombrowski C et al 2002 Hum Mol Genet 11:371; pathophysiology: Penagarikano O et al 2007 Annu Rev Genomics Hum Genet 8:109.

Fragile X Syndrome: ►fragile X chromosome

Fragment: A gap-free, contiguous tract of the genome without any alien insert.

Fragment Recovery Probability: The fragment recovery probability indicates the number of genomic fragments to be screened in order to recover a desirable one with a chosen probability. Probability = $1 - (1 - f)^n$, where f = the size of an average fragment divided by the size of the genome, n = the required number of fragments to be cloned. Example: $P = 0.95$, average fragment size 1×10^6 Da, and the size of the genome is 2.6×10^9 Da. Then: $n = \ln(1 - P)/\ln(1 - f) = \ln(0.05)/\ln[1 - (1000000/2600000000)] \approx 7787$, i.e., about 7,787 clones will include the wanted one by a probability of 95%. ►restriction enzymes, ►DNA library

Fragmentation Ladder: A collection of peptide fragments of different length but common terminus. These can be produced during mass spectrometric analyses. ►mass spectrometry

Fragmentin-1: A cytotoxic serine protease; it can trigger apoptosis in combination with perforin. ►perforin, ►apoptosis, ►ICE, ►granzyme, ►RNK1-1; Jans DA et al 1998 J Cell Sci 111:2645.

Fragmentin-2 (granzyme B): Cytotoxic T cells and natural killer lymphocytes destroy their targets with the cooperation of perforin and fragmentins. ►fragmentin-1, ►T cells; Jans DA et al 1996 J Biol Chem 271:30781.

Fragrances: Fragrances occur in all types of organisms and serve various adaptive purposes. Among animals, the pheromones are a means of communication and are used both as attractants and repellents. In plants, the fragrances may be the means of aiding



Figure F43. *Levandula*

pollination or dispersal but also as insect repellents. Chemically, the fragrances are diverse. Many plant fragrances are mono-terpenes such as citral, thymole (in thyme), linalol, and 1,8-cineol (in lavender). In the *Menthas* carvon, piperitones, menthone, menthole, and terpene rings represent the scents. In the *Eucalyptus* species, geraniols and cineols occur. In petunia plants, benzenoids convey the sweet fragrance emitted in the evenings and night. It is regulated by gene ODORANT1, a member of the MYB family. The same gene can activate also the promoter of 5-enol-pyruvateshikimate-3-phosphate synthase involved in flower pigment synthesis (Verdonk JC et al 2005 Plant Cell 17:1612). In the majority of the species of plants, the fragrances represent chemical complexes. Their inheritance is usually complex and frequently in the hybrids, the parental fragrances are hard to recover. By inserting the linalol synthase gene into snapdragon, bergamot scent was expressed. ▶pheromones, ▶olfactogenetics,

▶shikimic acid, ▶bergamottin, ▶taste; Vainstein A et al 2001 Plant Physiol 127:1383; evolution of flavors and scents: Gang DR 2005 Annu Rev Plant Biol 56:301; plant and fungal volatiles and physiological roles: Science 311:803–819 [2006].

Fraility: Fraility is the unobserved heterogeneity among the individuals in a population or family that affects the survival times and may seriously affect the relative risk between or among groups, especially under certain stress conditions.

Frameshift Mutation: Insertion or deletion of bases changing the reading frame of the code words, leading to new amino acid sequences from the site toward the carboxyl end of the polypeptide (see Fig. F44). If one or two bases are either lost or gained, the genetic message from that site is generally garbled, whereas if the loss or gain involves triplets there is a possibility to continue reading in a normal manner. Frameshift mutations are caused frequently by acridine dyes and cross-linking mutagens. The discovery of frameshift mutagens contributed to the recognition that the genetic code relies on nucleotide triplets. Frame shift mutation can be represented by the following folly:

Frameshift can also occur post-transcriptionally during translation and can produce two proteins with overlapping sequences by modification of tRNA at the E site in viruses and in eukaryotes (Bekaert M, Rousset J-P 2005 Mol Cell 17:61). ▶mutation, ▶base substitution, ▶deletion mutation, ▶duplication, ▶insertional mutation, ▶genetic code, ▶codon, ▶reading frame, ▶SNIPS, ▶acridine dye, ▶cross-linking; Crick FHC, Brenner SJ 1967 J Mol Biol 26:361; Farabaugh PJ 1996 Annu Rev Genet 30:507; Hoffmann GR et al 2001 Mutation Res 493:127.

Frameshift Suppressor: Generally, insertion(s) or deletion(s) of nucleotides that are capable of restoring the normal reading frame within the gene. ▶frameshift mutation, ▶suppressor mutation, ▶reading frame

Frameshift, Translational: ▶overlapping genes

Frameshifting, Ribosomal: The ribosome changes the frame of reading of the mRNA. In some cases, it is

| | |
|-------------------|--|
| Normal text | JOE AND BOB ATE THE BIG HOT DOG AND DID NOT SIP ICE TEA |
| Deletion & shift | JOE AND BOB ATE THE BIG HOT DOG AND IDN OTS IPI CET EA (lost D) |
| Addition restores | |
| meaning behind it | JOE AND BOB ATE THE BIG HOT DOG AND IDN OTS SIP ICE TEA (gained S) |

Figure F44. Frameshift mutation

called programmed frameshift because it is an efficient feature of the ribosome. Frameshifting occurs in viruses, prokaryotes and eukaryotes. It can shift upstream (−1) or downstream (+1) or it can even hop over a certain tract of nucleotides. As a consequence, the reading of the message may be normal in the upstream and downstream regions except the short tract involved in frameshifting. The protein product may appear as if it were based on two overlapping reading frames of the DNA. This mechanism can correct for frameshift mutations; its overall frequency has been estimated to 3×10^{-5} but in some gene its frequency may be much higher (Farabaugh PJ 1996 *Annu Rev Genet* 30:507). Pseudoknots may block the entry of the mRNA entrance to the ribosome and in the process, hinder the translocation of the mRNA and cause a deformation of the tRNA at the ribosomal P site. Also, it can affect the elongation factor eEF-2 (Namy O et al 2006 *Nature [Lond]* 441:244). ▶frameshift mutation, ▶eEF-2, ▶pseudoknot, ▶ribosome

Framework Amino Acids: The framework amino acids of antibodies secure the scaffolding of the hypervariable region but do not involve the CDR sequence. ▶antibody, ▶immunoglobulins, ▶CDR; Holmes MA et al 2001 *J Immunol* 167:296; Jung S et al 2001 *J Mol Biol* 309:701.

Framework Map: The framework map includes several (or only one) collection(s) of genes or DNA sequence groups (RFLP, microsatellites) that are used to position loci or sequences (STS) relative to these panels. ▶STS, ▶microsatellite, ▶RFLP, ▶radiation mapping, ▶skeletal map

Francisella tularensis: A bacterium has Gram-negative strains that cause tularemia, it is potentially a very dangerous agent of bioterrorism. It has two genes, *tolC* and *ftlC*, which determine multiple drug resistance. A sequence-defined, near-saturation transposon mutant library of *F. tularensis novicida*, a subspecies that causes a tularemia-like disease in rodents revealed 16,508 unique insertions, an average of >9 insertions per gene, which is a coverage nearly twice that of the greatest previously achieved for any bacterial species. Insertions were recovered in 84% (1,490) of the predicted genes. An analysis of genes lacking (or with few) insertions identified nearly 400 candidate essential genes, most of which are likely to be required for growth on rich medium and which represent potential therapeutic targets (Gallagher LA et al 2007 *Proc Natl Acad Sci USA* 104:1009). ▶bioterrorism, ▶biological weapons, ▶insertion elements; Gil H et al 2006 *Proc Natl Acad Sci USA* 103:12897; genomics: <http://bbrp.llnl.gov/bbrp/html/microbe.html>.

FRAP (TOR, RAFT1): ▶FK506

FRAP (fluorescence recovery after photo bleaching): In FRAP, cells are stained by fluorochromes and bleached locally by laser beams to study the organization of nuclei, diffusion of various proteins, and viscosity within the cell. ▶FRET, ▶FCS; Lippincott-Schwartz J et al 2001 *Nature Rev Mol Cell Biol* 2:444.

Fraser Syndrome (FRAS1, FS1, human chromosome 4q21): A heterogeneous malformation (4 loci in mouse) involving cryptophthalmos (eyeball is hidden by skin without differentiated eyelids), syndactyly, and kidney defects. The FS1 locus encodes mutations affecting the extracellular matrix by premature termination of this protein. The locus is homologous with *bl* in mice. The FS1 protein, the glutamate receptor interaction protein (GRIP1), and the cytoplasmic multi-PDZ scaffolding protein seem to jointly affect the Fraser symptoms (Takamiya K et al 2004 *Nature Genet* 36:172). ▶PDZ, ▶extracellular matrix, ▶cryptophthalmos; McGregor L et al 2003 *Nature Genet* 34:203.

Fraser-Like Syndrome (FREM2, 13q13.3): FREM2 syndrome is a heterogeneous disease and in mouse at least five loci exist (Jadeja S et al 2005 *Nature Genet* 37:520). ▶kidney disease, ▶genital anomaly syndromes, ▶hypertelorism, ▶Wilms tumor, ▶Denys-Drash syndrome

Frasier Syndrome (WT1, 11p13): A rare dominant/recessive male pseudohermaphroditism and progressive glomerulopathy displaying normal female external genitalia, streak gonads, and XY karyotype. It involves facial anomalies (hypertelorism), underdeveloped kidneys, fusion of the labia pudendi (the fleshy borders at the mons pubis of the external female genitalia), enlargement of the clitoris (the female erectile body [homologous to the penis of males]), defective fallopian tubes (connecting the ovaries with the uterus) and ovaries, etc. The affected individuals frequently develop gonadoblastoma. It is a mutation of the Wilms tumor gene. The WT1 gene encodes a zinc finger transcription factor. ▶kidney disease, ▶gonadoblastoma, ▶genital anomaly syndromes, ▶hypertelorism, ▶Wilms tumor, ▶Denys-Drash syndrome; Zugor V et al 2006 *Aktuelle Urol* 37 (1):64; Niaudet P and Gubler MC 2006 *Pediatr Nephrol* 21:1653.

Frataxin: ▶Friedreich ataxia

Fraternal: Fraternal refers to brothers; it is also used to describe dizygotic twins as fraternal twins, even when

one or both of the twins are girls (in the latter case, the biologically correct usage should be “sororal twins” but it is not used). ▶twins, ▶twinning

Fratricide (allolysis): Bacteria can evolve by taking up foreign DNA by a process of transformation. The DNA uptake is regulated by a quorum-sensing pathway and becomes competent for DNA internalization. Before reaching this state, the cells release a competence-stimulating peptide (CSP) into the environment. Genes of the *Com* operon (*ComDE*) sense CSP and further stimulate its expression. About two-dozen genes of the more than 100 *Com* are involved directly in the uptake. After secretion of CSP, the competent cells release the product of the *cibC* gene, *CibAB* (competence-induced bacteriocin). This bacteriocin lyses non-competent cells by the production of a hemolytic factor Ply. Ply also signals to the host through Toll-like receptor 4. The lysis of the fraternal cells apparently improves the fitness of the resistant cells by cannibalizing the contents of the lysed cells and making genetic transformation easier. Such fratricide occurs in *Streptococcus pneumoniae* and *Bacillus subtilis* (Guiral S et al 2005 Proc Natl Acad Sci USA 102:8710). ▶quorum, ▶sensing, ▶lysis, ▶bacteriocin, ▶transformation genetic, ▶competence of bacteria, ▶*Streptococcus pneumoniae*, ▶*Bacillus subtilis*

FRAX: Fragile X chromosome. ▶fragile X syndrome

FRAXA: ▶fragile X syndrome

FRAXE: A fragile X syndrome associated with the long arm of the human X chromosome based expansion of CCG repeat tracts and hypermethylation of a CpG island, resulting in a rare form of mental retardation. ▶trinucleotide repeats

Frazzled (*fra*, chromosome 2 of *Drosophila*): A netrin receptor expressed all over the embryo and one that distributes netrin in a pattern different from the place of expression of netrin. ▶netrin

Freckles: Freckles are ephelides, which are small, pigmented spots occurring usually on young, fair-skinned redheads or blonds and usually show up less conspicuously later. Solar lentigines are due to spotty photo-damage and increase in frequency with age (age spots). Stimulation of the melanocortin-1 receptor (MC1R, 16q24.3) by the α -melanocyte-stimulating hormone and pro-opiomelanocortin peptides may lead to increased synthesis of the black eumelanin instead of the red pheomelanin. The latter may promote the synthesis of free radicals in response to ultraviolet exposure and increase the risk of melanoma. There is substantial variation among MC1R alleles and susceptibility to melanoma.

Freckles may be due also to other several genes. ▶lentigine, ▶melanocyte, ▶melanocortin, ▶opiomelanocortin, ▶melanoma, ▶xeroderma pigmentosum; Bastiaens M et al 2001 Hum Mol Genet 10:1701.

Free Energy (G): The energy that can be obtained from a system for other purposes. Metabolism can accumulate energy by synthesis of ATP, which in turn drives many cellular processes. ▶entropy, ▶enthalpy, ▶ATP

Free Radical: An atom or group of atoms with an unpaired electron, and is therefore extremely reactive. Free radicals may be produced by exposure of wet tissues to ionizing radiation and thus leading to physiological and genetic damage of the cells. ▶superoxide, ▶ROS

Freeman-Sheldon Syndrome (arthrogryposis): is characterized by deformities (contractures) of the limbs, face, and other structures. Mutations (MYH3, 17p13.1) in the embryonic myosin heavy chain can account for it (Toydemir RM et al 2006 Nature Genet 38:561). One form has been mapped to human chromosome 5.5-pter-15p1. Distal arthrogryposis (Sheldon-Hall syndrome) displays clinical symptoms of finger and toe abnormalities (clenched fist, camptodactyly, etc) caused by defects in troponin, and is encoded at 11p15.5 or by myosin heavy chain 3 (MYH3). ▶arthrogryposis, ▶camptodactyly, ▶troponin

Freemartin: A somewhat masculinized sterile bovine (cattle, sheep, goat, pig, etc.) female born as twin with a male. The sterility is attributed to the circulation of blood containing male-specific antigens and hormones (see Fig. F45). Freemartins do not occur in humans, although women treated with male hormones to prevent miscarriage have been reported to



Figure F45. Somewhat masculinized freemartin cow

deliver female babies that after puberty might have shown some secondary virile characteristics. Hormonal interactions between opposite-sex human fetuses known to influence female morphology and behavior can also have negative effects on daughter fecundity and, hence, maternal fitness (Lumma A et al 2007 Proc Natl Acad Sci USA 104:10915).

The exact origin of the term is unclear. In old English, a spayed heifer (neutered bovine female) was called martin. Also, St. Martin has been regarded as a protector of rogues (off-type creatures, deviants). In Scottish, ferry-cow means a cow [temporarily] barren. ►hormones in sex determination, ►puberty, ►spaying; Ennis S et al 1999 Res Vet Sci 67:111; Kobayashi J et al 1998 Mol Reprod Dev 51(4):390; Vigier B et al 1988 Reprod Nutr Dev 28(4B):1113.

Freeze Drying (lyophilization): A procedure for the preservation of biological specimens, bacteria, and enzymes that involves freezing at about -50°C and dehydrating under high vacuum in a specially constructed equipment. The preserved samples are usually sealed in glass under vacuum for further storage. Generally, the activity of the enzymes is well maintained and the bacterial cells can be revived even after years of storage. Animal sperm may be preserved this way, stored at room temperature and used for fertilization by intracytoplasmic injection into eggs.

Freeze Etching: Freeze etching is different from freeze fracture inasmuch as it allows the electronmicroscopic study of membrane surfaces rather than internal structures. The specimens are frozen in liquid nitrogen, the material is cracked, and the water is removed by sublimation in a freeze dryer. The etched parts are shadowed and viewed in the electron microscope. An improved version of this procedure involves *rapid freezing* with a copper block (-269°C , liquid helium) after being slammed against it and then lyophilized. This way the internal cell parts and filaments can be well visualized. ►freeze drying, ►electronmicroscopy, ►membranes

Freeze Fracture: A technique for preparing membrane-containing specimens for electronmicroscopic examinations. The specimen is frozen in liquid nitrogen under the protection of antifreeze (cryoprotectant) to prevent ice crystal formation and concomitant distortion. After cracking the frozen blocks, some surfaces of the broken pieces expose the interior of cellular membrane bilayers. The membrane faces are then shadowed with platinum, and after the organic material is removed, it can be viewed by electronmicroscopy. ►electronmicroscopy, ►shadowing, ►membranes

French Pressure Cell: Used for breaking up cell suspensions in combination with a hydraulic press at $\sim 20,000$ lb/inch pressure.

Frequency-Dependent Selection: ►selection types, ►apostatic selection

Frequency Distribution: Representation of a population in classes according to the frequency of individuals in each class. ►normal distribution, ►Poisson distribution, ►negative binomial

Frequentist: A statistical test of the likelihood of a hypothesis by weighting the number of supporting hypotheses against all hypotheses tested. (See Schimek MG 2004 Methods Inf Med 43:439).

FRET (fluorescent resonance energy transfer): A fluorophore donor molecule, which has an absorption maximum at a shorter wavelength, can be excited and then can transfer the energy of an adsorbed photon non-radioactively to an acceptor molecule which has an excitation maximum at a longer wavelength. The distance over which FRET can be measured is about 40 to 100 Å, and in general it depends on the 1/6 power of the distance but it is modified by several factors. This technology enables visual monitoring of protein interactions. ►fluorochromes, ►DABCYL acid, ►two-hybrid system, ►FRAP, ►FCS, ►nanotechnology; Periasamy A, Day RN 1999 Methods Cell Biol 58:293; Jares-Erijman EA, Jovin TM 2003 Nature Biotechnol 21:1387.

Freund Adjuvant: is a water—light-weight mineral oil emulsion. An antigen is added into water phase and the oil phase contains an emulsifier. Sometimes dry, dead *Mycobacterium butyricum* is also added to the oil. This preparation boosts the immune reaction in case of weak or small amounts of the antigen. ►antigen

Friedreich Ataxia (FRDA): FRDA, along with optic nerve atrophy and deafness, is an autosomal dominant disease at 6p23. An autosomal recessive form (9q13) is a rare ($\sim 2 \times 10^{-5}$) brain-spinal chord degenerative malfunction, characterized by hypoaffective knee and ankle jerks, poor coordination of the limbs, spasms, etc. The heterozygosity for the recessive form is as high as $\sim 10^{-2}$. Most of the cases are point mutation in the gene encoding the 210 amino acid frataxin iron-binding protein, but this condition frequently involves GAA repeats in the first exon/introns. The normal range of the FRDA repeats is 7–22 but in disease this increases to 200–900 or more. The increase of the trinucleotide repeats interferes with transcription. Some special polyamides may increase transcription by altering DNA conformation of genes with GAA repeats or by chromatin opening (Burnett R et al 2006 Proc Natl

Acad Sci USA 103:11497). The DNA forms a triplex structure, which leads also to increased mutability. The defect is concerned with a phosphatidylinositol-4-phosphate kinase and mitochondrial iron homeostasis. Frataxin may be associated with insulin resistant diabetes. The critical protein has been located to the mitochondria where it increases the concentration of iron and decreases respiration; it is an iron protein chaperone and protects aconitase (Bulteau A-L et al 2004 Science 305:242). The accumulated iron reacts with H_2O_2 resulting in lesions to proteins, lipids and mtDNA. ▶ **fragile sites**, ▶ **ataxia telangiectasia**, ▶ **epilepsy**, ▶ **phosphatidylinositol**, ▶ **trinucleotide repeats**, ▶ **diabetes**, ▶ **AVED**, ▶ **aconitase**; Bradley JL et al 2000 Hum Mol Genet 9:275; Patel PI, Isaya G 2001 Amer J Hum Genet 69:15; Salkamoto N et al 2001 J Biol Chem 276:27171; Puccio H, Koenig M 2002 Current Op Genet Dev 12:272.

Friend Murine Leukemia: Friend Murine leukemia is caused by the replication competent helper virus, F-MuLV (Friend murine leukemia RNA virus) and the replication-defective spleen focus-forming virus (SFFV). Pathogenicity depends on the chimeric SFFV envelope protein, gp55 in the presence of the erythropoietin receptor. Susceptibility is controlled by several Fv (Friend virus) loci. ▶ **FMS**, ▶ **oncogene**, ▶ **leukemias**

Frizzled: The *frizzled* gene determines the orientation of the hair follicles and its mutation leads to waves, whorls, and tufts, each comprising many hundreds of hairs in mice. ▶ **polarity**, ▶ **Wingless**; Strutt DI 2000 Mol Cell 7:367.

Frog: *Rana pipiens* $2n = 26$, *Rana temporaria* $2n = 26$. *R. esculenta* and *R. catesbeiana* are considered food delicacies, but some toads secrete poisonous or irritating substances as a defense. ▶ **toad**; <http://vize222.zo.utexas.edu/frog.html>.

Frond: A leaf-like thallus of lichens or leaves of ferns.

Frontonasal Dysplasia: Sporadic, multifactorial, or dominant head lesions (cranium bifidum), hypertelorism; it is frequently associated with other syndromes. ▶ **cranium bifidum**, ▶ **hypertelorism**

Frontotemporal Dementia and Parkinsonism: ▶ **Pick disease**

FRP: A human phosphatidylinositol kinase. ▶ **PIK**

FRS: Fos-regulating kinase. ▶ **FOS**

Fructanes: Fructose polymers in plants. ▶ **inulin**

fru (fruitless): *Drosophila* mutation determining courtship behavior of males. It is not expressed in females. It is involved with male-specific neural circuitry in

the brain (Kimura K-I et al 2005 Nature [Lond] 438:229). ▶ **sex determination**, ▶ **pheromones**

Fructose: A monoketo-hexose, present in the disaccharide saccharose. It plays key roles in metabolism through phosphorylated derivatives (fructose-1-phosphate, fructose-6-phosphate, fructose-1,6-bisphosphate, etc.). Fructose utilization is not impaired in diabetes (see Fig. F46). Fructose is about twice as sweet-tasting as glucose and its use may reduce the caloric intake. The “corn sweeteners” contain fructose, industrially produced from starch. Fructose and fructose-containing food and beverages, especially at acid pH and by heating or just by long storage may liberate furans, furaldehyde, and levulinic acid that may be toxic. The Fig. F47 displays the breakdown products of fructose, autoclaved for 20 minutes; HMF = hydroxymethyl furfural, HAF = hydroxyacetyl furan. Furfural is actually an insecticide. Levulinic acid LD₅₀ intraperitoneally is 450 mg/kg for mouse. ▶ **fructose intolerance**, ▶ **fructosuria**, ▶ **aspartame**, ▶ **saccharin**, ▶ **diabesity**; Rédei GP 1974 Annals Bot 38:287; carbohydrate pyrolysis product toxicity detection: Glatt H et al 2005 Mutation Res 580:41.

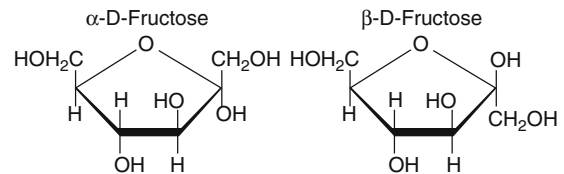


Figure F46. Fructose

Fructose-2,6-Bisphosphatase: The bisphosphatase breaks down fructose-2,6-bisphosphate. It is a tissue-specific bifunctional enzyme also possessing 6-phosphofructo-2-kinase activity. ▶ **phosphofructokinase**; Lee Y-H et al 2003 J Biol Chem 278:523.

Fructose Intolerance (hereditary fructose intolerance): A human chromosome 9q22.3 recessive disorder caused by a deficiency of the enzyme fructose-1-phosphate aldolase. The patients begin to sweat, tremble, feel dizzy and nauseous 20 minutes after ingesting fructose. The immediate clinical findings are fructosuria, hypophosphatemia (abnormally low amounts of phosphate in the blood), aminoaciduria (amino acids in urine), fructosuria (moderate amounts of fructose in urine), hyperbilirubinemia (excess of bilirubin [red bile pigment] in blood), etc. The chronic symptoms include jaundice, enlargement of the liver (hepatomegaly), vomiting, dehydration, edema (excessive fluid in the tissues), ascites (fluids in the abdominal cavity), seizures, fructose accumulation in the urine (fructosuria) and in the blood

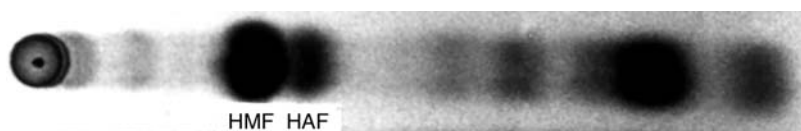


Figure F47. Heat-induced degradation products of fructose

(fructosemia), cirrhosis (destruction of cells and increase of connective tissues) in the liver, etc. The patients may be quite normal on a diet low on fruits, honey, or fructose-containing sweeteners, but consuming fructose may make them sick and infants may even die if the feeding formula contains fructose. The breakdown products (mainly furfural) of autoclaving cause the apparent toxic effect of fructose in plant cell cultures. Bacteria deficient in the phosphoenolpyruvate/glycose phosphotransferase system are unable to utilize fructose. ▶[fructosuria](#), ▶[aldolase](#); Santamaria R et al 2001 *Biochem J* 359(pt3):823.

Fructosuria (essential fructosuria, 2p23.3-p23.2): A rare autosomal disorder (prevalence is about 8×10^{-6}). The biochemical basis of this non-debilitating anomaly is a deficiency of fructokinase.

Fruit: The matured ovary of plants (may include also other parts of the flower); with the exception of the seed within, it is genetically maternal tissue. ▶[flower differentiation](#), ▶[gametogenesis in plants](#)

Fruit Fly: *Drosophila melanogaster* $2n = 8$; *D. ananassae* $2n = 10$; *D. melanica* $2n = 10$; *D. obscura* $2n = 10$; *D. pseudoobscura* $2n = 10$; *D. virilis* $2n = 10$; *D. willistonii* $2n = 6$. ▶[Drosophila](#), ▶[karyotype evolution](#)

Fruit Ripening: The consequence of changes in the composition and softening of the cell walls of fruits. The increase in respiration involves an increase in the production of the plant hormone ethylene, which affects the expression of a number of genes, notably polygalacturonase (PG), 1-aminocyclopropane 1-carboxylic acid synthase (ACCS), and 1-amino cyclopropane 1-carboxylic acid oxidase (ACCO; tomato gene pTOM13). By transforming tomatoes with a single PG antisense construct, PG activity could be reduced to 1%. However, for a more efficient control of ripening, the amount of the other enzymes should also be reduced to decrease ripening that is under polygenic control. For commercially effective storage without softening ripe-harvested tomato fruits, the use of the antisense RNA of the LE-ACS2 and LE-ACS4 loci was required. The berries stored at 20°C remained firm for months but could mature fully, when exposed either to ethylene (C_2H_4) or its analog (C_3H_6). The fruits so handled were practically indistinguishable by color, scent, and

consistency from vine-ripened fresh fruits. ▶[anti-sense technology](#), ▶[plant hormones](#), ▶[ethylene](#); Ferrándiz C et al 1999 *Annu Rev Biochem* 68:321; Giovannoni J 2001 *Annu Rev Plant Physiol Plant Mol Biol* 52:725.

Fruiting Body: The collective name of fungal organs (perithecium, cleistothecium, apothecium, locule) containing the haploid reproductive spores. (See mentioned items).

Frustration: Interference by the phagocytotic activity of opsonins. ▶[opsonins](#)

Frye Test: A legal ruling concerning admissible scientific evidence to the court. According to the *Frye v. United States* (D.C. Cir. [1923] 293 Fed. 1013) ruling, new scientific methods must be generally accepted by the scientific community before evidence from such methods is admissible in the courts. This became a highly controversial issue because “general acceptance” is difficult to define. Criminal defense lawyers frequently argue that electrophoretic pattern of proteins and DNA fingerprints, and their statistical evaluation should not be presented to the jury because some scientists may dissent about certain aspects of the data. ▶[forensic genetics](#), ▶[DNA fingerprinting](#), ▶[ceiling principle](#), ▶[Daubert rule](#)

FrzE: *Myxococcus xanthus* kinase affects FrzE and FrzG proteins regulating bacterial motility and development. (See McBride MJ 2001 *Annu Rev Microbiol* 55:49).

FSH (follicle stimulating hormone or follitropin, 2p21-p16): FSH controls ovarian follicles, estrogen secretion, menstrual cycles, spermatogenesis, and D2 cyclin. Ovarian and testicular tumors have high levels of cyclin D mRNA. FSH deficient males have small testes, yet fertile to a variable degree. The 54-kb gene has 10 exons and encodes the 695-amino acid protein. ▶[animal hormone](#), ▶[follicle](#), ▶[ovary](#), ▶[menstruation](#), ▶[gametogenesis](#), ▶[differentiation](#), ▶[NGFI-A](#), ▶[cell cycle](#), ▶[gonadal dysgenesis](#); Driancourt MA 2001 *Theriogenology* 55:1211; FSH structure: Fan QR, Hendrickson WA 2005 *Nature [Lond]* 433:269.

F_{ST}: An index for population diversity. For human autosomal loci it is ~15–20%, for mtDNA ~19%,

and for the Y chromosome ~65%. The complement of these percents indicates approximately the variations shared by any random-picked population and the rest of the human race. F_{ST} for diploids = $1/(1 + 4Nv)$, and for Y and mitochondrial [haploid] systems $F_{ST} = 1/(1 + Nv)$, where N is the effective population size (N_e), v = the sum of migration and mutation (or more precisely $m + \mu - m\mu = v$). ▶Eve foremother, ▶Y chromosome, ▶mutation rate, ▶migration, ▶effective population size, ▶diversity, ▶coalescent, ▶ G_{ST} , ▶ R_{ST} ; Weir BS, Hill WG 2002 Annu Rev Genet 36:721.

F

F-Statistics: ▶F

F-Table: ▶F distribution

FTDP-17: ▶Pick disease, ▶tau

F-Test: ▶F distribution

FTICR (Fourier-transformed ion cyclotron resonance mass spectrometer): FTICR is used for the determination of the molecular masses of hundreds of proteins in one run (see Fig. F48). ▶MALDI; Schmid DG et al 2000–2001 Biotechnol Bioeng M71:149.

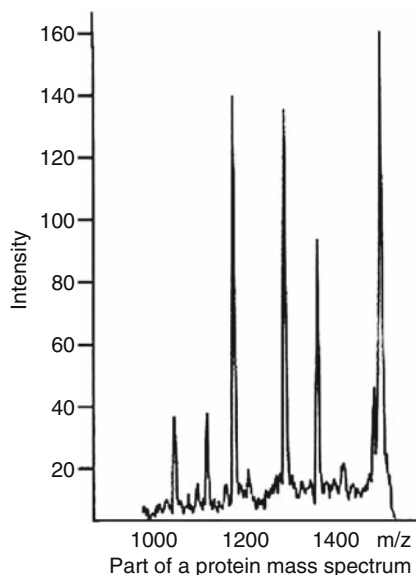


Figure F48. Part of protein mass spectrum

FT-IR (Fourier transform infrared spectroscopy): A very sensitive method for the detection of intramolecular changes as function of time is converted into function of angular frequencies. ▶Raman spectroscopy, ▶tumorigenesis, ▶electron density map

FTMS (Fourier transform mass spectrometry): FTMS is suitable for the identification of the mass of intact proteins. This type of analysis is particularly useful because it can obviate bias in mass due to alterations during the purification, e.g., oxidation of methionine

residues. ▶proteomics; Jensen PK et al 1999 Anal Chem 71:2076.

FTP (file transfer protocol): Ftp enables the connection between computers and Internet.

FtsK: FtsK mediates coupling bacterial chromosome segregation with cell division.

FtsY: Prokaryotic transport chaperone protein, related to mammalian SRP54. The related bacterial Ffh is ribonucleoprotein, binding to FtsY in a GTP-dependent manner. ▶SRP, ▶GTP, ▶protein sorting; Millman JS et al 2001 J Biol Chem 276:25982.

FtsZ: ▶tubulins

Fuchsia: The ornamental plant which Gregor Mendel was examining while being photographed in 1862 with his monasterial colleagues (see Fig. F49). This plant has 2n chromosome numbers 22, 56, 66, and 77. It was lucky for Mendel that he did not experiment further with this erratic material, which would not have permitted the type of studies he conducted with the stable pea.



Figure F49. This ornamental species has large number of variations in flower shape and color and probably that fact attracted Mendel's interest

Fuchsin (triaminotrimethylmethane): A red cytological stain.

Fucose: A 6-deoxy sugar. It is present in several antigenic glycoproteins and may be associated with several immunoglobulins and present in plant cell walls (see Fig. F50).

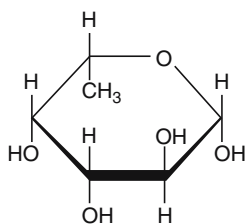


Figure F50. L-fucose

Fucosidase (FUCA2, 6q25-qter): A regulator of α -fucosidase in plasma and fibroblasts. It hydrolyzes fucose linkages in glycoproteins and glycosphingolipids. ▶sphingolipids

Fucosidosis (FUCA1): A recessive, human chromosome 1p34 (and a pseudogene at 2q31) defect of α -fucosidase, causing neurodegeneration and angiokeratoma, although some forms are less detrimental. It is a lysosomal storage disease. The accumulation of fucose is detectable in the amniotic fluid. ▶amniocentesis, ▶angiokeratoma, ▶lysosomal storage diseases

Fucosyltransferase (FUT2, FUT1, 19q13.3): In fucosyltransferase, deficiency, the H blood antigen is absent. There are at least seven other FUT genes in the human genome, scattered among the chromosomes. O-fucosyltransferase 1 also acts as a chaperone for the folding of the Notch receptor (Okajima T et al 2005 Science 307:1599). ▶Bombay blood group, ▶ABH antigen, ▶Secretor, ▶CD15, ▶chaperone, ▶Notch

Fugu rubripes: ▶pufferfish

Fukuyama Muscular Dystrophy: ▶muscular dystrophy

Full Mutation: In trinucleotide repeats the entire length of the repeat is altered rather than a part of it. ▶trinucleotide repeats, ▶FMR1

Full Sib: Brothers/sisters with identical mother and father. ▶sib

Fumagillin (C₂₆H₃₄O₇): Fungal antibiotic and inhibitor of angiogenesis. It inhibits methionine aminopeptidase-2, a metalloenzyme cleaving methionine from the N end of proteins. ▶angiogenesis; Owa T et al 2001 Curr Med Chem 8:1487.

Fumarate Hydratase (fumarase, FH): FH is encoded in human chromosome 1q42.1, but both cytoplasmic and mitochondrial forms of the enzyme exist; probably due to the alternative processing of the transcript. Its deficiency results in mental and physical impairment. ▶mitochondrial diseases in

humans, ▶leiomyoma; Sass E et al 2001 J Biol Chem 276:46111.

FUN GENES (functions unknown genes): ▶orphan genes, ▶orphan receptor

Funaria hygrometrica (Bryophyte): The chromosome numbers of bryophytes vary, 14, 28, 56.

Functional Cloning: In the first step of functional cloning, the protein encoded by the gene is isolated, its amino acid sequence is then determined, and on that basis synthetic probes are generated. With the aid of the probe the gene is fished out from a DNA library. ▶gene isolation, ▶synthetic probe

Functional Genomics: Functional genomics studies the function of all open reading frames revealed by DNA genome-wide sequencing. For this purpose, transposable elements, chemical and physical mutagenesis, and knockouts are being used. All techniques are currently not applicable to all organisms. In *Drosophila* insertional mutations (using P elements) has been accomplished for >25% of the vital genes by 1999 and ~85% is expected. ▶genomics, ▶hybrid dysgenesis, ▶insertional mutation, ▶knockout; Spradling AC et al 1999 Genetics 153:135.

Functional Networks: Functional networks display functional relations among several (many) proteins based on *rosetta stone sequences*, *phylogenetic profiles*, and if applicable, *gene neighbor methods* (see Fig. F51). Eventually, the over-simplified relations of protein ① to other numbered proteins can be represented as shown by the chart. ▶networks

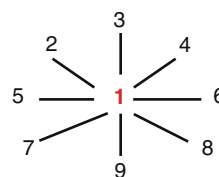


Figure F51. Functional network

Functional Redundancy: According to this hypothesis, relevant functions may be carried out by gene products with highly similar activity but the genes being members of separate regulatory circuits would make the system more flexible than a combinatorial control of development. ▶combinatorial gene control

Functionality of Mutagens: The number of chemical groups reacting in mutagenesis. ▶nitrogen mustard, ▶sulfur mustard

Function-Valued Trait: A function-valued trait can be best described by a function of some variable(s), e.g., by the phenotypic changes during aging.

Fundamental Theorem of Natural Selection: ►natural selection

Fundamentalism: The religious or ideological belief that regard as the only absolute right what is written in holy books (Bible, Koran), or in the works of the basic ideologues (e.g., Marx, Engels, Lenin). Accordingly, only creationism explains correctly the genesis of life, provides specific guidelines to human ethics and ideology or political or economical theory, respectively. ►creationism, ►lysenkoism; Bouchard TJ et al 1999 Twin Res 2(2):88.

Fundus Flavimaculatus: ►ABC transporters

Fungal Diseases in Humans: Fungal diseases can occur due to primary infectious agents or opportunistic fungi. Infection and pathogenicity is affected by a number of factors of the pathogen and the host. Fungal infections became more relevant in humans due to the spread of acquired immunodeficiency. Dectin-1, a mammalian ITAM-containing, non-Toll-like receptor, recognizes fungal zymosan, a cell wall component containing β -glucans, α -mannan, and mannoproteins. Card9 is a key transducer of Dectin-1 signaling and controls innate anti-fungal immunity. An alternative receptor is Carma1 (Narayan P et al 2006 Mol Cell Biol 26:2337). Both Dectin-1 and Carma1 activate the NF- κ B pathway to the T cell receptor with coupling to Bcl10 and MALT1 proteins (Gross O et al 2006 Nature [Lond] 442:651). ►acquired immunodeficiency, ►CARD, ►ITAM, ►Toll, ►NF- κ B, ►BCL, ►MALT, ►glucan, ►mannan, ►innate immunity; van Burik J-AH, Magee PT 2001 Annu Rev Microbiol 55:743; Hull CM, Heitman J 2002 Annu Rev Genet 36:557.

Fungal Incompatibility: Fungal incompatibility is based on the interaction of the products of non-allelic genes, and thus prevents self-fertilization, similar to the outcome of S alleles of plants. In *Ustilago maydis* (a pathogen of maize), stable dikaryons can be formed only between different mating type alleles of a multiallelic *b* locus recognized by pheromones. The same *b* locus is also responsible for plant pathogenicity. The *bE* and *bW* alleles encode different homeodomain proteins. The E variants and W variants differ primarily in the N-terminal amino acids. Activity requires that the E and W allele products dimerize and this can happen only in appropriate allelic combinations; the majority of the over 300 combinations are active. In other fungi several multiallelic gene pairs coding for interacting homeodomains have been discovered; in yeast only two

mating types *a* and α exist. *Vegetative incompatibility* prevents the fusion of hyphae in case of *het* alleles or alleles carrying non-allelic *het* genes in their nuclei. ►fungal life cycle, ►incompatibility vegetative, ►dikaryon, ►heterokaryon incompatibility; Glass NL et al 2000 Annu Rev Genet 34:165.

Fungal Life Cycles: Fungal life cycles display an enormous variety of specializations in the various taxonomic groups and cannot be represented here (see Fig. F52). The general scheme is, however, relatively simple and shared by all fungi. ►hypha

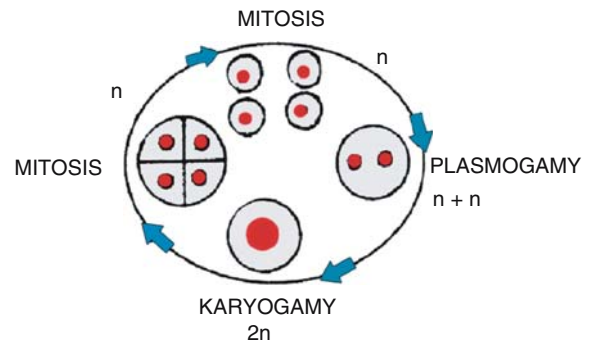


Figure F52. Fungal life cycle. The approximately 2,000 genera of fungi have a variety of modes of reproductions that share some basic similarities. Between 9 o'clock and 3 o'clock are the haploid phases (*n*). Haploid cells fuse at 3 o'clock (plasmogamy) but the nuclei are still separate and a dikaryon (*n* + *n*) is formed. In a following step, at 6 o'clock nuclear fusion takes place (karyogamy) and the cell becomes diploid (*2n*). This is followed by meiosis (9 o'clock) yielding four haploid sexual spores that may divide again by mitosis (12 o'clock) before the spores are released. These sexual spores may differentiate and the cycle is reinitiated

Fungi Imperfecti: Fungi without known sexual reproduction mechanism. (See Taylor JW et al 1999 Annu Rev Phytopath 37:197).

Fungus (plural fungi): Eukaryotic thallophytes, yet separate subkingdom from plants and bacteria. Fungi include many saprophytic, parasitic, and pathogenic species of enormous variety in structure and function. Fungal genetics has provided and is providing understanding for basic genetic phenomena such as recombination, biochemical pathways, cell cycle, etc. Yeasts and other ascomycetes are among the most important tools of modern genetic research. (See early fungal phylogeny: James TY et al 2006 Nature [Lond] 443:818; genomes: <http://www.fgsc.net/outlink.html>).

Funiculus: A vascular stalk of the plant ovule (see arrow); a cord-like structure, and in animals also including the umbilical cord, etc. (see Fig. F53).

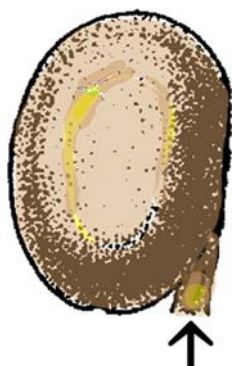


Figure F53. Funiculus

Fur Color: The color of the fur of animals is determined by the melanin pigments formed in the melanocytes and the migration of the melanoblasts. The various genes involved then modify, reduce, or intensify pigmentation. In addition, the actual visible color depends on the dorso-ventral distribution of the pheomelanin and eumelanin pigments. Superimposed on these are species- or genotype-specific striping, spotting, lyonization, temperature-sensitivity, etc. ▶melanin, ▶pigmentation of animals, ▶hair color, ▶agouti; <http://www.informatics.jax.org/wksilvers/>.

Furanocoumarins: ▶bergamottin, ▶grapefruit

Furin: A Golgi-associated proteinase; it may activate stromelysin and activation of virulence factors of pathogens. Furin has an important role in antigen processing for presentation to the cytotoxic T lymphocytes. Furin processes the BRI-L and BRI-D fibrillogenic precursors of dementia peptides. A furin-like protein mediates the cleavage of Notch receptor and furin convertase defect leads to hypertension. ▶Golgi, ▶dementia, ▶stromelysin, ▶T cell, ▶antigen processing and presentation, ▶Notch, ▶anthrax; Gil-Torregosa BC et al 1998 J Exp Med 188:1105; Bassi DE et al 2001 Proc Natl Acad Sci USA 98:10326; Thomas G 2002 Nature Rev Mol Cell Biol 3:753.

FUS3: A protein kinase of the MAPK family. Indirectly, it arrests yeast cells in G1 prior to mating and it down-regulates Ty transposition. *Fus*^{-/-} mutants of mice develop B cell defects, chromosomal instability, and perinatal death. ▶signal transduction, ▶MAPK, ▶STE, ▶Kss, ▶Ty; Cherkasova V, Elion EA 2001 Curr Genet 40:13.

Fusarium species: Plant pathogenic fungi. *F. oxysporum* can also cause skin and eye infection in animals and humans. They form septate hyphae, chlamydospores, and macroconidia. (See *Fusarium graminearum* database: <http://mips.gsf.de/genre/proj/fusarium/>).

Fushi tarazu (ftz): *Drosophila* mutation of the pair-rule class; every other body segment is missing at the blastoderm stage. The photograph (courtesy of Dr. Y. Nishida et al. 1999 Genetics 153:763) displays the seven wild type segments encoded by the gene (see Fig. F54). ▶morphogenesis in *Drosophila*, ▶SF-1, ▶pair rule genes

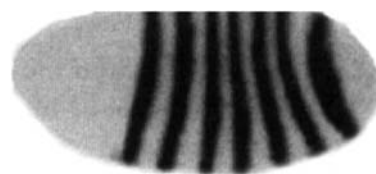


Figure F54. *Fushi tarazu*

Fusicoccin: The toxin of the fungus *Fusicoccus amygdali*; an activator of plasma membrane H⁺ ATP-ases. It causes H⁺ secretion, and K⁺ influx into guard cells and thus opening of stomata of plants. (Meinhard M, Schnabl H 2001 Plant Sci 160:635)

Fusidic Acid (C₃₁H₄₈O₆): An antibiotic (ramycin) isolated from *Fusidium coccineum*. This compound mimics the effect of the *rel*⁻ (relaxed control) mutations and also permits the synthesis of guanosine polyphosphates (ppGpp, pppGpp), ribosomal RNA, and ribosomal protein. Tetracycline has a similar effect. ▶antibiotics, ▶stringent control, ▶relaxed control; Duvold T et al 2001 J Med Chem 44:3125.

Fusigenic Liposome: The fusigenic liposomes are similar to the liposome vectors, except they are engineered to carry on their surface hemagglutinating neuroaminidase (HNA) and a fusion protein. The hemagglutinating Japanese virus (HVJ) and the Sendai virus produce these proteins and make them capable of fusing with the cell membrane at neutral pH. HNA is required for binding to cell receptors containing sialoglycoproteins or sialolipids. The fusion protein is in an inactive form until it is hydrolyzed to two polypeptides, F1 and F2; F1 interacts with cholesterol to facilitate fusion, and then the DNA carried by the liposome is delivered into the cell. ▶liposome, ▶sialic acid, ▶Sendai virus, ▶hemagglutinin, ▶cholesterol, ▶cytofectin; Kono K et al 2001 Gene Ther 8:5.

Fusin (LESTR, HUMSTR, CXCR4, stromal-derived factor [SDF1]): A co-receptor of the CD4 antigens

required for fusion with the membrane and entry of a virus (HIV) into a cell. It is a heterotrimeric GTP-binding protein. ▶CD4, ▶CD8, ▶HIV, ▶acquired immunodeficiency syndrome, ▶RANTES, ▶MIP; Dragic T 2001 J Gen Virol 82(p8):1807.

Fusion of Somatic Cells: (see Fig. F55) ▶cell fusion

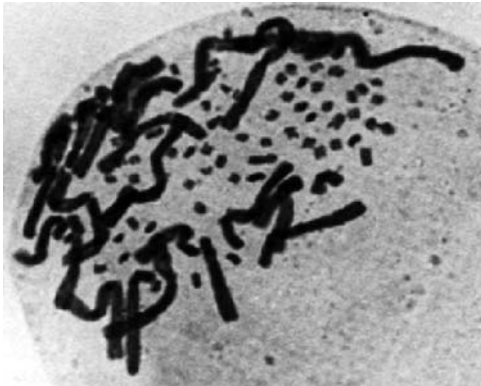


Figure F55. Soybean (short) and Vetch (long) chromosomes in fused somatic cells. (Courtesy of Dr. O.L. Gamborg et al. 1977 C.R. Hebd. Séances Acad. Sci. Paris Ser. D. 285:319)

Fusion Protein: A fusion protein is synthesized when neighboring genes are transcribed and translated together. It contains full or incomplete parts of two normal proteins. It may also refer to a group of proteins mediating membrane fusion in cells. Fusion of ligands (e.g., transferrin) for lymphocyte cell surface receptors with particular immunoglobulins (IgG3) may potentiate the delivery of antibody beyond certain (e.g., brain) barriers to the blood. Antibody_cytokine fusion may be useful in targeting tumors for destruction. Fusion of proteins with autofluorescent proteins is a powerful tool for the study of protein-protein interactions, conformational changes and other aspects of protein dynamics (Keppler A et al 2004 Proc Natl Acad Sci USA 101:9955). ▶gene fusion, ▶transcriptional gene fusion vectors, ▶translational gene fusion vectors, ▶read-through proteins, ▶chromosome breakage, ▶cancer, ▶leukemias, ▶ferritin, ▶immunoglobulins; labeling in vivo: Keppler A et al 2003 Nature Biotechnol 21:86.

Fusion Transcript: A fusion transcript may result from transcription of chromosomal translocations, retroposon insertion, and transcriptional gene fusion brought about by insertion of transformation vectors. Fusion transcripts are detectable by paired-end diTAG analysis.

Fusome: A structure that is formed in the germline cell of insects during the mitotic divisions. It anchors the mitotic divisions leading to the formation of the nurse cells and the oocyte. After the divisions are completed, it fades away. Antibodies to spectrin, a filamentous membrane protein, can detect its existence. ▶nurse cell, ▶morphogenesis, ▶spectrin; Grieder NC et al 2000 Development 127:4253.

Futile Cycle: An apparently useless chemical reaction in the cell, e.g., fructose-6-phosphate is phosphorylated to fructose diphosphate and simultaneously it is hydrolyzed back to fructose-6-phosphate, resulting in cleavage of ATP into ADP and Pi (unnecessary ATPase activity). The futile cycles may, however, confer regulatory role in functional networks. ▶substrate cycle; Samoilov M et al 2005 Proc Natl Acad Sci USA 102:2310.

Fuzzy Inheritance: A statistical term used for cases when linkage information is computed by allele sets and by using set recoding. (See Nature Genetics 11:402[1995]).

Fuzzy Logic: As per fuzzy logic, either one, or another different event can occur, e.g., frameshift or in-frame decoding of the mRNA, or the translation is either terminated or read through. ▶recoding, ▶pseudo-knot; Zimmermann HJ 1996 Fuzzy Set Theory and Its Applications, Kluwer, Boston, Massachusetts.

Fv (fragment variable): A functional antibody molecule, composed of light and heavy chain antigen-binding sites of one region of the antibody separated from the rest by proteolysis. The single-chain (scFvs) of the light (V_L) and heavy chains (V_H) can be engineered to bind together by 8–15 amino acid linkages and can be cloned by various vectors. These engineered antibodies have, however, somewhat reduced immunogenicity. These molecules may have applicability for radiolabeling and imaging of tumors and for the generation of immunotoxins. ▶antibody, ▶antibody engineering

Fv Protein: A homodimeric 175-kDa sialoprotein binding to the variable domains of immuno-globulin heavy chains. ▶sialic acid, ▶immunoglobulins

FVB Mouse: The FVB mouse is a not-inbred strain; frequently used for genetic transformation.

φX174: A single-stranded DNA bacteriophage with overlapping genes. Its genome has been the first to be completely sequenced (see Fig. F56) (Sanger F et al 1978 J Mol Biol 125:225).

Because of the simplicity of its genome (5,386 bases), it has been used for many purposes in genetics. Recently mice cell lines transgenic for φX174 have been promising in the study of

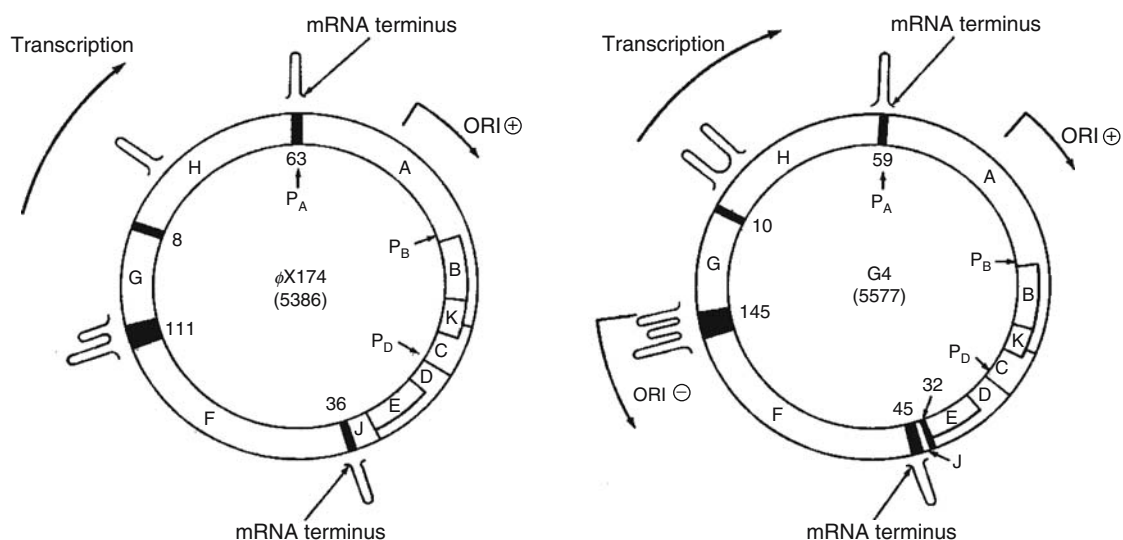


Figure F56. The physical map of bacteriophage ϕ X174 with 10 genes *a* to *h*. although some of the genes overlap each other (or included), there are non-genic (intergenic) sequences (shown in solid black). The related G4 phage is similar. (Courtesy of Godson, N.G. 1980, Stadler Symp. 12:143)

chemically induced forward mutation (Valentine CR et al 2002 Environ Mol Mutagen 39:55). The entire functional ϕ X174 genome has been assembled from synthetic oligonucleotides (Smith HO et al 2003 Proc Natl acad Sci USA 100:15440). ▶bacteriophages, ▶poliovirus, ▶synthetic genes

FXR (fragile x-related protein): A part of the RISC complex. ▶RISC, ▶fragile X chromosome; Caudy A et al 2002 Genes Dev 16:2491.

FXTAS: ▶fragile X chromosome

Fyb: ▶SLAP; Griffith EK et al 2001 Science 293:2260.

FYN: The FYN oncogene is a member of the Src non-receptor protein tyrosine kinase gene family. The protein controls memory and learning. Low level of Fyn results in greater sensitivity to alcohol effects. ▶Src, ▶Csk, ▶protein tyrosine kinase, ▶palmitoylation; Arold ST et al 2001 J Biol Chem 276:17199.

FYVE: A protein domain of phosphatidylinositol-3-phosphate-containing membrane proteins recruiting other proteins involved in signal transduction. ▶signal transduction; Stahelin RV et al 2002 J Biol Chem 277:26379.

Historical vignette

Mary F Lyon 2002 Annu Rev Genomics Hum Genet 3:1

...“Cambridge also had as Professor of Genetics, RA Fisher, the eminent statistician and mathematical geneticist. He is known now in mouse genetics for Fisher’s exact test and the maximum likelihood method of linkage estimation. He gave a course of lectures, which were largely incomprehensible.”

G

G: ▶ **guanine**. G also denotes generations after mutagenic treatment of mice, G₀, G₁, G₂, etc. This designation is somewhat confusing with the pre-empted cell cycle symbols. ▶ **cell cycle**

g: General intelligence. ▶ **intelligence quotient**, ▶ **human intelligence**

γ: ▶ **gamma**

g²: ▶ **genetic determination**

G418 (C₂₀H₄₀N₄O₁₀ · 2H₂SO₄): An aminoglycoside antibiotic. ▶ **geneticin**

G3139: An 18-mer full-phosphorothioate deoxyoligonucleotide (5'-TCTCCCAGCGTGC GCCAT-3' *Genta*, San Diego, California) with sequence antisense to the first six codons of the open reading of gene BCL-2, and it is used for therapy of lymphomas. ▶ **Bcl-1**, ▶ **lymphoma**, ▶ **antisense technologies**, ▶ **phosphorothioate**

G3854: A 20-mer full-phosphorothioate deoxyoligonucleotide with sequence antisense to open reading frame of gene BCL-2, and it is used for therapy of lymphomas. It is similar to G3139 but two nucleotides longer. ▶ **Bcl-1**, ▶ **lymphoma**, ▶ **antisense technologies**, ▶ **phosphorothioate**

G Banding: A chromosome staining method using Giemsa stain (a complex basic dyes, containing azures, eosin, glycerol and methanol), after pretreatment with the proteolytic enzyme, trypsin, it permits the identification of dark cross-bands that vary among the individual eukaryotic chromosomes and usually facilitates their identification even when their length and arm ratio is similar (see Fig. G1). The darkly stained bands represent (AT-rich) heterochromatin. ▶ **chromosome banding**, ▶ **stains**, ▶ **rye**

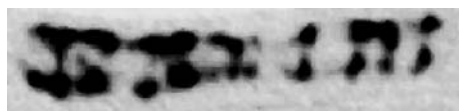


Figure G1. G-Banded human chromosome

G Box: A guanine-rich upstream cis element regulating transcription. Commonly it has the structure GA [CAACGTC] GC. The G-box activator protein binds to the framed core sequence. It is commonly found in environmentally sensitive genes. ▶ **Simian**

virus 40, ▶ **CAAT box**, ▶ **regulation of gene activity**, ▶ **phytochromes**

Gbuilder: A nucleotide sequence visualization tool based on Java application of DNA clusters in EST data. ▶ **Java**, ▶ **EST**; Muilu J et al 2001 *Genome Res* 11:179.

G Element: ▶ **non-viral retrotransposable element**, ▶ **retrotransposons**, ▶ **retroposons**

g Factor: ▶ **human intelligence**

g Force: ▶ **centrifuge**

G₀ Phase: The state of a pause for the cell before it enters the G₁ phase and until divisional activities start again after mitosis. ▶ **cell cycle**

G₁ Phase: The first phase of the cell cycle following mitosis (C value = 2). ▶ **cell cycle**

G₂ Phase: The phase following DNA replication during the cell cycle (C value = 4). ▶ **cell cycle**; O'Connell MJ et al 2000 *Trends Cell Biol* 10[7]:296.

G4 Phage: A single-stranded DNA phage (5507 bases), ~67% related to φX174. ▶ **bacteriophages**, φX174; Godson GN et al 1978 *Nature [Lond]* 276:236.

G Proteins: They are guanine nucleotide binding proteins that serve as intermediaries in biological signaling pathways. The signal is received by *receptors* and the *G-proteins* forward it by mediation of different number of intermediaries to the *effectors* that regulate genes in response to the signals. G-proteins are activated by aluminum fluoride and the α subunit can be ADP-ribosylated by mediation with the aid of bacterial toxins (cholera, pertussis).

The large G-proteins are heterotrimeric (α, β, γ) and control the opening and closing of the signal transduction pathways by changing the attached GDP ⇌ GTP. In the GTP-associated form, they have key role in signal transduction from receptors to effectors. The proteolysis of the large G proteins is regulated by RGS protein signaling and subject to N-end rule (Lee MJ et al 2005 *Proc Natl Acad Sci USA* 102:15030). There are also low molecular weight small G-proteins with a single (α) subunit. G-protein (G_s) is involved in the regulation of the level of the enzyme adenylyl cyclase and thus cAMP and cAMP-dependent protein kinase. The G_i form is involved in the inhibition of adenylyl cyclase; G_{iia2} is required for insulin function. The light-activated GTPase activity is mediated by the G_t-protein, also called transducin. G-proteins stimulate the hydrolysis of phosphoinositides with the aid of phospholipase C. Ca²⁺ also mediates by G-proteins and cAMP degradation by cyclic nucleotide phosphodiesterase indirectly. G-proteins also regulate ion channels.

When a proper ligand binds to a transmembrane receptor, the trimeric G-protein dissociates into a β and an α subunit. The α subunit stimulates adenylyl cyclase, the first the transition of GDP to GTP, and later the transition of GTP to GDP through the mild GTPase activity. In the G-GDP state reassociation of the three subunits follows. G-proteins regulate also Ca^{2+} metabolism and indirectly control allosteric effector proteins. Several human diseases are associated with defects in the G proteins (pituitary tumors, McCune-Albright syndrome, Albright hereditary osteodystrophy, puberty precocious) or with defects in the G protein receptors (hypercalcemia, hypercalciuria, hyperparathyroidism, diabetes insipidus, retinitis pigmentosa, color blindness, glucocorticoid deficiency, opiate addiction, hypertension, myocardial ischemia, chronic heart disease). The human genome seems to include 800 to 1,000 G protein receptors. The most common among them ($\sim 89\%$) are rhodopsin-like molecules, the secretin-like molecules ($\sim 7\%$) and the metabotropic-glutamate-receptor-like proteins ($\sim 4\%$). These proteins, because of their key role in the regulation of metabolic pathways and disease development are important targets of existing and future drugs. Dozens of genes are involved with coding and regulation of G protein subunits, scattered among several human chromosomes. Many of the G protein-coupled receptors are without introns suggesting that retrogenes code for them. Mutations in exons may alter splicing sites remote from the mutation and thus create new variants. G proteins have important roles in both animal and plant cells, however, plants have much fewer genes encoding the trimeric G protein subunits. Several human diseases implicate G protein malfunctions. ▶G region, ▶G' region, ▶G'' region, ▶ G_α , ▶ G_i , ▶ G_q , ▶ G_s , ▶ G_o , ▶ G_i -protein, ▶GTPase, ▶cAMP, ▶adenylate cyclase, ▶rhodopsin, ▶signal transduction, ▶N-end rule, ▶calmoduline, ▶receptor, ▶effector, ▶cholera toxin, ▶pertussis toxin, ▶GTP, ▶phosphodiesterase, ▶ion channel, ▶adenylate cyclase, ▶cell cycle, ▶retrogene, see also the mentioned diseases under separate entries; Sp SR 1997 Annu Rev Biochem 66:639; Bockaert J, Pin JP 1999 EMBO J 18:1723; Farfel Z et al 1999 New England J Med 340:1012; Dohlman HG, Thorner J 2002 Annu Rev Biochem 70:703; Knoblich JA 2001 Cell 107:183; Peterson YK et al 2002 J Biol Chem 277:6767; Assmann SM 2002 Plant Cell 14:S355; Chalmers DT, Behan DP 2002 Nature Rev Drug Discover 1:599; G proteins in plants: Assmann SM 2005 Science 310:71; G protein signaling in yeast: Slessareva JE, Dohlman HG 2006 Science 314:1412; GEF and GAP regulation of G proteins: Bos JL et al 2007 Cell 129:865; http://www.hsls.pitt.edu/guides/genetics/tools/protein/information/URL1118091522/info?print_format=false;

G protein ligands: <http://gdds.pharm.kyoto-u.ac.jp/services/glida/>.

G Quartet (guanine quartet): Guanine-rich nucleotide sequences may form four-stranded complexes, stabilized in Hogsteen structures. The G quartets may be formed in phosphorothioate octamers such as $\text{S-T}_2\text{G}_4\text{T}_2$ or from other sequences like $\text{GTG}_2\text{TG}_3\text{-TG}_3\text{TG}_3\text{T}$ (see Fig. G2). These quartets or double quartets may be potent viral inhibitors. The latter may block HIV1 integrase. Guanine-rich sequences are common in the telomeres, transcription regulatory regions, and immunoglobulin switching areas, etc. Antisense RNAs containing G quartets seem to suppress to various degrees MYC and MYB cellular oncogenes, HIV integrase, etc. G quartets may regulate the translation of the mRNA transcript of Fragile X gene and thus, control synaptic activity of neurons in the brain. Despite the presence of well-defined non-guanine base quartets in a number of NMR and X-ray structures, the data suggests that most non-guanine quartets do not participate favorably in structural stability, and that these quartets are formed only by virtue of the docking platform provided by neighboring G-quartets (Gros G et al 2007 Nucleic Acids Res 35:30:64). ▶antisense technologies, ▶Hogsteen pairs, ▶oncogenes, ▶HIV, ▶immunoglobulins, ▶Fragile X chromosome, ▶NMR; Horvath MP, Schultz SC 2001 J Mol Biol 310:367; G-quartet-rich sequences: <http://bioinformatics.ramapo.edu/grsdb/index.php>.

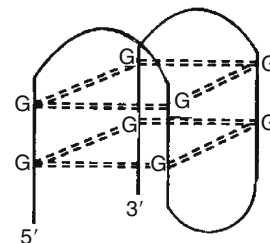


Figure G2. Quartet

G Region: Consensus N-K-X-D (see Amino Acid Symbols) in GTP-binding proteins that interacts with guanine in GTP. ▶G-proteins

G' Region of GTP Binding Proteins: With highly conserved consensus D-X-X-G-Q (see Amino Acid Symbols) it involves GTP-ase function and may affect oncogenicity. ▶signal transduction, ▶G-proteins

G''Region: G'' region in RAS interacts with GTP through the E-T-S-A-K (see Amino Acid Symbols) consensus. In some G-proteins H(F/M)-T-C-A

(T/V)-D-T may be the corresponding functional area.

► **G-proteins**

G8 RNA: ► **thermal tolerance**

γ Satellite: The repetitive heterochromatin in the pericentromeric area.

G Test: It is a goodness of fit test but instead of calculating the χ^2 in the common way the probability of p is divided by $\hat{p} = L$ (likelihood), and $G = 2 \ln(L) = 2(\ln 10) \log L$ and the distribution is approximated by the χ^2 distribution in large samples. Instead of G sometimes the symbol I (information) is used. ► **chi square**, ► **information**; Sokal RR, Rohlf FJ 1969 Biometry, Freeman, San Francisco, California.

GA: ► **gibberellic acid**, ► **plant hormones** (see Fig. G3).

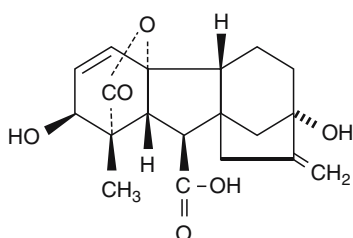


Figure G3. Gibberellic acid

G_α: The G-protein involved in hormonal stimulation of adenylate cyclase and may regulate ion channels or phospholipase C. The human G_s 1α gene contains 13 exons and 12 introns in a total size of 20 kbp. G_α types: G_iα, G_oα, G_xα, G_tα, G_α₁₂ and G_α₁₃ are subunits, which are stimulated by the p115 RhoGEF. The latter bound to p115RhoGEF catalyzes G nucleotide exchange on RHO but this may be inhibited by activated by G_α₁₃. These are very highly conserved proteins across phylogenetic ranges. In G_sα only 1/394 amino acid difference was found between man and rat, and the protein is entirely identical between humans and bovines. ► **G-proteins**, ► **RGS**, ► **p115**

GABA (γ-aminobutyric acid): It plays an important role in neurotransmission of vertebrates and invertebrates. In the nematode *Caenorhabditis* a series of *unc* (uncoordinated movement) genes respond to GABAergic neuronal effects. GABA_A receptors mediate synaptic inhibition but upon intense activation, they may excite rather than inhibit neurons. GABA controls Cl⁻ ion channels by efflux (depolarization and excitation of the nerve cell) and by influx (hyperpolarization and reduced excitability). By an increase of the level of GABA_A receptor α4

premenstrual anxiety and susceptibility to seizures decrease. Progesterone also acts as a sedative by enhancing GABA function. Heteromeric GABA receptors (GABA_BR1a/b—GABA_BR2), in cooperation with G proteins, regulate potassium and calcium ion channels. The nineteenth century alcoholic beverage, absinthe, containing wormwood oil (thujone) is antagonistic to the GABA_A receptor channels and that explains its convulsant and other neurological effects. GABA transaminase (16p13.3) is responsible for the catabolism of GABA and its deficiency leads to neuronal disorders. There are at least 13 GABA receptors encoded in different human chromosomes. It seems that GABA has a role also in the guidance of pollen tube to the plant ovule. ► **glutamate decarboxylase deficiency disease**, ► **epilepsy**, ► **Caenorhabditis**, ► **neuron**, ► **cleft palate**, ► **neurotransmitter**, ► **ion channels**; Ganguly K et al 2001 Cell 105:521.

Gαβγ: Heterotrimeric G-proteins and the three subunits are of 39–52, 35–36 and 7–10 kDa size, respectively. In mammalian cells, several genes are known for each subunit and their cDNAs may generate additional variations by alternative splicing. ► **G proteins**, ► **splicing**

GABA Transaminase: (16p13.3): ► **GABA aminobutyrate transaminase**

GABP: These are GAA sequence- (or their extension) binding heterotetrameric DNA-binding proteins (GABPα/β), members of ETS domain protein families (about 40) regulating gene transcription in a combinatorial manner with other proteins. The α subunit actually binds DNA whereas the ankyrin repeats in β recruit other protein domains. ► **transcription factors**, ► **ETS oncogenes**, ► **ankyrin**, ► **combinatorial gene control**

GABRIEL: A computer program designed to apply domain-specific and procedural knowledge for the analysis of DNA microarray data (Pan K-H et al 2005 Proc Natl Acad Sci USA 99:2118).

GAD: (Genetic Association Database, <http://geneticassociationdb.nih.gov>, <http://hpcio.cit.nih.gov/gad.html>): GAD contains information on association of genes with human diseases, primarily for medical professionals and also for the public. Anyone can submit information that will be reviewed before inclusion.

GADD45: It is a p53-inducible protein. It also binds PCNA. Deficiency of Gadd45a in mice leads to chromosomal instability, increased radiation sensitivity (cancer), and exencephaly. The GADD genes are induced by stress, inflammatory cytokines, tumor necrosis factor, transforming growth factor, and several cytokines. ► **PCNA**, ► **p53**, ► **exencephaly**; Takahashi S et al 2001 Cancer Res 61:1187; Kovalsky O et al 2001 J Biol Chem 276:39330.

GADD153 (growth arrest and DNA damage): A cellular enhancer-binding protein mediating stress of growth and differentiation. Under stress, it may be activated by phosphorylation of Ser⁷⁸ and Ser⁸¹ residues and consequently enhanced transcription and inhibited adipose cell differentiation. It is the same as CHOP. GADD is activated under varied stress conditions. It may act also as an oncoprotein by suppressing differentiation, especially in various gene fusions brought about by chromosomal translocations. ► [enhancer](#), ► [DNA repair](#), ► [chromosome breakage](#), ► [cancer](#); O'Reilly et al 2000 *Am J Physiol Lung Cell Mol Physiol* 278:L552; Jousse C et al 2001 *Nucleic Acids Res* 29:4341; Lu B et al 2004 *Nature Immunol* 5:38.

GADS: A CD3 signaling adaptor that links SLP-76 to LAT. ► [CD3](#), ► [SLP-76](#), ► [LAT](#)

GAF: A DNA satellite-binding regulatory protein.

GAG: ► [glycosaminoglycan](#)

gag: Group-specific antigen, a viral coat protein. ► [retroviruses](#)

GAGA: A multipurpose transcriptional activator binding to the GA/CT sites in the promoter. Its major function may be to rearrange the chromatin to facilitate transcription. GAGA activates chaperones and binds to the promoter of the *Ultrabithorax* and other *Drosophila* genes. ► [position effect](#), ► [morphogenesis in Drosophila](#), ► [heat-shock proteins](#), ► [heterochromatin](#); Basturia A et al 2001 *Development* 128:2163.

GAIA Theory: Organisms contribute to a self-regulating feedback that keeps the environment stable and suitable for life. The global environment (living and non-living) determines, however, the outcome of natural selection through interacting feedback processes. (See Downing K, Zvirinsky P 1999 *Artif Life* 5[4]:291).

Gain: A practical measure of heritability, frequently used by animal breeders. By this criterion heritability, $h^2 = (\text{gain})/(\text{selection differential})$. See graphical representation (After Lerner IM, Libby WJ 1976 *Heredity, Evolution and Society*, Freeman, San Francisco). The selection differential is the difference between the mean of the parental population and the mean of a portion of the parents selected for further reproduction to improve the herd. The gain/selection differential is often called *realized heritability*. The breeder may improve the gain either by increased heritability or by enhanced intensity of selection. Heritability estimates improve if environmental variation is kept at a low level by proper feeding and health care of the animals or appropriate tillage, fertilization,

weed and pest control in plants. The intensity of selection is increased if the proportion of the individuals selected for parents is reduced. Although this may appear to be an easy approach to improve selection gains, the small populations may increase inbreeding and becomes counterproductive. In large mammals, the males generally have more offspring than the females. By the use of artificial insemination, the breeding value of the males can be determined even more precisely than that of the dams (see Fig. G4). Generally, the estimates improve with the age of the animals because larger number of offspring is available for evaluation. In practice, the selection is aimed simultaneously at several traits. Often these traits are negatively correlated because high performance may make the animals (plants) more susceptible to disease. Thus, the gain in one trait may mean a loss in the others. Therefore, breeders frequently use a *selection index* that weighs each trait by a score and the total of the scores becomes the basis of the selection value. There are statistical methods for predicting the quantitative performance in a selective breeding program: $Y_o = \bar{Y} + Hn(Y_p - \bar{Y})$ where Y_o is the predicted average performance of the progeny, Y_p is the average of the two parental families selected, \bar{Y} = the average of the original population, Hn is heritability in the narrow sense. Example: the average number of eggs laid per year in a flock of chickens is 250, the heritability is 0.25, the average of the selected family of parents is 274, then the expectation for the offspring $Y_o = 250 + 0.25(274 - 250) = 256$. The genetic gain from mass selection is computed from the covariance: $(XY) = w = (1/2) 2\sigma_A$. For determining the covariance see correlation; σ^2_A = additive variance (see genetic variances); the plot-to-plot environmental variance is σ^2_e and the plant-to-plant environmental variance = $\sigma^2_{we} = \sigma^2_{wf} + \sigma^2_{me}$ and the genotype environmental variance, $\sigma^2_{G \times E} = \sigma^2_{A \times E} + \sigma^2_{D \times E}$.

If we consider the within-family variance = 0, then the gain for mass selection,

$$\Delta G_m = \frac{\frac{1}{2} i^2 A}{\sqrt{\sigma_A^2 + \sigma_D^2 + \sigma_{A \times E}^2 + \sigma_{D \times E}^2 + \sigma_e^2 + \sigma_{me}^2}}$$

and i = selection intensity, σ_D^2 = the dominance, $\sigma_{A \times E}^2$ = additive x environment, and $\sigma_{D \times E}^2$ = dominance x environment variances. This procedure is applicable to large populations at relative ease. In case of phenotypic recurrent selection, the equation for gain in mass selection above for cycle needs to be multiplied by 2 because the selection is applied to both parents. Additional formulas for other types of selection are to be found in Moreno-González J, Cubero, *J Plant Breeding*, pp. 281–313; Hayward MD et al eds 1993, Chapman & Hall, London, New York. ► [polygenes](#), ► [breeding value](#), ► [selection index](#),

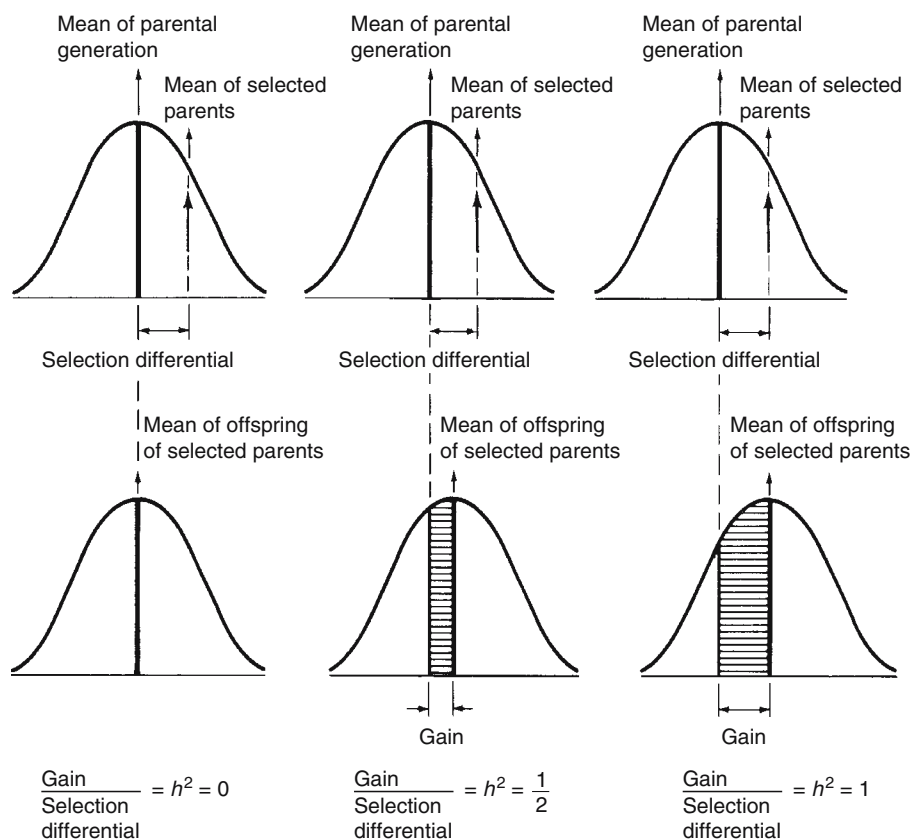


Figure G4. Gain

►quantitative genes, ►heritability, ►intraclass correlation, ►correlation

GAIN (Genetic Association Information Network): It involves private companies (Pfizer, Perlegen, Affymetrix, etc.) in a collaborative effort with the NIH to carry out genome-wide association studies for several common diseases. ►genetic association, ►genome-wide functional analysis, ►genome-wide location; http://www.fnih.org/GAIN/GAIN_home.shtml.

Gain-of-Function Mutations: Generally, mutations lead to loss of structures (for e.g., hairs or bristles) or certain function (e.g., auxotrophy). However, some of the homeotic mutants gain additional structures such as extra petals or stamens in flowers or legs on the head in *Drosophila*. These “gains” are the result of homeotic transdetermination regulated by altered transcription and/or transcript processing. ►transdetermination, ►transcription, ►processing, ►Huntington chorea, ►muscular dystrophy, ►homeotic genes, ►flower differentiation, ►loss-of-function mutation, ►dominant negative

GAL: ►galactose utilization

GAL4: A positive regulatory protein of the yeast galactose genes, it binds to a specific upstream regulatory DNA sequence. *GAL4* is activated by the interaction of Gal80p and Gal3p in the cytoplasm. In various constructs, introduced by transformation into other organisms, its activator domain is frequently utilized to boost the expression of selected reporter genes. Ubiquitylation of Gal4 seems to be required for elongation of mRNA. The F-box protein, Dsg1/Mdm30 mediates this turnover (Muratani M et al 2005 Cell 120:887). ►galactose utilization, ►activator proteins, ►reporter gene, ►transcriptional activator, ►Gene-Switch, ►p65, ►two-hybrid method, ►F-box; Hartley KO et al 2002 Proc Natl Acad Sci USA 99:1377; Peng G, Hopper JE 2002 Proc Natl Acad Sci USA 99: 8548; GAL3 and GAL80 regulatory functions: Ramsey SA et al 2006 Nature Genet 38:1082.

Gal α 1-3Gal: The terminal antigens present on the endothelial lining of blood vessels of majority of mammals, except humans and most primates because the latter higher animals do not have a functional 1,3-galactosyl transferase (GT). These antigens have the major role in organ graft rejection. In order to reduce

rejection, antisense technology may be used to block the synthesis of GT mRNA. Alternatively, an inhibitory ligand (aptamer) or an enzyme (H transferase) is used to add fucose (rather than galactose) to the molecule to compete in the reaction. The use of α -galactosidase may destroy the antigenic galactose terminals. ►immunity, ►xenotransplantation, ►grafting in medicine

Galactans: These are polymers of galactose. ►galactose, ►hyperacute reaction

Galactokinase Deficiency: Can be due to autosomal recessive defects at GALK1 (human chromosome 17q24) or GALK2 (chr. 15). Cataracts at infancy and hypergalactosemia occur due to this deficiency. Galactokinase converts galactose into galactose-1-phosphate. ►galactosemias, ►galactose

Galactose: One of the most common six-carbon monosaccharides differing from glucose only sterically at carbon-4 chiral centers (an epimer of glucose). It can be converted to glucose by an epimerase enzyme (UDP-Gal \rightarrow UDP-Glucose) (see Fig. G5). Galactosyl groups are present in some anthocyanin, collagens, and immunoglobulins. Lactose (the milk sugar) is a disaccharide of galactose + glucose, split by the enzyme lactase. ►galactosemias, ►galactose utilization, ►chirality, ►epimers, ►galactosidase, ►galactose [see formula], ►galactose utilization, ►epilepsy, ►eye diseases, ►genetic screening

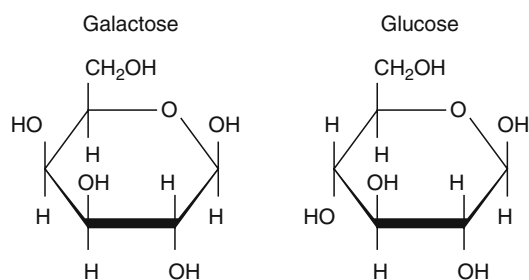


Figure G5. Galactose and glucose

Galactose Operon: ►galactose utilization

Galactose Utilization: Coordinately regulated in prokaryotes and eukaryotes. The galactose genes of *E. coli* are either clustered (*galE* [UDP-galactose-4-epimerase], *galEo* [operator], *galElp* [promoter], *galE2p* [promoter of *galEK*], *galK* [galactokinase], *galT* [galactose-1-phosphate uridylyltransferase]) all at map position 17 or *galR* [galactose regulator] at map position 61, *galP* [galactose permease] at map position 63, and *galU* [glucose-1-phosphate uridylyltransferase] at map position 27. In yeast, the uptake

of galactose is mediated by galactose permease (gene *GAL2*). In the presence of ATP, galactose is phosphorylated (Gal-1-P) by galactokinase (gene *GAL*). Galactose-1-phosphate (Gal-1-P) + uridine-diphosphoglucose (UDP-glucose) generate UDP-galactose + glucose-1-phosphate by the action of galactose-1-phosphate uridylyltransferase (gene *GAL7*) while the UDP-galactose-4-epimerase (gene *GAL10*) mediates the formation of UDP-glucose from UDP-galactose. Genes *GAL1*, *GAL7* and *GAL10* form a cluster in yeast chromosome 2 and *GAL2* is in chromosome 12. These yeast genes are coordinately inducible up to a 1000 fold by the presence of galactose although they are transcribed from separate promoters. Gene *GAL4* (linkage group 16) and gene *GAL80* (linkage group 13) regulate the GAL enzymes. *GAL4* is apparently a positive regulator of genes 1, 2, 7, and 10 whereas some *GAL80* mutations abolish the need for induction of the same genes and convert them either to constitutive forms or make them non-inducible. It is assumed that the normal role of the product of gene *GAL80* is to prevent the transcriptional activation by *GAL4* but the combination of the GAL1 protein with GAL80 protein inactivates the latter and then GAL1 activates GAL4, the activator of the system. This GAL1 protein is an enzyme as well as a regulator of transcription. The activation by *GAL4* depends on *upstream activating sequences* (UAS) located 200 to 400 base pair upstream of the genes, 1, 2, 7, 10 and *GAL80*. The presence of two UAS is sufficient for full expression (see Fig. G6). The consensus within the 17 bp palindromic (\leftrightarrow) UAS is:



Figure G6. Galactose UAS palindrome

The protein product of gene *GAL4* is about 100-kDA and it contains three essential domains. Amino acids from 1–65 are involved in DNA binding, residues 65–94 are concerned with dimerization. Amino acids 148–196 and 768–881 mediate activation of transcription (activation domain) and at the C-terminus, the sequence 851–881 also binds the *GAL80* gene. At the N-terminus, amino acid residues 10–32 display a Zinc-finger motif, common to binding proteins. At the C-terminus, there is a high density of acidic amino acids, a characteristics of regulatory proteins. The presence of inactivation by insertion elements in bacterial genomes was first recognized by a study of the *gal* operon in *E. coli*. ►galactose, ►operon, ►coordinated regulation, ►UAS, ►palindrome, ►IS elements, ►regulation of gene activity, ►Zinc fingers, ►binding proteins,

►two-hybrid method, ►galactosemia; Weickert MJ, Adhya S 1993 Mol Microbiol 10:245; Frey PA 1996 FASEB J 10:461.

Galactosemias: Autosomal hereditary diseases in humans caused by the deficiency of either the enzyme galactokinase (GALK, human chromosome 17q24) or more commonly galactose-1-phosphate uridylyltransferase (GALT, 9p1, 4q263). Consequently, galactose cannot be transformed into glucose. Since the milk sugar is a disaccharide of galactose and glucose, galactose accumulates in the blood and is excreted in the urine. The accumulating galactose causes severe intestinal problems and the accumulating galactose-1-phosphate may damage the liver, brain, eye lens (cataracts) and other organs. Unless this anomaly is detected right after birth, infant death may result. By a diet free of any source of galactose, damage may be prevented. This condition is quite common, about 4×10^{-4} . A human galactokinase gene GALK is responsible also for cataracts. Deficiency of the enzyme that converts UDP-galactose \rightleftharpoons UDP-glucose, galactose epimerase (GALE, chromosome 1p35-p36) also leads to galactosemia. GALT deficiency may cause neurological dysfunctions because the reduction of galactose available for galactosyl ceramides and glycosphingolipids and the accumulation of their precursors such as glucosyl ceramides. Deficiency of UDP-galactose:ceramide galactosyltransferase (CGT, 4q26) results in thinner myelin sheets and mild ataxias, low IQ, memory deficit, reduced visuo-motor coordination, etc. Galactosemia (GALT) may cause ovary dysfunction because of the higher than normal levels of the follicle stimulating (FSH) and luteinizing hormones. ►ceramides, ►myelin, ►ataxia, ►human intelligence, ►animal hormones, ►ceramides, ►sphingolipids, ►sphingolipidoses, ►lipid; Riehm K et al 2001 J Biol Chem 276:10634.

Galactosidase- β : Probably the best studied bacterial gene, *lac* involves the determination and control of the enzyme β -galactosidase (see ►*lac operon*). The enzyme α -galactosidase an α -galactosyl hydrolase (melibiase, α -galactoside galactohydrolase, ceramide trihexosidase) is deficient in patients suffering from Fabry's disease (Xq22). In the plasma and in most of the tissues the trihexosyl ceramides Gal-Gal-Glc-Cer or Gal-Gal-Cer (Gal = galactose, Glc = glucose, Cer = ceramide) accumulate in the tissues. In various organs, extensive deposition of lipids occur and the patients suffer skin lesions, pain, paresthesia (burning, prickling sensation). In the extremities, ectasia (dilation, distention) in the skin vessels, edema (accumulation of fluids) in the legs, hypohidrosis (diminished sweating), albuminuria (protein accumulation in the urine), hyposthenuria (lowered amounts of solids in the urine) occurs. Death

may result from renal failure. The disease is X-chromosome linked (q22). Heterozygous females have the same symptoms as hemizygous males but at reduced level. β -Galactosidase (a group of enzymes splitting galactosides, galactose linkages) activity is greatly reduced in patients affected by a group of human diseases called *gangliosidoses*. β -Galactosidase is a biological marker for cellular senescence. The general symptoms involve deterioration of psychomotor (brain and movement) activities, severe bony deformities and generally death by the age of two. These diseases occur in all ethnic groups as incurable autosomal recessive defects. Heterozygotes may be detected by β -galactosidase assays and the diseases can be identified by amniocentesis. ►galactose utilization, ►Fabry's disease sphingolipidoses, ►gangliosidosis general, ►Krabbe's leukodystrophy, ►lactosyl ceramidosis, ►*Lac operon*, ►Xgal; Pshezhetsky AV, Ashmarina M 2001 Progr Nucleic Acid Res Mol Biol 69:81)

Galactosyl Ceramide Lipidosis: ►Krabbe's leukodystrophy

1,3-Galactosyltransferase, α : Synthesizes α 1-3-galactose epitopes, which are the major antigens causing rejection of pig to human xenotransplants. Knocking out or mutation in the gene responsible for the enzyme may render the organs more suitable for xenotransplantation. The majority of mammals—with the exception of humans, apes and Old World monkeys—carry a gene for this enzyme. ►xenotransplantation; Phelps CJ et al 2003 Science 299:411.

Galago: ►Lorisidae

Galanin: A bioreactive peptide (in humans Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-His-Ala-Val-Gly-Asn-His-Arg-Ser-Asp-Lys-Asn-Gly-Leu-Thr-Ser). Its composition is somewhat different in pigs or rats. In humans, it inhibits acetylcholine and glutamic acid release. It also reduces excitability of spinal neurons and blocks voltage-activated Ca^{2+} -channels. It may be involved in behavioral and cognitive deficits in Alzheimer disease. Its effects in other mammals are similar. ►ion channels, ►Alzheimer disease, ►acetylcholine, ►glutamica; Steiner RA et al 2001 Proc Natl Acad Sci USA 98:4184.

Galectin: A β -galactoside binding protein regulating growth and immunological responses. It may induce apoptosis in activated human T cells. Galectin-1 and -3 are part of the spliceosome where they interact with the Gemin4 protein. ►apoptosis, ►T cell; Park JW et al 2001 Nucleic Acids Res 29:3595; Wang JL et al 2004 Biochim Biophys Acta 1673:75.

Gall: A generally undifferentiated tissue growth in plants, caused by infection. ► [crown gall](#)

Gallstone: ► [cholelithiasis](#)

GALT (gut-associated lymphoid tissue): ► [Peyer's patches](#)

Galtonian Inheritance: Francis Galton (1822–1911), father of quantitative genetics formulated the rules for Galtonian Inheritance in different ways. He recognized that his ideas on “ancestral heredity” were partly inconsistent with the observed facts. His application of the concept of regression to the inheritance of multifactorial traits remained essentially correct and contributed to the modern concepts of heritability. By rejecting Darwin's pangenesis and suggesting the concept of “stirpes”, he essentially laid the path to the concepts of hard heredity and particulate inheritance. His idea may still be applicable to the inheritance of organelle-coded functions: “We appear, to be severally built up out of a host of minute particles, of whose nature we know nothing, any one of which may be derived from any one progenitor, but which usually transmitted in aggregates, considerable groups being derived from the same progenitor. It would seem that while the embryo is developing itself, the particles, more or less qualified for each post, as it were in competition to obtain it. Also, the particle that succeeds must owe its success partly to accident of position and partly of being better qualified than any equally well-placed competitor to gain lodgment.” (Galton F 1889 *Natural Inheritance*, New York). ► [polygenic inheritance](#), ► [correlation](#), ► [heritability](#), ► [hard heredity](#), ► [sorting out](#), ► [pangenesis](#); Roberts HF 1965 *Plant Hybridization Before Mendel*. Hafner, New York; Kevles DJ 1995 *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, Harvard University Press, Cambridge, Massachusetts.

gam: ► [lambda phage](#), ► [Charon vectors](#)

GAMBIT (genomic analysis and mapping by in vitro transposition): By knowing the sequence of the genome and specificity of the target of a transposon, using transposons all the essential genes containing the target sequence can be inactivated and thus their function revealed. ► [targeting genes](#), ► [insertional mutation](#), ► [saturation mutagenesis](#); Kamichhane G et al 2003 *Proc Natl Acad Sci USA* 100:7213.

Gamborg Medium (B5): Developed for plant tissue culture, it is suitable for growing callus and different plant organs. Composition mg/L: KNO₃ 2500, CaCl₂·2H₂O 150, MgSO₄·7H₂O 250, (NH₄)₂SO₄ 134, NaH₂PO₄·H₂O 150, KI 0.75, H₃BO₃ 3.0, MnSO₄·H₂O 10, ZnSO₄·7H₂O 2.0, Na₂MoO₄·2H₂O 0.25, CuSO₄·5H₂O 0.025, CoCl₂·6H₂O 0.025,

Ferric-EDTA 43, sucrose 2%, pH 5.5, inositol 100, nicotinic acid 1.0, pyridoxine.HCl 1.0, thiamine. HCl 10, kinetin 0.1, 2,4-D 0.1 - 1.0. The microelements, vitamins and hormones may be prepared in a stock solution and added before use. For kinetin other cytokinins may be substituted such as 6-benzylamino purine (BA) or isopentenyl adenine (or its nucleoside), for 2,4-D (dichloro-phenoxy acetic acid), naphthalene acetic acid (NAA) or indole acetic acid (IAA) may be substituted or a combination of the hormones may be used in concentrations that is best suited for the plant and the purpose of the culture. For solid media use agar or gellan gum. Heat labile components are sterilized by filtering through 0.45 µm syringe filters. This medium may be purchased from commercial suppliers in a dry mix ready to dissolve. ► [Murashige & Skoog medium](#), ► [embryo culture](#), ► [cell culture](#), ► [cell fusion](#), ► [agar](#), ► [gellan gum](#), ► [plant hormones](#); Wetter LR, Constabel F (Eds) 1982 *Plant Tissue Culture Methods* Prairie Res Lab Saskatchewan, Canada.

Game Theory: Deals with decision-making under uncertainty. Before a decision is made, the probabilities of a set of actions, e.g., p(1) and p(2) must be assessed, generally by a subjective manner. An essential feature is a strategy that assures the maximal rewards for the good decisions. Such a procedure is most widely used in the business world (marketing) under competitive conditions. It may be applied also to natural sciences and evolution where exact statistical methods are not practical due to the variability and uncertainty of the conditions.

Decision-making involves computational tasks of the human brain and the Bayesian theorem provides statistical tools for the assessment of the roles of various kinds of uncertainties. In the neocortex and hippocampus of the brain, acetylcholine and norepinephrine have synergistic and permissive roles in assessing the *expected uncertainty* of environmental cues whereas norepinephrine is involved in the *uncertainty of the unexpected* based on a priory experience. Michel I. Posner, neurobiologist posited that a cue predicts a certain target by some degree of probability, called *cue validity*. Correctly cued target stimuli are processed more rapidly than incorrect ones. Acetylcholine level inversely varies with cue validity and thus indicates expected uncertainty. Physiological experiments with rodents and primates support this conclusion. Norepinephrine, in contrast, does not consistently interact with the probabilistic cuing task after the initial acquisition (Yu AJ, Dayan P 2005 *Neuron* 46:681). This model combines the physiological effects of neuromodulators and sensory cues for decision-making. ► [prisoner's dilemma](#), ► [winner's curse](#), ► [Bayes' theorem](#), ► [acetylcholine](#), ► [animal hormones](#); Binmore K, Samuelson L 2001

J Theor Biol 210(1):1; Sigmund K 2001 Theor Popul Biol 59:3; Stearns SC 2000 Naturwiss 87(11):476; Demetrius L, Grundlach VM 2000 Math Biosci 168(1):9.

Gamergate: Exceptional worker (reproductive female) in social insects that mates and can lay eggs. ► [social insects](#)

Gametangia: Sex organs of fungi; oogonium in the “female” and antheridium in the “male.”

Gamete: Haploid male or female generative cell (egg, sperm). Gametic fusion (formation of the zygote) takes place during sexual reproduction. The zygote (2n) has twice the number of chromosomes of the haploid (n) gametes. ► [gametogenesis](#), ► [fertilization](#), ► [germ cell](#)

Gamete Competition: If multiple gametes are available, their success in fertilization may be determined by genetically controlled viability or vigor. It occurs commonly among sperms of animals and plants, pollen tubes (certation) and also among eggs in multiparous animals or in plants where more than one megaspore of the tetrad may produce the egg. ► [certation](#), ► [meiotic drive](#), ► [selective fertilization](#), ► [preferential segregation](#), ► [segregation distorter](#)

Gametic Array: Gametic array of diploids, in case of independent segregation, can be determined by different procedures:

In a dihybrid: $(A + a) \times (B + b) = AB, Ab, aB, ab$ in a trihybrid: $(A + a) \times (B + b) \times (C + c) = ABC, ABc, AbC, Abc, aBC, aBc, abC, abc$ or using any type of gene symbols such as I/i, R/r A/a the combinations can be read from left to right by following the paths of the arrows and at right we obtain the gametic arrays (see Fig. G7). In general, in diploids, in case of independent segregation, the gametic output can be determined by $2n$ where n corresponds to the number of allelic pairs, e.g., in a trihybrid cross $2n = 2^3 = 8$ as derived above. For gametic array in autopolyploids and trisomics see autopolyploidy and trisomy, respectively. ► [Mendelian segregation](#)

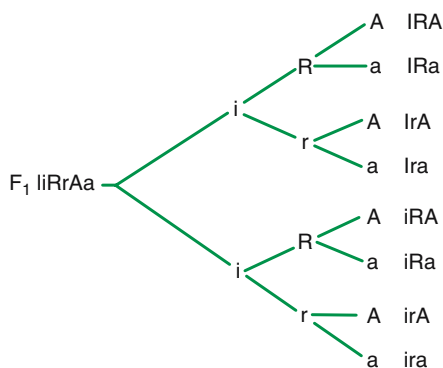


Figure G7. Derivation of gametic combinations

Gametic Lethal: Death at the egg or sperm stage. ► [zygotic lethal](#)

Gametocide: Any chemical that causes male sterility. They may be used in plant breeding to sparse the efforts of emasculation in large-scale hybridization or may be used as birth-control agents when applied shortly before copulation. Some gametocidal genes induce chromosome breakage during interphase. ► [male sterility](#)

Gametocyte: A cell that produces gametes. ► [Plasmodium](#)

Gametogenesis: The animal egg is formed by differentiation without further cell division from a haploid product of meiosis and so do the spermatozoa from the spermatids. (See Fig. G8 for development of the female and male gametes of higher animals and plants) Basically, gametogenesis in animals and plants shows substantial similarities because in both cases it is based on meiosis. The processes of gametogenesis are regulated in a complex manner by various hormones. In animals, the primordial germ cells colonize the gonads (spermatocytes and oocytes) through the mediation of chemokines such the stromal cell-derived factor-1 and its receptor CXCR4 (Ara T et al 2003 Proc Natl Acad Sci USA 10:5319). These chemokines control diverse other developmental processes too. More than 2,300 genes produce germ cell-specific transcripts (Schultz N et al 2003 Proc Natl Acad Sci USA 1000:12201). In *Caenorhabditis*, according to one study, 132 proteins are enriched during spermatogenesis and 444 during oogenesis whereas 370 are enriched during the formation of both types of gametes (Chu DS et al 2006 Nature [Lond] 443:101). Sparmatogonial stem cells transplanted into immature testes produce viable sperm cells even when the donor is rat and the recipient is mouse. Through such a procedure the xenogeneically produced spermatozoa yielded viable rat offspring when microinjected into rat oocytes (Shinohara T et al 2006 Proc Natl Acad Sci USA 103:13624). In mice in addition to “actual stem cells”, which are normally self-renewing, a second population (“potential stem cells”) also exists, which is capable of self-renewing but do not self-renew in the normal situation. Potential stem cells rapidly turn over in normal testes, suggesting that they belong to the transit-amplifying, rather than the dormant, population. During the long natural course, actual stem cells are occasionally lost and compensated for by progeny of their neighbors (Nakagawa T et al 2007 Dev Cell 12:195). ► [spermiogenesis](#), ► [gametophyte](#), ► [germ cells](#), ► [histone variants](#), ► [protamines](#), ► [animal hormones](#), ► [GDNF](#), ► [Wolffian ducts](#), ► [Müllerian ducts](#), ► [hedgehog](#), ► [azoospermia](#), ► [atresia](#), ► [synergid](#), ► [CXCR](#), ► [SDF](#), ► [stem cells](#)

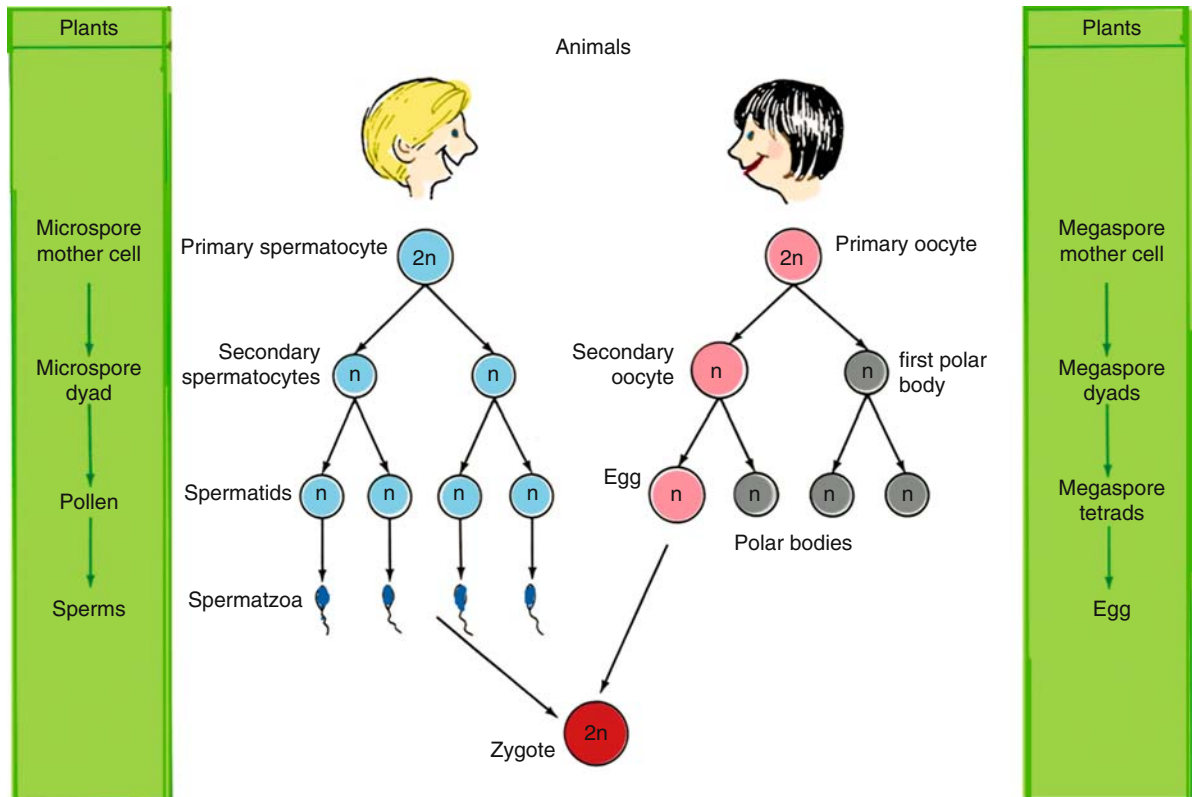


Figure G8. Comparative view of animal and plant gametogenesis

Gametophore: Leafy shoots of mosses bearing gametangia. ►gametangia

Gametophyte: The cells resulting from the meiosis of plants that have half the chromosome number of the zygotes. The gametophytes (megaspores, microspores) will form the gametes (egg and sperm). Selection at the gametophyte level is much more effective than in the sporophytic generation when the intended target of the selection is expressed at this developmental stage. The effectiveness of selection is particularly needed when the frequency of the gene selected for is low. Selection at the haploid level was apparently successful for tolerance to herbicides, toxins secreted by pathogens, alcohol dehydrogenase mutations, and possibly against certain stress effects. There are evolutionary variations in gametophyte structures (Friedman WE 2006 Nature [Lond] 441:337).

CHR11 chromatin remodeling factor is essential for the development of the female gametophyte in *Arabidopsis* (Huanca-Mamani W et al 2005 Proc Natl Acad Sci USA 102:17231). The effectiveness of selection is particularly needed when the frequency of the gene selected for is low. Selection at the haploid level.

In the somatic cells of flowering plants a germline-restrictive silencing factor (GRSF) suppresses the

expression of genes required for the function of the sperms by binding to the promoter of silencing sequences in lily and *Arabidopsis* (Haerizadeh F et al 2006 Science 313:496). Mutant *cdka1* pollen has only a single nucleus, which results in lack of fertilization of the diploid endosperm and consequently in seed sterility in *Arabidopsis* (Nowack MK et al 2006 Nature Genet 38:63). In the absence of the *FIS*-class genes the *cdka1* plants can produce reduced size maternal endosperm, which is smaller yet weakly functional (Nowack MK et al 2007 Nature [Lond] 447:312). See Figs. G9 and G10; ►sporophyte, ►cytoplasmic male sterility, ►male sterility, ►pollen competition, ►certation, ►gametophyte factor, ►incompatibility alleles

Gametophyte Factor: Affects the haploid gametophyte and may be responsible for reduced transmission of the chromosome (gamete) that carries it in a heterozygote. Gametophyte factors generally have more detrimental effect on the male but in rare cases the female is also influenced to various degrees. ►certation, ►gametophyte, ►meiotic drive, ►preferential segregation, ►selective fertilization, ►zygotic lethal, ►pollen-pistil interactions; Swanson R et al 2004 Annu Rev Genet 38:793.

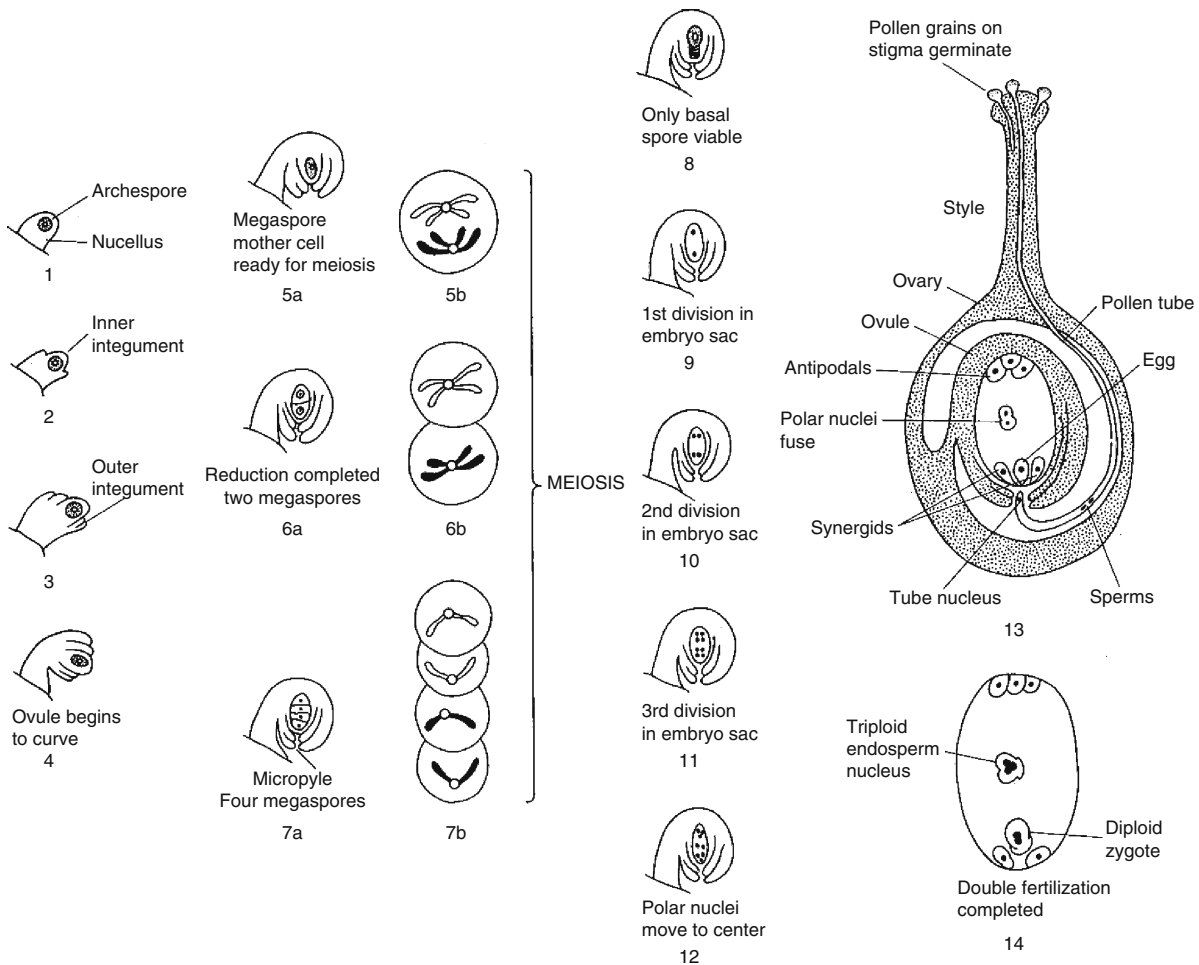


Figure G9. Development of the female gametophyte of higher plants. (The meiotic stages show only one bivalent)

Gamma (γ): The risk for a disease or other attribute associated with a particular genotype. ►[risk](#)

Gamma Distribution: Distribution of the amount of time until the x^{th} occurrence of an event by the Poisson distribution. It has been used to fit the evolutionary rate variation among protein sites. The gamma distribution and similar statistical concepts serve for the theoretical

$$f(x) = \frac{1}{\Gamma(n)} e^{-x} x^{n-1}, \text{ the } \Gamma(n) = \int_0^{\infty} e^{-x} x^{n-1} dx,$$

when n is an integer $\Gamma(n) = (n-1)!$

foundations for the t-distribution, F-test and chi square frequently used in genetic analyses. ►[Poisson distribution](#), ►[t-test](#), ►[F-test](#)

Gamma Field: An area or space where chronic exposure is usually provided from a source of electromagnetic radiation (e.g., ^{60}Co). Such a field may help in studies assessing the effects of long-term exposures on

various biological materials (mutation, chromosome breakage, physiological changes) in case of nuclear accidents. ►[electromagnetic radiation](#), ►[radiation effects](#), ►[radiation hazard assessment](#), ►[radiation protection](#), ►[gamma rays](#)

Gamma Interferon Activation Site (GAS): TTNCNNAA. ►[signal transduction](#), ►[Jak-STAT](#), ►[ISRE](#), ►[STAT](#), ►[interferon](#)

Gamma Rays: These are ionizing radiations (photons, electromagnetic radiation) emitted by isotopes (such as ^{137}Cs , ^{60}Co , and others). They are similar to X-rays but have much higher energy and have an ability to traverse even several centimeters of lead. Gamma rays from ^{60}Co (1.2 - 1.3 MeV) have a linear energy transfer 0.3 LET compared to hard X-rays (250 keV). [LET measures ionizing radiation in keV/nm path]. ►[physical mutagens](#), ►[electromagnetic radiations](#), ►[Volt](#), ►[eV](#)

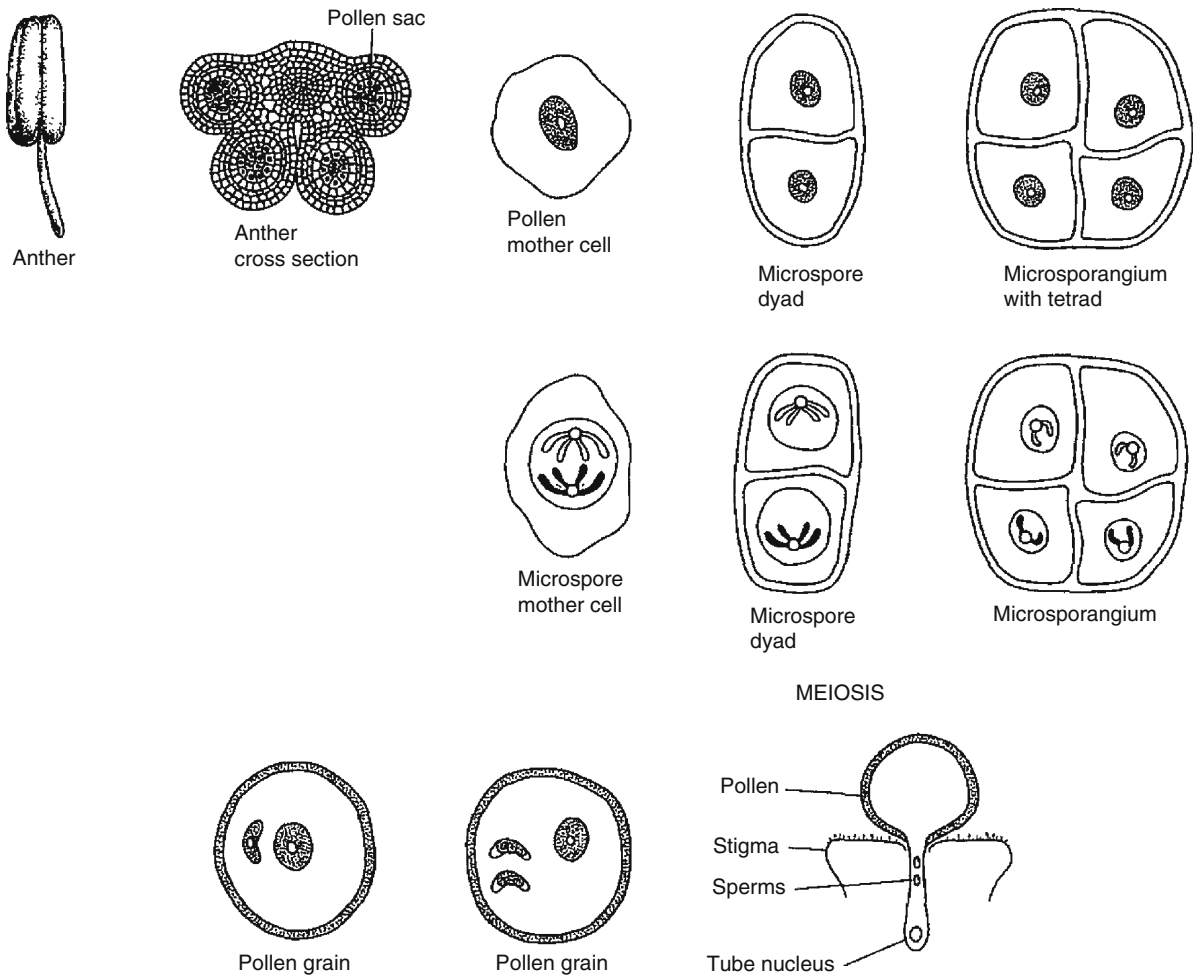


Figure G10. Development of the male gametophyte of higher plants. The meiotic stages (showing only one bivalent)

Gamma Selection Parameter: $\gamma = 2N_e s$ where N_e is the effective population size and s is the selection coefficient. ▶effective population size, ▶selection coefficient

Gammaglobulin: An immunoglobulin (IgG) consisting of either the light chains κ or γ and the heavy chains have one of the $C_{\gamma 3}$, $C_{\gamma 1}$, $C_{\gamma 2}$, $C_{\gamma 4}$ coded constant regions. ▶antibody, ▶immunoglobulins, ▶agammaglobulinemia, ▶immunodeficiency

Gammopathy: A condition of defective immunoglobulin (gammaglobulin) synthesis.

Gamodeme ▶deme

Gancyclovir: (GCV): A guanine analog, 9-[1,3-dihydroxy]-2-propoxymethylguanine) and a derivative of gancyclovir (2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6-H-purine-6-one, DCV). Both are antiviral (herpes) and anticancer drugs when incorporated into DNA because the analogs will prevent further replication of the genetic material

(see Fig. G11). GCV requires activation, usually by herpes virus thymidine kinase (HSV-TK) that converts it to a monophosphate form and subsequently cellular kinases mediate the production of the toxic triphosphate. ▶suicide vector, ▶adoptive cell therapy, ▶see shingles for acyclovir structure

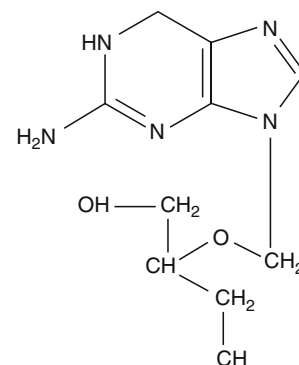


Figure G11. Gancyclovir.

Ganglion: A group of nerve cells outside the central nervous system.

Ganglioneuromatosis: ►MEN, ►tyrosine receptor kinase

Gangliosides: These are sphingolipids containing several units of acidic sugars attached to the fatty acid chain; they are common in nerve tissues. Their synthetic pathway is:

Uridine-diphosphate[UDP]-glucose + ceramide → glucosyl ceramide + UDP-galactose → galactosyl-glucosyl ceramide. Galactosyl-glucosyl ceramide + cytidine monophosphate-N-acetyl-neuraminic acid (CMP-NANA) → ganglioside G_{M3} . Ganglioside G_{M3} + UDP-N acetyl-galactosamine → ganglioside G_{M2} + UDP. Ganglioside G_{M2} + UDP galactose → ganglioside G_{M1} + UDP. Ganglioside G_{M1} + nCMP-NANA → higher gangliosides. If the sialic acid group (acetyl neuraminic acid, glucosyl neuraminic acid) is removed, asialogangliosides are generated. Several diseases, sphingolipidoses, are involved in their accumulation and breakdown. Ganglioside synthesis is indispensable for the normal development of the central nervous system and its absence leads to neurodegeneration and death. ►sphingolipids, ►sphingolipidoses, ►gangliosidoses, ►unfolded protein response, ►cancer gene therapy, ►Tay-Sachs disease; Kolter T et al 2002 J Biol Chem 277:25859.

Gangliosidoses: It includes a variety of forms. The general gangliosidosis Type I is β -galactosidase deficiency (3p21.33) disease leading to severe, progressive degeneration of the brain and death by the age of two. The overall symptoms resemble the Tay-Sachs disease caused by hexosaminidase A deficiency and the Niemann-Pick disease brought about by sphingomyelinase deficiency. The newborns already show abnormally low activity accompanied by facial and other edemas (fluid accumulation). The distance between the upper lip and nose is enlarged, the ears are set low, there is light hairiness on the front and neck, the spinal column is deformed, the fingers are short, poor appetite and lethargy and general weakness. The liver and spleen become enlarged. Type II juvenile gangliosidosis has a later onset, and death is delayed to age four to five. This form has also very low β -galactosidase levels yet another enzyme seems to be involved. In contrast to Type I disease, in Type II liver and spleen enlargement as well as bone deformities are absent. The heterozygotes can be identified by β -galactosidase assay and the recurrence may be avoided by genetic counseling. Type III is an adult form and it is controlled by a locus different from that of type I. Besides the autosomal Type III, there is an X-linked GM3-gangliosidosis and the latter affects young children. The classification of gangliosidoses

is quite complicated. ►GM-gangliosidoses, ►galactosidase, ►sphingolipidoses, ►sphingolipids, ►Tay-Sachs disease, ►Sandhoff's disease, ►spleen

Gap: An unknown sequence in between contigs, gapped genome. Before a first-draft sequence is produced filling must close the gaps in the sequences that may exist between contigs. ►contig, ►first-draft sequence, ►genome projects; Frohme M et al 2001 Genome, Res 11:901.

GAP: GTPase activating protein is encoded in the long arm of human chromosome 5. Tyrosine-phosphorylated GAP is in the cell membrane whereas the unphosphorylated is mainly in the cytosol. RHO and RAS-related GTPases are abundant in the cells and they regulate signal transduction and the cytoskeleton. ►RAS, ►RHO, ►GTP, ►signal transduction, ►GED, ►von Recklinghausen disease, ►RanGTPase; Ross EM, Wilkie TM 2000 Annu Rev Biochem 69:795.

GAP Genes: Gap genes in *Drosophila* have some segments missing or have fused segments (see Fig. G12). The body pattern is along the longitudinal axis (posterior→ anterior) of the wild type *Drosophila* embryo. Some of the gap mutations delete and/or modify the segments. ►morphogenesis, ►morphogenesis in *Drosophila*, ►knirps, ►Krüppel

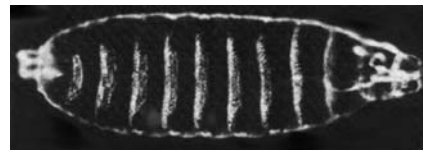


Figure G12. Body segments

Gap Junctions: The connecting channels (made of connexins) between apposed cells that permit the transfer of molecules and electric signals between cells. Peptides, such as the class I MHC molecules, up to 1,800 molecular weight may be transmitted between neighboring cells unless the three-dimensional structure interferes (Neijssen J et al 2005 Nature [Lond] 434:83). The same task in plants is assigned to plasmodesmata. Carcinogenic agents may block gap junctions. The function of gap junction can be monitored through transfer of fluorescent dyes or by complementation of nutrients. ►connexin, ►hemichannel, ►innexins, ►plasmodesma, ►CAM, ►MHC, ►Charcot-Marie-Tooth disease, ►oculodentodigital dysplasia; Kumar NM, Gilula NB 1996 Cell 84:381; connection formation: Shaw RM et al 2007 Cell 128:547.

Gap Penalty: When similarities are sought in nucleotide alignments for the sake of construction of evolutionary trees (or determine relatedness) and gaps are encountered, these are subtracted from the matches to avoid unwarranted conclusions regarding homologies.

GAPO Syndrome: Autosomal recessive defect characterized by retarded growth, reduced hair development (alopecia) toothlessness (pseudoanodontia) and progressive wasting of the optical nerves. It bears similarity to progeria. ►progeria, ►growth retardation, ►Gombo syndrome

G

Garden of Eden: The evolutionary theory supposes that the human population originated from single group and about 100,000 years ago, after passing through several bottlenecks, they differentiated into several subpopulations and dispersed from Africa. ►out-of-Africa hypothesis, ►multi-regional origin; Ambrose SH 1998 J Hum Evol 34:623.

Gardner Syndrome (APC, adenomatous polyposis of the colon; mutation in FAP): An autosomal dominant (human chromosome 5q21-q22, 8535 bp) familial polyposis of the colon (FPC). Mutation or deletion occurring at a frequency of about $2-3 \times 10^{-5}$ (in Ashkenazim populations the carrier frequency may exceed 7%), and it may cause adenomatous intestinal polyposis (a cancer) and breast cancer. Penetrance is very high and the prevalence in the general population is $\sim 1/8,000$. The syndrome includes several symptoms, especially if the genetic lesion extends to a larger segment in the region of several genes nearby. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) may be an early diagnostic sign. In some cases, the polyps are limited only to the colon but there are cases where other parts of the intestinal tract, the stomach, the forehead, soft bony tissues, epidermal cysts may also become tumorous. Some forms were associated with increased ornithine decarboxylase activity. Pre-symptomatic diagnosis may detect deletions by the use of appropriate DNA markers. Gene targeting experiments revealed the deletion of exon 14 of APC leads to rapid development of adenomas in mice. In the absence of the WNT morphogenetic signal, APC interacts with glycogen synthase kinase (GSK) and β -catenin. In this case, the Tcf (T cell transcription factor) and Lef (lymphoid enhancer factor) are blocked and the complex leads to tumor suppression. If APC is inactivated monomeric β -catenin appears in the cytoplasm and tumors are formed. Catenin seems to be a transcriptional co-activator of Tcf and Lef. The APC tumor suppressor has apparently a nuclear export function. The c-MYC oncogene is repressed by the wild type APC protein but activated by β -catenin

through Tcf-4 binding sites in the MYC promoter. APC appears to link microtubules (spindle fibers) to the kinetochore, more specifically the Bub protein, a mitotic checkpoint control kinase. This large gene locus includes 15 exons with phenotypic difference among the different allelic mutations/deletions and this causes some ambiguity in the nomenclature. APC is generally associated with chromosomal instabilities because mutation in the APC protein no longer controls the regular function of the kinetochore and its association with the spindle fibers. ►colorectal cancer, ►FAP, ►skin diseases, ►cancer, ►polyposis, ►Turcot syndrome, ►Muir-Torre syndrome, ►targeting gene, ►Cre/LoxP, ►exon, ►adenoma, ►WNT, ►catenins, ►conductin, ►kinetochore, ►spindle fibers, ►GSK, ►MYC, ►hereditary non-polyposis colorectal cancer, ►desmoid disease hereditary, ►mismatch repair; Bienz M, Clevers H 2000 Cell 103:311; Su L-K et al 2000 Am J Hum Genet 67:582; Livingston DM 2002 Nature [Lond] 410:536; Fearnhead NS et al 2001 Hum Mol Genet 10:721; Haigis KM, Dove WF 2003 Nature Genet 33:33.

Gargoylism: A defect in L-iduronidase such as in the Hurler and Hunter syndromes. ►mucopolysaccharidosis

Garlic (*Allium sativum*): A spice, $2n = 16$. Its alliin (allicin) component inhibits cystein proteinases and thereby may exert antibiotic effects on some parasitic microorganisms (see Fig. G13). Its ajoene (sulfur-rich) extract may be antimitotic, microtubule-regulatory, anti-hypertension and anticarcinogenic. ►onion; Li M et al 2002 Carcinogenesis 23:523; Ledezma E et al 2004 Cancer Lett 206:35; Macpherson LJ et al 2005 Current Biol 15:929.

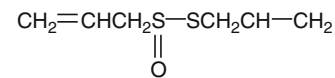


Figure G13. Alliin

GAS: ►gamma interferon activation site, ►interferons, ►signal transduction

Gas Chromatography: ►chromatography, ►gas-liquid chromatography

Gas-Liquid Chromatography (GLC): GLC is suited for the separation of volatile compounds according to their ability to be dissolved in the material of the column bed. An inert gas (helium) driven through the column carries the volatile compounds, and they are sequentially eluted and collected. Some material must be converted to more volatile derivatives before applied to the columns. This method has been

extensively used to separate and isolate fatty acids and other compounds. ►[chromatography](#)

Gastric Cancer (hereditary diffuse gastric cancer, HDGC, 16q22.1, 5q31.1): As the chromosomal locations indicate two forms of gastric cancer are known. One of them involves a methylation of 6–18 CpG nucleotides in the cadherin1 (CDH1, 16q22) promoter leading to inactivation. Predisposing genes: non-polypoid colon cancer, familial adenomatous polyposis, Peutz-Jeghers syndrome and the Cowden disease. ►[cadherins](#), ►[hereditary nonpolyposis colon cancer](#), ►[Gardner syndrome](#), ►[polyposis hamartomatous](#), ►[multiple hamartoma syndrome](#)

Gastrin: Hormones of 14 to 34 amino acid residues, released in the stomach and regulate stomach acid secretion, other enzymes and esophageal and gall bladder contraction.

Gastroenteritis: Inflammation of the lining of the stomach and intestines.

Gastrointestinal Stromal Tumor, Familial: ►[KIT oncogene](#)

Gastroschisis: A fissure of the abdominal cavity and some of the intestines are protruded through failure of the wall of the abdomen. The pattern of inheritance is unclear. ►[omphalocele](#)

Gastrula: An early stage of embryonic development following the blastula. Gastrulation patterns vary in different animal taxa. The general pattern is an invagination of the epithelial layer into the blastocoel (at the so-called vegetal pole) forming the endoderm that gives rise later to the gut. The outer layer, the epithelium, becomes the ectoderm that will form the epidermis and the nervous system. The cells in-between these two layers develop into a mesoderm that will differentiate into the notochord (a vertebral column or its substitute), into the connective tissues, bones, cartilages, fibers, muscles, the urogenital system and the vascular system, including the heart and blood vessels. Gastrulation of the human embryo takes place during the third week of embryonal development (in mice 6–7 days post coitum). In arthropods, gastrulation is followed by anterior-posterior segmentation and dorsal-ventral, medial-lateral identification of embryonal regions. ►[blastula](#), ►[morphogenesis](#), ►[coitus](#), ►[organizer](#), ►[embryo node](#), ►[p38](#)

GATA: Mammalian transcription factors mediating the formation of erythrocytes. GATA-1 (Xp11.23) recognizes the ^{GTATAG}_{ACTATC} or very similar upstream DNA sequences. Several other GATA factors have been identified also in other vertebrates. GATA-3 (10p15) is a human hematopoietic factor responsible also for the

differentiation of T cells of the immune system. Loss of GATA3 results in noradrenaline deficiency and embryonic lethality in mice. GATA factors may include 4 Zinc finger domains. Mutation in GATA1 results in dyserythropoietic anemia and thrombocytopenia. GATA-2 and GATA-3 regulate adipocyte differentiation and their deficiency may lead to obesity. GATA-4 (8p22-p23), GATA-5 and GATA-6 are expressed on the developing heart. ►[transcription factors](#), ►[hematopoiesis](#), ►[T cell](#), ►[T-bet](#), ►[DNA-binding protein domains](#), ►[erythropoietin](#), ►[dyserythropoietic anemia](#), ►[thrombocytopenia](#), ►[obesity](#), ►[transcriptional priming](#), ►[DiGeorge syndrome](#), ►[noradrenaline](#); Charron F, Nemer M 1999 *Semin Cell Dev Biol* 120:85; Molkenin JD 2000 *J Biol Chem* 275:38949; Patient RK, McGhee JD 2002 *Current Opin Genet Dev* 12:416.

Gatekeeper: ►[selectivity filter](#)

Gatekeeper Gene: It acts in the pathway of carcinogenesis by representing a certain threshold that must be passed before mutation of the tumor suppressor or activator gene(s) can mediate the development of the recognizable oncogenic transformation. Genes preventing other cellular processes are also called gatekeepers. ►[oncogenic transformation](#), ►[oncogenes](#), ►[transformation oncogenic](#), ►[progression](#), ►[cancer](#), ►[phorbol esters](#), ►[caretaker gene](#); Kinzler KW, Vogelstein B 1997 *Nature [Lond]* 386:761; Gomis-Ruth FX, Coll M2001 *Int J Biochem Cell Biol* 33 (9):939.

Gating in Cytometry: Used for typing different cells (e.g., CD4⁺, CD8⁺ lymphocytes) in cytometers. The gates permit the selective identification and counting of specific type on the basis of fluorochromes or antibody, etc. labels. The procedure may facilitate the clinical evaluation of the status of, e.g., AIDS patients. ►[acquired immunodeficiency](#); Bergeron M et al 2002 *Cytometry* 50:53.

Gateway Cloning: A procedure for large-scale identification of open reading frames (ORFeome) in order to annotate the genome and determine the protein-coding open reading frames. The outline of the protocol: 1. Collect a large set of open reading frames from databases. 2. Establish a large number of appropriate primers. 3. Carry out PCR on the cDNA library. 4. Clone recombinant sequences into *E. coli* plasmid vector. 5. Isolate the cloned plasmids. 6. Sequence tagged ORFs (OSTs) and obtain Phred score. 7. Align the ORFs on genomic sequences. 8. Identify thus the location of ORFs and can enter them into a database (Reboul J et al 2003 *Nature Genet* 34:35). ►[ORF](#), ►[ORFeome](#), ►[OST](#), ►[polymerase chain reaction](#), ►[Phred](#)

Gaucher Disease: A chromosome 1q21 recessive complex of glucosyl ceramide lipidoses. There are six genes and two pseudogenes within a 75 kb region and ten different crossing over sites and shared CACCA recombinational hot spots were detected (Tayebi N et al 2003 Am J Hum Genet 72:519). Glucosyl ceramide sphingolipids accumulate in the reticuloendothelial “Gaucher cells” because of deficiency of a β -glucosidase (glucosylceramidase). These Gaucher cells occur in the lymphoid tissues, spleen, bone marrow, inside the veins, lung alveoli and other tissues. The Type I disease occurs in various age groups and the most characteristic symptoms are enlargement of the spleen and bone anomalies. The neuronopathic or malignant Type II form appears before age of six months and results in death by the age of two. The cranial nerves and the brain stem are attacked although there is not much lipid accumulation in these tissues. The less severe juvenile form (Type III) may permit survival to the age of thirty years. Gaucher’s disease is of relatively common occurrence. Cure can be provided by enzyme replacement therapy. A mouse model indicates that transplantation of bone marrow or gene therapy through retroviral transduction either prevented or corrected the disease (Berglin Enquist I et al 2006 Proc Natl Acad Sci USA 103:13819). Prenatal diagnosis is feasible by the use of RFLP and enzyme assays. ▶sphingolipid, ▶sphingolipidoses, ▶glucosidase, ▶RFLP, ▶prenatal diagnosis, ▶lysosomal storage disease Jews and genetic diseases, ▶enzyme replacement therapy, Lewy body; Koprivica V et al 2000 Am J Hum Genet 66:1777.

Gaudens: *Oenothera lamarckiana* contains a ring of 12 translocation chromosomes and one bivalent (see Fig. G14). The translocations contain two complexes, *gaudens* (happy) conveys green color and *velans* (concealing) determines narrow leaves, pale color and disease susceptibility. The (complex) heterozygotes

appear normal. Because of the translocations and the recessive lethal genes they carry, half of the progeny is inviable (*gaudens/gaudens* and *velans/velans* homozygotes) and the other half (the balanced lethal translocation heterozygotes) breeds true and is of normal phenotype. ▶multiple translocations, ▶complex heterozygote, ▶*Oenothera*

Gaussian Distribution: ▶normal distribution

Gazella: In the Dorcas gazella (*Gazella dorcas*) and the Grant’s gazella (*Gazella granti*) the male has 31 chromosomes the female 30. In the *Gazella leptoceros* the males are $2n = 33$, the females $2n = 32$. The Thomson’s gazella (*Gazella thomsoni*) is $2n = 58$.

G_β: ▶G_{αβγ}

G-BASE: Genomic database of mouse, for access see Mouse Genome Database, Encyclopedia of the Mouse Genome. ▶mouse, ▶databases

G-Box Element: An upstream binding site (GA-CAACGTGGC) in plants of which the critical part is the CAACGTG core sequence that binds the G-box protein, a transcriptional activator.

GBP: GSK binding protein. ▶GSK

GC Box: GC BOX in eukaryotic promoters generally contain the 5'-GGGCGG-3' motif, a binding site for transcriptional regulator proteins.

GC (guanine-cytosine) Content: GC content of DNA contributes to the higher buoyant density of the molecules. In the DNA of the majority of eukaryotes, the GC content is about 40%. Higher organisms seem to display higher GC content yet genome size among eukaryotes does not involve higher GC content. It has been suggested that higher GC content affects the expression of genes but it could not be confirmed by more extensive analysis (Sémon M et al 2005 Hum Mol Genet. 14:421). ▶buoyant density, ▶density gradient centrifugation, ▶ultracentrifugation,

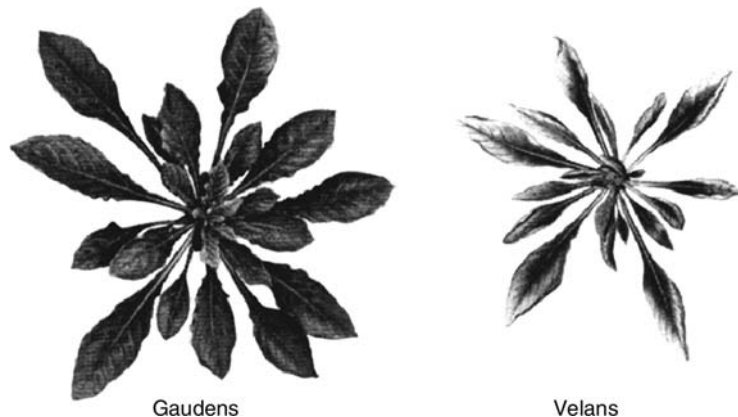


Figure G14. *Oenothera* pictures from deVries H 1913 Gruppenweise Artbildung, Borntraeger, Berlin

►DNA, ►base composition; GC identification tool:
<http://tubic.tju.edu.cn/GC-Profile/>.

GC Skew: $(G - C)/(G + C)$ indicating the not entirely random distribution of G and C on the two DNA strands. In *E. coli* there is 26.22% G in the leading strand whereas in the lagging strand it is 24.58%.

►DNA replication prokaryotes

GC-MS: Gas-liquid chromatography combined with mass spectrometry is an analytical procedure. ►gas-liquid chromatography, ►mass spectrum

GCN1/GCN20: A ribosome-binding complex bound by the N domain of GCN2 and it required for activation of the latter in starved yeast cells. (See Kubota H et al 2001 J Biol Chem 276:17591).

GCN2: It is dimeric and is required for the activation of GCN4. It has ribosome-binding, tRNA-binding, protein kinase and GCN2/GCN20-binding domains. Heatshock protein 90 assists its maturation folding. Its sequence is conserved across fungi, insects and mammals. (See Marbach I et al 2001 J Biol Chem 276:16944).

GCN4: The yeast transcription factor of a leucine zipper structure controlling the transcription of several genes. Its transcription is triggered by amino acid starvation when eukaryotic peptide elongation factor GCN2•eIF-2a becomes phosphorylated. The DNA binding site consensus for GCN4 is: $\begin{matrix} \text{ATGACTCAT} \\ \text{TACTGAGTA} \end{matrix}$ (See ►leucine zipper, ►eIF-2a, ►HRI, ►PEK; Yu L et al 2001 J Biol Chem 276:33257; Natarajan K et al 2001 Mol Cell Biol 21:4347).

GCN5: A yeast transcriptional co-activator with a histone acetyl transferase domain including amino acids 99–262 of the 439-amino acid protein (see Fig. G15). It consists of four antiparallel β-strands, an α-helix and a fifth β-strand. This domain is shared by other histone acetyltransferases as well as by other acetyltransferases such as an aminoglycoside 3-*N*-acetyltransferase and serotonin *N*-acetyltransferase belonging to the GNAT superfamily. It consists of four antiparallel β-strands, an α-helix and a fifth β-strand. This domain is shared by other histone acetyltransferases as well as by other acetyltransferases such as an aminoglycoside 3-*N*-acetyltransferase and serotonin *N*-acetyltransferase belonging to the GNAT superfamily. These enzymes transfer an acetyl group from Acetyl-CoA to a primary but different amino group. ►histone acetyl transferase, ►p300, ►aminoglycosides, ►acetyl CoA, ►TAF_{II}, ►transcriptional activators, ►enhanceosome; Kuo MH et al 2000 Mol Cell 6:1309.

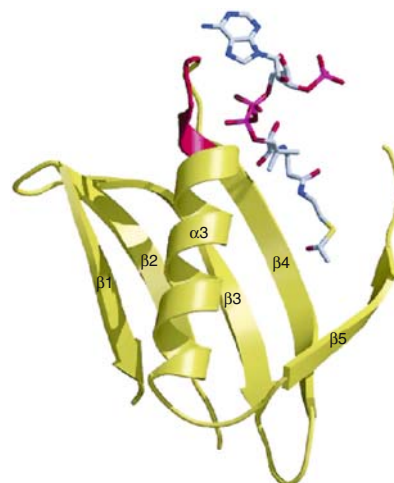


Figure G15. Crystal structure of GCN5 showing the four acetyl transferases. Courtesy of Drs. Sternglanz R and Shindelin H 1999 Proc. Natl. Acad. Sci. USA 96: 8807

G

GCR: G protein coupled receptor. ►G proteins

G-CSF (granulocyte-colony stimulating growth factor): A lymphokine, modulating the effect of growth factors, fetal and post-natal development. ►GM-CSF, ►M-CSF

GCSF (G-CSF): ►granulocyte colony stimulating factor, ►lymphokine

GD: ►hybrid dysgenesis

γδ Element (Tn1000): An insertion element (IE) of the bacterial F plasmid that may produce various Hfr bacterial strains either by co-integration or recombination. The pDUAL/pDelta vector series of the γδ family vectors have been successfully used for generating (nested) deletions in both strands of a cloned insertion sequence. The plasmid replication origin and γsome selectable marker(s) are located in both strands in such a way that none of the essential information would be outside the transposon. ►co-integration, ►Hfr, ►F factor, ►F plasmid, ►Tn3 family, ►nested; Broom J et al 1995 DNA Seq 5 [3]:185; Kumar P et al 2004 Biochemistry 43:247.

γδ T Cells: Express any of the Vγ and Vδ immunoglobulin genes, recognize non-peptidic antigens and the antigen. The γδ T cells do not need professional antigen presenting cells and do not require processing by MHC class I or class II molecules and their ligands in order to be recognized by them in contrast to the αβ T cells (Brandes M et al 2005 Science 309:264). The γδ T cells (~2–10% of all T cells) are very different from the most prevalent αβ T cells and they can be stimulated also by non-peptide antigens such as

phosphocarbohydrates, X-uridine and X-thymidine-5'-triphosphates (TUBBag3 and TUBbag4, respectively) and isopentenyl pyrophosphate. The $\gamma\delta$ T cell differentiation is promoted by the Sox13 transcription factor of the thymocytes whereas the same transcription factor opposes the development of the $\alpha\beta$ T cells (Melichar HJ et al 2007 Science 315:230). The molecules may be the product of nucleic acid salvage pathways and intermediates of the lipid metabolism. The $\gamma\delta$ T cells mount primarily an innate immune response but because they stimulate chemokines and secrete cytokines they promote also the acquired immune system ($\alpha\beta$ T cells). In the absence of $\gamma\delta$ T cells IgE and IgG1, IL-5 and eosinophils are reduced and mice in this condition does not show allergic asthma of the airways in response to peptidic allergens. The $\gamma\delta$ T cell receptor is different from that of the $\alpha\beta$ T cell receptor (Adams EJ et al 2005 Science 308:227). ▶ immunoglobulins, ▶ T cells, ▶ $\alpha\beta$ T cells, ▶ T cell receptor, ▶ salvage pathway, ▶ HLA, ▶ immune system, ▶ eosinophil, ▶ IL-5, ▶ allergen, ▶ asthma; Silva-Santos B et al 2004 Science 307:925; Allison TJ et al 2001 Nature [Lond] 411:820.

GDB: Genome database, the official depository of information of the human genome project. It can be accessed by Internet <http://gdbwww.gdb.org/>. (See also <http://www.ncbi.nlm.nih.gov/Entrez/>).

GDF (growth and differentiation factor): A member of the bone morphogenetic protein family. GDF5 mutations cause chondrodysplasia. ▶ BMP

GDEPT: Gene delivered enzyme-prodrug therapy. ▶ prodrug

GDI (guanine nucleotide dissociation inhibitor): GDI inhibits the dissociation of GDP from certain G proteins. ▶ G protein, ▶ signal transduction, ▶ GEF

GDLD (gelatinous drop-like corneal dystrophy): A rare hereditary amyloidosis. ▶ amyloidosis

gDNA: ▶ genomic DNA

GNDF (glial-cell-line-derived neurotrophic factor): Assists in the maintenance of central dopaminergic, noradrenergic and motor neurons and peripheral and sympathetic neurons. It is a family with several functional members neurturin, perefirin and artemin. This protein is structurally related to the transforming growth factor (TGF- β) family and GDNF is a receptor tyrosine kinase. GDNF function requires a glycosylphosphatidylinositol-linked protein (GDNFR- α) and RET. It has been considered as a potential drug for Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease. GDNF also regulates spermatogenesis. ▶ dopamine, ▶ neuron, ▶ receptor tyrosine kinase, ▶ Parkinson's disease, ▶ amyotrophic lateral

sclerosis, ▶ Alzheimer's disease, ▶ kinase, ▶ TGF, ▶ RET oncogene, ▶ MEN; Hashino E et al 2001 Development 128:3773; Bahuau M et al 2001 J Med Genet 38:638; Lee CS et al 2005 Exp Neurol 191:65.

GDRDA: ▶ genetically directed representational difference analysis

GDP: Guanosine 5'-diphosphate

GE81112: An antibiotic consisting of four amino acids (3-hydroxyisovaleric acid, 2-amino-5-[(aminocarbonyl)oxy]-4-hydroxypentanoic acid, histidine and 5-chloro-2-imidazolyserine). It inhibits specifically peptide initiation on the 30S prokaryotic ribosomal subunit by interfering with the binding of the fMet-tRNA (Brandi L et al 2006 Proc Natl Acad Sci USA 103:39). ▶ antibiotics

GENC (genetically effective cell number): ▶ genetically effective cells

GED: GTPase effector domain located at the C-end of dynamin. ▶ dynamin, ▶ GTPase, ▶ GAP

GEF: Translation factor similar in function to eIF-2B. ▶ eI factors, ▶ TU

GEF (guanine nucleotide exchange [release] factor): It facilitates the dissociation of GDP from G proteins. It is similar to ▶ Cdc25. ▶ GDI, ▶ GAP, ▶ Cdc25, ▶ G protein, ▶ signal transduction, ▶ SOS, ▶ ARF, ▶ faciogenital dysplasia, ▶ cytohesins, ▶ SOS; Vetter IR, Wittinghofer A 2001 Science 294:1299; Brugnera E et al 2002 Nature Cell Biol 4:574; Vazquez-Prado J et al 2004 Methods Enzymol 390:259.

GEFITINIB: ▶ Iressa

Geiger Counter (Geiger-Müller counter): Registers the rate of disintegration of radioactive isotopes. They are necessary in all isotope laboratories, also for monitoring contamination and spillage (see Fig. G16). The counter also detects environmental pollution of radioactivity in case of fallout. It measures β radiation with efficiency of 30–45% and for γ radiation (shield closed) 5,000 counts per minute per milliröntgen (mR). A typical full-scale reading is 0.2 to 20 mR/hr. It is very useful equipment for surveying because of good sensitivity and within seconds response. Its shortcomings are energy dependence, saturation at high rates and interference by ultraviolet and microwave radiations. A special adaptation of the Geiger counter is the strip counter that detects radiation in chromatograms, membrane filters, blots, etc. ▶ scintillation counters, ▶ ionization chambers, ▶ radiation hazard assessment



Figure G16. Geiger counter

Geitonogamy: Pollination by neighboring plants of basically the same genetic constitution.

Gel Electrophoresis: Nucleic acid fragments are electrophoresed in agarose and polyacrylamide gels, depending on the size of the fragment. In agarose larger, in polyacrylamide smaller fragments can be separated, e. g., in 0.3% agarose 5–60 kb, in 0.7% 0.8–10-kb fragments can be analyzed. In 5% polyacrylamide 0.5–0.8-kb, in 2% 0.04–0.1-kb fragments can be resolved (see DNA fingerprinting). Proteins can be electrophoresed in various media (paper, starch, polyacrylamide) by charge or by size in polyacrylamide-sodium dodecylsulfate (SDS) gels. ▶[electrophoresis](#), ▶[two-dimensional gel electrophoresis](#)

Gel Filtration: Porous polymers such as Sephadex, Bio-Gel (commercially available in various pore sizes) can be used to separate high molecular weight DNA or proteins from smaller molecules (unincorporated dNTPs, linkers, etc.) The large molecule is excluded while the smaller fragments are retained on the gel during chromatography. For rapid purification it can be used in syringes. ▶[Sephadex](#), ▶[linker](#)

Gel Mobility Assay: ▶[gel retardation assay](#)

Gel Retardation Assay: Compared to DNA alone, DNA-bound protein retards the movement of the complex in the electrophoretic field (band shifting), and this way DNA-binding proteins can be isolated and analyzed. To the protein bound to DNA, other protein(s) may also bind making the complex increasingly slow moving from the start site. This process is called *supershift*. A more specific test uses DNA affinity chromatography. ▶[DNA-binding domains](#), ▶[DNA binding proteins](#), ▶[affinity chromatography](#), ▶[electrophoresis](#)

Gelatinase: ▶[metalloproteinases](#)

Gelding: Castrated male horse. ▶[castration](#)

Geleophysic Dysplasia: A mucopolysaccharidosis with happy face, dysotosis and heart problems. ▶[mucopolysaccharidosis](#); Wraith et al 1990 Am J Med Genet 35:153.

Gellan Gum: A synthetic polysaccharide, used for solidifying plant tissue and bacterial culture media (instead of agar). ▶[agar](#), ▶[embryo culture](#)

Gelsolin: An actin-binding protein that regulates the cytoskeleton. ▶[actin](#), ▶[cytoskeleton](#), ▶[amyloidosis](#), ▶[fodrin](#)

Gem: A GTP-binding protein, induced by mitogens; it is related to RAS. ▶[GTP](#), ▶[mitogen](#), ▶[RAS](#)

GEM91: A 25-mer antisense phosphorothioate. ▶[antisense technologies](#), ▶[phosphorothioates](#)

Gemini of Coiled Bodies: These consist of heterogeneous nuclear ribosomal proteins (hnRNP), coiled bodies, and “survival-of-motor-neuron” proteins (SMN). SMN forms are tightly associated with protein SIP1 (SMN interacting protein). SMN1 is located in human chromosome 5q13 and SMN2 is almost identical to SMN1 but lacks an exon-7 domain. SMN1 is frequently replaced by SMN2 in spinal muscular atrophy. ▶[coiled bodies](#), ▶[hnRNP](#), ▶[spinal muscular atrophy](#); Matera AG, Frey MR 1998 Am J Hum Genet 63:317.

Geminin: A ~25-kDa protein preventing aberrant replication of the chromosomes after the S phase of mitosis. It keeps in check Cdc6/18 and Cdt1. It accumulates during mitosis but it is degraded at the transition from metaphase to anaphase. After it is degraded, Cdc6/18 and Cdt1 rebuild and associate with the chromatin in preparation for the S phase. ▶[mitosis](#), ▶[cell cycle](#), ▶[Cdc6](#), ▶[Cdc18](#), ▶[Cdt](#), ▶[MCM](#), ▶[ORC](#), ▶[replication licensing factor](#); Wohlschelegel JA et al 2000 Science 290:2309; Luo L 2004 Nature [Lond] 427:749.

Geminiviruses: These contain single-stranded small DNA genomes (~2.7 kb). Some can infect monocots others infect dicots (see Fig. G17). Their capsules may be geminate (doubled) or their DNA may exist in two partially-identical (200 bases) rings. They may be used for plant vector construction. ▶[agroinfection](#); Lazarowitz SG 1992 Crit Rev Plant Sci 11:327.



Figure G17. Geminiviruses particles

Gemmules: An ancient term for hereditary units.

GenBank: Data bank for information on nucleic acid and protein sequences, Los Alamos Natl. Laboratory, Group T-10, Mail Stop K710, Los Alamos, NM 87545, USA, Tel: (505) 665–2177, e-mail: general inquiries genbank%life@lanl.gov, sequence submission and forms: gb-sub%life@lanl.gov. ▶[EMBL](#),

►DDBJ, ►ENTREZ, ►Sequin, ►sperm bank, ►databases; Dennis A et al 2005 Nucleic Acid Res 33:DB34; <http://www.ncbi.nlm.nih.gov/>, complete genomes: <http://www.ncbi.nlm.nih.gov/Genomes/index.html>, updating: update@ncbi.nlm.nih.gov/projects/collab/FT/inex.html, feature table: <http://www.ncbi.nlm.nih.gov>, description of features: <http://www.ncbi.nlm.nih.gov/collab/FT/index.html>, unfinished large scale genomic high-throughput products: <http://www.ncbi.nlm.nih.gov/HTGS/>.

Genboree: Human Genome Sequencing Consortium sequencing and annotation programs. (See <http://www.genboree.org/java-bin/login.jsp>).

Gencode: An integrated annotation of existing cDNA and protein resources to define transcripts with both manual review and experimental testing procedures.

Gender: The sexual type, e.g., female or male in societal or lexicographic context; in physiology or genetics the word sex is more appropriate.

Gender Dimorphism: Separate individuals represent the two sexes.

Gender Discrimination: The difference between males and females is a biological fact yet that does not justify the ethical and moral principle that equal contribution must be equally rewarded. It is unfair, however, to evaluate men and women by identical criteria because the majority of the social criteria are male-oriented and disadvantageous for women. In general, males and females carry the same chromosomes except the gene-poor Y chromosome and the dosage of the X chromosomes, which are in duplicate in a normal female but the X is present only in a single dose in the normal males and dosage compensation may not be perfect. Both male and female attributes have special advantages. Maleness, in general, have been associated with more aggressiveness, less empathy compared with femaleness. There is no evidence, however, for differences in originality of thinking or creativeness, therefore for the frequently found lower appreciation for women in leadership or scientific contribution is not justified. In certain positions, males (e.g., when great physical strength is an advantage) and in others female characteristics (e.g., dealing with young children) are more desirable. The social differences between the sexes are frequently called gender gap. The gender gap was historically larger than it is today and it is steadily diminishing in business and academics. During the last 30 years among 4,227 life-scientists, patenting by women was only 40% of that by men (Ding WW et al 2006 Science 313:665). ►discrimination genetic, ►dosage compensation; Lawrence PA 2006 PLoS Biol 4[1]:e19.

Gender Preselection: Separation of X- and Y-bearing sperms before fertilization. Success in such a procedure may prevent the transmission of X-chromosome linked genetic defects. It may become an alternative to ethically or morally objectionable procedures of negative eugenics (Anyhow, it should be called sex preselection.) ►eugenics, ►abortion; Fertility & Sterility 75:861–864 [2001].

Gender Trading: In hermaphroditic animals the individuals may donate sperm or oocyte or both.

Gene: A specific functional unit of the DNA (or RNA) potentially transcribed into RNA or coding for protein. A group of co-transcribed exons but due to alternative splicing, or exon shuffling, or overlapping, or using more than one promoter or termination signal, the same nucleic acid sequence may encode more than a single protein. A common structural organization of protein encoding genes in eukaryotes: ►enhancer, ►promoter, ►leader, ►exons, ►introns, ►termination signal, ►polyadenylation signal, ►downstream regulators

The vast majority of human genes are ‘mosaics’ containing 7–9 exons of 120–150 bps, each. In some genes the exon number and size can be much larger. In between exons there are 1000 to 3,500 bp long introns. The size of the introns may also be several times larger. The number of coding nucleotides varies between 1,100 to 1,300 but the larger genes may have much larger coding sequences. The exons + introns + 5′ and 3′ untranslated sequences combined, the genomic genes, in general, extend to 14–27 kb DNA. A large fraction of the human genes is alternatively spliced and thus the same “gene” may be translated into three or more kinds of proteins. In human chromosome 10, the average known gene has 4.76 transcripts but the *adducin 3* gene has 22 variants. The organization of other eukaryotic genes may vary quantitatively. Genic sequences are richer in GC nucleotides than the non-coding tracts. In prokaryotes, introns are rare and the size of the genes is smaller. Computational procedures might assist the identification of promoters and first exons in the human (and other) genomes. Genes generally originate by duplication that is followed by mutational alterations to gain a new function. Alternatively, new functions may arise by reorganization of exons or modules or by emergence of functional sequences from non-coding DNA tracts. Lateral transfer delivers genes from one organism to another. Although the gene is a rather stable complex molecule, its function is mediated, modulated and controlled by several proteins. The potential role of epigenesis in gene expression and development is steadily increasing. The concept of the gene is undergoing now further complications since it became known that most of

the DNA (rather than a small “genic” fraction) is transcribed into RNA and these RNAs seem to have hitherto not completely understood function in controlling the expression of genes (Kapranov P et al 2007 Science 316:1484). A new definition of the classical ‘beads on a string’ concept of gene has now emerged: “A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products” (Gerstein MB et al 2007 Genome Res 17:699). The idea of “number of genes” is becoming difficult to define not because of problems of sequences and annotation. The final product of gene expression can be somewhat elusive because transcripts of exons and introns are overlapping in different contexts. In addition, some components of an expressed gene may be situated away from the core and can be in a different chromosome. Thus, the number of genes may greatly increase if we do not count the components of these systems but the variety of intertwined products. Paradoxically, if the genes are counted according to the number of these expression modules, the number of genes becomes much fewer (Gerstein MB et al 2007 Genome Res 17:669). It is now understandable why the prescience of Richard Goldschmidt (1958) questioned whether corpuscular genes may actually exist and rather we have to accept that complex position effects and interacting systems determine the function of the genes. ▶[reaction norm](#), ▶[one gene—one enzyme](#), ▶[splicing](#), ▶[dystrophin](#), ▶[titin](#), ▶[gene number](#), ▶[ORF](#), ▶[pseudogene](#), ▶[lateral transfer](#), ▶[mosaic genes](#), ▶[epigenetics](#), ▶[microRNA](#), ▶[RNAi](#), ▶[overlapping genes](#), ▶[operon](#), ▶[regulon](#), ▶[gene-associated region](#), ▶[non-Mendelian inheritance](#), ▶[ENCODE](#); Snyder M, Gerstein M 2003 Science 300:248; Wolfe KH, Li W-H 2003 Nature Gen 33 (Suppl):255; Rédei GP et al 2006; Advances Genet 56:53; gene location–function: <http://www.cmbi.ru.nl/GeneSeeker/>, gene records of more than 3,500 taxa: http://www.ncbi.nlm.nih.gov/projects/Gene/gentrez_stats.cgi.

Gene Action: The type and mechanism of expression of genes.

Gene Activation: Turning genes on; initiates expression of genes.

Gene Activator Proteins: ▶[transcriptional activators](#)

Gene Alignment: Arranging the nucleotide sequences of functionally or by evolution-related genes, in such a manner that the homologous and non-homologous stretches of nucleotides can be assessed. ▶[homology](#), ▶[dot matrix](#)

Gene Amplification: ▶[amplification](#)

Gene and Protein Names: See <http://www.ba.cnr.it/keynet.html>.

Gene Assignment: Locating genes to chromosomes.

Gene-Associated Regions: Regions not part of the classical gene, yet retain an important role in gene function. Furthermore, they can contribute to the expression of several genes. Examples for such long-range elements are the Locus Control Regions (LCR) of beta-globin that contributes to the expression of several genes, and will likely be the case for many other enhancers as their true gene targets are mapped. It can also be applied to untranslated regions that contribute to multiple gene loci, such as the long spliced transcripts observed in the ENCODE region and *trans*-spliced exons (Gerstein MB et al 2007 Genome Res 17:669).

Gene Bank: ▶[GenBank](#), ▶[DDBJ](#), ▶[EMBL](#), ▶[sperm bank](#), ▶[databases](#)

Gene Block: A group of syntenic genes. Gene blocks can be preserved in their original linkage phase if they are within inversions because the single recombinants are generally inviable and the double recombinants are very rare within short regions. Paracentric inversion testers have been used to locate advantageous gene blocks for utilization in plant breeding projects. Inversion homozygotes are backcrossed with inbred stocks, and the F₁ is backcrossed with the inversion-homozygote tester. This progeny is half homozygous for the inversion and half is heterozygous for it. The two groups can be easily distinguished by genetic markers or by semisterility of the heterozygotes (if any crossing over takes place). If the heterozygotes surpass the parental forms in quantitative traits, the good performance is attributed to the inverted segment tested. Favorable gene blocks (quantitative gene loci, QTL) may also be identified by linkage to RFLP markers. During evolution, some gene blocks were rather well preserved. In chicken after > 300 million years of separation from the human lineages 13 segments still represent 72% of human chromosome 12. About 87% of chimpanzee and rhesus macaque sequences can be aligned with human chromosome 12 (Scherer SE et al 2006 Nature [Lond] 440:346). ▶[inversions](#), ▶[QTL](#), ▶[operon](#), ▶[gene cluster](#), ▶[RFLP](#)

Gene Cassette: A special type mobile genetic element, which carries, most commonly, only a single gene (e.g., antibiotic resistance) and a recombination sequence. For mobility, it depends on another element, the integron. ▶[integron](#); Recchia GD, Hall RM 1997 Trends Microbiol 5:389.

Gene Center: The geographical area where the greatest genetic diversity within a species is found, and

therefore it is considered as the evolutionary cradle of that species. ►evolution; Vavilov NI 1928 Verhandl V Internat Kongr Vererbungswiss Berlin, 1:342.

Gene-Centromere Distance: ►centromere mapping, ►tetrad analysis, ►alpha parameter

Gene Chips: ►DNA chips, ►microarray hybridization

Gene Circuits: A collection of genetically encoded proteins with regulated expression. In the *elementary gene circuit*, only a single specific transcription factor operates the gene under the influence of a signal. In a biological system the number of players may extend to numerous (hundreds) of proteins. ►Gene-Switch cassette, ►networks, ►oscillator, ►genetic network, ►synthetic biology; Sprinzak D, Elowitz MB 2005 Nature [Lond] 438:443.

Gene Cloning: The propagation of a piece of DNA, in identical copies, in a bacterial, viral or yeast (or other) vectors in order to increase its quantity. It is the same as molecular cloning.

Gene Cluster: Juxtapositioned genes sometimes with related function. ►operon, ►regulon, ►transcripton, ►immunoglobulin genes

Gene Conversion: A biological event that results in the change of one allele to another present in the homologous chromosome. It is a specific type of non-reciprocal recombination. As a consequence, the meiotic output is changing from 2:2 to 3:1 or if the conversion takes place in the opposite direction, to 1:3. In case an additional mitotic division following meiosis forms octads, other types of conversion asci can be identified (see Fig. G18: the left-most octad is normal; the other five indicate gene conversions). Gene conversion within a locus proceeds in a polarized fashion, following the direction of DNA replication. Gene conversion may involve *map expansion* because within very short distances the neighboring sites may be co-converted and thus reducing the chance of their separation. This is in contrast to classical recombination when the presence of multiple markers permits the detection of higher number of recombinational events. The conversion is characterized by *fidelity*, i.e., the converter and the converted alleles are identical. The 3:1 and 1:3 spore ratios in the tetrads generally occur with equal frequency, and this was named *parity*. Mitotic gene conversion may produce somatic sector(s). Although gene conversion is not a classical recombinational event itself, it is accompanied by exchange of markers at the flanking region in about half of the cases. It has been assumed that gene conversion not associated with recombination of flanking markers, the donor of genetic information may be a cDNA.

In yeast genes *RAD51*, *RAD55*, and *RAD57* activity is involved in mitotic recombination and gene conversion between two DNA molecules. In RNA-mediated gene conversion these are dispensable but gene *RAD1* (encoding an endonuclease) is required.

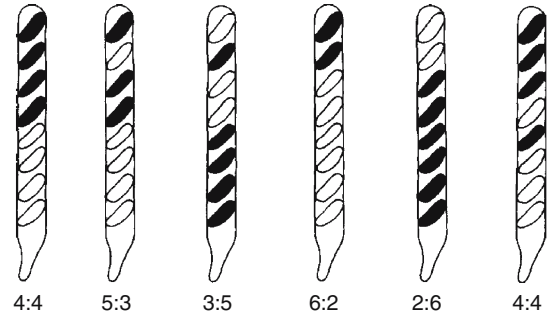


Figure G18. Gene conversion asci

Originally, gene conversion was discovered in ascomycetes, now it is believed to occur in other eukaryotes too but the identification of gene conversion is still the easiest on the basis of tetrad data (or half tetrads in *Drosophila* with attached X-chromosomes). The frequency of gene conversion may be highly variable from gene to gene ranging from less than 0.5% to a few percent in yeast. The average size of the converted segment may extend to 1000 bp. Not all aberrant spore output can be attributed to gene conversion. Polysomy, polyploidy, nondisjunction, premeiotic mitotic recombination, suppressor mutations, etc. may all produce aberrant asci similar to the results of gene conversion. The different types of gene conversions are best identified in the asci where meiosis is followed by an additional mitosis. The detection of gene conversion is relatively simple in organisms where the (pollen) tetrads are preserved (*Salpiglossis* or *Arabidopsis* mutants).

In some instances in human c4IIs, the frequency of gene conversion much exceeded that of homologous reciprocal recombination, verified by molecular analysis. Actually, at special hot spots within short chromosomal regions (HLA-DBP1 and the PAR pseudoautosomal region of the human Y chromosome) the frequency of recombination by crossing over was lower than that by gene conversion ($0.9\text{--}1.2 \times 10^{-3}$ versus $1.3\text{--}3.4 \times 10^{-3}$, respectively). At some other regions, the frequency of conversion was in the range of 5×10^{-5} . The conversion tract observed was minimum 300 bp to a maximum of 1,091 bp. The conversion appeared limited to sperm (meiosis) and was not observed in blood (mitosis). Other investigations detected gene conversion in somatic cells of animals. The conversion rate declined very rapidly

with increased distance. Sperm typing by PCR was used for the studies. The use of PCR technology may permit the detection of converted sequences within any eukaryotic gene even in the absence of tetrad analysis. The center of conversion events overlapped with the crossing over peaks. The results suggest similarities in the mechanism of gene conversion and crossing over (Jeffreys AJ, May CA 2004 *Nature Genet* 36:151). The mismatch repair of double-strand breaks may involve gene conversion. ▶[conversion asci](#), ▶[half conversion](#), ▶[recombination mechanisms](#), ▶[recombination models](#), ▶[sex circle model](#), ▶[PCR](#), ▶[mismatch repair](#), ▶[sperm typing](#); Fogel S et al 1971 *Stadler Symp* 1–2:89; Quintana PJE et al 2001 *Genetics* 158:757.

Gene Conversion, Ectopic: The interpretation for the variations in the non-recombining regions of the X and Y chromosomes in feline species. Since chromosome pairing is a requisite for the classical gene conversion, it is hypothesized that accidental pairing may occur. (See Slattery JP et al 2000 *Proc Natl Acad Sci USA* 97:5307).

Gene Copy Numbers: In lower organisms, the majority of the genes occur in single copies per genome yet, even in bacteria, ribosomal genes may be present in seven copies. In the amphibian oocytes, during the great need for protein synthesis ribosomal genes may be amplified 1,000 to 1,500 fold and form more than a thousand nucleoli. After meiosis this excessive amount of rRNA genes are discarded. In maize plants, there may be 10,000 to 20,000 copies of ribosomal genes per diploid cells. *Xenopus* may have 24,000 copies of the rRNA genes and 200 copies of each of the tRNA genes. *Drosophila* has about 500 copies of 5S RNA genes in the right arm of chromosome 2. Some particular sequences (SINE and LINE) occur in all eukaryotes in high numbers. In many higher eukaryotes, repetitive sequences may exceed 80% of the genome. Decreased copy number of the *Fcgr3* gene of rodents or the human homolog FCGR3B predisposes to glomerulonephritis in systemic lupus erythematosus (Aitman TJ et al 2006 *Nature [Lond]* 439:851). ▶[amplification](#), ▶[glomerulonephritis](#), ▶[lupus erythematosus](#), ▶[SINE](#), ▶[LINE](#), ▶[gene number](#); Romero D, Palacios R 1997 *Annu Rev Genet* 31:91.

Gene Delivery: The system of introduction of foreign gene(s) into a cell(s). ▶[transformation genetic](#), ▶[transfection](#), ▶[microinjection](#), ▶[biolistic transformation](#), ▶[electroporation](#), ▶[vectors](#), ▶[receptor-mediated gene transfer](#), ▶[cytofectin](#), ▶[liposomes](#), ▶[endocytosis](#)

Gene Density: In *Drosophila* 1/13.4 kb was reported but it is variable (1/5.6 to 1/78 kb); in the plant *Arabidopsis* 1/4.5 kb. It appears that in the human nucleus, the chromosomes with large gene density (e.g., 19/Mb) are more centrally located whereas the chromosomes with lower gene density (e.g., 18) are situated more at the periphery. The size of the chromosomes does not affect their position. The average human gene density is about 10/Mb, in chromosome 13 being 6.5 and in chromosome 22 being 26. In human chromosome 12 the size of the gene clusters vary; there 9 natural killer cell genes at 12p13.2-p12.3 and 14 keratin II genes at 12q13.3 whereas there are 3 aquaporin genes at 12q13.1 (Scherer SE et al 2006 *Nature [Lond]* 440:346). The marine chordate, *Oikopleura dioica*, has a minimum genome size of 51 Mb, about 15,000 genes and a very short life cycle (two to four days, depending on the temperature). Its gene density appeared only 1/5 kb, the lowest among chordates. Persistently open chromatin domains have more essential genes that enable reduced noise by avoiding transcriptional fluctuation associated with chromatin remodeling. Essential genes are rare in subtelomeric regions (Batada NN, Hurst LD 2007 *Nature Genet* 39:945). (See Boyle S et al 2001 *Hum Mol Genet* 10:211; Seo H-C et al 2001 *Science* 294:2506).

Gene Discovery: The completion of genome sequencing still does not reveal the function of all open reading frames. Functional genomics seeks the identification of what the individual or clusters of genes do within the cell. Because genes are expressed in complex networks new functions will be discovered for times to come. ▶[EST](#), ▶[UniGene](#), ▶[normalization](#), ▶[subtraction](#), ▶[genetic networks](#); Giallourakis; C et al 2005 *Annu Rev Genomics Hum Genet* 6:381; <http://www.geneatlas.org>.

Gene Disruption: ▶[insertional mutation](#), ▶[targeting genes](#), ▶[insertion elements](#), ▶[transposons](#)

Gene Distribution: Gene distribution in prokaryotes (*E. coli*, *Bacillus subtilis*) is unequal between the leading and lagging strands. The majority of the essential genes are expressed in the leading strand and the essentiality of function, and not the expression level, determines this strand bias. Some chromosomes and chromosomal regions display higher or lower gene density than the average. ▶[leading strand](#), ▶[lagging strand](#); Rocha EPC, Danchin A 2003 *Nature Genet* 34:377.

Gene Diversity: Estimated on the basis of allelic frequencies in a population. H = gene diversity at a locus, n = number of individuals, m = number of alleles at the locus, x_i = the frequency of the i th allele. For self-fertilizing species $n/(n-1)$ replaces $2n/2n-1$.

►evolutionary distance, ►diversity; Nei M Roychoudhury AK 1974 Genetics 76:379; Nei M 1987 Molecular Evolutionary Genetics. Columbia University Press, New York.

$$H = \frac{2n}{(2n-1)} \left(1 - \sum_{i=1}^m x_i^2 \right)$$

Gene Dosage: The number of identical and repeated genes in the genome. ►polyploidy

Gene Duplication: ►duplication

Gene Editing: Parts of natural genes are replaced or completed by synthetic DNA chains or a natural repair process eliminates gaps or mismatches in the DNA (called also proofreading). ►editing, ►DNA polymerases, ►mtDNA, ►RNA editing

Gene Evolution: The process by which once similar genes diverged or different genes assumed similar structure and function. The starting material is usually the duplication of gene or a chromosomal segment. During evolution, some genes are lost because their function is no longer needed in the altered environment. Parasites may exploit host functions and let some of their own functions and genes lapse. In some instances, host proteins are either hijacked for use by mobile elements or recruited to defend against them. Some yeast genes (e.g., those involved in DNA repair) may be subject to selective pressures imposed by mobile elements and could favor alleles that might be otherwise deleterious for their normal roles related to genome stability. NHEJ genes could have profound consequences for genome integrity in many organisms, making mutations that are subtly deleterious for NHEJ function nonetheless selectively favored because of their ability to combat mobile element insertions (Sawyer SL, Malik HS 2006 Proc Natl Acad Sci USA 103:17614). ►divergence, ►convergence of genes, ►duplication, ►NHEJ

Gene Expression: The realization of the genetic blueprint encoded in the nucleic acids. Gene expression may be modified, enhanced, silenced, and timed by the regulatory mechanism of the cell responding to internal and external factors. The *expression capacity* is the ratio of the maximal to minimal level of expression in response to signals. Usually it is the transcription of DNA into RNA. The number of genes expressed in one or more copies in human cell lines was estimated by 'massively parallel signature sequencing' to be 10,000 to 15,000. About 1/3 to 1/2 of the genes displayed cell specificity whereas half or more were generally expressed (Jongeneel CV et al 2003 Proc Natl Acad Sci USA 100:4702). Using RNAi technology, the 19,075 genes of *Caenorhabditis* were targeted. The data

indicate that about 40% of the genes are expressed at the early embryonic stage, 36% in the late embryos, 16% in the larvae, and 8% in the adults (Sönnichsen B et al 2005 Nature [Lond] 434:462). Interestingly, in *Arabidopsis* plants only 12% of the ethylmethane sulfonate induced mutations expressed at adult plant stages when 89.2% of the total estimated genes displayed mutant phenotype (Rédei GP et al 1984, p. 285, Mutation, Cancer, and Malformations; Chu HY, Generoso WM eds Plenum, New York).

Analysis of the sequence of regulatory elements 800 bp upstream of genes provides high probability for the prediction of their level of expression (Beer MA, Tavazoie S 2004 Cell 117:185). Regulation of gene expression differentiates evolutionary categories more distinctly than the base sequences of the DNA (Rifkin SA et al 2003 Nature Genet, 33:138). By the use of the *lac* bacterial gene or the aequorin (*GFP*) gene, gene activity can be visualized in living cells and the dynamics of transcription, RNA processing and DNA repair can be optically traced (Tsukamoto T et al 2000 Nature Cell Biol 2:871). Large scale co-expression of genes can be detected by regression analysis of microarray hybridization data (Persson S et al 2005 Proc Natl Acad Sci USA 102:8633). ►regulation of gene activity, ►protein synthesis, ►SAGE, ►FANTOM, ►microarray hybridization, ►massively parallel signature sequencing; Whitfield ML et al 2002 Mol Biol Cell 13:1977; Levsky JM et al 2002 Science 297:836; Bar-Joseph Z et al 2003 Proc Natl Acad Sci USA 100:10146; Gene Resource Locator; GEO [Gene Expression Omnibus]: <http://www.ncbi.nlm.nih.gov/geo/>; <http://www.HugeIndex.org/>; <http://www.biotech.nologycenter.org/hio/>; <http://expression.gnf.org/cgi-bin/index.cgi>; mouse: http://www.Informatics.jax.org/menus/expression_menu.shtml; mouse gene expression pattern database: www.genepaint.org/; complexity of gene expression: <http://www.bioinf.med.uni-goettingen.de/services/deep/>.

Gene Expression Maps: They combine topological information on expression, co-expression and correlation of gene expression with all possible intrinsic (e.g., developmental) and extrinsic (e.g., heat shock) factors. These maps then allow predictions on biological processes, functions and phenotypes. ►protein mapping; Kim SK et al 2001 Science 293:2087; Ihmel J et al 2002 Nature Genet 31:370.

Gene Expression Omnibus: The gene expression/molecular abundance repository supporting MIAME compliant data submissions, and a curated, online resource for gene expression data browsing, query and retrieval. ►MIAME, <http://www.ncbi.nlm.nih.gov/projects/geo/>; <http://www.ncbi.nlm.nih.gov/geo/>.

Gene Family: The number of genes (paralogous loci) closely related by structure and generally also by function. They probably originated through duplications, domain shuffling, splicing and fusion (and some divergence) during evolution. The members of these gene families are frequently (closely) linked but may also be dispersed in the genome. The complete genome sequences can now reveal the relationships impossible to detect by earlier methods. Amino acid sequence comparison for 25, 193 human proteins indicate that on average that the vast majority of them involve relationship to ~ 26 other proteins. The average number of related amino acids is 36.5 for the majority that are related (Britten RJ 2005 Proc Natl Acad Sci USA 102:5466). ▶orthologous loci, ▶paralogous loci, ▶duplication, ▶deletion, ▶exon shuffling, ▶paranome, ▶lateral transmission, ▶homoeologous chromosomes, ▶homoeologous alleles, ▶evolution of proteins, ▶protein families, ▶immunoglobulins, ▶protein isomorphs; Thornston JW, De Salle R 2000 Annu Rev Hum Genet 1:41.

Gene Farming: Cloning, transformation and propagation of genes in another species.

Gene Fission: May occur during evolution by splitting one gene into two parts. This process has taken place most frequently in thermophilic archaea. ▶gene fusion

Gene Flow: The spread of genes in a population by migration of individuals and cross-fertilization. Gene flow, depending on its intensity, may rapidly alter gene frequencies in a population. Gene flow may be hindered or prevented by geographic isolation, physiological factors (differences in sexual maturity and breeding seasons), genetically (by chromosomal rearrangements causing hybrid sterility, incompatibility alleles and differences in chromosome number [polyploidy]). In neighboring populations, at the overlapping borders, repeated backcrosses may occur resulting in *introgressive hybridization* and permanent inclusion of new alleles into the gene pool in one or more populations. The availability of transformation techniques may overcome the natural gene flow and transfect genes among taxonomic groups that were earlier unable to exchange genetic information because of complete sexual isolation. The wave of advance of an advantageous gene was calculated by RA Fisher: $r = \sqrt{2gm}$ where g = the initial growth rate and m = the migration rate per time and space. Molecular markers greatly facilitate tracing of the path of genes in human and other populations. Analysis of the mitochondrial DNA, X and Y chromosomes are the most useful tools for this purpose. ▶migration, ▶introgressive hybridization, ▶Wahlund's principle, ▶transformation, ▶Y chromosome, ▶X chromosome, ▶Eve mitochondrial

foremother, ▶out-of Africa; Wells RS et al 2001 Proc Natl Acad Sci USA 98:10244; Oota H et al 2001 Nature Genet 29:20; Weale ME et al 2002 Mol Biol Evol 19:1008; Goldstein DB, Chikhi L 2002 Annu Rev Genomics Hum Genet 3:129; Cavalli-Sforza LL et al 1994 The History and Geography of Human Genes, Princeton University Press, Princeton, New Jersey.

Gene-For-Gene: The relationship between host and pathogen. ▶Flor's model, ▶host-pathogen relation, ▶co-evolution

Gene Frequency: The frequency of a certain allele relative to all alleles at a locus within a particular population ▶allelic frequencies, ▶Hardy-Weinberg theorem, ▶selection, ▶drift, ▶genetic equilibrium, ▶forensic genetics, ▶DNA fingerprinting, ▶ceiling principle

Gene Function: The typical action of the product of the gene. Relying on the sequenced genomes and the proteomic technology, the correlation between the transcriptome and the metabolome can be experimentally studied. ▶transcriptome, ▶metabolome; Hirai MK et al 2004 Proc Natl Acad Sci USA 101:10205; gene function network tool:

<http://whipple.cs.vt.edu:8080/virgo>, analysis of genes against any set of function: <http://genetrail.bioinf.uni-sb.de/>.

Gene Fusion: Attaching to a structural gene by in vitro genetic engineering, a selected promoter or other element(s), or a promoterless structural gene is transformed into a host cell and expressed only if it can trap in vivo an appropriate host promoter (enhancer). The procedure permits a study of the nature of the fused heterologous genetic element. If gene fusion occurs between coding regions of two genes, the translation product becomes a *fusion protein* that contains amino acid sequences from two structural genes. This process may modify the function of the fusion protein. During evolution, the fused chimeric genes develop amino acid substitutions that are rare or missing from the ancestral mutants (Jones CD, Begun DJ 2005 Proc Natl Acad Sci USA 102:11373). Fusing ablation factors, such as ricin or diphtheria toxin to site- or tissue-specific promoters may facilitate the study of differentiation and development because certain cell types can be eliminated during critical periods. Gene fusion may occur during evolution. Fused genes are frequently scattered in the evolutionary ranks, indicating that they did not evolve by vertical common descent (Yanai I et al 2002 Genome Biol 3(5):res0024.1). Metabolic enzymes of *E. coli* fuse three-fold more commonly than other proteins. Gene fusion may have pathological consequences; the fusion of the breakpoint cluster genes with that of Abelson murine

leukemia viral oncogene leads to leukemia (CML). Recurrent fusion of the androgen-responsive promoter element of TMPRSS2 (a transmembrane protease serine 2) with members of the ETS oncogene family leads to prostate cancer (Tomlins SA et al 2005 Science 310:6744). Several cases of cancers are caused by chromosomal rearrangement (translocations) and fusion of different genic elements. ►transcriptional gene fusion vectors, ►translational gene fusion vectors, ►trapping promoters, ►fusion protein, ►read-through proteins, ►intergenic transcript, ►ablation, ►diphtheria toxin, ►gene fission, ►leukemia, ►prostate cancer, ►chromosomal rearrangement; Casadaban MJ 1976 J Mol Biol 104:541; Silhavy TJ et al 1984 Experiments with Gene Fusions, Cold Spring Harbor Lab., Cold Spring Harbor, NY, USA; Lavasani LS, Hiasa H 2001 Biochemistry 40:8438; gene fusion and translocation breakpoints: <http://genome.ewha.ac.kr/ChimerDB/>.

G

Gene Gun: ►biolistic transformation

Gene Identification: This may be required after a particular DNA tract has been sequenced but its function is unknown. The simplest approach is checking the DNA databases for homologous sequences among genes with known function. Extensive amounts of redundant sequences may make the comparisons difficult but computer programs are available to identify repeats in human genes (pythia@anl.gov or <ftp://ncbi.nlm.nih.gov>) or BASTX for other organisms: <http://www.cshl.org/genomere/supplement/harris.htm>. BLAST, FASTA can search databases. ►databases, ►Blast, ►Fasta, ►BLOCKS; Fickett JW 1996 Trends Genet 12:316.

Gene Indexing: Organizing information on groups of genes according to sequences/ functions/EST using Unigene, STACK and HGI. ►Unigene, ►STACK, ►HGI, ►expressed-sequence tag; Haas SA et al 2000 Trends Genet 16:521; <http://genest.molgen.mpg.de/>; <http://www.tigr.org/tdb/tgi>.

Gene Interaction: A common misnomer; in most cases the products of the genes interact—with a few exceptions such as gene insertion, gene fusion, etc. ►gene product interaction, ►epistasis, ►modified Mendelian ratios, ►morphogenesis in *Drosophila*, ►networks

Gene Isolation: The first gene isolation was reported in 1969. The *Lac* gene of *E. coli* was inserted in reverse orientation in bacteriophages λ and $\phi 80$ by a modification of specialized transduction. The DNA of these phages was extracted, denatured and the heavy chain of λ was combined with the heavy chain of $\phi 80$. Since the base sequences of the two phage strands were not

complementary, only the *Lac* sequences annealed, and the phage DNA sequences remained single-stranded. S_1 nuclease degraded the single strands but the double-stranded *Lac* gene was preserved in pure form. Somewhat similarly, genes from F' plasmids could also be isolated. These ingenious methods did not have general applicability. A more general procedure was developed by isolation cDNA from mRNA. The problem was that a eukaryotic cell might contain over 40,000 mRNA molecules at a time. To be reasonably certain (say at 99% probability) that the desired molecule is included, a very large number of molecules had to be isolated in order that the desired one be included:

$$[1 - (1/40,000)]^n = 1 - P = 1 - 0.99 = 0.01$$

hence

$$n = \frac{\log 0.01}{\log[1 - (1/40,000)]} \cong 184,213$$

where n is the number of molecules to be screened to find at least 1 at P (=0.99) probability.

The desired mRNA may be enriched by “cascade hybridization.” The mRNAs can be extracted from cells at different developmental stages. Also, substrate induction, heat shock, drug, hormone or pathogen caused induction can be used for enrichment of the mRNA. If a *DNA library* is available and the gene can be probed by colony hybridization, the fragments containing the gene or parts of it can be identified by the use of DNA probes. The simplest method of isolation of genes uses *heterologous probes*. Such a probe contains a homologous sequence of the gene to be isolated. The probe is labeled by *nick translation* using either radioactive nucleotides or biotinylation or any other non-radioactive fluorochromes or immunoprobes. The probe permits the selective isolation of the DNA fragment annealed with the probe. If the amino acid sequence of at least part of the gene product is known, synthetic probes can also be generated.

Genes can be labeled also by transposon mutagenesis or by insertional inactivation using transformation (transfection). In case close genetic or physical mapping information is available, the gene may be isolated by the use of overlapping YAC clones and “chromosome walking” (*map-based gene isolation*). Linker scanning can identify essential regulatory elements of the gene. The identity of the gene generally requires confirmation by in vitro translation and testing the function of the protein so obtained. ►biotinylation, ►chromosome walking, ►cloning, ►colony hybridization, ►cosmids, ►DNA library, ►DNA probes, ►fluorochromes, ►heterologous probes, ►immunoprobes, ►insertional mutation, ►linker scanning, ►nick translation, ►plasmid rescue, ►radioactive labeling,

►synthetic probes, ►transfection, ►transformation, ►transposon mutagenesis, ►YAC vectors, ►functional cloning, ►positional cloning, ►candidate gene, ►EST; Nieuwlandt D 2000 Curr Issues Mol Biol 2:9; Bimstiel ML. 2002 Gene 300:3.

Gene Knockout: ►knockout, ►gene disruption, ►targeting genes, ►excision vector, ►Cre/loxP

Gene Library: A collection of cloned genes. ►cloning

Gene Locus: ►locus

Gene Manipulation: ►genetic engineering

Gene Mapping: ►mapping genetic, ►mapping function, ►physical mapping

Gene Marking: The insertion of a stable retroviral vector into some stem cells, blood cells or other tissue and detect its functional state or contamination with neoplastic cells or immunological reaction, etc. It may serve—besides diagnostic purposes—therapeutic goals for hereditary disorders, viral infections. It can be employed for the introduction of drug-resistance genes and test the therapeutic index (maximal, optimal or toxic dose of pharmaceuticals). ►retroviral vectors

Gene Mutation: Molecular alteration within a gene (base substitution or frameshift, point mutation, substitution mutation). ►mutation

Gene Neighbor Method: This method infers functional linkage of genes from the information of genetic linkage. It is applicable primarily to prokaryotes where operons are relatively common.

Gene Nomenclature: See <http://www.gene.ucl.ac.uk/nomenclature/> for human genes/ or <http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/gdlw.pl>; ►gene symbols, ►databases

Gene Number: The number of genes per genome of an organism can be estimated on the basis of mRNA complexity, or by total sequencing of the genome. The estimates based on mRNA can be best determined when the entire genome is sequenced. By this method the single-stranded RNA phage, MS2 was found to have 4 genes. The gene number has been estimated also from mutation frequencies. If the overall induced mutation rate, for e.g., is 0.5 and the average mutation rate at selected loci is 1×10^{-5} then the number of genes is $0.5/(1 \times 10^{-5}) = 50,000$. Although this method has some errors, the estimates so obtained appear reasonable. On the basis of mutation frequency in *Arabidopsis* the total number of genes was estimated to be about 28,750 (Rédei GP et al 1984 in Mutation, Cancer, and Malformation, p. 306; Chu EHY & Generoso WM, (eds), Plenum). The number of protein-coding gene number of

Arabidopsis was estimated as 25,498 after sequencing the entire genome. The estimate after annotation has grown to 30,700 by June 2004 (TIGRE Annotation Database). By the late 1920s, John Belling counted 2,193 chromomeres in the pachytene chromosomes of *Lilium pardalinum* and assumed that this number corresponded to that of the genes.

In *Drosophila* ~17,000 genes were claimed on the basis of mRNA complexity. Based on the sequenced genome, the estimate was ~13,600. During the 1930s CB Bridges counted ~5,000 bands in the *Drosophila* salivary chromosomes and for many years it was assumed that each band represented a gene. Nucleotide sequencing of 69 salivary bands in the long arm of chromosome 2 of *Drosophila* pointed to the presence of 218 protein-coding genes, 11 tRNAs and 17 transposable element sequences within that ~2.9 Mb region. The shotgun sequencing of the *Drosophila* genome identified ~13,600 genes, encoding 14,113 transcripts because of alternate splicing. The number of protein-coding *Drosophila* genes was estimated to be ~14,000 (Yandell M et al 2005 Proc Natl Acad Sci USA 102:1566). In humans, 75,000–100,000 genes were expected on the basis of EST; of these about 4,000 may involve hereditary illness or cancer. The human gene number estimates in 2003 still varied from ~24,500 to ~45,00 (Pennisi E 2003 Science 301:1040). After the ‘completion’ of the sequencing the number was estimated between 28,000 to 35,000 yet the number of transcriptional units in humans appeared to be 65,000 to 75,000 (Wright FA et al 2001 Genome Biol 2(7):Research 0025). However, by 2004 the best estimate was 25,000–30,000. The finished euchromatic human genome seems to contain only about 20,000 to 25,000 genes (Nature [Lond] 431:931, 2004). Human chromosome 18 has the lowest gene density of 337 plus 171 pseudogenes (Nusbaum C et al 2005 Nature [Lond] 437:551). The ways of alternative splicing, the use of more than a single promoter (initiation codon) by the same DNA tract complicates the difficulties in estimation of functional units

In *Saccharomyces*, in the 5,885 open reading frames 140 genes encode rRNA, 40 snRNA and 270 tRNA (see also for revisions *Saccharomyces cerevisiae*). About 11% of the total protein produced by the yeast cells (proteome) has metabolic function, 3% each is involved in DNA replication and energy production, respectively; 7% is dedicated to transcription, 6% to translation and 3% (200) are different transcription factors. About 7% are concerned with transporting molecules and about 4% are structural proteins. Many proteins are involved with membranes.

In *Caenorhabditis* 19,099 protein-coding genes are predicted on the basis of sequencing of the genome.

The minimal essential gene number has also been estimated by comparing presumably identical genes in the smallest free-living cells *Mycoplasma genitalium* (482) and *Haemophilus influenzae* (1,749), both completely sequenced. In *Mycoplasma* 382 + 5 protein-coding genes are essential but 28% of the protein-coding genes have no known function (Glass JI et al 2006 Proc Natl Acad Sci USA 103:425). The minimal gene number among the ~4,000 in *Bacillus subtilis* appears to be 192 but another 79 are predicted to be essential (Kobayashi K et al 2003 Proc Natl Acad Sci USA 100:4678). Insertional inactivation mutagenesis indicated the minimal number to be ~265 to 300. Gene knockout indicates that some of the apparently minimally required genes of *Mycoplasma* are dispensable. Furthermore, only about 200 of the *Mycoplasma* genes are represented by orthologous genes in other organisms.

In *Caenorhabditis elegans* about 20 times more genes are indispensable for survival. In higher organisms, the number of open reading frames may be larger than the number of essential genes.

The gene number may not accurately reflect the functional complexity of a genome or organism because the combinatorial arrangement of proteins may generate great diversity and specificity. Many plants have about twice the number of genes of humans. ►gene, ►gene number in quantitative traits, ►transcriptome, ►genetic network, ►proteome, ►duplications, ►knockout, ►mtDNA; Cell 86:521 [1996]; Science 276:1962 [1997]; Adams MD et al 2000 Science 287:2185; Rubin GM et al 2000 Science 287:2204; Aparicio SAJR. 2000 Nature Genetics 25:129; Koonin EV 2000 Annu Rev Genomics Hum Genet 1:199; Akerley BJ et al 2002 Proc Natl Acad Sci USA 99:966; Moran NA 2002 Cell 108:583.

Gene Number in Quantitative Traits: It has been estimated by various complex statistical procedures (Mather, Jinks 1971 Biometrical Genetics, Chapman & Hall, London, UK) but none of the estimates are entirely reliable because the number of genes with minor contribution or greatly influenced by environmental effects, genetic linkage, etc. confound the picture. Perhaps the number of polygenes controlling one quantitative trait may not be more than five or six major genes rather than hundreds, postulated by some authors. Sewall Wright provided a very simple formula in 1913:

$$n = \frac{R^2}{8(s_1^2 - s_2^2)}$$

gene number (n) = where R is the difference between parental means, $[s_1]^2$ is the variance of the F_1 and $[s_2]^2$ is the variance of the F_2 generations.

An improved model of Zeng, considered linkage and variation in their effect where \bar{c} is the average recombination rate between loci and C is the coefficient of variation for the distribution. ►polygenes, ►QTL, ►gene number; Jones CD 2001 J Hered 92:274; Schliekelman P, Slatkin M 2002 Am J Hum Genet 71:1369.

$$\hat{n} = \frac{2\bar{c}\hat{n} + C2(\hat{n} - 1)}{1 - \hat{n}(1 - 2\bar{c})}$$

Gene Number Paradox: Although viruses and bacteria have fewer genes than eukaryotes, at first glance it appears unusual that the very simple nematode, *Caenorhabditis* has more (37%) genes than the much more complex *Drosophila*. The rice plant seems to show substantially more genes than humans, currently 37,544 seem to code for proteins. The cause appears to be in the difference of regulation, alternative splicing, and in a more elaborate array of transcription factor and transcriptional cofactors. The average human gene may be transcribed in three to four different ways. *Drosophila* seems to have about 1,000 transcription factors, whereas humans have more than 3,000. Ape's genomes are more than 99% identical to humans, although great deal of difference exists in the function of the nervous system, and in morphology. ►C value paradox; Levine M, Tjian R 2003 Nature [Lond] 424:147.

Gene Ontology (GO): A set of gene classification rules regarding their molecular function, biological role and cellular location. The same set of criteria is employed for the genomes of *Saccharomyces cerevisiae*, mouse, *Drosophila melanogaster*, *Arabidopsis*, etc. GOs include categories (and additional groups within the main entry) such as Nucleic Acid Binding Proteins, Cell Cycle Regulators, Chaperones, Motor Proteins, Actin Binding, Defense Proteins, Enzymes, Enzyme Activators, Enzyme Inhibitors, Apoptosis Proteins, Signal Transducers, Storage Proteins, Structural Proteins, Transporters, Ligands, Ubiquitin, Tumor Suppressors, Metabolism, Organelle Control, Developmental Regulators, Sensory Perception, Behavior, etc. ►genome projects, ►ontology; Ashburner M et al 2000 Nature Genet 25:215; Anonymous 2001 Genome Res 11:1425; WGS; <http://www.geneontology.org>; sequence ontology: <http://song.sourceforge.net/>; gene ontology annotation: <http://wego.genomics.org.cn/cgi-bin/wego/index.pl>; human and ten other organisms' gene partition: <http://bcl.med.harvard.edu/proteomics/proj/gopart/menu.php>; combination of information from 31 different species; converting between different database identifiers; finding orthologous genes from other species and searching a large body of public gene

expression data for co-expression: <http://biit.cs.ut.ee/gprofiler/>; functional profiling on the basis of several tools: <http://vortex.cs.wayne.edu/projects.htm>.

Gene Order in the Chromosome: It can be determined by three-point or multipoint testcrosses in eukaryotes or by similar principles in prokaryotes. Conservation of the order permits evolutionary inferences among species. ▶mapping genetic, ▶bacterial recombination, ▶chromosome walking, ▶physical map

Gene Pool: The sum of alleles that can be shared by members of an interbreeding population. ▶population genetics

Gene Prediction: Computer analysis of DNA sequences for matching known genes. ▶Genie, ▶GENSCAN, ▶FGENE, ▶GRAIL, ▶Mzef, ▶GenomeScan, ▶TWINSCANM, ▶SGP-1, ▶SLAM, ▶GeneWise, ▶Gnotator, ▶HMMgene, ▶Ace.mbly, ▶EST_GENOME, ▶annotation of the genome; Mathé C et al 2002 Nucleic Acids Res 30:4103; Guigó R et al 2003 Proc Natl Acad Sci USA 100:1140.

Gene Product: The transcript(s) of a gene and by extension the processed transcripts and even the translated polypeptides or RNAs. ▶processing, ▶transcript, ▶polypeptide, ▶RNA

Gene Product Interaction: It is responsible for epistasis, additive, complementary and suppressor type of modifications of Mendelian segregation ratios. These are frequently called gene interactions but actually, the gene products interact. Interaction among gene products is quite extensive in yeast 250 sequence-specific regulators were found to affect the expression of ~6,000 genes. It appears that genes are co-regulated at the level of transcription. ▶modified Mendelian ratios, see examples under ▶morphogenesis in *Drosophila*, ▶protein-protein-interaction, ▶microarray hybridization, ▶two-hybrid method, ▶networks, ▶genetic networks, ▶phage display, ▶proteomics, ▶interactome, ▶epistasis, ▶protein complexes; Adamkewicz JI et al 2001 J Biol Chem 276:11883; Ito T et al 2001 Proc Natl Acad Sci USA 98:4569; Minton AP 2001 J Biol Chem 276:10577; von Mering C et al 2002 Nature [Lond] 417:399; <http://www.genome.ad.jp/brite/>; <http://dip.doe-mbi.ucla.edu>.

Gene Rearrangement: ▶immunoglobulins, ▶phase variation, ▶sex determination in yeast, ▶transposons, ▶chromosomal rearrangements, ▶gene replacement, ▶targeting genes

Gene Regulation: ▶regulation of, ▶gene activity

Gene Relic: Usually a member of a multigene family that does not have all the elements necessary for function; it is actually a pseudogene. Their existence

is explained by losses during evolution. ▶pseudo-gene, ▶processed pseudogene

Gene Replacement: Accomplished with the aid of genetic vectors that carry a different allele and the flanking sequences of a chromosomal locus (see Fig. G19). This constitution permits intimate homologous pairing in the area. If double crossing over or gene conversion takes place, the allele in the vector may replace the one in the chromosome. Because the frequency of such an event is very low, selectable markers (*URA3* in the diagram in this integrating vector) must be used to screen out the replacement in a large population. For the selection, one may use an antibiotic resistance gene with a defect in the upstream area and in the vector the same but with a defect downstream may restore antibiotic resistance and that can selectively be isolated on media containing the antibiotic. By the use of the LoxP-Cre system, larger than 100 kb mouse chromosomal segment can be replaced by homologous human DNA tracts and the procedure called recombinase-mediated genomic replacement (RMGR) can be used to model human genetic diseases in mouse (Wallace HAC et al. 2007 Cell 128:197). ▶targeting genes, ▶localized mutagenesis, ▶site-specific mutation, ▶transformation, ▶Cre/LoxP, ▶FLP/FRT, ▶knockout, ▶homologous recombination, ▶site-specific recombination, ▶RMCE; Richardson PD et al 2001 Curr Opin Mol Ther 3(4):327.

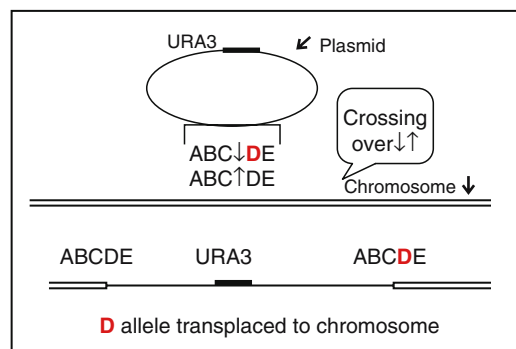


Figure G19. Gene replacement

Gene Rescue: ▶plasmid rescue, ▶marker rescue

Gene Resource Locator (GRL): A database on gene expression pattern, regulation, alternatively spliced transcripts. ▶gene expression, ▶regulation of gene activity; <http://grl.gi.k.u-tokyo.ac.jp>.

Gene Scanning: ▶linker scanning

Gene Sharing: An evolutionary process; a gene may acquire a new function without losing the original one, e.g., the crystalline protein gene $\delta 2$ in chickens

and ducks my have argininosuccinate lyase function as well as structural role in the eye lens (Piatigorsky J, Wistow G 1991 Science 252:1078).

Gene Silencing: ►silencer

Gene Size: It can be measured in different ways. If only the translated number of codons is considered, the smallest genes appear to be the 21 bp *mccA* coding for the antibiotic heptapeptide, microcin C7 (MW 1,177 Da) of *Enterobacteria* (Tenson T et al 1997 J Biol Chem 272:17425). Another is the pentapeptide encoded within the 23S ribosomal subunit by only 15 nucleotide pairs (González-Pastor JE et al 1994 Nature [Lond] 369:281). The largest mammalian genes, including introns and upstream and downstream regulatory sequences, may be in the range of hundreds of kbp. The human dystrophin gene with 2.34×10^6 bp includes 79 exons and it is probably the longest gene known (Tennnyson CN et al 1995 Nature Genet 9:184). Processed genes, reverse-transcribed from mRNA, are free of introns and other non-coding sequences are naturally shorter (Hollis et al 1982 Nature [Lond] 296:321). In human chromosome 7, the average gene length is 69,877 bp and it contains 10.1 exons with an average size of 261 bp. In human chromosome 10, the gene sizes vary from 1,776,209 bp (CTNNA3, CATENIN $\alpha 3$) to 859 bp (CLML5, CALMADULIN-LIKE 5). The longest exon is 9,763 bp (SH3MD1, SH3 multiple domain 1), the shortest is 3 bp (CDH23, CADHERIN 23). The “average” gene may have 400 codons and thus encode 46 to 48-kDa proteins. The 26,564 annotated human genes show an average of 8.8 exons and 7.8 introns. About 80% of the human exons are less than 200 bp. Less than 0.01% of the introns are less than 20 bp, and fewer than 10% are longer than 11,000 bp (Sakharkar MK et al 2004 In Silico Biol 4(2): 0032). The human genome of about 3×10^9 bp contains an estimated 25,000–30,000 genes. *Haemophilus influenzae* bacterium has 1,749 sequenced genes whereas budding yeast in its 1.8×10^7 genome encodes ~5,885 genes by 12,068-kb DNA; thus, its “average” gene is about 2,050 nucleotides long. By sequencing the genome of *Caenorhabditis* 1 gene was found per ~5-kb; the average intron number was found to be 5. In *Drosophila* upon completion of the sequencing of the “entire” genome, the average transcript size appeared to be ~3,058 bp with an average of ~4 exons. The intron sizes varied between 40 bp to > 70. The largest *Drosophila* protein, the cytoskeletal linker, Kakapo contains 5201 amino acids and the smallest is the 21-amino acid L38 ribosomal protein. The smallest gene numbers, four, are found in some viruses. ►introns, ►exons, ►genomic DNA, ►Enterobacteria, ►Mbp, ►dystrophin, ►ribosomal RNA, ►Haemophilus

influenzae, ►Saccharomyces cerevisiae, ►Aspergillus, ►exon, ►intron, ►gene

Gene Space: Regions of high gene density in the genome; generally it is rich in GC content. ►FANTOM, ►desert, ►jungle

Gene Substitution: The replacing of an old allele by a new one in a population, and chromosome substitution.

Gene Switching: It uses various ligands (tetracycline, rapamycin, estrogen analogs) that may down or regulate gene expression without turning it off. ►gene switch, ►tetracycline, ►rapamycin, ►estrogen

Gene Symbols: The abbreviated representation of the function of the genes or it designates it in a unique manner using a single or more letters. Very frequently, the allele that fails to carry out the normal function provides the name for the locus, e.g., the white eye locus in *Drosophila* is symbolized as *w* although the normal color of the eye is red. The symbols used vary in different organisms. Generally, the symbols begin with the first letter of the name and it is usually italicized. The recessive alleles in eukaryotes are symbolized with lower case letters whereas the wild type alleles either begin with a capital letter or all the letters are capitalized. Symbols of genes in the same chromosome strand are usually separated by a space in between them. Genes in the homologous strands customarily have a slash in between them (*a/b*). A semi-colon separates genes in non-homologous chromosomes and one space (*a; d*). Multiple alleles in *Drosophila* are designated by the same letter(s) representing the locus and further identified by superscripts, e.g., *w^a*, *w^{a2}*, *w^{aM}*, *w^{a79i}* or other additional distinctive signs. Recessive or dominant alleles in a series of mutant alleles are frequently symbolized as *a^R* or *a^D*, respectively. The common dominant allele may be designated also as *a⁺* or *A⁺*. Absence of a gene or lack of its function may be symbolized by a lower case letter such as *a⁻*.

Isoenzyme determining alleles may be designated as *Adh^F*, *Adh^S*, and the superscript indicating fast or slow run in the electrophoretic field. *Aⁿ* means null allele, *a^l* may be used for a lethal allele, if necessary with additional specifications. Non-allelic loci with similar phenotypes may be symbolized with the same letter(s) and subscripts: *a₁* and *a₂*. Also, non-allelic loci with similar phenotypes (mimics) may be symbolized as *tu-1a*, *tu-1b*, *tu-2*. Different loci encoding similar proteins may be designated with the same letters but attaching to the letters different numbers or by the addition of an abbreviated form of the molecular weight of the protein (*Hsp68*, *Hsp83*). Transpositions are symbolized with the designation of the original symbol followed in parenthesis the

new location: [*ry*⁺](*sd*), indicating that the *rosy* gene was moved from chromosome 3–52 location to the *scalloped* locus in chromosome 1–51.5. The designation of transformants follows that of transpositions. Modifier genes, such as suppressors may be designated as the symbol of the modifier, followed in parenthesis the gene modified: *su(lz*³⁴). Some symbols may carry also the name of the discoverer or the location of discovery of the mutation or the mutagenic agent used. Rv may indicate reversion in superscript. Capital letters and additional specifications designate chromosomal aberrations. Translocations (reciprocal interchanges between/among non-homologous chromosomes) are represented as *T(1;Y;3)* indicating that chromosomes 1 (X-chromosome), Y and 3 are involved. Each chromosome may be further specified using a capital letter superscript indicating the approximate position of the break point as P (proximal to the centromere), D (distal), or M (median). An X-chromosomal ring (of *Drosophila*) may be symbolized as *R(1)1*. Paracentric inversions are represented as *In(2L)* or *In(2R)*, depending whether the left or right arm of chromosome 2 is involved. *In(2L,R)* indicates pericentric inversion of chromosome 2. To this symbol, genes closest to the break points may be attached. For transposition (non-reciprocal transfer of chromosomal segments) the symbol is *Tn* and in parenthesis first the donor, followed by the recipient chromosome, e.g., *Tn(2;3)*. Again, the gene(s) involved may be included in the symbols. Deficiencies are symbolized by *Df* followed by the indication of the chromosome (arm) and locus involved: *Def(2R)vg*. Duplications are symbolized with *Dp* such as *Dp(3;1)* indicating that duplicated segment of chromosome 3 is located in the X-chromosome. When the duplicated segment has a centromere and it is a free element, it is symbolized with a letter *f*, e.g., *Dp(1;f)*. In case there are multiple repeats: *Dp(1;1;1)*. When a combination of multiple chromosomal rearrangements occur, they are indicated one after the other with a “+” sign between them. The location of break points may be designated by the euchromatic (1 to 102) or heterochromatic (h1 to h61) segment numbers. The older symbols in plants followed the customs in *Drosophila*. Recently, largely for convenience of typing or printing, the subscripts are substituted with a number written together with the gene symbol and the allelic number is attached hyphenated: *a2-5* the second *a* locus and allele 5 (rather than superscript 5). Mouse geneticists identify loci with three or four italicized letters, the first is capitalized. Human geneticists also use three or four (commonly not italicized) all-capital letter symbols with additional numbers. In Yeast and *Arabidopsis*, the new gene symbols use three italicized capital letters for the wild

type and three italicized lower case letters for the recessive alleles. In the majority of fungi the wild type alleles are designated with a superscript “+”. Allelic designation frequently follows the locus designation in parenthesis: *ilv(STL6)* or *pyr-3(KS43)*. Suppressor mutation symbols may include also the gene they modify: *su(met-7)-1*. The symbol *ssp* means super-suppressors. Mitochondrial mutations are designated as *mi*, and additional numbers. RFLP fragments are identified with an italicized three-letter symbol of the laboratory and a serial number. Transposable elements are symbolized similarly to the genes. In human genetics only capital letter symbols (no more than 4–5 letters) are used without sub- or superscripts. Hyphens or punctuations in the symbols are exceptional. Different loci by the same symbol are numbered, e.g., BPAG1, BPAG2. Alleles may be indicated by an asterisk after the symbol and followed by other designation e.g., ACY1*2. A slash between two symbols stands for the diploid genotype, hetero- or homozygous. Lack of synteny is indicated by semicolons(s) between the symbols. If linkage is unknown comma is used. Gene order is usually started from the short arm down.

Bacterial geneticists designate the loci with italicized three lower case letters followed by a capital letter: *lacI*, *lacZ*, *lacZ* indicating the lactose utilization operon regulatory (inhibitor), operator and the β -galactosidase genes, respectively. The letters *p*, *o*, *a*, stand for promoter, operator and attenuator, respectively.

Protein products of the genes are generally symbolized with the abbreviations of the genes but they are all in capitals or in yeast, the first letter is capital and the rest are lower case and not italicized.

Arabic numerals and chromosomes generally designate linkage groups by Roman numerals. In some publications, the linkage groups may not be correctly identified with particular chromosomes.

Gene symbols have been periodically revised in some organisms and this may make reading the older literature difficult. Creating new symbols is a cheap attempt to gain citations. If new symbolism is warranted that should not be used retroactively to published and used symbols. It is quite unfortunate that many genes have multiple synonyms and symbols. ▶*Drosophila*, ▶databases [plants–Mendel], gene nomenclature assistance; for *Caenorhabditis*, Horvitz HR et al 1979 Mol Gen Genet 175:129; mouse, Maltais LJ et al 2002 Genomics 79:471; humans, Wain HM et al 2002 Genomics 79:64; <http://www.gene.ucl.ac.uk/nomenclature>; www.flynome.com.

Gene Synthesis: The generation of nucleotide sequences by the methods of organic chemistry. These sequences—and their variations—can then be tested

for function after transformation into suitable host cells (see Fig. G20). The first entirely synthetic genes coded for tRNAs. Gene may be carried out also in a different and much simpler way. Sometimes an investigator wishes to remove or add a restriction enzyme recognition site or alter the coding properties so a different amino acid would be inserted into the protein. The desired sequence can be synthesized by using pairs of 10–15mer oligonucleotides and anneal them at the 3′-ends of long oligonucleotides as templates and primers. At the same time, several sequences can be generated each up to 400 nucleotides and then ligated before transforming them into a vector. The simplest diagrammatic representation is as follows:



Figure G20. Gene synthesis. Annealed, then use T7 DNA Polymerase and proceed with synthesis

On programmable microchips, multiple genes (21) can be synthesized (Tian J et al 2004 Nature [Lond] 432:1050). ▶genes synthetic, ▶synthetic genes, ▶DNA chips, ▶microfluidic; Uhlmann E 1988 Gene 71:29.

Gene Tagging: Gene tagging places an insertion or transposable element or any other DNA sequence into a gene with the aid of genetic transformation (transfection). When the inserted sequence is known and can be probed by molecular hybridization and/or genetical inactivation or altering the function (insertional mutation), it can identify the target gene. Some insertions going into intergenic or untranslated (intron) regions may not affect the expression of the gene involved. ▶labeling, ▶probe, ▶insertional mutation, ▶targeting genes, ▶biolistic transformation, ▶transformation genetic, ▶transposons; Johnson GC et al 2001 Nature Genet 29:233.

Gene Targeting: A method of transformation using cell-specific promoter attached to the prospective transgene in the vector. The goal is to localize the transgene expression to only one type of cells. ▶promoter, ▶transformation genetic, ▶gene replacement, ▶targeting genes, ▶targeted gene transfers, ▶knockout, ▶localized mutagenesis, ▶excision vector, ▶Cre/loxP, ▶FLP/FRT; Reynolds PN et al 2001 Nature Biotechnol 19:838.

Gene Therapy: The insertion of a functional gene into an organism for the purpose of correcting or compensating for genetic defect or combat or prevent infection. In contrast to biochemical compensation for

a genetic defect (e.g., use of insulin), gene therapy may provide a dynamic supply of the missing or deficient metabolite rather than in discrete shots. The vector RetroTet-Art was designed to modulate the expression of the transgene by employing the tetracycline inducible system as well as the p16 growth arrest protein (Rossi FM et al 1998 Nature Genet 20:389). The most important requisite of gene therapy is the correct identification of the genotype responsible for the phenotype determined by clinical means. It can be carried out either in somatic cells or in the germline (gametes, zygotes). Germline gene therapy may be risky because of various chromosomal rearrangements may be caused in the transgenic cells. There is, however, a possibility to achieve some of the goals of introducing into the gametes or zygotes genetically engineered DNA. In vitro fertilization followed by screening of the 8-cell stage embryos for some of the defects present in the heterozygous families may permit the transfer into the uterus only those embryos, which are free from the genetic defect. This procedure avoids most of the risks of directly manipulating the genome, and it is the technology used by natural selection during evolution. The methods potentially available are microinjection of (foreign) DNA or transformation with retroviral or adenovirus vectors, liposomes (see transformation of animals; human gene transfer) and gene replacement by homologous recombination. Another possibility is “knockout” when the function of a deleterious gene is eliminated by insertional inactivation or deletion. The technology is available for transformation or in vitro mutation that can be followed by injecting embryonic stem cells into blastocytes that are introduced into the uterus of a female to develop genetically modified embryos and eventually viable offspring. Recently introduction of —into mice with induced tyrosinemia—hepatic cells that could proliferate in the defective liver was successful in the laboratory with a model organism. The transformation technology needs refinements before it can be widely applied to humans. Polyelectrolyte films such as poly(L-glutamic acid/PLG) and poly(L-lysine/PLL) in the presence of charged cyclodextrin seem to be effective delivery vehicles for DNA. Such construct may be maintained at elevated level in the specific target environment and facilitate internalization of the DNA into the nucleus (Jessel N et al 2006 Proc Natl Acad Sci USA 103:8618).

The current gene therapy protocols (several hundreds available) involve altering the somatic cells. The techniques of embryo implantation are widely used to overcome female inability of conceive without surgical assistance. Before implantation, these fertilized embryos may be then tested for

expression of transferred remedial genes. These procedures may become potentially useful for preventing the expression of genetic diseases under the control of single genes such as the Lesch-Nyhan syndrome, Tay-Sachs disease, cystic fibrosis, muscular dystrophy, Gaucher's disease, β -thalassemia, ADA, melanoma, neuroblastoma, multiple myeloma, lymphoma, breast cancer, colorectal cancer and several others. An ADA patient treated by gene therapy appeared relatively well and survived more than ten years after the use of retroviral transformation although her immune system was below normal. Autologous CD34⁺ and functional ADA gene transplantation by umbilical cord blood resulted in low frequency (1–10%) of ADA expressing T lymphocytes, too low to be effective for a cure. Polyethylene-glycol-conjugated ADA enzyme treatment was much more effective yet not without undesirable effects. Liposomal vectors carrying the human leukocyte antigen (HLA)-B7 and the β_2 microglobulin cDNA to tumors can express these genes (see Fig. G21). One lentiviral vector contains an antibody for special cell recognition and a mutant viral glycoprotein, which is inactivated in binding ability to its receptor but retains its ability to trigger pH-dependent membrane fusion. Such a vector recognizes the target cell membrane and attaches to it. The antibody induces endocytosis. There the fusogenic molecule of the vector responds to the low pH and triggers membrane fusion and virus can enter the cytosol. After reverse transcription and migration to the nucleus the vector can integrate into the host genome and the transgene can be inherited (Yang L et al 2006 Proc Natl Acad Sci USA 103:11479).

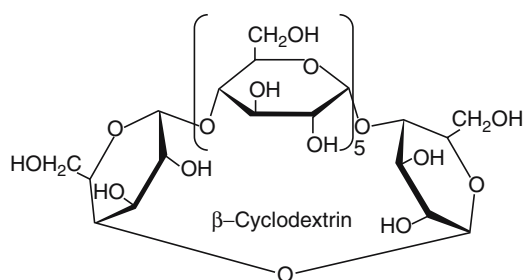


Figure G21. β Cyclodextrin

SCID-X1 patients were transfused by hematopoietic stem cells, expressing the CD34 surface marker and transfected by a defective Moloney retroviral vector carrying the γ c cDNA of the SCID-X1 human gene (Cavazzana-Calvo M et al 2000 Science 299:669). The CD34 cells are capable of differentiating into all types of blood cells. The SCID-X1 gene is a cytokine receptor. The patients so treated displayed normal lymphocytes and immune reactions

ten months after the treatment. Actually, in three months they were able to leave the complete isolation of the hospital. The apparent success of this treatment—compared to the earlier attempts described above—was due to improvements in the cell culture techniques (using Flt3 protein). Flt3 is a natural embryo cell growth factor. The new method avoided the administration of polyethylene glycol-conjugated ADA enzyme that exerted earlier a toxic effect by deoxyadenosine. Another important technical improvement was the use of transfected stem cells rather than mature transgenic T cells. More recently, highly efficient endogenous human gene correction (SCID) has been reported by the use zinc finger nucleases. Library of zinc finger proteins have been engineered for the recognition of unique chromosomal sites and fused to a nuclease domain. Such a construct can bring about double-strand breaks in the DNA required for homologous recombination. A plasmid-carried corrective DNA can thus replace the defective gene. Actually, 7% of IL2R γ genes, responsible for SCID, were corrected in both X chromosomes and expressed the right mRNA and protein (Urnov FD et al 2005 Nature [Lond] 435:646).

In 2002, acute lymphoblastic leukemia was observed in some of the children so treated (Science 298:34). The leukemia was caused in two cases by insertional mutation affecting the Lmo12 oncogene and in two instances into the IL-2rg gene. In one case, integration took place at both of these sites. It seems these cytokine receptors enhance leukemia (leukemogenesis). Davé UP et al 2004 (Science 303:333) are optimistic regarding the use of this type of therapy because the frequency of harmful insertions is relatively low. Clinical trials in the USA continue with careful consideration given to each case. In several European countries, temporary bans have been lifted or new rulings were suggested in 2004. Unfortunately, since then additional leukemia cases have been reported. Adverse effect of the gamma c gene subunit of the T cell antigen receptor (7p15-p14)—contained by the vaccine—has been suspected in the leukemogenic effects in some case. These adverse experiences cause a halt in this type of gene therapy and limit its application to cases where other approaches failed.

Using adenovirus vector with the human cystic fibrosis transmembrane conductance regulator (CFTR) resulted in expression of the gene for nine days in the nasal or bronchial membranes. With retroviral vector the low-density lipoprotein (LDL) receptor, important for familial hypercholesterolemia, has been successfully transformed and functioned. Promising initiatives were made by treatment of patients with retroviral vectors carrying interleukin-4 (IL-4) to fibroblasts resulting in infiltration

of the tumor with CD3⁺ and CD4⁺ T cells and cell adhesion molecules. The treatment resulted in some trials in the increase of CD8⁺ tumor-specific cytotoxic T lymphocytes (CTL) and eosinophils as well as CD16⁺ killer cells. Another approach is using intrabodies. As a treatment of the HIV-1 virus infection, intrabodies are directed to the lumen of the endoplasmic reticulum of the cells where they prevent the secretion of the gp160 glucoprotein precursor (a viral envelope protein) and its transport to the cell surface. Using anti-gp120 intrabodies the gp120-gp160 envelope proteins of the virus may be neutralized. Anti-tat antibody fragments introduced into the cells may prevent the activation of transcription by the viral TAT and the cellular NF- κ B proteins. Intrabodies against the Rev splicing element may also reduce the replication of the virus. Intrabodies against fusin may hinder HIV entry into the cells. The somatic cell genetic therapy may target cancer cells with interleukins, tumor necrosis factor, granulocyte macrophage colony stimulating factor to reinforce the immune system or use monoclonal antibodies against cancer cells equipped with toxins or sources of radiation (see lymphocytes; magic bullet). Some of the genes that are suitable for germline modification may be targeted to specific organs for alleviating or to overcome the symptoms of the disease. In some cases, e.g., neurological disorders, *ex vivo* methods have been sought of for the restoration of the normal function (in Alzheimer disease) of nerve growth factor (NGF) or transplanting dopamine-producing tissue (in Parkinson disease). Bone marrow transplantation may alleviate or reverse the course of lysosomal storage diseases. In the future, targeting the medication to specific cells, tissue or organs may gain increased significance because it will permit greater effectiveness and higher dosage without side effects. Purified genetically engineered myoblasts and myofibers can be propagated *ex vivo* and re-injected into the body. The multinucleate muscle cells may make possible the delivery of two or more different small vectors (e.g., AAV), which may be simultaneously expressed within the same cell and their product(s) released into the circulatory system to treat not only muscle but also other problems (Ozawa CR et al 2004 J Clin Invest 113:516).

One problem of gene therapy is that the cell defense mechanism may inactivate the introduced gene by methylating their promoters or immunologically neutralize the foreign proteins. Integration of the vector into tumor suppressor genes results very rarely in cancerous transformation. Other problems arise by unexpected reconstitution of the retroviral pathogenicity through recombination of the vector and endogenous human viruses. These latter problems are reduced by the use of DNA (rather than retroviral) vectors.

Some of the adenoviral vectors contain a much-truncated DNA to prevent viral replication and reduced immunological response against the vector but other adenoviral proteins are actually immunosuppressors and their deletion may cause the elimination of the vector by the host cells. Currently the adeno-associated and the lentiviral vectors may be most promising.

Somatic gene therapy involves apparently smaller risks. The possible harmful consequences of germline alterations are much more difficult to assess. Some gene therapy protocols combine the procedure with chemical treatment. Introduced into a cancerous brain, by a viral vector, working only with dividing cells, the herpes simplex virus thymidine kinase (HSTK) gene, it is assured that the vector lands only in the tumor cells because the normal cells do not divide. After the establishment of the transgene the patients are treated with ganciclovir. This drug after phosphorylation by HSTK can be incorporated into the DNA but it prevents then DNA replication resulting in the selective death of the cancer cells. Recombinant proteins may be used to remedy diverse metabolic defects. Ideally, the protein supply should be as under natural conditions, i.e., the amount would be variable in response to the need. For success of such treatments it is usually important that the protein would be rapidly secreted in response to orally administered drugs and the secretion would be rapidly stopped after discontinuation of the drug. Moreover, the protein must not incite an immunologically adverse reaction. Enzyme replacement or enhancement may be effective for lysosomal storage diseases (Desnick RG, Schuman EH 2002 Nature Rev Genet 3:954).

Recently, in utero treatments of fetuses afflicted by α -thalassemia or severe combined immuno deficiency (SCID), which may harm the developing embryo before or immediately after birth, respectively, have been considered. Such treatments may have still unknown side effects both on the fetus and mother. Some defects involving differentiation of limbs or brain (e.g., Greig's syndrome) occur early during pregnancy and may not be obvious until it is too late to apply any treatment. The α -Antitrypsin deficiency is manifested in adult stage and then oral administration of 4-phenylbutyric acid facilitates the release of antitrypsin from the endoplasmic reticulum and as a "chemical chaperone" may prevent the injuries resulting from AAT deficiency.

Human neural progenitor cells can be modified to release glial cell derived neurotrophic factor (GDNF) under an inducible promoter. After partial lesion of the dopamine system of rats, the engineered cells were transplanted into the brain of rats. Two weeks after implantation the engineered cells migrated within the striatum and released physiologically

relevant level of GDNF and facilitated survival of the neurons, and after eight weeks it even migrated to the substantia nigra. Loss of dopaminergic neurons in the substantia nigra is usually associated with Parkinson disease. The same type of cells survived for three months in the brain of aged monkeys and released GDNF. This technology shows promise to eventual cure of Parkinson disease currently largely incurable (Behrstock S et al 2006 *Gene Therapy* 13:379).

Some people oppose gene therapy on biological and/or ethical grounds. The arguments against gene therapy stem from the fears of unforeseeable damage to the human gene pool and the possibility of using these procedures for “genetic enhancement”. Genetic enhancement would have similar goals as eugenics and eventually may be exploited to create “super-soldiers” or other antisocial individuals with “uniform” genetic makeup. These fears are frequently fanned by political agenda or by unfounded speculations. The argument in favor of gene therapy is that it provides means to prevent the perpetuation of “disease genes” by specifically targeting the single defects. It may result not only in elimination of suffering but may also reduce health maintenance cost on the long run. In case of somatic gene therapy, unintended insertions into the germline may happen rarely. The US Federal Drug Administration proposed that such insertion should be limited to less than 50 per μg of DNA employed and genetically this may mean less than 1 insertion/6,000 sperm. It is true that not all possible consequences of gene therapy have been seen in an evolutionary history. The same criticism may also apply to several drugs that are part of current medical practice. Many of the medicines have physiological and genetic side effects (e.g., diagnostic and therapeutic X-rays, several antibiotics, anticancer drugs, etc.) yet the benefits are supposed to outweigh their risks. In human gene transfer, there are some potential risks of new constructs to develop by recombination with the viral vector. In some cases, the decision is very difficult, e.g., human dwarfism can be cured by the application of growth hormones or by functional growth hormone genes. Dwarfism is not an acute life-threatening anomaly yet it interferes in many ways with the normal fulfillment of life. The question arises then how far social philosophy should be permitted to affect the life of an individual. Animal models can be successfully applied for the testing of the physiological and biochemical consequences of gene therapy but it may not detect all the consequences for human behavior and mental abilities. One possibility appears the repair of disease genes at the site of the defect. Single-stranded DNAs, double-stranded DNA, DNA-RNA hybrid constructs, artificial chromosomes have been designed that may repair the defective nucleotides through site-specific

recombination. Although the numerous repair attempts are promising and some initial successes have been reported, the efficiency of the system is not sufficient for clinical applications (Liu L et al 2003 *Nature Rev Genet* 4:679). Thus, gene therapy still has to face not just biological, technical problems but ethical ones as well. The public often mistrusts new technologies, especially when the application suffers initial mishaps. The freedom of scientific inquiry and the innate human striving for knowledge should not be prevented, however, for any reason. Although the same caution may be necessary as it was applied with the techniques of “recombinant DNA”. Some of the problems to be solved include the development of more effective vectors and extrapolating successfully from animal models to humans. Sporadic tragic misfortunes (Teichler Zallen D 2000 *Trends Genet* 16:272) with the application of this technology cannot be a rational cause for opposing these innovative and promising medical research efforts. By July 2002, there were no US Government-approved gene therapy product on the market (Cimons M 2002 *Nature Med* 8:646), and none by 2008. The approximate share of the various genetic vectors in gene therapy experiments: retroviruses 40%, adenovirus 26%, liposomes 14%, plasmids 9%, vaccinia virus 5%, adeno-associated virus 2%, fowlpox virus 2%, canarypox virus 1%, RNA 1%, herpes simplex virus 0.3%. Gene therapy has potential applicability not only to hereditary diseases but also for a wide variety of acquired illnesses. (See diseases and terms under specific entries; ►hemo-
philia, ►thalassemia, ►rheumatoid fever, ►hyperten-
sion, ►Niemann-Pick disease, ►Tay-Sachs disease,
►transformation genetic, ►human gene transfer,
►transfection, ►receptor-mediated gene transfer, ►ul-
trasonics, ►immunostimulatory DNA, ►ex vivo,
►viral vectors, ►non-viral vectors, ►adeno-asso-
ciated, ►virus, ►retroviral vectors, ►onco-retroviral
vectors, ►MoMuLV, ►lentivirus vectors, ►liposome,
►T cells, ►molecular breeding, ►hysteresis, ►im-
mune system, ►adoptive cell therapy, ►cell, ►sickle
cell anemia, ►mosaic, ►epitope, ►cancer gene
therapy, ►biomarker, ►intrabody, ►ribozyme,
►HIV, ►NF- κ B, ►Rev, ►phenotypic knockout,
►ganciclovir, ►immunization genetic, ►antivector
cellular immunity, ►targeting genes, ►targeting vec-
tor, ►polyethyleneimine, ►nanoparticles, ►thalasse-
mia, ►SCID, ►adenosine deaminase deficiency
[►ADA], ►disaccharide intolerance, ►mitochondrial
gene therapy, ►ornithine transcarbamylase, ►muscu-
lar dystrophy, ►IUGT, ►ART, ►informed consent,
►public opinion, ►enzyme replacement therapy,
►antisense technologies, ►RNAi, ►locked nucleic
acids, ►SCID, ►zinc finger nuclease, ►stem cell,
►mitochondrial diseases in humans; Anderson WF
2000 *Science* 288:627; *Am J Hum Genet* 2000 87:272;

Romano G et al 2000 Stem Cells 18:19; Hanazano Y et al 2001 Stem Cells 19:12; Factor PH ed 2001 Gene Therapy for Acute and Acquired Diseases, Kluwer, Boston; Pfeifer A, Verma IM 2001 Annu Rev Genomics Hum Genet 2:177; Opalinska JB, Gwirtz AM 2002 Nature Rev Drug Discovery 1:503; neuronal gene therapy: Sapolsky RM 2003 Nature Rev Neurosci 4:61; viral vectors: Thomas CE et al 2003 Nature Rev Genet 4:346; advances on vectors and therapeutic applications; Smyth Templeton N ed 2004 Gene and Cell Therapy, Marcel Dekker, New York; Verma IM, Weitzman MD 2005 Annu Rev Biochem 74:711; OBA; CBER; genetic medicine; O'Connor TP, Crystal RG 2006 Nature Rev Genet 7:261; Criggler-Najjar syndrome; RAC; <http://www4.od.nih.gov/oba/rac/clinicaltrial.htm>; <http://www.advisorybodies.doh.gov.uk/genetics/gtac/index.htm>.

Gene Therapy for Infectious Diseases: Gene therapy is most commonly directed against hereditary diseases or other acquired conditions for what drugs are not sufficiently effective. Gene therapy may be designed against pathogenic microorganisms too. The available or potentially working approaches to be considered are: transformation by resistance genes, DNA vaccination, suicide genes, use of lytic phage, antibody genes, increase the production of metabolites that interfere with the development of the disease, use of antisense technology, RNAi, transgenesis for antimicrobial peptides, ribozyme-mediated cleavage of RNA, activation of antimicrobial defense genes, increase the dosage of antimicrobial genes, inactivate receptors required for infection, recruit antagonists of parasites, etc. A great variety of possible strategies may be developed. (See terms listed in separate entries in this book; Kaslow DC 2004 Trans R Soc Trop Med Hyg 98:593).

Gene Titration: Determining the quantitative expression of gene(s) as a function of dosage. ▶dosage effect, ▶titration; Yinduo J et al 2001 Science 293:2266; Shiao AL et al 2005 J Virol 79:193.

Gene Transfer: ▶transformation, ▶human gene transfer, ▶gene transfer lateral

Gene Transfer by Microinjection: It was the principal means of transformation of animals in the 1980s. Today gene targeting and other procedures are preferred (see Fig. G22). (See diagram, ▶transformation genetic [animals], ▶gene replacement, ▶targeting genes

Gene Transfer, Lateral: The transmission of genes and genetic elements by infection, plasmids, transposable elements and the acquisition of mitochondria and chloroplasts during evolution. ▶infectious heredity, ▶plasmids, ▶organelle sequence transfer, ▶evolution

Gene Trap Vectors (entrapment vector): These are equipped with a reporter gene that can insert at a splice acceptor site. The resulting gene fusion may facilitate the transcription of the reporter gene. It may be used with (mouse) embryonic stem cells to detect genes expressed during early development (Hansen J et al 2003 Proc Natl Acad Sci USA 100:9918). Actually, this procedure can tag any gene even if it is not expressed. ▶ES, ▶gene fusion, ▶insertional mutation, ▶reporter gene, ▶OMNIBANK; Medico E et al 2001 Nature Biotechnol.19:579; Stanford WL et al 2001 Nature Rev. Genet 2:756; Lai Z et al 2002 Proc Natl Acad Sci USA 99:3651.

Gene Trapping: A vector cassette consisting of a promoterless reporter gene and/or a selectable marker

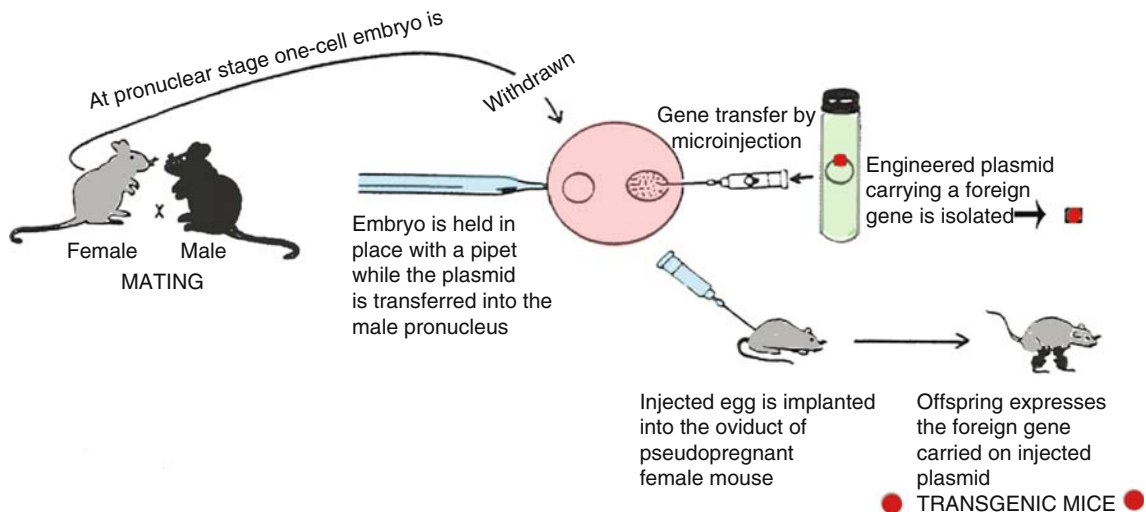


Figure G22. Gene transfer by microinjection

flanked by an upstream splice acceptor site and a downstream transcriptional termination sequence is used. When inserted into an intron of a target gene, the cassette is expressed from the host promoter fused to and easily recognized by the expression of the reporter. Since it contains a termination signal (such as for polyadenylation), the protein product is truncated. The insertion represents a tag on the disrupted target gene. Such a system permits tagging of a large number of genes across the entire genome of an organism. In plants, any somatic cell can be regenerated into intact seedlings. In animals, the targeting may use site-specific recombination system limited to somatic cells to avoid germline mutations. In self-fertilizing plants, the transferred gene or the knockout can become homozygous in the following generation of selfing. In mice, it is commonly used for knocking out genes. In bisexual animals, homozygosity can be achieved by mating of individuals that are heterozygous for the mutation. In mouse, embryonic stem cells can be genetically manipulated in vitro and offspring can be obtained by injecting the stem cells into early embryos. ▶[splicing](#), ▶[promoter](#), ▶[trapping promoters](#), ▶[targeting genes](#), ▶[knock-out](#); Schnütgen F et al 2005 Proc Natl Acad Sci USA 102:7221.

Gene Tree: It reveals when a population was divided into two subgroups on the basis that one of the subgroups has a particular mutation(s) and the other does not. Such an analysis can be continued for any number of genes. ▶[evolutionary tree](#), ▶[population tree](#)

Genealogy: The list and description of successive ancestors in a family. An extensive study of Icelandic populations of the last 300 years indicates a faster evolutionary rate for the matrilinear than the patrilinear descendants based on mtDNA and Y chromosome haplotype data. ▶[pedigree](#), ▶[coalescent](#); Helgason A et al 2003 Am J Hum Genet 72:1370.

GeneCards: ▶[GeneNote](#), ▶[EST](#), <http://genecards.weizmann.ac.il/genetide-bin/tide.cgi>.

GeneChip: ▶[microarray hybridization](#)

GeneDB: The sequences and annotations by the Sanger Institute Pathogen Sequencing Unit (PSU). (<http://www.genedb.org/>).

GeneEMAC: A computerized method for the monitoring of gene expression during development by external marker-based automatic congruencing (EMAC). (See Streicher J et al 2000 Nature Genet 25:147).

Genefinder: A computer program for finding genes within DNA sequences on the basis of identifying likely splicing sites, translation starts, coding potential, intron sizes, etc., by statistical criteria based on log likelihood ratios. The prokaryotic gene

finder GISMO combines searches for protein family domains with composition-based classification based on a support vector machine. GISMO is highly accurate and highly sensitivity and specific. It performs well for complete prokaryotic chromosomes, irrespective of their GC content, and also for plasmids as short as 10 kb, short genes and for genes with atypical sequence composition (Krause L et al 2007 Nucleic Acids Res 35:540). ▶[lod score](#), ▶[support vector machine](#); Rogic S et al 2001 Genome Res.11:817.

Genelet: ▶[SVD](#)

Geneology: The recorded or inferred steps of descent from ancestors, a family history ▶[pedigree analysis](#), ▶[evolutionary tree](#)

GeneNote: A database of human gene expression in normal tissues. ▶[GeneCard](#), ▶[Recon](#); <http://bioinfo.weizmann.ac.il/genecards>.

General Acid-Base Catalysis: The proton transfer from and to a molecule, water excepted.

General Recombination: The recombination between homologous sequences. ▶[illegitimate recombination](#), ▶[recombination genetic](#), ▶[gene conversion](#)

General Transcription Factors: ▶[transcription factors](#)

Generalized Transduction: It can be mediated by either temperate or virulent bacteriophages. The phage infects a donor bacterium (step 1) carrying the wild type allele (a^+) and then lyses it (step 2). Some phage shells scoop up *at random* only or almost only *any* bacterial DNA fragment rather than phage DNA (see Fig. G23). When these unusual phages infect a recipient cell, they can transfer the donor bacterial gene into the recipient (step 3). The transduced DNA and the indigent DNA can synaps (step 4) if they are homologous and by a double exchange replace the recipient's gene with that of the donor. This step then completes the generalized transduction. In case the donor DNA carries alleles $\underline{a}^+ \underline{b}^+$ and the constitution of the recipient is $\underline{a} \underline{b}$ recombination frequencies can be calculated as shown by the formula:

$$\frac{(a + b)(ab^+)}{(a^+b) + (ab^+) + (a^+b^+)}$$

With generalized transduction recombination can be estimated only within very short intervals, e.g., within genes. ▶[marker effect](#), ▶[pac sites](#), also ▶[specialized transduction](#), ▶[abortive transduction](#), ▶[bacterial](#), ▶[recombination frequency](#); Lederberg J et al 1952 Cold Spring Harbor Symp Quant Biol 16:413; Burke J et al 2001 Proc Natl Acad Sci USA 98:6289.

Generation Time: The time required for a cell division in continuous culture or the period from birth of an

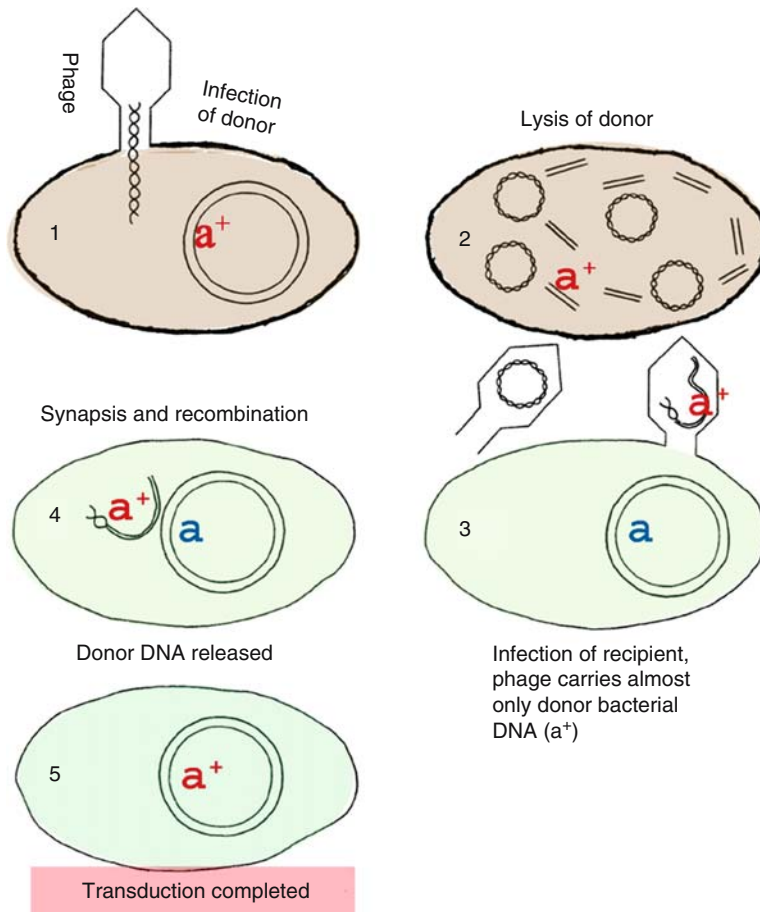


Figure G23. Generalized transduction

individual to the birth of its offspring (reproductive cycle).

GeneReviews: ►genetic testing

Genes, Good: They do not affect health adversely. Also, genes, which are transmitted and expressed in simple Mendelian fashion are called “good.” ►expressivity, ►penetrance, ►polygenic inheritance, ►QTL

Genes, Split: They contain introns; the vast majority of eukaryotic genes are therefore split into segments of exons. ►introns, ►exon

Genes, Synthetic: These have been produced since the 1970s. In 1976, Khorana synthesized the tyrosine suppressor tRNA genes of *E. coli* by classical methods or organic chemistry. In vitro synthesis of 26 oligonucleotide tracts were ligated into a 207 bp DNA containing the 86 nucleotide sequence of the gene plus leader, promoter and the terminator sequence. This gene turned out to be biologically

active and suppressed an amber mutation when transformed into bacterial cells. ►tRNA, ►suppressor tRNA, ►synthetic genes [for a diagram]; Ryan MJ et al 1979 J Biol Chem 254: 10803.

GENESCAN: A computer program for the detection of gene structure, transcriptional and translational splicing signals, exons, introns and intergenic regions of the mammalian genome on probabilistic basis. Multiple sequences are identified (Burge C, Karlin S 1997 J Mol Biol 268:78).

GeneScape: A computer program that seeks out miniset clones, DNA sequences, gene alignments to restriction maps and allows zooming from a display to the entire map of *E. coli*.

Gene-Scribe: A commercial transcriptional kit with a T7 phage RNA polymerase. It can be used to transcribe cloned genes without subcloning. ►EMBL3, ►λDASH, ►λFIX

Genesis: Used with several meanings such as inception, origin, the process of differentiation and development; also in composite words such as embryogenesis, morphogenesis, neurogenesis, etc.

Gene-Specific Repair Assay: Detects the presence of functional repair enzymes acting at a specific gene. The procedure: (i) expose cells (DNA) to mutagen/carcinogen, (ii) withdraw DNA after specific time periods, (iii) separate replicated and unreplicated DNAs on cesium chloride gradient ultracentrifugation, (iv) restriction enzyme digestion, (v) employ repair enzymes (uvrABC, T4 endonuclease, Fpg, endonuclease III), (vi) electrophorese DNA and on Southern blots probe the gene of interest, (vii) on the autoradiographed gel compare band intensities after allowed for repair as in (v). In the absence of repair, the intensity of the critical band in the gel is independent from the time allowed for repair whereas if repair is working the intensity of the band increases by the length of the period of incubation. ▶DNA repair, ▶uvrABC, ▶endonuclease, ▶Fpy, ▶density gradient centrifugation, ▶autoradiography; Anson RM, Bohr VA 1999 *Methods Mol Biol* 113:257; Ayala-Torres S et al 2000 *Methods* 22:135.

Gene-Switch Cassette: A construct facilitating turning genes on and off in a controllable manner. It encodes the DNA-binding domain of GALA4, the human progesterone receptor-ligand-binding domain and the activation domain of the human p65 protein gene. In the presence of the antiprogestin mifepristone (RU486) the chimeric molecule binds to the upstream activating domain (UAS) and in a ligand-dependent manner transactivates the appropriate downstream genes. The construct can be inserted into *Drosophila* by adenoviral or P vectors. A toggle switch system has been constructed in bacteria by the use of two repressible promoters arranged in a mutually inhibitory network. By chemical or temperature treatment, the system can be flipped between two stable states. Such system has potential application in biotechnology, gene therapy and biocomputing (Gardner TS et al 2000 *Nature [Lond]* 403:339). ▶GALA4, ▶progesterone, ▶RU486, ▶UAS, ▶p65, ▶transactivator, ▶tetracycline, ▶hybrid dysgenesis, ▶gene circuit; Roman G et al 2001 *Proc Natl Acad Sci USA* 98:12602; Osterwalder T et al 2001 *Proc Natl Acad Sci USA* 98:12596; Galimi F et al 2005 *Mol Ther* 11:142.

Genet: Genetically identical ramets that are clonal progeny of a single individual. ▶ramet

GeneTest: A publicly funded medical genetics information resource developed for physicians, other healthcare

providers, and researchers, available at no cost to all interested persons. According to GeneTest, in 2007 there have been 1,054 clinical tests and 297 research tests for 1,351 diseases. (See: <http://www.genetests.org/>; http://www.fnih.org/GAIN/GAIN_home.shtml).

Genethics: ▶ethics

Genetic Accommodation: Mutation or environmental effects cause the appearance of a novel adaptive phenotype through quantitative genetic changes. It is similar to genetic assimilation but unlike genetic assimilation, genetic accommodation results in increased environmental sensitivity of a plastic phenotype (Suzuki Y, Nijhout HF 2006 *Science* 311:650). ▶genetic assimilation, ▶polypheny

Genetic Assimilation: An adaptive mechanism in a population to fix genes as permanent parts of the genome by selection. An initially epigenetic (acquired-phenotypic) modification becomes fixed by heredity. ▶adaptation, ▶genetic accommodation, ▶assimilation, ▶fixation, ▶fixation index, ▶canalization, ▶epigenetic, ▶reaction norm, ▶plasticity, ▶fitness, ▶Baldwin effect; Palmer AR 2004 *Science* 306:828; Waddington CH 1953 *Evolution* 7:118.

Genetic Association: The correlation between the presence of a genetic marker and a certain type of multifactorial disease. For the trustworthiness of the conclusions large populations and high statistical probability are required (Dahlman I et al 2002 *Nature Genet* 30:149; Xiong M et al 2002 *Am J Hum Genet* 70:1257). ▶GAIN

Genetic Association Information Network (GAIN): GAIN is a public-private partnership of the Foundation for the National Institutes of Health, Inc., which includes corporations, private foundations, advocacy groups, concerned individuals, and the National Institutes of Health. This initiative will take the next step in the search to understand the genetic factors influencing risk for complex diseases. Through a series of whole genome association studies, using samples from existing case-control studies of patients with common diseases, the project will contribute to the identification of genetic pathways that make us more susceptible to these diseases and thus facilitate discovery of new molecular targets for prevention, diagnosis, and treatment. (See: http://www.fnih.org/GAIN/GAIN_home.shtml).

Genetic Background: All residual genes, besides the one(s) of special interest. It may be critical for

analysis because the background may affect (+/–) the expression of particular genes. Therefore, failure of identifying the background may make confirmation of the results impossible. It is improper in a scientific paper to state only that the material was purchased in a certain store.

Genetic Balance: ▶balance of alleles, ▶balanced lethals, ▶balanced polymorphism

Genetic Bar-Code: ▶DNA chip, ▶bar code

Genetic Block: Mutation in a gene may prevent or slow down the flow of a metabolic pathway. ▶null allele, ▶leaky mutant

G

Genetic Burden: Same as genetic load.

Genetic Cascade: Genes of a developmental pathway are activated in successive waves; the expression of “earlier” genes activates the next ones.

Genetic Circuits: ▶gene circuits

Genetic Circularity: A consequence of circular DNA genetic material, i.e., the genetic map has no ends

although one point is generally designated as origin.
▶DNA circular

Genetic Code: It consists of 64 contiguous nucleotide triplets; 61 specify 20 amino acids and three serves as signals for termination of translation on the ribosomes (see Table G1). The number of triplet codons for a particular amino acid varies from one to six. In animals, the 21st encoded (UGA) amino acid is selenocysteine and in Archaea and Eubacteria UAG may encode the 22nd amino acid, pyrrolysine. In addition, programmable ribozymes may attach non-natural amino acid to RNAs and incorporate them into engineered proteins (Bessho Y et al 2002 Nature Biotechnol 20:723). In an engineered *E. coli* bacterium the amber codon my direct the incorporation of the non-natural amino acid p-aminophenylalanine into protein at high efficiency (Mehl RA et al 2003 J Am Chem Soc 125:935). More than a dozen unnatural amino acids can be incorporated into proteins. The number of triplet codons for a particular amino acid varies from 1 to 6. It is of theoretical and of practical importance to amplify the genetic code beyond the “magic number”. Chemically modified, unnatural amino acids may alter protein function if

Table G1 The genetic code in RNA triplets

| 5' Nucleotide | Second nucleotide | | | | 3' Nucleotide | |
|---------------|-------------------|-----|-------|------|---------------|-------------------------|
| | U | C | A | G | | |
| U | Phe | Ser | Tyr | Cys | U | Ala = alanine (4) |
| | Phe | Ser | Tyr | Cys | C | Arg = arginine (6) |
| | Leu | Ser | ochre | opal | A | Asp = aspartic acid (2) |
| | Leu | Ser | amber | Trp | G | Asn = asparagine (2) |
| C | Leu | Pro | His | Arg | U | Cys = cysteine (2) |
| | Leu | Pro | His | Arg | C | Glu = glutamic acid (2) |
| | Leu | Pro | Gln | Arg | A | Gln = glutamine (2) |
| | Leu | Pro | Gln | Arg | G | Gly = glycine (4) |
| A | Ile | Thr | Asn | Ser | U | His = histidine (2) |
| | Ile | Thr | Asn | Ser | C | Ile = isoleucine (3) |
| | Ile | Thr | Lys | Arg | A | Leu = leucine (6) |
| | Met | Thr | Lys | Arg | G | Lys = lysine (2) |
| G | Val | Ala | Asp | Gly | U | Met = methionine (1) |
| | Val | Ala | Asp | Gly | C | Phe = phenylalanine (2) |
| | Val | Ala | Glu | Gly | A | Pro = proline (4) |
| | Val | Ala | Glu | Gly | G | Ser = serine (6) |

Thr = threonine (4)
Trp = tryptophan (1)
Tyr = tyrosine (2)
Val = valine (4)

RNA codons represent the universal genetic code for amino acids. The table shows the three nonsense codons (chain-termination codon, boxed) and 61 sense codons coding for amino acids. The numbers after the amino acids (right-most column) indicates the number of synonymous codons for each amino acid. methionine and tryptophan each have only..... 1
asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, lysine, phenylalanine, tyrosine, each has.....2
isoleucine has..... 3
alanine, proline, threonine, and valine have..... 4
arginine, leucine, serine all have..... 6 codons.
The codon usage is not random; it varies among organisms and genes

Table G2. Exceptional codon meanings

| <i>Mycoplasma capricolum</i> | <i>Tetrahymena thermophila</i> | <i>Euplotes octacarinatus</i> | Mitochondria | | | |
|------------------------------|--------------------------------|-------------------------------|---------------|-------------------|--------------|-------------------|
| | | | <i>Mammal</i> | <i>Drosophila</i> | <i>Yeast</i> | <i>Neurospora</i> |
| UGA: Trp | UAA: Gln | UGA: Cys | AUA: Met | AUA: Met | AUA: Met | CUN: Thr |
| | CAG: Gln | UAA: stop | AUU: Met | AUU: Met | CUA: Thr | |
| | UAG: Gln | UAG: absent | AUG: Met | AUG: Met | CUC: Met | |
| | | | AUC: Met | | CUU: Met | |
| | | | UGA: Trp | UGA: Trp | CUG: Met | |
| | | | AGA: stop | AGA: Ser | | |
| | | | AGG: stop | | | |

The UGA “universal” stop codon means Trp in the mitochondria of vertebrates, insects, molluscs, echinoderms, nematodes, platyhelminthes, fungi and ciliates. Selenocysteine is also coded by UGA in *E. coli* and mammals.

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incorporated in vivo in place of the natural ones. Modified special tRNAs and mutant aminoacyl tRNA synthetases may achieve incorporation. Mutations at the editing sites of *E. coli* tRNA^{Val} synthetase incorporated in higher than 29% aminobutyrate, a steric analog of cysteine into the site of cysteine (see Table G2).

Besides providing information for the primary sequence of amino acids in proteins, the genetic code includes parallel information for binding sequences for regulatory and structural proteins, signals for splicing, and RNA secondary structure. The universal genetic code can efficiently carry arbitrary parallel codes much better than the vast majority of other possible genetic codes. The ability to support parallel codes is strongly tied to the identity of the stop codons and to the minimization of the effects of frame-shift translation errors. Whereas many of the known regulatory codes reside in nontranslated regions of the genome, it seems that the protein-coding regions can readily carry abundant additional information (Itzkovitz S, Alani U 2007 Genome Res 17:405).

►code genetic, ►amino acid symbols in proteins sequences, ►genetic code second, ►xDNA, ►evolution of the genetic code, ►initiation codon, ►magic number, ►tRNA, ►codon, ►aminoacyl-tRNA synthetase, ►unnatural amino acids, ►decoding; Knight RD et al 2001 Nature Rev Genet 2:49; Wang L et al 2001 Science 292:498; Döring V et al Science 292:501; Wang L, Schultz PG 2004 Angew Chem Int Ed Engl 44:34; Yanofsky C 2007 Cell 128:815; For additional special differences and exceptions in the coding dictionary see <http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html>; and <http://www.ncbi.nlm.nih.gov/Taxonomy/Utils/wprintgc>.

cgi; mitochondrial codons: <http://darwin.uvigo.es/software/genedecoder.html>; ►microbial culture collections, sperm banks, ►code genetic, ►histone code

Genetic Code, Combinatorial: The transcription factor binding sites are assembled to form tissue-specific enhancer elements. ►enhancer, ►tissue-specificity, ►transcription factors

Genetic Code, Second: Determines the binding specificities of the transcription factors. ►aminoacyl-tRNA synthetase

Genetic Colonization: An infection of plants by *Agrobacteria* results in the expression of bacterial genes in the plant cells and the gene products, such as opines, and is utilized only by the bacteria. In population genetics, colonization means also the establishment of a breeding population in new habitat. ►*Agrobacterium*, ►transformation, ►opines; Harding RM, McVean G 2004 Curr Opin Genet Dev 14:667.

Genetic Complementation: ►complementary alleles, ►complementation groups, ►allelic complementation, ►complementation maps

Genetic Conflict Theory: The evolutionary conflict between maternal and paternal genes such as exists in imprinting. ►imprinting; Wilkins GF, Hasig D 2003 Nature Rev Genet 4:359.

Genetic Conservation: The preservation of species and subspecific genetic variations in protected areas, national parks, game reserves, botanical gardens,

zoos, seed depositories, culture corrections, sperm banks (Ryder OA 2005 Cytogenet Genome Res 108:6).

Genetic Correlation: Linked genes are expected to segregate together depending on the frequency of recombination. Members of the same family display correlation, and even assortative mating shows correlations although the latter may not be genetic. From the correlation between certain phenotypes the chromosomal location of genes can be predicted. The term genetic correlation in animal breeding is defined as a measure of the ratios of additive variances: $\text{Cov}(X,Y)/\sqrt{\text{Var}(X)\text{Var}(Y)}$. ▶correlation

Genetic Counseling: Provides information, medical diagnosis on hereditary bases, recurrence risk, family history, and possible management of genetic anomalies for the benefit of the family. It has no eugenic purpose and it does not make recommendations for decision; it merely informs the concerned individual(s). ▶counseling genetic, ▶risk, ▶recurrence risk, ▶utility index for genetic counseling; Mahowald MB et al 1998 Annu Rev Genet 32:547; Thornburn DR, Dahl HH 2001 Am J Med Genet 106:102; GENETests: http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genecounseling.shtml; <http://www.nlm.nih.gov/medlineplus/geneticcounseling.html>; <http://www.genetest.org/>.

Genetic Death: Genetic death occurs if an organism leaves no offspring or a gene is not transmitted to subsequent generations. ▶mutation beneficial, ▶mutation neutral, ▶fitness, ▶selection coefficient, ▶selection conditions, ▶transmission, ▶apoptosis; Hay BA et al 2004 Nature Rev Genet 5:911.

Genetic Determination (g^2): Similar to heritability in the broad sense (measured by intraclass correlation) where MS_b and MS_w stand for between and within strain mean squares, respectively. The $2n-1$ in the denominator is used in testing inbred strains to compensate for the increase of additive genetic variances during inbreeding. ▶intraclass correlation, ▶heritability, ▶variance

$$\frac{MS_b - MS_w}{MS_b + (2n - 1)MS_w} = g^2$$

Genetic Discrimination: Prejudicial treatment on the basis of phenotypic or genotypic constitution by employers, insurance companies or any other person or institution. ▶genetics and privacy, ▶bioethics; Nowlan W 2002 Science 297:195; Rothenberg KH, Terry SF 2002 Science 297:196; Wright Clayton E 2003 New Engl J Med 349:562). Genetic discrimination is also for the detection of differences in the

genetic material of cells, e.g., normal and cancer cells (Huang J et al 2004 Human Genomics 1:287).

Genetic Diseases: An estimated 4,000 human genes are directly or indirectly involved in the determination of human malformations and physical and mental disabilities. According to some estimates 15 to 20% of newborns are afflicted by some hereditary problems and a large fraction of the abortions are caused by chromosomal anomalies and/or recessive or dominant lethal genes. Approximately 25% of the hospitalizations are due to maladies with a genetic component. One study found that ~71% of the 4,224 children admitted to a hospital a significant genetic component of the illness they were treated for (McCandless SE et al 2004 Am J Hum Genet 74:121). After birth, defective enzymes have the largest share in the disorders. Anomalous genetic regulation accounts for the majority of the developmental defects. Amino acid replacement mutations (based on six human diseases) indicate that evolutionarily conserved sites are most common in human disease. From the degree of physicochemical alterations in the protein caused by missense mutation the grade of the disease or the likelihood of developing cancer can be predicted (Stone EA, Sidow A 2005 Genome Res 15:978). Polymorphic replacement mutations and silent mutations appear, however, randomly distributed. In several countries, population databases are being established with purpose to gain information on the interplay among genes and environmental factors and eventually to facilitate individualized medical treatment. Epidemiological observations indicate adulthood diseases are affected not only by genetic causes but also by early environmental factors such as conditions at the time of conception, fetal and infant environment as well as by adult life style (Gluckman PD, Hanson MA 2004 Science 305:1733). Very often genes are not the absolute cause of the disease because many of them can be prevented by proper life-style and preventive medication if disposition exists. The occurrence of genetic disease sometimes can be avoided or the risks reduced by proper education, premarital genetic counseling. During gestation, transcription factor and enzyme defects are the most prevalent fraction of diseases of the fetus. ▶eugenics, ▶gene therapy, ▶readthrough, ▶selection coefficient, ▶inbreeding, ▶consanguinity, ▶risk, ▶recurrence risk, ▶DALY, ▶prevalence, ▶genetics and privacy, ▶OMIM, ▶genetic screening; Miller MP, Kumar S 2001 Hum Mol Genet 10:2319; Perez-Iratxeta C et al 2002 Nature Genet 312:316; Dean M et al 2002 Annu Rev Genomics Hum Genet 3:203; Homophila; statistical tests for genome-wide identification

of disease genes: Marchini J et al 2005 Nature Genet 37:41; frequencies: <http://archive.uwcm.ac.uk/uwcm/mg/fidd/>; candidate disease genes:

[dhttp://disease.bork.embl-heidelberg.de/g2d/](http://disease.bork.embl-heidelberg.de/g2d/); disease genes: <http://dgcst.ceinge.unina.it/>.

Genetic Disorder: In the manifestation of the anomaly (disease) hereditary factors play major role. Single genes determine primarily some of the diseases; others are under the control of several genes. In either case, environmental factors can modify the expression of the disorder. ▶ [monofactorial inheritance](#), ▶ [polygenic inheritance](#), ▶ [QTL](#), ▶ [mitochondrial diseases in humans](#)

Genetic Dissection: Analyzes the mechanism(s) of genetic determination and control of biological traits, morphogenesis and/or other function(s) by the techniques of mutation, recombination and pattern of inheritance in pedigrees or populations. ▶ [one gene—one enzyme theorem](#), ▶ [morphogenesis in *Drosophila*](#), ▶ [metabolic pathways](#)

Genetic Distance: Genetic distance (d) can be measured by different procedures. One simplification is based on a geometric model is $d^2 = 1 - \sqrt{p_1 p_2} - \sqrt{q_1 q_2}$ where p and q represent the frequencies of the two alleles of a locus in populations 1 and 2, respectively. For actual determination of the distance between two populations more than one allelic pair must be considered. Genetic distance, F_{ST} is calculated also as $V_p / \bar{p}(1 - p)$ where V_p is the variance between gene frequencies in a set of n populations and \bar{p} = their average gene frequencies. ▶ [evolutionary distance](#), ▶ [evolutionary tree](#); Nei M 1972 Am Nat 106:283; molecular distances among some animals: <http://warta.bio.psu.edu/DED>.

Genetic Divergence: ▶ [divergence](#)

Genetic Diversity: The variations in the gene pool of a population or the genetic variations in the populations. ▶ [gene pool](#), ▶ [genetic variation](#), ▶ [genetic conservation](#), ▶ [diversity](#)

Genetic Drift: A change in gene frequencies by sampling error(s) of the gametic array so the genes are not maintained on the basis of their fitness or selective advantage they may convey but the selection is the outcome of chance. In case of two alleles, selection by chance alone is determined by the frequency of the alleles, the binomial distribution and population size. Thus, if the frequency of allele A is p and that of a is q the frequency of alleles by chance alone will follow the binomial distribution of $(p + q)^n$ where n = the number of individuals that leave offspring surviving

to the reproductive age; e.g., in case the allelic frequencies are equal and four individuals survive, the probability that all 4 will be homozygous recessives is 0.0625. ▶ [effective population size](#), ▶ [founder principle](#), ▶ [binomial distribution](#), ▶ [Pascal triangle](#), ▶ [Eve foremother](#); Cavalli-Sforza LL, Bodmer WF 1971 The Genetics of Human Populations, Freeman, San Francisco, California.

Genetic Endpoint: Classification of the types of genetic lesions such as mutation, chromosomal aberration, unscheduled DNA synthesis, etc. that are detected in mutagen testing. ▶ [bioassays in genetic toxicology](#)

Genetic Engineering: Construction of special chromosomes by cytogenetic manipulations, somatic cell fusions, or introduction of organelles into cells by mechanical means (genetic microsurgery). Isolation and propagation of DNA molecules in suitable hosts, molecular modification of genes and regulatory elements for special purposes, and transfer genes among diverse organism by bypassing the constraints of sexual reproduction and manipulate them for medical, industrial and agricultural use. ▶ [transformation](#), ▶ [cloning vectors](#), ▶ [homologous recombination](#), ▶ [chromosome substitution](#), ▶ [alien addition](#), ▶ [alien substitution](#), ▶ [alien transfer lines](#), ▶ [metabolite engineering](#), ▶ [protein engineering](#), ▶ [pathogen identification](#), ▶ [intercellular immunization](#), ▶ [intracellular immunization](#), ▶ [input trait](#), ▶ [gene therapy](#), ▶ [cancer gene therapy](#), ▶ [transgenic](#), ▶ [genomics](#), ▶ [biotechnology](#), ▶ [monoclonal antibody](#), ▶ [intein](#), ▶ [monoclonal antibody therapies](#), ▶ [targeting genes](#), ▶ [nuclear transplantation](#), ▶ [terminator technology](#), ▶ [scaffold](#), ▶ [GMO](#), ▶ [stem cells](#), ▶ [tissue engineering](#), ▶ [stem cells](#), ▶ [RAC](#), ▶ [synthetic biology](#)

Genetic Enhancement: ▶ [gene therapy](#), ▶ [plant breeding](#), ▶ [animal breeding](#), ▶ [eugenics](#)

Genetic Equilibrium: Exists when gene frequencies are stable for generations. (See also ▶ [mutations and genetic equilibrium](#)). In a panmictic diploid equilibrium population, the frequency of heterozygotes is twice the square root of the product of the frequencies of the two homozygous classes: $2 = H / \sqrt{D \times R}$ where H , D , R and stand for heterozygotes, homozygous dominants, and homozygous recessives, respectively (see Table G3). This is derived from the middle term of the Hardy-Weinberg formula, $2pq = h = 2\sqrt{p^2 q^2} = 2 \times \sqrt{D \times R}$ and hence $2 = H / \sqrt{D \times R}$.

This principle can graphically be represented (see Fig. G24). In an equilibrium population the frequency of heterozygotes is represented by a parabola as the proportion of the alleles vary from 0 to 1 to 0 as long the as three genotypes have equal fitness. With respect to an individual locus, equilibrium is attained

Table G3. Genotypic frequencies

The four populations represented in the body of the table below all have identical gene frequencies, $p = 0.8$, $q = 0.2$ yet the genotypic proportions are quite different. According to the definition in the text only population 4 is in equilibrium.

| Populations | Genotypic Frequencies | | |
|-------------|-----------------------|------|------|
| | AA | Aa | aa |
| 1 | 0.80 | 0.00 | 0.20 |
| 2 | 0.70 | 0.20 | 0.10 |
| 3 | 0.60 | 0.45 | 0.00 |
| 4 | 0.64 | 0.32 | 0.04 |

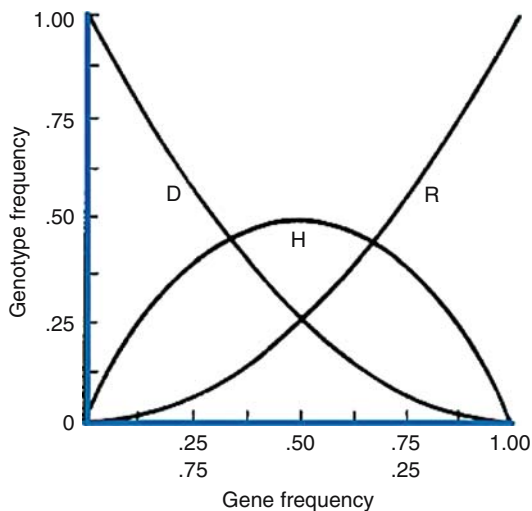


Figure G24. Genetic equilibria.

within one generation of random mating. As long as random mating prevails and there is no selection; gene and genotypic frequencies do not change and the Hardy-Weinberg principle prevails. Multiple loci require more generations to attain equilibrium. Also, equilibrium depends on the intensity of linkage among the loci. Progress toward equilibrium is delayed if the genes are sex-linked. If in the original mating the homogametic sex is homozygous for a recessive allele (X^aX^a) and the heterogametic sex carries the other allele (X^AY), the allelic frequencies in the two sexes will follow an oscillatory path during the generations because of the zigzag pattern of inheritance of the X chromosome. In equilibrium, the allelic proportions in the two sexes will be represented by the proportions of the X chromosomes.

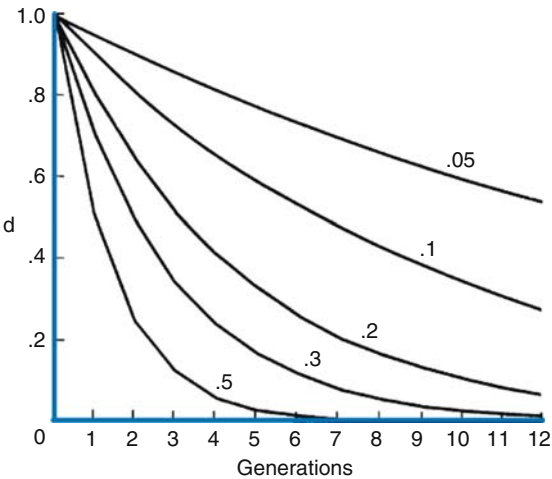


Figure G25. Progress toward genetic equilibrium in case two genes are linked in repulsion at zero generation time. At equilibrium the repulsion and the coupling phases are equal. Four of the curves (0.05 to 0.3) represent the courses to equilibria at various intensities of recombination; 0.5 indicates independent segregation. (Modified after Falconer, D.S. Introduction to Quantitative Genetics. Longman, London, UK)

Somewhat similar situation exists in hermaphrodites carrying self-sterility alleles (S) (see Fig. G25). The mating of plants self-incompatibility alleles (S) produce the offspring shown in the table (See Table G4) below.

Table G4. Self-sterility progenies

| Female | Male | Offspring |
|----------|-----------------------------|---|
| S_1S_2 | Either S_1S_3 or S_2S_3 | $\frac{1}{2} S_1S_3 + \frac{1}{2} S_2S_3$ |
| S_1S_3 | Either S_1S_2 or S_2S_3 | $\frac{1}{2} S_1S_2 + \frac{1}{2} S_2S_3$ |
| S_2S_3 | Either S_1S_2 or S_1S_3 | $\frac{1}{2} S_1S_2 + \frac{1}{2} S_1S_3$ |

Half of the progeny is the same as the male whereas the other half has a different constitution. The genetic constitution of the females does not reappear in the immediate progeny because of the self-sterility. Therefore, if the frequencies of the alleles are not identical, the genotypes most common among the parents will be the least frequent among their offspring although will reappear in advanced generations. Equilibrium is reached however if the frequencies of the alleles are equal.

In polyploids the progress toward equilibrium is quite complicated and can be determined according to

CC Li (First Course in Population Genetics, Boxwood Press, California). If the gametic output of an autotetraploid population is $G_0 \equiv x(AA) + 2y(Aa) + z(aa) = 1$, the frequency (p) of $A = x + y$ and the frequency (q) of $a = y + z$. The gametic proportions in the course of generations (n) is expressed as $d = (y^2 - xz) = y^2 - (p - y)(q - y) = y - pq$, and d is the index of divergence from the equilibrium condition. This index is reduced by $2/3$ during each generation of random mating. The gametic proportions and gene frequencies can thus be obtained as:

$$\begin{aligned} yn &= pq + dn = pq + \left(\frac{1}{3}\right)nd \rightarrow pq, \\ xn &= p - yn = p^2 - \left(\frac{1}{3}\right)nd \rightarrow p^2, \\ zn &= q - yn = q^2 - \left(\frac{1}{3}\right)nd \rightarrow q^2 \end{aligned}$$

►Hardy-Weinberg, ►linkage disequilibrium, ►autopolyploidy, ►sex-linkage, ►self-sterility, ►Wahlund's principle

Genetic Essentialism: A criticism of modern genetics for "equating" human (and other) beings with a molecular entity (DNA), including social, historical and moral complexities and responsibilities. In contrast, some physicians and ethicists emphasize the holistic approaches, which integrate also human consciousness. ►vitalism

Genetic Fine Structure: Analysis involves recombination within the boundaries of individual genes.

Genetic Fingerprinting: ►DNA fingerprinting

Genetic Hazards: ►risk, ►genetic risk, ► λ_s , ►recurrence risk, ►empirical risk, ►genotypic risk ratio, ►radiation hazard assessment, ►radiation effects, ►environmental mutagens, ►Kaplan-Meier estimator of survival, ►GMO

Genetic Homeostasis: The property of a population to maintain its genetic composition and resist changes in gene frequencies by phenotypic regulation under variable environmental conditions. ►homeostasis, ►canalization, ►artificial selection; Lerner IM 1954 Genetic Homeostasis, Wiley, New York.

Genetic Homology: The degree of similarity in the base sequences of DNA and RNA or the amino acid sequences in the proteins. ►DNA sequencing, ►RNA sequencing, ►protein structure, ►amino acid sequencing, ►homology, ►databases

Genetic Information: Instructions in the nucleic acids for the cellular machinery.

Genetic Instability: ►instability genetic

Genetic Interaction: Genetic interaction is becoming increasingly interesting in modern biology and needs new (bioinformatics) approaches for its genome-wide use. The global performance of four existing classes of inference algorithms using 445 *Escherichia coli* Affymetrix arrays and 3,216 known *E. coli* regulatory interactions from RegulonDB have been tested. The context likelihood of relatedness (CLR) algorithm can also be applied as a novel extension of the relevance networks class of algorithms. CLR demonstrates an average precision gain of 36% relative to the next-best performing algorithm. At a 60% true positive rate, CLR identified 1,079 regulatory interactions, of which 338 were in the previously known network and 741 were novel predictions (Faith JJ et al 2007 PloS Biol 5(1)e8). ►epistasis, ►gene product interaction, ►QTL, ►genetic networks, ►systems biology

Genetic Isolation: The lack of ability to interbreed (incompatibility) and/or hybrid inviability or sterility between/among different taxonomic groups. ►isolation genetic, ►speciation

Genetic Load: Sum of deleterious genes in the genome. Recessive alleles cannot generally be detected in the heterozygotes. These heterozygotes may continuously contribute homozygotes to the population and if the recessives are deleterious, they may adversely affect the fitness of the population; thus constituting a genetic load. The amount of hidden genetic variation is revealed by the coefficient of inbreeding. In F_1 , 100% of the population is heterozygous. In successive generations of selfing, the heterozygosity decreases by $(0.5)^n$ where n = the number of selfed generations (e.g., by F_5 there are four selfings). Thus, the sum of the heterozygotes = $1 - (0.5)^n$. The coefficient of inbreeding F , in the offspring of first cousins, is 0.0625 whereas among unrelated individuals it is presumed to be 0. Thus, if the mortality range in a certain age group is, say, 11% in the general population, and 16% among the children of first cousins, the difference is 5%. Therefore, $16 \times 0.05 = 0.80$, and 80% would be the average mortality if the coefficient of inbreeding would reach 100%. Recessive zygotic lethality requires homozygosity at the same locus (present in both parental gametes). According to the Hardy-Weinberg theorem, the frequency of the double recessive genotypes is expected to be q^2 , and the frequency of at least one lethal equivalent gene is then $\sqrt{0.80} \approx 0.89$. This indicates that almost 90% of the gametes carried a lethal gene or a combination of genes that cause lethality at homozygosity. On this basis, the genetic load of this population is close to one lethal equivalent factor per gamete. Other investigations estimated the genetic load to be twice as high in some

The frequency of deleterious alleles is proportional to the mutation rate and selection coefficient: $\hat{q}^2 = u/s$. By rewriting the formula, the mutational load of recessive alleles becomes $u = s\hat{q}^2$, and $\hat{q} = \sqrt{u/s}$.

The mutational load of dominant genes is $2u$. In the absence of dominance in a random-mating population, the mutational load is $L = 2u/(1 + u)$. The mutational load in the most common cases is proportional to the rate of mutation and not to the severity of the affliction.

G

populations. The amount of the genetic load may vary. It is affected by exposure to environmental mutagens, drugs, exposure to chemicals in the food chain (natural toxins or insecticides, pesticides) or in industrial pollutants, occupational hazards, presence of mutator genes (transposable elements), and natural or other types of radiations (X-rays, UV, etc.). Completely dominant lethal mutations do not contribute to the genetic load because they may eliminate the carriers of the genetic defect and thus no load is passed on to successive generations. Of course, some mutations may show intermediate types or conditional expression and may or may not contribute to the load. Some deleterious genes are closely linked to advantageous genes and thus transmitted beyond their merit by this "hitchhiking" effect. In such a situation, a recombinational load may exist. Environmental load is generated in highly variable environments where under certain conditions genes are selected that normally convey inferior fitness. Incompatibility load arises in cases of deleterious maternal—fetal interactions, such as those that may arise if the mother is Rh negative for this blood antigen and the fetus is positive or if the mother expresses phenylketonuria but the fetus is heterozygous (maternal epistasis). ▶allelic frequencies, ▶Hardy–Weinberg theorem, ▶mutation neutral, ▶mutation beneficial, ▶recombinational load, ▶selection coefficient, ▶fitness, ▶coefficient of inbreeding, ▶consanguinity, ▶incest, ▶genetic risk, ▶lethal equivalent, ▶Muller's ratchet, ▶incompatibility, ▶epistasis, ▶mutation in human populations, ▶death, ▶truncation; Cavalli-Sforza LL, Bodmer WF 1971 The genetics of human populations, Freeman, San Francisco; Muller HJ 1950 Am J Hum Genet 2:111; Drake JW et al 1998 Genetics 148:1667; Szafraniec K et al 2001 Proc Natl Acad Sci USA 98:1107; Kondrashov AS et al 2002 Proc Natl Acad Sci USA 99:14878.

Genetic Lottery: (Journalistic) chance of individuals to inherit certain genes in a population.

Genetic Manipulation: Application of genetic, cytological, or molecular techniques for constructing altered organisms. ▶genetic engineering, ▶chromosome engineering

Genetic Map: The relative position of genes or other chromosomal markers represented in a linear manner on the basis of recombination frequencies. ▶mapping genetic, ▶physical map, ▶mapping function, ▶deletion maps, ▶linkage group

Genetic Markers: Genetic markers help identify nuclear chromosomes, cytoplasmic organelles, and isolated cells on the basis of their inherited behavior and facilitate the identification of the genetic mechanisms involved in special phenomena, such as recombination, gene conversion, mutation, chromosomal rearrangements, genetic transformation, cell fusion, selection, etc.

Genetic Material: Either DNA (in eukaryotes and the majority of prokaryotes) or RNA (in some viruses). These nucleic acids can occur in either double or single-stranded forms. ▶RNA, ▶mtDNA, ▶ctDNA, ▶prion, ▶Watson and Crick model

Genetic Medicine: Genetic medicine aims to correct diseases by the use of DNA, RNA, or proteins. Inborn errors of metabolism were recognized since the beginning of the twentieth century and metabolic corrections or alleviations of the defect has been used by modified defect. Phenylketonuric patients were placed on phenylalanine-restricted diet, or in case of fructose intolerance, fructose-rich food was proscribed. Low-cholesterol diet and the use hydroxymethylglutaryl co-enzyme A (HMG CoA) inhibitor statins alleviate hypercholesterolemia. To avoid iron overload caused by the frequent blood transfusions in thalassemia, the iron chelating desferrioxamine proved useful. In several diseases, *protein augmentation* therapy corrected for the low level of a protein in the extracellular compartment; purified proteins were introduced into the body in case of endocrine disorders, immunoglobulin deficiencies, lysosomal storage diseases, and others. This approach was successful only when the administration was effective and simple, allergic or immunological reactions were not prohibitive, and the supply was adequate at reasonable cost. This type of therapy is applicable (at least in principle) to the approximately 1,800 human diseases involving a single major gene. The complex, multigenic quantitative diseases and chromosomal aberrations are generally not amenable to this type of corrections. Some of the disease sites are difficult to reach directly (e.g., in the brain in utero). Others, e.g., α -antitrypsin (ATT) deficiency is manifested in adult stage and then, oral administration of 4-phenylbutyric acid facilitates the release of antitrypsin from the endoplasmic

reticulum. Antitrypsin, as a “chemical chaperone”, may prevent the injuries resulting from AAT deficiency. Some injuries of the brain or spinal cord, or tissue degeneration (e.g., prion diseases, Parkinson disease, cardiac muscle defects, hematological anomalies, etc.) can eventually be remedied in humans, also by the use of embryonic or somatic stem cells. Gene therapy and stem cell mediated cures are generally expected to be effective for all variations within a specific monogenic disease. MicroRNA or RNAi technology must target specific sites (corresponding to that RNA) to be effective. ▶antisense technology, ▶microRNA, ▶RNAi, ▶gene therapy, ▶readthrough, ▶cancer gene therapy, ▶stem cell, ▶biomarker, ▶drug development, ▶SADR; O'Connor TP, Crystal RG 2006 Nature Rev Genet 7:261.

Genetic Milieu: ▶genetic background

Genetic Module: ▶module, ▶genetic network

Genetic Mosaic: An individual with cell patches of different genetic constitutions. It may come about by somatic mutation, movement of insertion- or transposable elements, somatic recombination, nondisjunction, deletion, etc. ▶individual entries, ▶chimera, ▶codominance

Genetic Network: The connections between DNA, RNA, protein, cis- and transacting regulators, operons, epistasis, signals and the signal transducing systems, and feedback, involving a large number of genetic and environmental inputs (see Fig. G26). M.

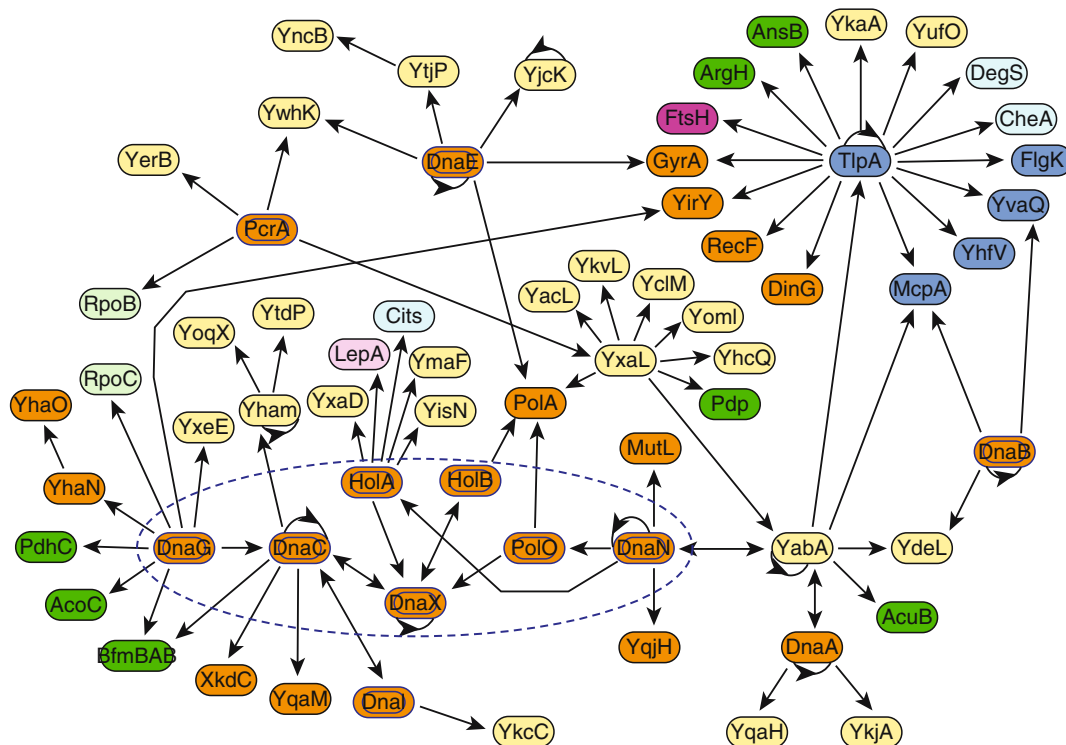


Figure G26. A network of 69 proteins involved in 91 specific interactions centered on the replication machinery of *Bacillus subtilis*. It shows the relations of DNA replication with recombination and repair, membrane-bound protein complexes, and signal transduction. The names, basic function, and location in the physical map of most of the specific proteins can be found in Kunst F et al 1997 Nature [Lond] 390:249, reporting the complete genome sequence of this prokaryotic genome. Two-hybrid tests were used to determine the interacting components. The arrows are oriented from bait to prey. Double blue lines designate the primary baits (with the exception of PriA and DnaD). The dashed black oval outlines the replisome. The number of the interacting components varies from 17 to 1. Details can be accessed by <http://www-mig.versailles.inra.fr/bdsi/SpiD>. The color code identifies functional categories. Orange: DNA replication/ recombination/ repair. Dark blue: mobility and chemotaxis. Light blue: signal transduction. Light green: transcription. Pink: protein synthesis. Dark green: metabolism of carbohydrates and amino acids. Purple: cell division. Yellow: unidentified functions. (From Marie-Françoise Noirot-Gros, Etienne Dervyn, Ling Juan Wu, Peggy Mervelet, Jeffery Errington, S. Dusko Ehrlich and Philippe Noirot 2002 Proc Natl Acad Sci USA 99:8342–8347. Courtesy of Dr. M.-F. Noirot-Gros, I.N.R.A., France. Copyright 1992 National Academy of Sciences, U.S.A.).

Demerec in 1933 said (J. Hered. 24: 369) “We know today, however, that no single gene has the sole responsibility for the appearance of any one character. The final effect is produced through the interaction of the whole complement of genes, although certain genes may have greater influence on the expression of certain characteristics than some other genes have.”

Genes involved in common processes tend to be expressed in detectable hierarchical waves. Exposure of yeast cells to Cd^{2+} induced 54 proteins, the majority of the sulfur assimilated by the cells was utilized for the formation of glutathione, and this reduced the production of other sulfur-rich proteins. The regulation takes place at the mRNA level. Glutathione is required for detoxification (Fauchon M et al 2002 Mol Cell 9:713). Interacting proteins may be identified experimentally by the two-hybrid system, TAP, three-dimensional structures, or by mass spectrometry.

Computational methods exist that reveal the co-inheritance of functional linkages across phylogenetic boundaries. By such procedures in yeast 3,875 linkages of 804 proteins have been revealed (Date AV, Marcotte EM. 2003 Nature Biotechnol 21:1055). In yeast, 4681 genes, i.e., ~81% of the genome, displayed ~34,000 probabilistic linkages (Lee I et al 2004 Science 306:1555). In *E. coli*, 74% of the known metabolic enzymes seem to be clustered in modules with an average pathway specificity of 84% (von Mering C et al 2003 Proc Natl Acad Sci USA 100:15428). On the basis of experimental data available or perturbation of the systems as the result of the recent molecular techniques, mathematics-aided models can be developed that may be applied to medical and biotechnological problems (Tegnér J et al 2003 Proc Natl Acad Sci USA 100:5944). Highly connected topological modules are combined into larger, less cohesive units and display similarities across different organisms. During development, multigenic feedback loops and spatial repressive control systems operate both periodically and constitutively in a dynamic manner (de Lichtenberg U et al 2005 Science 307:724). Behavioral traits of *Drosophila* displayed dramatically different interactions depending on the genetic background (van Swinderen B, Greenspan RJ 2005 Genetics 169:2151). The protein interaction networks are conserved in even unrelated species (Sharan R et al 2005 Proc Natl Acad Sci USA 102:1974). In 17 fungal genomes, cis-regulatory elements are conserved for several interacting modules. However in the ribosomal modules for dozens of promoters, new cis elements have emerged and switched on while retaining the functionality of the modules and shedding light on the evolution of regulatory

networks (Tanay A et al 2005 Proc Natl Acad Sci USA 102:7203). In some fungal species, the transcriptional network is altered by the loss of cis-regulatory functions (Ihmels J et al 2005 Science 309:938). A model of oscillatory signals may offer greater quantitative precision (Lipan O, Wong WH 2005 Proc Natl Acad Sci USA 102:7063). Herpes virus (Kaposi sarcoma-associated herpesvirus and varicella-zoster virus) proteins interact within their proteomes and with the human proteome (Uetz P et al 2006 Science 311:239).

Some network designs may require revisions when additional knockout(s) indicate no significant downstream consequence of the gene loss. In yeast, however, in some cases 4,000 double knockouts lead only to synthetic lethality (see Fig. G27) (Yeang C-H et al 2005 Genome Biol 6:R62).

The protein–protein interaction networks can facilitate understanding the pathogenic mechanisms involved in disease. In hereditary human ataxias and neural degenerations, Purkinje cell defects are

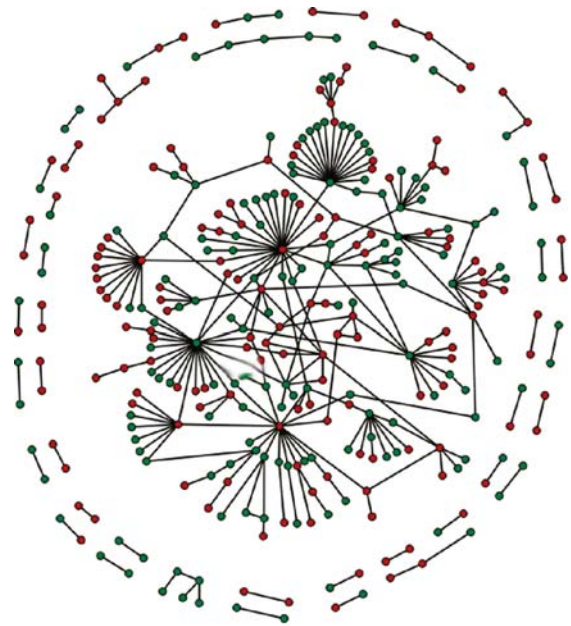
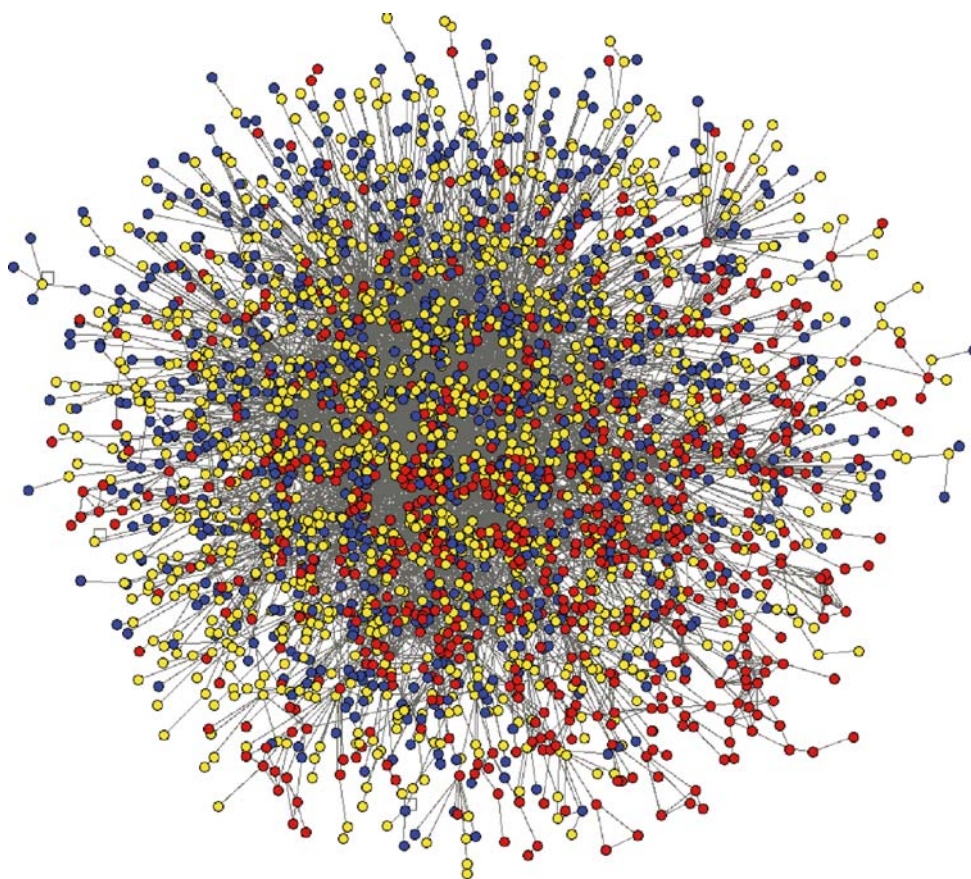


Figure G27. Genetic network of yeast nuclear proteins displaying 318 interactions of 329 proteins. Note the reduced links between highly connected proteins and the preference between highly connected and low-connected pairs of proteins. Green nodes correspond to viable null-mutations. Red nodes represent indispensable functions and their mutation is lethal. The map was constructed on the basis of two-hybrid data and the statistical properties of the interactions are discussed by Maslov S, Sneppen K 2002 Science 296:910. (Courtesy of Dr. Sergei Maslov)



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Figure G28. *Caenorhabditis elegans* interactive network (interactome) displaying approximately 5,500 interactions. The experiment involved the use of yeast two-hybrid method. The nodes (circles) of proteins are colored according to phylogenetic class. Red: ancient, yellow: multicellular and blue: worm specific sets. See for details Li, S. *et al.* 2004 Science 303:540; the illustration is the courtesy of Drs. Marc Vidal and Nicolas Bertin

involved. A study of 54 proteins of 23 genetically determined ataxias revealed 770 protein–protein interactions by stringent yeast two-hybrid system; 83% of the interaction could be verified also in mammalian cells (Lim J *et al* 2006 Cell 125:801 (see Fig. G28)). In *Caenorhabditis*, using RNAi interference of gene expression by simply feeding RNAi containing bacteria revealed that a few “hub” genes affected several others, including homologs of genes involved in hereditary diseases. The data indicated that these genes modify the state of the chromatin and can affect the expression of many functionally unrelated genes and provide new information on the complexity of human disease (Lehner B *et al* 2006 Nature Genet 328:896).

Regulatory interactions affect the evolution of proteins that can be different in coding properties (see Fig. G29).

Evolution of genetic networks may be based either on the *link dynamics* or on *node dynamics*. Comparison of genetic networks may be relatively

simple if the species are closely related, and it can be measured by sequence comparisons (see Fig. G30). In case the species are less closely related, unrelated sequences may assume similar function within the network. These problems of evolutionary analyses can be resolved by a Bayesian parameter inference. Correlation coefficients of gene expression measured on RNA microarrays can be used to assess quantitatively the divergence between humans and mice, even when there is loss or gain of genes (Berg J, Lässig M 2006 Proc Natl Acad Sci USA 103:10967).

A probabilistic method, called Geronemo, aims to identify the mechanism by which genetic changes perturb the regulatory network. Geronemo automatically constructs a set of coregulated genes (modules), whose regulation can involve both sequence variations and expression of regulators. By exploiting the modularity of genetic regulatory systems, it reveals regulatory relationships that are indiscernible when

genes are considered in isolation, allowing the recovery of intricate combinatorial regulation. By incorporating both expression and genotype of regulators, Geronemo captures cases where the effect of sequence variation on its targets is indirect. The results suggest that a significant part of individual variation of expression in yeast arises from the evolution of a small number of chromatin structure modifiers (Lee S-I et al 2006 Proc Natl Acad Sci USA 103:14062).

Time-series microarray expression experiments can provide dynamic information about the expression of thousands of genes that are activated or repressed in response to stimuli such as environmental stress. Transcriptional modules, subsets of transcription

factors (TF) and genes, such that genes in the same module tend to be similarly expressed and regulated by the same TFs across a number of experimental conditions. Integrated chromatin immunoprecipitation (ChIP-chip) data with expression data can identify active motifs and combinations of motifs and target genes under certain conditions. A computational method integrates the time-series expression data and ChIP-chip or motif information to infer an annotated *global* temporal map. This map describes the main transcriptional regulatory events leading to the observed time-series expression patterns and the factors controlling these events during a cell's response to stimuli (Ernst J et al 2007 Mol Systems Biol 3:74).

Mechanisms exist for signaling pathways that share components to respond specifically to any one stimulus. One of these mechanisms is insulation, i.e., the shared component(s) are relegated into distinct and specific macromolecular complexes or to different subcellular complexes. Another mechanism can be mutual inhibition to eliminate unwanted interactions between the pathways. These mechanisms can maintain the identity and specificity of different signaling pathways despite shared components (McClellan MN et al 2007 Nature Genet 39:409).

(See separate entries mentioned, ► [small-world networks](#), ► [networks](#), ► [cell model](#), ► [hub](#), ► [micro-array](#), ► [protein complexes](#), ► [protein interactions](#),

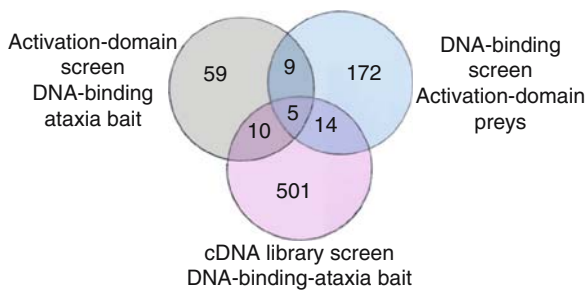


Figure G29. Yeast two-hybrid interactions for 54 ataxia-associated proteins

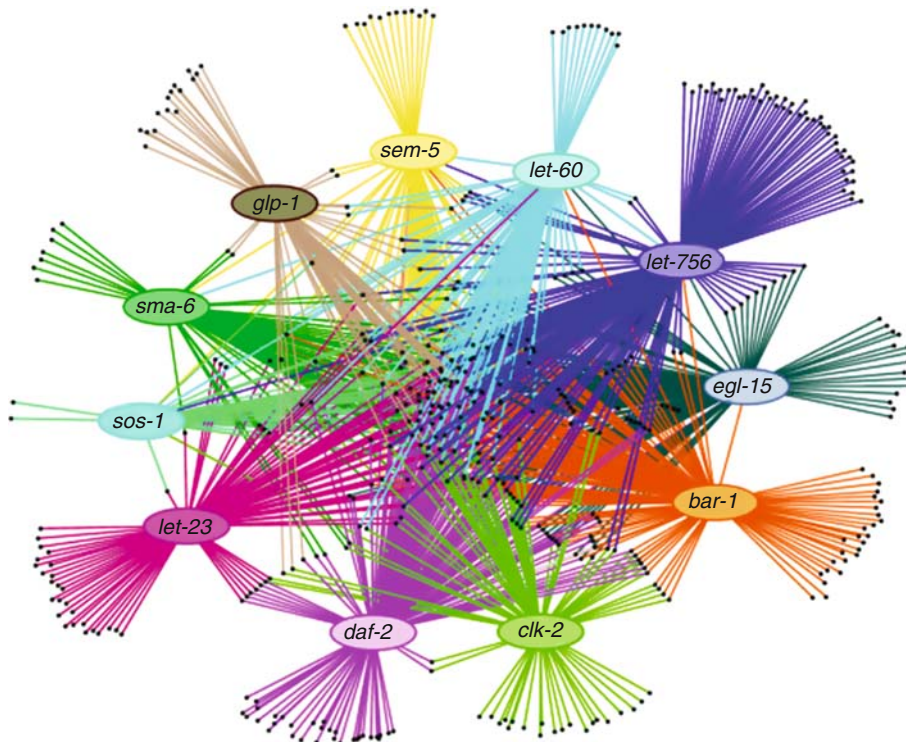


Figure G30. The SGI network. (From Byrne AB et al 2007 J. Biol. 6(3): 8)

►protein network, ►two-hybrid system, ►entropy, ►regulon, ►epistasis, ►interlogs, ►synthetic genetic arrays, ►probabilistic graphical models of cellular networks, ►autoregulation, ►proteome, ►transcriptome, ►überoperon, ►genome-wide location analysis, ►signal transduction, ►metagene, ►one gene-one enzyme theorem, ►HUPO, ►reactome, ►cooperative stability, ►knockout, ►synthetic lethal, ►synthetic genetic array, ►ataxia, ►ChIP, ►signal transduction; Kalir S et al 2001 Science 292:2080; Becskei A et al 2001 EMBO J 20:2528; Hasty J et al 2001 Nature Rev Genet 2:268; Davidson EH et al 2002 Science 295:1669; Gavin A-C et al 2002 Nature [Lond] 415:141; Saito R et al 2002 Nucleic Acids Res 30:1163; Guet CC et al 2002 Science 296:1466; Shen-Orr SS et al 2002 Nature Genet 31:64; Wyrick JJ, Young RA 2002 Current Opin Genet Dev 12:130; Dietmann S et al 2002 Current Opin Struct Biol 12:362; Valencia A, Pazos F 2002 Current Opin Struct Biol 12:368; Rison SC, Thornton JM 2002 Current Opin Struct Biol 12:374; Ravasz E et al 2002 Science 297:1551; Gilman A, Arkin AP 2002 Annu Rev Genomics Hum Genet 3:341; Hasty J et al 2002 Nature [Lond] 420:224; Pawson T, Nash P 2003 Science 300:445; Davidson EH et al 2003 Proc Natl Acad Sci USA 100:1475; regulatory module networks: Segal E et al 2003 Nature Genet 34:166; molecular networks in yeast: Galitski T 2004 Annu Rev Genomics Hum Genet 5:177; interaction network in *E. coli*: Butland G et al 2005 Nature [Lond] 433:531; yeast networks based of synthetic lethality: Boone C et al 2007 Nature Rev Genet 8:437; statistical evaluation of transcription regulatory signals: Garten Y et al 2005 Nucleic Acids Res 33:605, 18,183 interactions of *Caenorhabditis* genes computed from integrated interactome of yeast worm and fly information: Zhong W, Sternberg PW 2006 Science 311:1481; evolution of interactions: Weitz JS et al PLoS Biol 5(1):e11; molecular interaction database: <http://www.ebi.ac.uk/intact>; <http://dip.doe-mbi.ucla.edu>; <http://visant.bu.edu>; www.genepath.org; <http://string.embl.de>; <http://www.mgs.bionet.nsc.ru/mgs/gnw/genenet/>; commercial supplies: <http://www.biocarta.com/>; structural genomics: <http://sg.pdb.org/>; protein network: <http://www.cellcircuits.org>.

Genetic Nomenclature: ►gene symbols, ►databases, ►Genew; http://www.mblogic.net/point_of_view/1/.

Genetic Polymorphism: Gene loci (or chromosomal arrangements, organelles) in a population are represented by more than one (allelic) form. ►allele

Genetic Predisposition: Genetic predisposition implies that the genetic constitution is favorable for the development of a disease or anomaly.

Genetic Privacy: The right of an individual to keep his/her genetic record closed to the public. There are two aspects of this right: protection from discrimination by employers, insurance companies, etc.; and its possible hinderance of research on genetic disorders and development of new drugs. In the USA, law now recognizes “protected medical information.” ►genetic testing, ►wrongful life, ►ethics, ►privacy rules; Hall MA, Rich SS 2000 Am J Hum Genet 66:293; Skene L 2002 Trends Mol Med 8:48; Roche PA, Annas GJ 2001 Nature Rev Genet 2:392.

Genetic Profile: Electrophoretic pattern of microsatellites, restriction fragments, PCR products, etc. The purpose of the procedures is to detect potential health risks. It requires consent by the individuals or parents unless state law mandates screening. It should not violate privacy and should not be used for any kind of discrimination. ►electrophoresis, ►RFLP, ►PCR, ►genetic screening; Almond B 2006 Nature Rev Genet 7:67.

Genetic Recombination: ►recombination, ►recombination frequency, ►crossing over, ►bacterial recombination frequency, ►intragenic recombination, ►mapping genetic, ►illegitimate recombination, ►unequal crossing over, ►site-specific recombination, ►sister chromatid exchange, ►recombination variations of, ►recombination molecular mechanism prokaryotes, ►mtDNA, ►mitochondrial genetics, ►chloroplast genetics, ►recombination mechanisms eukaryotes, ►recombination models, ►gene conversion, ►targeting genes, ►homologous recombination, ►bacterial recombination frequency

Genetic Repair: ►DNA repair

Genetic Risk: The chance that an offspring will be affected by a hereditary defect. The risk can be inferred from the heritability of a particular gene or gene complex in a population. In case of simple Mendelian inheritance, for example in cystic fibrosis, in some Caucasian populations in genetic equilibrium, the frequency of this anomaly is $\approx 1/2,000 = 0.0005$. Thus, the frequency of the recessive allele is $\sqrt{0.0005} \approx 0.022 = q$. At genetic equilibrium, the frequency of carriers (heterozygotes) is $H = 2pq = 2 \times (1 - q) \times q = 0.043 = 1/23$. If a person heterozygous for such a deleterious gene ($q = 0.5$) marries a spouse by random choice ($q = 0.022$), the chance that they will have an afflicted offspring is $0.5 \times 0.022 = 0.011$, i.e., approximately $1/91$. If the same heterozygous person marries a first cousin who may have a 0.25 chance carrying the same allele, the probability that they will have an afflicted child may be as high as $0.5 \times 0.25 = 0.125$, i.e., $1/8$. If, however, an average Caucasian will have an offspring with an average Japanese spouse ($q = 0.004$) the probability that their child

would be afflicted by cystic fibrosis is only $0.022 \times 0.004 = 0.000088$ or $1/11,363$. The genetic risk will slowly rise with the application of medical care that compensates for the hereditary defects, e.g., administration of insulin to diabetics or by the use of gene therapy without replacing the defective gene(s). The remedial treatments will not much affect the incidence of rare diseases in the shorter term. If the incidence of a dominant human anomaly is 1×10^{-5} at the present, it may take 3,000 years (100 generations) to increase its prevalence to 1×10^{-3} . The incidence of recessive anomalies will rise at a much slower rate because the alleles are already sheltered from selection in the heterozygotes. The genetic risk can now be estimated with good precision if molecular information is available on the nucleotide sequences of a gene. E.g., in familial hypercholesterolemia in the gene encoding cardiac β -myosin, a substitution of Glu for Gly at position 256 involves only 0.56 chance for the penetrance of the disease, whereas a Gln \rightarrow Arg change at position 403 predicts a 100% penetrance and thus sudden death. ►genetic load, ►genetic counseling, ►empirical risk, ►risk, ►genotypic risk ratio, ►Hardy-Weinberg theorem, ►allelic frequencies, ►amniocentesis, ►clinical tests for heterozygosity, ►mutation rate, ►genetic screening, ►prenatal tests, ►transgenic, ►selection–medical care; Falconer DS 1965 *Ann Hum Genet* 29:51; Coulson AS et al 2001 *Methods Inf Med* 40(4):315.

Genetic Scanning: ►genotyping

Genetic Screening: This type of screening is applied to an asymptomatic population as (i) *prenatal tests* during pregnancy such as for mucopolysaccharidosis, muscular dystrophy, cytological tests for Down syndrome and fragile X conditions, ultrasound test for developmental anomalies, blood groups (Rh), and infections (syphilis, toxoplasmosis, cytomegalovirus). These tests may be mandated or voluntary. Screening of (ii) *newborns* aims to reveal whether they are afflicted by autosomal recessive disorders that require immediate medical attention to prevent severe later consequences. Most frequently the tests include biotinidase deficiency, congenital hypothyroidism, galactosemia, hereditary tyrosinemia, homocystinuria, maple syrup urine disease, phenylketonuria, and sickle-cell anemia. Law in the USA mandates some of these tests. Congenital adrenal hyperplasia, cystic fibrosis, hyperphenylalaninemia, arginosuccinase deficiency, galactokinase deficiency, phosphoglucomutase deficiency, homocystinuria, glucose-6-phosphate dehydrogenase deficiency and others (altogether more than 1000 diseases) may also be involved. The frequency of the genetic defects may vary in different ethnic groups and some of the tests are limited to families

where history provides clues to potential risk. The tests may be performed on blood withdrawn from the neonates by specialized laboratories using standard and reliable procedures such as ELISA, enzyme assays, immuno assays, Guthrie test and DNA tests, radioimmune assays, high-performance liquid chromatography, tandem mass spectrometry, cytological tests, etc. (iii) *Carrier testing* detects heterozygotes for “recessive” disorders in order to facilitate informed decisions by prospective parents regarding risks, especially in populations where the frequency of the deleterious genes is expected to be high, as in the cases of Tay-Sachs disease among Ashkenazi Jews (0.02), thalassemia in people of Mediterranean ethnicity occurring at frequencies exceeding 0.1 in high malaria areas, and cystic fibrosis with variable (generally about 0.02) frequency but much higher in ethnic populations with high degree of consanguinity. About 70% of those afflicted by cystic fibrosis had a CTT (Phe) deletion of codon 508 in exon 10 ($\Delta F508$). This assay is not yet used widely. (iv) *Presymptomatic* and susceptibility screening may be applied to younger individuals with liability to late onset genetic anomalies such as autosomal polycystic kidney disease, Charcot-Marie-Tooth disease, Huntington chorea, familial hypercholesterolemia, retinitis pigmentosa. Some tests predict susceptibility to diabetes mellitus, coronary heart disease, breast cancer, etc. In some countries, predictive premarital testing is mandated for some diseases. Some tests, e.g., Factor V Leiden (parahemophilia, 1q23, heterozygosity for the deficiency is in the range of 10^{-3} , homozygosity 10^{-6}) may involve venous thrombosis for women taking oral contraceptives and the test is not recommended (Grody WW et al 2001 *Genet Med* 3:139).

Testing for predispositions must require confidentiality because of the obvious relevance to finding jobs or health insurance. Genetic screening of individuals who do not have a family history of disorder may involve psychosocial and ethical issues. It is important that screening be conducted only for essential diseases or pre-disposition, for conditions that are medically treatable and for which, informed choices are available in case the test proves positive. Appropriate and safe procedure should be available, the test should not be objectionable to the population in general, and should be acceptable by the subjects. Genetic screening raises several ethical question regarding the right or advisability of withholding information, disclosure of the information to members of the family, what is the right to know or not to know by whom, and storage, safe-keep, and release of the information. (See terms used under specific entries, ►prenatal diagnosis, ►GMS, ►RDA, ►polymerase chain reaction, ►tandem mass

spectrometry, ►sperm typing, ►pre-implantation genetics, ►ART, ►false positive, ►false negative, ►cascade testing, ►eugenics, ►abortion medical, ►selective abortion, ►genetic counseling, ►genetic testing, ►Guthrie test, ►Guthrie card; Levy HL, Albers S 2000 Annu Rev Genomics Hum Genet 1:139; Pastinen T et al 2000 Genome Res 10:1031; Chace DH 2001 Chem Rev 101:445; McCabe LL, McCabe ERB 2004 Annu Rev Genomics Hum Genet 5:57; <http://mchb.hrsa.gov/screening/>; screening resources: <http://genes-r-us.uthscsa.edu/>).

Genetic Segregation: ►Mendelian segregation, ►modified segregation ratios, ►meiosis, ►preferential segregation, ►somatic segregation

Genetic Sexing Lines: Mechanical separation of insects by sex is often very difficult or nearly impossible at larger scale although this may be required for control by genetic sterilization. By genetic engineering, strains can be developed where under defined conditions, either the female or the male individuals can be selectively eliminated upon induction. ►sex-ing, ►autosexing, ►genetic sterilization; Robinson AS, Franz G 2000 In: Handler AM, James AJ (eds) Insect Transgenesis: Methods and Applications, CRC Press, Boca Raton, FL, p 307.

Genetic Similarity Index: The genetic similarity index expresses the similarities between different strains on the basis of the number of shared restriction fragments, identified by probes such as DNA minisatellite sequences, etc. ►minisatellite, ►microsatellite, ►probe, ►genetic distance

Genetic Stability: Genetic stability is good if the gene and chromosomal mutabilities are relatively rare, transposable elements are absent, and the population is in genetic equilibrium. ►mutability, ►genetic equilibrium, ►transposable elements, ►genetic homeostasis; Li SL, Rédei GP 1969 Theor Appl Genet 39:68.

Genetic Sterilization (sterile insect technique, SIT): In genetic sterilization, heavy doses of ionizing radiation (X-rays) break the chromosomes but do not necessarily kill the irradiated animals that are even capable of mating. However, because of the chromosomal rearrangements that follow, sterility or lethality may occur in their progeny, or, although the irradiated males may copulate, they cannot fertilize the eggs of the females and leave no offspring. This basic genetic knowledge was successfully applied to insect eradication. The screwworm (*Cochliomya hominivorax*), a tropical and subtropical parasite of warm-blooded animals, produces larvae that hatch in the wounds of livestock and cause great damage to the hide, making it inferior for the leather industry. Additional damage

results to agriculture by weight loss in cattle, sheep, and game; further, the fly may pose hazards even to people. The chemical control of this insect is difficult to achieve in live animals and not without danger of causing pollution and damaging health. Therefore, pupae were reared in a large laboratory and treated with about 7,500 R X-radiation, and every week two million irradiated males were released in the heavily-infested areas. The monogamous females so mated either failed to produce offspring, or more sophisticated chromosomal constructs were used to generate “genetic time bombs” (recurring genetic defects) that kept on killing the offspring due to chromosomal or genic defects (temperature-sensitive alleles).

In some areas and some years, this pest control was so effective that the screwworm population was reduced to 1% of that before the initiation of the program. A similar procedure was successfully applied for mosquito control as well. Particularly good results were observed in the control of lepidopteran insects with holocentric chromosomes where the delayed and sustained lethal effects could be best exploited.

Constructing a conditional lethal dominant genetic system may cause death without irradiation. The insect becomes lethal when specific conditions are met. In one construct designed in a *Drosophila* model, a tetracycline-repressible transactivator (tTa) protein was placed under the control of the Yp3 fat-body gene promoter. In the absence of tetracycline, any gene controlled by a tetracycline-responsive element (tRe) is normally expressed in the females. On a culture medium containing as low as 0.1 µg/mL tetracycline, females produced no progeny because the tTa prevented the synthesis of fat body (a yolk protein) that is required for storage of nutrients and for the insect immune system. The progeny of the males was not affected because they do not produce eggs and do not need fat body for fertility. In a similar manner, a mutant allele of the *male-specific lethal 2* gene (*msl-2^{NOPU}*), selectively killed the females by activating the dosage compensation mechanism in both males and females. By the same principles, insect-mediated (insect vector) human viral (Dengue fever, West Nile fever, Yellow fever), bacterial (Plague, Typhus, Lyme disease), protozoan (Malaria, Leishmaniasis, Sleeping sickness, Chagas disease), and worms-inflicted diseases (River blindness, Filariasis) may be controlled. With the increased knowledge of genetic transformation and the availability of various transposable elements, new approaches may open up in insect control. ►holocentric chromosomes, ►translocations, ►radiation effects, ►GSM, ►SIT, ►tetracycline, ►TetR, ►tTA, ►rtTA, ►sex determination, ►msl, ►high-dose/refuge strategy, ►refractory genes; Thomas DD et al 2000 Science 287:2474; Robinson AS 2002

Rev Mut Res 511:113; Horn C, Wimmer EA 2003 Nature Biotechnol 21:64; female-specific alternative splicing: Fu G et al 2007 Nature Biotechnol 25:353; Dyck, V., Hendrichs J, Robinson A (eds.) 2005 Sterile Insect Technique: Principles and Practice in Area-Wide Integrated Pest Management, Springer, Dordrecht, H.

Genetic Surgery: Genetic surgery replaces single or a few (defective) genes of an organism with the aid of (plasmid) vectors or introducing into cells foreign genetic material (organelles, chromosomes) with microsyringes or microcapillaries controlled by micro-manipulators under microscopes. ►gene replacement, ►gene therapy, ►genetic engineering, ►gene transfer by microinjection, ►targeting genes, ►transformation genetic

Genetic Switch: Mechanisms to turn genes on and off, based on interaction between specific DNA and protein sequences. ►regulation of gene activity, ►DNA binding proteins, ►DNA-binding protein domains, ►immunoglobulins, ►transposition, ►mating type determination in yeast, ►phase variation, ►Trypanosomas, ►Borrelia, ►serotype

Genetic Systems: Primarily the prevalent mode of reproduction (selfing, inbreeding, random mating, assortative mating, etc.). Generally, the mechanisms affecting variability (recombination, mutational mechanisms, etc.) are also included in this term. ►mating systems

Genetic Testing: Genetic testing may reveal the liabilities of an individual to certain diseases and genetic anomalies. The purpose of the tests can be diagnosis and/or risk assessment for symptomatic and asymptomatic cases, population screening, and reproductive decision-making. The test may consider family histories and environmental factors. Identification of carriers may be of particular importance for reproductive counseling. The results may aid prevention an/or treatment. Genetic information may facilitate the proper selection of drugs; e.g., mercaptopurine must be avoided for leukemia patients, and those deficient in thiopurinemethyl transferase. Cytogenetic, biochemical/pharmacogenetics and molecular tests can be used. DNA sequencing identifies alterations within genes, although heterozygotes may not necessarily bear a direct burden or risk. Microarray hybridization may also reveal genetic defects, although the tests are more expensive and the results may be ambiguous in case of heterozygosity of the diploid cells. Single strand conformation polymorphism and denaturing gradient gel electrophoresis are also applicable techniques. An individual may benefit from it because glucose-6-phosphate dehydrogenase deficiency may make a person more susceptible to

environmental oxidants (ozone, nitrogen dioxide). Thalassemias may increase the dangers of exposure to lead and benzene, porphyrias to chloroquine and barbiturates, pseudocholinesterase deficiency to organophosphate and insecticides, and so on. Molecular tests may reveal non-symptomatic heterozygosity for genetic diseases and may predict the risk for various disorders in the offspring. On the other hand, employers and health insurance companies may discriminate against individuals on the basis of genetic records. Genetic testing may not be applicable for the identification of certain anomalies or diseases, and the results of the tests for some conditions may not accurately predict the onset of a disease. With the approval of the Genetics and Insurance Committee of the United Kingdom, private health insurance companies in the UK already use seven tests for mutant alleles for the early onset Alzheimer disease, breast cancer, familial adenomatous polyposis coli, Huntington disease, and three other monogenic diseases. Those who are positive are obligated to pay higher premiums to obtain life insurance over £100,000 and have mortgage insurance. An extensive public welfare and healthcare system is available in the UK. Nevertheless, the ethical aspects of such a policy of insurance have been questioned. It must be recognized that genetic tests may not yet provide the wished answers to all health problems (Khoury MJ et al 2000 Genet Med 2:198), although 1,100 genetic tests had become available by 2007. Non-communication to patients of genetic risks may have legal liability to the physician or to the counselor (J. Clin. Oncology 21:2397 [2003]). Direct genetic testing of consumers (DTC) requires caution, and must not be considered without adequate context or counseling because some tests from laboratories of dubious quality mislead through unproven claims of benefit. In the USA, only about half of the states permit it (Hudson K et al 2007 Am J Hum Genet 81:635). ►genetic privacy, ►genetic screening, ►prenatal diagnosis, ►compliant mutation, ►refractory mutation, ►DNA sequencing, ►microarray hybridization, ►conversion, Yan H et al 2000 Science 289:1890; Cutler DJ et al 2001 Genome Res 11:1913; regulatory problems in genetic tests: Burke W, Zimmern RL 2004 Nature Rev Genet 5:955, <http://www4.od.nih.gov/oba/>, www.genetests.org, <http://www.geneclinics.org>.

Genetic Toxicology: ►gene-tox

Genetic Transfer: A genetic transfer may be mediated by the gametes during sexual reproduction, by cytoplasmic organelles, plasmids, episomes, infectious heredity, bacteriophages (transduction) or plasmids, fusion of somatic cells, transfer of isolated organelles,

transformation, vectors, viruses, retroviruses, prions, microinjection, electroporesis, and targeting genes.

Genetic Transformation: ►transformation genetic, ►transformation oncogenic, ►transfection

Genetic Transfusion: Transfer of organelles and cellular inclusions by protoplast fusion.

Genetic Translation: ►protein synthesis, ►regulation of gene activity

Genetic Tumors: More than two dozens tumor genes have been assigned to *Drosophila melanogaster* chromosomes 1, 2, and 3. The majority of these are not malignant and occur freely or attached to internal organs in the thorax and in the abdomen.

They are distinguished already at the third instar larva stage and persist through the life of the individuals. Most of the tumors become melanotic. The melanotic tumors determined by genes *mbn* and *Tum* have malignant characteristics. In several inbred mice strains, ovary tumors, testis tumors, B cell lymphoma, kidney adenocarcinoma, leukemia, and pulmonary tumors are under polygenic control. *Bilateral retinoblastoma* (tumor of the eyes) of humans is controlled by a dominant gene. Deficiencies involving the long arm of chromosome 13 may also induce retinoblastoma. Genes involved in the skin disease, *xeroderma pigmentosum*, is based on deficiency in the genetic repair mechanism. Initially the disease involves excessive freckle formation and may become tumorous. Exposure to ultraviolet light (sunlight) enhances the formation of skin tumors, particularly in fair skinned and albino individuals.

About 5–10% of human cancers (hereditary or sporadic) show definite genetic components. Cancer cells commonly display hypermethylation of promoter CpG islands and demethylation of the rest of the genome. The incidence of leukemia may increase in cases of trisomy or partial deficiency for chromosome 21. Both DNA (SV40, adenovirus, bovine papilloma virus, etc.) and RNA viruses (Epstein-Barr virus, retroviruses) can cause tumorigenesis in mammals. The loss or mutation in a gene controlling protein p53 may lead to tumorigenesis presumably due to lack of function of this suppressor gene. Genetic hybrids between the species of the platyfishes (*Xiphophorus*) are prone to develop melanoma. Approximately 30 species-crosses of tobaccos may produce tumorous offspring that form callus in vitro cultures without a requirement for phytohormones (see Fig. G31). In the *Nicotiana glauca* (2n = 24) × *N. langsdorffii* (2n = 18) hybrids, more than one locus is involved in tumor development. In the hybrids of *N. longiflora* (2n = 20) × *N. tabacum* (2n = 48), one chromosomal segment



Figure G31. Genetic tumors of interspecific tobacco hybrids. (Courtesy of Dr. H.H. Smith)

appears responsible for tumorigenesis. *N. saunderae* may inhibit the expression of tumors. In the majority of dicotyledonous and some monocotyledonous plants, agrobacterial infection and the insertion of the T-DNA of the Ti plasmid may lead to tumor formation by genetic transformation. Certain viral infections also result in tumorous growth in plants. Several insects stimulate the formation of gall tumors in plant tissues through their metabolic products. For the in vitro development of plant tumors, the additions of phytohormones (primarily natural or synthetic auxins) are required. Some cultures, however, become “habituated” after a course of culture and the exogenous auxin supply may no longer be required. The plant tumors are non-malignant. ►cancer, ►tumor, ►Knudson’s two-mutation theory of cancer, ►tumor suppressor, ►carcinogens, ►SV40, ►adenoviruses, ►retroviruses, ►reverse transcription, ►retinoblastoma, ►*Agrobacterium*; Purello M et al 2001; Oncogene 20:4877; Suhardja A et al 2001 J Neurooncol 52:195; Esteller M et al 2001 Hum Mol Genet 10:3001; Smith HH 1973 Brookhaven Symp 25:309.

Genetic Vaccine: ►immunization genetic

Genetic Variability: The ability or proneness (proclivity) to hereditary change. ►mutation, ►mutator genes, ►transposable elements, ►homeostasis, ►genetic homeostasis

Genetic Variance: Genetic variance is caused by the various effects of the genotype (V_g). The variance observed is usually the phenotypic variance (V_p) that

is the outcome of the mutual action of the genotype and the environmental variance (V_e). The genetic variance itself has three components: $V_g = V_a + V_d + V_i$, where V_a is the additive genetic variance or breeding value, V_d is the dominance variance, and V_i = interactions. The interactions can be epistatic effects among the individual quantitative traits and the effect of the environment on gene expression. The additive genetic variance may be expressed also as $V_a = 2pq^2(p[1-d] + qd)^2$ where t stands for displacement, The dominance variance $V_d = p^2q^2t^2(d-0.5)^2$. ▶variance, ▶midpoint value, ▶breeding value, ▶polygenes, ▶gain, ▶heritability, ▶displacement, ▶genotypic risk ratio

G

Genetic Variation: Hereditary differences within or between populations. Sequencing the genomes of many prokaryotic and eukaryotic organisms sheds light on earlier unforeseen variations such as SNIPS, minor duplications and deletions, and rearrangements in the chromosomes. For a review of human variations see: Serre D, Hudson TJ 2006 Annu Rev Genomics Hum Genet 7:443, <http://projects.tcag.ca/variation/>.

Genetical Genomics: Genetical genomics dissects regulation of transcription (Jansen RC 2003 Nature Rev Genet 4:145) by analysis of transcript expression pattern by high-throughput procedure (Jansen RC, Nap J 2001 Trends Genet 17:388) and segregation of genomic regions.

Genetically Directed Representational Difference

Analysis (acronym GDRDA): GDRDA targets and identifies traits that differ between congenic lines without prior knowledge concerning their biochemical

function. It determines linkage to known genes or to polymorphic DNA markers. ▶congenic, ▶DNA markers, RDA; Higo K et al 2000 Exp Anim 49[3]189.

Genetically Effective Cells: The cells of the germline that actually contribute to the formation of the gametes and thus to the offspring (see Fig. G32). The number of genetically effective cells can be determined in autogamous species on the basis of the segregation ratios after mutation. In case the genetically effective cell number (GECN) is 1, the segregation is either 3:1 or 1:2:1. If the GECN is 2, the segregation of dominant: recessives is 7:1, in case of GECN = 4, the expected ratio is 15:1 because only one of the cells of the germline segregates while the other cell(s) provide only non-mutant offspring. Thus, the pooled phenotypic numbers yield the 7:1 (4 + 3):1, and 15:1, (4 + 4 + 4 + 3):1 proportions. These ratios may be (slightly) altered if the transmission of the gametes carrying the recessive alleles is impaired, or if the viability of the recessive homozygotes is reduced. For the determination of GECN, the aberrant progenies should be left out of consideration. ▶planning of mutation experiments, ▶critical population size, ▶mutation rate; Rédei GP, Koncz C 1992 In: Koncz C. et al (eds) Methods in Arabidopsis Research, World Scientific, Singapore, p 16).

Genetically Effective Population Size: ▶effective population size

Genetically Modified Organisms: ▶GMO, ▶pest eradication

Geneticin (G418): An aminoglycoside antibiotic (see Fig. G33). ▶antibiotics, ▶aminoglycoside phosphotransferase, ▶kanamycin, ▶neomycin

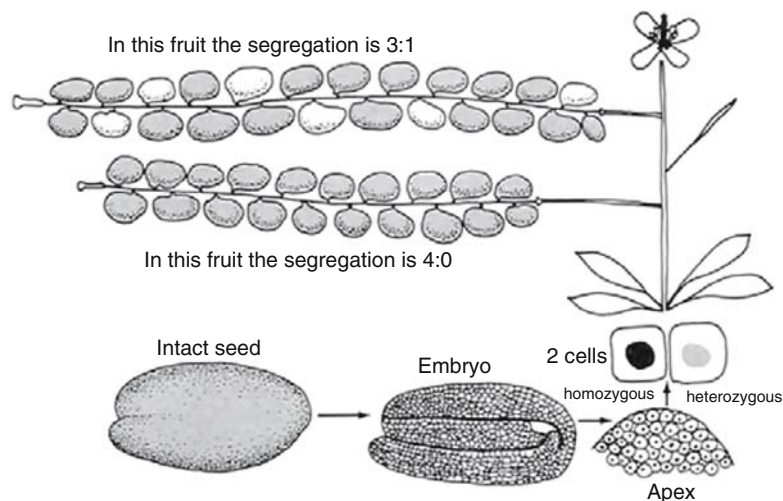


Figure G32. Segregation in case of two genetically effective cells

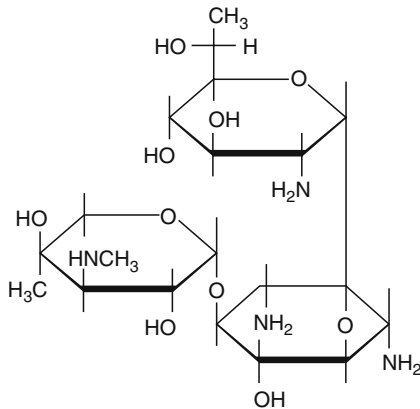


Figure G33. Geneticin

Genetics: The study of inheritance, variation, and the physical nature and function of the genetic material. William Bateson suggested the term in 1906 for the then entirely new discipline. [Professor Attila T. Szabó called my attention to a paper published in German in Brünn in 1819 (*Oekonomische Neuigkeiten und Verhandlungen* 22, April, p. 169–71) by Hungarian count Imre Festetics and used the expression “die genetische Gesätze der Natur” [the genetic rules of nature] in expounding his studies on heredity of farm animals.]

Genetics may be pursued as a basic science whose goals are only the discovery of new principle(s) and their integration into the store of knowledge. Alternatively, applied branches of genetics rely on established genetic principles and are used for agricultural (plant and animal breeding) or industrial (biotechnology) purposes, or for the improvement of human health (medical genetics). Applications of genetics are expanding into paleontology, archeology, and forensic areas. The tools of genetics are integrated today into all biological disciplines from taxonomy, evolution, cytology, development, behavior, and physiology, to biochemistry, biophysics, and molecular studies. Thus, genetics has escaped from its classical boundaries of heredity and cytology to become the core and unifying element of biology. ►heredity, ►inheritance, ►reversed genetics, ►population genetics, ►human genetics, ►medical genetics, ►clinical genetics, ►quantitative genetics, ►experiments, ►science, ►genetic engineering, ►synthetic genetics, ►criticism on genetics, ►GMO

Genetics and Privacy: The rapidly-accumulating information on risks based on various screening techniques and DNA sequencing may result in discrimination by insurance companies, potential

employers, and possibly by society in general. Therefore, there is considerable concern that such information not be divulged without the consent of the individual and the privacy be legally protected. ►bioethics, ►genetic privacy; Annas GJ 2001 *N Engl J Med* 345(5):385.

Genetics, Chronology of: A very broad overview includes only the most important milestones of basic genetics compiled somewhat subjectively. Paraphrasing GB Shaw, who would dare to say who is greater than Shakespeare? To keep the length minimal, applied aspects of genetics are not included. (See Rédei GP 1974 *Biol Zbl* 93:385; chronology of medical genetics through the career of a man: Victor McKusick 2006 *Annu Rev Genomics Hum Genet* 7:1).

200–300 B.C. Greek Philosophers discuss heredity

1694 Camerarius recognizes sex in plants

1761 Kölreuter reports thousands of attempted and (some) successful plant hybridizations

1839 Schleiden (plants) and Schwann (animals) discover cellular organization

1865 Mendel recognizes the basic principles of inheritance

1866 Haeckel points out the role of the nucleus in heredity

1869 Galton lays down the foundations of statistics-based inheritance

1871 Miescher reports about nuclein

1873-on Mitosis, meiosis, chromosome numbers, supremacy and continuity of chromosomes are recognized

1900 Mendel's work is rediscovered

1902 Sutton proposes the chromosomal theory of inheritance

1902 Benda recognizes mitochondria

1902 Garrod reports on alkaptonuria as an inherited biochemical trait

1906 Bateson suggests the term genetics

1909 Johannsen coins the terms gene, genotype, phenotype, and explains pure lines

1909 Correns and Baur discover non-Mendelian inheritance of chloroplasts

1910–11 Morgan discovers sex-linkage and crossing over

1910 von Dungern and Hirschfeld show that blood groups are inherited

1913 Sturtevant constructs the first linear map of 6 genes of the *Drosophila* X chromosome

1913–1925 Bridges and Sturtevant discover deficiency, nondisjunction, duplication, inversion, translocation

1926 Chetverikov and Helena Timoféeff-Ressovskaya found experimental population genetics

1926 D'Hérelle describes bacteriophages

1927 Landsteiner and Levine lay the foundations of immunogenetics

1927 Muller and then Stadler induce mutations by X-rays

1928 Griffiths observes bacterial transformation

1930-on Fisher, Wright, and Haldane, working independently, lay down the foundations of theoretical population genetics

1939-on Delbrück and Luria initiate phage genetics

1940 Beadle and Tatum conduct experiments leading to biochemical genetics and to the gene - polypeptide theory

1944 Auerbach and Robson discover chemical mutagenesis

1944 Avery, MacLeod and McCarty demonstrate that the transforming principle is DNA

1946 Lederberg and Tatum show bacterial recombination

1949 Chargaff discovers the variable base composition and A = T, G = C relations in different DNAs

1951 McClintock discovers transposable elements

1952 Lederberg reports transduction

1953 Watson and Crick construct a valid DNA model

1955 Fraenkel-Conrat and Williams prove that RNA can also be a genetic material

1956 Kornberg shows in vitro replication of DNA

1957 Taylor in plants, and in 1958 Meselson and Stahl show that DNA replication is semi-conservative

1957-on Beginning of the understanding of the machinery of protein synthesis

1960 Marmur and Lane hybridize nucleic acids

1960 Barski makes somatic cell hybrids

1961 Brenner and coworkers explain the nature of the mRNA

1961 Nirenberg and Ochoa laboratories independently demonstrate the nature of the genetic code

1961 Jacob and Monod propose the operon concept

1965 Southerland discovers cAMP and opens the ways into inquiries on signal transduction and transcription factors

1969 Shapiro et al. isolate the *lac* operon

1970 Temin and also Baltimore discover reverse transcription

1970 Khorana synthesizes in vitro a tRNA gene

1971 Danna and Nathans fragment SV40 DNA by a restriction enzyme discovered by Smith and Wilcox in 1970

1972 Transformation by recombinant DNA begins in the Cohen, Berg and Lobban laboratories using plasmid vectors

1977 Development of efficient DNA sequencing by Gilbert's and by Sanger's laboratories

1978 Shortle and Nathans make localized mutagenesis During the late 1970 Prusiner, S.B. isolates

the "scrapie" agent", which turns out to be an unorthodox infectious, hereditary protein, the prion, in violation of the 'nucleic dogma'

1980 Capecchi et al., Ruddle et al. transform mice

1980s Christiane Nüsslein-Volhard and E. Wieschaus based on earlier studies by EB Lewis establish a new approach to developmental genetics.

1981 Schell et al. transform plants by *Agrobacterium*

1981 Cech discovers ribozymes

1983 Varmus, Bishop and others identify c-oncogenes

1985 Mullis et al. develop the PCR procedure

1989 Saiki, Walsh & Erlich initiate microarray type analysis of amplified DNA with immobilized sequence-specific probes

1995-on Sequencing of complete DNA genomes of prokaryotes and also the eukaryote yeast

By 1996 Beginning of the mass identification of the function the sequenced genes. During the 1990s RNAi, microRNA and other small Interfering RNAs have been discovered in *Caenorhabditis*, plants and other organisms by several laboratories.

1999 the almost complete sequence of the 33.4 megabase human chromosome 22 was published by 217 authors. Craig Venter's Celera group, the Berkeley, Canadian and the European Genome Projects publish the first 'complete' sequence of the *Drosophila* genome. The sequencing of the *Arabidopsis* genome (2000) and the human genome (2001) followed this. On Apr. 14, 2003 completion of the Human Genome Project has been announced.

1999 marks the beginning of 'modular cell biology' and the development of genetic and protein networks by Hartwell LH and co-workers, Barabási A-L, Oltvai ZN and other laboratories, culminating in detailed functional networks of lower and higher eukaryotes by the laboratories of Chant, J. in 2003 and Vidal M 2004.

From 1996 on, the interest increased on the proteome, the complete complement of cellular proteins. Their number exceeds that of the genes because of the transcripts can be processed in multiple ways. How cells and organisms function will be fully understood when all genes will be annotated and the understanding of the complex, dynamic interactions within the proteome will unfold during the coming years. (See ENCODE 2007) It is a commonplace to say that genetics progresses at a breath-taking speed. Yet it is hard to give credit to the major current developments because there are so many and they are so intertwined.

During the preceding decades geneticists tried to reveal the function of single *good* genes or of genetically controlled pathways. By the turn of the millennium the field is turning toward synthesis and integration. The goal of the future research is not less than understanding the function of entire organisms

(proteome), including their descent and cooperation. In the coming years we can expect major progress in the understanding of developmental control (epigenetics), the organization and function of the nervous system, evolution, application of gene and cancer gene therapy, in developing more productive and safer agricultural plants and livestock, moving from databases to complex Information Systems. Although genetics is again in a golden age, the excitement may last indefinitely. Yet one must keep in mind the words of the immunologist Peter Medawar: wise people may have expectations but only the fools make predictions. (See Lander ES, Weinberg RA 2000 Science 287:1777).

Genetics, Digital: Digital genetics is the computer modeling of the behavior of virtual genes and their function, interaction, organization, mutation, recombination, and evolution. ►digital genes, ►avidian; Adami C 2006 Nature Rev Genet 7:109.

Genetics of Behavior: ►behavior genetics

Genetics of Cancer: ►cancer, ►genetic tumors, ►cancer gene therapy

Genetics, Public Understanding and Social Needs: In democratic societies public understanding of social and technological developments is of great importance because research and applications are influenced by the collective wisdom of individuals. Individual rights imply responsibilities. Because of rapid progress, it is increasingly more difficult to keep up with the current knowledge. Although newspapers, popular magazines, television, internet and various commercial resources are available for information transfer, the quality and trustworthiness of these resources are quite variable. Genetics knowledge is now available on the advantages and perils of various energy sources (atomic and fossil fuels), polluting industrial and agricultural chemicals (mutagens and carcinogens), drugs and side effects of medications, food processing, additives and food supplements. There is a continuous debate about the advantages and potential perils of genetically modified organisms. In the area of human health, the use of vaccination, microbial resistance to antibiotics, biological weapons, emergence of new pathogens, origin and risks of cancer, the problems of stem cell research, gene therapy, cancer gene therapy, artificial insemination, in vitro fertilization, preimplantation screening, twin studies, incest and inbreeding risks, genetic counseling, genetic testing and screening, hereditary and sporadic diseases and their penetrance and expressivity, pharmacogenetics and human individuality, race and disease prevalence, and concerns about eugenics, privacy, and ethics are areas where sound genetic information may facilitate forming

relatively best opinions. The sequencing and annotation of human and other genomes are expensive for society and citizens must be able to form sound judgments. Genetic principles in forensics, such as fingerprinting, DNA analysis, and testing of blood groups are frequently discussed without adequate information for laymen. There are genetic consequences of the use of various weapon systems (nuclear, chemical, biological, and conventional). Abortion and other means of medical practices too have certain consequences in human evolution. Evolution and its relation to faith and religions are often presented with conflicting views. Obviously, it is impossible to be an expert in the broad field of genetics and its application but there is a large array of condensed information to consult in this book and references cited. Schools (elementary through college or even graduate school) do not have time enough for dealing with all the existing problems and with those yet evolving. The review of Haga SB 2006 Nature Rev Genet 7:223 discusses teaching resources for genetics.

Généthon: Research Center for Genetics and Gene Therapy (Every, France, <http://www.genethon.fr/php/index.php>; <http://www.cephb.fr/ceph-genethon-map.html>).

GeneTide: ►GeneCard

Gene-Tox: Genetic toxicology; study of factors (physical and chemical agents) that are responsible for mutation and cancer or both. ►environmental mutagens, ►carcinogen, ►toxicogenomics, ►comparative toxicogenomics; gene-chemical interactions: <http://ctd.mdibl.org/>; <http://toxnet.nlm.nih.gov>; structure-searchable toxicity database: <http://www.epa.gov/nheerl/dsstox>).

GeneTrek: A method to sequence and annotate a small portion of the large genome to obtain information about its general nature (Liu R et al 2007 Proc Natl Acad Sci USA 104:11844).

GENEW (Human Gene Nomenclature Database): ►genetic nomenclature, ►gene symbols; <http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl>.

GeneWise: GeneWise compares genomic and protein sequences. ►gene; Birney E et al 2004 Genome Res 14:988; www.sanger.ac.uk/Software/Wise2/.

Genic Balance: The proportion of the sex chromosomes and autosomes has a crucial role in sex determination in some organisms (e.g., *Drosophila*). In *Drosophila* (1 X):(2 sets of auto-somes) means male, whereas (2X):(2 set of autosomes) = females (1:1). In general, all individuals with chromosomal ratios above 1 are females and those between 0.5 and <1 are inter-sexes.

In humans and mice, the XO is female while in *Drosophila* XO is male. In trisomics and nullisomics, the nature of the individual chromosome(s) present or absent makes a great difference in the phenotype.

►sex determination, ►trisomy, ►nullisomic, ►nullisomic compensation

Geniculate Body (geniculate nucleus): A knee-like structure in the brain where optic and auditory fibers are received.

Genie: A gene predictor program. ►GENSCAN, ►FGENE, ►MZEF; Reese MG et al 2000 Genome Res 10:529.

G

Genistein (4,5,7-trihydroxyflavone): A phytoestrogen (common in soybean products), an inhibitor of protein tyrosine kinases and frequently used for probing signal transduction pathways. ►leukemia BCP; X-ray crystallography: Manas ES et al 2004 Structure 12:2197.

Genital Anomaly Syndromes: In males, these syndromes may involve hypospadias or cryptorchidism or micropenis. In hypospadias the urethra may open at the lower side of the penis or between the anus and the scrotum. Cryptorchidism indicates that the testes do not descend from the abdominal cavity into the scrotum (the testicular bag). In females, commonly either the ovaries, uterus, or the fallopian tubes (connecting the ovaries with the uterus), or the vagina fail to develop normally, and clitoromegaly and fusion of the labia occur. ►hermaphroditism, ►pseudohermaphroditism, ►gonadal dysgenesis, ►Smith-Lemli-Opitz syndrome, ►Opitz syndrome, ►Wilms tumors, ►Robinow syndrome, ►Fraser syndrome, ►Wolf-Hirsch-horn syndrome, ►Bardet-Biedel syndrome, ►adrenal hyperplasia, ►trisomy, ►testicular feminization

Genius: According to the Latin meaning of the word, a genius is a guarding spirit influencing a person for better or worse. CD Darlington (1964) defined it as a person who “changes the environment of others for his own and even for succeeding generations, for his own species and even for the whole living world.” Francis Galton in his book *Hereditary Genius* (1869) came to the conclusion that eminence is biologically inherited. Darlington had a less asserting view “the sons of great men are given the best chances with the worst results”. Human intelligence cannot be exempted from the general biological laws (offspring-parent regression), although environment has great influence on the development of hereditary qualities. A good example is Marie Curie Skłodowska who became the first woman who received, along with her husband Pierre, the Nobel Prize for physics in 1903 (see Fig. G34). She received her second Nobel Prize

in 1911 for chemistry. In 1935, their daughter Irene and her husband Frédéric Joliot received the Nobel Prize for chemistry, and this indicated the roles of inheritance and assortative mating on the manifestation of a genius.



Figure G34. Marie Curie Skłodowska

Albert Einstein, probably the most influential physicist in history, was a slow child (suspected to be dyslexic) and neither of his two sons matched their father although, in his words, their mother Mileva was comparable to her husband in intellectual abilities (see Fig. G35). Actually the younger son, Eduard, an aspiring psychologist died in an asylum as a schizophrenic. His brother Hans Albert became a hydraulic engineering professor. An extensive study of Nobel-laureate and literary prize-winner families suggest that outstanding creativity is not much biologically inherited rather it may be influenced primarily by the same-sex parent (Rothenberg A, Wyshak G 2004 Can J Psychiatry 49(3):185). ►human intelligence, ►musical talent; Andreasen NC 2005 *The Creating Brain: The Neuroscience of Genius*, Dana Press, New York.



Figure G35. Mileva and Albert Einstein wedding picture (Courtesy of Joachim Reinhardt, University of Frankfurt, Germany)

Genmap: A computer program for mapping genetic data based on least squares. ►least squares

Genocopy: A genetically determined phenotype that imitates or resembles a similar phenotype, which is controlled by another gene. ►phenocopy

Genomatron: A gene-mapping machine.

Genome: A complete single set of genes of an organism (taxonomic unit) or organelle, also the basic haploid chromosome set. The size of genomes, in rounded nucleotide numbers, varies in the different taxonomic categories (See tabulation below).

The average genome size of birds is almost 1/3 that of mammals, mainly because the avian introns are shorter. Endosymbionts usually reduce the size of

their genomes during evolution. The nucleomorph of the chlorarachniophyte protist *Bigelowiella natans* is composed of only 373,000 bp representing the smallest eukaryotic nuclear genome. It has three chromosomes, 331 genes, and several very short introns in this endosymbiont within the chloroplast (Gilson PR et al 2006 Proc Natl Acad Sci USA 103:9566). The larger plant genomes contain many LTR retrotransposon families with >10,000 copies per haploid genome, whereas the smaller genomes contain few or no LTR retrotransposon families with >1,000 copies, suggesting that this differential potential for retroelement amplification is a primary

G

| | | |
|---|------------------------|-------|
| Human mitochondrion | 1.7×10^3 | bp |
| MS2 (single-stranded RNA bacteriophage) | 3.5×10^3 | bases |
| φ X174 (single-stranded DNA bacteriophage) | 5.4×10^3 | bases |
| SV40 (double-stranded animal DNA virus) | 5.2×10^3 | bp |
| Tobacco mosaic virus (single-strand RNA) | 6.4×10^3 | bases |
| Influenza virus (single-strand RNA, animals) | 1.4×10^4 | bases |
| λ (double-stranded DNA bacteriophage) | 4.9×10^4 | bp |
| Vaccinia virus (double-stranded DNA, animals) | 1.9×10^5 | bp |
| T2, T4 (double-stranded DNA phages) | 1.7×10^5 | bp |
| <i>Chlamydia</i> (bacteria) | 6.0×10^5 | bp |
| <i>Escherichia coli</i> bacterium | 4.7×10^6 | bp |
| <i>Calotrix</i> (bacteria) | 1.3×10^7 | bp |
| <i>Saccharomyces cerevisiae</i> (fungus, eukaryote) | 1.2×10^7 | bp |
| <i>Ostreococcus tauri</i> green alga | 1.3×10^7 | bp |
| <i>Drosophila melanogaster</i> (insect) | 9.0×10^7 | bp |
| <i>Caenorhabditis elegans</i> (nematode) | 1.0×10^8 | bp |
| <i>Arabidopsis thaliana</i> (higher plant) | $\sim 1.2 \times 10^8$ | bp |
| Rice | $\sim 4.0 \times 10^8$ | bp |
| Chicken | 1.05×10^9 | bp |
| Dog | $\sim 2.3 \times 10^9$ | bp |
| Mouse | $\sim 2.6 \times 10^9$ | bp |
| <i>Homo sapiens</i> | $\sim 2.9 \times 10^9$ | bp |
| Opossum (<i>Monodelphis domestica</i>) | $\sim 3.5 \times 10^9$ | bp |
| Toad (<i>Bufo bufo</i>) | 6.0×10^9 | bp |
| Maize (higher plant) | 2.5×10^9 | bp |
| Hexaploid wheat (n = 3x) | 1.7×10^{10} | bp |
| <i>Trillium luteum</i> (higher plant) | 6.5×10^{10} | bp |
| <i>Fritillaria davisii</i> (higher plant) | 1.5×10^{11} | bp |

factor in angiosperm genome size variation. Besides amplification of transposable elements, ejection of redundant copies by unequal homologous recombination and nonhomologous recombination determine the actual, extant genome size (Vitte C, Bennetzen JL 2006 Proc Natl Acad Sci USA 103:17638). ▶**mtDNA**, ▶**chloroplasts**, ▶**nucleomorph**, ▶**endosymbiont**, plants: Bennett MD, Leitch IJ 1995 Ann Bot 76:113; bacterial genomes: Casjens S 1998 Annu Rev Genet 32:307; Genetica Vol 115: issue 1 (2002); ▶**minimal genome size**, ▶**C value paradox**, ▶**human genome**, ▶**gene numbers**, ▶**Map Viewer**, ▶**genome sizes**; <http://www.cbs.dtu.dk/data/bases/DOGS/>; ▶**animal genome size**; <http://www.genomesize.com/search.php>; <http://www.ensembl.org/index.html>; number and organismal genomes sequenced and sequencing underway: <http://www.genomesonline.org/>.

Genome Analysis: Initially, genome analysis meant determining the origin of the component genomes in allopolyploid species on the basis of chromosome pairing, univalent(s) and multivalent associations, chiasma frequencies, chromosome substitution, chromosome morphology, chromosome banding, and hemizygous ineffective alleles. Today, it is used more generally for studying DNA base sequences, microsatellites, etc. (See terms under separate entries, genome elements such as ▶**intron splice sites**, ▶**3' untranslated regions**, ▶**promoters**, and ▶**cis-regulatory elements**, novel methods for predicting DNase I hypersensitive sites, for predicting noncoding RNA genes, including microRNA genes and their targets: Jones SM 2006 Annu Rev Genomics Hum Genet 7:315).

Genome Annotation: Identification of nucleotide sequences to reveal their function. ▶**annotation**; Stein L 2001 Nature Rev Genet 2:P493; Devos D, Valencia A 2001 Trends Genet 17:429; Zhang MQ 2002 Nature Rev Genet 3:698; Miller W et al 2004 Annu Rev Genomics Hum Genet 5:15.

Genome Bioinformatics (<http://genome.ucsc.edu/>): Genome bioinformatics carries information on human, *Caenorhabditis elegans* and *C. briggsae*, mouse, rat, zebrafish, yeast, and SARS genomes, including news and updates.

Genome Conservation: Genome conservation analyses the sequence and gene content among organisms and thus provide a reliable view on phylogenesis. ▶**phylogeny**; Kunin V et al 2005 Nucleic Acids Res 33:616.

Genome Database: ▶**Map Viewer**; human: <http://gdbwww.gdb.org>; integrated microbial genomes: <http://img.jgi.doe.gov/cgi-bin/pub/main.cgi>; genome databases of 468 organisms: <http://pedant.gsf.de>.

Genome Domain: Histone modifications, transcription pattern, and DNA replication timing can define discrete active and repressed functional domains ranging from 20 kb to 1 Mb in size within the human genome (ENCODE). Active and repressed domains differ markedly from one another with respect to annotated genomic features including gene content, CpG islands, the spectrum of repetitive elements, and the density of conserved nonexonic sequences (Thurman RE et al 2007 Genome Res 17:917). ▶**domain**, ▶**ENCODE**

Genome Equivalent: In a genome equivalent, the mass of the DNA/RNA is the same as that of a genome.

Genome Evolution: Evolution may be based on duplication of single genes or duplication of larger chromosomal segments including hundreds of genes. The duplication may be rearranged and modified to fill a need for evolutionary advantage in the particular environment. Exons and to a lesser extent, regulatory sequences, evolve slower than introns, which contain many mutations because generally having little or no function they are not subject to selection pressure. Some of the duplicated copies may also be lost. If an organism becomes a parasite, some of its genes are no longer needed because the host can provide the required function(s). In *Salmonella enterica*, the estimated DNA loss per generation was 0.05 bp but about 50 times higher in mutants defective in repair (MutS). Deletion ranged in size from 1 to 202 kb and were not involved with repeat sequences, indicating that the losses did not depend on RecA-mediated recombination (Nilsson AI et al 2005 Proc Natl Acad Sci USA 102:12112). Within a single bacterial phylum genome, sizes vary by more by an order of magnitude, e.g., 600 kb in *Buchnera aphidicola* to 7,000 kb in *Pseudomonas fluorescense* (Ochman H 2005 Proc Natl Acad Sci USA 102:11959). The sequenced genome of *E. coli* is 4,639,221 but megabase size variations occur in different isolates. The sequenced and annotated genomes of related organisms provide opportunities for analyses of the evolutionary paths. ▶**genome analysis**, ▶**evolution of the karyotype**, ▶**evolution**, ▶**gene evolution**; Dujon B et al 2004 Nature [Lond] 430:35.

Genome Hitchhiking: ▶**überoperon**

Genome Information Broker (GIB): A database for genomics of prokaryotes, fungi, and *Arabidopsis*. ▶**genomics**; <http://gib.genes.nig.ac.jp>.

GenomeInspector: A computer program for assessing distance correlations between large sets of sequence elements, which can be used for the identification and definition of basic patterns of functional units such as

promoters and transcription factors. (See Quandt K et al 1996 Comput Appl Biosci 12:405).

Genome-Linked Viral Protein: ►VPg

Genome Mutation: Genome mutation affects chromosome numbers. ►aneuploid, ►polyploid

Genome Organization: As per genome organization, although genes are situated in a linear order within the chromosomes, temporal and hierarchical spatial arrangement of the genome affects the turning on/off the functions. ►genome, ►chromosome territories, ►transcription factories, ►DNA looping, ►chromatin, ►euchromatin, ►heterochromatin, ►repetitive DNA; Misteli T 2007 Cell 128:787.

Genome Projects: Genome projects are focused on the physical mapping and sequencing of entire genomes of humans and other higher and lower eukaryotes as well as of prokaryotes. Upon completion of these projects, a detailed inventory of all genes will become available. This in turn will facilitate new generalization of organization and function of the cells and will permit the application of the new principles and the new technologies to human economic fields, as well as for preventing and curing diseases. The complete nucleotide sequence of the four genes of the MS2 RNA virus had been determined by 1976, and

by 1995 all the 1749 genes of *Haemophilus influenzae* bacterium had been sequenced. The genome of *Saccharomyces cerevisiae* yeast has also been completely sequenced.

The large eukaryotic genomes such as that of humans, containing about 3 billion bps are ordered first into sequential stretches by the use of overlapping fragments. The first step is breaking up the human chromosomal DNAs (average of 250 Mb) into 100–2,000 kb fragments and cloned them in YACs. The YACs are cleaved into an average of 40-kb fragments and cloned by cosmids. The contents of the cosmids are then cloned in 5–10-kb capacity double-stranded DNA plasmid vectors or into the single-stranded filamentous phage M13 vector of 1-kb load. The fragments at each step can be tied into contigs by “chromosome walking.” The nucleotide sequences of the smaller clones can be analyzed.

The entire human genome requires a minimum of about 3,000 YAC or 20,000 BAC or 75,000 cosmid or 600,000 plasmid or 3,000,000 M13 phage clones. An alternative approach, the complete sequencing is to proceed from sequence-tagged connectors (STC). The human chromosomes would be cloned in BAC vectors and sequence 300–500 nucleotides at the ends. The 600,000 BAC end sequences represent 10% of the genome and are scattered at

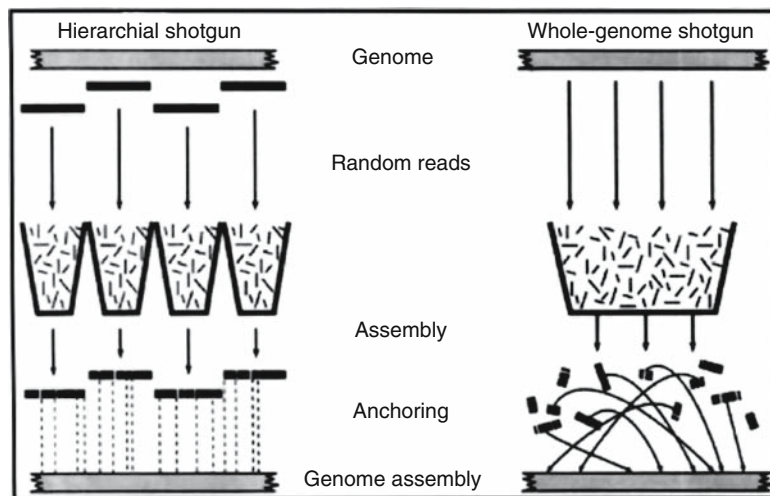


Figure G36. The human genome sequencing projects reported in Feb. 15, 2001 Science 295 and Nature [Lond] Febr. 16, 2001 used two somewhat different sequencing strategies. The *hierarchical shotgun* procedure cut up the genome into BAC clones and arranged them in a somewhat overlapping tiling path. Then after shotgun sequencing reassembled each BAC clone and then merged the sequences of adjacent clones. This had the advantage that all sequence contigs and scaffolds derived from a BAC belong to a single compartment with respect to anchoring to the genome. The *whole genome shotgun* strategy shotgun sequenced the entire genome and then reassembled the entire collection. With this method, each contig and scaffold is an independent component that had to be anchored to the genome. In general many scaffolds might have been difficult to anchor to the genome. (From Robert H. Waterston, Eric S. Lander, and John E. Sulston. 2002 Proceedings of the Natl. Acad. Sci. USA 99:3712-3716. Copyright 2002 National Academy of Sciences USA)

every 5-kb across the genome. They are called *sequence-tagged connectors* because they allow each BAC clone to be connected to about 30 others (150 kb insert/5 kb \cong 30, Mahairas GG et al 1999 Proc Natl Acad Sci USA 96:9739). The BAC inserts are digested by a restriction enzyme to determine their size. The sequencing templates have pUC18 based plasmids with \sim 2-kbp templates. A “seed” BAC is sequenced and checked. A “seed” BAC is sequenced and checked against the data of sequence-tagged connectors to identify the overlapping clones.

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In a following step, two BACs that show internal homology by the restriction enzyme digests and minimal overlap at their end are completely sequenced. By such a procedure the entire human genome could be sequenced in 20,000 clones. The advantage of this proposal (Venter JC Smit HO, Hood L 1996 Nature 381:364) is that some of the low-resolution mapping (YAC and cosmid steps) could be eliminated and automatic sequencing procedures could be applied, reducing cost and labors. Many groups worldwide could do the BAC clone sequencing. The already known sequence-tagged sites (STS) and expressed sequence tags (EST) could be readily located and additional genes could be easier placed. The procedure suggested would greatly facilitate the sequencing other smaller genomes of interest. The Perkin-Elmer Corporation and Craig Venter use very high efficiency DNA sequencing apparatuses (230ABI PRISM 3700) based on capillary electrophoresis (\sim 1,000 samples/day) and robotization and to expedite the process and substantially reduce the cost of sequencing. The completed sequencing information of entire genomes reveals that homologous genes from *Saccharomyces* to *Caenorhabditis*, *Drosophila*, *Homo* and *Arabidopsis* direct the majority, but not all, of cellular functions. Yet the regulation of the functions show differences to account for the differences among these organisms. The number of genes used by the different organisms varies. Apparently and unexpectedly *Arabidopsis* needs about twice as many genes as *Drosophila* and *Caenorhabditis* relies on nearly 45% more genes than *Drosophila*. *Drosophila* has about 700 transcription factors versus 500 in *Caenorhabditis*. Among the fully sequenced microbial genomes, on the average, about 25% of the open reading frames are unique to each organism. Dunham I 2000 in Trends Genet 16:458 tabulates a chronology of the innovations facilitating the realization of the genome projects. For the best understanding of the genome sequences comparative data of many species are very helpful. Unfortunately all species cannot be sequenced because of technical and financial cost. The species to be sequenced are chosen by several criteria: (1) phylogenetic relationships, (2) relevance to human biology,

(3) economic importance, (4) genome size and characteristics, (5) developmental and organizational specialization, (6) consideration for the more ancestral evolutionary forms. Unfortunately there are hard choices and no better criteria in the organismal selection (O’Brian SJ et al 2001 Science 292:21264). By 2006 more than 400 genomes have been sequenced and many other projects are underway. **physical mapping**, **YAC**, **cosmid**, **vectors**, **restriction enzyme**, **DNA sequencing**, **DNA sequencing automated**, **capillary electrophoresis**, **STS**, **EST**, **BAC**, **YAC**, **cosmid**, **DNA chips**, **contigs**, **seeding**, **parking**, **tiling**, **gap**, **finishing**, **clone validation**, **databases**, **shotgun sequencing**, **WGS**, **Gene Ontology**, **sequence-tagged connectors**, **scaffolds in genome sequencing**, **human genome**; Venter JC et al 1998 Science 280:1540; Mullikin JC, McMurray AA 1999 Science 283:1867; Adams MD et al 2000 Science 287:2185; Waterston RH et al 2002 Proc Natl Acad Sci USA 99:3712; Myers EW et al 2002 Proc Natl Acad Sci USA 99:3712; Internet guides to the majority of genome-related databases: Nature Genet 32 suppl. 1–79 [2002]; Birney E et al 2002 Annu Rev Genomics Hum Genet 3:293; Cozzarelli NR 2003 Proc Natl Acad Sci USA 100:3021; theory of species selection criteria for sequencing: McAuliffe JD et al 2005 Proc Natl Acad Sci USA 102:7900). <http://www.ncbi.nlm.nih.gov/genome/guide>; sequencing projects and related resources: <http://www.intlgenome.org/>; <http://compbio.ornl.gov/channel>; published genomes: <http://www.genomesonline.org/>; bacterial genomes: <http://xbase.bham.ac.uk/>; integrated genomes: <http://www.ebi.ac.uk/integr8/EBI-Integr8-HomePage.do?jsessionid=8F34D370D1F714C23FC63A07B65D67D0>.

Genome Reviews: Genome reviews contain information on sequencing and annotation of the majority of organisms: <http://www.ebi.ac.uk/GenomeReviews>.

GeneScan: Gene identification algorithm. Applicable to large genomes, including pertinent protein sequences. **gene prediction**; Yeh RF et al 2001 Genome Res 11:803.

GeneVar: GeneVar program is based on GeneWise and it analyzes an annotated genome, automatically identifies missed gene calls and sequence variants such as genes with disrupted reading frames (split genes) and those with insertions and deletions (indels). **GeneWise**, **base-calling**; Yu GX et al 2007 Nucleic Acids Res 35:3953.

Genome Scanning: Genome scanning comprises of cutting up the genome first by 8-bp-recognizing restriction endonuclease(s) into large fragments, followed by using more-frequent-cutter enzymes to generate physical information on the entire genome.

These fragments can then be used to establish a physical map. ► [physical map](#), ► [restriction enzyme](#), ► [gene finding](#); Rouillard JM et al 2001 *Genome Res* 11:1453; Beekman M et al 2001 *Genet Res* 77:129.

Genome Sequence Database (GSDb): <http://www.ncgr.org>; interrupted sequences in prokaryotes: <http://www-bio3d-igbmc.u-strasbg.fr/ICDS/>.

Genome Sequence Sampling (GSS): In GSS, chromosomal DNA, digested with several restriction enzymes, is cloned into cosmids. Hybridization with YAC clones of the same chromosomal DNA identifies all the cosmids that contain sequences present within the YAC. The cosmids are then broken down into contigs and their ends are identified by hybridization to pure cosmid DNA. The 300–500 bps of the ends are sequenced and aligned in sequence, permitting the generation of a rather high-density physical map.

Genome Size: ► [genome](#), ► [C value paradox](#); Gregory TR 2005 *Nature Rev Genet* 6:699; animals: <http://www.genomesize.com>; C value of plants: <http://www.kew.org/genomesize/homepage.html>; fungi: <http://www.zbi.ce/fungal-genomesize/>; ► [virus](#)

Genome Surveys: Sequences of genomic origin, rather than cDNA (similar to EST); the sequence represented may be interrupted when compared to genomic sequence: <http://www.ncbi.nlm.nih.gov/dbGSS/index.html>; genomic clones and libraries: <http://www.ncbi.nlm.nih.gov/genome/clone>.

Genome Transplantation: ► [mycoplasma](#)

Genome-Defence Model: In the genome-defence model, generally multiple, different transposable elements occur in all organisms and their movements from one chromosomal location to another may bring about rearrangements in the genome. The cell keeps these transpositions in check by methylation of the transposase, and thus restricts deleterious alterations in the genome. (See Miura A et al 2001 *Nature [Lond]* 411:212).

Genomere: A hypothetical subunit of genes, proposed by Eyster WH 1924 *Genetics* 9:372 for explaining the behavior of unstable genes. Demerec M 1935 *Bot Rev* 1:233 has argued against the plausibility of the existence of such particles, and the term has been abandoned. ► [unstable genes](#)

GenomeScan: A gene identification algorithm (Yef R-F et al 2001 *Genome Res* 11:803).

Genometrics: Biometric analysis of chromosomes. ► [biometry](#), ► [genomics](#); Roten C-A H et al 2002 *Nucleic Acids Res* 30:142; http://www.unil.ch/dmf/page14997_en.html.

Genome-Wide Analysis: ► [GWA](#)

Genome-Wide Functional Analysis: In genome-wide functional analysis, in contrast to hitting genes by random mutations, the procedures aim at specific genes by homologous recombination mediated gene replacement. Unfortunately, the efficiency of the latter procedure is quite variable among different organisms. An alternative approach is the use of RNAi (~300 nucleotide long double-stranded precursors), which can be injected, fed, or transferred by the use of plasmids into *Caenorhabditis* or *Drosophila*. In contrast to flies and worms, the introduction of long dsRNA in mammalian cells induces a non-sequence-specific interferon response and shut-down of translation. This response can however be bypassed by the direct introduction of Dicer products of short interfering RNAs.

The SID-1 protein (systemic RNA interference-deficient) of *C. elegans* may greatly facilitate the uptake (Feinberg EH, Hunter CP 2003 *Science* 301:1545). Insertional mutagenesis, degron, peptide aptamer inhibitors, or other function specific tags are also useful. The perturbed genes may be detected by high-throughput optical devices such as automatic microscopes, particle-size counters, reporter genes, fluorescent labels, FRET analysis, and cell sorters. Z-factor determinations may be a useful statistical device to assess the significance of differences of quantitative measurements. ► [RNAi](#), ► [insertional mutation](#), ► [targeting genes](#), ► [degron](#), ► [aptamer](#), ► [synthetic lethal](#), ► [FRET](#), ► [cell sorter](#), ► [Z](#), ► [mutagenesis](#), ► [genetic networks](#), ► [networks](#), ► [small-world networks](#), ► [probabilistic graphical models of cellular networks](#), ► [synthetic genetic array](#), ► [GAIN](#); Carpenter AE, Sabatini DM 2004 *Nature Rev Genet* 5:11; Friedman A, Perrimon N 2004 *Curr Opin Genet Developm* 14:470; technique for use in mouse: Wu S et al 2007 *Nature Genet* 39:922.

Genome-Wide Location Analysis: The genome-wide location analysis or genome-wide binding analysis reveals the genes bound in vivo by transcriptional regulators of the genome. The procedure may be epitope tagging and microarray hybridization. The 2343 promoter regions of the 6270 genes of yeast were found to bind one or more of the 106 transcriptional regulators. On the average, each regulator was found to bind 38 promoter regions. The Abf1 regulator bound 181 promoter sites. The Thi2 activator of thiamine biosynthesis, however, bound only three promoters. 295 combinations of two or more regulators may bind to common sets of promoters, thus regulating yeast genes in response to specific environmental inputs. The regulators may function in a sequential manner in which, one regulator may affect the promoter of a second regulator, which in turn may regulate a third promoter

and so on. Also, by inserting—by homologous recombination—structural genes fused to green fluorescent protein markers, the subcellular location of various proteins and groups of proteins can be determined (Huh W-K et al 2003 Nature [Lond] 425:686). The abundance of individual proteins detected by similar optical means is >50 to 10^6 molecules/yeast cell (Ghaemmaghani S et al 2003 Nature [Lond] 425:737). ▶transcription factors, ▶epitope tagging, ▶microarray hybridization, ▶ABF-1, ▶genetic networks; GAIN; Lee TI et al 2002 Science 298:799; Jorgenson E, Witte JS 2006 Nature Rev Genet 7:885.

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Genomewise: A program for the analysis of gene structure across cDNA and EST-defined spliced structure; it is suitable for annotation. ▶GeneWise; Birney E et al 2004 Genome Res 14988.

Genomic Clone: A genomic clone is prepared from chromosomal DNA, rather than from cDNA. ▶genomic DNA, ▶cDNA; <http://www.ncbi.nlm.nih.gov/genome/clone>.

Genomic Control: A statistical method for the estimation of population structure in a manner somewhat similar to case-control design or transmission disequilibrium tests. ▶case-control design, ▶transmission disequilibrium test; Bacanu SA et al 2000 Am J Hum Genet 66:1933.

Genomic Disorder: A genetically determined disease caused by deletions, duplications, inversions, translocations, transpositions in chromosomes.

Genomic DNA (gDNA): The native DNA including exons, introns and spacer sequences (versus the processed genes which are transcribed from mRNA to DNA by reverse transcription and have only the coding sequences). ▶processed genes, ▶reverse transcription

Genomic Exclusion: Genomic exclusion takes place in the ciliate *Tetrahymena pyriformis* in case one of the two mates has a defective genome (micronucleus) that is therefore not included in the meiotic progeny. The first progeny becomes heterokaryotic, having only the normal diploid micro-nucleus and an old macronucleus that is genetically not concordant with the micronucleus. After subsequent matings the normal micronucleus forms a macronucleus concordant with its own genetic constitution. As a result the strain is purged from the defect. ▶conjugation *Paramecia*; Cole ES et al 2001 J Eukaryot Microbiol 48(3):266.

Genomic Formulas: n = haploid, $2n$ = diploid, $3n$ = triploid etc. and $n-1$ or $2n-2$ = nullisomic, $2n-1$ monosomic, $2n+1$ = trisomic, $2n+2$ = tetrasomic,

etc., where n = haploid chromosome number. The basic chromosome number, however, is x and the diploids may be $2x = 2n$. ▶polyploids, ▶aneuploids

Genomic Fractionation: ▶RDA

Genomic Hybridization: ▶comparative genomic hybridization

Genomic Library: A set of cloned genomic DNAs; it is expected that a good library includes at least one copy of all the genes of a particular genome. ▶cloning, ▶genome, ▶fragment recovery probability

Genomic Medicine: Genomic medicine studies genetic variations in human populations concerning the genetic bases of disease. It is based on single nucleotide polymorphisms, oligonucleotide microarrays, molecular characterization of drug responses, etc. It uses global genomic information in connection clinical data to assess individual risks and multidimensional analysis for efficient management of disease. It combines predictive, preventive, and personalized medicine. ▶SNIP, ▶drug discovery, ▶medical genetics, needs and some available resources for practicing physicians: Guttmacher AE et al 2007 Nature Rev Genet 8:151.

Genomic Mismatch Scanning: ▶GMS

Genomic Profiling: The detection of concurrent occurrence of multiple generic variations that predispose humans to a particular disease. Identification of such genetic factors may assist in personalized medication and preventive means of health maintenance. The currently suggested commercial procedures have not yet been adequately tested. Although genomic profiling may have significance in the future, at present it is not entirely safe to follow some of the recommendations. (See Haga SB et al 2003 Nature Genet 34:347; <http://www.genovations.com/home/index.html>; <http://www.bankdna.com/>).

Genomic Prospecting: Searching of diverse species (e.g., different mammalian genomes) for DNA sequences, which could alleviate human disease with the aid of gene therapy. ▶gene therapy; O'Brien SJ 1995 Nature Med 1:742.

Genomic Screening: Genomic screening is used for the localization of genetics markers (genes). For *random genomic screening*, usually anonymous polymorphic markers are employed. For *directed genomic screening*, specific polymorphic markers, which have already been located in the vicinity of a targeted gene(s) are suitable. The best markers are easy to recognize, are highly heterozygous, and have established chromosomal location. In human genetics, the Généthon (http://www.genethon.fr/genethon_en.html) map containing more than 5,000 dinucleotide

markers covering the entire genome by ~ 2 cM average spacing is used. Alternatively, the Cooperative Human Linkage Project (CHLC, <http://www.chlc.org>) covers the genome by 3600 tri- and tetranucleotide markers with an average spacing of 1 cM. The Utah Human Genetics Institute (<http://www.genetics.utah.edu/home.html>) has developed tetranucleotide markers at 10–15 cM spacing. These spacings are average and are not evenly distributed. The standard sets of markers are called *mapping sets*. Using lod scores, a value of 3 is considered to be significant. In case when two genes are tested, the lod score probability may be corrected for more accuracy and should be $3 + \log 2 \approx 3.3$, and in case of say 20 genes it should be $3 + \log 20 \approx 4.3$. Sib pair data sets may be evaluated with the aid of the χ^2 procedure and the appropriate degrees of freedom, but general probability may be determined by using $\text{lod} = (\chi^2)/4.605$. ($2\ln 10 \approx 4.605$, and converts the lod scores to χ^2 with 1 degree of freedom. Lod score of 3 corresponds to a P value of 0.001, and $\chi^2 \approx 4.605 \times 3 \approx 13.83$). Jianfeng Xu et al. (1998) present the justification for the very high significance level of 0.001 as follows. If the human genome is 3000 cM and it is divided into sixty 50 cM segments and the studied locus is in one of them, then the chance for the location of this gene is $1/60 \approx 0.02$. In other words, under this assumption, the *a priori* chance of linkage for any single locus is $\sim 2\%$. According to Bayes' theorem, with a lod score of 3, the posterior probability for linkage is about 95%, a conventional limit for level of significance. Usually these linkage data are loaded with false positive results and the best statistical procedures have not been agreed upon or generally accepted. Directed genomic screening may identify *locational candidate regions* where the investigated genetic difference is likely to be situated. As a general rule large relative risk, determined by λ_S is very helpful in locating genes. ►physical mapping, ►mapping, ►minisatellite, ►microsatellite, ►microarrays, ►lod score, ►chi square, ►candidate gene, ► λ_S , ►Bayes' theorem

Genomic Stress: Genomic stress, such as dissimilar genetic backgrounds in hybrids, in vitro cell culture, etc., may activate dormant transposable elements and cause genetic instability. ►transposable elements, ►somaclonal variation

Genomic Subtraction: A method that removes from wild type DNA all the sequences that are present in a deletion mutant, but retains the wild type DNA sequences corresponding to the deletions by denaturing a mixture of wild type and biotinylated mutant DNA. Allowing the mix to reassociate, the biotinylated sequences are subtracted by several repeated cycles of binding to avidin-coated polystyrene beads

(that have great affinity for biotin). The remaining (non-biotinylated) DNA is wild type and contains only the sequences that were deleted in the mutant but present in the wild type. This DNA can then be amplified by PCR and studied by standard techniques of sequencing. This method also permits the isolation of genes affected by the deletion (caused by, e.g., ionizing radiation). ►physical mutagens, ►gene isolation, ►biotinylation, ►avidin, ►PCR, ►DNA sequencing, ►RDA, ►RFLP subtraction, ►subtractive hybridization; Kingsley PD et al 2001 Dev Growth Differ 43(2):133.

Genomic Variation: Genetic variation, chromosomal rearrangements, polyploidy, copy number estimates, and human genome variation: <http://www.sanger.ac.uk/humgen/cnv/data/>.

Genomics: The study of the molecular organization of genomic DNA and physical mapping. *Structural genomics* studies the folds of macromolecules, the three-dimensional shape of biological molecules with the aid of physical instruments (X-ray crystallography, etc.) and bioinformatics, and classifies these molecules into functional families (see Fig. G37).

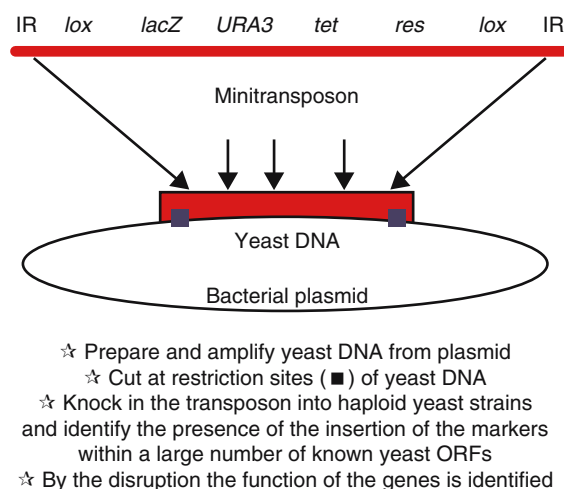


Figure G37. Identification of gene function

Biochemical genomics studies pools of purified proteins and the corresponding open reading frames (ORF). This is accomplished by generation and expression, e.g., a large set of glutathione-ORF fusion proteins are purified and mapped to a specific ORF and the proteins are further analyzed in subpools (Martzen MR et al 1999 Science 286:1153). *Chemical genomics* studies the effects of small molecules to ascertain their modulating effects on cellular states or on gene expression, preferably in high-throughput systems (Stegmaier K et al 2004 Nature Genet 36:257). The *functional genomics/physiological*

genomics deals with genome-wide functional analyses and integration of structure of the DNA and the molecular function and interaction of genes and gene products (Wu LF et al 2002 *Nature Genet* 31:255; Liang P et al 2002 *Physiol Genomics* 9:15). After the completion of sequencing of the organisms, interest is now turning to the determination of the function(s) of genetics. Such studies can now be conducted with high-throughput procedures (see diagram modified after Ross-Macdonald P et al 1999 *Nature [Lond]* 402:413). These types of methods can identify the function of thousands of ORFs in combination with macroarray analysis. This area of study integrates genetics, molecular biology, biochemistry, pharmacology (*pharmacogenomics*: designing drugs that best fit the genetic constitution of an individual), agriculture, medicine, and other disciplines. In 1996 alone, a half million patents were proposed from the field. *Epigenomics* studies the interaction between proteomes and genomes, global patterns of methylation, and methylation signals, and surveys this type of information in different species. *Comparative genomics/phylogenomics* seeks to determine (i) the number of distinct protein families encoded by different genomes, (ii) the distribution of the coding genes within the genomes and (iii) and how many of the genes are shared by the different genomes (Ureta-Vidal A et al 2003 *Nature Rev Genet* 4:251). *Orthogenomics* deals with the genomes of orthologous descent whereas *paragenomics* studies paralogous genomes. The study includes the composition and organization of protein domains in the different organisms. *Genetical genomics* involves expression profiles and marker-based fingerprints of each individual in a segregating population. The data are analyzed by QTL methods (Jansen RC, Nap JP 2001 *Trends Genet* 17:388). *Computational genomics* quantitatively or qualitatively measures a property of interest in ten or more inbred mouse strains. Genetic factors are then computationally identified in genomic regions where the pattern of genetic variation correlates with the distribution of trait values among the inbred strains analyzed. The extent of correlation between the trait values and strain groupings within each haplotype block is determined by analysis of variance (Wang J et al 2005 *Trends Genet* 21:526). *Nutrigenomics* has the goal to reveal the consequences of macro- and micronutrients on health and disease on different genotypes (Müller M, Kersten S 2003 *Nature Rev Genet* 4:315). *Toxicogenomics* seeks understanding the complexities in the biological system responding to toxic, mutagenic and carcinogenic factors. Special consideration is given to homologies of genes involved in controlling disease in the human genome, to sharing fundamental functions such as the cell cycle and structure, cell

adhesion, signaling, apoptosis, neuronal controls and the defense system (immune reactions). Finished genomic sequence is contiguous and has no more errors than 1/10,000 bases. ►genomic DNA, ►DNA sequencing, ►DNA chips, ►macroarray analysis, ►microarray hybridization, ►maldi/tof/ms, ►physical mapping, ►mass spectrometer, ►genome projects, ►gene numbers, ►duplications, ►proteome, ►SAGE, ►biotechnology, ►genetic engineering, ►ORF, ►Cre/Lox, ►knockin, ►X-ray diffraction analysis, ►orthology, ►paralogy, ►comparative genomics, ►TWINSCAN, ►bioinformatics, ►analysis of variance; Craig AG, Hoheisel JD 1999 *Automation: Genome and Functional Analyses*. Academic Press, San Diego, California; Trends Guide to Bioinformatics, Sup. Elsevier, 1998, Rubin GM et al 2000 *Science* 287:2204; Koonin EV 2001 *Curr Biol* 11:R155; Reboul J et al 2001 *Nature Genet* 27:227; Gopal S 2001 *Nature Genet* 27:337; genomics; Meyerowitz EM 2002 *Science* 295:1482; Aardema MJ, MacGregor JT 2002 *Mutation Res* 499:13; human genomics reviews: *Human Mol Genet* 15 Rev. issue 1; <http://www.functionalgenomics.org.uk/>; chemical genomics: <http://www.genome.jp/kegg/>; <http://gib.genes.nig.ac.jp/>; public population genomics: <http://www.p3gconsortium.org/>; structural genomics targets: <http://www.ysbl.york.ac.uk/sgTar/get/>; agriculturally relevant species: <http://www.agbase.msstate.edu/>; plant genomes: <http://mips.gsf.de/projects/plants>.

Genomics-Guided Transgenes (GGT): GGT are homologous genes obtained from native species or from related species. GGTs are expected to provide useful features to crops without potential drawbacks of induced mutant genes. ►transgene, ►GMO; Strauss SH 2003 *Science* 300:61.

Genomotyping: Genomotyping hybridizes the DNA of a particular strain/isolate to the genome of a sequenced standard line to assess the difference between the two.

Genophore: gene string not associated with large amounts of protein (bacterial chromosome). (See Ris H, Chandler BL 1963 *Cold Spring Harbor Symp Quant Biol* 18:1).

Genotator: is a program for sequence annotation and gene finding. ►gene prediction, ►annotation of the genome; <http://www.fruitfly.org/~nomi/genotator/user-manual.html>.

Genotoxic Chemicals: Genotoxic chemicals cause gene mutation, chromosomal aberration, and cancer. Genotoxic stress activates cell cycle checkpoints to allow time for repair, if possible. The most recommended tests involve bacterial mutation assays, in vitro test for chromosomal damage using mammalian

cells (rodent hematopoietic cells), and in vitro assay of mouse lymphoma $tk^{+/-}$ cells (MLA). Molecular effects of genotoxic chemicals can be assessed by single nucleotide polymorphism analysis. ►[gene-tox](#), ►[databases](#), ►[environmental mutagens](#), ►[mutagen assays](#), ►[SNIP](#), ►[cell cycle](#), ►[checkpoint](#), ►[pharmaceuticals](#); Müller L et al 1999 Mutation Res 436:195.

Genotype: The genetic constitution, the full set of genes.

Genotype Elimination: In genotypic elimination, statistical algorithms are used for the identification of genotypes that are inconsistent with the pedigree information. (See O'Connell JR, Weeks DE 1999 Am J Hum Genet 65:1733).

Genotypic Frequencies: ►[Hardy-Weinberg theorem](#)

Genotypic Mixing: In genotypic mixing, after infecting a cell with viruses of different genotypes, in a single viral capsid more than one type of viral DNA may be included. ►[rounds of matings](#)

Genotypic Risk Ratio (GRR): The total number of offspring affected/twice the number of affected homozygotes. ►[genetic hazards](#), ►[risk](#), ►[genetic risk](#), ►[empirical risk](#), ►[displacement](#)

Genotypic Segregation: ►[trinomial distribution](#)

Genotypic Value: A quantitative genetics term indicating the genetically determined component (G) of the phenotypic variation; phenotypic value (P) = G + E, where (E) stands for environmental variation. ►[midpoint](#), ►[breeding value](#), ►[additive effects](#)

Genotyping: Identification of the genotypic constitution at one or more loci by genetic, molecular, immunological, or any other means using cells, tissues, or whole organisms. Single-sperm genotyping permits detection of recombination in humans at large scale and sheds light on the extent of linkage disequilibrium. Naturally, this procedure does not reveal recombinational differences among females, if any. Quite commonly RFLP, mini- and microsatellites, trinucleotide repeats, single nucleotide polymorphism, and PCR are used. Immobilizing DNA on silicon chips and the use of MALDI has developed high-throughput methods. Statistical methods based on inheritance are available for the detection of genotyping errors (Douglas JA et al 2002 Am J Hum Genet 70:487; Sobel E et al 2002 Am J Hum Genet 70:496). ►[genotype](#), ►[RFLP](#), ►[SNIP](#), ►[PCR](#), ►[minisatellite](#), ►[microsatellite](#), ►[trinucleotide repeats](#), ►[DNA chips](#), ►[microarray hybridization](#), ►[MALDI](#), ►[haplotype analysis](#), ►[GWA](#); Tang K et al 1999 Proc Natl Acad Sci USA 96:10016; Ranade K et al 2001 Genome Res 11:1262; Beaulieu M et al 2001 Nucleic Acids Res 29:1114; Wolfe JL et al 2002 Proc Natl

Acad Sci USA 99:11073; genotyping errors and estimation of errors: Pompanon F et al 2005 Nature Rev Genet 6:847; Wang L et al 2007 Adv Exp Med Biol 593:105.

Gens (plural gentes): Organisms with shared relations (a sub-race).

GENSAT (<http://www.gensat.org/login.jsp>): is a gene expression atlas of the central nervous system.

Genscan: is a gene predictor program. (See Burle C, Karlin S 1997 J Mol Biol 268:78, <http://genes.mit.edu/GENSCAN.html>).

GENT Algorithm: The GENT algorithm generates contigs from optical mapping data. ►[contig](#), ►[optical mapping](#); Mathe C et al 1999 J Mol Biol 285:1977.

Gentamycin (gentamycin): A broad-spectrum aminoglycoside antibiotic. Gentamicin may facilitate reading through nonsense termination codons during translation. It may cause irreversible hearing loss that is preventable by aspirin (see Fig. [G38](#)). (See New England J Med 354:1856; ►[readthrough](#), formula).

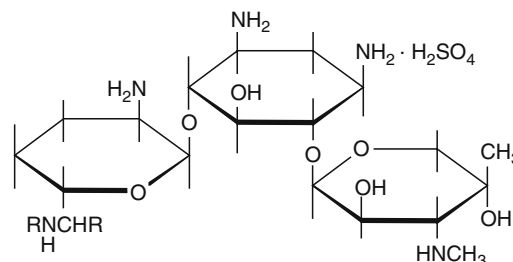


Figure G38. Gentamycin sulphate

Genus: A taxonomic category including usually several species of common descent. e.g., *Drosophila* (genus) *melanogaster* (species), the fruitfly most commonly used in genetics studies. Some genera are monotypic, however, inasmuch as they consist of a single species, e.g., *Arabidopsis*. ►[species](#)

Genus (in statistics): A topologically invariant property of a surface defined as the largest number of nonisotopic simple closed curves that can be drawn on the surface without separating it, i.e., the number of handles on the surface (Tuminello M 2005 Proc Natl Acad Sci USA 102:10421).

Gene2XML: A program, which converts ENTREZ GENE ASN1 into XML. ►[ASN.1](#), ►[XML](#); [ftp.ncbi.nih.gov/toolbox/ncbi/s\do5\(t\)ools/converters/by\s\do5\(p\)rogram/gene2xml/](ftp.ncbi.nih.gov/toolbox/ncbi/s\do5(t)ools/converters/by\s\do5(p)rogram/gene2xml/)

GEO (Gene Expression Omnibus): The GEO lists genes by name, type, organism, database, etc. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gds>.

Geographic Isolation: Geographically isolated populations cannot exchange genes because physical distance or other physical factors (mountain ranges, lakes, etc.) keep them apart. ► [speciation](#)

Geographical Race: A topologically separate population with distinctive gene frequencies.

Geological Age: ► [evolutionary clock](#)

Geological–Evolutionary Time Periods: (~ millions of years ago) formation of the Earth—4600—origin of Life—3000—Cambrian—600—Ordovician—450—Silurian—410—Devonian—345—Carboniferous—280—Permian—225—Triassic—190—Jurassic—135—Cretaceous—65—Eocene—36—Oligocene—Miocene—13—Pliocene—3—Pleistocene—0.01—Recent. ► [Archeozoic](#), ► [Pterozoic](#), ► [Paleozoic](#), ► [Mesozoic](#), ► [Cenozoic](#), ► [origin of life](#), ► [evolution prebiotic](#), ► [extinction](#), ► [evolution of the genetic code](#), ► [missing link](#)

Geometric Mean: ► [mean](#)

Geometric Progression: A series of elements increasing by the same factor, e.g., 2, 6, 18, 54 (i.e., by a factor of 3 in this example). ► [arithmetic progression](#)

Geometric Solids: (see Fig. [G39](#)).

Surface: $\square 6a^2$; $\square 2(ab + ac + bc)$; $\square 2\pi r((h + r))$; \square base surface + $[(ah)/2 \times n]$

$\square r\pi(r + s)$; \square side areas $\times 4$; $\square \pi[r^2 + (r + r_1)s + r_1^2]$

Volume: $\square a^3$; $\square a \times b \times c$; $\square r^2\pi h$; \square base surface $\times h$; $\square (r^2\pi h)/3$,

$\square h/3(aba) \sqrt{(axa)(a1xa1) + (a1xa1)}$; $\square (\pi h)/3(r^2 + rxr1 + (r1)^2)$

*SPHERE: surface: $4r^2\pi$; volume: $(4/3)r^3\pi$ ($\pi \cong 3.132857$). ► [circle](#)

George III: This mad king of England (1738–1820) might have been a victim of porphyria. ► [porphyria](#)

Geotropism: Growth influenced by gravity; positive (+) geotropism directed toward and negative (–) away

from gravity. Plant roots grow downward (+) and the shoots upward (–).

GEP: Guanine nucleotide exchange proteins.

Gephyrin (93 kDa): Peripheral nervous system membrane protein binding the inhibitory β subunit of the motor neural glycine receptor to tubulin in the cytoskeleton encoded in human chromosome 14 (Heilig R et al 2003 Nature [Lond] 421:601). It is also used for a co-factor that regulates molybdenum-dependent enzymes. ► [cytoskeleton](#), ► [tubulin](#), ► [neuron](#); Sola M et al 2001 J Biol Chem 276:25294.

Geranyl Pyrophosphate: A precursor of farnesyl pyrophosphate. Two molecules of farnesyl pyrophosphate join by the pyrophosphate end and squalene is formed through the elimination of both pyrophosphates. Squalene is then cyclicized to form lanosterol before being converted into cholesterol. ► [prenylation](#), ► [cholesterols](#)

GERBICH (Ge blood group): The Ge blood group is distinguished by its encoding β and γ sialoglycoproteins (glycophorins). These red blood cell membrane proteins are suspected of being the receptors of the *Plasmodium falciparum* merozoite (malaria-causing protozoon). ► [blood group](#), ► [malaria](#); Mayer DC et al 2001 Proc Natl Acad Sci USA 98:5222.

Gerbil: *Gerbillus cheesmani* $2n = 38$; *Gerbillus gerbillus* $2n = 43$ male, 42 female.

Germ: (Pathogenic) microorganism or an initial cellular structure capable of differentiation and development into a special organ or organism.

Germ Cells: The reproductive (sex) cells of eukaryotes, such as spores, eggs, and spermatozoa. The spores frequently come about by non-sexual processes such as the conidia of fungi and may not function like sex cells. The egg and spermatozoa are direct or indirect products of meiosis that have undergone a process of differentiation without division, e.g., the spermatozoa of animals arise from the spermatids and the sperms of plants are formed by post-meiotic division of the microspore nuclei. The eggs of animals arise by an additional division of the haploid secondary oocytes.

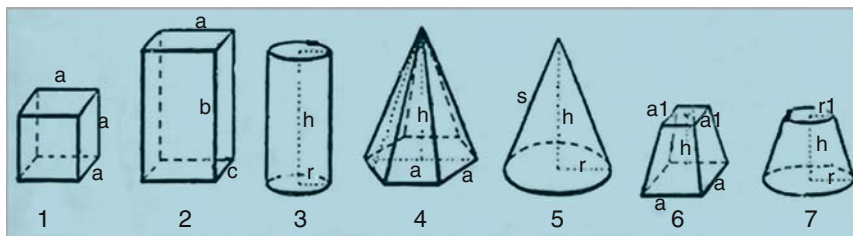


Figure G39. Geometric solids

Primordial germ cells of animals are sexually undifferentiated and can develop into oogonia or spermatogonia by mitosis before the meiotic path is set. Retinoic acid causes germ cells in the ovary to enter meiosis and initiates oogenesis. In the fetal testis, a retinoid-degrading enzyme (CYP26B1) retards meiosis and ultimately spermatogenesis takes place. Thus retinoid levels specify germ cell fate during gonad development (Bowles J et al 2006 Science 312:596). In mice, the *Stra8* gene (stimulated by retinoic acid 8) controls the transition into meiosis in both sexes. In females *Stra 8* is expressed in embryonic ovaries just before meiosis whereas in males it is expressed in the testes after birth (Koubova J et al 2006 Proc Natl Acad Sci USA 103:2474).

Primordial germ cells of mouse obtained from fetuses 8.5 p.c. when transplanted into the seminiferous tubules of infertile mice permitted the production of fertile offspring (Chuma S et al 2005 Development 132:117). The spermatogonial stem cells of animals can divide throughout life and produce spermatozoa. Adult testicular germ cells of the fish, trout (*Oncorhynchus mykiss*), contain spermatogonial stem cells, which when transplanted into the peritoneal cavity of newly hatched male or female embryos differentiated into functional spermatozoa in males and into functional eggs in the female recipients, and were capable of producing normal offspring (Okutsu T et al 2006 Proc Natl Acad Sci USA 103:2725). The egg of plants is formed through three divisions from one of the haploid megaspores. ► [gametogenesis](#), ► [germ plasm](#), ► [conidia](#), ► [egg](#), ► [sperm](#), ► [spore](#), ► [megaspore](#), ► [microspore](#), ► [histone variants](#), ► [protamines](#), ► [embryoid body](#), ► [p.c.](#); Raz E 2003 Nature Rev Genet 4:690; Santos AC, Lehmann R 2004 Current Biol 14:R578; germline transmission of genetically modified primordial germ cells: van de Lavoie M-C et al 2006 Nature [Lond] 441:766; conserved gametogenesis transcriptome in humans mouse and rat: Chalmel F et al 2007 Proc Natl Acad Sci USA 104:8346; genome browser: <http://www.germonline.org/index.html>.

Germ Layers: Gastrulation forms the most inner layer, *endoderm*, the surface layer, *ectoderm* (epithelium), and the in-between mesenchyme cell layer the *mesoderm*. Some embryologists attribute the differentiation to the neural crest. ► [gastrula](#), ► [neural crest](#)

Germ Plasm: Development (in *Drosophila*) begins with the formation of the primordial germ cells also called pole cells. The syncytial nuclei congregate at the posterior segment of the pole. Cellularization begins after about two hours. During gastrulation, the germ cells move to the embryonic gonad and form the germline stem cells. In both males and females, after four rounds of cell divisions 16 cells are formed. In

the male, all 16 contribute to sperm formation. In the female these 16 cells remain interconnected but only one becomes an oocyte, while the 15 others become polyploid nurse cells and nourish the oocyte. The oocyte proceeds with meiosis. About 80 maternal (somatic) follicle cells surround the oocyte and nurse cells. The development of the germ plasm (the cytoplasmic determinants of the germ cells) is controlled by the interacting products of a series of genes. ► [morphogenesis in *Drosophila*](#), ► [germ cells](#), ► [germline](#), ► [germplasm](#), ► [Drosophila](#)

German (germen): Closely related, such as having the same parents. ► [cousin german](#)

German Measles: ► [rubella virus](#)

Germanium: The location of the pro-oocytes which through mitotic divisions gives rise to the oocysts, one of which, becomes the oocyte. ► [oocyte primary](#), ► [karyosome](#)

Germinal Center: A group of naive (uncommitted) B cells. When activated by a specific antigen, they may develop into either memory B cells after antigen selection or become plasma cells. In the presence of interleukin-1,-10, and CD40 ligands they become memory B cells. By removal of CD40 ligand, the cells differentiate into plasma cells. A rapidly growing center also includes antigen-specific helper T cells. CD21 may be required for the B cells to survive in the germinal center. The germinal center has an open structure that enables competition for rare high-affinity B cells to participate in antigen responses (Schwickerts T et al 2007 Nature [Lond] 446:83). ► [T lymphocyte](#), ► [clonal selection](#), ► [antigen](#), ► [CD40](#), ► [CD21](#), ► [plasma cell](#), ► [memory immunological](#), ► [OBF](#), ► [somatic hypermutation](#), ► [B lymphocyte](#); Schebesta M et al 2002 Curr Opin Immunol 14:216.

Germinal Choice: Germinal choice is the idea that parents should not necessarily rely on their own gametes for producing offspring but adopt eggs, sperms, or even fertilized eggs from superior gene pools as a practical measure of positive eugenics. ► [sperm bank](#), ► [in vitro fertilization](#), ► [eugenics](#), ► [ART](#); Stock G 2005 Reprod Biol Online 10(1):27.

Germinal Mutation: Germinal mutation occurs in the germline, gonads, or in the gametes. ► [germline](#), ► [gonad](#), ► [gamete](#)

Germinal Vesicle: The large nucleus of the amphibian oocyte. This nucleus contains the three eukaryotic RNA polymerases and can also transcribe exogenous (microinjected) DNA. The oocyte then translates the mRNAs into a variety of proteins. ► [in vitro translation systems](#)

Germinoma: The neoplasm of the male or female gonads. ►gonad

Germline: The cell lineage that contributes to the formation of the gametes. In the majority of animals, the germline is determined very early in the zygote although the embryonic stem cells have pluripotent capability. In mice, the germ cells originate from extra-embryonic ectoderm under the influence of an inducible transmembrane protein encoded by the *fragilis* gene. Then gene *stella* is expressed in the cells that are restricted to the germline. The latter gene represses homeobox genes in the cells and thus they retain pluripotency (Saitou M et al 2002 Nature [Lond] 418:293). The segregation of the germline from the soma line involves the degradation of CCCH finger proteins in the soma by the ZIF-1 protein complex, which interacts with cullin-dependent ubiquitination system. In the germline, the PAR-1 kinase protects these proteins (DeRenzo C et al 2003 Nature [Lond] 424:685).

According to some views, plants do not have germline, certainly not in the sense of animals, because the generative cell lineage is not set aside definitely in early development and plant cells may retain totipotency for almost the entire life of the individuals. Nevertheless, by “fate maps”, the cell lineages giving rise to megaspores and microspores of plants can be traced to origin. In *Drosophila*, for the development of the germline the product of the *nanos* (*na*) gene locus is essential. In animals, the germline progenitor cells and gonadal somatic cells form the embryonic gonads, which develop into gamete-producing organs. In the embryonic gonads of *Drosophila*, 101 genes are expressed preferentially out of which 39 were expressed predominantly in the germline, whereas 58 in the somatic cells and 45 genes in both lineages (Shiegenobu S et al 2006 Proc Natl Acad Sci USA 103:13728). If mutation occurs in the germline, the genetically mosaic tissue may produce different gametes. Some mutations, which appear recessive in the somatic tissues may display reversal and function as dominant. In such cases, selection is possible before the formation of the gametes. ►cell lineages, ►*Drosophila* life cycle, ►genetically effective cell number, ►morphogenesis in *Drosophila*, ►germ plasm, ►gonads, ►gametogenesis, ►stem cells, ►somatic embryogenesis, ►CCCH protein, ►cullin, ►PAR, ►ubiquitin, ►Keimbahn for illustration; Lin H 1997 Annu Rev Genet 31:455; Saffman EE, Lasko P 1999 Cell Mol Life Sci 55:1141; Extavour C, García-Bellido A 2001 Proc Natl Acad Sci USA 98:11341; Crittenden SL et al 2002 Nature [Lond] 417:660.

Germline Transcripts (sterile RNA): Germline transcripts are not translated into protein. These specific

guanine-rich RNAs are transcribed from the immunoglobulin heavy chain S (switch) sequences in the B lymphocytes. These RNAs of 1 to 10-kb in length and containing repeats of 20 to 100 bp, anneal with the cytosine-rich DNA template. The sterile transcripts—although have similar overall structure—are specific for each switch sequence preceding a heavy chain gene, and each mediates in cis position class switching of a specific heavy chain gene. It has been hypothesized that these RNA-DNA hybrids are the recognition sites for the endonuclease that cuts the DNA double strands in the process of class switching.

►immunoglobulins, ►antibody gene switching, cis arrangements; Tracy RB et al 2000 Science 288:1058.

Germplasm (Keimplasma): The sum of the genetic determinants transmitted through the gametes to the progeny. In a broader sense, it is used for the designation of a collection of genotypes of organisms usable as plant and animal breeding resource.

►genotype, ►germ plasm

Gerontology: The clinical, biological, and sociological study of aging. ►aging, ►apoptosis, ►Hayflick's limit

Gerstmann-Sträussler Disease (GSD): A chromosome 20p12-pter dominant brain disease with substantial similarities to the Creutzfeldt-Jakob disease. There are some apparent differences inasmuch that in GSD there are numerous multicentric tuft-like plaques in the cerebral and cerebellar cortex, in the basal ganglia, and in the white matter of the brain. GSD appears to involve a greater recurrence risk than the Creutzfeldt-Jakob disease. ►Creutzfeldt-Jakob disease, ►scrapie, ►prion, ►encephalopathies, ►encephalopathy bovine spongiform

Gestation: The time from fertilization of the ovum (ova) to the delivery of the newborns in viviparous animals. The average term of gestation, in days: opossum 13, hamster 17, mouse 19, rat 21, rabbit 31, giant kangaroo 39, dog 61, cat 63, guinea pig 68, sow 114, sheep and goat 151, Virginia deer 215, Rhesus monkey 164, chimpanzee 238, woman 267, cow 284, mare 340, and elephant 624. There may be substantial deviations from these averages. Some of the differences in literature data are due to either biological or developmental variations, or the information indicates the time between ovulation and birth. ►hatching time in poultry

Gestational Drive (green beard effect): As per gestational drive, maternal genes recognizing and favoring special genes of the offspring, already during gestation, and favoring or disfavoring a genetic constitution may lead to consequences somewhat similar to meiotic drive. Population geneticists do not generally accept the concept. ►meiotic drive, ►green beard effect

GFAP (glial fibrillary acidic protein): GFAP affects myelination of the peripheral nerve cells and brain and its defect causes long-term depression. ▶myelin, ▶depression, ▶leukemia, ▶inhibitory factor; Headley SA et al 2001 J Comp Pathol 125(2–3):90.

GFF (General Feature Format): A document software format for finding in higher organisms a variety of recognition methods that give scores to likely signals (starts, splice sites, stops, motifs, etc.) or to extended regions (exons, introns, protein domains etc.), and then combine these to give complete gene, RNA transcript, or protein structures. Normally, the combination step is done in the same program as the feature detection, often using dynamic programming methods. To enable these processes to be decoupled, a format called GFF (“Gene-Finding Format” or “General Feature Format”) was proposed as a protocol for the transfer of feature information. (See http://www.sanger.ac.uk/Software/formats/GFF/GFF_Spec.shtml).

GFP: ▶green fluorescing protein

GGAs: Proteins that sort mannose phosphate receptors (MPR) into vesicles budding from the transgolgi network (TGN). The proteins are eventually delivered to endosomal and lysosomal compartments. The GGA is composed of a VHS (VPS27, Hrs, STAM) domain at the NH₂ end and a GAT domain that is flexibly hinged to a GAE domain at the carboxyl end. The GGA is moved to the transgolgi membrane after the GAT (transporter) domain interacts with the ARF-GTP (ADP-ribosylation factor–guanosine triphosphate) complex on the TGN membrane. The VHS domain binds the acidic cluster dileucine motif (ACLL) of the MPR. The GGA recruits at the GAE hinge a clathrin triskelion and accessory proteins γ -synergin (controlling clathrin-coated vesicle traffic) and the endosome fusion regulator protein rabaptin 5. ▶mannose phosphate receptor, ▶transgolgi network, ▶endocytosis, ▶lysosome, ▶triskelion; Tooze SA 2001 Science 292:1663.

γ -Glutamyl Carboxylase (GGC): The enzyme required for the post-translational modification of vitamin K dependent proteins used for blood clotting and bone proteins. ▶vitamin K-dependent blood clotting factors

GH: Growth hormone such as the hGH (human, encoded in 17q22-q24) or rGH (rat) growth hormones. ▶hormone response elements, ▶hormones, ▶pituitary dwarfism, ▶growth hormone relapsing hormone, ▶GHRH, ▶GHRHR

Ghost: An empty phage capsid without its genetic material. Also, electronic noise.

Ghost QTL: An erroneous localization result obtained by QTL analysis. ▶QTL

G_h: G protein with GTP-binding signaling function and transglutaminase activity. ▶G-protein

Ghrelin: An acetylated, 28-amino acid secretagogue produced in the hypothalamus that releases growth hormone from its receptor. It promotes feeding and is an antagonist of leptin. Ghrelin regulates neuropeptide Y and agouti-related protein neurons. The fatty acid synthase inhibitor, C75, blocks the synthesis of ghrelin. Oxyntomodulin suppresses it. ▶secretagogue, ▶growth hormone pituitary, ▶leptin, ▶agouti, ▶neuropeptide Y, ▶obesity, ▶obestatin, ▶oxyntomodulin; Inui A 2001 Nature Rev Neurosci 2:551; Hosoda H et al 2003 J Biol Chem 278:64; Hu Z et al 2005 Proc Natl Acad Sci USA 102:3972.

GHRH (growth hormone release hormone, 20q11.2): GHRH stimulates the release of growth hormones from the pituitary. Antagonists of GHRH receptors suppress cancerous proliferation. Somatostatin inhibits growth hormone secretion. ▶animal hormones, ▶pituitary, ▶somatostatin, ▶brain human, ▶GH; GHRH antagonists with improved antitumor activity: Zarandi M et al 2006 Proc Natl Acad Sci USA 103:4610.

GHRHR (growth hormone-releasing hormone receptor, 7p15-p14): GHRHR results in dwarfism. Several variants are known. ▶dwarfism, ▶GH; Szepesházi K et al 2001 Endocrinology 142:4341.

gi: An identification number in the GenBank data base that is used in addition to the accession number. This permits a closer identification of later discovered variations in a particular sequence to which—as new information becomes available for that particular DNA—a string of gi-s may be added. ▶accession number, ▶asn.1, ▶GenBank, ▶identifier syntax

G_i Protein: A member of the trimeric G-protein family; it activates adenylate cyclase and thus opens K⁺ channels. The $\beta\gamma$ subunits activate the ERK/MAPK signal transduction path through tyrosine kinase. This pathway responds positively to RAS and antagonized by RAP1. ▶G-proteins, ▶signal transduction, ▶adenylate cyclase, ▶ion channels, ▶RAS, ▶RAP1

GI₅₀: A chemical dose that provides 50% growth inhibition, e.g., for a certain cancer cell line.

Giant Axonal Neuropathy (GAN, 16q24): A recessive sensory and motor disease of the central and peripheral nervous system. Its onset is at early childhood and usually causes death by late adolescence of curly haired individuals. It causes swelling of the axons due to a defect in the protein gigaxonin affecting the axonal cytoskeleton. Gigaxonin binds to

ubiquitin-activating enzyme E1 through its amino-terminal BVTB domain, and the carboxyterminal kelch repeat interacts with the light chain of microtubule-associated protein 1B (MAP1B). Over-expression of gigaxonin enhances the degradation of MAP1B, and loss of gigaxonin has the opposite effect (Allen E et al 2005 Nature [Lond] 438:224). A similar disease also afflicts some German Shepherd dogs. ▶neuropathy, ▶BTB, ▶microtubule, ▶kelch motif

Giant Chromosomes: Polytenic chromosomes and lampbrush chromosomes. ▶lampbrush chromosomes, ▶polytenic chromosomes, ▶salivary gland chromosomes

Giant Platelet Syndrome (Bernard-Soulier syndrome, 22q11.2, 17pter-p12): The giant platelet syndrome is caused by deficiency of a major platelet glycoprotein (glycoprotein Ib-β, GP1BB), resulting in a bleeding disorder. ▶thrombophilia, ▶May-Hegglin anomaly, ▶thrombocytopenia

Giardia: *Giardia* is an intestinal protozoan parasite causing sensitive people severe, debilitating diarrhea and abdominal pain (see Fig. G40). It generally infests through unsanitized water. Its genome is less than 12 Mb. The *G. lamblia* genome is tightly packaged. Bidirectional transcription is a common feature and produces, not only the appropriate downstream sense transcript, but also leads to the production of either an upstream sense transcript (for promoters between genes in a head-to-head arrangement) or an upstream sterile antisense transcript (for promoters between genes in a head-to-tail arrangement). Bidirectional transcription seems to contribute to the abundance of sterile antisense transcripts observed (Teodorovic S et al 2007 Nucleic Acids Res 35:2544). The cells do not have mitochondria but mitosomes. ▶mitosome, ▶*Entamoeba*, ▶*Trichomonas*; Adam, RD 2007 Clin Microbiol Rev 14: 447.



Figure G40. *Giardia* (Courtesy of CDC Public Health Image Library)

GIB: ▶Genome Information Broker (<http://gib.genes.nig.ac.jp>).

Gibberella fujikuroi: A plant-pathogenic fungus that produces by its normal metabolism the plant hormones gibberellins. ▶plant hormones

Gibberellins: ▶plant hormones, ▶*Gibberella fujikuroi*, ▶dwarfism, ▶florigen; Rojas MC et al 2001 Proc Natl Acad Sci USA 98:5838; Richards DE et al 2001 Annu Rev Plant Physiol Mol Biol 52: 67; Olszewski N et al 2002 Plant Cell 14:S61; genes and enzymes in fungi and plants; Tudzynski B 2005 Appl Microbiol Biotechnol 66:597 (see Fig. G41).

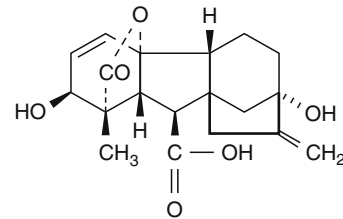


Figure G41. Gibberellic acid

Gibbon: ▶Pongidae, ▶primates

Giemsa Stain: The Giemsa stain contains azure II, azure-eosin, glycerol, and methanol. The dark bands appear to be poor in GC and the light, rich in GC content. ▶G banding, ▶chromosome banding, ▶rye; Niimura Y, Gojobori T 2002 Proc Natl Acad Sci USA 99:797.

Gierke's Disease: ▶glycogen storage disease type I

GIFT (gamete intrafallopian transfer): A method of artificial insemination. ▶artificial insemination, ▶ART

GIGA: Prefix for 10⁹ size or quantity.

GigAssembler: An algorithm suitable for preparing the human genome working draft, including about 88% of the 400,000 initial contigs. ▶contig, ▶human genome, ▶genome projects; Kent WJ, Haussler D 2001 Genome Res 11:1541.

Gilbert Syndrome: A very common human chromosome 2, dominant hyperbilirubinemia, similar to the Crigler-Najjar syndrome and probably controlled by genes allelic to it. ▶Crigler-Najjar syndrome, ▶Dubin-Johnson syndrome, ▶hyperbilirubinemia

Gilles de la Tourette Syndrome: ▶Tourette disease

Gillespie Equation: The Gillespie equation can be used to estimate the stochastic regulation of chemical reactions, including interacting gene systems. The paper cited here presents a computational simpler

form. (See Gillespie DT 2001 J Chem Phys 115:1716).

Gin: An invertase. ►invertases

Ginger (*Zingiber officinale*, $2n = 2x = 22$): Perennial rhizome spice. It dilates blood vessels, relieves pain, reduces flatulence, increases perspiration, and it is a stimulant. ►phenolics

Ginkgo biloba: An ornamental tree in the USA. Its leaves are considered as herbal medicine for neurological disorders associated with aging such as Alzheimer disease, hearing and memory loss, attention deficit, etc. Its flavonoids appear to be effective scavengers of free radicals. Microarray hybridization was found to reveal higher level of tyrosine/threonine phosphatase and other mRNAs involved in up-regulation of activity in the brain cortex of mice upon consuming leaf extracts. Ginkgos are very old species. (See Watanabe CMH et al 2001 Proc Natl Acad Sci USA 98:6577; Zhu Z, Zheng S 2003 Nature [Lond] 423:821).

GIP: A G protein subunit, and a potential oncoprotein. ►G protein, ►oncoprotein

GINs: One of the accessory factors for replication by DNA polymerases ϵ and α ; it is a heterotetrameric complex consisting of Sld5, Psf1 (partner of Sld5-1), Psf2, and Psf3. ►SLD; Chang YP et al 2007 Proc Natl Acad Sci USA 104:12685.

GIP (glucose-dependent insulinotropic polypeptides): GIPs mediate insulin secretion. (See Hinke SA 2001 Biochim Biophys Acta 1547:143).

Giraffe (*Giraffa camelopardalis*): $2n = 30$; the *Okapia johnstoni* is $2n = 45$.

Girdle Bands: Concentric rings of thylakoids. ►chloroplasts, ►thylakoids

GIRK (G-protein-gated inwardly rectifying K^+ channel): A heterotrimeric guanine nucleotide-binding protein. ►ion channels, ►G proteins; Seeger T, Alzheimer C 2001 J Physiol 535[pt 2]:383.

GIS (gene identification signature): See Liu T-B, Ruan Y 2005 Nature Meth 2:105; ►transcriptome

GISH: Genomic in situ hybridization (see Fig. G42). It may identify chromosomes in species hybrids and reveal crossovers among homoeologues. ►in situ hybridization, ►FISH, ►genome, ►homoeologous chromosome

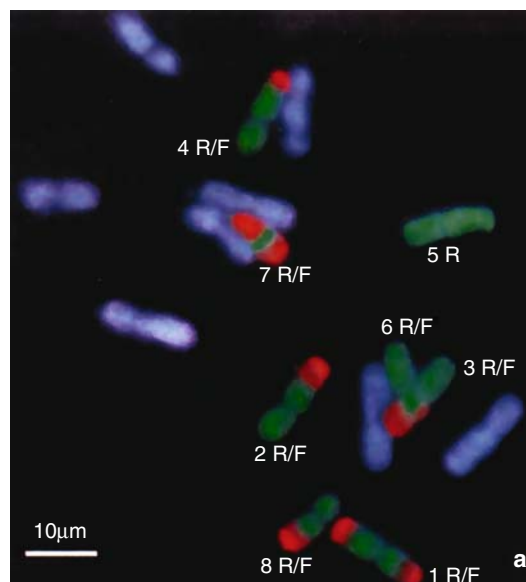


Figure G42. GISH. Introgression of *Allium fistulosum* chromosomes into *A. cepa*, mediated by bridging cross to *A. roylei*. The *A. fistulosum* chromosomes are labeled red (biotin, CY3), *A. roylei* shows green fluorescence (FITC) and *A. cepa* chromatin is blue (DAPI). (From Khrustaleva LI, Kik C 2000 Theor Appl Genet 100:17–26. Copyright Springer Verlag, 2000)

GIS-PET: Gene-identification signature analysis using paired-end ditags. Paired-end ditags from the two ends of each expressed transcript (18 bp from 5' end and 18 bp from 3' end) are extracted, concatenated, and subjected to sequencing analysis. ►GIS, ►paired-end diTag

giSNP (genetically indistinguishable SNP): About 50% of SNPs in human chromosome 20 shows at least one SNP partner in perfect linkage disequilibrium within < 20 kb clusters. Such giSNPs may make difficult the association mapping of disease genes. (Lawrence R et al 2005 Genome Res 15:1503). ►SNIPs, ►linkage disequilibrium

Gitelman Syndrome (16q13): Hypocalciuria, hypomagnesemia, and hypertension. ►Bartter syndrome, ►Liddle syndrome, ►hypoaldosteronism, ►hypertension, ►hypokalemia

GITR (glucocorticoid-induced tumor necrosis factor receptor-related, 1p36.3): GITR regulates cell proliferation, differentiation, and cell survival. Its ligand is AITR (activation-inducible TNFR). ►TNF; Nocentini G et al 2000 DNA Cell Biol 19(4):205.

GIY-YIG: A family of homing endonuclease with a GIY (X_{10-11})-YIG amino acid motif. These enzymes occur in T4 bacteriophage, either free, or within mobile group I introns. They occur in fungal and algal

mitochondrial introns and in algal chloroplasts. ▶**homing endonucleases**; Chevalier BS, Stoddard BL 2001 *Nucleic Acids Res* 29:3757.

Glanzmann's Disease: A variety of blood platelet anomalies determined by autosomal recessive genes. The overall symptoms include bleeding under the skin (ecchymosis), tiny, round and flat purplish (later yellow or blue) spots under the skin caused by blood release (petechia), bleeding of the tooth gum (gingiva), nosebleeds (epistaxes), gastrointestinal bleeding, excessive uterine bleeding (menorrhagia), or bleeding from the uterus at irregular intervals (metrorrhagia). The platelets may appear normal yet their number is reduced (thrombocytopenia). Sometimes the size of the platelets increases and their shape becomes abnormal and they appear isolated rather than aggregated. ▶**platelet abnormalities**, ▶**hemophilias**, ▶**von Willebrand disease**, and other terms under separate entries.

Glast: Na⁺-dependent transporters of glutamate and aspartate; GLASTs may have 68% homology with another glutamate transporter GLT. β-Lactam antibiotics increase the expression of glutamate transporters and may protect against some neurological diseases (Rothstein JD et al 2005 *Nature [Lond]* 433:73). ▶**transporters**, ▶**β-lactamase**, ▶**antibiotics**, ▶**neurological disorders**; Gegelashvili G et al 2001 *Progr Brain Res* 132:267; structure of *Pyrococcus* homolog: Yarnol D et al 2004 *Nature [Lond]* 431:811.

Glaucoma: Glaucoma may be controlled by autosomal dominant or recessive genes and may be manifested at birth, during juvenile years, or in adults (see Fig. G43). The incidence of the different forms may vary from 10⁻⁴ to a couple of percent in the general population, usually presenting a higher risk in adult life. The most general features are opacity of the eye lens caused by a gray gleam on the iris and an increased intraocular pressure, which eventually distorts the vision. In the early stages or in any mild forms, the anterior chamber of the eye is open (open angle glaucoma). This stage may pass into an intermittent form that may be transient but can last for several months, and eventually the angle becomes closed resulting in great pressure and swelling of the



Figure G43. Glaucoma. (From Bergsma, D. ed. 1973 *Birth Defects. Atlas and Compendium*. National Foundation-March of Dimes)

cornea accompanied by substantial pain. Eventually, if untreated, total blindness may follow.

Testing the eye (intraocular) pressure before the visible onset of the condition may monitor it. In some cases, the increased intraocular pressure does not result in glaucoma and in some individuals glaucoma develops without eye pressure. In the early stages, the majority of people are unaware of the disease. The penetrance and expressivity of this disease is highly variable. The basic defect is degeneration of the optic nerve in the retinal ganglion cells. Amyloid β (Aβ) has an important role in retinal ganglion cell apoptosis (Guo L 2007 *Proc Natl Acad Sci USA* 104:13444). Radiation treatment of the receiver (1000 rad in two doses to whole body) and syngeneic (T cell-depleted) bone marrow injection from donor was found to provide very successful treatment in mice (Anderson MG et al 2005 *Proc Natl Acad Sci, USA* 102:4566). The most common forms of glaucoma are not monogenic but show complex inheritance due to multiple genetic and environmental factors. The gene (GLC1A) coding for juvenile open angle glaucoma (JOAG) was assigned to human chromosome 1q23-q25. GLC1B is at 2cen-q13 and GLC1C at 3q. The GC3B (buphtalmos) locus is at 1p36. The gene encodes the trabecular (supportive connective tissue) meshwork-inducible glucocorticoid response (TIGR) or myocilin. The dominant glaucoma at 6p25 encodes a forkhead type transcription factor. For early detection of glaucoma, the endothelial leukocyte adhesion molecule (ELAM-1, 1q23-q25) test has been suggested. ▶**eye diseases**, ▶**syngeneic**, ▶**FKH**, ▶**amyloids**, ▶**Axenfeld-Rieger anomaly**; Jacobson N et al 2001 *Hum Mol Genet* 10:117; Libby RT et al 2005 *Annu Rev Genomics Hum Genet* 6:15.

GLC: ▶**gas liquid chromatography**

Gle1: ▶**RNA export**, ▶**export adaptors**

Gleason Score: A classification of prostate cancer on the basis of histology with predictive value for progression. (See Gleason DF 1992 *Hum Pathol* 23:273; prostate cancer).

Gleevec (Glivec, Imatinib, STI-571): An inhibitor of Abelson murine leukemia virus oncogene-encoded tyrosine kinase and an anticancer drug effective against some sarcomas and hematopoietic cancer (see Fig. G44). In some cases, cardiac failure may result from this drug. It is an inhibitor of platelet-derived growth factor receptor (PDGFR) and cancers where this growth factor is involved. Resistance may arise to the drug through mutation in the kinase domain. The new drug BMS-3548725, however, is effective against most of the cells resistant to Gleevec (Shah NP et al 2004 *Science* 305:399). Recently,

some physicians reported improvement of diabetes II in a few patients treated by Gleevec. The drug seems to be a potent inhibitor of differentiated myeloid leukemic cells (CML), but does not deplete leukemic stem cells (Michor F et al 2005 Nature [Lond] 435:1267). A new generation of inhibitor of CML is Desatinib. For gastrointestinal tumors, Sutent may replace Imatinib. ►hematopoiesis, ►leukemia, ►diabetes, ►genetic medicine, ►biomarkers; Capdeville R et al 2002 Nature Rev Drug Discovery 1:493.

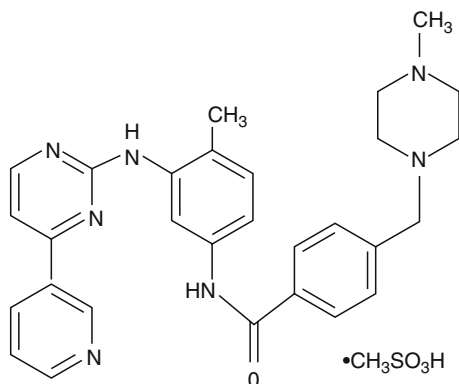


Figure G44. Gleevec

GLGF Repeats: Same as DHR domain or PDZ domain. (See Tochio H et al 2000 J Mol Biol 295:225).

GLI1 Oncogene (glioma): GLI1 has been located to human chromosome 12q13. It is highly amplified in gliomas. GLI2 in chromosome 2q14 (appears homologous to the *Krüppel* gene of *Drosophila* encoding a DNA-binding protein, regulating embryo morphogenesis). Similarly, GLI2 is also expressed in embryonal carcinomas but not in late developing ones. GLI3 (7q13) is apparently not an oncogene but it is involved in the Greig syndrome and in the Pallister Hall syndrome. Other homologous genes were also found in the human genome, altogether six loci in five different chromosomes. Some of the homologs (GLI4, 8q24.3) are denoted as HKR (human *Krüppel*). Gli transcription factors are suspected in the transduction of sonic hedgehog signals. Carboxy-terminal deletions in Gli3 facilitate its association with SMADs. ►oncogenes, ►*Krüppel*, ►Greig's cephalopolysyndactyly syndrome, ►Pallister-Hall syndrome, ►Rubinstein-Taybi syndrome, ►nevoid basal cell carcinoma, ►hedgehog, ►sonic hedgehog, ►syndactyly, ►polydactyly, ►DNA-binding protein domains, ►SMAD, ►glioma; Kim Y-S et al 2002 J Biol Chem 277:30901.

Gliadin: ►zein, ►glutenin

Glial Cell (neuroglia): Glial cells can be either astrocytes or oligodendrocytes or microcytes; the first two have supportive roles, the latter phagocytize the waste products of the nerves. Glial cells modulate synaptic transmission though an acetylcholine binding protein. ►FGF, ►acetylcholine

Glimmer: A program for locating (bacterial) genes based on interpolated Markov models. ►ORF, ►Markov chain statistics; Salzberg SL et al 1998 Nucleic Acids Res 26:544; <http://glimmer.sourceforge.net/>.

Glioma: A tumor of the tissues supporting the nerve cells (astrocytes) but it may spread beyond these. The glioma may be benign yet the malignant forms lead to rapid death. The most active glioma (glioblastoma multiformis, GBM) develops by an interaction of Ras and Akt in mice. GBM, although highly heterogeneous, can be grouped into rapidly progressing and slow progressing groups on the basis of expression ~70 genes, especially FABP7, and it can serve as a prognostic marker (Liang Y et al 2005 Proc Natl Acad Sci USA 102:5814). Gliomas seem to secrete glutamate that activates the NMDA receptors and further facilitates the expansion of the tumor. Surgery, radiation treatment supplemented with chemotherapy, and gene therapy with adenoviral vector carried herpes simplex virus thymidine kinase (HSVTK) and gancyclovir are used, but none give entirely satisfactory results. Bone morphogenetic protein inhibits glioblastoma stem cell proliferation (Piccirillo SGM et al 2006 Nature [Lond] 444:761). ►cancer gene therapy, ►GLI oncogene, ►angiogenesis, ►adenovirus, ►gancyclovir, ►RAS, ►Akt, ►FABP, ►NMDA, ►p110α, ►CD133, ►bone morphogenetic protein; Lam PYP, Breakfield XO 2001 Hum Mol Genet 10:777; Holland EC 2001 Nature Rev Genet 2:120; Takano T et al 2001 Nature Med 7:1010.

glnA: Bacterial glutamine synthase.

glnAp2, glnAp1: Major and minor glutamine synthase promoters, respectively, in bacteria.

Global Genetic Effects: Global genetic effects involve most or all of the genome. With the availability of microarray hybridization a very large number of gene loci can be studied (Rockman MV, Kruglyak L 2006 Nature Rev Genet 7:862). ►microarray hybridization, ►QTL

Global Single Cell Reverse Transcription-Polymerase Chain Reaction (GSC RT-PCR): The aim of the GSC RT-PCR method is to determine differences in gene expression among individual cells within a population of cells. This may be of interest for determining the process of metastasis, changes in gene expression during development, etc. A description of the procedure

can be found: Brailo LH et al 1999 *Mutation Res Genomics* 406:45. Although much difference is detectable among different cells, the components of the procedure introduce substantial variations too.

►microarray hybridization, ►SAGE

Globins: Ancestral protein molecules that diverged over a billion years ago into the oxygen-carrying muscle protein myoglobin and into the respiratory hemoglobins of the red blood cells. The neuroglobin, encoded at human chromosome 14q24, is expressed predominantly in the brain. The hemoglobin α locus is at human chromosome 16pter-p13.3, the β locus is at 11p15.5, δ is at 11p15.5, θ is at 16pter-13.3, the ζ is at 16pter-p13.3, and the ϵ is at 11p15.5. ►myoglobin, ►hemoglobin, ►leghemoglobin, ►haptoglobin, ►LCR, ►thalassemia, evolution of globins: Vinogradov SN et al 2005 *Proc Natl Acad Sci USA* 102:11385; <http://globin.cse.psu.edu/>.

Globo H: A glycosphingolipid present in breast cancer, ovarian, gastric, pancreatic, endometrial, prostate and small cell lung carcinomas. It may be employed in cancer vaccines. ►cancer gene therapy; Keusch JJ et al 2000 *J Biol Chem* 275:25315.

Globoid Cell Leukodystrophy: ►Krabbe's leukodystrophy

Globoside: Glycosphingolipid with the most common structure: acetylgalactoseamine-galactose-galactose-glucose-ceramide. ►sphingolipids, ►ceramides; Puri V et al 2001 *J Biol Chem* 154:535.

Globozoospermia (round-headed spermatozoa): A developmental anomaly caused by the loss of α' subunit of casein kinase II. This enzyme has many substrates and is involved in numerous metabolic controls. (See Larson KL et al 2001 *J Androl* 22 (3):424).

Globulin: Salt-soluble proteins with many diverse cellular functions.

Glofish: A genetically modified zebrafish expressing a red fluorescent protein transgene under a muscle-specific promoter, a pet novelty. ►transgene, ►zebrafish

Glomerulocystic Kidney Disease, Hypoplastic, Familial (GCKD, 17 cen-q21.3): Dominant mutations in the hepatocyte nuclear factor-1- β gene causing chronic renal failure, renal cysts and diabetes-like symptoms. ►HNF, ►kidney diseases

Glomerulonephritis: An autosomal dominant kidney disease associated with very sparse hairs and red lesions due to dilation of the blood vessels (telangiectasis). This disease (membrano proliferative glomerulonephritis) is frequently associated with

reduced levels of C3 complement component. More recent information indicates that the Fc γ R (fragment crystalline gamma receptor) of the antibody molecule is the most critical factor in the disease. Complement factor H-deficient mice showed significant reduction of nephritis if deficient in C5 but not in C6. Antimurine C5 antibody reversed renal injury (Pickering MC et al 2006 *Proc Natl Acad Sci USA* 103:9649). The dominant IgA nephropathy (6q22-q23) occurs at a frequency of 1×10^{-3} and may cause death in ~20% of the afflicted, despite dialysis.

►hair, ►kidney diseases, ►skin diseases, ►telangiectasis, ►complement, ►antibody, ►immunoglobulins, ►gene copy number

Glomerulosclerosis, Focal and Segmental, Familial:

Glomerulosclerosis involves increased urinary protein excretion and decreasing kidney function or even morbid kidney defects. The α -actinin gene at human chromosome 19q13.1 may be one of the causes for the stronger than normal binding of this protein to filamentous actin. Another dominant locus is in chromosome 11q22-q24 (encoding a transient receptor potential cation channel) and a recessive steroid-resistant NPHS2 gene has been assigned to 1q25-q31. The latter locus encodes the transmembrane protein podocin. ►actinin, ►actin, ►kidney diseases; Winn MP et al 2005 *Science* 308:1801.

Glomerulus (plural glomeruli): Cluster of blood vessels or nerve fibers.

Gloves: Gloves are frequently recommended for laboratory work when handling hazardous material or when contamination by hands must be avoided. Remember that surgical latex gloves easily develop invisible holes and permit unseen contamination of the hands. (Mercury penetrates latex disposable gloves in 15 seconds.) Latex gloves may cause (serious) allergic reactions to about 10% of the regular users and food allergies may aggravate it. Longer than 15-minute use of a latex glove may result in leakage. Organic solvents damage some plastic gloves and they may develop holes easily. For most operations neoprene gloves provide the greatest safety. For very hazardous material, the use of double gloves may be advisable. Washing hands after the removal of the gloves is recommended. (See laboratory safety).

GLT: ►GAST

Glucagon: A polypeptide hormone secreted by the α cells of the pancreas when the level of blood glucose sinks below a certain level. The hormone then increases the concentration of blood sugar by breaking down glycogen with the cooperation of epinephrine. ►epinephrine, ►animal hormones, ►cAMP, ►diabetes mellitus

Glucan: A polymer (repeating units) of glucose, the same as glucosan. ►[glucosan](#)

Glucanase: Glucan-digesting enzyme. ►[glucan](#), ►[host–pathogen relation](#)

Glucocorticoid: A kidney cortex hormone which regulates carbohydrate, lipid, and protein metabolism, muscle tone, blood pressure, the nervous system, etc. It inhibits the release of adrenocorticotropin, slows down cartilage synthesis, and mitigates inflammation, allergy and various immunological responses. Cortisol (hydroxycortisone) is an important natural glucocorticoid, whereas dexamethasone is a synthetic product that is two orders of magnitude more potent than cortisol. The glucocorticoid-mediated immunosuppression involves the activation of the I κ B α gene and an increase of its cytoplasmic protein product. When the nuclear regulator factor NF- κ B is active (because of the expression of TNF), its inhibitor, the I κ B α protein is degraded and NF- κ B moves into the nucleus and activates the immune system. Dexamethasone—in contrast with natural glucocorticoids—causes an increased transcription of I κ B α . Thus, the NF- κ B translocation to the nucleus is inhibited, leading to less nuclear NF- κ B and reduction of inflammation because the immune system is suppressed. Familial and sporadic glucocorticoid deficiencies are caused by defective adrenocorticotrophic hormone receptors. Glucocorticoids can affect serotonin levels and brain function. The deficiency of the glucocorticoid receptor (94-kDa, encoded at 5q31) causes cortisol and dexamethasone resistance. The melanocortin unresponsiveness is due to receptor deficiency at 18p11.2. The glucocorticoid receptor is an indispensable transcription factor, and it can attach to naked DNA as well as to nucleosomal structures. ►[adrenocorticotropin](#), ►[NF- \$\kappa\$ B](#), ►[I \$\kappa\$ B](#), ►[cortisol](#), ►[dexamethasone](#), ►[opiocortin](#), ►[immunosuppression](#), ►[apoptosis](#), ►[Cushing syndrome](#), ►[calreticulin](#), ►[immunophilins](#), ►[GRE](#), ►[stress](#), ►[serotonin](#), ►[allergy](#)

Glucocorticoid Response Elements (GRE): GREs are located generally about 100 to 2,000 nucleotide pairs upstream from the transcription initiation site (the human growth hormone response element is within the transcribed region). These elements, such as the mammary tumor virus (MTV), metallothionein (MTIIA), tyrosine oxidase (TO), and the tyrosine amino transferase receptor element, respond to different activating proteins as indicated by their names. Despite differences in structure they share a consensus: CGTACANNNTGTTCT. ►[hormone response elements](#), ►[regulation of gene activity](#), ►[DNA looping](#), ►[mammary tumor virus](#), ►[metallothionein](#),

►[tyrosine aminotransferase](#); Herrlich P 2001 *Oncogene* 20:2465.

Glucogenic Amino Acids: Glucogenic amino acids can be converted into glucose or glycogen through pyruvate (alanine, cysteine, glycine, serine, tryptophan), α -ketoglutarate (arginine, glutamine, histidine, proline), succinyl CoA (isoleucine, methionine, threonine, valine), fumarate, (phenylalanine, tyrosine) and oxaloacetate (asparagine, aspartate). ►[amino acids](#)

Glucokinase (GK): GK phosphorylates glucose to form glucose-6-phosphate. Heterozygosity for GK mutation in the fetus may cause mild hyperglycemia and may reduce insulin secretion by the fetus resulting in reduced intrauterine growth. In case of maternal glucokinase mutation, hyperglycemia stimulates fetal insulin secretion and increase in growth. ►[insulin](#); Grimsby J et al 2003 *Science* 301:370.

Gluconeogenesis: Gluconeogenesis is the synthesis of sugars from non-carbohydrate precursors (such as oxaloacetate, pyruvate, citrate, malate, TORC).

Glucosan (polyglucosan): Different types of polysaccharides (starch, glycogen, cellulose) containing repeating glucose subunits.

Glucose (glycose): A 6-carbon sugar (dextrose), an aldohexose. Besides being a source of energy, it induces and represses many genes. In chemostat cultures of yeast on galactose media, by small pulses of glucose additions, ~25% of the genes changed their expression (monitored by microarrays) primarily due to five transcription factors (Ronen M, Botstein D 2006 *Proc Natl Acad Sci USA* 103:389). Glucose influx triggers gene expression changes in hepatocytes to suppress endogenous glucose production and convert excess glucose into glycogen or fatty acids to be stored in adipose tissue. This process is controlled by insulin. Glucose also regulates the activity of ChREBP, a transcription factor that modulates lipogenesis. Glucose binds and stimulates the transcriptional activity of the liver X receptor (LXR), a nuclear receptor that coordinates hepatic lipid metabolism (Mitro N et al 2007 *Nature [Lond]* 445:219). ►[galactose](#) [for formula], ►[insulin](#), ►[lipidogenesis](#)

Glucose Effect: A form of catabolite repression when as long as glucose is available in the nutrient medium, the synthesis of enzymes involved in the utilization of other carbohydrates is prevented. The preferential growth on, e.g., glucose is followed by a temporary pause before the utilization of another carbon source is commonly called *diauxic growth*. Glucose may act at three levels: (1) inhibits the uptake of inducer molecules by relying on the dephosphorylated component of the phosphoenolpyruvate-dependent

glucose phosphotransferase. (2) Lowers the level of cAMP and its receptor and activates indirectly adenylate cyclase. (3) Increases the level of catabolites that repress the synthesis of inducible enzymes. In fungi, the mechanism of glucose effect may be mediated through the function of hexokinase. In yeast, *SNF1* (sucrose non-fermenting) encoding a transactivator protein (protein threonine/serine kinase) gene can relieve *SUC* and *GAL* glucose repression. The Mig1/CREA Zinc-finger DNA-binding protein, Glc7 protein phosphatase and the Tup1 general suppressor have also been implicated in the regulation. Two glucose signaling loci (*gsf1* and 2) also affect the glucose repression of *SUC2* and *Gall10*. Glucose suppression has been analyzed in prokaryotes and lower and higher eukaryotes, animals as well as plants. The *PRL1* locus of *Arabidopsis* encodes an α -importin WD protein that regulates glucose/sucrose sensitivity as well as hormone responses in the plant. ►feedback control, ►repression, ►catabolite repression, ►Zinc finger, ►Tup1, ►WD-40, ►SW1, ►transactivator, ►SUC2, ►GAL; Ronne H 1995 Trends Genet 11:12; Németh K et al 1998 Genes & Development 12:3059; Stülke J, Hillen W 1999 Curr Opin Microbiol 2:195; Rolland F et al 2002 Plant Cell 14:S185.

Glucose Induction: Glucose sensors *SNF* and *RGT1* genes monitor glucose in the cell membrane of yeast. Glucose most likely causes a conformation change in these proteins by attaching to their N-terminal domains outside the cell membrane. Both of these are transmembrane proteins with their C-terminus tail within the cytoplasm. That tail probably recruits the Hxt glucose transporters. The transcriptional suppressor Zn-finger protein, Rgt1, represses the *HXT* glucose transporter genes and the SCF^{Grr1} complex inhibits Rgt1 (regulator of transport) when a low concentration of glucose appears in the culture medium. (SCF is an acronym for Skp1, Cdc53 and Cdc34; it includes an F-box protein. Grr is a Cdc34-dependent protein factor of ubiquitination of cyclins). Then, *HXT* genes are activated. When the level of sucrose is increased beyond a certain level, the Mig1 suppressor system becomes active. When the concentration of glucose becomes high, Rgt1 turns into an activator of *HXT1*. ►glucose effect, ►SNF, ►SCF, ►Skp, ►Cdc34, ►Cdc53, ►F-box, ►glucose transporters; Vaultont S et al 2000 J Biol Chem 275:31555.

Glucose Repression: ►glucose effect

Glucose Tolerance Test: ►diabetes

Glucose Toxicity: Normally, insulin regulates the physiological range of glucose in the cells. When the level of glucose is raised for a longer period of

time, glucose toxicity results. Glucose may generate reactive oxygen species (ROS). Antioxidants as well as binding transcription factors PDX-1/STF and RIPE-3b1 to the insulin promoter may increase insulin production and reduce toxicity. (See Shimoi K et al 2001 Mutation Res 480–481:371).

Glucose Transporters: GLUT (12p13.3) is a 49-kDa protein involved in moving glucose. GLUT2 (3q26.1-q26.3) is another solute/sugar carrier (Fanconi-Bickel syndrome). GLUT1 (1p35-p31.3) mediates sugar transport to the brain across the blood/brain barrier membrane. The GLUT4 (17p13) defect seems to be involved in the resistance to insulin in diabetes type 2. GLUT5 (1p36.2) is a fructose transporter. GLUT10 (20q13.1) deficiency upregulated TGF. ►diabetes, ►BBB; Brown GK 2000 J Inher Metab Dis 23:237; Coucke PJ et al 2006 Nature Genet 38:452.

Glucose-Galactose Malabsorption (GGM): ►SGLT

Glucose-6-Phosphate Dehydrogenase: The first enzyme in the pentosephosphate pathway that converts G-6-P into 6-phosphoglucone- δ -lactone (see Fig. G45). The final product of the pathway is D-ribose-5-phosphate, and NADPH is also generated. Although about 90% of the cellular glucose in mammals is converted to lactate by glycolysis, 10% is driven through the pentose phosphate path and this is the principal reaction to provide the erythrocytes with NADPH for the reduction of glutathion. The deficiency of the enzyme caused by Xq28-chromosomal genes was first identified as a hemolytic anemia caused by the antimalarial drug 8-aminoquinoline. Most of the afflicted individuals are essentially asymptomatic until exposed to drugs such as certain analgesics, sulfonamides, antimalarial drugs (atabrine), quinine, etc., or afflicted by other diseases (see Fig. G46). G-6-P dehydrogenase deficiency is widespread in human populations, probably because the heterozygotes and hemizygous males are protected against falciparum malaria by a 46–58% reduction of the infectious disease. Heterozygotes (XX) may display lyonization. In the Jewish populations of Kurdistan, Caucasus, and Iraq, the frequency of the defect reached 58.2, 28.0 and 24.8%, respectively, whereas in geographical areas free of malaria it was generally less than 2%. Cavalli-Sforza and Bodmer estimated that G-6-P dehydrogenase deficiency conveyed an extremely high 0.15% selective advantage against malaria (Saunders MA et al 2002 Genetics 162:1849). A similar sequence is situated in human chromosome 17 and it may be a pseudogene. ►analgesic, ►malaria, ►selection coefficient, ►selection conditions, ►pentose phosphate pathway, ►glycolysis, ►glutathion, ►glycogen storage

diseases, ►atabrine; Tishkoff SA et al 2001 Science 293:455; <http://www.rubic.rdg.ac.uk/g6pd/>.

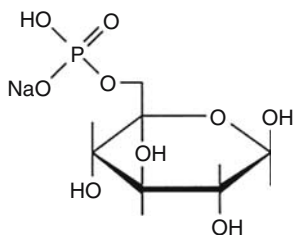


Figure G45. Glucose-6-phosphate

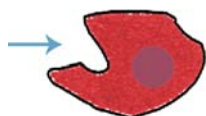


Figure G46. G-6-P deficient erythrocyte peripheral "BITE"

Glucose-Phosphate Isomerase: ►phosphohexose isomerase

Glucosidase (GCS1): An enzyme that digests 1,2-N-linked glycoproteins and other glucose linkages; in humans it is encoded in chromosome 2p13-p12. ►acid maltase, ►Pompe diseases, ►Gaucher disease

Glucosides: When D-(+) glucose is treated with an alcohol (methanol) and HCl, methyl D-(+)glucoside is formed that still has one methyl group attached, yet its properties resemble that of an acetal. Acetals may be formed from aldehydes and they are common in different plants. Cardiac glucosides present in plants such as *Digitalis*, *Scilla*, etc. have cardiotonic effect (strengthen heart function) and used as medicine. Many of the plant glucosides are highly toxic and cause anorexia (loss of appetite), nausea, vomiting, salivation, diarrhea, headache, drowsiness, delirium, hallucinations, and possibly death. Glycosides linked to cyanides also occur in common food plants such as beans, apricot, and almond seed, etc. Forage plants such as Sudan grass, white clover, etc. may contain enough cyanide to kill a 50 kg animal if it eats 1 to 2 kg fresh plant material. Through plant breeding efforts, the synthesis of the glucoside (lotoaustralin) may be blocked or the production of the enzyme linamarase may reduce the toxicity. ►lotoaustralin, ►cyanide; Tattersall DB et al 2001 Science 293:1826.

Glycosylation: Attaching glucose to another molecule. Defective N-glycosylation is the cause of mucopolisaccharidosis II and impacts the immune systems. Glycosylation has many important consequences on plant metabolism. ►mucopolisaccharidosis, ►glycosylation,

►congenital disorders of glycosylation; Lowe JB 2001 Cell 104:809; congenital disorders: Jaeken J, Matthijs G 2007 Annu Rev Genomics Hum Genet 8:261.

Glucuronic Acid: A derivative of uronic acid (a derivative of glucose) and it is present in glucosaminoglycans (see Fig. G47). ►mucopolysaccharidosis, ►GUS

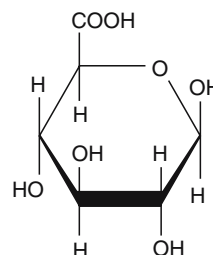


Figure G47. D-glucuronic acid

Glume: The lower-most bract of the grass florets (see Fig. G48). The glume is generally free from the fruit, in some cases however, it may be firmly associated with the kernels.

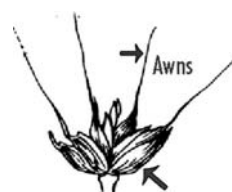


Figure G48. Glumes

GluR: ►glutamate receptor

GLUTs: Insulin-dependent glucose transporters encoded by the genes SLC. GLUT may be homologous to the cJun amino-terminal kinase-interacting protein JIP. MAPK81P1 (11p11.2-p12), a potential SLC transactivator, may be a major gene for type-2 diabetes. There are also several other glucose transporters. ►insulin, ►MAPK, ►diabetes, ►MODY, ►MAPK; Doege H et al 2001 Biochem J 359[pt2]:443)

Glutamate ($\text{HOOCCH}[\text{NH}_2]\text{CH}_2\text{CH}_2\text{CONH}_2$): An uncharged derivative of glutamic acid, which also has a key role as a nitrogen donor in the cell. The glutamate neurotransmitter activates the glutamate receptors (iGluR) regulating ion uptake and (mGluR) nerve synaptic strength and frequency. Mitochondrial glutamate facilitates insulin secretion. ►amino acids, ►glutamine, ►glutamate synthase, ►glutamate synthetase, ►neurotransmitter

Glutamate Decarboxylase Deficiency Disease (GAD):

A pyridoxine-dependent epilepsy. The two enzymes require the cofactor pyridoxal phosphate. These enzymes convert glutamic acid into γ -aminobutyric acid (GABA) that controls neurotransmission in vertebrates and invertebrates. The phenotype is autosomal recessive (GAD1 at 2q31, GAD2 at 10p11.23).

►epilepsy, ►GABA, ►amino acid metabolism

Glutamate Dehydrogenase (M_r 330,000):

Glutamate dehydrogenase catalyzes oxidative deamination of glutamate in the mitochondria, resulting in the formation of α -ketoglutarate. The reaction requires NAD^+ or $NADP^+$ as cofactors and is regulated allosterically by GTP and ADP. Then in turn, α -ketoglutarate and ammonia may again form glutamate. If the concentration of NH_3 is low, glutamate dehydrogenase cannot function to an appreciable extent. In such a case, NH_3 plus glutamate are converted to glutamine by non-adenylylated glutamine synthetase. In the presence of high amount of NH_3 , glutamine synthetase is adenylylated and becomes inactive and in this form it represses its own synthesis (autoregulation). In its non-adenylylated state (when the level of ammonia is low), it represses glutamate dehydrogenase instead. From glutamine and α -ketoglutarate, glutamate can be synthesized by glutamate synthase in the presence of $NADPH + H^+$. Glutamate synthase also serves as an inducer for tryptophan permease, which together with tryptophan transaminase may also contribute to glutamate synthesis. In its non-adenylylated state, glutamine synthetase activates also the histidine utilization operon (*hut*). This operon also yields glutamate and ammonia. In humans, a small multienzyme family codes this enzyme (GLUD); its level is relatively high in the brain. The principal and functional *GLUD1* is located in human chromosome 10q23. This gene is homologous to mouse locus *Glud-2* in chromosome 14. ►UTase, ►glutamate synthase, ►olivopontocerebellar atrophy, ►autoregulation

Glutamate Formiminotransferase: An autosomal recessive deficiency of this enzyme leads to the accumulation of formiminoglutamate and folic acid in the urine and in the serum causing physical and mental retardation (see Fig. G49). ►amino acid metabolism, ►mental retardation

Glutamate Oxaloacetate Transaminase (GOT2): GOT2 is encoded in human chromosome 16q21 but the protein is mitochondrially located. In many plants and lower animals, the enzyme is mitochondrially

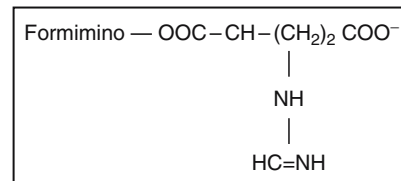


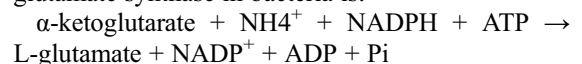
Figure G49. Formiminoglutamate

coded. Pseudogenes were found at two locations in human chromosome 1 and in chromosome 12.

►mtDNA, ►aspartate aminotransferase mitochondrial, ►tyrosine aminotransferase

Glutamate Receptors (GluR): GluR are cation channels mediating the post-synaptic current in the central neurons. Certain mutations in GluR-B subunits lead to increased calcium uptake and concomitant seizures if, e.g., the position 586 arginine prevents editing of pre-mRNA. The glutamate receptors are tetrameric. GluR genes with 63% to 16% homology to animal GluRs have been identified in both monocot and dicot plants with role in light signal transmission. ►neurotransmitters, ►NMDA, ►GABA, ►ion channels; Borges K, Dingledine R 2001 J Biol Chem 276:25929.

Glutamate Synthase: Glutamate synthase catalyzes the reaction that leads to: α -ketoglutarate + glutamine + $NADPH + H^+ \rightarrow 2$ glutamate + $NADP^+$. The result of the combined action of glutamate synthetase and glutamate synthase in bacteria is:



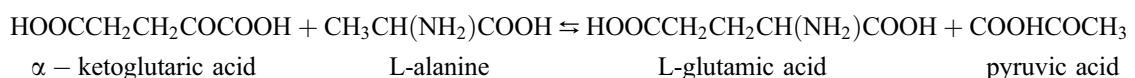
►glutamate dehydrogenase, ►glutamine, ►autoregulation

Glutamate Synthetase: Glutamate synthetase in *E. coli* is a ca. 800,000 M_r protein containing flavin, iron, and S^{2-} . ►glutamate synthase, ►glutamate dehydrogenase, ►glutamic acid, ►glutamine, ►autoregulation

Glutamate Transporter: ►GLAST

Glutamate-Pyruvate Transaminase (GPT1): GPT1 catalyzes the reversible reaction:

The soluble enzyme is encoded in human chromosome 8q24.2-qter. Cytosolic and mitochondrial forms exist. It is also called alanine aminotransferase (AAT1). ►amino, ►acid metabolism; ►glutamine; ►alanine aminotransferase



Glutamic Acid: $\text{HOOC} \cdot \text{CH}(\text{NH}_2) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ (L(+), amino-glutaric acid)

Glutaminase (GLS): An enzyme converting glutamine into glutamic acid and it has been mapped to human chromosome 2q32-q34. It is activated by phosphate and may affect the neurotransmitter role of glutamate. ▶ amino acid metabolism, ▶ glutamine, ▶ glutamic acid

Glutamine: $\text{HOOC} \cdot \text{CH}(\text{NH}_2) \cdot (\text{CH}_2)_2 \cdot \text{C}(\text{O})\text{NH}_2$. ▶ glutamic acid

Glutamine Amidotransferases: A group of enzymes with two domains, one binds glutamine and the other binds another molecule. After cleaving ammonia from glutamine they transfer it to the other substrate, generally in the presence of ATP.

Glutamine-Repeat Diseases: ▶ Huntington's chorea, ▶ Kennedy disease, ▶ dentatorubral-pallidolusian atrophy, ▶ olivopontocerebral atrophy, ▶ Macho-Joseph disease, ▶ fragile sites, ▶ trinucleotide repeat

Glutamyl Ribose-5-Phosphate Glycoproteinosis: An ADP ribose protein hydrolase deficiency resulting in proteinuria and neurological disorders. It is also regarded as a lysosomal storage disease. It may be X-linked. ▶ lysosomal storage diseases

Glutamyl-tRNA Synthetase (QARS): The enzyme charging the cognate tRNA with glutamic acid; it is encoded in human chromosome 1q32-q34. ▶ aminocyl tRNA synthetase

Glutaraldehyde: ▶ fixatives

Glutaredoxin: Glutaredoxin catalyzes NADPH-dependent reduction of disulfides usually in a complex with glutathione and glutathione reductase. ▶ thioredoxin, ▶ DsbA

Glutaricacidemia (GA): GAI autosomal recessive (19p13.2) glutaryl-CoA dehydrogenase deficiency results in increase in glutaric acid in the blood and in the urine resulting in neurodegenerative disorders. GAIC encoded in human chromosome 4q32-qter involves deficiency in the electron transfer flavoprotein oxidoreductase. GAIIA (15q23-q25) causes the excretion, besides glutaric acid, also lactic, ethylmalonic, isovaleric and different forms of butyric acids. Similarly, an X-linked (Xq26-q28) acyl-CoA dehydrogenase deficiency results in the abnormal excretion of glutaric and other organic acids. ▶ glutaricaciduria, ▶ aminoacidurias

Glutaricaciduria: An autosomal recessive glutaryl-CoA dehydrogenase deficiency leading to accumulation of glutaric acid in the urine, degeneration of the nervous system, and impairment of muscle functions. Limiting amino acid intake may alleviate the

symptoms. An autosomal dominant form (15q23-q25) was identified as a defect in an electron-transfer flavoprotein. Some glutaricacidemias are also called glutaricaciduria, e.g., glutaryl-CoA dehydrogenase deficiency (GAI, 19p13.2). Glutaricaciduria IIC (GAIIIC) was assigned to 4q32-qter. ▶ neuromuscular diseases, ▶ aminoacidurias, ▶ glutaricacidemia

Glutathione: Glutathione or γ -L-glutamyl-L-cysteinylglycine is a reducing agent that protects SH groups in proteins. About 10% of the blood glucose is oxidized to 6-phosphogluconate by glucose-6-phosphate dehydrogenase (G6PD) using NADP^+ , and the reducer NADPH keeps glutathione reduced. Deficiency of G6PD results in destruction of red blood cells and thus anemia. Glutathione is indispensable for development. Protozoa with anaerobic metabolism lack glutathione and mitochondria. ▶ glucose-6-phosphate dehydrogenase; Meister A 1988 J Biol Chem 263:17205; Spector D et al 2001 J Biol Chem 276:7011.

Glutathione Peroxidase (GPX1): GPX1 was assigned to human chromosome 3p21.3 (earlier it was assigned to 3q11). Its deficiency causes hemolysis and jaundice. The frequency of the GPX1 gene is >0.5 in Mediterranean Jewish populations but it is <0.2 in Northern Europeans. Locus GPX2 is in 14q24.1, GPX2 is in 5q32-q33.1, and GPX4 is in 19p13.3. The ailment may also be caused by selenium-deficient diet. ▶ hemolytic anemia, ▶ glutathione reductase, ▶ glutathione synthetase, ▶ deficiency

Glutathione Reductase (GSR): The GSR gene was located to human chromosome 8p21. Its deficiency results in hemolytic anemia. In insects thioredoxin substitutes for GSR. ▶ hemolytic anemia

Glutathione Synthetase Deficiency: A form of human chromosome 20q11.2 recessive hemolytic anemia and/or 5-oxoprolineuria. It may also result in excess metabolic pyroglutamic acid in the urine and in a variety of ailments. GST2 (γ -glutamylcysteine synthetase) gene was assigned to human chromosome 6p12 also causes hemolytic anemia. ▶ hemolytic anemia, ▶ glutathione, ▶ anemia

Glutathione-S-Transferases (GST): A family of enzymes metabolizing and detoxifying mutagens and carcinogens (some alkylating agents, cisplatin, carbonyl, peroxide, and epoxide groups) GST 3 was assigned to 11q13, GST2 to 6p12, GST1, GST4, GST5 all at 1p13.3. GSTPL (glutathione transferase-like enzyme) is encoded in 12q13-q14. These enzymes, despite different locations of the coding units, show homology. GST is also used for protein labeling. It is extremely stable and facilitates the solubilization of proteins fused with. ▶ multidrug resistance, ▶ cisplatin

Glutathionuria (GGT): A recessive defect (human chromosome 22q11.1-q11.2) in γ -glutamyl transpeptidase enzyme and accumulation of glutathione in the urine.

Gluten: A mixture of several seed proteins in cereals. The main fractions are the alcohol-soluble gliadin and the alkali-soluble glutenin. The proportion of the components is genetically determined and defines nutritional value and baking quality. ►glutenin, ►zein

Glutenin: Glutenin is about half of the seed storage protein in wheat; it is soluble in 70% ethanol and alkali but insoluble in water. It is a polymer of extremely large molecular weight, up to tens of millions. Its composition bears similarity to the muscle protein titin, comprising about 27,000 amino acid residues. The similarities based on (PEVK) proline, glutamate, valine, and lysine sequences may be attributed to the fact that both proteins require great elasticity in the bread dough. It was (indirectly selected by humans) to retain gas bubbles in the dough to return to the original position after extension. In wheat, gliadin occurs with glutenin. The former conveys resistance to extension while the latter provides the softness and viscosity of the dough. ►gluten, ►gliadin, ►celiac disease, ►Triticum, ►resilin; Kobrehel K et al 1992 Plant Physiol 99:919.

Glycan: A general old term for polysaccharides. Glycans associated with proteins have very important role in the cell (immune system, transport, etc.) and defects in their synthesis or association are involved in a large number of human diseases (galactosemia, fucosidosis, etc). ►lectins, ►polysaccharide, ►immune response; Lowe JB, Marth JD 2003 Annu Rev Biochem 72:643; bacterial glycans in immune response: Comstock LE, Kasper DL 2006 Cell 126:847; glycans technologies: Prescher JA, Bertozzi CR 2006 Cell 126:851.

Glycemia: Blood sugar content.

Glycerol ($\text{CH}_2\text{OH}-\text{CHOH}-\text{CH}_2\text{OH}$): An intermediate in carbohydrate and lipid biosynthesis.

Glycerol Kinase Deficiency (GKD, Xp21-p21.2): Physical and mental retardation, osteoporosis, myopathy, eye defects, and hyperglycerolemia. Chromosomal deletions may overlap with several other genes in the region of the X chromosome. ►contiguous gene syndrome; Gaudet D et al 2000 Am J Hum Genet 66:1558.

Glycerophospholipid: Glycerophospholipids are formed when fatty acids are esterified to glycerol and a polar alcohol is linked to it by phosphodiester bond. They are parts of cell membranes (synonymous with phosphoglycerides).

Glycine Biosynthesis: Glycine ($\text{NH}_2\text{CH}_2\text{COOH}$) is synthesized by hydroxymethyltrans-ferase from serine ($\text{HOCH}_2\text{CH}(\text{NH}_2)\text{COOH}$), while tetrahydrofolate is converted to N^5,N^{10} methylene tetrahydrofolate. The transferase gene has been located to human chromosome 12q12-q14, whereas the tetrahydrofolate cyclases are in human chromosomes 8q21, 18qter. Glycine is synthesized alternatively from CO_2 and NH_4 by glycine synthase in the liver of vertebrates. ►glycinemia ketotic, ►hyperglycinemia

Glycine max (soybean): A leguminous plant (basic chromosome number 20). The seed contains 20 to 23% oil and its protein content (meal) may exceed 40%. It is one of the most important source for vegetable oil products and textured proteins for human food. Also, it is used as supplements to animal feed mixtures.

Glycinemia, Ketotic (PCC): PCC is caused by two genes at two human chromosomal locations (PCCB at 3q21-q22 and PCCA at 13q32). The biochemical defect is propionyl-CoA carboxylase deficiency. This enzyme's primary known role is the generation of D-methyl-malonyl-CoA, which is epimerized into the L form and subsequently by a mutase—with vitamin B12 cofactor—to succinyl-CoA. These processes concomitantly somehow produce ketosis, hypoglycemia, and hyperglycinemia. The symptoms are growth retardation, vomiting, lethargy, protein intolerance, low level of neutrophilic leukocytes, reduction in platelet number, etc. ►ketoacidosis, ►amino acid metabolism, ►glycine biosynthesis, ►methylmalonicaciduria, ►hyperglycinemia

Glycocalyx: A carbohydrate-rich membrane glycoprotein-lipid layer of prokaryotic and eukaryotic cell surface.

Glycoform: Proteins with differences in glycosylation. ►glycosylation

Glycogen: The main storage polysaccharide in animal cells. About 7% of the wet weight of the liver is glycogen and glycogen is present in the muscle cells too. It is branched at every 8 to 12 residues. As needed, glycogen is hydrolyzed into glucose to supply energy, with the aid of enzymes that are associated with its granular form. Glycogen is synthesized from glucose-6-phosphate by first being changed into glucose-1-phosphate by phosphoglucomutase. Then UDP-glucose pyrophosphorylase converts G-1-P and UTP into UDP-glucose and pyrophosphate (PPi). Glycogen synthase then converts UDP-glucose into glycogen. *Glycogen synthase a* is the dephosphorylated active form of the enzyme, whereas the phosphorylated *glycogen synthase b* is inactive. The reaction requires a primer of α 1-4 polyglucose and the protein glycogenin. The branching is generated by

branching enzymes amylo-(1→4) to (1→6) transglucosylase or glycosyl-(4→6) transferase. The glycogen metabolism is regulated by glucagon and insulin in the liver and mainly by epinephrine and insulin in the muscles. The level of glucagon is regulated by cAMP. *Glycogen synthase kinase-3* regulates glycogen and protein synthesis by insulin and modulates transcription factor AP-1, CREB, the dorso-ventral patterning of embryogenesis, and apoptosis. ▶epinephrine, ▶insulin, ▶diseases, ▶AP, ▶CREB, ▶Akt, ▶PTG; Weston CR, Davis RJ 2001 Science 292:2439.

Glycogen Storage Diseases: Several hereditary defects have been identified as being associated with the synthesis and catabolism of glycogen: 1. *von Gierke's disease* (type I glycogen storage disease, 17q21) involves a deficiency of glucose-6-phosphatase, determined by an autosomal recessive gene (see Fig. G50). The patients develop liver enlargement (hepatomegaly as indicated by the extended abdomen, see photo), subnormal level of blood sugar content (hypoglycemia), increased levels of ketone bodies (acetone) in tissues and fluids (ketosis), as well as high amounts of lactic and uric acids in the blood. 2. *Type II glycogen disease* (Pompe disease, GAA, chromosome 17q25.2-q25.3) is determined by an autosomal recessive condition causing a deficiency of lysosomal α -1,4-glucosidase (acid maltase). Infants develop excessive enlargement of the heart (cardiomegaly) because of the deposition of glycogen in the lysosomes and, under severe conditions, in the heart. By the age of two they succumb to cardiorespiratory failure. The defect can be diagnosed prenatally from amniocentesis. A milder form of the disease exists, with prolonged survival. Intravenous injection of the normal GAA gene in an adenovirus vector construct significantly alleviated the disease in a mouse model. 3. *Type III glycogen disease* (see Forbes disease) is also caused by autosomal recessive (1p21) mutations. The basic physiological defects involve, in variable forms, the glycogen debranching process. The symptoms are not as severe as in Type II disease and the patients may survive longer; with age some of the symptoms may even be somewhat alleviated. 4. *Type IV disease* involves a 3p21 recessive defect of the glycogen branching enzymes. The progressive destruction of liver cells is accompanied by an increase in connective tissues and the liver substance (cirrhosis). An increase in the size of the liver and spleen and accumulation of fluids in the abdominal cavity (ascites) results in death before age two. 5. In *Type V McArdle's disease* (chromosome 11q13), the homozygosity of autosomal recessive glucose-6-phosphate translocase gene causes variable symptoms accompanied by glycogen accumulation. Phosphorylating activity in the muscle tissues is deficient. Painful cramps accompanying physical

exercise are the first symptom of the disease, the onset of which is around age 20. There is no hypoglycemia or increase of lactate in the blood but some patients excrete myoglobins in the urine. 6. *Type VI* (chromosome 14q21-q22) patients accumulate glycogen and some show reduced phosphorylating activity. 7. *Type VII disease* (Tarui disease), determined by chromosome 12q13.3 recessive genes, resembles Type V disease but the patients have reduced phosphofructokinase activity as well. 8. *Type VIII glycogen storage disease* is caused by a Xp22.2-p22.1-chromosomal recessive gene and thus affects primarily males. It is based on a leukocyte phosphorylase b activation deficiency. Some glycogen diseases involve multiple enzyme defects. These diseases are frequently associated with muscle weakness and various other adverse effects. ▶glucose-6-phosphate dehydrogenase, ▶glycogen, ▶epilepsy, ▶acid maltase deficiency, ▶neuromuscular disease, ▶enzyme replacement therapy



Figure G50. Glycogen storage diseases

Glycogen Synthase: ▶glycogen

Glycogenosis: The term “glycogenosis” is used to designate glycogen storage diseases. ▶glycogen storage

Glycolipid: A lipid with a carbohydrate group. Glycolipids are derivatives of sphingosine with one or more sugar. ▶sphingosine

Glycolysis: The catabolic pathway from carbohydrates to pyruvate; anaerobic breakdown of glucose for the synthesis of ATP. ▶Embden-Meyerhof pathway, ▶pentose monophosphate shunt

Glycome: The sugar chains in the cell, including glycosylated proteins, chaperones, and lipids. The size of glycomes exceeds that of proteins by orders of magnitude. Large numbers of human diseases are caused by disorders of the glycome (Freeze HH 2006 Nature Rev Genet 7:537). ▶glycosylation, ▶phosphomannomutase deficiency, ▶phosphomannose isomerase, ▶glycosyltransferases, ▶mannosyltransferases, ▶glycosidase, ▶lissencephaly,

►Ehlers-Danlos syndrome, ►exostosis, ►Kniest dysplasia, ►glycolipids, ►mucopolidoses, ►mucopolysaccharidosis, ►galactosemia, ►fructose intolerance, ►Marfan syndrome, ►muscular dystrophy; ►Walker-Warburg syndrome, ►thrombocytopenia, ►leucopenia, ►leukotrienes, ►epilepsy; <http://www.glycosciences.de/>; <http://www.glyco.ac.ru/bcsdb/>.

Glycophorin: A 131 amino acid transmembrane glycoprotein. Serological glycophorin assays have been developed to detect somatic mutations. Glycophorin-spectrin/actin bridge determines membrane shape and stability. ►spectrin, ►actin; Gerber D, Shai Y 2001 J Biol Chem 276:31229.

Glycoprotein: Proteins with covalently linked carbohydrate(s). ►proteoglycan; <http://www.cbs.dtu.dk/data/bases/OGLYCBASE/>.

Glycosaminoglycan (synonym mucopolysaccharide): A heteropoly-saccharide alternating *N*-acetylglucosamine + uronic acid and *N*-acetylgalactosamine + uronic acid (glucuronic acid). This family of compounds includes chitins, chondroitin sulfate, heparan, heparin, hyaluronic acid, keratans, and keratin (see Fig. G51). Chemokines interact with glycosaminoglycans and play roles in inflammation, and in developmental and homeostatic functions. ►exostosis, ►mucopolysaccharidosis, ►proteoglycan, ►chemokines, ►glucuronic acid, ►hyaluronidase deficiency; Constantopolous G, Dekaban AS 1975 Clin Chim Acta 59[3]:321; Handel TM et al 2005 Annu Rev Biochem 74:385.

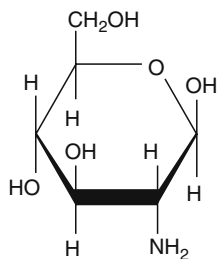


Figure G51. Glucosamine

Glycose: The generic name of monosaccharides, e.g., glucose, fructose, mannose, etc.

Glycosidase: Glycosidase digests glycosidic bonds and transfers of glycosyl moieties from a donor sugar to an acceptor of another sugar or other molecule(s).

Glycosidic Bond: A sugar linked to either alcohol or purine, or pyrimidine or sugar through an oxygen or nitrogen atom. (See conformation maps: <http://www.glycosciences.de/modeling/glycomapsdb/>).

Glycosome: Peroxisomes (microbodies) filled with glycolytic enzymes. ►glycolysis, ►microbody

Glycosphingolipids: Glycosphingolipids are present in plasma membrane rafts and caveolae and play an important role in differentiation and development ►sphingolipid, ►caveolae, ►RAFT

Glycosuria: An incompletely recessive defect in glucose reabsorption by the kidney, resulting in high sugar level in the urine. ►phlorizin, ►disaccharide intolerance

Glycosylases: Enzymes involved in excision of damaged purines and pyrimidines from the sugar-phosphate backbone of DNA. Different enzymes work on different bases (see Fig. G52). The uracil-DNA glycosylases (human gene UNG, chromosome 12q23-q24) remove uracils formed by spontaneous or induced deamination of cytosine, to avoid U-G mispairing potentially leading to GC→AT transitions.

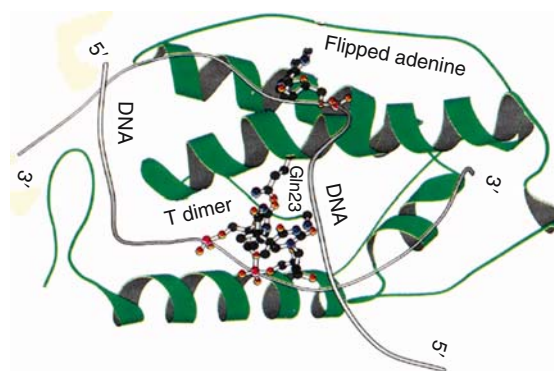


Figure G52. T4-pdg (pyrimidine dimer glycosylase/AP lyase, a TDG) X-ray crystal structure as a ribbon diagram. The DNA is distorted and the flipped-out adenine and the thymine dimer are shown as ball and sticks. The 3' and 5' indicate the directions of the DNA strands. Gln23 is a mutant amino acid residue. (Courtesy of Lloyd, RS, see also McCullogh AK et al 1999 Annu Rev Biochem 68:266)

It works in the nucleus and the mitochondria as well. The thymine-DNA glycosylase (TDG/UDG, 12q24.1) is one of the most efficient of these repair enzymes. The enzyme pushes and pulls out the improper uracil nucleotide from the major groove of the DNA. Subsequently,

TDG excises U, AP endonuclease cleaves the DNA backbone, deoxyribo-phosphodiesterase removes the 5'-phosphate group, and DNA polymerase β replaces the correct nucleotide and ligase finishes the job. It has been estimated that in a human cell 100 to 500 cytosine residues are deaminated daily. MUG (mismatch-specific uracil DNA glycosylase, human

chromosome 12) removes uracil/thymine when mispaired with guanine. The human hSMUG1 operates primarily at single strands of DNA during replication and transcription. MBD4 glycosylase (3q21) may remove mismatched U or T nucleotides. The 3-methyladenine-DNA glycosylase (gene AAG/MPG, chromosome 16p-telomere) works on N-3- and N-7 methylation adducts of purines (including hypoxanthine) and cyclic adducts. The pyrimidine hydrate-DNA glycosylase removes damaged or altered pyrimidines. OGG1 (oxoguanine glycosylase, 3p25.3/ 3p26.2) removes 8-oxoguanine across cytosine. MYH (1p32.1-p34.3) glycosylase excises adenine when misincorporated across oxoguanine. The formamidopyrimidine-DNA glycosylase (NTHL1, 16p13.3-p13.2) excises oxidatively damaged purines such as 8-oxoguanine, 8-hydroxyguanine, thymine glycol, and cytosine glycole, but requires the cofactor XPG (xeroderma pigmentosum G, 13q33). This DNA glycosylase also removes deaminated 5-methylcytosines that are common in eukaryotic DNA. All these excision repair enzymes maintain the working conditions of the human cells each of which suffers more than 10,000 damages each day. The yeast or *E. coli* glycosylases have similar functions but the proteins involved are different in size. ▶excinucleases; ▶AP endonucleases; ▶endonuclease III; ▶endonuclease VIII; ▶DNA repair; ▶mismatch repair; ▶transition; ▶adduct; ▶base flipping; ▶X-ray repair; ▶RAD27; ▶pyrimidine dimer; ▶cyclobutane ring; McCullough AK et al 1999 Annu Rev Biochem 68:255; Hollis T et al 2000 Mutation Res 460:201; Ischenko AA, Saparbaev MK 2002 Nature [Lond] 415:183; MuTM glycosylase: Banerjee A et al 2006 Science 311:1153.

Glycosylation: The attachment of sugars to proteins either through a hydroxyl group of serine or threonine (O-glycosylation, Ser[Thr]-O-GlcNAcylation), or to the amide group of an asparagine (N-glycosylation). Glycosylated proteins have many different types of cellular functions. O-glycosylation occurs in proteins of the nuclear pore, in RNA polymerase II, transcription factors, oncoproteins (tumor suppressors), chromatin proteins, microtubule-associated proteins, cytoskeletal binding proteins, tyrosine phosphatase, SV40 T antigen, estrogen receptors, etc. Some antibiotics (tunicamycin) interfere with the process. Glycosylation increases the stability of proteins and may facilitate antigen recognition, appropriate folding, signal transduction, nerve function, etc. It plays an important role in the function of the immune system in the reproductive cell paths and several other health-related metabolic functions. A search for glycosylation in the Human Gene Mutation Data Base revealed 77 genes with 142 glycosylation

mutations that seem to affect disease susceptibility (Vogt G et al 2005 Nature Genet 37:692). ▶glycoform, ▶glycosylation, ▶glycome, ▶sialic acid, ▶mycobacterium; Rudd PM et al 2001 Science 291:2370; Lübke T et al 2001 Nature Genet 28:73; Varki A 2006 Cell 126:841; glycosylation in health and disease: Ohtsubo K, Marth JD. 2006 Cell 126:855; glycobiology reviews: Nature [Lond] 446:1030–1051.

Glycosyltransferases: Enzymes adding glucose to proteins and lipids involved in the formation of lipopolysaccharides used for bacterial cell wall. The ABO blood group alleles also encode glycosyltransferases (also the B gene product adds galactose). These enzymes shape the cell surface, determine cell to cell contacts, play some role in cancer, and have an important function in various sphingolipidoses. ▶sphingolipidoses, ▶ABO blood group; Cosgrove DJ 1999 Annu Rev Plant Physiol Plant Mol Biol 50:391; may catalyze reversible reactions: Zhang C et al 2006 Science 313:1291.

Glyoxalase: Glyoxalase I adds SH group from glutathione to the aldehyde carbonyl of methylglyoxal. The thioester product is then hydrolyzed by glyoxalase II (see Fig. G53). Glyoxal: OHCCCHO. Methylglyoxal: CH₃COCHO. ▶enzyme design

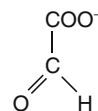


Figure G53. Glyoxylate

Glyoxylate Cycle: The glyoxylate cycle converts acetate into succinate and finally to carbohydrate. ▶Krebs-Szentgyörgyi cycle

Glyoxysome: Vesicles in plant seeds and special type of microbodies (peroxisomes) in plants mediate the conversion of fatty acids to succinic acid to produce peroxiacetyl CoA and glucose through the glyoxylate cycle. ▶microbody, ▶glyoxylate cycle

Glyphosate: ▶herbicides, ▶GMO

Glypicans: Transmembrane proteins with phosphatidyl inositol distal to the membrane and heparan sulphate outside but proximal to the membrane. Glypican-1, -3, -5 are encoded at human chromosomes 2q35-q37, Xq26, and 13q31-q32, respectively. In mice, glypican-3 regulates a quantitative trait locus (QTL) involved in the body mass determination (Oliver F et al 2005 PLoS Biol 3(5):e135). ▶phosphatidylinositol, ▶heparan sulphate, ▶syndecan, ▶Simpson-Golabi-Behmel syndrome; Filmus J, Selleck SB 2001 J Clin Invest 108[4]:497.

GLYT: Glycine-specific transporters to the nervous system; they may be inhibitory neurotransmitters through a ligand-gated Cl^- channels, activated by glycine or may modulate glutamate-mediated neurotransmission. ►transporters, ►ion channels; Hanley JG et al 2000 J Biol Chem 275:840.

GM: ►GMO

GMENDEL: A computer program for analysis of segregation and linkage. (See Hered J 81:407 [1990]).

GM1-Gangliosidosis: ►gangliosidosis type I

GM2-Gangliosidosis: ►Tay-Sach disease, ►Sandhoff disease

GM3-Gangliosidosis: ►gangliosidosis type III, ►Sandhoff disease

GM3 Synthase: GM3 synthase produces gangliosides and glycolipids. Homozygous mutations cause infantile-onset epilepsy. ►epilepsy; Simpson MA et al 2004 Nature Genet 36:1225.

GMHT: (genetically modified herbicide-tolerant plants) have an agronomic advantage by facilitating the elimination of undesirable weeds from crops but they may adversely affect the population of wild birds that feed on weed seeds. ►GMO

GM-CSF: The granulocyte-macrophage colony stimulating growth factor is a lymphokine. ►lymphokines, ►macrophage, ►granulocyte, ►M-CSF, ►M-CSF, ►G-CSF; Collins SJ et al 2001 Blood 98:2382.

GMO: Genetically modified organisms; a name actually used for transgenic plants and animals (see Fig. G54). Consumers may oppose genetically modified (GM) food, fearing that the products may cause allergic reactions (e.g., Brazil nut albumins in transgenic soybean). The modified organisms develop antibiotic resistance (in case antibiotic resistance genes were used in the transformation vectors) or the transgene may be transcribed and translated into harmful substances. Lectins and alkaloids in the GMO may create human or environmental hazards (e.g., transmitting glyphosate herbicide-resistance by cross-pollination to weeds [*Cruciferae*], harming useful insects [e.g., neuropteran lacewings] or other species such as the Monarch butterfly [by Bt]). Ecologists have expressed concerns about the potential selective advantage of genetically modified plants in the natural environment. In a 10-year-long study of rape, maize, beet, and potato carrying various transgenes, it was found, however, that in general these were no more invasive than conventional crops (Crawley MJ et al 2001 Nature [Lond] 409:682). Although the actual extent of cross-pollination between transgenic and wild type plants is difficult to determine, indirect

assessment may be feasible and useful (Wilkinson MJ et al 2003 Science 302:457).



Figure G54. Monarch (*Danaus*) butterfly larva

Transgenic rice producing more β -carotene and accumulating more iron may not entail any danger, but can reduce malnutrition, anemia, and some kinds of blindness in the underdeveloped areas of the world. It is worth considering that the transgenic organisms may be easier, cheaper, and safer to produce because of they offer resistance to pests and diseases and facilitate the curtailing of hunger. The extensive use of chemical pesticides may be reduced. Insect-resistant GM rice yields more and protects the health of farmers because pesticides do not harm the workers (Huang J et al 2005 Science 308:688). These opposing facts may mandate some regulations and/or labeling of the products and further research to clarify the cost/benefit dilemmas. Genetically modified proteins in excess of 0.1% are detectable by ELISA and PCR detects DNA modifications when present at 0.01% in the sample. By 2005, more than 12% of the crops were transgenic and the acreage has been increasing since, without any evidence of harm to the consumer (Raven PH 2005 Proc Natl Acad Sci USA 102:13003).

Rainbow trout (*Onorhynchus*) or salmon carrying engineered growth hormone genes may grow dramatically larger, especially the non-domesticated forms, which had not been subjected to selection for increased productivity. Genetically engineered cows may produce milk with higher β - and κ -casein (Brophy B et al 2003 Nature Biotechnol 21:157). One study of cattle produced by somatic cloning (offspring obtained by transfer of somatic cell nuclei into enucleated eggs and subsequent pregnancy and birth) was analyzed in detail in comparison with sexually produced progeny for the normal milk composition, including antibodies. No significant differences were detected. In the comparative analysis of the meat no significant differences were found, except higher fatty acid components in the muscles and the increase mesentery fat (in the membranes covering internal organs) of the modified animals. Internal organs were histologically analyzed for possible pathological changes and abnormalities. In the kidney and urinary ducts, calculi (mineral stones) were found in the clones but these were often detected in normal beef

cattle. This relatively small-scale study does not indicate differences beyond the range of natural variations of the breeds (Tian XC et al 2005 Proc Natl Acad Sci USA 102:6261). Another study with potatoes transgenic for insulin-type fructans (sucrose: sucrose 1-fructosyl transferase and fructan:fructan 1-fructosyltransferase) indicated overall substantial similarity in composition compared to the non-transgenic (original) cultivar, as demonstrated by gas chromatography, capillary electrophoresis, and mass spectrometry (Catchpole GS et al 2005 Proc Natl Acad Sci USA 102:14458).

One must keep in mind that a type of genetic modification, selection, raised the sugar content of beets from ~2% to ~20% from the middle of the eighteenth century to the present. Similarly, purposeful plant breeding increased maize production from about 1.25 metric tons/hectare to ~15 tons since the 1930s. The “green revolution” doubled cereal production since the 1960s. Nevertheless, even today about 40,000 children die daily from malnutrition-related diseases. Obviously, technological progress will involve a trade-off. The only question is whether it is worth the exchange. There was a general fear in the 1970s about the use of recombinant DNAs even for laboratory purposes. Most of these fears turned out to be unfounded but certain types of genetic engineering (e.g., using toxin genes) can be carried out only in a highly controlled environment and only when there is a special, justified need. The arguments against and for genetically modified organisms must be based on scientifically validated facts, rather than on political views or preconceived notions. Existing information indicates relatively fast (100–150 days) decomposition of most (60–70%) of the Bt toxin in soil and even in plant tissues. Paracelsus/Theophrastus of Hohenheim (1493–1541), the ‘Luther of Medicine’, remarked: “Guilty is he who does not know it properly and who does not apply it properly” (see Fig. G55).



Figure G55. Paracelsus

Interestingly, William Shakespeare in his play *Winter's Tale* (1611) (Act. 4, Scene 4) addressed the problem of genetically modified organisms:

“POLIXENES

Say there be;

Yet Nature is made better by no mean

But Nature makes that mean: so, over that art

Which you say adds to Nature is an art

That Nature makes. You see, sweet maid; we marry

A gentler scion to the wildest stock,

And make conceive a bark of baser kind

By bud of nobler race: this is an art

Which does mend Nature change it rather, but

The art itself is Nature.” (I am indebted to Professor AT Szabó for calling my attention to this quotation).

The genetic and ethical problems relevant to inheritable genetic modification of humans can be accessed on the WEB: <http://www.aaas.org/spp/sfrr/projects/germline/report.pdf>. ▶Asilomar conference, ▶biohazards, ▶pollen, ▶chloroplast genetics, ▶recombinant DNA and biohazards, ▶xenotransplantation, ▶targeting genes, ▶stem cells, ▶nuclear transplantation, ▶transplantation of organelles, ▶biotechnology, ▶*Bacillus thuringiensis*, ▶Bt, ▶gene therapy, ▶input trait, ▶pest eradication, ▶refuge, ▶RBF, ▶terminator technology, ▶T-GURT, ▶patent, ▶fructans; Wolferbarger LL, Phifer PR 2000 Science 290:2088; Quist D, Chapela IH 2001 Nature [Lond] 414:541; Dale PJ et al 2002 Nature Biotechnol 20:567; Hare PD, Chua N-H 2002 Nature Biotechnol 20:575; Vasil IK 2003 Nature Biotechnol 21:849; environmental contamination: Stewart CN et al 2003 Nature Rev Genet 4:806; transgenic livestock: Clark J, Whitelaw B 2003 Nature Rev Genet 4:825; public concerns with GMOs: Hails R, Kinderlerer J 2003 Nature Rev Genet 4:819; <http://www.nbiap.vt.edu>; www.usia.gov/topical/global/biotech; <http://usbiotechreg.nbi.gov/>; <http://www.colostate.edu/programs/lifesciences/TransgenicCrops>.

GMP: Guanosine monophosphate.

GMS (genomic mismatch scanning): A method designed to scan large genomic DNA samples for differences in order to identify alterations, e.g., those responsible for hereditary disease. The principles are as follows: two DNA samples (diseased and healthy) are digested with restriction endonuclease. Fragments of one of the samples are methylated. Then both samples are denatured and allowed to hybridize. From re-annealed DNA only those strands are subjected to further study, which are hybrids (i.e., one of the two strands is methylated but other is not). These hybrids are exposed to bacterial mismatch repair enzymes that recognize mismatches and at that site nick the unmethylated strand. The nicked strands

are then removed and the intact duplexes retained. These would be expected to include the desired marker(s). The method is very elegant in principle but cannot yet be applied to the very complex human genome with great amount of redundancy and complexity. Single genetic regions can, however, be studied with the aid of array hybridization. ►RDA, ►mismatch repair, ►genetic screening, ►array hybridization; Mirzayans F, Walter MA 2001 *Methods Mol Biol* 175:37.

Gnotobiota: The known microbes (animals and plants) associated with laboratory animals. The animals might be raised under germfree conditions and infected with a single, specific bacterium.

GnRHA (gonadotropin-releasing hormone agonist): When administered at a constant rate, GnRHA shuts down mammalian reproductive functions and induces a condition resembling the menopause. It can be employed as a fertility-controlling agent but must be supplemented with periodic treatments with other hormones to prevent menopause-like side effects. It can be also used to save an implanted ovum or zygote by preventing ovulation. GnRHA has many other medical applications. ►gonadotropin releasing factor, ►egg donation, ►in vitro fertilization, ►ART, ►menopause, ►menstruation; Smits J et al 1992 *Hum Reprod* 1:49.

GNRP (guanine nucleotide releasing protein): It is involved in signal transduction with RAS and affect several cellular functions. A rather detailed review of its basic function is in Quilliam RL et al 2002 *Progr Nucleic Acid Res Mol Biol* 71:391). GNRP, when activated by receptor tyrosine kinase in the signal transduction pathway, a RAS protein switch is turned on. ►RAS, ►signal transduction; Marshall M 1995 *Mol Reprod Dev* 42[4]:493.

GO: A dormant stage of cell divisions in fission yeast. ►cell cycle, ►*Schizosaccharomyces pombe*

GO: ►gene ontology

G_o Protein: A subunit of the trimeric G-protein; it activates K⁺ channels and shuts down Ca²⁺ ion channels. Mutations in the gene encoding it cause behavioral anomalies in *Caenorhabditis* similar to those caused by a defect in the serotonin receptor. The main symptoms are hyperactivity, premature egg laying, and male impotence due to defects in neuronal and muscle functions. ►signal transduction, ►ion channels, ►serotonin, ►G_α

GO Units: ►gene ontology

Goat (*Capra hircus*): 2n = 60. It was probably the first large herbivorous domesticated animal. (See MacHugh DE & Bradley DG 2001 *Proc Natl Acad*

Sci USA 98:5382, <http://locus.jouy.inra.fr/cgi-bin/lgbcmapping/common/intro2.pl?Base=goat>).

Goat-Sheep Hybrids: The domesticated sheep (*Ovis aries*, 2n = 54) can be impregnated by the domesticated goat (*Capra hircus*, 2n = 60), but the hybrid embryo rarely develops normally although, occasionally some hybrids do grow up. ►animal species hybrids; Hancock JL et al 1968 *J Reprod Fertil* 3:29; Ilbery PL et al 1967 *Aust J Biol Sci* 20:1245.

GOBASE: An organelle genome database. ►organelle genetics, ►OMIA; <http://megasun.bch.umontreal.ca/gobase/>; <http://gobase.bcm.umontreal.ca/>.

GOGAT: Glutamine-2-oxoglutarate transferase. ►nitrogen fixation

Goiter, Familial: A collection of various metabolic anomalies involving enlargement of the thyroid gland that may become obvious by viewing the neck. The defect may involve various dominant or recessive mutations in the thyroglobulin gene. The thyroglobulin gene (TG) is located in human chromosome 8q24 extending to about 300-kb genomic DNA, containing 37 exons and large introns. The dimeric thyroglobulin protein has a molecular weight of ca. 660,000. This protein is iodinated at tyrosine residues to form mono- and diiodotyrosines. *Thyroxine* is a tetraiodothyronine but *triiodothyronine* is also formed upon activation by peroxidase. The iodinated proteins are transported by the blood, increase the metabolism, and regulate the function of the nervous system, kidney, liver and heart. *Hyperthyroidism* occurs due to the overproduction of iodinated thyroglobulin hormones, resulting in goiter, fast heart rate, fatigue, muscular weakness, heat intolerance and sweating, tremors, and emotional instability. Excessive secretion of thyroid hormones is referred to by the synonymous *Graves* or *Basedow* disease, with susceptibility controlled by several sites (14q31, 6p21, 7q, 8q, 10q, 2q33, 20q13, Xq21). The New Graves Disease maps to 18q21. The latter condition may or may not be genetic, although its frequency may be quite high (0.008). The basic defect may involve autoimmunity of the receptor of the hormone. *Hypothyroidism* is the consequence of the underproduction of the thyroid hormone, resulting in fatigue, lethargy, low metabolism, cold-sensitivity, and menstrual problems in females. This condition may lead to *cretinism*, which is most commonly caused by failure of releasing *thyrotropin*, the glycoprotein thyroid-stimulating hormone of the anterior pituitary. Cretinism also means an arrest of physical and mental development, and is caused by this hormonal deficiency.

Hypothyroidism may also lead to deafness. Defects in deiodination of iodotyrosines could also cause hypothyroidism. *Permanent congenital hypothyroidism* has a prevalence of ~ 3 to 4×10^{-4} in newborns and unless it is caused by hypothalamic or pituitary defects, it is accompanied by over-expression of the thyroid-stimulating hormone and lower-than-normal thyroid function or thyroid dysgenesis. Thyroid therapy is required within the first two months to prevent neurological damage (cretinism). In some cases, mutation of the Pax8 gene at human chromosome 2q12-q14 has been detected. PAX8 seems to be required for the differentiation of endoderm primordia into thyroxine-producing follicular cells. Goiter-like diseases are known in the majority of mammals. Thyroxine binding globulin is encoded in human chromosome Xq28 and a thyroxine binding serum globulin is autosomal. The multinodular goiter—with 5:1 female:male ratio—has been assigned to Xp22. [▶hyperthyroidism](#), [▶Hashimoto disease](#), [▶animal hormones](#), [▶tyrosine](#), [▶thyroid stimulating hormone](#), [▶PAX](#), [▶NIS](#), [▶Pendred syndrome](#), [▶CTLA-4](#); Tomer Y et al 1997 J Clin Endocr Metab 82:1645; Vaidya B et al 2000 Am J Hum Genet 66:1710.

Gold Standard Test: The gold standard test in clinical trial involves (i) random allocation of the treatment, (ii) concurrent control and (iii) double blind trial of the drug or the treatment. [▶double-blind test](#)

Goldberg-Hogness Box: [▶Hogness box](#)

Goldenhar Syndrome: Autosomal dominant and recessive forms with different expressions of facial and other developmental deformities.

Golgi Apparatus: Flat vesicles (cisternae) containing cellular storage and transport material involved in glycosylation, sulfation, proteolysis, etc., in animals (see Fig. G56). Although the model shown indicates transport in one direction, evidence is accumulating for transport by the cisternae from the cell membrane toward the endoplasmic reticulum. The *coat protein I* (COPI) and SNARE seem to play important role in the transport. The homologous structures in plants are frequently called dictyosomes. Some of the Golgi structures are located next to endoplasmic reticulum and are called *cis Golgi*; others occur at a distance (*trans Golgi*). In these vesicles, some proteins are modified after the completion of their synthesis in the endoplasmic reticulum. In the stacked fragments, some of the functions seem compartmentalized (Yano H et al 2005 Proc Natl Acad Sci USA 102:13467). The Golgi complex is inherited by fragmentation of the elements into small vesicles, which are distributed at random during mitosis. According to more recent observations, the distribution may not be entirely random. The fragments were found to aggregate around the mitotic spindle pole and the motor proteins pulled them into the daughter cells. After cytokinesis, Cdc2 supposedly phosphorylates the

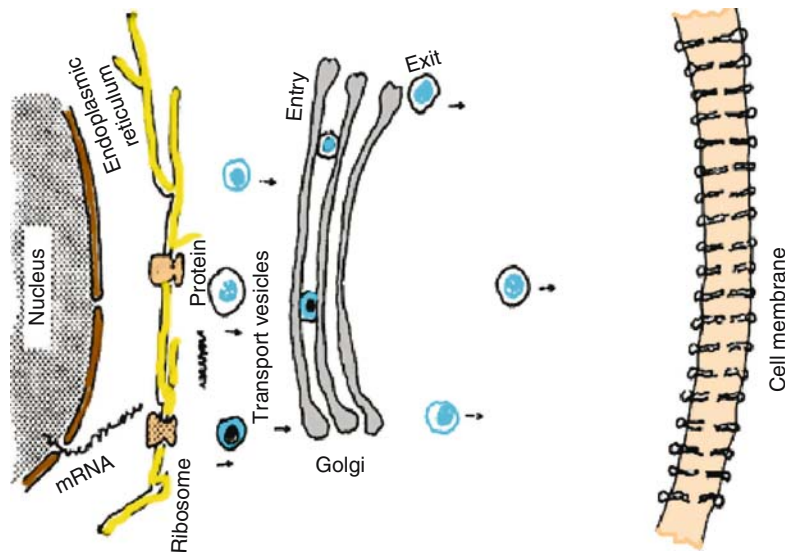


Figure G56. Transport function of the Golgi apparatus. From the nucleus, through the nuclear pores, mRNA reaches the ribosomes sitting on the endoplasmic reticulum (ER). The protein synthesized may enter the lumen of the ER with the assistance of a signal peptide transfer particle-mediated system. The proteins may emerge then in transport vesicles to enter the Golgi at the cis side end, exit at the "bulbous" ends of the stacked membrane vesicles. In the Golgi the proteins are glycosylated and modified post-translationally

p115 receptor and then of the fragments the Golgi structure is reconstituted probably via the endoplasmic reticulum. The exact mechanisms are not generally agreed upon, however.

►endoplasmic reticulum, ►dictyosome, ►cell structure, ►trans-Golgi network, ►cis-Golgi, ►RAB oncogene, ►SNARE; Allan BB, Balch WE 1999 Science 285:63; Roth MG 1999 Cell 99:559; Müsch A et al 2001 EMBO J 20:2171; Allan VJ et al 2002 Nature Cell Biol 4:E236; Shorter J, Warren G 2002 Annu Rev Cell Mol Biol 18:379; Golgi maturation: Losev E et al 2006 Nature [Lond] 441:1002; Matsuura-Tokita K et al 2006 Nature [Lond] 441:1007.

G

G_{oif}Protein: A trimeric G-protein; stimulating cAMP in the control of olfactory neurons. ►G-proteins, ►olfactory, ►olfactogenetics

GOMBO Syndrome: Autosomal recessive growth retardation with eye, brain, skeletal, and mental defects. ►growth retardation

Gomori's (Gömöri's) Stain: Gomori's stain is used primarily for histological localization of phosphatases and lipases in sectioned specimens by the light microscope. The trichrome stain contains, in 200 mL H₂O, chromotrope 2R (2[phenylazo]chromotropic acid) 1.2g, fast green 0.6 g, phosphotungstic acid 1.6g, and glacial acetic acid 2mL. ►stains, ►histochemistry; Gomori G 1950 Am J Clin Path 20:665.

Gonadal Dysgenesis: The failure of normal differentiation of the gonads (ovary, testis). It is a common cause of sterility in aneuploids. Gonadal dysgenesis of XY chromosomal constitution occurs in mammalian females. They have "streak gonads" and fail to develop the secondary sexual characteristics. Gonadal neoplasias are frequent in these individuals. It has been shown that the testis-determining factor resides in a Y-chromosomal segment and either deletion or base substitution may lead to an inactive human SRY (Yp11.3) product, a DNA binding protein involved in testis determination. Transfection of the TDY (the mouse homolog of SRY) DNA into XX mouse was found to induce male development. Gonadal dysgenesis may occur also in XX females, which have higher than normal level of gonadotropins and underdeveloped male gonads. In XY females (GDXY, Xp22.11–21.2) gonadal dysgenesis causes multiple developmental anomalies and hypermuscular appearance. Premature ovarian failure (2p21-p26) is a mutation in the follicle-stimulating hormone receptor. The cause of the dysgenesis may reside either in autosomal recessive genes or in the sex chromosomes. Mutation in the human desert hedgehog (12q12-q31.1) may lead to partial gonadal dysgenesis and neuropathy. ►H - Y

antigen, ►FSH, ►testicular feminization, ►Swyer syndrome, ►Turner syndrome, ►Smith-Lemli-Opitz syndrome, ►hermaphroditism, ►pseudohermaphroditism, ►SRY, ►SOX, ►campomelic dysplasia, ►gonad, ►hedgehog, ►sex reversal

Gonadoblastoma: A rare type of neoplasm containing germ cell, immature Sertoli-like cells, and cells resembling the granulosa cell of the ovarian follicles. Mutation in a 1–2 Mb fragment encoding the testis-specific protein (TSPY) near the centromere in the short arm of the human Y chromosome may be responsible for it. ►Frasier syndrome

Gonadotropin: A group of hormones that regulate gonadal and placental functions. ►MSAFP, ►GnRHA, ►puberty

Gonadotrophin: Same as gonadotropin.

Gonadotropin-Releasing Factor: ►luteinizing hormone-releasing factor

Gonadotropin-Releasing Hormone Agonist: ►GnRHA

Gonads: The organs of gametogenesis, such as ovary and testis. In *Drosophila*, the male gonad includes about 15, the female about 12 cells that further proliferate during embryonic differentiation, and there are 60–110 primordial germ cells by the late instar stage (see Fig. G57). In the mouse, the primordial germ cells appear seven days after mating (dpc). In the female, the primordial germ cells stop mitosis 13–15 dpc and meiosis is initiated immediately. Spermatogenesis begins 5–6 days after birth and on the 9th day proleptotene spermatocytes appear.

By day 18, haploid spermatids are formed followed by spermiogenesis. The general pattern of gonadal development is similar in mammals too, as shown in the diagram. The testes and the ovary differentiate from sex neutral structures. From the Müllerian ducts, the fallopian tube, and at its base the uterus develops, while the primitive gonad is converted into the ovary. From the Wolffian duct, the vas deferens, and at its base the seminal vesicles are formed, and the primitive gonad is converted into testis. In the drawing (for saving space) only half of the female and male sexual apparatus is shown. At the undifferentiated stage, the steroidogenic factor, SF-1, the Wilms tumor 1 Zinc-finger protein, and the homeobox gene Lim-1 are important. During the sexual differentiation stage, the Y chromosomal testis determining gene, SRY, the autosomal male sex differentiation factors SOX9, glucoprotein WNT4 (female), WT1 (male), SF-1, and a general sexual differentiation factor, DMRT1 play key roles.

Müllerian inhibitory substance inhibits testosterone synthesis in the female, whereas promotes it in the male. The Dax-1 protein (originally considered as an

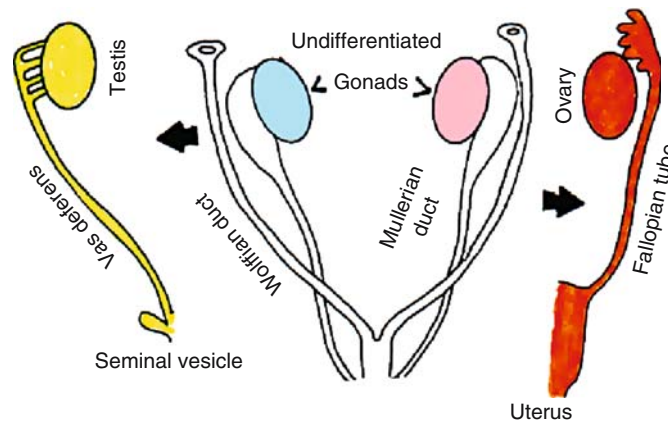


Figure G57. Gonads. The diagram was redrawn after H. Eldon Sutton & RP Wagner 1985 Genetics. A Human Concern. Macmillan, New York

ovary promoting substance) at higher dosage suppresses male development. The InsL3 protein has a role for the gubernaculum (a ligament) facilitating the descent of the testes into the testicular bag, the scrotum. Numerous other proteins are also involved.

►Müllerian duct, ►Wolffian duct, ►gametogenesis, ►cell cycle, ►germline, ►dpc, ►mismatch repair, ►sex, ►sex reversal, ►GDNF, ►puberty; Roberts LM et al 1999 Am J Hum Genet 65:933; Koopman P 2001 Curr Biol 11:R481; Mackay S 2000 Int Rev Cytol 200:47; Kobayashi A, Behringer RR 2003 Nature Rev Genet 4:969; Brennan J, Capel B 2004 Nature Rev Genet 5:509; <http://www.germonline.org/>.

Gonidia: Specialized asexual reproductive cells.

Gonioblast: A cell resulting from asymmetric division in the germline; the original stem cell gives rise by division to a new stem cell and to the gonioblast, which is destined for differentiation.

Gonochoirism: As per gonochorism, normally the species has separate male and female individuals. ►dioecious, ►hermaphrodite

Gonocytes: Progenitors of the spermatogonia. ►spermatogonia, ►gametogenesis

Gonosome: The sex chromosomes as distinct from the autosomes. ►autosome, ►sex chromosome

Gonotaxis: A genetically controlled ability of eggs or spermatozoa to be preferentially involved in the formation of a zygote. ►meiotic drive

Gonzalo of Spain: A great grandson of Queen Victoria of England who inherited from his grandmother, Beatrice, the classic X-chromosomal hemophilia gene and died by hemorrhage in an automobile accident at age 20. ►hemophilia, ►anticoagulation factors, ►Queen Victoria

Good Genes: The expression “good genes” has a double meaning: (i) genes that are advantageous for the individual or for evolution (eugenics), and (ii) genes with good penetrance and expressivity and thus facilitating analysis of their inheritance and function. ►penetrance, ►expressivity

Goodness of Fit Test: ►chi square

Goodpasture Syndrome: An autosomal recessive autoimmune reaction of the basement membrane of the renal glomeruli and the lung. The basic defect is in the α -chain of collagen type 4. Although some cases indicated familial occurrence, most likely they were exposed to similar (viral, bacterial hydrocarbon) environmental factors. ►autoimmune disease, ►collagen, ►basement membrane, ►Wegener granulomatosis; Papiris SA et al 2007 Critical Care 11:213)

GOOSE: *Anser anser*, $2n = 80$.

Gooseberry (*Ribes* spp): Tart berry fruits; $2n = 2x = 16$.

Gopher: Genetic information databases, accessible through INTERNET electronic networks. Software for gopher is free and can be obtained with FTP (file transfer protocol) by gopher@boombox.micro.umn.edu. (The name comes from a ground squirrel).

Gordon Syndrome (PHA2A, 1q31-q42): The Gordon syndrome involves hypertension and high salt concentration in the blood with normal filtration rate in the kidneys. It is also called pseudohypoaldosteronism II. Similar disorders occur at 17q21-q22 and 12p13. ►hypertension, ►pseudohypoaldosteronism, ►Liddle syndrome

Gorilla: ►Pongidae, ►primates

Gorlin-Chaudhry-Moss Syndrome: A very rare autosomal recessive craniofacial dysostosis (head malformation), excessive hairiness, heart and lung defect

(patent ductus), and hypoplasia (reduced growth) of the female external genitalia. ►hypertrichosis, ►craniosynostosis

Gorlin-Goltz Syndrome ►nevroid basal cell carcinoma

Gossypium: (cotton): A member of the *malvaceae* family of plants. Economically the most important are the long staple upland species, *G. hirsutum* ($2n = 4x = 52$) that produces 95% of the cotton fibers, and *G. barbadense*, an extra long staple (Sea Island; Egyptian) cotton (also a tetraploid), contributes about 5% of the world fiber. There are 30 diploid species. *G. herbaceum* and *G. arboreum* carry the *A* genome and are the only diploids with spinnable lint. The *B* genome is represented by North-African and Cape Verde Islands species. The *C* genome occurs in Australian diploids. *D* genome plants occur in Mexico, Peru, Galapagos Islands, and the USA. The *E* genome species occur in North Africa, Arabia, and Pakistan. The *F* genome is represented by a single African species. The new world tetraploids contain the *A* and *D* genomes. Most of the cottons are naturally cross-pollinated but tolerate inbreeding. The various genomes are distinguished primarily on the basis of chiasma frequencies and the number of univalents in the species hybrids, although some chromosome morphological differences also exist. The seed of the plants would be potentially useful for food but it contains the toxic gossypol (terpenoids), which provides protection against herbivorous insects. RNAi technology can disrupt gossypol biosynthesis in cottonseed by interfering with the expression of the δ -cadinene synthase gene during seed development (see Fig. G58). This genetic modification does not affect gossypol level in the leaves but reduces it to apparently safe level in the seeds. (Sunilkumar G et al 2006 Proc Natl Acad Sci USA 103:18504; ►terpene; <http://www.tigr.org/tdb/tgi/>).

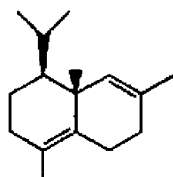


Figure G58. Cadinene

Gout: A complex hereditary disorder of the joints leading to arthritis caused by overproduction and/or underexcretion of uric acid. In one autosomal recessive gout, glucose-6-phosphatase is deficient. In the X-linked gout, hypoxanthine-guanine phosphoribosyl transferase deficiency exists (see Fig. G59). Some gout is associated with increased

turnover of nucleic acids. Autosomal dominant and polygenic forms are also known. Gout may be asymptomatic initially but at later stages the joints and the kidney may become permanently injured. (See Fig. G59). The first sign is pain in the great toe but it may spread to other parts of the foot and also to the wrists and other body parts. The prevalence may vary in different populations from 0.2 up to 10%. The serum urate level may vary from 6 to over 9 mg/100 mL serum. Generally, fewer women than men suffer from it, but in women the gout may be more severe and destructive. If the diet is very low in proteins, gout may not appear. The uric acid crystals (urate) activate the Hageman factor in the viscous fluid (synovia) of the joints that in turn sets into motion a series of events leading to inflammation. Uric acid crystals activate the inflammasome (Martinon F et al 2006 Nature [Lond] 440:237). In chickens that lack the Hageman factor or in dogs with suppressed number of leukocytes (leukopenia), the inflammatory reaction fails, indicating the role of these factors in gout attack. After the first attack, the gout symptoms apparently disappear for weeks or many months, only to return with greater strength. The chronic arthritic gout may produce ulcerating tophi (a chalky urate deposit) in the joint and may cause severe deformation of the affected area. Urates may be deposited also in kidneys, cartilage, and bone tissues. Tophi may be present at the fingertips, palms, soles, eyelids, nasal cartilages, and in the eye. Rarely, it is also observed in and on the penis, the aorta, on the heart wall (myocardium), valves, tongue, the entrance of the larynx (epiglottis), and vocal cords. Urate deposits occur in between the vertebral disks and cartilages. There is very little or any urate in the spinal cord or in the nervous system. In the kidney medulla, urate crystals may accumulate and kidney stones may be formed (lithiasis) in 20 to 40% of the affected persons. Gout is frequently associated with obesity, and hyperuricemia is common in case of diabetes mellitus. Hyperlipoproteinemia and high triglyceride levels are common in gout. Alcoholism may aggravate hyperuricemia. Serum urate levels are about the same in people of European origin, in North-American Indians, Hawaiians, Japanese, and Chinese. In some Polynesians and Australian aborigines and South-American Indians, the urate level may be higher. Overproduction of uric acid is correlated to the availability of L-glutamine and phosphoribosyl-1-pyrophosphate that are rate-limiting precursors in purine biosynthesis. Uric acid is dramatically overproduced in case of (partial) deficiency of hypoxanthine-guanine-phosphoribosyl-transferase (HPRT). Glucose-6-phosphatase and glutathione reductase also increase uric acid synthesis.

Exposure to lead may increase the occurrence of gouty arthritis due to inflammation of the kidney (saturnine gout). Starvation, Down's syndrome, and psoriasis (a skin disease causing silvery scaling and plaques) may increase uricemia. Acute attacks of gout may be successfully treated with colchicine and allopurinol, an inhibitor of xanthine oxidase. Both of these compounds may be highly toxic. Gout due to genetically determined factors is called primary gout, the secondary gout is the result of ingestion of certain chemicals and drugs. Many famous historical persons were apparently afflicted by gout: Medici, Newton, Darwin, Luther, Calvin, Benjamin Franklin, Cotton Mather (who reported plant hybrids in America in 1721), and others. Recently by the use of scanning electronmicroscopy in the mummified finger tip of the Holy Roman Emperor Charles V (King Charles I of Spain), uric acid crystals were positively identified after almost a half a millennium, explaining the cause of the illness of this powerful ruler (Ordi J et al 2006 New England J Med 355:516). His seated pose on a special chair, painted by the famous artist Titian, also supports other historical records of his debilitating affliction. ▶[Lesch-Nyhan syndrome](#), ▶[colchicine](#), ▶[antihemophilic factors](#), ▶[Hageman factor](#), ▶[inflammasome](#); Chen SY et al 2001 Metabolism 50:1203.



Figure G59. Gouty fingers

gp: In general, the abbreviation for glycoprotein; the gp is usually followed by a number.

gp: Gene of phage, e.g., the first gene of λ phage entering the capsid is *gpNu*. ▶[lambda phage](#)

GP32 Protein (of phage T4): GP32 protein is required for (i) configuration of the single-strand DNA (ssDNA) to accommodate the replisome, including DNA polymerase, (ii) to melt adventitious secondary structures, (iii) to protect ssDNA from nucleases, and (iv) to facilitate homologous recombination. ▶[replication fork](#), ▶[replisome](#)

gp39: Same as the CD40 ligand.

gp120: The HIV glycoprotein that activates B lymphocytes with receptors carrying variable heavy chain

(V_H3) immunoglobulins. ▶[HIV](#), ▶[immunoglobulins](#), ▶[B lymphocytes](#)

gp130: A ~101-kDa (without glycosylation) subunit of the interleukin 6 family receptors, encoded at 5q21. It is a signal transducer chain for IL-6, IL-11, LIF, OSM, and CNTF. ▶[interleukins](#), ▶[APRF](#); Chow D-c et al 2001 Science 291:2150.

Gp190: A ~121-kDa (without glycosylation) subunit of various cytokine receptors, encoded at 5p12-p13.

GPA: Genes of yeast homologous to G α cDNAs, involved in mammalian G-protein coding. GPA1 protein is 110-, and GPA2 is 83-amino-acid longer at the N termini than the mammalian proteins. GPA1 may be involved in mating signal transduction, GPA2 controls cAMP level. GPA1 (α subunit of G-protein) plays a negative role (growth arrest) in mating signal transduction, whereas the *STE4/STE18* (β , γ subunits) are responsible for a positive transducing signal (enhancement) for mating. ▶[G proteins](#), ▶[cAMP](#), ▶[STE](#), ▶[mating type determination in yeast](#)

GPCR (G protein-linked receptors): ▶[signal transduction](#)

G6PD: The glucose-6-phosphate dehydrogenase deficiency is responsible for one type of hemolytic anemia in humans; it is controlled by a sex-linked recessive gene (map location X28). It catalyzes the reaction $G6P + TPN^+ + H_2O \rightleftharpoons 6\text{-phosphogluconic acid} + TPNH + H^+$. ▶[Zwischenferment](#), ▶[glutathione](#), ▶[glucose-6-phosphate dehydrogenase](#), ▶[malaria](#)

GPI Anchors: Glycosyl-phosphatidylinositol cell surface-membrane proteins.

G1ps: G1 (gap 1) pre-synthetic phase (preceding S phase) of mitosis. ▶[cell cycle](#), ▶[mitosis](#)

GPR: Co-receptors of HIV and SIV. ▶[acquired immunodeficiency syndrome](#)

G-Quadruplexes: Four-stranded guanine-rich structural elements of the telomeres. G-quadruplexes may be directly involved in gene regulation at the level of transcription. In promoter regions of more than 40% of the human genes (1 kb upstream of the transcription start site), one or more quadruplex motifs exist. The promoter quadruplexes are strongly associated with nuclease hypersensitive sites. Regions of the human genome that are both nuclease hypersensitive and within promoters show 230-fold enrichment of quadruplex elements, compared to the rest of the genome (Huppert JL, Balasubramanian S 2007 Nucleic Acids Res 35:406). ▶[telomeres](#), ▶[telomerase](#), ▶[promoter](#), ▶[tetraplex](#); Parkinson GN et al 2002 Nature [Lond] 417:876.

G_q-Protein: A member of the trimeric G-protein family; activates phospholipase C- β and responds to

acetylcholine. ►G-proteins, ►signal transduction, ►phospholipase; ►acetylcholine, ►acetylcholine receptors

Graafian Follicle: Small sac-like structures on the ovary of mammals containing a mature egg (secondary oocyte). The release of the egg is called ovulation and afterwards the follicle is transformed into a corpus luteum. ►luteinization, ►corpus luteum

Gradient Centrifugation: A technique of separation of cells, subcellular organelles, and macromolecules on the basis of their density and shape by centrifugation. High-speed centrifuges may separate the larger particles while for macromolecules ultracentrifuges are used. The medium of separation may be sucrose, percol, cesium salts, etc. The material is placed on the top of the medium, which is made in various concentrations in steps; i.e., first we place in the centrifuge tube 60% sucrose, layer on top of it 40%, then 20% solutions. Alternatively, cesium salts may be used at an average density of the macromolecule. In the latter case, during high-speed centrifugation the medium forms a continuous density gradient. In either case, the material will accumulate either at the top of the step (layer) which has higher density than the substance to be separated or it will accumulate as a band in the medium that corresponds to the density of the macromolecule (DNA, ribosomes, viral particles). ►ultracentrifuge, ►buoyant density, ►DNA density

Grading Up: In the process of grading up an animal breed is repeatedly backcrossed with males of another, more desirable livestock to improve its productivity and/or quality. ►gain

Gradualism: As per gradualism, evolution is supposed to proceed by slow acquisition of adaptive mutations in the Darwinian sense. (See Darwinian evolution; punctuated evolution).

Graeco-Latin Square: An experimental design similar to the Latin Square (see Fig. G60). Three or more variates, e.g., A, B, C, each are tested under three or more different treatments, e.g., 1, 2, and 3, and the results are usually evaluated by analysis of variance. One such arrangement is shown in the box. ►Latin Square, ►analysis of variance, ►factorial experiments

| | | |
|----------------|----------------|----------------|
| A ₁ | B ₂ | C ₃ |
| B ₃ | C ₁ | A ₂ |
| C ₂ | A ₃ | B ₁ |

Figure G60. Layout of simple Graeco-Latin square

Graft: Transplantation of plant or animal tissues by surgical means.

Graft Hybrid: Chimera produced by fusion of two genetically different cells in tissues. The followers of the Mitchurin, Lysenko, and Glushchenko's group of Soviet ideologues postulated non-chimeric type graft hybrids. They referred to them also as vegetative hybrids, and claimed that grafting alters the hereditary material of both graft and scion. These claims were not reproducible by appropriate methods of experimentation, and several of the results were due either to ignorance or deliberate deception. When the mitchurinian experiments were re-examined under well-defined conditions, no acceptable evidence indicated the existence of vegetative hybridization (Stubbe H 1954 Kulturpflanze 2:185; Böhme H 1957 Ztschr Pflanzg 38:37). Certainly, viruses can be transmitted between stock and scion by grafting and this may result in an altered phenotype. But, this can hardly be considered a genetic alteration. Infection of plant (or other cells) by genetic vectors containing foreign genes can result in transgenic individuals because of the transfer of DNA. The "plastic substances" of vegetative hybridizers have no substance in the twenty-first century when all assertions need proof to become acceptable. The assertion (Liu Y 2006 Adv Genet 56:101) that doubts about graft hybridization were "squarely contradicted by a substantial body of reliable experimental evidence (Landman 1963)" is not justified in view of the experiments reviewed and the conclusions of Landman (1963 BioScience 43:696) who does not even mention graft hybridization, although he reviews old and new evidences for inheritance of acquired characters, including "epinucleic inheritance". Liu acknowledges, "Further evidence will be required to elucidate molecular mechanisms underlying graft hybridization". Unfortunately, even the data on graft hybridization are highly questionable. Linnaeus stated already in 1735 "Knowledge... built on opinion only, will not stand". Unsubstantiated findings are not just scientifically unacceptable but may be very detrimental to applications in agriculture or medicine. ►acquired characters

Graft Inheritance: ►cortical inheritance

Graft Rejection (GVHD): The manifestation and result of histoincompatibility between transplanted tissues: host-versus-graft disease. If oocytes of an individual mouse are stimulated to parthenogenetic development, histocompatible tissue can be produced (Kim K et al 2007 Science 315:482). ►cytotoxic T cells, ►HLA, ►MHC, ►mixed lymphocyte reaction, ►microcytotoxicity assay, ►therapeutic cloning, ►graft-versus-host disease, ►stem cells, ►MHC

GVHD (graft versus hoist disease): ►graft rejection

Grafting: Grafting transfers one piece of tissue or an organ from one place to another within the body or to another body. Horticulturists have practiced grafting of plants as a means of propagation. Grafted roses and other ornamentals, as well as fruit trees assure the maintenance of genetic uniformity in the grafts where multiplication by seed would produce a heterogeneous offspring because of heterozygosity at multiple loci. Some grafts are horticulturally advantageous because the rootstock may be resistant to soil-borne pests and can secure crops in more valuable varieties of *Vitis vinifera* grapes. *Vitis rotundifolia*, a wild grape stock, may be 20 fold more resistant to the *Dactylospheera vitifolii* root parasite than the standard varieties. Grafting may be used to propagate inviable plants on appropriate stocks and to study the physiological interactions between scion and stock in such complex processes as flowering response, etc. Macromolecules such as viruses may move from stock to scion through plasmodesmata. mRNA may move through the phloem and mutant phenotype may be expressed in the scion. ▶transplantation, ▶grafting in medicine, ▶graft hybrids; Kim M et al 2001 Science 293:287.

Grafting in Medicine: Grafting is practiced in modern medicine by transplanting skin, kidneys, liver, heart and other organs. Allografts are generally incompatible with the host immune system. The immune response is controlled by a large number of genes that are part of the major histocompatibility gene families. Experimental studies on tissue transplantation are carried out with inbred strains of mice (see congenic resistant). The histocompatibility genes are codominant and F_1 hybrids between different inbred lines may accept graft from both parents, whereas the two parental lines may be incompatible with each other. F_1 hybrid generally accepts grafts also from the offspring from the later generation. The incompatibility is inherited in a Mendelian manner and 3/4 of the F_2 individuals are compatible with one or the other parent and 1/4 are not. If the number of independent histocompatibility loci is (n) , $(3/4)^n$ = the number of histocompatible individuals in F_2 and in a backcross it is $(1/2)^n$. There are some confounding factors, however. Within some highly inbred lines, skin grafts from male to female may be rejected but not from female to male. This may be due to “male-specific” antigens encoded by the Y chromosome. Also, tumor tissues may be rejected when skin grafts are accepted because of tumor-specific antigens. Heterotopically (placed to a non-regular position) transferred hearts and kidneys may be accepted when skin grafts are rejected. Even apparently accepted graft may produce very low level of antibodies. Allogeneic inhibition may also occur, i.e., parental

animals fail to accept transplants from their offspring, but the offspring may accept the transfer from that parent. Most of these principles of grafting were derived from studies on inbred mice strains. Grafts have another interest for medicine with the discovery of the regenerative capacity of stem cells. ▶HLA, ▶allogeneic, ▶mixed lymphocyte reaction, ▶microcytotoxicity assay, ▶therapeutic cloning, ▶stem cells, ▶zoonosis, ▶cell therapy, ▶organ culture; Quisenberry PJ et al 2001 Ann NY Acad Sci 938:54.

Graft-Versus-Host Disease (GvH): GvH may arise when the grafted tissue damages the host because of the immune reaction. GvH may also be beneficial by eradicating the residual leukemia cells though the mediation of T cells and the HLA molecules of the major histocompatibility system. ▶graft rejection, ▶HLA, ▶TIP; Kärre K 2002 Science 295:2029.

GRAIL: A gene locator/annotation program. ▶gene prediction

Gram Molecular Weight: Grams of a compound equal to its molecular weight: mole.

Gram Negative/Gram Positive: Classification of bacteria depending on retention of the Gram stain (gentiana violet after an iodine stain, and then extracted by acetone or alcohol) (see Fig. G61). The outer membrane of the Gram-positive bacteria (stain blue-purple) does not have lipopolysaccharides but these are present in the membrane of Gram-negative bacteria (stain pink-red). The cell wall of Gram-positive bacteria contains peptidoglycans and teichoic acid. *Gram-positive bacteria: Streptococci, Staphylococci, Pneumococci, Corynebacterium, Mycobacterium, Bacillus anthracis, B. cereus, Listeria, Actinomyces, Streptomyces*, etc. *Gram-negative bacteria: Neisseria, Enterobacteriaceae (E. coli, Salmonella, Shigella), Haemophilus, Bordetella, Yersinia, Vibrio cholerae, Pseudomonas, Brucella, Proteus, Campylobacter, Legionella*, etc. ▶peptidoglycan, ▶teichoic acid



Figure G61. Gram-positive cells

Gram Stain: ▶bacteria, ▶Gram negative/Gram positive

Gramene (rice and other grasses database): <http://www.gramene.org>.

Grana (sing. granum): Dark green pile of flattened membrane vesicles (thylakoids) in the chloroplasts (see Fig. G62). ▶chloroplast, ▶chloroplast genetics

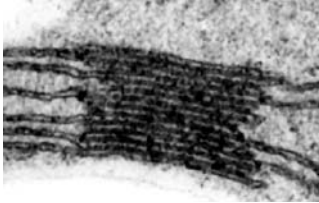


Figure G62. Granum

Grandchildless-Knirps Syndrome: In *Drosophila*, maternal effect genes cause embryonic lethality by eliminating pole cells and one or more abdominal segments. ▶morphogenesis, ▶pole cells, ▶maternal effect genes

Granddaughter Design: An analysis of genetic linkage of quantitative loci to (usually) DNA markers among the granddaughters. The markers are identified in grandsires and sons but quantitative analysis is carried on the daughters of sons. ▶QTL, ▶least squares, ▶RFLP, ▶maximum likelihood method applied to recombination; Weller JI et al 1990 J Dairy Sci 73:2525; Cappieters W et al 1998 Genetics 149:1547)

Grande: The wild type cells of yeast in comparison with the petite mitochondrial mutants deficient in respiration. ▶petite, ▶mtDNA

Granin: Calcium-binding acidic proteins (21 to 76-kDa) in the Golgi network. Their function is processing secreted proteins and they are subject to processing by converting into biologically active peptides. The granin consensus bears similarity to breast cancer gene proteins, BRCA1 and 2. ▶Golgi, ▶breast cancer; Rosa P, Gerdes HH 1994 J Endocrinol Invest 17[3]:207.

Grantham's Rule: Highly expressed genes preferentially use, from the synonymous codons, those that have a pyrimidine at the third position of the triplets. ▶genetic code, ▶codon usage, ▶synonymous codons; Grantham R et al 1981 Nucleic Acids Res 9:r43.

Grantham's Classification: Classification of amino acids on the basis of substitution frequencies in proteins, atomic weight ratio of non-C elements in end groups or rings to C atoms in side chains, polarity, and mol volume. Substitution frequencies agree much better with the chemical properties than with

the minimum base differences in their codons. Fixation of mutations involving non-similar amino acids is relatively rare. (See Grantham R 1974 Science 185:862).

Granule Exocytosis: ▶cytotoxic T cells

Granulocyte-

Macrophage Colony Stimulating Growth Factor: GM-CSF (18–30-kDa monomeric glycoprotein, encoded at human chromosome 5q21-q32) activates the cells of the granulocyte pathway. Binding of GM-CSF to its receptor dimerizes the receptor and leads to activation of the Jak-STAT pathway of signal transduction. A small nucleotide, SB 247464, may serve as a non-peptidyl inducer of the oligomerization of the receptor. It may be involved in the maturation or function of special antigen presenting cells. ▶lymphokines, ▶neutropenia, ▶signal transduction, ▶antigen presenting cell; Tian SS et al 1996 Blood 88:4435; Roth MD et al 2000 Cancer Res 60:1934; Trapnell BC, Whitsett JA 2002 Annu Rev Physiol 64:775.

Granulocytes (polymorphonuclear leukocyte): Specialized white blood cells such as neutrophils, eosinophils, and basophils. They contain numerous lysosomes and secretory vesicles (granules) and play an important role in the defense system of the animal body. ▶lysosome, ▶neutrophils, ▶eosinophils, ▶C/EBP

Granulomatous Disease, Chronic (CGD): A group of X-chromosomal (Xp21.1) recessive conditions involving chronic infections, based on defects in NADPH-oxidase subunits of the neutrophils and other phagocytotic leukocytes. If the normal enzyme is activated it generates superoxide that is converted to antimicrobial hydrogen peroxide. The 91-kDa-membrane glycoprotein, a phagocyte oxidase (gp91^{phox}, p47^{phox}, p40^{phox}, p67^{phox}), is a part of the cytochrome b system. The autosomal (16q24) recessive type is deficient in cytochrome b α -subunit (CYBA) and the neutrophil cytosol factor deficiency (NCF1) form is located in chromosome 7q11.23. A third CGD (NCF2) was assigned to 1q25. The Duchenne muscular dystrophy gene may involve CGD and several other genes have bearing on the disease. ▶neutrophil, ▶leukocyte, ▶superoxide dismutase, ▶hydrogen peroxide, ▶McLeod syndrome, ▶muscular dystrophy, ▶contiguous gene syndrome; Grizot S et al 2001 J Biol Chem 276:21627.

Granulolysin: ▶cytotoxic T cell

Granum in Chloroplasts (plural grana): The multilayered thylakoids appear as dark "grains" in the chloroplasts viewed by the light microscope. ▶chloroplasts, ▶chloroplast genetics; see photo at grana.

Granzymes: Cytotoxic T cell serine proteases and perforin responsible for apoptosis by activating the precursor (CPP32) of the protease cleaving poly (ADP-ribose) polymerase. Granzyme B is activated in T cells and in the active form cytolytic CD8⁺ T cells (CTL) destroy infecting particles. Besides Granzyme A and B, perforin is important for the action of CTLs. Granzymes cleave lamins and may be responsible for cytolysis. Granzyme A initiates mitochondrial damage leading to apoptosis (Martinvalet D et al 2005 Immunity 22:355). ▶CTL, ▶ICE, ▶apoptosis, ▶perforin, ▶caspase, ▶cathepsin, ▶lamins; Kam CM et al 2000 Biochim Biophys Acta 1477:307; Zhang D et al 2001 Proc Natl Acad Sci USA 98:5746.

Grapefruit: *Citrus paradisi*, 2n = 18, 27, 36. Grapefruit juice has beneficial dietary value because of high antioxidant content and lowering the level of blood plasma lipids (Gorinstein S et al 2005 J Agric Food Chem 53:3223). Because of furanocoumarin/bergamottin content, it may interfere with or increase intestinal absorption of several drugs (statins, antihistamines, calcium channel blockers, cyclosporin, sildenafil, multidrug transporter P-glycoproteins, etc.) and the fruit and the drugs should not be taken simultaneously or within several hours of each other. ▶bergamottin, ▶drug interaction; Romiti N et al 2004 Life Sci 76:293; Bailey DG, Dresser GK 2004 Am J Cardiovasc Drugs 4(5):281; drug interaction with grapefruit juice: Anonymous 2005 Obstet Gynecol 105(2):429.

Grapes: *Vitis vinifera*, 2n = 38; the *Muscadina* species, 2n = 2x = 40. The condensed tannins/proanthocyanidins, which are a products of the flavonoid pathway in red wines have protective effects against heart disease involving ventricular fibrillation and tachycardia (Pataki T et al 2002 Am J Clin Nutr 75:894). ▶resveratrol; diversity and history of grape wines: This P et al 2006 Trends Genet 22:511; Sandler M, Pinder R (eds) 2002 Wine: A Scientific Exploration. Taylor & Francis, London, UK; <http://mpss.udel.edu/grape/>.

Grapes, Seedless: Normal diploids but a gene prevents the division of the embryo, presumably because of shortage of hormones (stenospermocarp). ▶seedless fruits

Graph Theory: Graph theory represents metabolic or genetic networks as nodes (vertices) connected by links of edges (arcs). The graph theory has many applications, including in biology. ▶networks, ▶genetic networks; Wilson R, Beineke L 2004 Topics In: Algebraic Graph Theory, Cambridge Univ. Press, New York, Solymosi J 2005 Proc Natl Acad Sci USA 102:8075.

Grasses (cultivated for herbage): Blue grass (*Poa pratensis*) 2n = 36–123; Italian ryegrass (*Lolium multiflorum*) 2x = 14; meadow fescue (*Festuca pratensis*) 2x = 14; orchardgrass (*Dactylis glomerata*) 4x = 28; perennial ryegrass (*Lolium perenne*) 2x = 14; smooth brome (*Bromus inermis*) 8x = 56; tall fescue (*Festuca arundinacea*) x = 7, 2n = 42; timothy (*Phleum pratense*) 6x = 42. ▶gramene

Grasshoppers (*Orthoptera*): Grasshoppers are suitable objects of cytological and evolutionary investigations because of the large size and number of chromosomes. (n = 13 to 57 in males that are of XO constitution); *Melanopus differentialis* 2n = 24. The variation in chromosome number is supposed to be due to chromatin reorganization rather than to polyploidy. (See <http://www.haibei.org/brim/grashopp/look.asp>).

Gratuitous Inducer: A substrate analog of an inducible enzyme that may trigger transcription of the gene concerned, such as IPTG (isopropyl thiogalactoside) for the *Lac* operon, although it is not metabolized by the *z* gene of the operon. ▶inducer, ▶*Lac* operon; Horton N et al 1997 J Mol Biol 265:1.

Grazone: A female meiosis regulatory WD type Zinc-finger protein distantly related to Cdc20 that binds to the cortex promoter during meiosis and early embryo development. Meiosis fails when it mutates. ▶WD-40, ▶DNA-binding proteins, ▶CDC20; Harms E et al 2000 Genetics 155:1831; Chu T et al 2001 Genesis 29:141.

Graves Disease (Grave's disease): ▶goiter

Gravitropism: A tendency of plant organs such as roots to grow in the direction of terrestrial gravitation. The mechanism of this response is unclear although amyloplasts and other cytoplasmic characteristics have been suggested as possible receptor sites. ▶statolith, ▶phototropism; Kato T et al 2002 Plant Cell 14:33; Yano D et al 2003 Proc Natl Acad Sci USA 100:8589.

Gravity: Either hypo- or hypergravity may cause chromosomal damage in human cells.

Gray Crescent: A pale area in some amphibian eggs, opposite to the sperm entry; at this point will the dorsal parts be initiated. ▶dorsal

Gray Matter: A butterfly-shaped neuronal tissue of the hippocampus; it is surrounded by the axonal *white matter*. Its anomalies may lead to psychomotor retardation, seizures that are resistant to anticonvulsant therapy. Some of the hereditary infantile seizures respond dramatically to large doses of vitamin B₆ (pyridoxine). Differences in the frontal gray matter of individuals are under genetic control and increased

size appears positively correlated with cognitive abilities. ►[brain human](#), ►[neuron](#); Thompson PM et al 2001 *Nature Neurosci* 4:1253.

Gray Units: Units of ionizing radiations; 1 Gy = 100 rad absorbed dose. ►[R](#), ►[rad](#), ►[rem](#), ►[Sievert](#)

GRB (growth factor receptor-bound protein): A vertebrate adaptor protein with SH2 and SH3 binding domains; it is a downstream receptor kinase. It mediates the activation of guanine nucleotide exchange ($GTP \rightleftharpoons GDP$) on RAS, a homolog of the *Drosophila* protein DRK. ►[DRK](#), ►[signal transduction](#), ►[SH2](#), ►[SH3](#); Jahn T et al 2001 *J Biol Chem* 276:43419; Kessels HWHG et al 2002 *Proc Natl Acad Sci USA* 99:8524.

GRE (glucocorticoid receptor element): GRE is situated upstream from the TATA box gene regulatory tract. ►[backtracking](#), ►[glucocorticoid](#), ►[glucocorticoid response element](#); Herrlich P 2001 *Oncogene* 20:2465.

Greek Alphabet (with Roman counterparts): (see Table G5).

Greek-Key: A protein configuration where β -sheets are connected across the end of a barrel. ►[barrel](#)

Green Beard Effect: An idea that some unique traits are specially favored by the parents' altruistic behavior during evolution. In general, other individuals of the population, irrespective whether they carry it themselves, recognize the "green beard" gene (gene product). ►[gestational drive](#), ►[kin selection](#), ►[altruistic behavior](#); Dawkins R 1976 *The Selfish Gene*, Oxford Univ. Press, New York, Nee S 1989 *J Theor Biol* 141:81; Sinervo B et al 2006 *Proc Natl Acad Sci USA* 103:7372.

Green Processes: Green processes do not have serious environmental impacts.

Green Fluorescent Protein: ►[aequorin](#), ►[Renilla GFP](#), ►[drFP583](#)

Green Revolution: The development of new plant (cereal crop) varieties which, because of the shorter and stronger stems and improved disease resistance, permitted more intensive agricultural practices (use of higher doses of fertilizers, irrigation, etc.) and resulted in 2–3 fold increases in grain yield. (See Khush GS 2000 *Nature Rev Genet* 2:815; Evenson RE, Gollin D 2003 *Science* 300:758).

Greenberg Dysplasia: ►[hydropsectopic calcification–motheaten skeletal dysplasia](#)

Greenhouse Gases: Greenhouse gases are faulted as the main causes of global warming. Carbon dioxide and methane were thought to be primarily responsible.

Table G5. The Greek and corresponding Roman characters

| Greek | | | Roman |
|-----------|--------------------|---------|-------|
| | α | alpha | a |
| | β | beta | b |
| Γ | γ | gamma | G g |
| Δ | δ | delta | D d |
| | ϵ | epsilon | e |
| | ζ | zeta | z |
| | η | eta | e |
| Θ | $\theta \vartheta$ | theta | Th th |
| | ι | iota | i |
| | κ | kappa | k |
| Λ | λ | lambda | L l |
| | μ | mu | m |
| | ν | nu | n |
| Ξ | ξ | xi | X x |
| | \omicron | omicron | o |
| Π | π | pi | P p |
| | ρ | rho | r |
| Σ | σ | sigma | S s |
| | τ | tau | t |
| | υ | upsilon | y |
| Φ | ϕ | phi | F f |
| | χ | chi | ch |
| Ψ | ψ | psi | Ps ps |
| Ω | ω | omega | O o |

Therefore, extended forestation was believed to be able to reduce CO_2 level in the atmosphere. Now it appears that green plants produce large amounts of methane that counteracts the beneficial effects of forestation (Lowe DC 2006 *Nature [Lond]* 439:149; Keppler F et al 2006 *Nature [Lond]* 439:187). Thus, President Ronald Reagan's ridiculed remarks about plants being the cause of warming of the globe appears prescient.

Greig's Cephalopolysyndactyly Syndrome (GCPS): GCPS is dominant in the short arm of human chromosome 7p13. It involves polysyndactyly and malformation of the head without mental defects. Molecular analysis indicates that the anomaly is concerned with GLI3 oncogen, a CREB-binding

protein. The protein product of the *cubitus interruptus* locus of *Drosophila*, involved in the regulation of limb development is also a homolog. ▶[hedgehog](#), ▶[Rubinstein-Taybi syndrome](#), ▶[GLI oncogene](#), ▶[morphogenesis in *Drosophila*](#), ▶[polydactyly](#), ▶[polysyndactyly](#), ▶[Pallister-Hall syndrome](#), ▶[cubitus interruptus](#)

Grey Matter: ▶[gray matter](#)

Grid: A surface evenly lined by parallel horizontal and vertical lines, such as, e.g., in microarray slides.

GRID (general repository for protein interaction database): <http://biodata.mshri.on.ca/grid/>.

Gridding: Aligning spots on a grid. ▶[grid](#)

GRIM (gene associated with interferon-retinoic acid-induced cell mortality): ▶[interferon](#), ▶[retinoic acid](#); Zhang J et al 2003 Proc Natl Acad Sci USA 100:9342.

GRIP (glutamate receptor interacting protein): GRIP contains seven PDZ domains interacts with C end and links AMPA to other proteins. GRIP lacks catalytic functions. ▶[AMPA](#), ▶[CARM](#); van Beeren HC et al 2000 FEBS Lett 481:213.

Griscelli Syndrome: Recessive 15q21 mutation causing anomalous pigmentation and T lymphocyte and macrophage function aberrations (hemophagocytic syndrome). The basic defect is in the RAB27A guanosine triphosphate-binding protein. Defects at the same site may also involve myosin 5a, a motor protein. The former lesion involves immune defects, the latter is concerned with neurological impairment. The hypopigmentation and the immunological problems appear to be related to lysosomal defect. ▶[RAB](#), ▶[lysosomes](#), ▶[Warburg micro syndrome](#); Anikster Y et al 2002 Am J Hum Genet 71:407; Stinchcombe J et al 2004 Science 305:55.

Griseofulvin: Strong inhibitor of fungal mitosis but weak as human spindle microtubule inhibitor and displays relatively low toxicity (see Fig. G63). It has been used against ringworm infections. In human tumor cells, it blocks cell cycle progression at G2/M and can cause apoptosis and it is a potential anti-cancer drug (Panda D et al 2005 Proc Natl Acad Sci USA 102:9878).

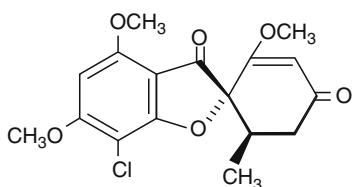


Figure G63. Griseofulvin

GRK1 (rhodopsin kinase): GRK1 is involved in the desensitization of G protein-mediated signaling. ▶[rhodopsin](#), ▶[GRK2](#)

GRK2 (G protein-coupled receptor kinase 2): GRK2 controls signaling from activated receptors to downstream effectors. (See for crystal structure: Tesmer VM et al 2005 Science 310:1686).

GRM: General regulator of mating type in yeast in cooperation with PRTF. ▶[mating type determination in yeast](#), ▶[PRTF](#)

gRNA (guide RNA): gRNA has a role in the kinetoplast, mitochondrial DNA of some protozoa. It mediates the pan edited primary RNA transcripts substantially by modified U additions or deletions but some short sequences (50–100 bases) may remain homologous to the primary transcript. These sequences are apparently anchored to the 3'-end and thus pairing may get started. Additional homology may occur in the middle (20–30 bases) and at the 5'-end (ca. 10 bases). These gRNAs may serve as templates for editing. The process requires a series of enzymatic steps. Free uridine triphosphates are the source of the Us inserted and they are added to the 3' ends generated by enzymatic cleavage. ▶[kinetoplast](#), ▶[Trypanosoma](#), ▶[Leishmania](#), ▶[RNA editing](#), ▶[pan editing](#), ▶[mtDNA](#); Müller UF et al 2001 EMBO J 20:1394; Bloom D et al 2001 Nucleic Acid Res 29:2950; Decatur WA, Fournier MJ 2003 J Biol Chem 278:695.

grow: Hamster gene activated by mitogens ▶[KC](#), ▶[N51](#), ▶[MGSA](#)

GRO α : ▶[melanoma growth-stimulating factor](#)

GroEL: A homo-tetradecameric chaperonin, composed of 57 kDa subunits of three functional domains each, arranged as a hollow cylinder of two stacked rings with seven-fold symmetry in *E. coli*. It binds to the smaller GroES molecule. GroEL and GroES are encoded in the same operon of *E. coli* (see Fig. G64). Although the information for folding resides in the primary structure of proteins, the GroEL–GroES complex facilitates the realization of this potential. In *E. coli*, ~250 proteins interact with GroEL but most of these can utilize the upstream chaperone trigger factor and DnaK for folding (Kerner MJ et al 2005 Cell 122:209). ▶[chaperone](#), ▶[chaperonin](#), ▶[protein folding](#), ▶[DnaK](#), ▶[trigger factor](#); Feltham JL, Gierash LM 2000 Cell 100:193; Farr GW et al 2000 Cell 100:561.

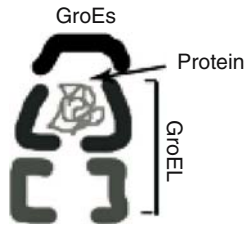


Figure G64. GroES and GroEL structure

GroES: A 10-kDa monomer. (See diagram).

G

Groucho: In *Drosophila*, groucho is a somewhat limited in scope corepressor protein responsible for extra bristles and ocelli above the eyes of the flies. It can act with Hairy, Engrailed, and Dorsal although the interacting domains in Hairy and Engrailed are different. Its mammalian homologue is TLE1 and it is structurally and functionally related to Tup1 of yeast. ▶corepressor, ▶ocellus, ▶Tup1, ▶engrailed, ▶hairy [morphogenesis in *Drosophila* {30}], ▶dorsal [morphogenesis in *Drosophila* {3}]

Groundnut (peanut, *Arachis hypogea*): About 40 – 70 species, $2n = 2x = 20$; some have higher ploidy. Some people are allergic to peanut protein that binds immunoglobulin (IgE) in the intestinal mucosa resulting in histamine release, which may cause contraction of the smooth muscles of the airways and anaphylactic reaction. It should be promptly counteracted by epinephrine to prevent serious consequences that may include death. (See Burow MD et al 2001 Genetics 159:823).

Ground State: Stable, normal, not excited form of an atom, molecule, or gene.

Group Selection: Group selection may occur when the behavior of individuals influences their own fitness and the fitness of related individuals and is selected by Nature accordingly. ▶altruistic behavior, ▶kin selection, ▶nepotism

Group Transfer Potential: Ability of a compound to donate an activated group (e.g., phosphate or acyl).

Growth: ▶cell growth, ▶growth curve, ▶exponential growth, ▶invasive growth

Growth Cone: The tip of growing axons. ▶axon

Growth Curve: Cell multiplication may start at an exponential rate under ideal conditions for proliferation, then it reaches a stationary phase (growth flattens) and only maintenance of the cell population takes place (S curve) (see Fig. G65). The exponential growth is named so because an exponent of base 2 can mathematically define the growth. Thus, after 10 divisions of a cell the expected number is 2^{10} . In case

the initial cell number was 100, after exponential growth, the number of cells 10 generations later would be $2^{10} \times 100 = 1024 \times 100$. Alternatively, growth may decline and the level of the population decreases. In higher organisms, such growth curves can be observed only in isolated cell cultures. In differentiated tissues the growth has structural limitations.

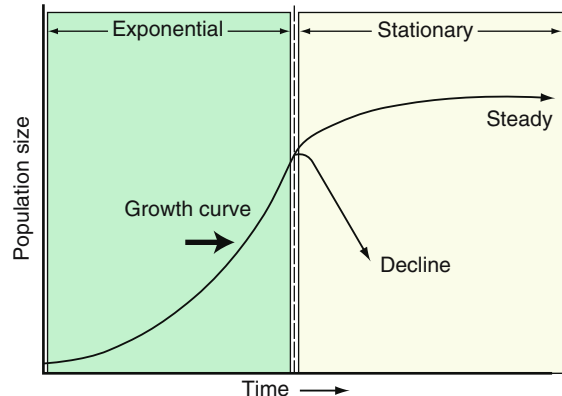


Figure G65. Growth curve

Growth Factors: ▶FGF, ▶PDGF, ▶EGF, ▶IGF-I, ▶IL-2, ▶IL-3, ▶NGF, ▶TGF, ▶erythropoietin, ▶cell cycle, ▶growth hormone pituitary, ▶brassinosteroids, ▶epidermis

Growth Hormone, Pituitary: The gene complex for the hormone is in human chromosome 17q23-q24 and encodes a 190 amino acid protein, human growth hormone (hGH), and also the somatotropin, a chorionic growth hormone (191 amino residue with ≈85% homology to hGH), and a growth hormone-like protein (GHL, 22-kDa). The expression of the hormone gene complex is regulated by the 33-kDa growth hormone transcription factor (GHF1) and growth factor response protein (GFRP1). The hGH is released by a 44-amino acid growth hormone-release factor (GHRF) encoded at chromosome 20p12. ▶pituitary dwarfism, ▶pituitary, ▶brain human, ▶secretagogue, ▶ghrelin, ▶Rowley-Rosenberg syndrome, ▶Gapo syndrome, ▶prion

Growth Hormones: Growth hormones and receptors are associated with many cellular proliferative processes and nuclear localization of the growth hormone receptors is associated with various types of cancer (Conway-Campbell BL et al 2007 Proc Natl Acad Sci USA 104:13331). ▶animal hormones, ▶plant hormones, ▶nuclear receptors

Growth Retardation: Reduction in the rate of increase in size, cell multiplication, differentiation and development. ►retardation, ►Rowley-Rosenberg syndrome, ►GAPO syndrome, ►Gombo syndrome

Growth-Associated Kinase: An M-phase histone-1 kinase, functions at its peak in mitotic M phase but its activity ebb at other phases; it is also active during meiosis. ►histones, ►mitosis

GRP: Heat shock glycoproteins of the HSP family. GrpE is itself not a chaperone but as ADP-ATP exchanges factor it is part of the DnaJ-DnaK chaperone complex of prokaryotes and the replication machinery of phage lambda. Its homologs are present in prokaryotes as well as in the mitochondria of yeast, insects, and mammals. The mammalian Grp94 (member of the Hsp90 family of proteins) chaperones are a small number of proteins and are suspected to be involved in antigen presentation and tumor rejection. ►heat-shock proteins, ►HSP, ►DnaK, ►Mge1, ►Droel, ►Hsp90, ►antigen processing and presentation, ►endoplasmic reticulum

GRP: General receptors of phosphoinositides. ►phosphoinositides

Grunstein-Hogness Screening: Grunstein-Hogness screening involves in situ lysis of bacterial colonies on nitrocellulose filters (or other membranes) and non-covalent attachment of the probe DNA to that support medium. ►Benton-Davis plaque hybridization, ►probe; Elvin P et al 1988 Br J Cancer 57:36.

G_s Protein: A stimulatory G protein; when bound to GTP it stimulates the activity of adenylate cyclase, the membrane bound enzyme, which generates cAMP. G_s has α , β and γ subunits, the GTP/GDP binding site being on the α subunit. When GDP is at the nucleotide-binding site, adenylate cyclase activity ceases. Displacement of GDP and replacement by GTP (mediated by the hormone, epinephrine) restores the active form. At this stage, the α sub-unit with bound GTP dissociates from β and γ . ►G-proteins, ►adenylate cyclase, ►signal transduction, ►oogenesis

GSC (genome structure correction): A method to adapt statistical tests to make fewer assumptions about the distribution of features on the genome sequence. This provides a conservative correction to standard tests. ►genome sequence sampling

GSC RT-PCR: ►global single cell reverse transcription-polymerase chain reaction

GSD (genetically significant dose): GSD determines the effectiveness of a mutagenic exposure. ►mutation rate, ►doubling dose, ►genetic hazards, ►genetic load, ►mutation spontaneous

GSEA (gene set enrichment analysis): GSEA detects modest but coordinate expression of groups of functionally related genes. The relevant genes are ranked according to difference in expression between two conditions of interest. The null hypothesis is that the expression is random between the two groups. The alternative hypothesis is that the rank of the affected individuals of the pathway members is associated with the diagnostic criteria used for the characterization. The extent of the association is measured by a non-parametric test. The maximum enrichment score (MES) is evaluated after random permutation of the diagnostic labels between the groups. The actual MES is then compared to the distribution of the enrichment score over all pathways tested. Subramanian A et al (2005 Proc Natl Acad Sci USA 102:15545) described an improved version and the procedure (software) is freely made available. On the basis of microarray information, the genome-wide factors involved in a pathway, e.g., leukemia or lung cancer can be predicted. ►null hypothesis, ►cluster analysis; Mootha VK et al 2003 Nature Genet 34:267.

GSH: Reduced glutathione. ►glutathione

GSK3 (glycogen synthase kinase 3 β): A protein encoded by *Drosophila* gene *zeste white* (z^{W3} , chromosome 1-1); homologous proteins are present in other animals. It is assumed that GSK is mediating a step in the intestinal polyposis carcinogenic pathway. It also regulates global protein synthesis. GSK3 β is involved in the induction of mammalian neurogenesis in embryonic stem cells targeted by 4,6-disubstituted pyrrolopyrimidine (Ding S et al 2003 Proc Natl Acad Sci USA 100:7632). GSK-3 β mediates the establishment and maintenance of neuronal polarity and its inhibitors may be suitable targets to promote the generation of new axons after neural injury (Jiang H et al 2005 Cell 120:123). Therapeutic concentration of lithium (LiCl) inhibits GSK-3 α by interfering with the γ -secretase cleavage of amyloid precursor protein (APP). GSK-3 α also phosphorylates the tau protein, the main component of the neurofibrillary tangles in Alzheimer disease. Thus GSK-3 α may control two steps in the development of Alzheimer disease (Phiel CJ et al 2003 Nature [Lond] 423:435). Levels of Akt-GSK3 β reduction appear to be a factor in schizophrenia (Emamian ES et al 2004 Nature Genet 36:131). AKT-activated GSK also regulates apoptosis. The anti-apoptotic BCL-2 family proteins control the permeabilization of the outer membrane of the mitochondria, whereas the pro-apoptotic BAX and BAK are required for permeabilization. GSK-3 phosphorylates MCL-1 (member of the BCL-2 family of proteins), leading to its degradation by the proteasome and facilitating the release of cytochrome c and apoptosis (Maurer U et al 2006 Mol Cell

21:749). ►polyposis adenomatous intestinal, ►translocation initiation, ►conductin, ►GBP, ►Alzheimer disease, ►tau, ►secretase, ►stem cell, ►AKT oncogene, ►neurogenesis, ►adipocyte, ►apoptosis, ►cleft palate, ►BCL-2, ►BAX, ►BAK, ►epiloia

GSM (genetic sexing mechanism): A method of insect control by producing translocation between the Y chromosome and the X chromosome. The Y translocation serves as a dominant selectable marker and reduces the fertility of the female. ►genetic sterilization, ►autosexing

GSMA (genome search meta-analysis): A linkage analysis procedure based on non-parametric ranking of lod scores or other recombination values. ►lod score, ►non-►parametric tests, ►meta-analysis of linkage, ►affected-sib-pair; Levinson DF et al 2003 Am J Hum Genet 73:17.

gsp: c-oncogene; its product is the α -subunit of G-proteins. ►G-, ►c oncogene

GSP: Gene-specific primer. ►directed mutation, ►c-oncogene

GSS: ►genome sequence sampling

G_{ST}: An index of genetic diversity similar to F_{ST}. (See F; Nei M 1973 Proc Natl Acad Sci USA 70:3321).

GST: ►glutathione-S-transferase

GSTB (Genome Sequence Data Bank): The GSTB maintains nucleotide sequence information on genes and clones ►GenBank; ►NCBI

GT – AG RULE (Chambon's rule): The Chambon's rule states that the first two and the last two nucleotides of introns are GT and AG, respectively; some exceptions are known. ►intron, ►exon

GTL (genome to life): A US Department of Energy project that aims to shed light on the biological mechanisms of microbes and microbial systems under dynamic conditions, in order to use the information for assisting public needs in solving problems of health and the environment. (See <http://DOEGenomesToLife.org/>).

G_t-Protein (transducin): A member of the trimeric G-protein family; it activates cGMP phosphodiesterase in photoreceptors. ►G-proteins; ►rhodopsin

GTBP (G/T mismatch-binding protein): GTBP is encoded in human chromosome 2 and its mutations lead to genetic instability at single nucleotide sites. ►mismatch, ►DNA repair, ►hereditary non-polyposis colorectal cancer

GTF (general transcription factors): Proteins that are required for the initiation of transcription by RNA

polymerase I (TFIs), RNA polymerase II (TFIIs), and RNA polymerase III (TFIIIs). ►transcription factors

GTP: Guanosine triphosphate (see Fig. G66).

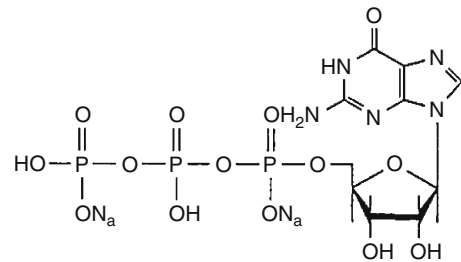


Figure G66. GTP

GTPase: ~60 proteins mediating the conversion of GTP into GDP. These enzymes regulate translation, signal transduction, cytoskeletal organization, vesicle transport, nuclear import, and protein translocation across membranes, etc. Two different GTPases may modulate each other's activity. ►RAS, ►RAC, ►RHO, ►RAB, ►RAN, ►RASA, ►dynamins, ►Arf, ►GAP, ►GEF, ►SAR, ►G proteins; Yang Z 2002 Plant Cell 14:S375.

GTPase-Activating Protein (GAP): GAP increases GTP hydrolysis to GDP by several orders of magnitude in signal transduction. ►signal transduction

GTP Binding Protein Superfamily: The GTP binding protein superfamily includes transitional factors, transmembrane signaling proteins, Ras proteins, and tubulins. ►signal transduction, ►E region of GTP-binding proteins

GTP Cyclohydrolase Deficiency (14q22.1-q22.2): The recessive deficiency of guanosine triphosphate cyclohydrolase I results in hyperphenylalaninemia because tetrahydrobiopterin is not converted into dihydroneopterin triphosphate by a process requiring GTP. The disorder involves low urinary pterines, serotonin, and dopamine levels. The afflicted individuals show convulsions, muscular hypotonia of the trunk but hypertonia of the limbs. Oral L-erythro-tetrahydrobiopterin may alleviate some of the symptoms. ►phenylalanine, ►hyperphenylalaninemia, ►pteridines, ►biopterin, ►serotonin, ►dopamine, ►hypotonia, ►hypertonia

Guam Disease: An autosomal dominant complex syndrome displaying the characteristics of amyotrophic lateral sclerosis, Parkinsonism, and dementia, and discovered in Guam. Environmental conditions such as a low calcium and magnesium in the diet and consumption of the Cycas plants seem to favor toxic metal accumulation in the central nervous

system and appears to favor the onset. ►neurodegenerative diseases

Guanidinium Chloride: Guanidinium chloride is used in molecular genetics similarly to guanidinium isothiocyanate for isolation of undegraded RNA. ►RNA extraction

Guanidinium Isothiocyanate: Guanidinium isothiocyanate is used for the isolation of RNA. It breaks up cells, dissociates nucleoproteins, and inactivates tough RNase enzymes (at 4 M solutions) in the presence of the reducing agent β -mercaptoethanol. ►RNA extraction

Guanine: The purine base in DNA and RNA (see Fig. G67). ►glycosylases

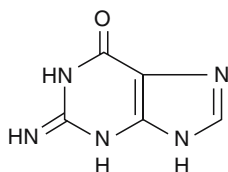


Figure G67. Guanine

Guanine Methyltransferase: The guanine methyltransferase methylates the mRNA cap. ►cap

Guanine Nucleotide Binding Protein (16q13, 6q21.3, 20q13.2, 7q21, 22q11.2, 1p13, 3p21, 19p13): The guanine nucleotide binding protein mediates signal transduction on G proteins.

Guanine Nucleotide-Exchange Protein (11p23.3, 19q13.3): The guanine nucleotide-exchange protein catalyze the reaction $GTP \rightleftharpoons GDP$. The large Rho family of G proteins generally contains a Dbl (MCH2) domain and a pleckstrin homology (PH) domain. ►G protein, ►MCH2, ►Rho, ►brefeldin

Guanine Nucleotide Releasing Protein (GNRP, 11q13): GNRP hydrolyzes GTP, bound to G proteins, into GDP. ►signal transduction

Guanosine: The nucleoside of guanine.

Guanosine Tetraphosphate, Guanosine Penta

Phosphate (ppGpp, pppGpp): ppGpp and pppGpp are effectors of the stringent response. ►stringent response; Chatterji D, Ojha AK 2001 Curr Opin Microbiol 4:160.

Guanylate Cyclase: Guanylate cyclase mediates the formation of cyclic guanosine monophosphate, cGMP.

Guanylic Acid: Guanine nucleotide.

Guanylyl Transferase: Guanylyl transferase attaches GTP to the mRNA cap. ►cap, ►GTP

Guard Cell: ►stoma

Guard Hypothesis: The guard hypothesis postulates that the requirement for a specific protein to activate the plant resistance gene when it encounters an avirulence gene of a pathogen and it guards against the suppression of the plant defense mechanism by any bacterial effector.

Guava (*Psidium guajava*): Subtropical, tropical, small, allogamous fruit tree; $2n = 2x = 22$.

Guessmer: Usually 30–7-base long synthetic oligonucleotides representing limited degeneracy and using neutral bases (inosine) at sites of ambiguity. The nucleotide sequence is generated on the basis of information of amino acid sequences in the protein. This label can be used for screening for specific coding sequences (genes). If the codons would be picked at random, the synthetic sequence would represent at least 76% homology by chance, but by considering codon usage of the organism, the homology may be over 90%. The probes are labeled with the aid of polynucleotide kinase or primer extension with the Klenow fragment. ►probe, ►primer extension; O'Farrell PA et al 1997 Biochem Biophys Res Commun 239:810.

Guest Peptide: ►CD tagging

Guest RNA: ►CD-tagging

Guest Tag: ►CD-tagging

Guide RNA: Guide RNA chaperones the alignment of splicing by attaching either to the intron or to the exon sequences of the transcript. ►RNA editing, ►gRNA, ►intron, ►splicing; Kabb AL et al 2001 Nucleic Acids Res 29:2575.

Guillain-Barré Syndrome: A sporadic or familial autosomal dominant. It is a de-myelinating neuropathy arising after infection by *Campylobacter jejuni*. ►Campylobacter

Guillardia: A filamentous alga.

Guinea Pig: *Cavia porcellus*, $2n = 64$ (see Fig. G68).



Figure G68. Guinea pig

Gunther Disease: ►porphyria (erythropoietic porphyria, 10q25.2-q26.3)

GURT: ► **T-GURT**

GUS: The tetrameric glycoprotein acid hydrolase, β -glucuronidase enzyme (gene) is frequently used as a reporter for the in vivo testing of promoters, identifying site-specific expression, or monitoring the excision of transposable elements. Several substrates of the enzyme are useful for releasing a blue color upon activity of GUS. Deficiency of the enzyme in mammals leads to lysosomal storage diseases. ► **lysosomal storage diseases**, ► **gene fusion**, ► **reporter gene**, ► **aging**; Jefferson RA et al 1987 EMBO J 6:3901; Schenk PM et al 2001 Plant Mol Biol 43:399.

Gustatory: “Gustatory” refers to something involving the sensation of taste. ► **taste**

Gustducin: ► **taste**

Gut: The gastrointestinal tract or the developmentally primitive (early) digestive tract composed of fore-, middle-, and hindgut sections. The mammalian gut endoderm forms different ‘buds’ giving rise to the liver, lung, pancreas, thyroid, and gastrointestinal tissues. The developmental fates are determined by the additional growth factors recruited. The microbial flora (10 to 100 trillion microbes/gut) has important function in gastrointestinal health and disease, and substantial variations exist in these populations among individuals (Eckburg PE et al 2005 Science 308:1635; Bäckhead F et al 2005 Science 307:1915). ► **microbiome**, ► **oral bacterial films**

Guthrie Test: Guthrie test detects phenylketonuria because if the blood contains phenylalanine, the analog β -2-thienylalanine does not interfere with the growth of *Bacillus subtilis*. ► **phenylketonuria**, ► **genetic screening**

Guthrie Cards: Guthrie cards are used for genetic testing/screening of newborns—from dry blood samples—for about 30 hereditary disorders.

Gutless/Gutted Vector: Usually a viral vector without nearly any viral gene, which would have been required for viral replication. Such vectors require helpers for trans-complementation and propagation. ► **HDAd**

Guttation: In the process of guttation, water ascending through the xylem vessels of plants may drop from the leaves when relative humidity increases. ► **transpiration**, ► **cohesion-tension**

Guttmacher Syndrome (preaxial deficiency, postaxial polydactyly and hypospadias, 7p15-p14.2): A special hand-foot-genital syndrome, apparently due to mutation in the HOXA13 gene. ► **polydactyly**,

► **hypospadias**, ► **hand-foot-genital syndrome**; Guttmacher AE 1993 Am J Med Genet 46:219.

GVG: A transcription factor constructed of the yeast GAL4 DNA-binding domain, the trans-activation domain of herpes virus VP16, and the hormone-binding domain of the glucocorticoid receptor. ► **galactose utilization**, ► **VP16**, ► **glucocorticoid response elements**, ► **dexamethasone**

GW Body (GWBs): 182-kD proteins characterized by multiple glycine (G)-tryptophan (W) repeats and an RNA recognition motif that binds messenger RNAs and have a role in mRNA degradation (Eystathiou T et al 2003 RNA 9:1171).

GWA (genome-wide association, GWAS): GWAS uses mapping linkage to the level of expression across a genome(s). The analysis may involve various markers, including single-nucleotide polymorphism, and determines the regression of the markers and the trait of interest (Evans DM, Cardon LR 2006 Trends Genet 22:350). Statistical and computer programs are now available for studying the association between known phenotypes and molecular biology markers (Pearson JW et al 2007 Amer J Hum Genet 80:126). This relatively new approach is less expensive for the analysis of complex traits than direct genotyping although it may be adversely affected by microarray-based errors (McGregor S 2007 Eur Hum Genet 15:501). A GWA study of British populations in 2007, including 2,000 individuals for each of seven major diseases and a shared set of 3,000 controls, identified 24 independent association signals at $P < 5 \times 10^{-7}$: one in bipolar disorder, one in coronary artery disease, nine in Crohn’s disease, three in rheumatoid arthritis, seven in type 1 diabetes, and three in type 2 diabetes. The information indicates that this is a new powerful approach for understanding human pathophysiology (Nature [Lond] 447:661). ► **QTL**, ► **genotyping**, ► **microarray hybridization**, ► **human subjects privacy protection**; US federal guidelines concerned with GWA: <http://grants.nih.gov/grants/gwas/index.htm>; privacy protection: Lowrance WW, Collins FS 2007 Science 317:600.

Gy: Gray units of radiation; 1 Gy = 100 rad. ► **rad**

Gy: Billion years of geological time.

Gymnosperm (*Coniferophyta*): Plants with seeds, which are not enclosed in an ovary. Typical representatives are the pine trees ($2n = 24$).

Gymnothecium: The fruiting body of some ascomycetes fungi; it may cause skin infections. ► **perithecium**, ► **cleistothecium**, ► **ascogonium**

Gynander: Same as gynandromorphy, *Drosophila* gynandromorph image from Morgan T et al 1925 Bibliographia Genetica 2:1.

Gynandromorph: Sex mosaic (part male/part female); same as gynander. They are the result of the loss one of the X-chromosomes during development of *Drosophila* and other organisms where the XO chromosomal constitution leads to the development of male phenotypic characteristics (see Fig. G69). The loss of the X-chromosome reveals the recessive alleles present in the remaining homolog. These sex mosaic individuals can be exploited for fate mapping. The right side of the diagram of the fly shows male characteristics and has a ruby eye because the left sector is X0. The left side depicts like female (XX). ▶fate mapping, ▶lyonization, ▶variegation; Szabad J, Fajsz J 1982 Genetics 100:61.

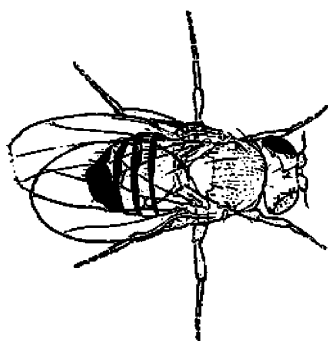


Figure G69. Gynandromorph

Gynecomastia: Increased development of the mammary gland of males caused either by estrogen accumulation and/or reduction of testosterone (see Fig. G70). Deficiency of a gene encoding hydroxysteroid dehydrogenase III (9q22) and increased expression of the cytochrome P450 (CYP, 15q21.2) aromatase subunit may be responsible for pseudohermaphroditism and gynecomastia. X-linked inheritance with male transmission has also been suggested. A transient mild form may not be abnormal during puberty. Several statues of the young pharaoh, Tutankhamen (fourteenth century BC), reveals bilateral gynecomastia and the somewhat bloated stomach suggests the likelihood of celiac disease (see Fig. G71). Gynecomastia can be corrected by plastic surgery (Yavuz M et al 2006 Ann Plast Surg 57 [4]:370). ▶pseudohermaphroditism male, ▶Klinefelter syndrome, ▶Kennedy syndrome, ▶animal hormones, ▶steroid dehydrogenase/ hydroxysteroid dehydrogenase, ▶aromatase; black and white photo showing a young male with gynecomasty on one side of his chest; photo by courtesy of Dr. C. Stern.

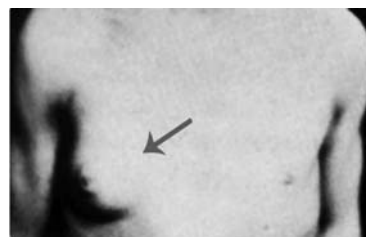


Figure G70. Gynecomastia



Figure G71. Tutankhamen

Gynodioecious: A gynodioecious population consists of both hermaphroditic and female individuals, and is generally determined by nuclear and mitochondrial genes. ▶hermaphrodite; Taylor DR et al 2001 Genetics 158:833.

Gynoeceum: The carpels and structures enclosed by them in flowers. ▶fruits; Ferrándiz C et al 1999 Annu Rev Biochem 68:321.

Gynogenesis: Reproduction by parthenogenesis, i. e., the sperm does not fertilize the egg but stimulates the cleavage of the unreduced egg (pseudogamy). Also, embryos developed by transfer of male pronuclei into the egg, and thus diploid are called *gynogenones*, in contrast to *parthenogenones* (gynogenotes), which arise from parthenogenesis. ▶apomixis, ▶parthenogenesis, ▶androgenesis, ▶EP

Gypsy: A somewhat diverse ethnic group migrating from the Indian subcontinent north and southward, presumably before the ninth century, to Asia and to Egypt, and from there to most of the northern hemisphere, although they are now found all over the world. Their Indian origin is asserted by orally transmitted legends. Linguistic evidence indicates Sanskrit roots. Y chromosomal and mtDNA information

support Indian origin. Their ethnic identity has been preserved by cultural and genetic isolation. Haldane JBS (1935) used ABO blood type frequencies to show that the Hungarian Gypsies are more closely related to some Eastern Indian populations than to that of Hungary although some of them lived in that country since the early fifteenth century. They prefer to be called Roma. ► [ethnicity](#); Kalaydjieva L et al 2001 Eur J Hum Genet 9[2]:97; Gresham D et al 2001 Am J Hum Genet 69:1314.

Gypsy Retroposon: ► [copia](#), ► [insulator](#)

Gyrase: A DNA topoisomerase II that reverses the direction of coiling in DNA, resulting in negative supercoiling. ► [DNA replication](#), ► [transcription](#), ► [supercoiling](#), ► [topoisomerase](#); Gellert M et al 1979 Proc Natl Acad Sci USA 76:6289; Kirchhausen T et al 1985 Cell 3:933; Williams NL, Maxwell A 1999 Biochemistry 38:13502.

G

Historical vignettes

“William Curtis, British botanist, described a weed called *Arabidopsis thaliana* as having ‘no particular virtues or uses’. More than 200 years later, he could not have been proved more wrong.”

The Guardian, UK, quoted after Jane Alfred, Editor of Nature Rev. Genet. 2001, 2:86.

Herman N Eisen 2001 in Annu. Rev. Immunol. 19:1

“...the self-correcting character... is inherent in the scientific enterprise. This aspect of science seems at times to be utterly incomprehensible to journalists, politicians, and the public at large—as I was to find out painfully many years later...”

H

H: A heavy chain of a double-stranded DNA.

H1, H2A, H2B, MacroH2A, H3, H4: H1 and H5 are variants of H1 histones. ► [histones](#)

h (Planck constant): An energy quantum of radiation that relates it to the frequency of the oscillator that emitted it. $E = h\nu$ where E is the energy quantum, ν is its frequency, numerically 6.624×10^{-27} erg/sec.

h: Also indicates the human homolog of a gene or protein standing in front of the symbol.

H-2: The major histocompatibility gene cluster in the mouse is located to chromosome 17, proximal to the centromere within a segment of about 1.3 cM consisting of about 2,000 kb DNA. They encode cell surface glycoproteins that have a major role in recognition and immune response to foreign antigens. The gene order in this cluster encoding Class I, Class II and Class III and Class I-like polypeptides is:

K-A-E-C2-Bf-SLP-OH-C4-TNF-D-D2-D3-D4-L-Q-T-T1a-centromere. The transplantation antigens are the Class I proteins coded for by genes K, D and L. The Class II proteins, encoded by genes A and E, occupy the surface of B and T lymphocytes and the macrophages and participate in cell immune responses. The Class III proteins coded for by genes C2, Bf, SLP, OH, and C4 are the complement proteins of the serum involved in the lysis of foreign material after the recognition by the antibody. The Q and T loci determine the so-called differentiation antigens present in the blood cells. TNF is the tumor necrosis factor gene. ► [HLA](#), ► [antibody](#), ► [lymphocytes](#), ► [TNF](#); Fischer K et al 1997 Annu Rev Immunol 15:851.

h²: The symbol of heritability; it is derived historically from Sewall Wright's definition of heritability as the ratio of the standard deviations of the additive and phenotypic variances, $h^2 = V_A/V_P$. Heritability is not a squared entity, and h^2 stands for heritability and not for its square. More at ► [heritability](#), ► [correlation](#), ► [offspring-parent regression](#), ► [intraclass correlation](#), ► [heritability estimation in humans](#)

H Test: An H test defines, statistically, the effect of hitchhiking on the evolution of genomes. H is the average difference between θ_π , which is based on the average frequency of heterozygosity and influenced most by the average intermediate frequency variants, and $\hat{\theta}_H$, which is influenced mainly by the average high-frequency variants. Under neutrality the

expected difference between the two estimators of θ is zero, but following the hitchhiking event $\hat{\theta}_H$ and $\hat{\theta}_w$ (the total number of segregating sites) should be $>\theta_\pi$. ► [hitchhiking](#); Fay JC, Wu C-I 2000 Genetics 155:1405.

H Value Paradox: The H value paradox expresses the tendency of homology across a genome and it may indicate a late specific expansion after losing some of the evolutionarily ancestral genes. ► [C value paradox](#), ► [N value paradox](#); Petrov DA 2001 Trends Genet 17:23.

HA: ► [hemagglutinin](#)

HAART: Stands for highly active antiretroviral therapy.

Habitat: An area in nature where an organism(s) occur(s) naturally. ► [source habitat](#), ► [sink habitat](#)

Habituation (accoutumance à l'auxine, anergie à l'auxine): Plant tissues, after prolonged culture, may dispense of the continued reliance on exogenous auxins for proliferation. This alteration does not involve somatic mutation yet it bears similarity to oncogenic transformation. In animal cells, the SV40 T antigen loss after a period of time still may not cease proliferation in the absence of the oncoprotein. ► [tissue culture](#), ► [somatic mutation](#), ► [transformation oncogenic](#), ► [tumor](#), ► [oncoprotein](#), ► [SV40](#); Gautheret RJ 1955 Rev Gen Bot 62:1.

Habrobracon: ► [wasp](#)

Habsburg Lip: The protruding lower lip and the undershot lower jaw were transmitted among male and female members of this European dynasty up to the twentieth century. The coin shown here represents Maximilian I (1459–1519) (see Fig. H1). (See Thompson EM, Winter RM 1988 J Med Genet 25:838).



Figure H1. The Habsburg lip on a coin of Maximilian I

HAC (hyperpolarization activated channels): ► [I_h](#)

HAC (human artificial chromosome): Critical elements (telomeres, centromeres, and replicator) must be present. HACs can eventually be used to ferry

desirable genes to human cells for medical purposes. A useful human artificial chromosome should be much smaller than the smallest chromosome in the natural genome in order to transfer genes into human cells, yet it should be big enough to carry large human or mammalian genes and some regulatory sequences. Minichromosomes of ~4 Mbp appear stable but those below 2.5 Mbp seem unstable. The useful HAC is expected to be stable through mitosis and possibly even through meiosis. This requires a minimal functional centromere and telomeres. The centromeric DNA (α -satellite) is variable in length in the different human chromosomes but in order to function may have to comprise ~150 kbps. It should not incite an adverse immunological reaction in the recipient cell. For experimental manipulation it is desirable that the HAC be easily transferable to any type of cell, including, e.g., yeast cells. ▶**YAC**, ▶**BAC**, ▶**PAC**, ▶**human artificial chromosome**, ▶**minichromosome**, ▶**MAC**, ▶**HAEC**, ▶ **α -satellite**, ▶**DT40**, ▶**vectors**; Henning KA et al 1999 Proc Natl Acad Sci USA 96:7125; Shen MH et al 2000 Curr Biol 10:31; Csonka E et al 2000 J Cell Sci 113(18):3207; Mejia JE et al 2001 Am J Hum Genet 69:315.

HAC1: A basic leucine zipper protein; is a transcription factor that binds to the UPR element in the promoter of the UPR genes. ▶**unfolded protein response**

H/ACA Box: Nonprotein-coding RNAs, which include small nucleolar RNAs (snoRNAs), small Cajal body-specific RNAs (scaRNAs), and a homologous class of RNAs in archaeal organisms. Typical box H/ACA RNA exhibits a common hairpin-hinge-hairpin-tail secondary structure with the H (ANANNA) motif in the single-stranded hinge region and an ACA triplet located 3 nucleotides upstream of the 3' termini. The majority of known H/ACA RNAs play important roles in the posttranscriptional modification of rRNAs and snRNAs. H/ACA snoRNAs direct the conversion of uridine to pseudouridine at specific residues of eukaryotic ribosomal RNAs and Pol III-transcribed snRNA U6, whereas H/ACA scaRNAs guide the formation of Pol II-transcribed spliceosomal nuclear RNA. Some H/ACA RNAs process ribosomal RNAs. In humans, 100 H/ACA RNAs have been identified, and most of which are located within the introns of protein-encoding genes. Retrotransposition seems to have played a pivotal role in the mobility and diversification of H/ACA RNA genes. In the human genome 202 sequences derived from box H/ACA snoRNAs (Luo Y, Li S 2007 Nucleic Acids Res 35: 559). ▶**noncoding RNA**, ▶**snoRNA**, ▶**Cajal body**, ▶**pseudouridine**

Hae II: A restriction enzyme with recognition site
 $\begin{array}{c} \text{A} \\ \text{G} \end{array} \text{GCGC} \downarrow \begin{array}{c} \text{T} \\ \text{C} \end{array}$

Hae III: A restriction enzyme with recognition site GG↓CC.

HAEC (human artificial episomal chromosome): The HAEC was constructed by using the replicational origin of the Epstein-Barr virus. Such a construct may carry over 300-kb inserts and may be maintained in human cells without integration (as an episome) in the genome. ▶**Epstein-Barr virus**, ▶**episome**; Wade-Martins R et al 2000 Nat Biotechnol 18:1311.

Haem: Iron-porphyrin; occurs in different forms (see Fig. H2). Chlorophyll contains Mg porphyrin. ▶**heme**, ▶**chlorophyll**

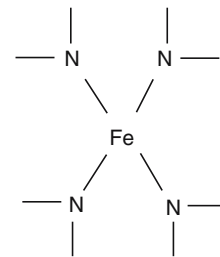


Figure H2. Heam

Haematopoietic Growth Factor: ▶**IL-3**

Haematoxinil: ▶**hematoxylin**

Haemochromatosis: ▶**hemochromatosis**

Haemophilus influenzae: Gram-negative bacterium and an early object of genetic transformation. The first free-living organism completely sequenced by 1995. Its genome includes 1,830,137 bp. (See Fleischmann RD et al 1995 Science 269:496).

Hailey-Hailey Disease (HHD, benign pemphigus): An autosomal dominant skin disease involving vesicle formation generally on the neck, groin, and armpits. The benign disease is precipitated by infection by the fungus *Candida albicans*, but antifungal, antibacterial drugs may also initiate it. Mutation in an ATP-powered ion pump sequestering calcium into the Golgi apparatus causes HHD. ▶**skin diseases**, ▶**pemphigus**

Hair: The human hair has a high- and a low-sulfur protein; the former is about 40% of the hair proteins. In some animal hairs a high-tyrosine protein also occurs. Hair develops from multipotent clonogenic keratinocytes, which are similar to multipotent stem cells. Hair follicle progenitor cells are maintained in an undifferentiated state by the transcription factor Lhx2 (Rhee H et al 2006 Science 312:1946). Regeneration of lost hair follicles was considered unlikely. After wounding of mouse skin, in the presence of functional *Wnt* gene de novo follicle formation occurs from epithelial cells (Ito M et al

2007 Nature [Lond] 447:316) promising new approaches to treating hair loss in mammals. ▶hair color, ▶hair whorl, ▶alopecia, ▶hypotrichosis, ▶hypertrichosis, ▶baldness, ▶De Lange syndrome, ▶glomerulonephritis with spare hairs, ▶hairy ears, ▶hairy elbows, ▶hairy nose, ▶hairy palms and soles, ▶hair-brain syndrome, ▶catenins, ▶keratin, ▶widow's peak; Fuchs E et al 2001 Develop Cell 1:13; Jave-Suarez LF et al 2002 J Biol Chem 277:3718; Tumber T et al 2004 Science 303:359; Fuchs E 2007 Nature [Lond] 445:834.

Hair Color in Humans: Strikingly blond and red hair colors (prevalence about 2% or less) appear to be autosomal recessive but the latter may have some expression in the heterozygotes. Red hair is hypostatic to brown and black. Brown hair appears to be autosomal dominant and it is closely linked to green eye color. Dark hair appears to be dominant. The babies' first hair may not be concordant with that of later years. The relative proportions of the reddish pheomelanin and the black eumelanin pigments determine the hair color. Their level is controlled by the melanocyte stimulating hormone (MSH) and its receptor (MC1R). Environmental factors (temperature, sunshine, diseases) may also affect transiently the color. Graying of the hair is usually preceded by aging, however, precocious graying may be determined by dominant genes and it may be a symptom shared by several syndromes such as the Waardenburg and the Werner syndromes; pernicious anemia (a vitamin B12 deficiency) may also cause it. Graying in the aged is caused by defective self-maintenance of the melanocyte stem cells (see Fig. H3). Pax3 and Mitf (positive regulator of tryptophan and tyrosinase transcription) molecules balance melanocyte stem cell maintenance and differentiation (Steingrimsdottir E et al 2005 Cell 121:9). In case of deficiency of the anti-apoptotic Bcl2, the process is greatly accelerated (Nishimura EK et al 2005 Science 307:720).

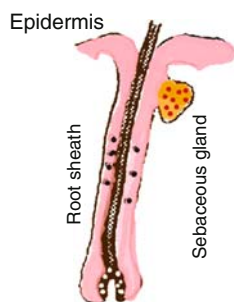


Figure H3. Hair follicle. The black circles are melanocyte stem cells. The white spots are mature melanocytes. The sebaceous gland lubricates the hair.

Actually, the inheritance of human hair is determined by many loci. In human chromosome 19 alone there are 6 loci homologous to fur color genes of the mouse. ▶pigmentation in animals, ▶forelock white, ▶albinism, ▶melanin, ▶aging, ▶hypostasis, ▶BCL2, ▶Pax; Sturm RA et al 1998 Bioessays 20 (9):712; Flanagan N et al 2000 Hum Mol Genet 9:2531; Healy E et al 2001 Hum Mol Genet 10:2397.

Hair Whorl: May be clockwise, that is autosomal dominant over counterclockwise rotation. Hair pattern is controlled by the *frizzled 6* gene and homologs, which are receptors of the *Wnt* gene. ▶hair, ▶wingless; Guo N et al 2004 Proc Natl Acad Sci USA 101:9277.

Hair-Brain Syndrome (trichothiodystrophy, BIDS): A condition characterized by autosomal recessive brittle hair, low intelligence, short stature, reduced fertility and reduced cystine-rich protein in the hair and nails. ▶hair, ▶stature, ▶trichothiodystrophy

Hairpin: A double-stranded structure in nucleic acids brought about by folding back of palindromes like a hairpin. At the end, where the arrow is pointed → C, the unpaired structure may be digested by S₁ single-strand-specific nuclease. ▶S₁ nuclease, ▶palindrome, ▶pseudohairpin

Hairy Ears: Hairy ears (see Fig. H4) occur primarily in the male humans and have been thought to be due to Y-chromosomal (holandric) gene(s) or to two genes in the homologous segments of the X and Y chromosomes. Most likely it is determined by autosomal dominant factors and sex-influenced inheritance. ▶sex-influenced, ▶holandric genes. [Photo is courtesy Dr. Curt Stern.]



Figure H4. Hairy ear

Hairy Elbow: An autosomal dominant hairiness on the elbows associated with short stature. ▶hair

Hairy Nose: Autosomal dominant (?) hairs on the nose tip; onset after puberty in the male only. ▶hair

Hairy Palms and Soles: Apparently autosomal dominant, male transmitted, site-specific hairiness. hair.

Hageman Factor: A protein (M_r ca. 80,000) present in the blood plasma and serum of the majority of mammals, but absent in dolphins, killer whales and birds. It is involved in the blood coagulation pathway; it also affects vascular permeability, dilates blood vessels, contracts smooth muscles, provokes pain, promotes the migration of leukocytes, induces fibrinolysis (dissolution of fibrin), etc. ▶[antihemophilic factors](#), ▶[Hageman trait](#); Schousboe I et al 1999 Thromb Haemost 82:1041; Gaffney PJ et al 1999 Haemostasis 29:58.

Hageman Trait: The Hageman trait is controlled by an autosomal recessive gene causing deficiency of the Hageman factor in the blood. Normally, the individuals lacking this factor do not show any disease symptom although blood coagulation is slow in the laboratory. No therapy is required, yet, in case of surgery, it is advisable to keep at hand appropriate blood or plasma. ▶[Hageman factor](#)

Haldane's Mapping Function: $(1 - e^{-m}) 0.5 = y$ (recombination fraction), where m is the number of exchanges, e is the base of the natural logarithm. Hence, $(1 - e^{-m}) = 2y$, and $e^{-m} = 1 - 2y$ and $m = -\ln(1 - 2y)$ and the corrected map distance estimate is $x = m/2$ because each exchange produces maximally 50% recombination. This formula does not take into account interference and thus frequently overestimates map distances. The graph (see Fig. H5) permits reading directly the recombination frequencies corrected by Haldane's mapping function.

Different organisms may require different mapping functions (Stahl FW Genetic recombination, Freeman, San Francisco, California). ▶[Kosambi's mapping function](#), ▶[mapping functions](#), ▶[recombination frequencies](#), ▶[mapping genetic](#), ▶[coefficient of coincidence](#)

Haldane-Muller Principle: The seriousness of the consequences of a mutation is not its deleterious effect because a dominant lethal mutation is eliminated immediately, but its probability of death. Thus moderately disadvantageous mutations may be maintained for many generations and in each generation they may adversely affect the fitness and eliminate a number of individuals. ▶[genetic load](#)

Haldane's Rule: When, in the F_1 offspring of two different animal races, one sex is absent, or sterile, that sex is the heterogametic one. The cause is not an imbalance between autosomes and sex-chromosomes, rather it is due to the somewhat general fact that lethality is usually completely recessive whereas deleterious mutations may show a series of less debilitating effects that may also be expressed in heterozygotes. Another interpretation in some species is the "the faster male" theory, i.e., the sex-specific, male fertility genes evolve faster than those responsible for female fertility. It has been suggested that the reduction in the heterogametic class is due to sex transforming genes. This mechanism may play some but apparently insignificant role. Another interpretation pointed to dosage compensation, which may

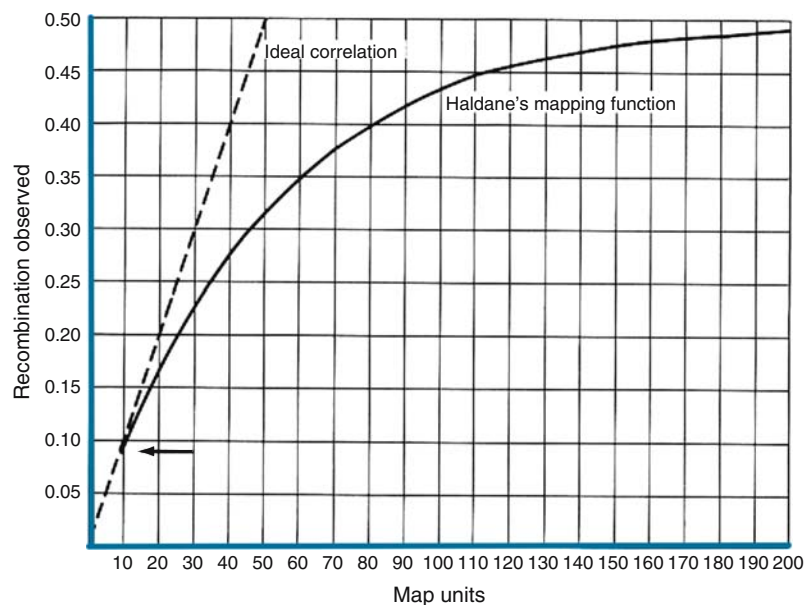


Figure H5. Read the point of intersection between the recombinant fraction observed (ordinate) line and the solid line curve corresponding to the mapping function and project the point to the bottom line representing map units. For example, 0.3 recombination corresponds to about 45–46 map units. (After Haldane JBS 1919 J Genet 8:299)

break down in crosses between distantly related species. This interpretation is contradicted by the fact that Haldane's rule is observed in the ZW sex determination system albeit dosage compensation is not evident. Furthermore, in mammals, the X chromosome inactivation in the females ►[Lyon hypothesis](#) and the hypoactivation of the X chromosome in the hermaphroditic *Caenorhabditis* are kinds of female dosage compensation. X-Y and Y-Autosome incompatibilities may account, to some extent, for the sterility of species hybrids but not for their viability. Meiotic drive has also been invoked as a possible cause without general acceptance. There are some examples of cytoplasmic effects, independent of heterogamety, although they may affect heterogametic individuals ►[segregation distorter](#), ►[infectious heredity](#). With rare exceptions, Haldane's rule is generally valid. ►[sex-chromosomes](#), ►[sex determination](#), ►[hybrid inviability](#), ►[hybrid sterility](#); Haldane JBS 1922 J Genet 12:101; Laurie CC 1997 Genetics 147:937; Naisbit RE et al 2002 Genetics 161:1517.

Half-Chromatid: A half-chromatid involves only one of the strands of the DNA double helix in the chromatid. The expression of mutation is delayed by one division if it occurs in a half-chromatid and it may result in somatic sectors after replications. chromatid.

Half Conversion: In yeast the tetrad contains 2 *A*, 1 *a* and 1 *A/a* heteroduplex sectorial spores. ►[gene conversion](#)

Half-Life: In general, half-life is the time required for the decay of one half of a compound; the decay, e.g., of a promutagen or procarcinogen may lead to the formation of an even more active mutagen and/or carcinogen. The half-life of H^3 and C^{14} is 12.4 and 53,700 years, respectively, and that of P^{32} 14.3, P^{33} 25.4 and I^{131} 8, I^{125} is 60 days respectively. The half-life $T_{1/2} = 0.693/\lambda$, and λ = the characteristic disintegration constant for the specific isotope. The radioactivity is gradually decreasing by time and the correlation between the number of half-lives passed and the chart (see Fig. [H6](#)) shows the amount of radioactivity still remaining. The mean and median half-life of 3,751 proteins of yeast was ~43 min but in 161 unstable proteins it was only ~4 min (Belle A et al 2006 Proc Natl Acad Sci USA 103:13004).

►[evolutionary clock](#), ►[isotopes](#), ►[radiocarbon dating](#), ►[mRNA](#)

Half-Mutant: Half-mutant is a Hugo de Vries' term for the new types that arose relatively frequently in *Oenotheras* with translocation rings. The half-mutants produced normal (translocation-ring) and sterile progenies due to recombination between the differential segment and its homolog in another chromosome within the ring resulting in smaller rings and other chromosomal changes. When the non-crossover original translocation ring was recovered in the egg and sperm, the offspring was the same as the original complex heterozygotes. ►[complex heterozygote](#)

Half-Sibs: Half-sibs share only one biological parent; they are half-sisters or half-brothers. ►[sibling](#)

Half-Tetrad Analysis: Tetrad analysis is feasible in a limited number of organisms where the four products of meiosis can be separately recovered either as a tetrad or, after a post-meiotic division, as an octad, a phenomenon common in ascomycetous fungi. In *Drosophila*, half-tetrad analysis can be carried out in the presence of attached X chromosomes (See Fig. [H7](#)). In this case, the products of meiosis have either two attached X chromosomes or are nullisomic for the X chromosome. X-chromosomal genes are inherited as a block unless recombination takes place. Flies heterozygous for attached X-chromosomal genes can become homozygous only after crossing over and producing two different nonparental gametes from a single meiocyte. This type of recombination provided the first direct evidence that genetic recombination takes place at the 4-strand stage of meiosis.

Half-tetrad analysis has been adapted to a plant (*Medicago*) case using four RFLP markers in situations when restitution nuclei were observed at a high frequency. Three of the markers were linked (chromosome 1) and the fourth was independent (chromosome 6). The analysis permitted the localization of the centromere. Trisomics may also be used for half-tetrad analysis. Molecular analysis of individual secondary oocytes by PCR may also reveal gene positions. ►[tetrad analysis](#), ►[gene-centromere distance](#), ►[attached X chromosomes](#), ►[restitution nucleus](#), ►[disomic](#); Nullisomic, Zhao H, Speed, T.P. Genetics 150:473.

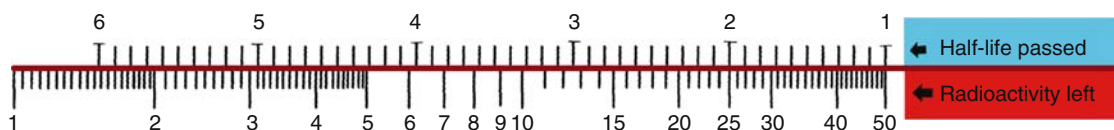


Figure H6. Half-life. The chart depicting the correlation between the number of half-lives passed and the amount of radioactivity that still remains

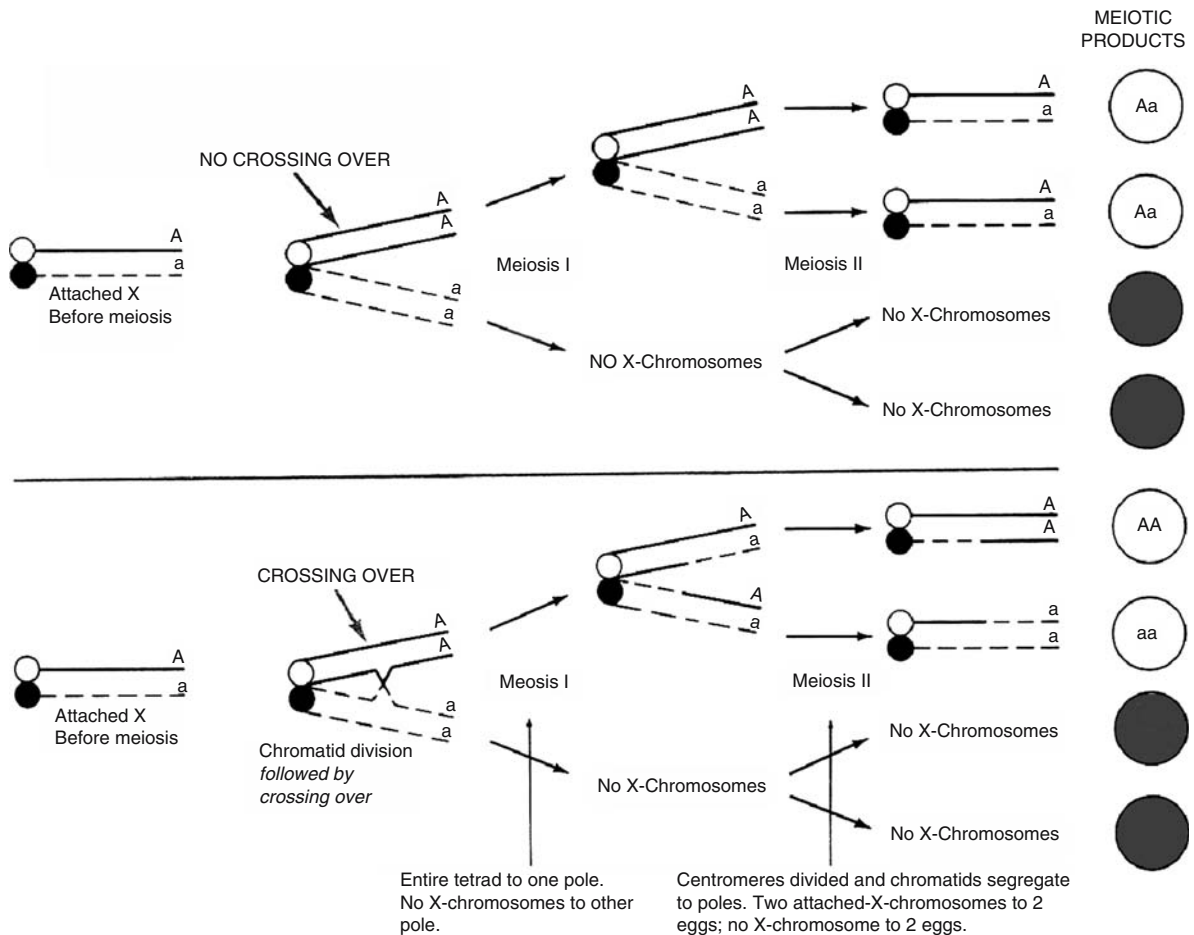


Figure H7. Half-tetrad analysis in *Drosophila*. Because the centromeres of the attached x chromosomes are stably fused, they cannot pass to opposite poles during anaphase I. Segregation of the chromatids is equational at anaphase II. Instead of four viable meiotic products, only two X-disomic and two lethal, nullisomic gametes are formed. If the two attached chromosomes carry different alleles, all the non-crossover gametes will be the same and only the crossovers will be of two nonparental types. (After Shult EE, Lindegren CC 1959 Can J Genet Cytol 1:189)

Half-Translocation: A half-translocation is the half of an original reciprocal translocational event. Such a situation occurs, e.g., when a presumably reciprocal interchange takes place between the proximal region of an X chromosome and the small 4th chromosome of *Drosophila*, but one of the translocated strands is not recovered because it gets lost during segregation of chromosomes into the functional gamete. ▶[translocation chromosomal](#)

Half-Value Layer: The half-value layer reduces the transmission of radiation to half.

Hallermann-Streiff Syndrome: Characteristics include, most likely, an autosomal recessive bird-like face, long, narrow nose, cataracts, sparse hairiness, occasionally

teeth by birth and proportionate dwarfism. ▶[dwarfs](#), ▶[tooth](#)

Hallervorden-Spatz Disease (neuroaxonal dystrophy): Human chromosome 20p12.3-p13 located recessive brain atrophy accompanied by involuntary movement and early death. The brain accumulates iron in the basal ganglia probably due to defects in the panthotenate kinase gene. ▶[Lewy body](#), ▶[synuclein](#), ▶[ferritin](#); Zhou B et al 2001 Nat Genet 28:345.

Halophyte: A salt-tolerant or salt-resistant plant species.

Halo Assay: A substance is placed at a spot to a microbial culture plate and inhibition of growth or reverse mutations appear as a circle around the spot (see Fig. [H8](#)).

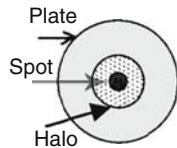


Figure H8. Halo assay

Halothane Gene: The halothane gene controls malignant hyperthermia syndrome in pigs (in chromosome 6). Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) is an anesthetic applied by inhalation. ►PSE

Haltere (singular), **Halteres** (plural): Halteres are balancing organs. *Ultrabithorax* (*Ubx*) controls haltere size by restricting *Decapentaplegic* (*Dpp*) by increasing the amount of *Dpp* receptor, *thickveins* (Crickmore MA, Mann RS 2006 Science 313:63). (See Fig. H9; ►morphogenesis in *Drosophila*).

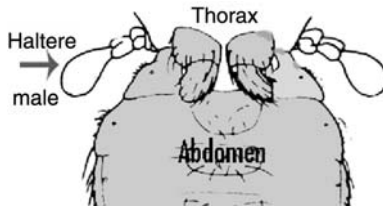


Figure H9. Haltere

Halvorson 5: A nutrient concentrate for yeast g/L $(\text{NH}_4)_2\text{SO}_4$ 20, K_2HPO_4 43.5, succinic acid 29, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 1.99, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 5.11, *trace elements* 5 mL [containing mg/0.5 L $\text{Fe}_2(\text{SO}_4)_3$ 307, MnSO_4 280, $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$], pH 4.7. This medium is usually diluted five times.

HAMA (human anti-mouse antibody): A human antibody response against murine monoclonal antibodies. The HAMA complexes are usually rapidly cleared from the human body and may incite allergic reactions or even anaphylactic shock. Engineered rodent antibodies may overcome the problems. Human antibodies are better because they are compatible with the complement system and ADCC. ►monoclonal antibody, ►complement, ►ADCC, ►humanized antibody

Hamartin: ►epiloia

Hamartoma: A tissue overgrowth (of darker color).

Hamiltonian Path: A directed graph if and only if there is a sequence of a one-way path beginning with *vin* (vertex in) and ending at *vout* and enters every other vertex exactly once. This mathematical method may serve the basis for designing a molecular (DNA)

computer that may assist in developing very complex combinatorial approaches to manipulating macromolecules, e.g., designer enzymes. ►DNA computer, ►RNA computer; Liu Q et al 2000 Nature [Lond] 403:175.

Hamilton's Rule: ►inclusive fitness

Hammerhead: ►ribozymes

HAMP Domains (histidine kinases, adenylyl cyclases, methyl-accepting chemotaxis proteins and phosphatases): HAMP domains are in the C-terminal end of transmembrane segments. HAMP occurs in thousands of proteins connecting extracellular sensing with intracellular signaling. It operates with signal transduction. ►signal transduction; Hulko M et al 2006 Cell 126:929.

Hamster: *Cricetulus griseus* (Chinese [gray] hamster) $2n = 22$; *Mesocricetus auratus* (Syrian [golden] hamster), $2n = 44$.

Hand Clasping: Some authors claimed that it is genetically determined whether the left- or right-hand fingers (the latter more common among females) are on top when hands are clasped. The control may be autosomal dominant or polygenic. ►handedness

Handcuffing: The products of plasmid replication associated with *incA* and *incC* (incompatibility factors of replication) that cause antiparallel pairing of the two DNAs preventing replication until the "handcuffs" are disrupted. (See Chatteraj DK 2000 Mol Microbiol 37:464).

Handedness: About 93% of the human population is right-handed; left-handedness is higher among younger age groups than in the older age groups indicating greater longevity of right-handed individuals. Right-handedness most frequently is associated with clockwise orientation of the hair whorls on the scalp. Lefties and ambidextrous individuals display either clockwise or counterclockwise hair swirls. The inheritance of handedness is unclear; it was attributed to polygenic control (2p12-q11, Francks C et al 2003 Am J Hum Genet 72:499), and it has been suggested that it is due to a homozygous recessive state, the heterozygotes being ambidextrous (able to use both hands with equal facility). In *Arabidopsis*, left-right asymmetry of leaf twisting is controlled by the intradimer interface of α -tubulins 4 and 6 (Thitamadee S et al 2002 Nature [Lond] 417:193). (See Klar AJS 2003 Genetics 165:269).

Hand-Foot-Genital Syndrome (Hand-Foot-Uterus syndrome, HFU, 7p15-p14.2): A rare condition with dominant malformations of hands, feet, fingers, toes, vaginal septum and uterine anomalies in girls, hypospadias in boys, common infections of the

urinary tract, and other variable symptoms. The mutation affects a HOXA13 gene. ►[hypospadias](#), ►[homeotic genes](#), ►[Guttmacher syndrome](#)

Hand-over-Hand Model: One way that motor proteins may move along microtubules. The two-headed kinesin may move ahead by alternative steps of its two heads and thus exchanging leading and trailing roles ►[kinesin](#), ►[motor protein](#), ►[microtubule](#); Asbury CL et al 2003 Science 302:2130.

Hanging Drop Slide: The material to be examined microscopically hangs from the cover slip into the concavity of the slide in a drop of a solution (see Fig. H10).

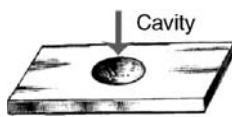


Figure H10. Hanging drop slide

Hap: A positive control protein of transcription (46 kDa), attached to one or two sites in the DNA. It generally associates with heatshock protein70 (Hsp70). Its murine homolog is BAG-1.

Haplodiploidy: In some social insects (Hymenoptera), the males (drones) are haploid (because they develop from unfertilized eggs) whereas the females (queen and workers) are diploid (because they hatch from fertilized eggs). Consequently, usually full sisters (progeny of a single mating) are more closely related to each other and less closely related to their brothers than to their daughters and sons. In the wasp, *Bracon hebetor*, the females are normally heterozygous for genes of sex determination. Inbreeding in such populations may result in homozygosity of the sex-determining genes and male diploidy. In *Nasonia vitripennis* there is a “selfish” supernumerary chromosome, PSR (paternal sex ratio chromosome). When PSR males produce offspring with normal females only haploid males occur because the paternal chromosome set, except the PSR chromosome, is eliminated. When PSR males mate with triploid females the offspring becomes diploid males. In *Nasonia* females can develop from unfertilized eggs and these are haploid (Beukeboom LW et al 2007 Science 2007 315:206). ►[sex determination](#), ►[complementary sex determination](#); Smith NG 2000 Heredity 84(2):186; Bordenstein; SR et al 2003 Genetics 164:223.

Haplogroup: A group of haplotypes which share some sequence variation. ►[haplotype](#)

Haploid: A haploid contains only a single complete set(s) of chromosomes ►[monoploid](#). The gametes are haploid; the meiotic products of polyploids are often called *polyhaploid*. Many of the fungi are haploid during most of their life cycle, except after fusion of the nuclei in dikaryotes preceding meiosis. ►[meiosis](#), ►[fungal life cycle](#). Haploid individuals among diploids show up spontaneously at low frequency. Haploid lines are very rare in animals *although* haploid frog cell lines have been used in cultures. In the spider mite *Brevipalpus phoenicis* most of the populations are haploid females caused by infection by the bacteria *Cytophaga-Flavobacterium-Bacteroides*. Once antibiotics cure the females of the bacterium they are converted to male individuals (Weeks AR et al 2001 Science 292:2479). The spontaneous frequency of haploids varies among different lines of the same species. A high frequency of haploids occurs in crosses involving the wild barley, *Hordeum bulbosum*, and certain wheat varieties crossed with the grass *Aegilops caudata* (*Triticum dichasians*). Wheat pollinated by maize also yields haploid wheat. In these crosses one of the genomes (e.g., *H. bulbosum*) is eliminated at high frequency. Haploid plants have been obtained in many species in an artificial culture of immature pollen or microspores and anthers. The microspores can be cultured without separation from the anthers, although separation of the pollen sacs may improve their development because the anther walls may contain growth inhibitors. From these haploid cells haploid plants can be regenerated. Successful embryogenesis is generally easier if the cultures are initiated at the uninuclear stage of the microspore. Haploid plants may actually be obtained through two different routes from microspores: either by so called *direct androgenesis* when the haploid male cells are guided through embryogenesis directly or, alternatively, through indirect androgenesis wherein the haploid initial cells can be converted to callus and from the callus plants are generated. The latter procedure is less desirable because during callus growth, spontaneous chromosome doubling and other types of chromosomal anomalies frequently occur. If the microspores are exposed to colchicine or other agents that block the mitotic spindle, chromosome doubling may be induced. Haploid cell cultures have great advantages for mutation studies because all the recessive mutations are detectable without the masking effect of the dominant alleles at the loci. Similar advantages are available in the use of hypoploid animal cell cultures, such as derived from XY males where X-chromosomal genes are present in a single dose or, e.g., in the culture of Chinese hamster ovary cells (CHO) when individual chromosomes are spontaneously be eliminated. Although

effective screening methods are available in animal cells (BUdR, antibiotic, temperature), regeneration of animals from isolated cells cannot be accomplished in culture, except from stem cells or via nuclear transplantation. Haploids may have a great advantage in plant breeding work because by doubling the chromosome numbers, in a single step, 100% homozygosity results. Ordinarily, by self-fertilization or inbreeding 6 to 8 cycles result in only 98 to 99% homozygosity ($0.5^6 \cong 0.0156$ heterozygosity). S.S. Chase developed a successful method for selective isolation of haploid maize. Female flowers, recessive for several markers and easily recognizable in the kernels, are pollinated by the corresponding dominant stocks (*A*, *B*, *Pl*, *R*). Kernels that fail to show the paternal markers in the endosperm are discarded because they originated by unintended selfing. The seedlings displaying the dominant paternal markers are also discarded because they are most likely diploid. The true haploids thus arise from fertilization of the endosperm nucleus by the dominant sperm, but the egg that develops into an embryo without fertilization yields seedlings with maternal traits only (thus haploid). After doubling their chromosome number, homozygotes are obtained. Some caution may be required in critical studies because through spontaneous mutation some variations may arise in these otherwise completely homozygous lines. Haploidy may also be induced by pollination with heavily irradiated pollen or pollen damaged by other means. Some genotypes display a proclivity for spontaneous androgenesis. ►androgenesis, ►apomixis, ►anther culture, ►embryo culture, ►embryogenesis somatic, ►selective medium, ►antibiotic resistance, ►bromouracil, ►conversion, ►doubled haploid, ►sex determination; Hall DW 2000 Genetics 156:893.

Haploidization: The reduction of the chromosome number to the haploid level.

Haploid-Specific Genes: Haploid-specific genes are turned on in response to mating factors (yeast). The responding consensus is 50 bp upstream of the translation initiation site. ►mating type determination in yeast, ►consensus, ►upstream, ►translation

Haplo-Insufficient: The gene in a single dose (such as in hemizygotes) cannot assure its normal function and may even be lethal. Haplo-insufficiency may also lead to tumorigenesis or to disease by reduced ability of tumor suppression or genetic repair. ►Turner syndrome, ►DiGeorge syndrome, ►Waardenburg syndrome, ►familial hypercholesterolemia, ►Chotzen syndrome, ►polycystic kidney disease, ►hemizygous ineffective, ►PCR-mediated gene replacement

Haplontic: During most of its life the organism is haploid. ►haploid

Haplopappus gracilis: A composite plant with only two pairs ($n = 2$) of good-size chromosomes. Due to self-incompatibility genes, its culture is somewhat inefficient.

Haplotype: A set of genes in each chromosome of the genome inherited ordinarily as a block. (The term was most commonly used in immunogenetics.) Originally, it represented the haploid set of genes of the MHC (multiple histocompatibility) antigens. It is generally assumed that individual genes within a haplotype would display collinearity with homologous genes of other haplotypes of the same species. This expectation may not be valid, however, since it has been shown that, e.g., at and around the *bz* locus of maize substantial nucleotide heterogeneity occurs (Fu H, Dooner HK 2002 Proc Natl Acad Sci USA 99:9573). ►HLA, ►SNIPs, ►association test, ►linkage disequilibrium, ►hapmap; Gabriel SB et al 2002 Science 296:2225; <http://www-gene.cimr.cam.ac.uk/clayton/software/>.

Haplotype Analysis: A haplotype analysis infers the relative position of genes and DNA markers by assuming a minimum number of crossing overs along the chromosome. Haplotype analysis may be very useful for the identification of human disease genes. ►crossing over, ►linkage disequilibrium; Daly MJ et al 2001 Nat Genet 29:229; Johnson GC et al 2001 Nat Genet 29:233; Ding C, Cantor CR 2003 Proc Natl Acad Sci USA 100:7449.

Haplotype Blocks: An average of ~5,000 to ~20,000 base pair segments of the genome are preserved by lack of recombination. These blocks display characteristic variations within populations or species groups. About 50% of the haplotype blocks are preserved in the populations of the three main continents (Europe, Asia and Africa). About 72% are shared in Europe and Asia but in Africa 28% of the blocks are limited in occurrence to certain geographic regions.

Human populations in Africa display the greatest and most unique variation. The analyses of the blocks reveal evolutionary and demographic histories. Recombinational hot spots are found at the boundaries of these blocks (Pääbo S 2003 Nature [Lond] 421:409). The linkage disequilibrium is high in the large human haplotype blocks while it is low in the short ones. Using SNP markers their association with disease factors can determine functional polymorphism by appropriate algorithms (Zhang K et al 2003 Am J Hum Genet 73:63). Large human data sets indicate that some regions conform well to the haplotype block concept, others do not because there is an extensive variation in recombination rates across the genome (Wall JD, Pritchard JK. 2003 Am J Hum

Genet 73:502). ►association map, ►HapMap, ►hot spot, ►linkage disequilibrium, ►SNIPs

Haplotyping: Haplotyping is the determination of the genotypic constitution of a haplotype. ►haplotype

HapMap: The HapMap is based on haplotype patterns of SNIPs. The goal is to find connections between single nucleotide polymorphism haplotypes and disease, and possibly a response to therapeutics. There are two approaches: (i) the direct approach which seeks a correlation between the disease and putative variations, and (ii) the indirect approach that wishes to establish an association between particular genomic regions and a particular disease. Approach (ii) is more practical and it detects variants of candidate genes and chromosome regions across the genome. Also, the indirect analysis reveals that most of the variants occurred in, and were preserved from, the ancestral chromosome where the mutation occurred. In the SNIPs (displaying an average frequency of 0.1%), either a C or T most commonly occurs at a particular site. In the human genome at an estimated 10 million sites both of these alleles (C and T) occur at higher than 1% frequency. These common SNIPs constitute 90% of the variations in the human populations. The mutation rate per a particular site is about 10^{-8} . Only about 10^4 generations have elapsed since any two humans separated from the most recent common ancestor and there is a high chance that the neighboring alleles in the ancestral chromosomes are still preserved in this haplotype. Such conservatism is present despite recombination and additional mutations during the course of evolution. As a consequence, few carefully chosen SNIPs (*tag SNIPs*) can identify the most relevant haplotypes. These common SNIPs are apparently older than the rare ones and by virtue of linkage disequilibrium are shared among populations. Such studies will be carried out among different ethnic groups with careful consideration to individual and group sensitivities. HapMap DNA samples can be used to select SNIPs tags for genome-wide association studies in many samples around the world. The tags picked from the HapMap DNA samples capture rather well the variation in other samples too (de Bakker PIW et al 2006 Nature Genet 38:1298). ►haplotype analysis, ►association mapping, ►SNIPs, ►PAF, ►Perlegen Sciences; Carlson CS et al 2003 Nature Genet 33:518; Cardon LR, Abecasis GR 2003 Trends Genet 19:135; The International HapMap Consortium 2005 Nature [Lond] 437:1299; HapMap use for defining human variations: Kruglyak L 2005 Nature Genet 37:1299; Conrad DF et al 2006 Nat Genet 38:1251; <http://www.hapmap.org/>; <http://hapmart.hapmap.org/BioMart/martview>.

Happiness: Happiness is most likely genetically determined because the correlation between monozygotic and dizygotic twins was found to be 0.44 and 0.08, respectively. It has been suggested that happiness may be determined by the D4 dopamine receptor and unhappiness is related to the control of serotonin metabolism. ►dopamine, ►serotonin

HAPPY (haploid genome equivalent and polymerase chain reaction): HAPPY is an in vitro method of mapping DNA fragments. The fragments are generated from genomic DNA by irradiation and classified by size with the aid of pulsed-field gel electrophoresis. The fragments are distributed into a 96-well panel. The panel members are amplified by PCR and then screened for specific new STS markers. LOD scores test co-segregation. The procedure is very efficient. The disadvantage of the methods—which may later be overcome—is that the pre-amplification of the genomic DNA results in new STS markers. These STS markers are flanked by interspersed repeat elements and are thus not identical to known STS markers and reflect the distribution of interspersed repeats rather than the standard maps. (►STS, ►PCR, ►lod score, ►pulsed field gel, ►radiation hybrids; Dear PH, Cook PR 1993 Nucleic Acids Res 21:13; Walter G et al 1993 Nucleic Acids Res 21:4524; Dear PH et al 1998 Genomics 48:232).

Happy Puppet Syndrome: An abandoned, derogatory name of the Angelman syndrome. ►Angelman syndrome

Hapsburg Lip: ►Habsburg lip

Hapten: A small molecule that, in association with a protein (carrier), can act as an antigen. Alone, haptens are only antigenic but not immunogenic. The hapten-carrier is the basis of the immune response to the complex. ►antigen, ►immune system, ►affinity labeling, ►affinity maturation; <http://bioinformatics.charite.de/superhapten/>.

Haptoglobin: A mammalian serum protein composed of two α and two β chains. The $\alpha 1$ chain contains 84 amino acids and differs from the $\alpha 2$ chain which is nearly double in size in the presence of the Hp^2 allele due to a duplication in an intercalary segment, presumably brought about by an unequal crossing over event during its evolution. The $\alpha 2$ chain occurs only in humans and it is thus most likely to be of relatively recent origin. This protein is attached to hemoglobin and has a role in recycling heme. The HP gene was located to human chromosome 16q22. A number of electrophoretic variants have been identified. The frequency of the gene responsible for the $\alpha 1$ chain varies a great deal in ethnic populations.

►globin, ►hemoglobin, ►plasma proteins, ►unequal crossing over

Haptotaxis: The movement of cells is determined by the concentration gradient of a cell adhesion molecule.
►CAM

Hard Disk: A permanently sealed disk of the computer; it operates faster than floppy disks and has a large capacity. ►disk

Hard Heredity: Inheritance determined by permanent genetic material such as DNA and RNA, rather than the diffuse hypothetical gemmules, pangenes, etc., hypothesized before the acceptance of Mendelian genetics. ►Mendelian laws, ►pangenes, ►gemmules, ►soft inheritance

Harderoporphyria: A variant form of coproporphyria where the relative amount of excreted coproporphyrin is less in favor of the other intermediate in heme biosynthesis, harderoporphyrin. ►coproporphyria, ►porphyria; Lamoril J et al 2001 Am J Hum Genet 68:1130.

Hardware: Hardware constitutes physical equipment such as the computer machine. ►software

Hardy-Weinberg Equilibrium: The genotype and gene frequencies remain constant from generation to generation because there is random mating between individuals and neither selection nor mutation or migration affect the composition of the population.
►Hardy-Weinberg theorem

Hardy-Weinberg Theorem: For one allelic pair $p^2 + 2pq + q^2$ where p is the frequency of the dominant and q is the frequency of the recessive allele ($1 - p$). If the genotypic frequencies are available, the allelic frequencies can be derived because the two types of homozygotes have two copies of the alleles concerned whereas the heterozygotes have one of each. In the case of three alleles at a locus, such as in the ABO blood group, the frequency of the i^O recessive allele is $r = \sqrt{\frac{O}{N}}$. Since the combined frequencies of i^O and I^A is $r^2 + 2pr + p^2$ the frequency of the i^A allele is $p = \sqrt{\frac{A+O}{N}} - r$, and therefore the frequency of the allele, by subtraction, becomes $q = 1 - p - r$. O, A, and B are the actually observed numbers of the representatives of the blood groups and N is the population size. In the case of trisomy the various possible genotypes will be given by $(p_1A_1 + p_2A_2)^3$ after the expansion of this binomial. It is often critical for human genetic analysis to estimate accurately the possible deviation from the Hardy-Weinberg equilibrium. An exact stratified test for diallelic markers, such as single-nucleotide polymorphisms (SNPs), and an exact test for homogeneity

of Hardy-Weinberg disequilibrium is available. Applying these methods to data from Perlegen and HapMap—a combined total of more than five million SNP genotypes, with three to four strata and strata sizes ranging from 23 to 60 subjects—this exact stratified test provides more robust and more powerful results than those obtained by either the minimum of exact test P values over strata or approximate stratified tests that sum measures of departure from equilibrium (Schaid DJ et al 2006 Amer J Hum Genet 79:1071). ►allelic frequencies, ►ABO blood group, ►HapMap, ►Perlegen sciences, ►stratification

Hare: *Lepus americanus* $2n = 48$; *Lepus townsendii* $2n = 48$ (see Fig. H11).

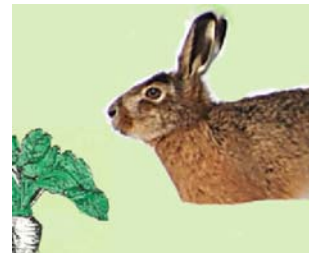


Figure H11. *Lepus europaeus*

Harelip: A hereditary cleft of the upper lip (see Fig. H12). The maxilla (upper jaws) and palate (the partition of the oral and nasal cavity) may also be affected. The incidence in the general population varies between 0.04 to 0.08% and the recurrence risk among brothers and sisters is about 0.2%. It is somewhat more common among males than females. Harelip is a sex-influenced trait. Haploinsufficiency for SUMO1 leads to harelip and cleft palate in mouse (Alkuraya FS et al 2006 Science 313:1751). ►cleft palate, ►sex-influenced, ►haploinsufficient, ►SUMO; Van der Woude syndrome, [photo after RJ Gorlin, Univ. Minnesota].



Figure H12. Harelip

Harlequin Fetus: ►Ichthyosis

Harlequin Staining of Chromosomes: The Harlequin staining of chromosomes results in different coloration of sister chromatids as the result of one or two

cycles of replication in the presence of the nucleoside analog 5-bromodeoxyuridine (BrDU). The chromatids replicated in the presence of BrDU absorb less of the fluorescent stain Hoechst 33258 than the chromatid that has replicated in the presence of thymidine. On a black and white photo negative, the chromatid free of BrDU appears lighter and darker in the print than the one that incorporated BrDU. Thus, chromatids containing one, two or no BrDU can be distinguished. Therefore, such a staining permits the detection of sister-chromatid exchange. ▶[sister chromatid exchange](#), ▶[bromouracil](#); Rachel AJ et al 1991 *Mutation Res* 264:71; Jordan R et al 1999 *Biotechniques* 26:532.

H

Hartnup Disease (11q13): An autosomal recessive disorder involving photosensitivity, rash, cerebellar ataxia (impaired muscle coordination by the brain), and aminoaciduria (see Fig. [H13](#)). The uptake of methionine and tryptophan and, to some extent, of other neutral amino acids by the intestines is reduced. It is diagnosed by urine analysis for increase in neutral amino acids. Its prevalence is about 4×10^{-5} . ▶[tryptophan](#), ▶[light-sensitivity diseases](#), ▶[ataxia telangiectasia](#); photograph from Bergsma D ed 1973 *Birth Defects*, March of Dimes Foundation.



Figure H13. Hartnup disease

Harvest Index: The harvest index refers to proportion of the economically and directly usable productivity of crops, e.g., grain versus straw. It has also been defined as the ratio of dry weight of the harvestable organs to the total dry weight.

Harvey Murine Sarcoma Virus (transformation gene): The Harvey Murine sarcoma virus was originally derived from rats and it is found to encode a 21-kDa oncoprotein (p21) or RAS. The human homolog was mapped to chromosome 11p14.1. ▶[RAS](#), ▶[p21](#)

Harvey: A *Drosophila* transposable element (7.2 kb). ▶[transposable elements](#)

Haseman-Elston Regression: A method to study the linkage between QTLs and markers. ▶[QTL](#); Haseman JK, Elston RC 1972 *Behavioral Genet* 2:3.

Hashimoto Thyroiditis: An autoimmune disease of the thyroid gland controlled by several loci; some of them affect Graves disease too. ▶[autoimmune](#)

[disease](#), ▶[goiter](#); Tomer Y et al 2003 *Am J Hum Genet* 73:736.

Hassall Corpuscles: Hassall corpuscles express thymic lymphopoietin in the stroma (TSLP) and activate CD11c-positive dendritic cells to make CD80 and CD86. The active dendrites induce the proliferation and differentiation of CD4⁺ CD8⁻ CD25⁻ thymic T cells into CD4⁺ CD25⁺ FOXP3⁺ regulatory T cells. The induction also requires CD80, CD86, and interleukin-2. The corpuscles thus mediate selection for medium to high affinity self-reactive T cells (Watanabe N et al 2005 *Nature [Lond]* 436:1181). (See terms under separate entries).

Hat: ▶[histone acetyltransferase](#), ▶[nucleosomes](#), ▶[histones](#), ▶[coactivator](#)

HAT Medium: Hat medium of animal cell culture contains hypoxanthine, aminopterin and thymidine. It has been extensively used for the isolation of bromodeoxyuridine and azaguanine resistant mutants and complementary fused cell lines by the rationale outlined in the figure (see Fig. [H14](#)). ▶[selective isolation](#), ▶[bromodeoxyuridine](#), ▶[azaguanine](#), ▶[aminopterin](#)

Hatching Time of Poultry: The eggs of chicken hatch in three weeks; turkey, goose and duck eggs require four weeks incubation.

HAUSP: A herpesvirus-associated ubiquitin-specific protease.

Haustorium (plural haustoria): Those organs of parasites (see Fig. [H15](#)) (e.g., fungi) that penetrate the periplasmic space of the host cells for the purpose of absorbing nutrients. In parasitic plants (*Striga asiatica*) quinone may serve as a signal to the expression of the expansion gene and the cellulose fibers are modified to form haustoria. (See Voegelé RT et al 2001 *Proc Natl Acad Sci USA* 98:8133).

Haw River Syndrome: The same as dentatorubral-pallidolusian atrophy.

Hawkinsinuria (4- α -hydroxyphenylpyruvate hydroxylase deficiency): The hawkinsin is a 2-L-cystein-S-yl-1, 4-dihydroxycyclohex-5-en-1-yl acetic acid. On a restricted phenylalanine and tyrosine diet the dominant condition greatly improves. It is a childhood disease.

Hawthorne Effect: The persons involved in a treatment know about the treatment and their behavior may be thus affected.

Hay Fever: ▶[allergy](#)

Hayflick's Limit: Human cells usually die in culture after 50 to 60 or fewer cell cycles. Cancer cells

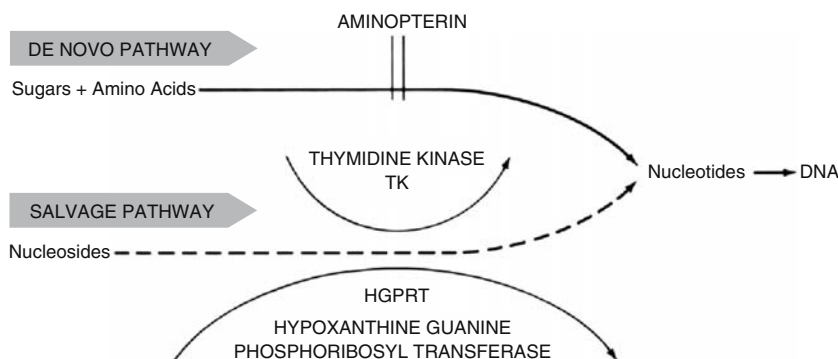


Figure H14. Alternative pathways of nucleic acid biosynthesis. The upper *de novo* pathway can be selectively blocked by aminopterin, an inhibitor of dehydrfolate reductase (an enzyme essential for the biosynthesis of thymidylate). In case of such a block, pyrimidines and purines may still be synthesized through the salvage pathway from nucleosides. Tk (thymidine kinase) can make thymidylic acid and hgprt (hypoxanthine guanine phosphoribosyl transferase) can supply guanylic acid. In case *tk* is inactivated by mutation (*tk*⁻), the cells become resistant to 5-bromodeoxyuridine because the cells cannot convert it into a nucleotide analog. Similarly, if hgprt is inactivated (*hgprt*⁻) by mutation the guanine analog, 8-azaguanine cannot be incorporated into DNA and thus the cell will be resistant to it. Therefore, on hat medium, both bromodeoxyuridine and azaguanine resistant mutant cells can selectively be isolated

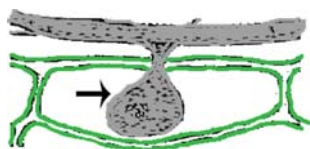


Figure H15. Haustorium grows through epidermis

are ordinarily not subjected to such a limit by senescence. ▶immortalization, ▶hybridoma, ▶senescence, ▶aging, ▶apoptosis; Shay JW, Wright WE. 2000 Nat Rev Mol Cell Biol 1:72.

Haynaldia villosa: A diploid wild grass ($2n = 14$) carrying the V genome. It can directly be crossed with tetraploid wheats and the AABBVV hybrids can be backcrossed with hexaploid wheat (AABBDD); AABBDD + 7V additions can thus be generated. ▶addition lines, ▶Triticum; photomicrogram in Fig. H16.

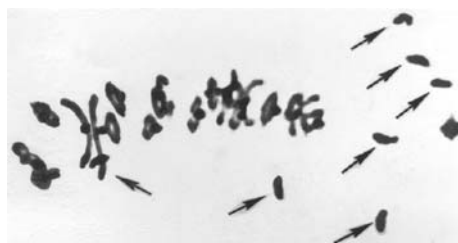


Figure H16. Haynaldia addition chromosomes marked by arrows. (Courtesy of Dr. ER Sears)

Hay-Wells Syndrome (3q27): The dominant ankyloblepharon-ectodermal defects-cleft lip/palate. Mutations in p63 may be involved. ▶ankyloblepharon, ▶p63, ▶ectrodactyly; McGrath JA et al 2001 Hum Mol Genet 10:221.

Hazard Function: $\hat{h}(t) = (\text{number of individuals exposed within time } t) / (\text{number of survivors within the same period of time})$.

Hazardous Chemicals: ▶chemicals hazardous, ▶environmental mutagens, ▶biohazards

Hazelnut (*Corylus* spp): A monoecious shrub with edible nuts; $2n = 2x = 28$.

HBV: The hepatitis B virus. ▶hepatitis

HCK: ▶SRC kinase family of oncogenes

HCP: A non-receptor tyrosine phosphatase. ▶B lymphocyte

HC-Pro: ▶post-transcriptional

HCT: ▶CDH1

HDA1, HDA2, HDA3: All three are histone 3 and histone 4 deacylating enzymes of yeast. ▶DHAC, ▶histone deacetylation

HDAd (helper-dependent adenovirus): HDAd is deficient in the functions required for replication and the helper compensates for the missing functions. Such "guttled" viruses are used as vectors for gene therapy.

Hdj2: A mammalian homolog of DnaJ. It may chaperone translocation into the Golgi apparatus and the nucleus. ▶chaperones, ▶DnaK, ▶Golgi apparatus

HDL: ►high-density lipoprotein, ►Tangier disease

hDNA: hDNA is used in two ways: as human DNA or heteroduplex DNA. ►heteroduplex

H-DNA: A protonated molecule; apparently without a natural biological role. ►DNA types

H-DNA: H-DNA may be formed as a triplex tract when either pyrimidines (PY) or purines (PU) abound in the DNA single strands. The PY-rich strand may fold back and pair with the PU-rich tract or vice versa (see Fig. H17). The 3' halves (PY3') contribute preferentially to the triplex. ►trinucleotide repeats, ►triplex, ►nodule DNA

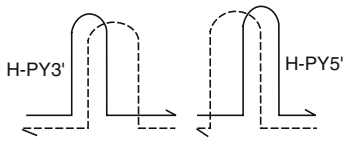


Figure H17. H-DNA

Head/Face/Brain Defects: ►Prader-Willi syndrome, ►holoprosencephaly, ►de Lange syndrome, ►Angelman syndrome, ►Miller-Dieker lissencephaly, ►Walker-Wagner syndrome, ►Opitz syndrome, ►Smith-Lemli-Opitz syndrome, ►Opitz-Kaveggia syndrome, ►Borjeson syndrome, ►fragile X chromosome, ►Langer-Giedion syndrome, ►Coffin-Lowry syndrome, ►Aarskog syndrome, ►cranioorodigital syndrome, ►otopalatodigital syndrome, ►craniometaphyseal dysplasia

Headful Rule: Bacteriophages replicate their DNA in concatamers but the phage head (capsid) has a limited storage capacity and, therefore, the molecules have to be cut to “headful” lengths. Bacteriophages, herpesviruses and other large double-stranded DNA viruses pump the DNA into the capsids by molecular motors that generate pressure, ten times in excess of bottled champagne (Lander GC et al 20067 Science 312:1791). ►concatamer, ►lambda phage, ►packaging of phage DNA; ►Droge A, Tavares P 2000 J Mol Biol 296:103; Coren JS, Sternberg N 2001 Gene 264:11.

Hearing Deficits: ►deafness

Heart Disease: Heart disease affects about 1% of the population and only a little less of the newborns; for about 15%, it is lethal. The majority of heart diseases involve either hypertrophy of the heart muscles or ventricular dilation. The myocytes after differentiation do not replicate any more but can increase their size leading to hypertrophy upon stress. Under healthy conditions Ca^{2+} regulates cardiac contraction and relaxation through an elaborate path. The

mammalian heart cannot regenerate in contrast to that of zebrafish that can regenerate when up to 20% is amputated. According to classical developmental ideas, different mammalian heart tissues arise from separate precursor lineages under the control of a unique combination of transcriptional networks. Newer information indicates the LIM homeobox islet gene (*Is/1*) of the mouse determines alternative multipotent progenitor cells that can lead to cardiac, smooth muscle and endothelial cell diversification suggesting a potential for stem cell therapy (Moretti A et al 2006 Cell 127:1151).

Many genes are involved in the development of the heart (see Fig. H18) and platelet-derived growth factors are upregulated during the process (Lien CL et al 2006 Plos Biol 4(8):e260). Congenital heart disease frequently occurs as a component of various syndromes. About 2% of the cases are caused or precipitated by environmental effects and various diseases (alcoholism, lithium, thalidomide, retinoic acid [a derivative of vitamin A]), trimethadione (anticonvulsant drug), viral infections (rubella), maternal diabetes and phenylketonuria, trisomics (21, 8, 13), Turner syndrome, deletions by the DiGeorge syndrome, asplenia, patent ductus, Holt-Oram syndrome, Ellis-van Creveld syndrome, mucopolysaccharidosis, Danon disease, Pompe’s disease, endocardial fibroelastosis, coarctation of the aorta, Noonan syndrome, LEOPARD syndrome, Fallot’s tetralogy, mitral prolapse, myotonic dystrophy, Jervell and Lange-Nielsen syndrome, Opitz-Kaveggia syndrome, etc.

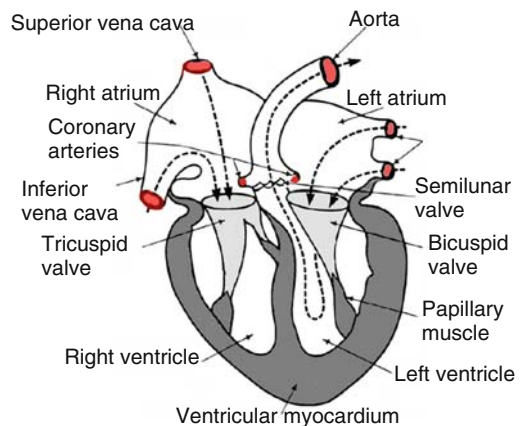


Figure H18. Heart

►coronary heart disease, ►myocardium, ►cardiovascular disease, ►phospholipase, ►atherosclerosis, ►hypertension, ►atrial septal defect, ►GATA, ►supravalvular aortic stenosis, ►mitral prolapse, ►hypertrophic cardiomyopathy, ►arrhythmogenic right ventricular cardiomyopathy, ►long QT

syndrome, ►nemaline myopathy, ►aneurysm, ►platelet-derived growth factor, ►mitochondrial diseases in humans; and the syndromes named above; Srivastava D, Olson EN 2000 *Nature (Lond)* 407:22; Chien KR 2000 *Nature (Lond)* 407:227; Nicol RL, Olson EN 2000 *Annu Rev Genomics Hum Genet* 1:179; Molkentin JD, Dorn GW 2001 *Annu Rev Physiol* 63:391; *Nature [Lond]* 2002, 415:198–240, structural and functional mutations in heart disease: Ahmad F et al 2005 *Annu Rev Genomics Hum Genet* 6:185, evolution of the heart: Olson EN 2006 *Science* 313:1922, heart differentiation and development: Srivastava D 2006 *Cell* 126:1037, <http://www.fsm.it/cardmoc/>.

Heartbreaker (*hbr*): A nontranslated, short (314-bp) insertion element in several grasses (maize and other cereals). It is present in ~4,000 copies in the maize genome. It is suspected to be responsible for a significant portion of the polymorphism observed. ►MITE, ►transposable elements plants; Zhang Q et al 2000 *Proc Natl Acad Sci USA* 97:1160.

Heat Repeats: A repeated element first discovered in the following proteins: huntingtin, translation elongation factor EF3, the A subunit in protein phosphatase 2A (PP2A), and TOR1, a target for rapamycin. Similar repeats have since been found in different proteins of several species. ►Huntingtin, ►EF3, ►TOR, ►rapamycin; Andrade MA et al 2001 *J Struct Biol* 134:[2–3]:117.

Heat Shock Elements: ►HSE

Heat-Shock Proteins (hsp): Heat-shock proteins are most commonly molecular chaperones that under heat stress inhibit or prevent denaturation of other proteins by binding to interactive surfaces and thus securing that these chaperoned proteins maintain their structure required under normal, no stress conditions. A heat-shock transcription factor (HSF1), peptide chain elongation factor eEF1A, and heat-shock RNA (HSR1) mediate, primarily, the expression of heat-shock proteins (Shamovsky I et al 2006 *Nature [Lond]* 44):556). The production of heat-shock proteins to this type of stress is very rapid because the hsp70, hsp26, hsp27 genes of *Drosophila* are initiating transcription in anticipation of heat by a halted 20 to 40 nucleotide transcript that can be then readily elongated. Hsp70 (see Fig. H19) is stalled near the promoter under un-induced conditions but,

upon heat shock, RNA polymerase Pol II is readily released by TFIIS and additional Pol II molecules as well as transcription factors are recruited to the initiation site (Adelman K et al 2005 *Mol Cell* 17:103). Some Hsp proteins may have other functions as well. Hsp110 is present in prokaryotes and eukaryotic organelles in response to stress. Hsp90 family members bind ATP and are involved in autophosphorylation, although in animals they are immunophilins (binding to immune-suppressive antibiotics such as cyclosporin). Hsp70 members are made in all types of organisms and their main role is to mediate the folding of nascent proteins. The heptameric hsp60 molecules participate in the molding of proteins using $ATP \rightleftharpoons ADP$ for energy. The hsp40 proteins may be involved in sorting polypeptides. The smaller hsp proteins may form aggregates before acting on other molecules. Prokaryotes do not contain the very smallest hsp proteins. The hsp genes are classified into families on the basis of the molecular weight of the proteins (in kDa) encoded by them.

For the small heat-shock proteins ►sHsp. Under high temperature stress heat-shock proteins may accumulate to 15–20% of the total cellular proteins. Their formation is tightly regulated by both positive and negative controls. In *E. coli* the heat signals activate the $E\sigma^{32}$ RNA polymerase and the *rpoH* operon whereas misfolding activates the $E\sigma^E$ (σ^{24}) operon. Besides elevated temperature (5–10°C above normal), heat-shock responses may also be elicited by toxic chemicals, metabolic inhibitors and analogs, microbial or viral infections, various injuries, cancer, aging and developmental events. During heat shock, normal protein synthesis may be selectively repressed. ►HSE, ►Hsc, ►transcription factors inducible, ► σ , ►chaperone, ►thermal tolerance, ►cold shock, ►HSP, ►Hsp70, ►Hsp90, ►Hsc66, ►DnaJ, ►sHsp, ►elongation factors, ►immunophilin, ►spastic paraplegia; Nagao RT, Gurley WB 1999 In Reynolds PHS (ed) *Inducible gene expression in plants*, CABI, Wallingford, UK, p 97; Macario AJ, Conway-Macario E 2000 *Int J Clin Lab Res* 30[2]:49; Queitsch C et al 2002 *Nature [Lond]* 417:618; Srivastava P 2002 *Annu Rev Immunol* 20:395, <http://www.heatshock.net/>.

Heat Tolerance: Some lower eukaryotes and some prokaryotes can tolerate temperatures close or even above the boiling point of water. Their special ability

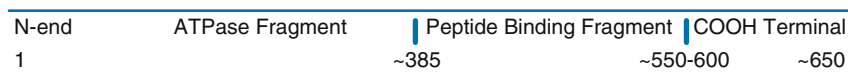


Figure H19. Generalized structure of an Hsp-70 protein

enables them to survive under the blazing temperature of the equator or in hot springs. In the warm soil of the Yellowstone National Park the fungus, *Curvularia protuberata*, controls the high temperature tolerance (65°C) of the grass, *Dicanthelium lanuginosum*, when the fungus harbors a double-stranded RNA mycovirus (Márquez LM et al 2007 Science 315:513).

Heavy Chain: ►antibody, ►Watson-Crick model, ►DNA heavy chain

Heavy Chain of DNA: ►DNA heavy chain

Hebbian Mechanism: An old hypothesis proposed by Donald Hebb (1949) for the memory function of the brain as a series of excitations of axons resulting in firing of other nerve cells and resulting in long-term potentiation. ►memory; Rao RP, Sejnowski TJ 2001 Neural Comput 13:2221.

Hec: An 80 –kDa, coiled-coil nuclear protein. It interacts with Smc1 and Smc2 and apparently controls chromosome segregation. ►spindle

HECT: A protein domain present in ubiquitin ligases. ►ubiquitin

Hedgehog: *Erinaceus europaeus*, 2n = 48 (see Fig. H20).



Figure H20. Hedgehog

hedgehog (*hh*, 3–81): A segment polarity type embryonic lethal mutation in *Drosophila*. The product of the wild type allele of *hh* encodes a signaling molecule that is processed by auto-proteolysis into two active species. By the action of the C-terminal domain of the protein it is cleaved into two and the N-terminal signaling domain covalently binds a cholesterol moiety. This binding is required for neutralizing the effects of Patched and Smoothed proteins that would block the signaling pathway. The Cholesteryl-Hedgehog-Patched-Smoothed complex displays differences in tissue distribution and instructs adjacent cells to express the organizing signal encoded by the *decapentaplegic* (*dpp*) locus. The Hh protein is secreted under the control of the *En* (engrailed) protein. The *en* locus is continuously expressed in the posterior part of the embryo. The anterior part of the embryo expresses the *ci* (*cubitus*

interruptus) locus, which encodes a zinc-finger binding protein of the Gli family of transcription factors. If *ci* is not expressed the *hh* gene product shows up and posterior compartment properties appear without the expression of the *en* signal. Increased levels of *ci* products induce the expression of *dpp* independently from *hh*. Expression of the normal *ci* product in the anterior cells results in limb development by limiting the expression of *hh* to posterior cells and mediating the ability to respond to the protein signal of the *hh* locus. *Ci* transduces the Hh signal by activating the *dpp* and *ptc* (*patch*) genes. The Patch gene product and the cyclic AMP-dependent protein kinase A interfere with inappropriate expression of *dpp* if an Hh product is not available. The *ci* product at low level represses *dpp* and at higher concentration appears to be an activator of the same gene. Hh induces both decapentaplegic (dorsal compartment) and wingless (ventral compartment) and these two modulate each other's function to assure normal axial development. The product of the *patched* (*ptc*) gene is the receptor of Hh and *smoothed* (*smo*) is a signaling component of *Ptc*. Hip (hedgehog-interacting protein, ~78 kDa) has a somewhat similar role as *Ptc*. The human gene EXT-1 (and the apparently homologous *Drosophila* gene *Ttv*) seems to regulate the embryonic movement of the *hh* protein. EXT encodes a protein apparently involved in the cell surface glycosaminoglycan (GAG) synthesis. The *hh* gene has at least three homologs in humans and other vertebrates: the Sonic hedgehog (SHH, 7q36, patterns the neural tube, early gut endoderm, posterior limb buds). Indian hedgehog (*Ihh*, 2q33-q35) is expressed primarily in cartilage and Desert hedgehog (*Dhh*, 12q13.1) is expressed primarily in the testes. *Ihh* in mouse mediates progesterone signaling in the uterus (Lee K et al 2006 Nature Genet 38:1204). The *hh* signaling system is present in many invertebrates and vertebrates but it is absent from *Caenorhabditis*. Upon autocatalytic processing, Hh releases a 19-kDa ligand with cholesterol linked to its C-end. It is assumed that Hh works in *Drosophila* as a raft for intracellular transport. Basal cell carcinoma and medulloblastoma cancers are frequently associated with mutation of Hh. An RNAi system applied genome-wide, revealed hundreds of new regulators of Hh (Nybakken K et al 2005 Nature Genet 37:1323). (See more about ►*ptc*; ►*decapentaplegic* under ►nevoid basal cell carcinoma, ►holoprosencephaly; Gli in ►Greig's cephalopolysyndactyly syndrome, ►cubitus interruptus, ►Rubinstein syndrome, ►engrailed in ►morphogenesis in *Drosophila*, ►sonic hedgehog, ►tumor suppressor pathway, ►cholesterol, ►glycosaminoglycan; McMahon AP 2000 Cell 100:185; Kalderon D 2000 Cell 103:371;

Ingham PW 2001 Science 294:1879; Bale AE 2002 Annu Rev Genomics Hum Genet 3:47, review; Lum L, Beachy PA 2004 Science 304:1755, signaling pathway: <http://www.hedgehog.sfsu.edu>.

HEI (hybrid element insertion): The left end of one hybrid dysgenesis-causing P element of *Drosophila* in *trans* position can move with the left end of another P element as a unit and causes viable exchanges or inviable rearrangements. The exchange products may be due also to hybrid excision and single strand repair synthesis (HER). The HEI model may account for male recombination in *Drosophila*. ▶ [male recombination](#), ▶ [hybrid dysgenesis](#), ▶ [DNA repair](#); Tanaka MM et al 1997 Genetics 147:1769.

Heisenberg's Uncertainty Principle: Developed in the 1920s by the German physicist Werner Heisenberg for quantum mechanics. In its simplest form: an atomic particle moves at a *p* momentum (speed) and has a certain *x* position on its track. These properties (*p* and *x*) cannot be measured with certainty because whenever a measurement is made the system is disturbed. Therefore, all measurements are loaded with some errors, some uncertainties. This concept was developed for interpretation of nuclear fission but it may have relevance for studies of biological systems too.

HeLa Cell Line: An immortalized human cancer cell line which originated in 1951 from a highly malignant cervical carcinoma of patient Henrietta Lacks who died the same year. The line, however, is maintained all over the world indefinitely. Many of the HeLa cell lines have been contaminated—by error or by deception—with cells of different origin. Now, with improved forensic laboratory techniques these can be identified by high probability. ▶ [immortalization](#); O'Brien SJ 2001 Proc Natl Acad Sci USA 98:7656; Masters JR 2002 Nat Rev Cancer 2:325.

Helical Twist: The angle between neighboring DNA base pairs; it is within the range of 24° and 51° with a mean of 36.1 ± 5.9.

Helicases: Helicases are enzymes unwinding the double helix of a nucleic acid for replication and transcription, repair, recombination, and in reactions associated with binding and hydrolysis of DNA. About 60 helicases have been identified; some unwind DNA and RNA hybrids. *E. coli* bacterium encodes about 12 different helicases, and all organisms have several types (see Fig. H21).

The activity of a helicase may be coordinated with DNA polymerase and the complex may travel at about 1,000 nucleotide/second. The RecQ family of helicases is implicated in mutator functions and chromosomal rearrangements such as occurring in

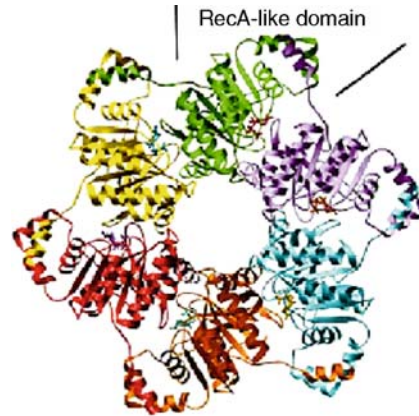


Figure H21. Phage T7 hexameric helicase motor protein. (From Waksman, G et al. 2000 Nature Struct. Biol. 7:20)

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the Bloom's syndrome, Cockayne syndrome, Xeroderma pigmentosum B and D, and others. ▶ [DNA replication in prokaryotes](#), ▶ [chromosomal rearrangements](#), ▶ [DEAD-box](#), ▶ [Bloom syndrome](#), ▶ [Werner syndrome](#), ▶ [Cockayne syndrome](#), ▶ [xeroderma pigmentosum](#), ▶ [Rothmund-Thompson syndrome](#), ▶ [ABC excinuclease](#), ▶ [Rep](#), ▶ [recA](#), ▶ [SRS2](#), ▶ [recombination molecular mechanism in prokaryotes](#), ▶ [branch migration](#), ▶ [unwinding protein](#), ▶ [CDC45/CDC46-Mcm](#); Patel SS, Picha KM 2000 Annu Rev Biochem 69:651; von Hippel P, Delagoutte E 2001 Cell 104:177; van Brabant AJ et al 2000 Annu Rev Genomics Hum Genet 1:409; Mohaghegh P, Hickson ID 2001 Hum Mol Genet 10:741; Enomoto T 2001 J Biochem 129:501; Wu L, Hickson ID 2006 Annu Rev Genet 40:279; structure, function: Singleton MR et al 2007 Annu Rev Biochem 76:23.

***Helicobacter pylori*:** A bacterium (strain 26695) with a completely sequenced genome of 1,667,867 bp and 1,590 ORF (Nature 388:539 [1997]). Strain J99 is also sequenced (1,643,831 bp, Nature 397:176 [1999]). The latter has a 24,036-bp smaller genome. The genic difference between the two strains is about 6–7% and half of these are clustered in a hypervariable region. These common pathogens are tolerant to high acidity and are responsible for peptic ulcers and possibly gastric carcinoma but may also be harmless. The *H. pylori* strain causing atrophic acute superficial gastritis (1,596,366 bp) has also been sequenced (Oh JD et al 2006 Proc Natl Acad Sci USA 103:9999). O-glycan of the gastric mucin has an antibiotic effect against the bacterium (Kawakubo M et al 2004 Science 305:1003). The carcinogenic effect may be brought about by increased gastric acidity and interleukin-1. The damaged stomach epithelia may recruit bone marrow cells, which may become

metaplastic and dysplastic (Houghton J et al 2004 Science 306:1568). *H. pylori* can produce an antibacterial peptide (a cecropin), bearing similarity to ribosomal protein RplL1. A protein-protein interaction map using yeast two-hybrid assay has been developed for over 46% of the proteome by 2001. The *H. pylori* antigen-binding adhesin (BabA) has increased affinity for O blood group and this fact explains the increased incidence of gastric inflammation among some Amerindians who have predominantly O blood group (Aspholm-Hurtig M et al 2004 Science 305:319). The Nobel Prize for Physiology and Medicine in 2005 was awarded to BJ Marshall and Robin Warren for the discovery of the role of this bacterium in duodenal and gastric ulcers. Anatomically modern humans were already infected by *H. pylori* before their migrations from Africa and it has remained intimately associated with their human host populations ever since (Linz B et al 2007 Nature [Lond] 445:915). ►ORF, ►*E. coli*, ►antimicrobial peptides, ►ABO blood group, ►adherence reaction, ►dysplasia, ►metaplasia, ►gastric cancer; Rain J-C et al 2001 Nature 409:211; Ernst PB, Gold BD 2000 Annu Rev Microbiol 54:615; Del Giudice G et al 2001 Annu Rev Immunol 19:523; *Helicobacter hepaticus* genome sequence: Suerbaum S et al 2003 Proc Natl Acad Sci USA 100:7901; <http://genolist.pasteur.fr/>.

Helitrons: ►rolling circle

Helix (of macromolecular structure): A coil of a three-dimensional ribbon; the DNA double helix is similar to a staircase with the steps corresponding to the bases and the strings of the staircase representing the sugar-phosphate backbone of the two polynucleotide chains; thus it is not a simple spiral. Besides the commonly seen double-helix structure, a nucleic acid can also assume triple and quadruple helical structures. Telomeric and centromeric DNA can show quadruplex structure in guanine- and cytosine-rich sequences. These sequences have potentials for binding different ligands. RNA quadruplexes offer chances for binding both outside and inside of the groove of the quadruplex. Quadruplexes can also bind each other at the termini and extend their length. RNA quadruplexes can display bulges at the end of the 5' structure and can result in the formation intercalated octaplexes (Pan B et al 2006 Proc Natl Acad Sci USA 103:3130). ►DNA, ►triplex, ►triple helix forming oligonucleotides, ►Watson and Crick model, ►collagen

Helix Bundle Proteins: ►integral membrane protein

Helix Destabilizing Protein (RF-A): A single-strand binding protein instrumental in DNA replication. ►DNA replication, ►binding proteins, ►RF-A

Helix-Loop-Helix: Helix-loop-helix are polypeptides, each with three-partite structures; two of the helices are connected through a loop in each component of the dimer; the third helix of the components is rich in basic amino acids and this end binds to the DNA. The monomers thus appear as HOOC-helix-loop-helix positively charged helix-NH₂. They recognize the CANNTG (E-box) sequence in the DNA. The H-L-H proteins may form dimers and recognize two different neighboring DNA-binding sites. The proteins may saddle into the major groove of the DNA through their positively charged amino acids in the α helix of the NH₂ terminus. Basic helix-loop-helix proteins (>250) control transcription of genes involved in a great variety of cellular functions. ►DNA-binding protein domains, ►regulation of gene activity, ►helix-turn-helix motif; Lodent V, Vervoort M 2001 Genome Res 11:754.

Helix-Turn-Helix Motif: H-T-H motifs are parts of regulatory proteins of prokaryotes and homeodomains of eukaryotes. One α -helix (*recognition helix*) fits into the major groove of the DNA and the other is positioned at a right angle above it and it allows interaction with other proteins. The other monomer of the dimeric structure is binding to the next major groove along the DNA. There are large varieties of these proteins in bacteria and eukaryotes yet they contain a conspicuous symmetrical structure formed of antiparallel β sheets or α -helices separated by a turn of several amino acids. H-T-H motifs occur in the homeodomain proteins, in various repressors (λ *ci* and *cro* proteins, in the *E. coli* catabolite activator [CAP] proteins, etc.). ►DNA-binding protein domains, ►regulation of gene activity, ►lac operon, ►lambda phage, ►DBP, ►monomeric, ►DNA grooves, ►protein structure

Helminthosporium maydis: Fungus is the causative agent of the maize disease, southern corn leaf blight. Plants with the T (Texas) cytoplasmic male sterility are extremely susceptible to the disease and suffer serious damage. ►cytoplasmic male sterility, ►cms

Helper Plasmid: ►binary vector

Helper T Cell: ►T cell

Helper Virus: A helper virus provides the functions that a defective virus particle lacks.

Hemagglutinin: Hemagglutinins are proteins that cause agglutination of the red blood cells such as antibodies, lectins, and certain viruses (influenza, mumps, etc.). Variations in hemagglutinins due to amino acid substitutions are important factors in viral infectivity and the ability of the cells to make antibodies against them. ►fusogenic liposome,

►antibody, ►antigen; Skehel JJ, Wiley DC 2000 *Annu Rev Biochem* 69:531.

Hemangioblast: Mesodermal stem cells giving rise to blood vessels, hematocytoblasts (hemocytoblasts) and endothelial cell lineages. ►angiogenesis, ►blood, ►hematocytoblast; Huber TL et al 2004 *Nature [Lond]* 432:625; Vogeli KM et al 2006 *Nature [Lond]* 433:337.

Hemangioma: Several forms of neoplasias of blood vessels under autosomal recessive gene control in humans. ►angioma, ►Kasabach-Merritt syndrome

Hematocytoblast (hemocytoblast): Totipotent stem cells of blood. ►blood, ►stem cell, ►angiogenesis, ►hemangioblast

Hematopoiesis: The process of blood formation. It is a homeostatic process as new cells are formed and old ones are removed by apoptosis. After a certain age the blood volume does not expand. The major regulatory factors in this process are cytokines. Growth factors include the Kit ligand, the various macrophage factors. Large-scale culture of CD34⁺ produces normal, functional red blood cells from stem cells of peripheral blood and bone marrow (Giarratana M-C et al 2004 *Nature Biotechnol* 23:69). ►G-CSF, ►GM-CSF, ►M-CSF, ►interleukins, etc., ►bone marrow, ►Gleevec, ►PTEN; Metcalf D, 1998 *Stem Cells* 16:314; Christensen JL et al 2004 *PLoS Biol* 2:368; <http://bioinformatics.med.ohio-state.edu/HemoPDB/>.

Hematopoietic Receptors: Hematopoietic receptors bind hormone (GH, PRL, EPO, G-CSF) or cytokine (interleukin) ligands and are involved in cellular signaling. They may be homodimers (α -chain) and or heterooligodimers (α and β chains). (See mentioned items under separate entries).

Hematopoietic Stem Cells (HSC): HSCs can give rise to blood cells. By QTL analysis in mouse, a stem cell proliferation locus (Scp2) was identified in chromosome 11, corresponding to 5q31.1 in humans. The deletion of this region is associated with myelodysplastic syndrome and acute myeloid leukemia. The Scp2 locus is subject to cis- and trans-regulation by several genes and allelic forms. Hematopoietic CD34 human stem cells from bone marrow, when implanted into developing chicken spinal chord, differentiated into neurons (Sigurjonsson OE et al 2005 *Proc Natl Acad Sci USA* 102:5227).

Latexin (*Lxn*, human chromosome 3q25.3; is an endogenous carboxypeptidase inhibitor), is a gene whose differential transcription and expression is associated with the allelic differences in the mouse hematopoietic cell number. Expression is inversely correlated with the number of HSCs. The ectopic

expression of *Lxn* using a retroviral vector decreased stem cell population size. Clusters of SNPs upstream of the *Lxn* transcriptional start site, at least two of which are associated with potential binding sites for transcription factors, regulate stem cells. Thus, promoter polymorphisms between the B6 and D2 alleles may affect *Lxn* gene expression and consequently influence the population size of hematopoietic stem cells (Liang Y et al *Nature Genet* 39:178). Methylated histones H3K4 and acetylated histone AcH3, and unmethylated CpG dinucleotides colocalize across defined regulatory regions of lineage-affiliated genes in HSC and these active epigenetic histone modifications either accumulated or were replaced by increased DNA methylation and H3K27 trimethylation in committed progenitors consistent with gene expression (Attenu JL et al 2007 *Proc Natl Acad Sci USA* 104:12371). ►stem cells, ►QTL, ►cis, ►bone marrow, ►histones; Bystrykh L et al 2005 *Nature Genet* 37:225.

Hematoxylin: A histological and cytological stain in different formulations (Delafield's hematoxylin, Haidenhain hematoxylin, iron hematoxylin, etc.). ►stains

Heme: A iron or magnesium-porphyrin prosthetic group in hemoglobin, cytochromes, and chlorophyll, respectively. The majority of free-living eukaryotes synthesize heme but *Caenorhabditis* and other worms may depend on their food supply for it (Rao AU et al 2005 *Proc Natl Acad Sci USA* 102:4270). ►haem [for structure].

Hemeralopia: ►day blindness

Hemerythrin: A circulatory transport, non-heme iron protein in some non-vertebrates. ►heme, ►hemoglobin, ►hemocyanin Kurtz DM 1992 *Adv Comp Env Physiol* 13:151.

Hemicellulose: A polymer of neutral polysaccharides present in the plant cell wall matrix. (See Dhugga KS et al 2004 *Science* 303:363).

Hemichannels: Hemichannels are open half-gap junctions that permit the flux of ions and <1-kDa molecules. ►channel, ►gap junction

Hemiclonal (hybridogenetic species): *Rana esculenta* (European edible green frog) arises from the hybrid of *Rana ridibunda* x *R. lessonae*. In *R. esculenta*, before meiosis, one of the parental genomes is eliminated before DNA synthesis and after duplication of the remaining genome meiosis takes place. Thus, the gametes are produced from only one of the genomes. Backcrossing to the parental species whose genome was eliminated then reforms the hybrid. In case of exposure to ionizing radiation the *R. esculenta*

individuals may lose up to ~50% of its DNA and thus make it possible to measure the extent of radiation fallout with the aid of flow cytometry. The *Poeciliopsis* fishes and the *Bacillus rossius-grandii* stick-shape insects are also hybridogenetic. The latter may also reproduce by parthenogenesis, gynogenesis, or androgenesis. ▶parthenogenesis, ▶gynogenesis, ▶androgenesis; Giorgi PP 1992 Nature [Lond] 357:444; Vinogradov AE, Chubinshvili AT 1999 Genetics 151:1123.

Hemifusion: A step toward fusion of membranes or viruses. First, the membranes dock and the outer membrane leaflets mix (hemifusion) followed by pore opening and mixing of contents. The entire process may be preceded by trans-SNARE pairing. ▶SNARE; Reese C et al 2005 Nature [Lond] 436:410.

Hemiglobin: ▶methemoglobin

Hemiknot: A means of stabilizing a DNA tract by threading one end of the duplex through another (see Fig. H22). (Diagram modified after Lyubchenko YL et al 2002 Nucleic Acids Res 30:22).

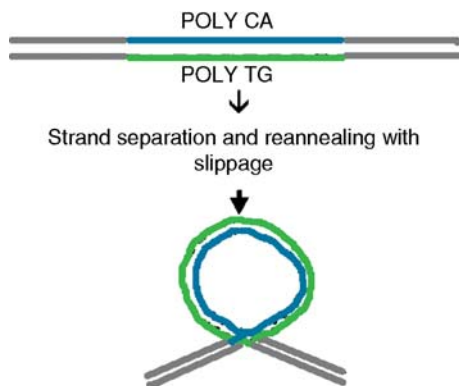


Figure H22. Hemiknot

Hemimetabolous: The insect hatches as a miniature adult and grows to the imago size. ▶imago, ▶holometabolous

Hemimethylated: Only one of the two DNA strands is methylated. ▶methylation of DNA, ▶demethylation

Hemin (ferriprophyrin chloride, $C_{34}H_{32}ClFeN_4O_4$): Hemin is used for the treatment of porphyria and the preparation of rabbit reticulocyte lysate. ▶porphyria, ▶haem, ▶rabbit reticulocyte in vitro translation

Hemin Regulated Inhibitor: ▶HRI

Hemiobiotrophy: For infection the parasite requires live cells but later it can grow on the ones killed.

Hemizygous: Gene(s) present in a single dose in an otherwise diploid cell or organism (e.g., X-chromosome-linked genes in an XY male or XO cells). ▶dosage compensation

Hemizygous Ineffective: A special class of recessive mutations in allopolyploids. These recessive alleles are not expressed in monosomics (hemizygotes) and in case of nullisomics the dominant wild type is expressed for these loci. Their expression requires two doses of these recessive alleles and never displays pseudodominance. Thus, the hemizygous ineffective alleles resemble recessive suppressor mutations in diploids. Recessive mutations in allopolyploids are generally of this type because the homoeologous loci cover up the mutations at the other corresponding genes. ▶allopolyploid, ▶monosomic, ▶nullisomic, ▶pseudodominance, ▶suppressor gene, ▶homoeologous alleles; Sears ER 1972 Symp Biol Hung 12:72.

Hemochromatosis (HFE/HLAH, haemochromatosis): A disease of iron accumulation, accompanied by cirrhosis (fibrous condition) of the liver, diabetes, dark pigmentation of the skin, heart abnormality, and cancer. If diagnosed early by determining plasma iron and ferritin (a red 80,000 M_r serum protein with 2 iron-binding sites to transport iron, also called siderophilin), it is curable by lowering the iron level through venesection (phlebotomy), letting out blood by cutting the vein. The recessive gene HFE is located within the HLA-H complex in human chromosome 6p21.3. The frequency of the gene is about 6 to 10% with an incidence of homozygosity of 2–3 per 1,000 births. The HFE2 locus is at 1q21 and HFE3 is at 7q22 encoding (TFR2) transferrin receptor-2. Neonatal hemochromatosis (8q21.3) has very complex expression due to modifying effects. The solute carrier family member, ferroportin (FPN1, 2q32), may be involved in dominant hemochromatosis. ▶HLA, ▶Menke's disease, ▶Wilson disease, ▶liver cancer, ▶ferritin, ▶ferroportin, ▶transferrin, ▶hepcidin, ▶anemia, ▶metal metabolism and disease; Njajou OT et al 2001 Nature Genet 28:213; Muckenthaler M et al 2003 Nature Genet 34:102.

Hemocyanin: A copper-containing protein in several invertebrates that is used to bind O_2 in a way similar to hemoglobin. ▶keyhole limpet hemocyanin, ▶hemoglobin, ▶hemerythrin; van Holde KE et al 2001 J Biol Chem 276:15563.

Hemocyte: The collective name of blood cells in higher animals or the lymph of insects.

Hemocytometer: A special microscope slide with compartments (see Fig. H23) of known exact volume when a coverglass is laid over. It is used for the

microscopic counting of the number of blood cells, or any other suspended cells, or protoplasts in a certain volume.

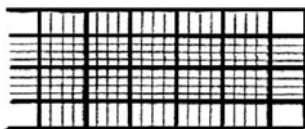


Figure H23. Compartments of hemocytometer

Hemodialysis: The removal of certain components of the blood in a machine through a semipermeable membrane by virtue of their differential rate of diffusion. ► **plasmaphoresis**

Hemoglobin: Oxygen-transporting heme proteins (M_r 64,500) in the red blood cells. The four polypeptide chains are attached to four heme prosthetic groups (Fe_2^+ state). The human adult hemoglobin consists of two α (141 amino acids) and two β (146 amino acids) polypeptide chains, whereas in the early embryo the polypeptide composition is $\zeta\zeta\epsilon\epsilon$. The ζ (zeta) is α -like, the ϵ (epsilon) is β -like. By the eighth week of gestation the embryonal hemoglobin is replaced by fetal hemoglobin with a structure $\alpha\alpha\text{G}\gamma\text{A}\gamma$; (the latter ones are β -like). Just before birth these two γ chains are replaced by β - and δ -globin chains. By the age of six months after birth 97–98% of hemoglobin A (HbA) is $\alpha\alpha\beta\beta$ and about 2% is $\alpha\alpha\delta\delta$ (HbA₂), and a very small amount is still fetal hemoglobin (HbF). Thus, there are two gradual developmental switches in the β -like genes but only one in the α -like genes. These changes are programed as the sites of the synthesis shift from the yolk sac of the embryo to the liver, spleen and bone marrow of the fetus and finally to the bone marrow in adults. The two gene families, α and β , of hemoglobin include α , γ , ζ and θ (θ , theta, unknown function) were located to human chromosome 16p13, and β , δ , ϵ and γ are at chromosome 11p15.5.

Both the α family of genes ($\rightarrow \zeta, \psi\zeta, \psi\alpha, \psi\alpha, \alpha 2, \alpha 1, \theta$) and the β family ($\rightarrow \epsilon, \text{G}\gamma, \text{A}\gamma, \psi\beta, \delta, \beta$) include pseudogenes (ψ) and are transcribed in the order as shown by the arrow. Hundreds of different amino acid substitutions and deletions are known in the globin chains and some of them lead to hemoglobinopathies, or blood diseases. One of the most famous among them is a substitution of valine for glutamic acid at residue 6 of the β chain (Hemoglobin S). This is responsible for a hydrophobic change on its surface resulting in an abnormal quaternary association of the subunits. When the oxygen level is reduced, the subunits polymerize into a linear array of fibers that alters the normally doughnut-shaped red blood cells to assume a sickle shape and therefore it is called *sickle cell anemia* in a homozygous condition. In

a heterozygous state it is called the *sickle cell trait*. The sickling erythrocytes are inefficient in oxygen transport. In the arteries, normal hemoglobin is 95% saturated with oxygen, in the venous blood—on the return to the lung—the saturation is about a third less.

Over 3 million Americans carry this abnormal HbB gene and there are many millions more all over the tropical and subtropical regions of the world where malaria is common. The heterozygotes are apparently at a selective advantage when infested with the *Anopheles* mosquito that spreads the causative protozoon, *Plasmodium falciparum*. A milder form of sickling, expressed only in the homozygotes, is caused by another mutation called hemoglobin C (HbC, $\beta 6\text{Glu} \rightarrow \text{Lys}$). HbC also protects against falciparum malaria. Other variants are HbD and HbE. Many other amino acid substitutions that have been identified on the basis of altered electrophoretic mobility or amino acid substitutions at precisely identified residue sites in either of the chains may not involve a disease. In the M hemoglobins, the oxygenated molecule has hereditary deficiencies of NADH-methemoglobin reductase activity and remains largely charged with oxygen. The stability of the hemoglobin molecules depends mainly on the close fit of the hemes to the globin chains that would be thermolabile at 50 °C. Mutations affecting the tight fit of the heme pocket may cause the formation of methemoglobin or the loss of the heme. Such unstable hemoglobins are, e.g., the Hb Zürich in which at β -chain residue 63 His changed to Arg. Hb Köln β 98 has a Val \rightarrow Met substitution. The increase in positive charge (e.g., Hb Zürich) favors the loss of heme. In case of Hb Hammersmith β 42, Phe \rightarrow Ser substitution, there is no change in charge yet instability occurs. Instabilities were associated with α chain substitutions too, e.g., in Hb Boston 58 His \rightarrow Tyr. Other anomalies include *hereditary persistence of high fetal hemoglobin* (HPFH). In the latter case, numerous types of variations exist. It appears that deletions involving a regulatory region of 3.5 kb at 5' to the δ gene may be a very important factor for the high expression of fetal hemoglobin. In one form, all the cells are equally affected whereas in the *heterocellular* hereditary persistence of fetal hemoglobin (HHPFH), only some of the cells display this anomaly. Certain point mutations in the γ -globin gene promoter are capable of maintaining the expression of this gene during adult erythropoiesis, a condition called *non-deletion hereditary persistence of fetal hemoglobin*. Among these, the British form of HPFH carrying a T \rightarrow C point mutation at position -198 of the A-globin gene promoter results in 4–10% fetal hemoglobin in heterozygotes. HPFH -198 bind specifically to DNMT1 (DNA methyltransferase 1), RAP74 (the largest subunit of the general transcription factor (TFIIF), the coactivator p52, nuclear matrix

protein SNEV, and a CDC5-like protein. Sp1 was not found among the proteins identified (Olave AI et al 2007 J Biol Chem 282:853)

In the Lepore hemoglobins $\delta\beta$ or $\beta\delta$ fusion products were observed, indicating the possibility of unequal crossing over between these DNA sites. Another type of hemoglobin anomalies involves the slow rate or lack of synthesis of one or the other hemoglobin chains resulting in thalassemias. The HBA gene is located to human chromosome 16p13.33-p13.11 whereas the HBB, HBD and HBG genes are in 11p15.5. Senescent or damaged erythrocytes are disposed of by macrophages in the bone marrow to protect from the oxidative and toxic effects of heme. Heme is converted into bilirubin and iron.

H

Hemoglobins are ubiquitous in animals and are highly variable. In humans, hemoglobin occurs in muscle cells, but in the carp it is found also in the brain. A different type (truncated) of hemoglobin also occurs in prokaryotes, protozoa, algae and higher plants, but is absent in archaea or metazoa. ►globin, ►methemoglobin, ►thalassemia, ►anemia, ►sickle cell anemia; Hardison RC 1996 Proc Natl Acad Sci USA 93:5675; Watts RA et al 2001 Proc Natl Acad Sci USA 98:10119; Modiano D et al 2001 Nature [Lond] 414:305; Wittenberg JB et al 2002 J Biol Chem 277:871; <http://globin.cse.psu.edu>.

relatively easily. Over 90% of the soluble proteins in blood plasma are globins. The still nucleated erythrocytes and the reticulocytes mainly synthesize globin mRNA. Amino acid sequence variants were detected in these proteins at the beginning of protein sequencing. Since globin genes occur both in animals and in plants, evolutionary studies became attractive. The number of amino acids in globins of plants as well in animals is fairly close: soybean leghemoglobin 143, seal myoglobin 153, human α 141, human β 146. Also, there are sequence homologies in the primary structure of the chains that with aid of estimated average replacement data the evolutionary time could also be quantitated. In vertebrates the globin genes have two introns at around the 30th amino acid-coding region and another around the 100th. In plants there are 3 introns, two at about the same location and a third near the middle in between. The size of the introns varies substantially from 99 triplets of the middle intron of the leghemoglobin, to 4,800 of the first intron in seal myoglobin. In vertebrates the heme binding is in the second exon, closer to the 3'-end. The residues required for tetramer association are in exon 3. (See Fig. H24; ►globin, ►hemoglobin, ►leghemoglobin, ►myoglobin, ►evolutionary clock, ►evolutionary tree; Hardison R 1998 J Exp Biol 201 [pt 8]:1099).

Hemoglobin Evolution: Molecular genetics which evolved from the early studies (late 1940s) has shown that globin genes could be obtained in pure forms

Hemoglobin, Fetal, Persistence of: The condition may be restricted to some of the cells (heterocellular) or it may involve all the cells (pancellular). Fetal

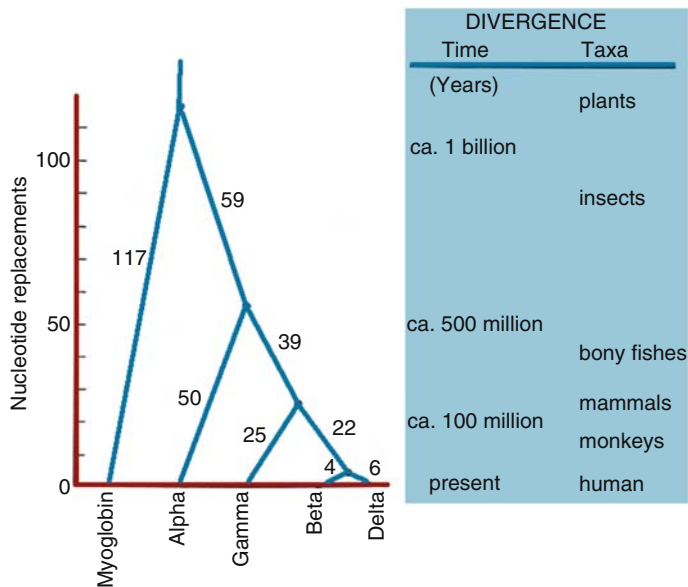


Figure H24. Evolution of hemoglobins. The numbers at each node indicate the numbers of the presumed nucleotide replacements in the genetic code during evolution. The time of divergence is estimated on average amino acid replacement data and evolutionary clocks. (After Fitch WM, Margoliash E 1970 Evol. Biol 4:67)

hemoglobin is a normal protein, only its persistence is a disorder. It may have point mutations or various types of deletions. The DNA may have either the G- γ gene without the presence of A- γ , - δ , - β , or it may retain the G- γ gene and also the A- γ , - δ , - β , or it may have the G- γ and the A- γ but the δ and β are missing. The phenotype depends primarily on the genes present than on the missing ones. ►hemoglobin, ►GATA; Ikunomi P et al 2000 Gene 261:277.

Hemoglobin Switching: During development various different hemoglobin genes are activated resulting in the formation of the different fetal and eventually adult types. ►hemoglobin; Ristaldi MS et al 2001 EMBO J 20:5242.

Hemoglobinopathies: Hemoglobinopathies are diseases that involve hemoglobins. ►hemoglobin, ►methemoglobin, ►thalassemia, ►anemia, ►hemophilia, ►paroxysmal nocturnal hemoglobinuria, ►sickle cell anemia, ►hemophiliacs, ►hemoglobin, ►fetal, ►persistence of

Hemolin: An immunoglobulin-like molecule in insects. ►immunoglobulins

Hemolymph: Blood-like fluids in insects and other invertebrates. It also has a role in defending against pathogens by dispersing to the sites of infection the secreted antimicrobial peptides and melanin. ►antimicrobial peptides; Vierstraete E et al 2004 Proc Natl Acad Sci USA 101:470.

Hemolysins: Hemolysins are proteins secreted by pathogenic bacteria. They cause the formation of pores in the mammalian cell membranes and dissolve red blood cell membranes. ►erythrocyte, ►lysin

Hemolysis: The disruption of the membranes of erythrocytes by antibodies, the hemolysin enzyme, and chemicals. ►hemolytic disease

Hemolytic Anemia: A disease may have several causes such as emphysema, sensitivity to high temperature, Rh blood type, and other autoimmune diseases, etc. ►anemia, ►hemolysis, ►phosphohexose isomerase, ►glutathione synthetase deficiency, ►glutathione peroxidase, ►glutathione reductase, ►pyruvate kinase deficiency, ►autoimmune diseases, ►hexokinase deficiency

Hemolytic Disease: ►erythroblastosis fetalis, ►Rh blood type, ►Su blood type

Hemolytic Uremic Syndrome (HUS): Hemolytic anemia, hypertension, and acute kidney failure are the main

clinical symptoms. In the dominant form (1q32), the complement factor H is defective. ►complement

Hemophagocytotic Lymphohistiocytosis, Familial: ►histiocytosis

Hemophillias: Hemophillias are hereditary bleeding diseases caused by a deficiency of one or another antihemophilic blood-clotting protein factors. The classic *hemophilia A* (deficiency of antihemophilic factor VIII, encoded at Xq28) has a prevalence of about 1/10,000. The estimated mutation rate is about $2-3 \times 10^{-5}$. Somatic mosaicism may occur in 25% of the patients (Leuer M et al 2001 Am J Hum Genet 69:75). The most famous case of hemophilia involved the descendants of Queen Victoria of England (see Fig. H25). She was heterozygous for the gene (probably through a new mutation) and transmitted it through marriage to the Russian, German, and Spanish royal families. ►pedigree chart

The inept handling of Russia's social problems by Tzar Nicholas II of Russia has been attributed partly to his preoccupation with, and worries about, the affliction of his son Tzarevitch Alexis by hemophilia. Thus, a single recessive gene might have had contributed indirectly to the largest upheaval in the social order of the world. The so-called *Christmas disease* (named after the family Christmas [deficiency of antihemophilic factor IX]), hemophilia B is also an X-chromosome linked disease (Xq27.1-q27.2).

The latter defect is about 1/5 to 1/10 as frequent as the classic hemophilia. These diseases are generally expressed in the males (because of X-chromosomal hemizygosity). Heterozygotes also have generally lower amounts of the proteins responsible for the condition, and thus the carriers can be identified in most cases. The estimated average mutation rate for hemophilia B is $\mu = 7.73$, for males $\nu = 18.8$, and for females $u = 2.18$ per gamete per generation, $\times 10^{-6}$ (Green PP et al 1999 Am J Hum Genet 65:1572). Transitions were 7.3×10^{-9} , transversions 6.9×10^{-9} , deletions/insertions 3.2×10^{-10} (Gianelli F et al 1999 Am J Hum Genet 65:1580). The temporarily effective therapy involves treatment with an antihemophilic factor. For gene therapy—using Moloney retroviral or adenovirus vectors—the B domain of Factor VIII is deleted from the cDNA and only a 170-kDa section is used of the total of 293-kDa. The transcription of the Factor VIII sequences may be repressed presumably by MAR action. Transplantation of embryonic day 42 pig spleen tissue into hemophilic mice model (SCID) led to complete alleviation of hemophilia within two to three months after transplant, as demonstrated by tail bleeding and by assays for factor VIII blood levels. These results provide proof of principle to the concept that transplantation of

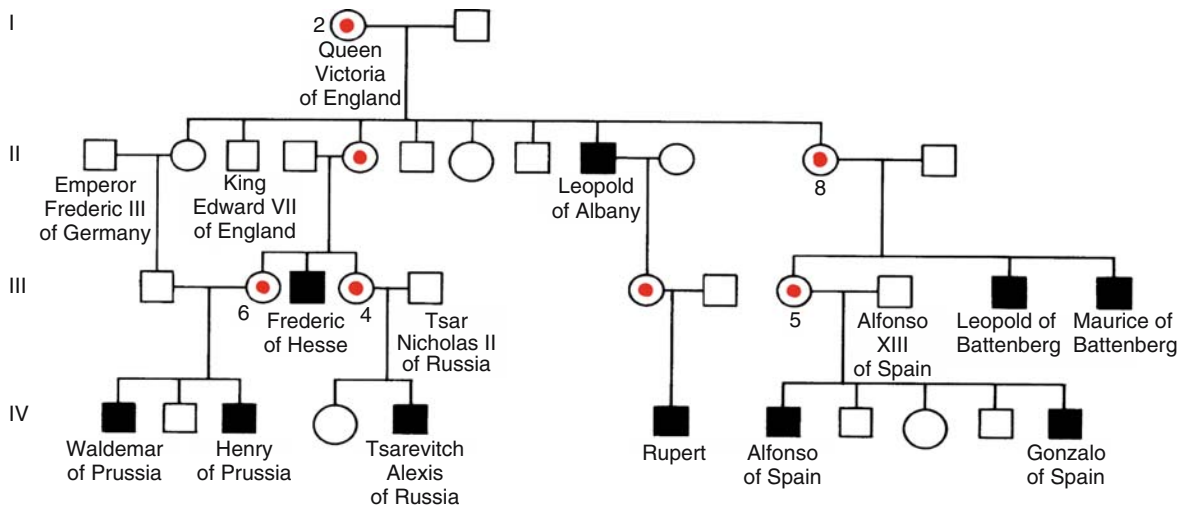


Figure H25. Descendants of Queen Victoria. The family of Queen Victoria of England. Hemophiliac male descendants are represented by black squares. The circles, with a dot inside, stand for the carrier females, 8: Beatrice, 7: Alice, 6: Irene, 5: Victoria, 4: Alexandra, 3: granddaughter Alice

a fetal spleen, obtained from a developmental stage before the appearance of T cells, could provide a novel treatment modality for genetic deficiencies of an enzyme or a factor that can be replaced by the growing spleen tissue (Aronovich A et al 2006 Proc Natl Acad Sci USA 103:19075).

Gene therapy has also been explored for factor IX (Christmas disease); the adeno-associated vector carrying the factor IX gene into skeletal muscles had beneficial effects and no toxicity in phase I clinical trials. The latter has the advantage for being a much smaller protein (454 amino acids). In certain cases the therapy is difficult because the patients may produce significant amounts of the so-called circulating anticoagulant (IgG type antigen) that counteracts the beneficial effects of the clinically transfused blood or the supplied blood factors. Prenatal diagnosis is potentially feasible after 10 weeks by DNA analysis and physical mapping or blood samples can be studied for factor VIII. ▶**antihemophilic factors**, ▶**blood clotting pathways**, ▶**X-chromosomal linkage**, ▶**Hageman trait**, ▶**PTA deficiency**, ▶**prothrombin deficiency**, ▶**Stuart factor**, ▶**vitamin K-dependent clotting factors**, ▶**coumarin-like drug resistance**, ▶**MAR**, ▶**parahemophilia**, ▶**afibrinogenemia**, ▶**dysfibrinogenemia**, ▶**fibrin-stabilizing factors**, ▶**von Willebrand's disease**, ▶**Glanzmann's disease**, ▶**thrombopathic purpura**, ▶**thrombopathia**, ▶**hemostasis**, ▶**platelet abnormalities**, ▶**pseudohemophilia**, ▶**transversion**, ▶**retroviral vectors**, ▶**adenovirus**, ▶**gene therapy**, ▶**clinical trials**, ▶**adeno-associated virus**; New England J Med 2001 345[14].

Hemopoiesis: Same as hematopoiesis.

Hemorrhage: Bleeding.

Hemostasis: The checking or arrest of blood flow. Hereditary diseases involved in hemostasis are the hemophilias, platelet abnormalities, the Nishimura factor, Tatsumi factor, Fletcher factor, Dynia factor, Flood factor, thrombocytopenia, May-Hegglin anomaly, and another number of bleeding anomalies that are characterized by abnormal bleeding such as the Fanconi disease, Meekrin-Ehlers-Danlos syndrome, von Willebrand disease, osteogenesis imperfecta, telangiectasia hereditary hemorrhagic, Osler-Rendu-Weber syndrome, pseudohemophilia, and stroke. (See the mentioned items under separate entries; ▶**venom**; McEver RP 2001 Thromb Haemost 86:746).

Hemp: ▶*Cannabis sativa*

Henbane: *Hyoscyamus niger* (2n = 33, 34); a member of the *Solanaceae* family of plants requiring both vernalization and long photoperiods for flowering (see Fig. H26). It is a source of the hyoscyamine and scopolamine alkaloids (ca. 0.04% in the leaves). The Egyptian henbane, *Hyoscyamus muticus*, has higher alkaloid content (0.5%) and also contains hyoscyperin and choline. These alkaloids are used as a smooth muscle relaxant and a sedative. Hyoscyamine (synonym atropine) has a low lethal oral dose of 5 mg/kg in humans, LD50 intravenously in mice is 95 mg/kg. ▶**alkaloids**, ▶**vernalization**



Figure H26. Henbane leaf and flower

Henden's Node (primitive knot): A group of cells in the primitive streak, contributing to the formation of head, notochord, and endoderm of the embryo. ▶ [primitive streak](#), ▶ [organizer](#), ▶ [notochord](#), ▶ [endoderm](#); Shilo BZ 2001 Cell 106:17.

Henderson-Hasselbalch Equation: $\text{pH} = \text{pK} + \log[(\text{A}^-)/(\text{HA})]$, where pH is the hydrogen ion concentration, pK is an equilibrium constant (1/K), (A^-) is a proton acceptor and HA is a proton donor. This equation expresses the relations between pH and ratio of acid to base in a solution.

Hennigian Cladistics: Basically, a version of the parsimony method of analyzing evolutionary pathways. ▶ [maximum parsimony](#), ▶ [parsimony](#), ▶ [cladistics](#); Mishler BD 1994 Am J Phys Anthropol 94:143.

Henrietta Lacks: ▶ [HeLa cell line](#)

Henry of Prussia: The great-grandson of Queen Victoria of England. Henry of Prussia was afflicted with hemophilia. ▶ [hemophilia](#)

HEPA Filter (high-efficiency particulate air): A HEPA filter traps particles, notably microbes, of the air.

Hepadnavirus (hepatotropic DNA virus): Liver-targeting viruses (~3 kb) that replicate via an RNA intermediate. ▶ [hepatitis](#)

Heparan Sulfate: Repeated disaccharide units composed of glucosamine linked to uronic acid or either to (sulfated) glucuronic acid or (sulfated) L-iduronic acid. Heparan sulfates may be present in mucopolysaccharides and thus in the extracellular matrix. Heparan sulfate proteoglycans are coreceptors in cell adhesion, motility, proliferation, differentiation and morphogenesis, and regulate tumor growth and metastasis. Bacteria, viruses, and parasitic protozoa

bind to the cell-surface heparan sulfate proteoglycans (HSPG). Heparan sulfate proteoglycans may serve as receptors for viral surface fibers and mediate the uptake of the RNA or DNA of the transformation vector. The enzyme heparanase can break down the heparan sulfate meshwork and facilitate the metastasis of cancer cells. In addition, it aids angiogenesis. Heparanase inhibitors are therefore expected to interfere with the development and invasiveness of cancer (see Fig. H27). ▶ [iduronic acid](#), ▶ [glucuronic acid](#), ▶ [mucopolysaccharidosis](#), ▶ [exostosis](#), ▶ [angiogenesis](#), ▶ [metastasis](#), ▶ [Wingless](#), ▶ [syndecan](#), ▶ [glypican](#), ▶ [exostosis](#), ▶ [Simpson-Golabi-Behmel syndrome](#); Bernfield M et al 1999 Annu Rev Biochem 68:729; Liu D et al 2002 Proc Natl Acad Sci USA 99:568; Kramer KL. Yost HJ 2003 Annu Rev Genet 37:461.

Heparin: A mucopolysaccharide consisting of repeated units of uronic acid (glucosamine) and glucuronic acid disulfate. It is secreted into the bloodstream primarily by the liver and it has anticoagulant effects. It is employed as an anticoagulant medicine, and in the molecular biology laboratory it is used (with or without dextran) for in situ hybridization. In Southern hybridization it is used as a blocking agent on nitrocellulose (but usually not on nylon) membranes. Heparin may inhibit metastasis of cancer cells. ▶ [in situ hybridization](#), ▶ [Southern hybridization](#), ▶ [heparan sulphate](#), ▶ [metastasis](#)

Heparin Cofactor II (HCF2, 22q11): Several cofactors facilitate the anticoagulant function of heparin. ▶ [thrombophilia](#)

Heparinemia: The accumulation of heparin in the blood often causing problems in blood clotting and thus bleeding. ▶ [hemostasis](#), ▶ [platelet anomalies](#), ▶ [blood clotting pathways](#)

Hepatitis: The neonatal giant cell hepatitis (8q21.3) is a hemochromatosis due to deficiency in steroid biosynthesis. ▶ [steroid dehydrogenase](#), ▶ [hemochromatosis](#)

Hepatitis B Virus (HBV): A member of the hepadnavirus family. The double-stranded DNA genome is ~3.2 kb. The double-layered mature infectious form

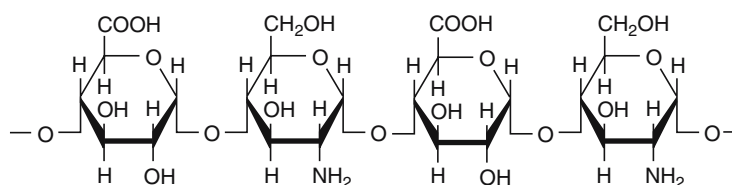


Figure H27. Non-sulphated heparin

is called Dane particle. HBV is replicated through a process of reverse transcription: DNA \Rightarrow RNA \rightarrow single-strand DNA \Rightarrow partially double-strand DNA. The viral DNA may be episomal or it may integrate into the cellular DNA of the host cell by random non-homologous recombination. The virus does not kill the cell upon integration, rather it causes a stable transformation and replicates along with the chromosomes. Infection may increase liver cancer development 5 to 30-fold or more. It is endemic in South-East Asia, tropical Africa and along the Amazon River in South America. Transmission is through body fluids (oral ingestion, blood transfusion, sexual contact, nursing) of the infected persons. The incubation period is one to six months. The disease caused involves fever, vomiting, jaundice, arthritis, etc. Some individuals recover completely but remain carriers and may have a high chance of developing cirrhosis or liver cancer. There are about 350 million chronic HBV carriers worldwide and about one million die annually from complications caused by the infection. The development of effective DNA immunization seems to be a desirable goal. Currently, vaccines based on viral subunits are being used. The HAV and the HCV virus are single-stranded RNA viruses. ►liver carcinoma, ►immunization genetic, ►retroid virus; Ganem D, Schneider RJ 2001 In: Knipe DM, Howlery PM (eds) *Fundamental Virology*, Lippincott Williams & Wilkins, Philadelphia, gene expression, pp 1285; Uprichard SL et al 2003 *Proc Natl Acad Sci USA* 100:1310; particle organizations: Gilbert RJC et al 2005 *Proc Natl Acad Sci USA* 102:14783; http://www.hpa-bioinfodatabases.org.uk/hepatitis_open/main.php.

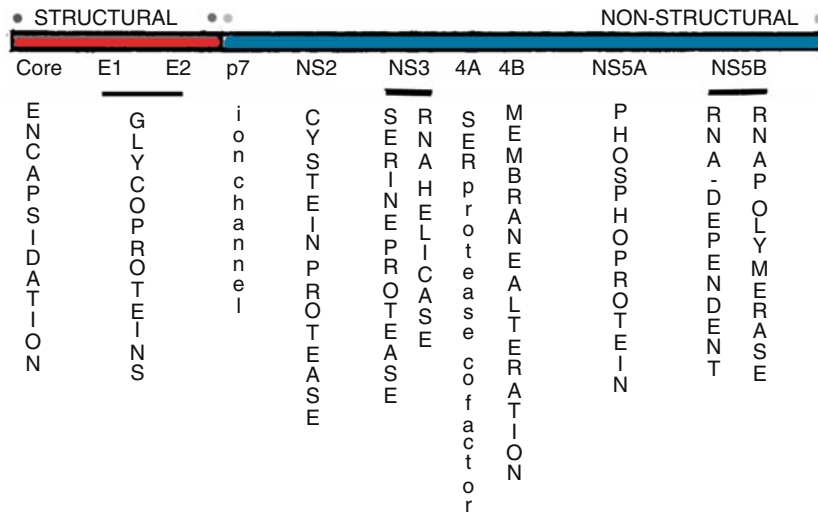
Hepatitis C Virus (HCV): A member of the Flaviviridae family. HCV infects only humans and chimpanzees; there are no small animal disease models. Its positive-strand RNA genome of ~9.5-kb nucleotides, encodes a polyprotein of 3010–3033 residues. A serine protease processes its polyprotein and this is required for its replication. Inhibition of the protease may be a means for defense (Lamarre D et al 2003 *Nature [Lond]* 426:186). Unfortunately, in a single infected individual about a trillion virus particles are produced daily and each of them may be different from the template strand by one mutation. An estimated 1–3% of the world population is infected by it and chronic infection may lead to liver diseases and cancer. Hepatitis B and C viruses seem to be responsible for 50 to 70% of the cases of hepatocellular carcinomas. Immunization is not available because of the great variety of mutant forms present in the infected individuals. Currently, interferons (IF) are used as a medication but many isolates are resistant to it because the E2 viral coat protein can inhibit the

RNA-inducible protein kinase (PKR). Interferon and ribavirin combination improves treatment effectiveness (Dixit NF et al 2004 *Nature [Lond]* 432:922). IF normally activates PKR that would block the translation initiation factor eIF2 α . R. De Francesco G Migliaccio (2005 *Nature [Lond]* 436:953); Houghton and M Abrignani S 2005 (*Nature [Lond]* 436:961) have summarized newer therapies. Thus, E2 conveys resistance to interferon by facilitating protein synthesis in the cell in the presence of IF. Other pathways of resistance may also exist. HCV can replicate in cell cultures when adaptive mutation(s) occur. Inhibition of geranylation of several host proteins disrupts HCV replication and may promise therapeutic use (Ye J et al 2003 *Proc Natl Acad Sci USA* 100:15865). Although replication in cell cultures of subgenomic particles was earlier known, the complete replication of the full-length genomes in cell cultures has now become known (Lindenbach BD et al 2005 *Science* 309:623; Lindenbach BD et al 2006 *Proc Natl Acad Sci USA* 103:3805). The feasibility of in vitro culture appears to be an important step toward overcoming the debilitating human disease. Recombinant HCV-like particles (HCV-LPs) containing HCV structural proteins (core, E1, and E2) (see Fig. H28), produced in insect cells, resembled the putative HCV virions and were capable of inducing strong and broad humoral and cellular immune responses in mice and baboons in small-scale experiments (Elmowalid GA et al 2007 *Proc Natl Acad Sci USA* 104:8427). ►positive-strand virus, ►eIF2 α , ►PKR, ►claudin; WHO 1999 *J Viral Hepat* 6:35; Barbato G et al 2000 *EMBO J* 19:1195; *Nature* Insight summary of current information: *Nature [Lond]* 436:930–978; interferon pathway targeting by HCV: Meylan E et al 2005 *Nature [Lond]* 437:1167; sequence and immunology database: <http://hcv.lanl.gov/content/hcv-db/index>; European Hepatitis C: <http://euhcvdb.ibccp.fr>.

Hepatitis Delta Virus (HDV): The hepatitis delta virus has a closed circular RNA genome of 1.7 kb packaged into folded and base-paired rods. It codes for two proteins that are edited from a single RNA transcript. The editing is carried out by a double-stranded-RNA-adenosine deaminase. This virus cannot be packaged without the hepatitis B virus. ►hepatitis B virus

Hepatocerebral: Involves the liver and brain

Hepatocyte: A type of liver cell; they are arranged in folded sheets, facing blood-filled spaces (sinusoids). The hepatocytes are responsible for synthesis, degradation, and storage of many substances. The detoxification in the hepatocytes, with the assistance of cytochrome P450, may also produce ultimate mutagens and carcinogens as part of the process.



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Figure H28. Hepatitis C Virus map. (Redrawn after Lindenbach & Rice 2005 Nature [Lond] 436:933)

Hepatocytes also secrete the bile that mediates the absorption of fats. The forkhead transcription factors, Foxa1/Foxa2, are required for competence within the foregut endoderm for the onset of liver development (Lee CS et al 2005 Nature [Lond] 435:944). Partially hepatoectomized rodent livers are induced to regeneration (Huang W et al 2006 Science 312:233) by increase in bile acid supply and the farnesoid X-activated nuclear bile acid receptor FXR (human chromosome 12q). Severely immunodeficient fumarylacetoacetate hydrolase (Fah)-deficient mice have been constructed which, after pretreatment with a urokinase-expressing adenovirus, could be very successfully engrafted (up to 90%) with human hepatocytes from multiple sources, including liver biopsies. The human cells could then be serially transplanted from primary donors and made to repopulate the liver for at least four sequential rounds. The expanded cells displayed typical human drug metabolism and appear to be a promising model for the study of human liver diseases (Azuma H et al 2007 Nature Biotechnol 29 July doi:10.1038/nbt1326).
 ►hepatoma, ►scatter factor, ►farnesoid X receptor

Hepatocyte Growth Factor (HGF): A mitogen and morphogen, it controls processes in the liver and placental development. Its receptor is a heterodimeric transmembrane protein tyrosine kinase. It has numerous functions such as organ regeneration, angiogenesis, and metastasis of tumors. Also, it is a “scatter factor” because it dissociates epithelial cells and stimulates cell motility. ►scatter factor, ►mitogen, ►morphogen, ►metastasis, ►MET oncogene; Cao B et al 2001 Proc Natl Acad Sci USA 98:7443.

Hepatoma: A liver tumor; originally, it is the transition stage between the generally benign adenoma and the

malignant carcinoma of the liver. Ovarian hormones suppress hepatoma development and therefore male mice and men show five-fold higher incidence of hepatocarcinomas. Myc-induced hepatocarcinoma displays sustained regression and normal-appearing differentiation upon inactivation of Myc, but upon reactivation of the oncogene cancerous growth returns (Schachaf CM et al 2004 Nature [Lond] 431:1112). ►liver cancer, ►chi elements

Hepatomegaly (enlargement of the liver): ►glycogen storage diseases, ►lipodystrophy

Hepatotoxicity: Toxicity to the liver.

Hepcidin (HAMP, 19q13): An antimicrobial peptide of 84 amino acids that processed into mature cysteine-rich peptides of 20, 22, and 25 amino acids. Its deficiency leads to hemochromatosis because of its regulatory role in iron intake. Hepcidin synthesis is stimulated most importantly by IL-6, but IL-1 is also effective (Lee P et al 2005 Proc Natl Acad Sci USA 102:1906). Hemojuvelin, a bone morphogenetic protein coreceptor, regulates hepcidin levels (Babbitt JL et al 2006 Nature Genet 38:531). ►hemochromatosis, ►ferroportin, ►IL-6, ►IL-1, ►bone morphogenetic protein; Roetto A et al 2003 Nature Genet 33:21.

HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid): HEPES is used for the preparation of buffers in the pH range 7.2–8.2.

Heptamer: ►immunoglobulins

HER (hybrid excision and repair): ►HEI

her: A mutation that converts X0 *Caenorhabditis* males into females.

HER2: Synonymous with ERBB2 (avian erythroblastosis leukemia viral oncogen homolog, 17q21.2); ►**ERBB1**. The HER2 gene may be amplified by 25% in breast cancer (Meng S et al 2004 Proc Natl Acad Sci USA 101:9393). HER2-mediated metastasis is upregulated by receptor CXCR4 and the inhibition of this receptor suppresses metastasis (Li YM et al 2004 Cancer Cell 6:459). Also HER2/ERBB2 protein tyrosine kinase associated in breast cancer with the kinase CHK/MATK (19p13.3). The HER2 gene also encodes the autoinhibitor herstatin. Fatty acid synthase (FAS) inhibition suppresses HER2 overexpression in cancer (Menendez JA et al 2004 Proc Natl Acad Sci USA 101:10715). ►**tumor-associated antigen**, ►**ETS**, ►**EGFR**, ►**CXCR4**, ►**breast cancer**, ►**metastasis**; Tzahar E et al 1997 EMBO J 16:4938.

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HER3 (c-Erb-b3): HER3 and other HER proteins are human epidermal growth factor receptor tyrosine kinases and can drive cancer growth (Singer E et al 2001 J Biol Chem 276:44242). When HER2 is inactivated HER3 may take over the role of HER2 (Sergina NV et al 2007 Nature [Lond] 455:437).

Herbaceous: Plant tissue without woody components.

Herbal: Old books with descriptions of plants considered mainly for spice or medicinal use.

Herbarium: A museum collection of dried plant specimens, classified, identified, and described.

Herbicides: Herbicides are chemicals that regulate plant growth. The first herbicides were synthetic auxins (dichlorodiphenyl trichloroacetic acid, 2,4-D). Some of the general type weed killers, e.g., 3-amino triazole, were very potent human carcinogens although they did not respond as positive in the majority of short-term mutagen-carcinogen assay systems. Some herbicides kill plants as germination inhibitors (pre-emergence weed killers such as atrazine). Atrazine interferes with electron transport in photosystem II (photosynthesis) and may disrupt sex hormones. About 20 species of weeds have developed resistance to atrazine since its introduction in agricultural practice in the 1950s. Recently, atrazine was replaced by glyphosate (ROUNDUP), an inhibitor of the biosynthesis of aromatic amino acids by blocking enol-pyruvylshikimate-3-phosphate synthase (EPSP). Glyphosate tolerance is controlled by glyphosate N-acetyl transferase (Castle LA et al 2004 Science 304:1151). Few plant species have yet to develop a resistance to glyphosate.

DICAMBA (3,6-Dichloro-2-methoxybenzoic acid; toxic and carcinogenic) (see Fig. H29) is effective as

glyphosate and other widely used herbicides. The genetically engineered bacterial gene DMO (dicamba monooxygenase) is capable of inactivating dicamba when expressed from either the nuclear genome or chloroplast genome of transgenic plants. The enzyme inactivates the herbicide before toxic levels are reached in treated transgenic crop plants (Behrens MR et al 2007 Science 316:1185).

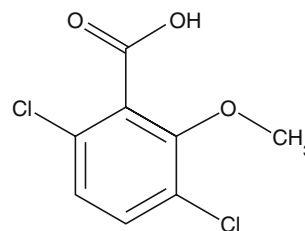


Figure H29. Dicamba

In glyphosate resistance wheat showed pre- and post-infestation relief against leaf rust (*Puccinia striiformis* and *Puccinia triticina*) and also suppressed Asian soybean rust (*Phacopsora pachyrhizi*) in limited trials (Feng PCC et al 2005 Proc Natl Acad Sci USA 102:17290). (Glyphosate is also effective against some protozoa, e.g., *Plasmodium falciparum*.) Sulfonylureas are selective herbicides of dicotyledonous plants—non-toxic to animals—and they inhibit the acetolactate synthase/acetohydroxyacid synthase enzyme (ALS) in the branched pathway of leucine, valine, and isoleucine (McCourt JA et al 2006 Proc Natl Acad Sci USA 103:569). By a highly selective isolation system resistant mutants were obtained. Resistance under field conditions can be a serious problem. The non-selective herbicide glufosinate-ammonium (phosphinothricin, BASTA) specifically inhibits the glutamine synthetase enzyme (GS). The plants accumulate highly toxic levels of ammonia. The dinitroanilin herbicides (trifluralin, oryzalin) depolarize cytoskeletal tubulins. Three base mutations in its host target molecule results in resistance against this herbicide. Herbicide research took advantage of transformation techniques by developing bacterial EPSP transgenic crop plants (cotton, sorghum, maize, alfalfa, canola, tomato, sugar beet) to make them resistant to glyphosate while the weeds are eliminated. Even greater resistance to glyphosate can be assured by introducing, into crop plants, the *Bacillus licheniformis* gene encoding glyphosate N-acetyltransferase (GAT). The resistance of cultivated plants against sulfonylureas could also be enhanced four-fold by insertion of the ALS gene. The high level of activity of these enzymes permits the transgenic plants to escape death. BASTA resistance was engineered into plants using a gene from *Streptomyces* bacteria that inactivates the

herbicide by acetylation, and, as a consequence, toxic levels of ammonia do not accumulate. Hydantocidin, a spironucleoside, binds to the regulation site of adenylosuccinate synthetase and thus blocks purine biosynthesis in the cells. The overexpression of an ATP-binding cassette efflux protein and apyrase facilitates multiherbicide (and some other chemicals) detoxification and thus generates resistance (Windsor B et al 2003 *Nature Biotechnol* 21:428). Acetyl-CoA carboxylase (ACCase)-inhibiting herbicide resistance for grass weeds was correlated with any of the following five amino acid replacements in the plastids: Ile-1,781-Leu, Trp-1,999-Cys, Trp-2,027-Cys, Ile-2,041-Asn, and Asp-2,078-Gly. Some of the same replacements conferred resistance to aryloxyphenoxypyrone (APP) and cyclohexanedione herbicides in oats and wheat (Liu W et al 2007 *Proc Natl Acad Sci USA* 104:3627).

There is always the possibility that the herbicide-resistance transgene escapes from the crop plants to related weed species by cross-fertilization through the pollen. This risk can be greatly reduced if the resistance transgene is inserted into chloroplast DNA. The large majority of plants do not transmit plastids through the pollen. Another potential advantage of chloroplast transformation is the increased number of transgene copies per cell. Transformation of chloroplasts and mitochondria (by biolistic methods) is somewhat more difficult than introducing foreign genes by agrobacterial vectors into the plant cell nucleus. ▶bialaphos, ▶spironucleoside, ▶transformation, ▶biolistic transformation, ▶transformation of organelles, ▶intein, ▶*Agrobacterium*, ▶vectors, ▶tubulins, ▶acetyl-CoA carboxylase; molecular basis of Roundup resistance: Funke T et al 2006 *Proc Natl Acad Sci USA* 103:13010; Palumbi SR 2001 *Science* 293:1786; herbicide resistance: Gressel J, Levy AA et al 2006 *Proc Natl Acad Sci USA* 103:12215; <http://www.dnr.state.wi.us/org/land/er/invasive/info/herbicides.htm>.

Herbivore: An organism feeding on plants. Insects or higher animal herbivores may cause economic damage. One study indicates that koalas do not like eucalyptus trees with high concentrations of formylated phloroglucinol compounds (see Fig. H30) or low concentrations of nitrogen (Moore BD, Foley WJ 2005 *Nature [Lond]* 435:488). ▶insect resistance, ▶koala

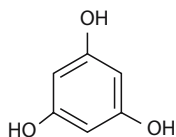


Figure H30. Phloroglucinol

Herceptin (ERBB2, Trastuzumab): An anti-HER2 antibody to control the development of breast cancer and other cancers. It is commonly used with conjugates such as Paclitaxel (a taxol derivative). ▶HER2, ▶breast cancer, ▶ERBB, ▶taxol

Hereditary: Hereditary means being biologically inherited because of the genetic constitution of the family. Being hereditary does not imply perfect transmission to, and expression in, the progeny. The phenotype observed depends on the gene concerned and the environmental factors modifying their expression. The gene(s) responsible for a phenotype may be transmitted without expression under some conditions(s) and the condition still may be hereditary. ▶familial, ▶congenital, ▶reaction norm, ▶heritability, ▶penetrance, ▶expressivity, ▶epigenesis

Hereditary Nonpolyposis Colorectal Cancer (Lynch syndrome, HNPCC, MSH2 chromosome 2p16 and in MLH1 chromosome 3p21, MSH6 in 2p15): HNPCC is accompanied by a high rate of mutation in microsatellite sequences. The mutability is caused by deficiency in mismatch repair controlled by four loci, MSH2, MSH6, GTBP, MLH1, and to a lesser extent by PMS1 and PMS2 (7p22), homologous to microbial enzymes, MutS and MutL. Hypermethylation of the human MLH1 promoter is a frequent cause of insufficient repair. In a family in three successive generations germline allele-specific and mosaic hypermethylation of the *MSH2* gene was detected, without evidence of DNA mismatch repair gene mutation. Three siblings carrying the germline methylation developed early-onset colorectal or endometrial cancers, all with microsatellite instability and MSH2 protein loss. Pyrosequencing showed different methylation levels in different somatic tissues, with the highest level recorded in rectal mucosa and colon cancer tissue, and the lowest in blood leukocytes. Detection of transmission of this condition failed earlier indicating that this case was a hereditary epimutation (Chan TL et al 2006 *Nature Genet* 38:1178). Its prevalence is about 2×10^{-3} . The hereditary nature of HNPCC is determined by the Amsterdam criteria. ▶colorectal cancer, ▶microsatellite, ▶polyposis, ▶Amsterdam criteria, ▶mismatch repair, ▶epimutation, ▶trinucleotide, ▶Gardner syndrome, ▶gastric cancer, ▶histone deacetylase, ▶Muir-Torre syndrome, ▶Turcot syndrome; de la Chapelle A, Peltomäki P 1995 *Annu Rev Genet* 29:329; Scott RJ 2001 *Am J Hum Genet* 68:118; Wagner A et al 2003 *Am J Hum Genet* 72:1088.

Hereditary Tyrosinemia: ▶tyrosinemia

Heredity: The study of the storage, transmission, and expression of genetic information. ► [inheritance](#), ► [genetics](#), ► [reverse genetics](#)

Heregulins (glial growth factor/neuroglin differentiation factor/NDGF): Heregulins are transmembrane protein tyrosine kinase receptor ligands (44 kDa, encoded at human chromosome 8p22-p11) present in breast carcinoma and fibrosarcoma cell lines. They bind to the NEU/ERBB2 oncogene. ► [ERBB1](#), ► [\[ERBB2\]](#), ► [oncolytic virus](#); Lee H et al 2001 *Cancer Res* 61:4467.

Herfindahl Index: The Herfindahl index is “the sum of squares of the patent shares (in percentage terms) of each patent assignee (range 0 to 10,000), where 10,000 represent “monopolist” with 100% of patents owned by assignee and low numbers represent more fragmentations” (Jensen K, Murray F 2005 *Science* 310:239). ► [patent](#)

HERG: A human, inward rectifying K⁺ ion channel, responsible for the LQT2 syndrome, encoded in chromosome 7q35–36. HERG is also a regulator of tumorigenesis and apoptosis. ► [ion channels](#), ► [LQT1](#), ► [LQT3](#), ► [Jervell and Lange-Nielsen syndrome](#); Wang H et al 2002 *Cancer Res* 62:4843.

Heritability (h^2): Heritability is generally defined as the ratio of the additive genetic variance and the phenotypic variance (narrow-sense heritability). In some cases only the ratio of the total genetic variance and the phenotypic variance can be determined (broad-sense heritability). Heritability can be estimated by offspring-parent regression, intraclass

correlation and by special methods in humans. Heritability below 0.25 is considered low and above 0.75, high (see Table H1). Generally, heritability of genes barely affecting fitness (e.g., spotting of the fur coat) is higher than for those traits that are important for reproductive success (fertility). The broad-sense heritability of intelligence displays variations during development. In children it may be 40–50%, but by adolescence it may climb to 60–70% or above. The estimates of heritability are valid only for the population that provided the information. In different populations different sets of polygenes may exist and they may provide different heritability estimates. In experimental animals and plants, generally, the narrow sense heritability is used because that is much more predictive.

► h^2 , ► [heritability in the broad sense](#), ► [heritability in the narrow sense](#), ► [correlation](#), ► [intraclass correlation](#), ► [heritability estimation in humans](#), ► [realized heritability](#), ► [QTL](#), ► [behavior genetics](#); <http://www.sfbr.org/solar/index.html>; human variation: www.hgvs.org/; sequence variation database: www.ebi.ac.uk/mutations/.

Heritability, Broad Sense: The total, genetically determined fraction of the phenotypic variance. ► [variance](#), ► [genetic variances](#)

Heritability Estimation in Humans: This may be important in the study of various anthropometric traits, and other polygenically determined conditions such as weight, height, behavior, various types of mental illness, epilepsy, heart disease, diabetes, etc. Since monozygotic twins are expected to be identical

Table H1. Selected heritability estimates in various animals and plants

| HUMANS | | CATTLE | | MAIZE | |
|------------------|------|-----------------|------|---------------|------|
| schizophrenia | 0.75 | white spots | 0.95 | plant height | 0.51 |
| epilepsy | 0.50 | milk production | 0.43 | kernel number | 0.40 |
| MOUSE | | conception rate | 0.03 | yield | 0.29 |
| tail length | 0.60 | SWINE | | ear number | 0.20 |
| litter size | 0.15 | litter number | 0.20 | SOYBEAN | |
| DROSOPHILA | | weaning weight | 0.10 | maturity | 0.75 |
| abdomen bristles | 0.50 | CHICKEN | | plant height | 0.62 |
| egg number | 0.20 | egg weight | 0.75 | oil percent | 0.55 |
| SHEEP | | egg number | 0.25 | seed weight | 0.54 |
| wool length | 0.55 | viability | 0.10 | | |

genetically, any variation between them is supposed to be environmental. Dizygotic twins are of the same age exactly but genetically as different as any other sibs. Thus, heritability (h^2) is calculated frequently as:

$$\frac{\text{variance of dizygotics} - \text{variance of monozygotics}}{\text{variance of dizygotics}} = h^2$$

or

$$\frac{\text{percent monozygotic concordance} - \text{percent dizygotic concordance}}{100 - \text{dizygotic concordance}} = h^2$$

or using the correlation coefficients (r) of monozygotic twins reared together (r_{mzt}) and reared apart (r_{mza}):

$$\frac{(r_{mzt}) - (r_{mza})}{1 - (r_{mza})} = h^2$$

The interpretation in all of these cases has some limitations. The estimate is valid only if the variance is of the additive type because direct estimation, in the absence of controlled matings, cannot be carried out. In the presence of dominance variance, the genetic determination will be underestimated in the two formulas given above. Because the common assortative matings in human populations leads to positive correlation between the parents it thus overestimates heritability. The heritability estimates may be biased if major genes are also involved. Furthermore, environmental variation may not be the same for monozygotic (identical) twins as for dizygotic ones. Generally, it has been difficult to find large enough numbers of twins for precise comparisons. Also, it must be kept in mind that in humans, just as in other organisms, heritability measured in one population, even for the same trait, may not be valid for another population. It would be of great interest to know the heritability of human diseases. Unfortunately, many complicating, nongenetic factors are involved in the development of complex diseases such as cancer (Hemminki K et al 2006 *Nature Rev Genet* 7:958). ▶correlation, ▶intraclass correlation, ▶ h^2 , ▶monozygotic twins, ▶heritability in the broad sense, ▶heritability in the narrow sense, ▶variance, ▶confidence interval, ▶standard error, ▶heritability of some human polygenic disease susceptibility such as blood pressure, ▶lipids, ▶glycemia; pulmonary functions: <http://www.nhlbi.nih.gov/about/framingham/policies/pagetwelve.htm>.

Heritability, Narrow Sense: Narrow-sense heritability is the genetically determined fraction of the phenotypic variance, excluding nonfixable interactions such as due to overdominance. ▶heritability, ▶heritability broad sense

Heritable Translocation Tests as Bioassays in Genetic

Toxicology: Animals exposed to mutagens are tested for sterility or semi-sterility and also examined cytologically for multivalent association during diakinesis to metaphase I in the spermatocytes. Since many of these translocations are transmitted to the progeny, this procedure permits an assessment of how much particular mutagenic agents increase the genetic load of mammals, and potentially of humans too. ▶chromosome breakage in bioassays for genetic toxicology

Hermansky-Pudlak Syndrome: A rare, recessive, human chromosome 10q23 disease, although in some endemic populations (Puerto Rico, Switzerland) its prevalence is $5-6 \times 10^{-4}$. Another locus is at 3q24. In the mouse about 16 loci are involved with the HP syndrome. It involves pigmentation defects (ocular albinism, freckles but the inability to get tanned), predisposition to bruising and bleeding, ceroid storage defects, large and abnormal melanocytes, lower platelet count, and defective lysosomes. Survival is usually limited to 20–25 years. The defect seems to involve a transmembrane protein and lysosomal secretion defect may be involved. This syndrome bears similarities to the Chádiak-Higashi syndrome. ▶Chádiak-Higashi syndrome, ▶albinism, ▶melanocyte, ▶pigmentation of animals, ▶platelet, ▶lysosome, ▶ceroid, ▶lysosomal storage diseases; Anikster Y et al 2001 *Nature Genet* 28:376; Huizing M et al 2001 *Am J Hum Genet* 69:1022.

Hermaphrodite: Both male and female sex organs are present in the same individual. If the same plant bears both male and female flowers but individual flowers are either male (pollen producer) or female (egg producer), it is called monoecious. Hermaphroditism is the most common form of sexual differentiation in plants, but normally it is very limited in the animal kingdom (to flatworms, nematodes, some annelids and crustaceans, etc.) (see Fig. H31). In true hermaphroditism the same individual develops both ovarian and testicular structures. Its frequency is low in mammals, including humans. The majority of human true hermaphrodites have a 46XX constitution and about $\frac{1}{4}$, 46XY; the remaining groups have sex chromosomal mosaicism and are considered to be males by appearance until puberty. In the majority of cases pseudohermaphroditism is observed, i.e., the sex chromosomal constitution does not match the gonadal phenotype. The chromosomally XY individual appears feminine in many ways or the XX individual appears virile. Pseudohermaphroditism may arise by mutation in, or by translocation of, the SRY gene, mutation in the Müllerian duct inhibitor substance gene, defects in the androgen receptor or deficiency in the testosterone 5 α -reductase.

►intersex, ►pseudohermaphrodite male, ►testicular feminization, ►freemartins, ►sex ratio, ►sex reversal, ►sex determination, ►gonadal dysgenesis, ►Müllerian ducts, ►Wolffian ducts; Mittwoch U 2001 J Exp Zool 290:484.



Figure H31. Hermaphrodite pig by courtesy of Dr. L. Lojda

Heroin: A highly addictive drug. ►poppy

Herpes: A family of double-stranded (linear) DNA (see Fig. H32) viruses with 120–250-kbp genetic material (HSV-1; ca. 75 genes); the capsid is made of about 30 polypeptides. The viruses replicate in the cell nucleus that protrudes through the nuclear membrane into the endoplasmic reticulum. HSV-1 evades the host immune system by the expression of the gE-gI Fc receptor and binds to the Fc region of immunoglobulin G. HSV-1 gE-gI is a heterodimer. gE is a 530 residue protein including a ~401 residue portion followed by a single transmembrane helix and a ~94-residue C-terminal tail. gI has ~370 residues including a ~248 residue extracellular followed a single transmembrane helix and a ~94-residue tail.

The C-terminal CgE ectodomain of gE binds to the $C_H^2-C_H^3$ region of the mammalian antibody's Fc region. The binding is bipolar, i.e., gE-GI is bound to Fc and to a specific gC or gD viral antigen. The bipolar binding at neutral or slightly acid pH protects and helps the spreading of the virus (Sprague ER et al 2006 PLoS Biol 4(6):e148).

There are more than 100 types of herpes viruses and many are serious pathogens; some benign forms are also common in humans. The herpes virus associated with Kaposi sarcoma encodes a chemokine (vMIP-II) that binds to a broad spectrum of chemokine receptors and can thereby block the entry of other viruses (e.g., HIV) into the cells. Most humans harbor latent herpes viruses from early infections during their life. These latent forms rarely erupt in infection again. Latent infection of mouse with viruses similar to the Epstein-Barr virus and cytomegalovirus become resistant to *Listeria monocytogenes* and *Yersinia pestis* bacteria through the continued production of the antiviral interferon- γ (Barton ES et al 2007 Nature [Lond] 447:326).

Herpes Type 1 is responsible for cold sores and Type 2 for obnoxious and painful eruptions in the genital area. The Epstein-Barr virus, a member of the family, is held responsible for nasopharyngeal (nose-throat) carcinoma. The cytomegalovirus, which usually causes mild symptoms, is also a herpes virus, as are also equine and gallid herpes (the latter is responsible for the Marek's disease of poultry [discovered by József Marek, Hungarian veterinary professor]). The herpes simplex virus 1 (HSV-1, 152 kbp) is used as a therapeutic genetic vector to deliver and express genes in the central nervous system, selective destruction of cancer cells, and for prophylaxis against

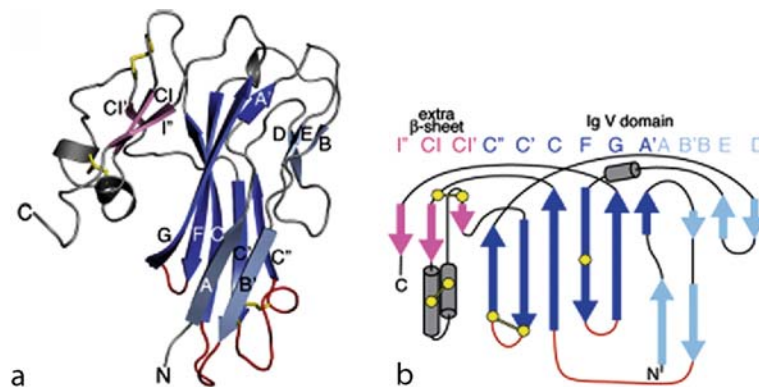


Figure H32. Ribbon diagram of the CgE structure of HSV-1. β -strand D, E, B, B' and A are light blue, strands A', G, F, C, C' and C'' are dark blue, strands CI', CI and I'' are pink. α -helices are gray. Disulphide bonds are yellow and the three CDR loops (as defined in Ig V domine structures) are red. At right CgE topology. β -strands are shown as arrows and colored as at left. α -helices are gray cylinders. Cysteines are yellow circles with disulphide bonds by yellow lines between paired cysteines. (From Sprague ER, Wang C, Baker D & Bjorkman PJ 2006 PLoS Biol 4(6):e148)

HSV and other infectious agents. The carrying capacity of the HSV vector is about 15–30 kb DNA. The *E. coli* origin of replication permits its propagation in bacteria. For successful propagation in eukaryotic cells, helper HSV-1 is used but it contains either mutations or deletions to avoid its lethal cytotoxic effects. Nevertheless, reversions may occur but in the best helper stocks back mutation is in the 10^{-6} to 10^{-7} range. pHSV amplicon may also be propagated with the assistance of cosmid vectors, which may contain all the essential genes of the virus in fragments but lack the packaging signal. Therefore, lethal infectious virions cannot be reconstituted yet they assure the propagation of the pHSV vector (see Fig. H33) in various types of cells. The newer types of pHSVs may accommodate several genes although generally passengers larger than 15 kb are undesirable. Also, several cell-specific promoters have been employed to facilitate more precise targeting. Another version of the pHSV carries a functional IE3 gene required for the production of the ICP protein (infected cell protein) regulators of transcription and translation. This gene is deleted in the helper virus and it can propagate only by complementation with pHSV. As a consequence, a higher proportion of pHSV is obtained after transfection. Yet another construct of pHSV also contains the inverted terminal repeats (ITR) of the adeno-associated virus (AAV) as well as the AAV *rep* gene. Such a construct integrates specifically into the human chromosome at site 19q13 and behaves there as a stable provirus without disrupting any essential function of the human genome.

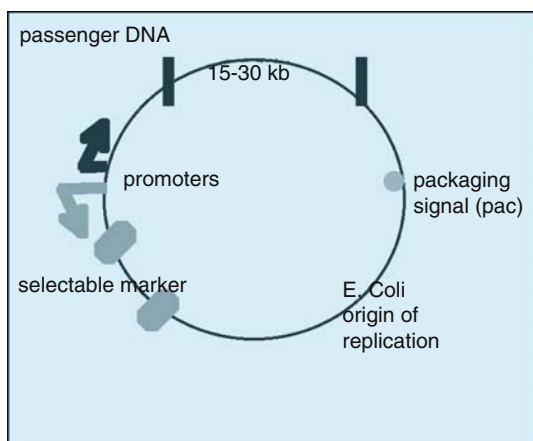


Figure H33. Outline of herpes simplex vector, pHSV

Several herpes viruses of the varicella virus group evade cytotoxic T cells by interfering with TAP, a heterodimer of ATP-binding cassette transporter. Normally, MHC class I- β_2 -microglobulin is involved in antigen-presentation to the T lymphocytes and in

the absence of the transport, the MHC I molecules are not loaded with peptide antigen. Herpes simplex virus 1 and 2 encode a cytoplasmic protein, IPC47, that competes effectively with peptide binding to the TAP heterodimer and the transport system ultimately ubiquitinated. Human cytomegalovirus relies on an endoplasmic reticulum-resident type I membrane protein, US6, for the inhibition of TAP by conformational alteration of the transporter complex and that prevents translocation. The murine γ -herpesvirus 68-encoded K3 protein destabilizes MHC class I molecules, TAP and tapasin, and eventually degrades the system. The bovine herpesvirus, the pseudorabies virus and the equine herpesvirus encode the glycoprotein, UL49.5, which evades the killer lymphocytes by impeding the TAP-driven peptide import into the endoplasmic reticulum. Thus all these viruses save their invading ability by different proteins and basically by the same principle, by preventing effective antigen-presentation to killer lymphocytes (Koppers-Lalic D et al 2005 Proc Natl Acad Sci USA 102:5144). ▶Epstein-Barr virus, ▶Marek's disease, ▶cytomegalovirus, ▶gene therapy, ▶Kaposi sarcoma, ▶shingles, ▶chemokines, ▶VP16, ▶LAT, ▶viral vectors, ▶adeno-associated virus, ▶amplicon, ▶TAP, ▶MHC, ▶antigen presenting cell, ▶antibody, ▶killer cell, ▶ubiquitin, ▶tapasin, ▶HVEM, ▶cleft palate; Boehmer PE and Lehman IR 1997 Annu Rev Biochem 66:347; Brune W et al 2000 Trends Genet 16:254; Albà MM et al 2001 Genome Res 11:43; Wolfe D et al 2004 Methods Mol Biol 246:339.

Hers Disease: ▶glycogen storage diseases Type VI

Hershey-Chase Experiment: This experiment demonstrated that only the T2 phage DNA uptake was necessary to reproduce phage in *E. coli* and the phage coat protein was not required. It thus proved that DNA is the genetic material of this bacteriophage (Hershey AD, Chase M 1952 J Gen Physiol 36:39).

Hershey Circle: A nicked phage λ DNA circle in the bacterial host. ▶nick

Hertz (Hz): The unit of the number of cycles in alternating electric currents. In the USA the standard is 60 Hz. 1 megahertz (MHz) is 1 million pulses/second. Modern personal computers employ 300–600 or even much higher MHz microprocessors.

HERV (human endogenous retrovirus): ▶endogenous virus; <http://herv.img.cas.cz>.

Hesitation, Transcriptional: ▶pausing transcriptional

He-T Sequences: Repetitive DNA in the heterochromatin and near the telomeres of *Drosophila*. ▶heterochromatin, ▶telomere

HeT-A: Polyadenylated 6-kb retroposons (no LTR) specific for the telomeres of *Drosophila*, belonging to the family of LINE elements. The 2.8-kb open-reading frame encodes a zinc-finger protein but no reverse transcriptase. Thus, for transposition, it is expected to depend on this function, coded elsewhere in the genome. ▶telomere, ▶retroposon, ▶LINE, ▶zinc finger, ▶TART

Heteradelphian: Conjoined twins or other rare teratological anomalies such as extra limbs without hereditary basis.

Heteroalleles: Nonidentical alleles, which may recombine (involve different nucleotide sites in a cistron). ▶allele, ▶cistron

Heterobrachial: When the two arms of the chromosomes are not identical in length (see Fig. H34). ▶chromosome arm, ▶isobrachial, ▶chromosome morphology



Figure H34. Heterobrachial chromosome

Heterocaryon: ▶heterokaryon (the desirable spelling).

Heterocatalysis: A catalytic process resulting in a product different from the starting material, e.g., the function of enzymes yields a compound different from the substrate or the enzyme. ▶autocatalytic function

Heterocellular: A body or tissue made up of different cells.

Heterochromatin: Parts of the chromosome that stain dark even during interphase (heteropycnotic). The *constitutive heterochromatin* remains in a highly condensed state in all the cells of an organism. Heterochromatin usually reduces recombination and transposon insertion and may affect the expression of adjacent genes (position effect). It contains repetitive and methylated DNA that is usually not transcribed and translated; it is assumed to contain monotonous satellite DNA that is generally rich in AT sequences. It is frequently localized to both sides of the centromeres and to the telomeres. The centromeric heterochromatin of *Drosophila* contains blocks of satellite DNA interrupted at 20- to 200-kb middle-repetitive sequences and by single complete transposable elements. Certain chromosomal regions,

such as most of the Y chromosomes and the B – chromosomes, are heterochromatic. The constitutive heterochromatin can be seen as distinctly and characteristically located cross bands of the chromosomes after stained with Giemsa or other stains. Facultative heterochromatin may be in a relaxed state when it is expressing some information in some cells at certain developmental stages but not under other conditions. The mammalian X chromosome, displaying dosage compensation, becomes heteropycnotic in the additional copies, e.g., in the normal females one of the two X chromosomes is heterochromatic although both of the X chromosomes can be expressed in the males when they are present in a single dose (XY) or in the XO females the single X chromosome is not heteropycnotic. In XXX trisomic individuals two are heteropycnotic and in XXXX superfemales three are heteropycnotic and show two or three Barr bodies, respectively, when in the normal females (XX) there is only one Barr body. The facultative heterochromatinization in the two X chromosomes permits the expression of one or the other alleles of a gene associated with these chromosomes and this results in a variegation called lyonization. The function of heterochromatin has been investigated since the 1930s but no general function could be assigned to it, probably because there are different functional properties of this material, collectively identified as heterochromatin. Most commonly, regulatory and structural roles were attributed to heterochromatin. Lyonization proves some regulatory role. The position effect shows that genes transferred to heterochromatic regions can be silenced. This silencing may be permanent in a stable position effect; presumably the transposed gene lacks the appropriate environment (promoter) for transcription. A multi-enzyme complex (SHREC) with a core of four proteins mediates transcriptional gene silencing of heterochromatin (Sugiyama T et al 2007 Cell 128:491). In case of variegation type position effect (PEV), it was assumed that some binding proteins functioning between the homologous chromosomes have a trans-sensing role in the phenomenon. Both strands of the heterochromatin DNA can be transcribed but one of them may be processed into siRNA and amplified by RdRP and recruited the RITS pathway (Lippman Z, Martienssen R 2004 Nature [Lond] 431:364). RNA polymerase II seems to be required for RNAi-dependent heterochromatin assembly (Kato H et al 2005 Science 309:467). The role of heterochromatin in crossing over remains confusing because both enhancing and suppressing effects on the phenomenon have been observed. Heterochromatin being the site of polygenes has been suggested but not demonstrated

conclusively, unless it is accepted on the basis that some of the redundant genes are heterochromatinized. It came to light recently that centromeric heterochromatin (but not the telomeric) has a role in the disjunction of achiasmate chromosomes. The GAGA transcription factor has been implicated in stimulating variegation type position effect of heterochromatin. The *kl*, *k* and *cry* fertility genes of *Drosophila* seem to be in the Y-chromosomal heterochromatin and the ribosomal gene repeats, *bb* (bobbed), can be found in both the X and Y chromosomes. The enhancer of the second chromosomal (2–54) segregation distorter (*Sd*) locus (*Esd*) and also the activator of *Sd*, responder (*Rp*, 2–56.61), were localized in the heterochromatin. The euchromatic abnormal ovule (*abo*, 2–44) mutations can be normalized by the *ABO* heterochromatic repeats in the X and Y chromosomes. (Hoskins RA et al 2002 Genome Biology 3(12): research0085.16) reported 297 protein-coding genes and six non-protein coding genes in the heterochromatin of *Drosophila*. These genes are different from other *Drosophila* genes in as much that they contain clusters of transposable elements and very large introns (Tulin A et al 2002 Genes Dev 16:2108; Reugels AM et al 2000 Genetics 154:759). The heterochromatic regions generally enclose several transposons and retrotransposons. ATPase DDM1 (decrease in DNA methylation) controls the transposable elements, and the methylation is guided by siRNAs (small interfering RNA). Typically, euchromatin is associated with acetylated histones and with histone H3 dimethylation on lysine 4. In heterochromatin, histone H3 is dimethylated on lysine 9. The transitions between these two states control, epigenetically, the development (Lippmann Z et al 2004 Nature [Lond] 430:471). In rice plants a chromosome 8 that suffered a misdivision contains much reduced repetitive DNA tracts and facilitates the sequencing of this heterochromatic region usually refractory to this procedure. In this region the CENH3 (a generally centromere-specific H3 histone protein gene) as well as several other active genes have been revealed (Nagaki K et al 2004 Nature Genet 36:138). The best-known component of heterochromatin is the heterochromatin-associated protein (HP1), which assists the expression of other heterochromatin genes. Trimethylation of histone H3 lysine 9 creates a binding site for HP1 and contributes to gene silencing by the recruitment of histone methylase (Nakayama J-i et al 2001 Science 292:110). HP1 exists in the isoforms α , β and γ and these are released from chromatin during the mitotic cycles after phosphorylation of histone H3 at Ser¹⁰. However, in the pericentromeric region HP1 α is partly retained. Aurora B kinase is responsible for the serine 10

phosphorylation and the release of HP1 (Fischle W et al 2005 Nature [Lond] 438:1116; Hirota T et al 2005 Nature [Lond] 438:1176).

At the amino end of histone methylase there is about a 50-amino acid sequence (*chromodomain*), a reminder of the Polycomb protein of *Drosophila*. The chromo-ATPase/helicase-DNA-binding proteins (CHD) of humans have two chromodomains to bind to the H3-lysine-4-methylated tails (Flanagan JF et al 2005 Nature [Lond] 438:1181). The chromoshadow domain is located at the C-terminus that is apparently involved in the organization of heterochromatic complexes. Heterochromatin formation requires the deposition of histone in nucleosomes of the newly synthesized DNA (see Fig. H35). The chromatin assembly factor (CAF) and anti-silencing factor (Asf1p), RttP and other proteins serve as chaperones for histones but the PCNA replication factor also controls silencing (Huang S et al 2005 Proc Natl Acad Sci USA 102:13410). ▶satellite DNA, ▶Barr body, ▶lyonization, ▶knob, ▶banding, ▶position effect, ▶silencer, ▶telomeric silencing, ▶*Su(var)*, ▶RAP polygenes, ▶achiasmate, ▶locus control region, ▶GAGA, ▶position effect, ▶PEV, ▶RIGS, ▶histone deacetylase, ▶nucleosome, ▶chromodomain, ▶Aurora, ▶bromodomain, ▶SET, ▶Sbfl, ▶pro-chromosome, ▶centromere, ▶cohesin, ▶boundary elements, ▶CAF, ▶ASF1, ▶PCNA, ▶RITS, ▶histone methyltransferases, ▶insulator, ▶misdivision, ▶epigenesis, ▶RNAi, ▶RITS; McCombie WR et al 2000 Cell 100:377; Hennig W 2000 Chromosoma 108:1; Henikoff S 2000 Biochim Biophys Acta 1470:1; Nielsen AL et al 2001 Mol Cell 7:729; Grewal SI, Elgin SC 2002 Current Opin Genet Dev 12:178; RNAi and heterochromatin: Lippman Z, Martienssen R 2004 Nature [Lond] 431:364; Matzke MA, Birchler JA 2005 Nature Rev Genet 6:24; Grewal SI, Jia S 2007 Nature Rev Genet 8:35; formation of heterochromatin review: Shiv S et al 2007 Nature [Lond] 447:399; annotated sequence of 24 Mb *Drosophila* heterochromatin: Smith CD et al 2007 Science 316:1586; 200 coding and non-coding genes in non-satellite and pericentromeric heterochromatin of *Drosophila*: Hoskins RA 2007 Science 316:1625.

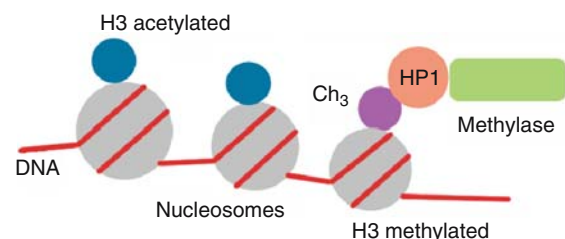


Figure H35. Heterochromatinization

Heterochromia Iridis: (see Fig. H36) ►eye color

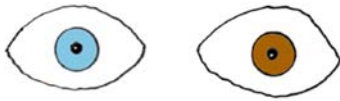


Figure H36. Heterochromia iridis

Heterochromosomal Recombination: Involves segmental exchange between repeats within non-homologous chromosomes. ►homologous recombination, ►illegitimate recombination

Heterochronic Expression: The heterochronic expression of genes controls the timing of developmental events.

Heterochronic Mutant: A heterochronic mutant expresses its genetic information with a timing pattern different from that of the wild type, or it regulates development by a (+) or (−) control. Heterochrony has both developmental and evolutionary significance. Heterochrony also bears resemblance to homeotic mutations affecting spatial morphology rather than temporal changes. Heterochronic mutations may orchestrate cell lineage patterns, timing of hormone production, and/or the phasing of the developmental program(s). By studying heterochrony of development the evolutionary pattern in different species can be revealed. ►homeotic genes, ►cell lineages; Pasquinelli AE, Ruvkun G 2002 Annu Rev Cell Dev Biol 18:495.

Heterochronic RNA: Regulates the transition from one developmental phase to another. These RNAs occur in the majority of species with some exceptions, e.g., *E. coli*, *Saccharomyces cerevisiae*, and *Arabidopsis*. In *Caenorhabditis*, the 22-nucleotide *lin-4* RNA controls the transition from the first to the second larval stage. For the progress from the late larval stage to adult cell the 21-nucleotide *let-7* RNA is required. These two RNAs are not homologous to each other but they are complementary to the 3' untranslated sequences of protein-coding genes and negatively affect their expression. These RNAs have single or multiple homologous sequences in humans, *Drosophila*, zebrafish, etc. ►RNAi; Pasquinelli AE et al 2000 Nature [Lond] 408:86.

Heteroclitic Antibody: A heteroclitic antibody binds to an antigen that is different but similar to the one which induced its formation.

Heterocyclic Amines: Heterocyclic amines include mutagens and carcinogens. Some are formed during high-temperature cooking and frying of meat and fish.

Heterocyst: A terminally differentiated cell, e.g., the nitrogenase protecting cells of filamentous cyanobacteria. ►nitrogen fixation; Wolk CP 1996 Annu RevGenet 30:59.

Heterodimer: A protein with two different polypeptide subunits.

Heterodisomy: ►uniparental disomy

Heterodox Chromosomes: The special structures such as polytenic, lampbrush, sex, etc., chromosomes.

Heteroduplex: Base-paired polynucleotide chains with the two strands of different origins; they may not be entirely complementary (see Fig. H37). In case the heteroduplex area includes different alleles, post-meiotic segregation may occur resulting in aberrant ascospore octads or sectorial colonies from single (haploid) spores. ►Meselson-Radding model of recombination

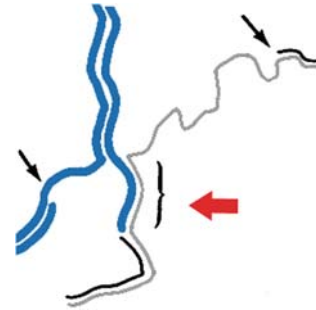


Figure H37. Heteroduplex

Heteroduplex Analysis (heteroduplex tracking, HTA, HMA, QHTA): A method of mutation detection. DNA sequences containing even a single mismatch may move more slowly in the electrophoretic gel when compared with a corresponding homoduplex. ►mismatch, ►electrophoresis, ►mutation detection, ►SNIP

Heteroduplex Rejection: The differences in base composition between recipient and donor decrease the formation of stable transformants.

Heteroencapsidation (transencapsidation): Heteroencapsidation occurs when the viral coat and the enclosing genetic material do not match by origin.

Heterofertilization: Heterofertilization occurs when genetically different sperms fertilize the polar nucleus and egg of plants and, therefore, the egg and the endosperm become non-concordant ►gametophyte, ►embryosac

Heterogametic Sex: Heterogametic sex produces both X (Z) and Y (W) chromosome-containing gametes, or

gametes with X and without X if the diploid has the chromosomal constitution XO. ▶sex determination, ▶MR

Heterogamy: Heterogamy is disassortative mating; it is also the alternation between sexual and parthenogenetic modes of reproduction. ▶disassortative mating, ▶parthenogenesis, ▶homogamy

Heterogeneity: A population or family is segregating for genes of one or more loci. The appearance of phenocopies may confound genetic conclusions. Genetic heterogeneity may be due to mutation in different genes controlling the same developmental or biochemical pathways and resulting in similar phenotype although caused by different molecular mechanisms. Several human diseases (syndromes) are based on mutations in different genes. ▶phenocopy, ▶context genetic, ▶syndrome

Heterogeneous Nuclear RNA: ▶hnRNA

Heterogenote: ▶endogenote

Heterograft: The donor and recipient of the graft are different species. ▶graft, ▶allograft, ▶isograft, ▶grafting in medicine

Heterohybrid DNA: One of the annealed strands is methylated, the other is not.

Heterohybridoma (trioma): Heterohybridoma is obtained by fusing a human lymphoid tumor cell with a mouse myeloma cell. The purpose of generating such a cell is to obtain cell lines which produce more and more stable antibodies than the lines obtained by fusion with rodent cells alone. The production of human monoclonal antibodies may have several problems. There are ethical obstacles which come in the way of immunizing humans with disease markers. It is difficult to harvest appropriate immune cells from the spleen or lymph nodes, and when peripheral blood is used it contains relatively few B lymphocytes. Furthermore, the blood B cells carry IgM on their surface and therefore display low affinity IgM antibodies. In addition, the human myeloma cells proliferate slowly and may express their own immunoglobulins and therefore make purification difficult too. Using murine myeloma cells may be only a partial solution although they may not secrete their own antibody, but they may cause the loss of human chromosomes resulting in the inability of human antibody production. ▶monoclonal antibody, ▶hybridoma, ▶Epstein-Barr virus, ▶lymphocytes, ▶immunoglobulins, ▶myeloma, ▶somatic cell hybrids, ▶hybrid hybridoma; Jessup CF et al 2000 J Immunol Meth 246:187.

Heteroimmune: When a lysogenic bacterium has a normal prophage and the λ dgal transductant, and

the two have different repressors, the transduction is heteroimmune. One species of animals was immunized by another species or the antigen (of any type) used evokes a pathological change. ▶lambda, ▶ λ dgal, ▶specialized transduction, ▶HFT; Yoshida Y, Mise K 1984 Microbiol Immunol 28[4]:415.

Heterokaryon: A cell with more than one nucleus per cell of more than one type. This is of common occurrence in fungi when two different haploid cells undergo plasmogamy or when somatic cells of other organisms fuse and the cell fusion is not followed by fusion of the nuclei (see Fig. H38). ▶dikaryon, ▶homokaryon, ▶fungal life cycle, ▶somatic cell hybrids; Beadle GW, Coonradt VL 1944 Genetics 29:291.

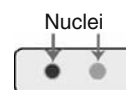


Figure H38. Heterokaryotic cell

Heterokaryon Incompatibility: Heterokaryon incompatibility results when the fusion of opposite mating-type (A and a) vegetative hyphae results in growth inhibition or cell death. ▶incompatibility, ▶fungal incompatibility, ▶hypha, ▶heterokaryon

Heterokaryon Test: When two marked cells are fused and subsequently uninucleate cells are selected. If the nuclei are not fused and recombined, yet the uninucleate progeny still carry both parental markers, the markers must be carried by the cytoplasm.

Heterolabel: A sister chromatid exchange can be identified if the two sister chromatids are different by harlequin staining. ▶sister chromatid exchange, ▶harlequin staining of chromosomes

Heterologous Gene Expression: The transcription/translation or regulation of a gene(s) introduced from another source, e.g., in gene therapy or metabolic engineering.

Heterologous Probe: A heterologous probe is used for the identification, localization, isolation, and cloning of specific genes in an organism by employing a labeled (radioactive, fluorescent) nucleotide sequence of presumably similar structure and function, from another species. ▶probe

Heteromorphic Bivalent: Morphologically distinguishable members of a homologous chromosome pair (see Fig. H39). ▶bivalent



Figure H39. Heteromorphic bivalents

Heteromultimeric: Proteins with nonidentical subunits, encoded by different genes.

Heteroplasmy: The extranuclear genetic material within a eukaryotic cell is not homogeneous but contains genetically different components in analogy to heterozygosis (see Fig. H40). Pathogenic mutations in the mtDNA occurred at a frequency of $\sim 1.3 \times 10^{-4}$ in England. Heteroplasmy, to the extent of 1% or more, was detected in 13.8% of a sample of 253 human individuals and some individuals displayed triplasm, i.e., had three types of mtDNA in the hypervariable region of the mtDNA populations (Tully LA et al 2000 Am J Hum Genet 67:432). Cell fusion, microinjection of somatic mitochondria into pronucleus-stage embryos and nuclear transfer may generate heteroplasmy that may be transient or persistent (Steinborn R et al 2002 Genetics 162:823). Selection would be expected to eliminate inferior mitochondria yet some variation (neutral?) seems to be maintained, although in the majority of cells or bodies homoplasmy seems prevalent. Mitochondrial mutations are subject to genetic drift (Brown DT et al 2001 Am J Hum Genet 68:533) because, during oogenesis, only very few mitochondria are transmitted. Heteroplasmy for mitochondrial encephalopathy was detectable in 87% of the affected tissue (skeletal muscles) but only 0.7% in the unaffected blood. Deletions of the mtDNA are rarely transmitted to the offspring but point mutations (MELAS) reappear by random drift. The exhumed remains of Tsar Nicholas of Russia and his brother Georgij Romanov's

mitochondria displayed two populations of mtDNA with both C and T at position 16,169, respectively. Heteroplasmy may involve differences between individuals and groups but even within different organs of the same individual. Heteroplasmy may involve a single base or several. Human diseases involving defective mitochondria in heteroplasmic state may potentially be temporarily remedied by selective destruction of the defective mtDNA using a specific restriction enzyme. ▶mitochondria, ▶chloroplast, ▶Romanovs, ▶DNA fingerprinting, ▶homoplasmy, ▶paternal leakage, ▶mitochondrial diseases in humans; Chinnery PF et al 2000 Trends Genet 16:500; Brown DT et al 2001 Am J Hum Genet 68:533; Srivastava S, Moraes CT 2001 Hum Mol Genet 10:3093; Schwartz M, Vissing J 2002 New England J Med 347:576.

Heteroplastic: When within the same cell more than one type of chloroplasts exist as a consequence of mutation in the ctDNA or cell fusion. ▶chloroplast genetics, ▶ctDNA

Heteroploid: The chromosome number deviates from the normal.

Heteropolymer: A synthetic polynucleotide containing more than a single type of bases.

Heteropolysaccharide: A heteropolysaccharide contains more than one kind of monosaccharide.

Heteropycnosis: One chromosome or part of it is darkly stained when the rest of the chromosome(s) absorb(s) little or no stain at a particular stage. Dark staining at interphase is an indication of tight coiling and being in an inactive state. ▶heterochromatin, ▶Barr body, ▶pycnosis; Zaccharias H 1990 Chromosoma 99:24.

Heteroscedasticity: Heterogeneity (inequality) of the variances in a group of samples.

Heteroselection: In a population, selection for heterozygotes may prevail and improve its ability to respond to new environmental challenges. ▶selection, ▶homoselection

Heterosis: Heterosis is frequently defined as the superiority of the F_1 hybrids over the mid-parent value (see Fig. H41). This definition expresses heterosis as Σdy^2 where d is the dominance effect at all loci and y is the difference of gene frequency between the two parental populations. This mathematical definition assumes that only dominant genes are responsible for heterosis. In agricultural practice, the breeders and growers require that the hybrids surpass in performance any known parental types and overdominance and epistasis may also be involved ▶hybrid vigor. There is no unanimity in the literature in interpreting the biological basis of heterosis.



Figure H40. Heteroplasmy

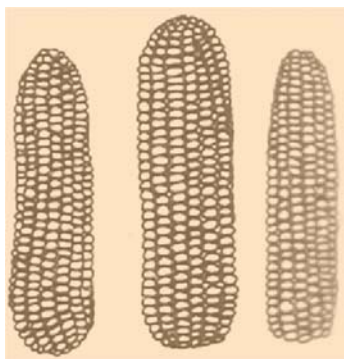


Figure H41. Heterosis

Perhaps the majority favors the dominance or epistasis interpretation; there is incontrovertible evidence also for monogenic or overdominant mechanism. Large-scale introgression analysis of tomato species led to the conclusion that overdominance is prevalent in quantitative trait loci for yield and fitness (Semel Y et al 2006 Proc Natl Acad Sci USA 103:12981). Heterosis was known for ages and was systematically exploited in agricultural practice by cross-pollination between open pollinated, distinct varieties of maize. Since the second decade of this century inbred lines of maize were used for the production of single-cross hybrids. A single-cross is the F1 generation of two inbreds. Inbreeding reduces the vigor of the inbreds but the single-cross may surpass not just the parental inbred lines but also the open-pollinated varieties from which the inbreds were isolated by several years of selfing in plants or brother-sister mating in animals. During the process of inbreeding, a progressive increase toward homozygosity takes place. Also, the different inbreds become homozygous for different alleles of the population. Therefore, not all inbreds are capable of contributing valuable genes to show heterosis. The breeders must select for inbred lines that produce superior hybrids, i.e., they have good combining ability. The *specific combining ability* means that a certain inbred contributes to valuable hybrids only with a particular, and other, inbred line. *General combining ability* implies that an inbred yields high in combination with many other inbreds. Heterosis was most successfully exploited in maize breeding where it was practically difficult and expensive to use F1 hybrids for commercial production. In the late 1910s it was discovered that *double-crosses* were also very productive and it is much more economical to generate seeds in large quantities for agronomic production. A double-cross is the intercross of two F1 lines such as (A x B) x (C x D). In order to obtain 100% hybrid seeds, first the plants had to be

detasseled, the male inflorescence, the tassel, had to be cut off before shedding pollen and when the female inflorescence (silks) were receptive, they had to be pollinated. This manual operation was very inefficient and costly. When cytoplasmic male sterility and fertility restorer genes were discovered, cross-pollination could be carried out economically at a large scale. Before hybrid corn was introduced into commercial production the yield per hectare in the USA was about 1,400 kg. By the time the use of hybrid corn became practically universal, the yield increased from five- to ten-fold. Heterosis is now exploited in many other plant species, including some autogamous species such as tomatoes. Hybrid vigor is also commercially utilized in the poultry and pork industries. Both positive and negative heterosis of molecules has also been revealed. Generally, negative heterosis is hybrid inviability in inter-species or laboratory-bred offspring. The latter has been exploited for genetic sterilization of pests. Large-scale (13,999) cDNA analyzed by microarray hybridization indicated that additive, dominance, and overdominance all could contribute to hybrid performance in maize (Swanson-Wagner SA et al 2006 Proc Natl Acad Sci USA 103:6805). ▶inbreeding, ▶maize, ▶cytoplasmic male sterility, ▶hybrid vigor, ▶overdominance and fitness, ▶tassel, ▶genetic sterilization; Gowen JW (ed) 1952 Heterosis, Iowa State College Press, Ames IA; Li SL, Rédei GP 1969 Theor Appl Genet 39:68; Rhodes D et al 1992 Plant Breed Revs 10:53; Comings DE, MacMurray JP 2000 Mol Genet Metab 71:19; Lippman ZB, Zamir D 2007 Trends Genet 23:60.

Heterospecific: Belonging to another species.

Heterosporic: Produces both micro- and macrospores.
▶microspore, ▶macrospore

Heterostyly: The anthers in a flower are at a height different (generally lower) from that of the stigma in order to avoid self-pollination (inbreeding). ▶incompatibility alleles

Heterotachy: The pattern of variation at a molecular site through time of evolution.

Heterotaxy (heterotaxia): Partial asymmetries in the placement (situs) of single visceral organs, e.g., different organs are oriented independently. ▶isomerism, ▶situs inversus viscerum, ▶connexin; Aylsworth AS 2001 Am J Med Genet 101:345.

Heterothallism: Heterothallism in lower eukaryotes (fungi) is comparable to dioecy in higher plants, or bisexuality in animals, i.e., the plus and minus mating type spores are carried by different individuals (thalli, colonies). This definition does not require that the species would have sexual organs (that many fungi

lack), nor are these spores immediate meiotic products. In case of relative heterothallism the union of genetically different nuclei is favored. ► [homothallism](#), ► [pseudohomothallism](#)

Heterotopia: The misplaced location of a tissue or organ. Hereditary nodular, periventricular heterotopia (Xq28) in the cerebral cortex is a serious health problem that results in epilepsy. The basic defect is in filamin-A synthesis. ► [filamins](#)

Heterotopic Graft: A piece of tissue is transplanted to a location different from its original site. ► [graft](#)

Heterotrophs: Heterotrophs cannot meet all their requirements from inorganic nutrients.

Heterotropic: An allosteric enzyme needs more than its substrate for modulation. ► [allostery](#), ► [modulation](#)

Heterozygosity, Average: Heterozygosity varies in an outbreeding population in *Drosophila* as well as in man; many genes are homozygous whereas heterozygosity at some other loci may vary from 0.10 to over 0.70. In a random mating population heterozygosity (H) for a locus can be estimated: $H = 1 - \sum_{i=1}^k x_i^2$

where x_i = frequency of the i^{th} allele, k = the number of alleles, e.g., if the frequencies of the alleles A1 (0.4), A2 (0.2), A3 (0.3) and A4 (0.1) then $H = 1 - (0.4^2 + 0.2^2 + 0.3^2 + 0.1^2) = 1 - 0.3 = 0.70$. In case the size of the population is very small the following formula may give somewhat better estimate: $H = 2n / (2n - 1)(1 - \sum \hat{x}_i^2)$ where \hat{x}_i = the frequency of the i^{th} allele and n = the number of alleles studied. ► [utility index of polymorphic loci in genetic counseling](#), ► [counseling genetic](#)

Heterozygosity-Fitness Correlation: This model assumes that heterozygosity is a major contributor to fitness in a population. An opposing assumption is that fitness is due to the association between certain marker genes and selectively advantageous loci. ► [fitness](#); David P 1998 *Heredity* 80:531.

Heterozygote: An individual with different alleles at one or more gene loci. Segregation identifies it genetically. From the frequency of the heterozygotes, carriers of a recessive disease allele, the approximate frequency of the afflicted (homozygous recessive) can be predicted on the basis of the Hardy-Weinberg theorem; e.g., if a population 1/50 ($2pq = 0.02$) is a carrier the expected approximate frequency of the disease is about 10^{-4} . DNA sequencing may identify it molecularly. ► [homozygote](#), ► [Hardy-Weinberg theorem](#)

Heterozygote Advantage: ► [hybrid vigor](#), ► [heterosis](#), ► [selection coefficient](#), ► [fitness](#), ► [inbreeding coefficient](#)

Heterozygote Proportions: In the F_2 of a monofactorial cross the genotypic proportions are 1AA:2Aa:1aa. If propagation is continued by selfing, the frequency of homozygotes will increase (inbreeding) and that of the heterozygotes will decrease as discovered by Mendel. The proportion of each homozygote (AA or aa) relative to the heterozygotes (Aa) will be in compliance with the formula: $[(2^{n-1}) - 1]:[2]$ where n stands for the number of filial generations. Apply this formula to F_2 : $[(2^{2-1}) - 1]:[2] = 1:2$ and by F_6 : $[(2^{6-1}) - 1]:[2] = 31:2$. (Note that the F_1 was not produced by selfing.) The proportion of both types of homozygotes combined relative to the heterozygotes will be 2:64 at one locus. The same results can also be obtained another way: 0.5^{n-1} , thus, the frequency of heterozygotes at a single locus, in F_6 , will be $0.5^{6-1} = 0.03125$ that is the same as 2/64 obtained above. In case the average effective population size (N_e) is known the heterozygosity remaining after n generations can be determined as $[1 - 1/(2N_e)]^n$. ► [inbreeding](#), ► [inbreeding progress of](#), ► [effective population size](#)

Heterozygous: In a diploid or polyploid the alleles at a locus are not identical; a similar condition may exist in haploids (merozygotes) carrying duplication or a plasmid with the same locus. ► [homozygous](#), ► [Mendelian segregation](#)

HETS: Stands for heterozygotes.

Heuristic Search: A sequential estimation of the shortest branches of an evolutionary tree starting with a single individual and then choosing others. It is carried out usually with the PAUP computer program. ► [PAUP](#), ► [evolutionary tree](#), ► [exhaustive search](#)

Hevea brasiliensis (rubber plant): A major source of latex in plants grown mainly in Asia and West Africa for the production of natural rubber (a polymer of cis-1,4 polyisoprene $[C_5H_8]_n$). The origin of the plant is South America. The basic chromosome number $x = 18$ but 9 has also been suggested. Some of the species are either diploid, $2n = 36$ or triploid, $2n = 54$.

Hexaploid: A hexaploid has six basic sets of chromosomes (genomes) in its cells (chromosome number = $6x$). Hexaploids are generally allohexaploids, i.e., each pair of the sets are of different evolutionary origin. For example, in the somatic cells of the common bread wheat (*Triticum aestivum*) $2n = 42$ contain 6 x 7 chromosomes of the AABBDD genomic composition. In the allohexaploid wheat the three genomes each synthesize benzoxazinones. Their products are not exactly the same, however, and

they correspond to the original progenitors, indicating that these genes evolved before the polyploidy series were formed (Nomura T et al 2005 Proc Natl Acad Sci USA 102:16490). Autohexaploids would have problems with multivalent association, unequal disjunction and consequently with sterility. ►polyploidy, ►allopolyploid, ►*Triticum*

Hexasomic: When one particular chromosome is present in six copies within a cell. ►aneuploid

Hexokinase: A hexokinase phosphorylates glucose to glucose-6-phosphate using an ATP donor. HK1, HK2, and HK3 genes are in human chromosomes 10q22, 2p12, and 5q35.2, respectively. HK deficiency may lead to hemolytic anemia. ►AKT

Hexon: A capsomer with six neighbors in the viral capsid. ►capsomer, ►penton

Hexosaminidase A and B: Hexosaminidase A and B are lysosomal enzymes involved in the breakdown of ganglioside sphingolipids forming about 6% of the membrane lipids in the gray matter of the brain and present in smaller amounts in other tissues. ►gangliosides, ►Tay-Sachs disease, ►Sandhoff's disease, ►lysosome

Hexose: A hexose is a sugar with a 6-carbon backbone, e.g., glucose galactose or fructose. ►galactose

Hexose Monophosphate Shunt: ►pentose phosphate pathway

Hfr: The high-frequency recombination strain of a bacterium. The sex element (F plasmid) is integrated into the bacterial chromosome resulting in about a thousand-fold more efficient transfer of the bacterial chromosome with the integrated F⁺ element into the F⁻ recipient cell. The transfer of the chromosome makes recombination possible but, unlike in eukaryotic crossing over, only one of the recombinant strands is recovered.

The sex factor and the bacterial chromosome are transferred in a unidirectional manner. The F element can be integrated into the bacterial chromosome at different map positions and it may be transferred either clockwise or counterclockwise (see Fig. H42). The transfer involves a process of a rolling circle type of replication. The genes closest to the point of the initiation of transfer are transferred first in proportion to their distance from that point. The transfer point is generally in the middle of the sex element, so for the recipient cell to receive the intact F requires the transfer of the entire Hfr plasmid. The rate of transfer depends also on the nature of a particular Hfr element. The complete transfer of the entire bacterial genome, plus the F element, is about 4,700,000 nucleotides and requires about 90–100 minutes. (See also the

diagram; ►rolling circle, ►replication, ►mob, ►conjugation, ►conjugation mapping, ►bacterial recombination frequency, ►F plasmid; Hayes W 1953 Cold Spring Harbor Symp Quant Biol 18:75).

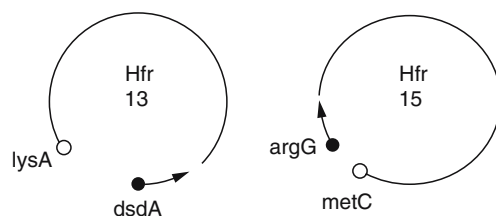


Figure H42. Two different Hfr groups, 13 and 15. The arrows on the dots indicate the direction of the transfer and the gene first transferred. The open circles show the position of the markers last transferred. In *E. coli* more than two dozen Hfr strains are known

H

HFS Cells: HFS cells are human fibroblast cells transformed by replication/transcription origin deficient SV40 DNA. They produce T antigen (Tag) and thus can provide helper functions for replication to high copy number minireplicons containing only viral replicational origins. ►SV40, ►replicon

HFT: A high frequency transducing lysate. Normal lambda phage and the defective λdgal phage can transduce bacteria. Upon induction both λdgal and normal phages can be released at about equal frequencies because the wild type phage can provide the information missing in the defective λ DNA. The two types of particles can be separated by CsCl density centrifugation because the density of the wild type particles is about 1.7 g/cm³, whereas that of the defective may be as low as 1.3. ►specialized transduction, ►LFT, ►lambda phage, ►high-frequency lysate

HGF (hybridoma growth factor; hepatocyte growth factor): The HGF receptor is the product of the Met oncogene. The hepatocyte growth factor may interfere with the neoplastic activity of the c-myc oncogene in mouse. ►signal transduction, ►hybridoma, ►hepatocyte, ►macrophage-stimulating factor, ►Met, ►hepatocyte growth factor, ►Ron, ►HNF

HGI (Human Gene Index): Gene indexing, <http://www.tigr.org/tdb/hgi/index.html>.

HGMD (human gene mutation database): See <http://www.hgmd.cf.ac.uk/ac/index.php>.

HGP (human genome project): ►genome projects; <http://www.ncbi.nlm.nih.gov/genome/guide>.

HGPRT: ►hypoxanthine-guanine phosphoribosyltransferase; the same as HPRT.

Hhal: A restriction enzyme that has the same recognition site as CfoI: GCG↓C.

HHV8 (KSHV): The human herpes virus 8 (~165 kb); it is consistently associated with Kaposi sarcoma. It has no in vitro transmission. It may inactivate the complement, induce IL-6, MIP-1 α , β , RANTES, BCL2, Cyclin D2, and inhibit interferon signaling. ►Kaposi sarcoma, ►Cd21/CR2, ►IL6, ►MIP-1, ►RANTES, ►BCL2, ►cyclin D, ►interferon, ►interferon receptor, ►Jak-Stat, ►signal transduction

Hibernation: Hibernation in mammals involves decreased metabolic rate and survival up to ~6 months without food and low body temperature of close to 0° C. In ground squirrel (*Spermophilus*) the heartbeat may be lowered to just a couple percent of the rate of that during aroused state and oxygen consumption becomes ~1/40th of normal. The activity of the genes controlling pyruvate dehydrogenation is turned down and the activity of pancreatic triacylglycerol kinase is turned on to switch to energy source of adipose tissues rather than from carbohydrates. (See Andrews MT 2004 Biochem Soc Trans 32 (6):1021). In nonhibernating mammals (mouse) a similar state (torpor) may also be evoked by long circadian dark cycles (Zhang J et al 2006 Nature [Lond] 439:340). A hibernation protein complex in the brain controls seasonal (circannual) hibernation rather than by body temperature and it actually protects the animals from the harmful effects of low body temperature (Kondo N et al 2006 Cell 125:161).

HIC (hypermethylated in cancer, 17p13.3): A zinc-finger protein regulating embryogenesis and differentiation. It is deleted in the Miller-Dieker syndrome. ►Miller-Dieker syndrome

Hickory (*Carya* spp.): A hardwood forest and shade trees, 2n = 32, 36.

Hidden Markov Model (HMM): A probabilistic model for a protein or RNA family. In a HMM graph the nodes are “states” and the edges are “transitions”. The total probability is the sum over all paths. ►Markov chain statistics

Hide-and-Release Variation: The decrease in function of the heatshock protein Hsp90 capacitates the expression of silent mutation in genes chaperoned by Hsp90 (Queitsch C et al 2003 Nature [Lond] 417:618).

Hieracium: A genus of the Compositae family with many weedy species in America and Europe (see Fig. H43). Several of them have a euploid chromosome number (e.g., *H. japonicum* 2n = 18). The apomicts have chromosome numbers 2n = 27, 36 and 45. Apomixis in *Hieracium caespitosum* is controlled at two principal loci, one of which regulates events

associated with the avoidance of meiosis (apomeiosis) and the other, an unlinked locus that controls events associated with the avoidance of fertilization (parthenogenesis). AFLP bands identified as central to both loci were isolated, sequenced, and used to develop sequence-characterized amplified region (SCAR) markers (Catanach AS et al 2006 Proc Natl Acad Sci USA 103:18650). These apomicts, studied by Gregor Mendel, upon the recommendation of Carl Nägeli, Professor of Botany at the University of Munich, caused great worries to Mendel concerning the validity of his discoveries about inheritance because the apomicts failed to segregate as expected. Thus Nägeli, despite his great fame, almost thwarted the development of genetics with plants as he also argued against the existence of hard heredity in bacteria by advocating his theory of pleomorphism, meaning that these organisms lacked fixed genetic material and vary freely. If Nägeli's theory had been accepted, it would have also foiled the development of bacteriology and medicine. ►Mendel's laws, ►pleomorphism, ►AFLP, ►parthenogenesis



Figure H43. *Hieracium auranticum* herbal illustration

Hierarchical Cluster Analysis: Compares pair-wise large sets of data to determine similarities and homogeneity in genetic-metabolic information. ►cluster analysis; Eisen MB et al 1998 Proc Natl Acad Sci USA 95:14863.

Hierarchical Shotgun Sequencing: This procedure is based on mapped clones generated by BACs. The main advantage of this conservative approach versus the whole genome shotgun procedure is that several laboratories can work simultaneously on the project. The International Human Genome Sequencing Consortium relied on it. ►shotgun sequencing

HIF (hypoxia-inducible factor): A transcription factor binding to the 5'-ACGTG-3' element and it is

involved in oxygen homeostasis under anoxic (low-oxygen) conditions by inducing glycolysis, erythropoiesis, and angiogenesis. HIF-1 regulates cytochrome oxidase subunits (Fukuda R et al 2007 Cell 129:111). Blocking the interaction between HIP and its transcriptional coactivator CREB binding protein, p300, disrupts HIF activity (Kung AL et al 2004 Cancer Cell 6:33). The HIF1A α subunit is encoded in humans at 14q21-q24, the HIF2 (EPAS1) α subunit is at 2p21-p16. In the presence of the wild type allele of HIF, hypoxia and hypoglycemia reduce cell proliferation controlled by p53, p21 and Bcl-2 proteins, but the inactivated HIF genes do not affect p27 and GADD153. Prolyl hydroxylase domain (PHD) enzymes regulate HIF by proteasome-dependent degradation of E3 ubiquitin ligases, Siah 1a/2 enzymes (Nakayama K et al 2004 Cell 117:941). Prolyl hydroxylation generates ubiquitin ligase binding sites in the von Hippel-Lindau tumor suppressor protein, resulting in the decay of HIF α . Some tumors containing HIF display reduced apoptosis and increased proliferation under anoxia because of the different response of genes to the homeostatic effect of HIF (Moeller BJ et al 2006 Cancer Cell 8:99). In contrast, HIF-2 α increased angiogenesis and yet enhanced apoptosis in rat gliomas; the net effect was tumor suppression. Therefore, HIF inhibitors may not be advisable for cancer therapeutic strategies (Acker T et al 2005 Cancer Cell 8:131). [►homeostasis](#), [►glycolysis](#), [►erythropoiesis](#), [►hypoglycemia](#), [►p53](#), [►p21](#), [►p27](#), [►GADD153](#), [►Bcl-2](#), [►apoptosis](#), [►CBP](#), [►hypoxia](#), [►von Hippel-Lindau syndrome](#); Wenger RH 2000 J Exp Biol 203:1253; Ramírez-Bergeron DL, Simon MC 2001 Stem Cells 19:279; Semenza GL 2001 Cell 107:1; Kaelin WG Jr 2005 Annu Rev Biochem 74:115; Pouyssegur J et al 2006 Nature [Lond] 441:437; review: Keith B, Simon MC 2007 Cell 129:465.

High-Content Screening: High-content screening bears similarity to high-throughput analysis but the properties of the tested compounds is tested by cell cultures, which register reactions by multiple biological criteria and not only by chemical reactivity. [►high-throughput analysis](#); Dove A 2003 Nature Biotechnol 21:859.

High-Density Lipoprotein (HDL): High-density lipoprotein is located in particles rich in various proteins and relatively low in cholesterol and cholesteryl esters. HDL is the benign lipoprotein; atherosclerosis is inversely related to the concentration of HDL. Lipoprotein lipase and endothelial lipase mutations may result in lower levels of HDL. The SR-BI scavenger receptor controls the amount of HDL and the concentration of cholesterol in the bile cells. The familial high-density lipoprotein deficiency syndrome

(FHA, 9q22-q31) is characterized by a susceptibility to coronary heart disease because of the low level of HDL cholesterol in the blood. The ABC transporters are apparently responsible for the normal balance between cholesterol export and LDL import. It is assumed that HDL promotes and facilitates the process of reverse cholesterol transport (RCT), whereby excess macrophage cholesterol is channeled to HDL and ultimately returned to the liver for excretion in the bile and feces (Lewis GF, Rader DJ 2005 Circulation Res 96:1221). Mutation of the ABC1 transporter accounts also for the Tangier disease. [►cholesterol](#), [►apolipoproteins](#), [►lipids](#), [►lipase deficiency](#), [►Tangier disease](#), [►LDL](#), [►hypertension](#), [►atherosclerosis](#), [►ABC transporters](#), [►SR-BI](#); Sacco RL et al 2001 JAMA 285:2729.

High Dose/Refuge Strategy: A high dose/refuge strategy has been designed to prevent the development of resistance in insect populations against toxins synthesized by transgenic plants for their protection against insects. The resistance gene is engineered to a high degree of resistance and dominant inheritance. Any mutation for countering the resistance is expected to be recessive and thus not selected effectively because in the heterozygotes the recessive allele is not expressed. Or, even if the counter-resistance is intermediate the high toxin level is expected to be lethal or deleterious to them. The refuge strategy is expected to reduce the genetic survival (fitness) of the counter-resistance. The refuge is the presence of nontoxic plants that allow the reproduction of the susceptible insects. When there are substantial numbers of susceptible insects, the rare recessive counter-resistant individuals will mate with them and there is a reduced probability for mating between two counter-resistant individuals. Therefore, the counter-resistant phenotypes will not be propagated and will eventually be eliminated. This strategy is very attractive theoretically yet under the conditions of the natural environment it may have limitations. (See Rauscher MD 2001 Nature [Lond] 411:857; [►insect resistance in plants](#), [►genetic sterilization](#), [►Cochliomya hominivorax](#)).

High-Energy Bond: Upon hydrolysis the covalent linkage liberates large amounts of free energy, e.g., the phosphodiester bond of ATP, thioester linkage in acetyl Coenzyme A. [►phosphodiester](#), [►thioester](#)

High-Frequency Lysate: When a temperate bacteriophage excises from the bacterial chromosome it may pick up an adjacent site. For example, bacteriophage λ may gain, from *E. coli* map position 17, a *galactose* gene, but because of the reciprocal recombination a piece of its own genetic material, required for lysogeny, may be left behind. Thus, the new phage

becomes *λdgal* (lambda-deficient-galactose). Such a phage particle may multiply vegetatively but its infecting ability is reduced. When a helper phage is inserted into the bacterial chromosome next to *λdgal*, the wild type phage gene may compensate for the defect and a *double lysogenic bacterium* is produced. Upon induction (to liberate phage), a *high-frequency lysate* containing the two types of the phages is produced with high transducing ability. ▶ [specialized transduction](#), ▶ [lambda phage](#); Hartman PE 1963 in: *Methodology in Basic Genetics*, Burdette BJ (ed) Holden-Day, San Francisco, CA, pp 103.

High-Frequency Transducing Lysate: HFT.

H

High-Lysine Corn: The seed proteins of cereals are composed of four major fractions in variable but frequently in closely equal amounts: prolamine (zein in maize, gliadin in wheat), glutenin, albumin, and globulin. In maize, the genetically determined lysine content is highly variable and subject to increase and decrease by selection for high or low zein content, respectively. Two families of genes *opaq* (*o*) and *floury* (*f*) scattered over the maize map are particularly influential in reducing the low-lysine protein fractions with the concomitant increase (doubling or more) of the percentage of this essential amino acid and that of tryptophan as well. In some *f12* lines the level of methionine is also substantially higher. Particularly beneficial effects are due to genes *o2*, *o7*, *f12*, and *f13*. In wheat, in mol/10⁵ g protein the lysine contents are: ca. gliadin 5.0, glutenin 17.6, albumin 78.4, and globulin 98.0. The *o2* maize itself also has a disadvantage, namely, the liability of the kernel to physical damage. In the Quality Protein Maize (QPM), genetic modifications make the kernels vitreous and more damage resistant. One genetic modifier is near the terminus of the long arm of chromosome 7 and it encodes a 27-kDa γ-zein, which is present in two- to three-fold amounts in QPM. The kernel structure—among other factors—is modified also by altered branching of amylopectin (Gibbon BC et al 2003 *Proc Natl Acad Sci USA* 100:15329). Cereals with improved nutritional values are desirable for feeding of animals and more importantly for the production of cereal food for human populations suffering from malnutrition as a result of protein deficiency in the diet (kwashiorkor). ▶ [essential amino acids](#), ▶ [kwashiorkor](#), ▶ [amylopectin](#), ▶ [zein](#); Coleman CE et al 1995 *Proc Natl Acad Sci USA* 92:6828; O'Quinn PR et al 2000 *J Anim Sci* 78:2144; Zarkadas CG et al 2000 *J Agric Food Chem* 48:5351.

High-Mobility Group of Proteins (HMG): This group of proteins is associated with functionally active chromatin and renders the genes more sensitive to DNase and probably to RNase II. HMGs also

promote the elongation of the RNA transcripts. They are regulated by cell-cycle-dependent phosphorylation, affecting their ability to bind to DNA. HMG proteins are important for growth and development. A large number of transcription factors contain HMG-like domains. The specificity of these proteins varies but a common feature is that they distort the DNA structure and have an affinity for distorted DNA structures. The change in DNA electrophoretic mobility is correlated with this altered structure. Thus, HMGs have both regulatory and structural functions. Recurrent rearrangements of the HMGI-C group were detected in some benign tumors (lipomas). There are three groups of these proteins: HMGI-C (12q15), HMGI, and HMGI(Y) encoded at 6p21. ▶ [chromatin](#), ▶ [nonhistone proteins](#), ▶ [cell cycle](#), ▶ [coactivator](#), ▶ [transcription factors](#), ▶ [FACT](#), ▶ [SOX](#), ▶ [DNA bending](#), ▶ [elongation factors](#), ▶ [lipomatosis](#); Bustin M 1999 *Mol Cell Biol* 19:5237; Reeves R et al 2001 *Mol Cell Biol* 21:575; in inflammation: Jiang W, Pisetzky DS 2007 *Nat Clin Rheumatol* 3:52.

High-Performance Liquid Chromatography (HPLC): A mixture of compounds is applied to chromatographic columns with strong ion exchange resins. The solvent is forced through the resin under pressure for rapid and sharp separation of the components of the mixture. The eluates are electronically scanned and identified. Denaturing high-performance liquid chromatography can be used to detect structural differences between mutant and wild type molecules. ▶ [chromatography](#)

High-Quality Sequence: A (final) stage of the contiguously sequenced genome that has an error rate of only ~10⁻⁴. ▶ [first-draft sequence](#), ▶ [genome projects](#)

High-Throughput Analysis: High-throughput analysis permits the study of large amounts of facts by the use of (generally) automated equipment, using the tools of bioinformatics, and working on the basis of combinatorial chemistry. ▶ [combinatorial chemistry](#), ▶ [high content screening](#)

Highly Repetitive DNA: Such DNA contains a high degree of redundancy and reassociates very rapidly after denaturation. ▶ [SINE](#), ▶ [LINE](#), ▶ [annealing](#), ▶ [C₀t value](#)

Hill Reaction: The Hill reaction occurs when illuminated chloroplasts evolve oxygen and reduce an artificial electron acceptor (ferricyanide → ferrocyanide). It was an important tool to study the mechanism of photosynthesis, namely, that the evolved oxygen comes from water rather than from CO₂ and it demonstrated that isolated chloroplasts can perform part of the reactions. It also

revealed the light-activated transfer of an electron from one substance to another against a chemical-potential gradient. ► [photosynthesis](#)

Hill-Robertson Effect (interference): The selection at one locus may hinder the choice of a favorable allele at another linked gene in a population in the absence of recombination. ► [hitchhiking](#), ► [genetic drag](#); Hill WG, Robertson A 1966 Genet Res 8:269.

Hilum: A depression or pit where vessels and nerves enter an organ; the place (↓) where the plant seed (see Fig. H44) is connected to its stalk in the fruit.



Figure H44. Hilum

him: A high incidence of male mutation in *Caenorhabditis* has a high level of nondisjunction in XX hermaphrodites and thus produces XO males. ► [nondisjunction](#), ► [chromosomal sex determination](#), ► [Caenorhabditis](#)

Himalayan Rabbit: The Himalayan rabbit carries temperature-sensitive tyrosinase genes controlling pigmentation.

The extremities, paws, ears, and tail having lower blood circulation and concomitant lower body temperature develop darker pigmentation (see Fig. H45). A similar pattern of pigmentation occurs in other rodents and in Siamese cats. Tyrosinase is a copper enzyme (also called polyphenol oxydase) and is involved in the formation of 3,4-dihydroxyphenylalanine (DOPA) that is responsible for the production of melanin in the hair and skin and darkening of wounded fruits and other plant tissues. ► [albinism](#), ► [piebaldism](#), ► [Siamese cat](#), ► [pigmentation of animals](#), ► [temperature-sensitive mutation](#)



Figure H45. Himalayan rabbit

HindIII: A restriction enzyme with recognition site shown at A↓AGCTT.

H-InvDB: An integrative annotation of human genes, description of gene structures, details of novel alternative splicing isoforms, non-protein-coding RNAs, functional domains, subcellular localizations, metabolic pathways, predictions of protein three-dimensional structure, mapping of known single nucleotide polymorphisms (SNPs), identification of polymorphic microsatellite repeats within human genes, and comparative results with mouse full-length cDNAs. (See Imanishi T et al 2004 PloS Biol 2(6):e162; <http://www.h-invitational.jp/>).

Hindbrain (rhombencephalon): The caudal part of the brain. It includes the cerebellum, pons (metencephalon), and the medulla oblongata (myelencephalon). ► [brain human](#)

HiNF (histone nuclear factor): A 48-K M_r protein, identical to interferon regulatory factor IRF-2. ► [IRF-2](#), ► [histones](#)

Hinge: ► [antibody](#)

Hinny: She-ass (2n = 62) x stallion (2n = 64) hybrid. The reciprocal (mare x jackass) is called mule (see Fig. H46). Mules are easier to produce because the jackass willingly mates with the mare but the stallion mates with the she-ass only under special circumstances (blindfolded). The hybrids' body resembles more closely the female parent as an apparent cytoplasmic influence. These sterile hybrids—known since the beginning of human civilization—may retain some sexual drive and occasionally fertility has been reported in backcrosses with either the jackass or the stallion. The jackass backcrosses are entirely sterile but the backcrosses with stallions appear more normal. Nuclear transplantation using horse oocytes and mule embryonal fibroblast nuclei has resulted in apparently normal offspring after normal gestation (Woods GL et al 2003 Science 301:1063). The advantages of the mule and hinny are that they are stronger and yet as resistant to stressful conditions as the donkey, and they can thrive on much less feed than the horse. The adults are generally



Figure H46. Hinny (left), mule (right)

healthier than the horse and well adapted to work under primitive conditions. These hybrids do not require iron hoof plates (horseshoes). They are more obstinate than the horse although they are shrewd and better self-disciplined under conditions scary to horses. ► [mule](#), ► [animal species hybrids](#), ► [nuclear transplantation](#); Rong R et al 1988 Cytogenet Cell Genet 47[3]:134.

HINT: An autoproteolysis and protein-splicing domain. (See Kroiher M et al 2000 Gene 241:317).

Hip: A 41.3-kDa cytosolic protein interacting with Hsc70; it is homologous with DnaJ. ► [Hsc](#), ► [DnaK](#), ► [molecular chaperone interacting complex](#), ► [huntingtin](#)

H

Hip Dislocation, Congenital: An autosomal dominant complex with a prevalence of about 0.001/live births. Generally involves laxity of joints.

Hippel-Lindau Syndrome: ► [von Hippel-Lindau syndrome](#)

Hippocampus: A seahorse-shaped, ventral-temporal gray matter part of the brain including seven layers of tissues. It is the presumed site of memory-amnesia-learning deficit, etc. During mouse hippocampal development, 1,926 genes displayed dynamic changes—by microarray analysis—and seem to be involved in neuronal proliferation, differentiation, and synapse formation. ► [brain human](#), ► [memory](#), ► [microarray hybridization](#), ► [synapse](#); Mody M et al 2001 Proc Natl Acad Sci USA 98:8862.

Hippopotamus (*Hippopotamus amphibius*): 2n = 36.

HIR: Genes involved in histone and nucleosome assembly at 22q11.2. ► [histones](#); Ray-Gallet D et al 2002 Mol Cell 2002 9:1091.

Hirschsprung's Disease (megacolon): Hirschsprung's disease occurs in several forms involving megacolon (large and dilated terminal section of the intestine), microcephaly (reduced head size), short stature, coloboma of the iris (the iris has two distinct colors) and unequal development of the two sides of the face, obstructed anus (the terminal end of the intestine) and bladder. In Hirschsprung's disease, in case of RET mutations, ganglia are absent from the colon of humans and mice. The symptoms may not all occur in each individual and were attributed most commonly to autosomal recessive endothelin receptor (chromosomal deletion 13q1-q32.1), and less frequently to autosomal dominant mutation (human chromosome 10q11.2) in the RET oncogene (receptor tyrosine kinase), or even to multifactorial inheritance. The RET loss mutation may have a dominant negative effect. A mutation at 9q31 appears to regulate the penetrance of RET. A noncoding element in the first

intron of the RET gene increases the disease risk twenty-fold (Sproat Emison E et al 2005 Nature [Lond] 434:857). Mutations in the glial cell-derived neurotrophic factor (GDNF), encoded in human chromosome 5p13.1-p12 may also have a minor role in the disease. Prevalence is about 1/5000 but among sibs about 1/25. The chance for males to be affected is three to five times higher than in females. Its incidence is high in Down's syndrome (6%) and in piebaldism. This disease also occurs in horses and mice and probably in pigs. Endothelin-3 mutations (20q13.2-q13.3) or defects in the endothelin converting enzyme (1p36.1) may also be responsible factors. In the complex Waardenburg-Hirschsprung disease, Waardenburg-Shah syndrome mutations in the SOX10 gene have been detected. One form is controlled by the Smad-interacting protein (Sip1) encoded at 2q22. The complex Hirschsprung disease may be the outcome of mutations of more than a single gene. ► [eye diseases](#), ► [coloboma](#), ► [stature in humans](#), ► [diabetes mellitus](#), ► [RET oncogene](#), ► [psoriasis](#), ► [hypogammaglobulinemia](#), ► [piebaldism](#), ► [endothelin](#), ► [Shah-Waardenburg syndrome](#), ► [aganglionosis](#), ► [SOX](#), ► [dominant negative](#), ► [Smad](#); Wakamatsu N et al 2001 Nature Genet 27:369; Gabriel SB et al 2002 Nature Genet 31:89.

Hirsh Suppressor: A mutation in *E. coli* tryptophanyl tRNA at G24A (a non-anticodon site) permitted it to pair with the UGA stop codon as well as with the wild type UGG codon and insert tryptophan into the amino acid sequence.

Hirsute: The word means hairy.

HIS Oncogenes (HS2): HIS oncogenes were identified in mouse chromosomes 2 and 19 from leukemia cells. The human homolog was assigned to 2q14-q21. ► [oncogenes](#), ► [leukemias](#)

HIS OPERON: A coordinately regulated gene cluster. In *Salmonella typhimurium*

gene order on the map: *E* (2) *I* (3) *F* (6) *A* (4) *H* (5) *B* (7,9) *C* (8) *D* (10) *G* (1)

and the numbers in parenthesis after each gene indicate the order of the biosynthetic steps the genes mediate. The substrates and products in the pathways are ordered below:

(1) PHOSPHORIBOSYL PYROPHOSPHATE + ATP → (2) PHOSPHORIBOSYL-ATP → (3) PHOSPHORIBOSYL-AMP → (4) PHOSPHORIBOSYL-FORMIMINOAMINOIMIDAZOLE-4-CARBOXAMIDE RIBONUCLEOTIDE + GLUTAMINE → (5) ? → (6) IMIDAZOLE GLYCEROL PHOSPHATE + AMINOIMIDAZOLE-4-CARBOXIAMIDE RIBONUCLEOTIDE → (7) IMIDAZOLEACETOL PHOSPHATE → (8) L-HISTIDINOL PHOSPHATE → (9) L-HISTIDINOL + PHOSPHATE

→ (10) L-HISTIDINE. ► *hut operon*; Alifano P et al 1996 Microbiol Rev 60:44.

Histamine (HA): A decarboxylated histidine (see Fig. H47). A vasodilator (expands blood vessels) mediates the contraction of smooth muscles. It is released in large amounts as part of the allergic response. In allergic persons an immunoglobulin E (IgE)-dependent histamine-releasing factor (HRF) is produced by lymphocytes. HA exerts its effect through four G protein-coupled receptors designated HA receptor H1, H2, H3, and H4. Compared with wild-type animals, mice with a disrupted HA H3 receptor (H3RKO), the expression of which is normally confined to cells of the nervous system, develop more severe disease and neuroinflammation. This effect is associated with dysregulation of blood-brain barrier permeability and increased expression of MIP-2, IP-10, and CXCR3 by peripheral T cells (Teuscher C et al 2007 Proc Natl Acad Sci USA 104:10146). Histamine H3 receptor agonists (imetit) (see Fig. H48) may be effective for treatment of obesity and diabetes (Yoshimoto R et al 2006 Proc Natl Acad Sci USA 103:13866). ► *basophils*, ► *mast cell*, ► *hypersensitive reaction*, ► *allergy*, ► *obesity*, ► *diabetes*, ► *blood-brain barrier*, ► *MIP-1a*, ► *IP³*, ► *CXCR*; Marek J et al 2001 Nature [Lond] 413:420.

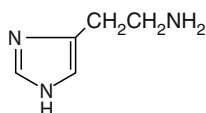


Figure H47. Histamine

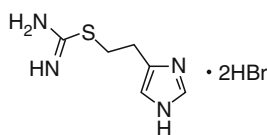


Figure H48. Imetit

Histidase (histidine ammonia-lyase): ► *histidinemia*

Histidine Kinase: A signal-transducing molecule of two components. One of the components, in response to environmental cues, autophosphorylates a histidine in the catalytic domain. The phosphate is then transferred to an aspartate within the second component, which is a response regulator, binding to another cellular protein to induce a cellular response. The histidine kinase may either be a transmembrane signal receptor or a cytoplasmic protein receiving the signal indirectly from another transmembrane receptor. In yeast, the histidine kinase, SLN1, seems to be a transmembrane protein with the kinase domain in the

NH₂ end region. It is joined to a response regulator domain at the COOH end. It appears that the sensor part is outside the cell and the kinase and the response regulator are within the cytoplasm. In yeast downstream of the histidine kinase (SLN1) the Ssk1 protein, normally phosphorylated by SLN1, is then inactive but when it is not phosphorylated it controls other protein(s) in the signal transduction pathway. Besides Ssk1, the mitogen-activated *HOG1* gene also encodes another SLN1 suppressor. HOG1 appears to be a homolog of MAP (mitogen activated protein kinase) and also Pbs2 which seems similar to the MAP kinase kinase (MAPKK). The ETR1 (ethylene response) histidine kinase gene of the plant *Arabidopsis* is organized after the yeast pattern and this histidine kinase gene is a signal transducer for ethylene. Downstream in the pathway acts the CTR1 (constitutive triple response) gene encoding a serine-threonine kinase negative regulator of ETR1. ► *histidine*, ► *histidine operon*, ► *signal transduction*, ► *ethylene*, ► *phytohormones*, ► *MAP*; West AH, Stock AM 2001 Trends Biochem Sci 26[6]:369.

Histidine Operon: ► *His operon*

Histidinemia: Histidinemia is caused by a deficiency of histidase enzyme (histidine ammonia-lyase) involved in the removal of a NH₃ from histidine. It frequently causes mental retardation and neurological abnormalities. Identification, by enzyme assays, is feasible prenatally. Its pattern of inheritance is not entirely clear. However, an autosomal recessive gene was assigned to human chromosome 12q22-q23. Its prevalence is 1 in 20,000 to 40,000 and in some isolated populations the heterozygote frequency was estimated to be as high as 3%. Histidinemia symptoms may be caused also by nongenetic factors. Histidase alleles were described in chromosome 10 of the mouse. ► *amino acid metabolism*

Histidyl tRNA Synthetase (HARS): Histidyl tRNA synthetase charges tRNA^{His} by histidine. Its gene is in human chromosome 5. ► *aminoacyl-tRNA synthetase*

Histiocytoid Lipidosis (familial cardiac lipidosis): A mitochondrial cardiomyopathy caused by accumulation of lipids in the heart muscle fibers. ► *mitochondrial diseases in humans*, ► *cardiomyopathies*; Reid JD et al 1968 J Pediatr 73:335.

Histiocytosis: A heterogeneous autosomal recessive lethal defect of the immune system, involving uncontrolled activation of the T cells and macrophages, fever, enlargement of the spleen and the liver (hepatosplenomegaly), reduction in the number of blood cells (cytopenia), and neurological disorders. The HPLH1 gene was assigned to 9q21.3-q22 and to

10q21-q22. The erythrophagocytotic lymphohistiocytosis gene was mapped to 11p13 and to 11q25, respectively. The complex disease was described also as familial hemophagocytotic lymphohistiocytosis (FHL, 10q21-q22) and familial histiocytotic reticulosis. The basic problem in FHL appears to be due to deficiency in perforin. ▶perforin; Göransdotter Ericson K et al 2001 Am J Hum Genet 668:590.

Histoblasts: Cell groups that give rise to dorsal epidermis (tergites) and ventral epidermis (sternites), respectively. ▶epidermis

Histochemistry: Histochemistry determines tissue components on the basis of in situ analysis of their chemical reactions by color and/or by specific antibodies. Histochemical techniques are useful tools to study developmental mechanisms (see Fig. H49). ▶Gomori's stain, ▶aequorin

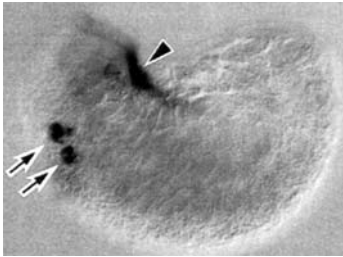


Figure H49. Histochemical localization of alkaline phosphatase enzyme in whole mount preparation of the annelide (*Tubifex*) embryo. (Courtesy of Professor T. Shimizu)

Histocompatibility: ▶HLA, ▶(human leukocyte antigen), ▶leukocytes

Histone Acetylase: ▶histone acetyltransferases

Histone Acetyltransferases (HAT): Histone acetyltransferases are acylate amino acid (lysine, serine) residues in the nucleosomes. They contribute to the remodeling of the nucleosomal structure and facilitate transcription. HAT has a preference for Lys5 and Lys12 or Lys16 (at dosage compensation) in Histone 4. In the active chromatin histone 2a is less acylated than in the inactive one. Acetylated histones permit better DNA access for transcription factors and other proteins modulating gene expression. Histone H3 acetylation of lysine at the entry–exit site of DNA in the nucleosomes facilitates the recruitment of SWI/SNF chromatin remodeling complex (Xu F et al 2005 Cell 121:375). H3 lysine 56 acetylation appears to be needed for the repair of chromosomal DNA damage (Masumoto H et al 2005 Nature [Lond] 436:294). H3K56 acetylation is promoted by yeast protein Rtt109 in cooperation with Asf1 (Driscoll R et al

2007 Science 315:649). Some histones are acetylated at the chromatid location but histone acetylation also takes place in the cytoplasm before entering the nuclei. The RNA polymerase II holoenzyme complex also contains HAT activity. HATs may belong to the GNAT family of proteins (Gcn5-related acetyltransferases) of four conserved motifs. The MYST family (MOZ, Ybf2/Sas3, Sas2, Tip60) shares structural similarity with HATs. HATs may also acetylate several non-histone proteins. HATs play a role in development and in carcinogenesis. ▶GCN5, ▶SAGA, ▶Msl, ▶NuA, ▶p300, ▶CBP, ▶TFII 230/250, ▶PCAF, ▶nucleosomes, ▶promoter, ▶histones, ▶E1A, ▶CAC, ▶chromatin remodeling, ▶bromodomain, ▶dosage compensation, ▶ADA, ▶elongator, ▶acetyltransferases, ▶Asf1, ▶SWI/SNF; Imhof A et al 1997 Curr Biol 7:689; Berger SL 1999 Curr Opin Cell Biol 11:336; Brown CE et al 2000 Trends Biochem Sci 25:15; Roth SY et al 2001 Annu Rev Biochem 70:81; Davie JR et al 1999 Biochem Cell Biol 77:265; An W, Roeder RG 2003 J Biol Chem 278:1504; dynamics of histone acetylation and transcription: Clayton AL et al 2006 Mol Cell 23:289; site-specific acetylation and deacetylation: Shahbazian MD, Grunstein M 2007 Annu Rev Biochem 76:75.

Histone Code: The posttranslational modification of the N-termini of histones H2A, H2B, H3, and H4 may result in altered regulation of genes and altered epigenetic signaling. A study of lysines 5, 8, 12, and 16 substitutions for arginine in the tail of H4 histone, mimicking positively charged, unacetylated lysine states and changes in gene expression detected by microarray analysis, indicated the following. Only lysine 16 mutations had specific consequences for transcription. On the other hand, lysine 5, 8, and 12 affected the transcription in a cumulative manner of about 1,200 genes. Thus, the histone code was specific only for the lysine 16 site in yeast (Dion MF et al 2005 Proc Natl Acad Sci USA 102:5501). ▶histones, ▶epigenetics; He S et al 2003 Proc Natl Acad Sci USA 100:12033; Vu TH et al 2004 Hum Mol Genet 13:2233.

Histone Deacetylases (HDAC): Histone deacetylases are components of the transcriptional suppression system in the inactive chromatin. Both HDAC1 and HDAC2 form a complex with DNA topoisomerase II. There are at least nine HDACs in mammalian cells. The methyl-CpG-binding protein MeCP2 seems to be associated with histone deacetylase activity. Mutations of HDAS2, due to truncation of the protein, reduce its expression and make it more resistant to histone deacetylase inhibitors. Histone deacetylase defects are found in some cancer cells (e.g., nonpolyposis colorectal cancer) and such drugs may not be effective (Ropero S et al 2006 Nature Genet

38:566). The retinoblastoma protein may bind to the E2F transcription factors and the complex then apparently represses the promoters of cell cycle S phase genes. It may activate silenced genes, such as those showing position effect by centromeric or telomeric heterochromatin, and inactive X chromosomes in the mammalian females, imprinting and inactivated tumor suppressor genes. The steroid receptor coactivator (SRC-1) is required for the expression of these enzymes. Protein HDRP (HDAC-related protein) is associated with HDAC4, shares ~50% identity with the non-catalytic NH²-domain of HDAC4 and HDAC5, and seems to be a transcriptional repressor. SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) and NCoR (nuclear receptor corepressor) activate HDAC3. The HDAC3 activation domain (DAD) includes a special motif and a SANT-like (SWI3, ADA2/NCoR/TFIIIB). In addition, it requires a surface exposed lysine residue for activation but not for interaction (Codina A et al 2005 Proc Natl Acad Sci USA 102:6009). Histone deacetylase 7 is expressed in the vascular endothelium and represses matrix metalloproteinase 10 and thereby maintains the integrity of blood vessels (Chang S et al 2006 Cell 126:321). Histone deacetylation and acetylation are not limited to the nucleosomal site including the promoter of a gene but both processes may have somewhat global effects. Blocking histone deacetylation by an antisense construct in *Arabidopsis* resulted in pleiotropic expression of several genes. HDAC inhibitors also inhibit tumors (Bolden JE et al 2006 Nature Rev Drug Discovery 5:769). The inhibition of histone deacetylase (by trichostatin) prevents homologous recombination and survival of cells but does not affect nonhomologous end-joining repair (Yaneva M et al 2005 Nucleic Acids Res 33:5320). ▶DHAC1, ▶HDA1, ▶HOS, ▶RPD, ▶E2F, ▶histone, ▶heterochromatin, ▶nucleosome, ▶chromatin remodeling, ▶ORC, ▶SRC-1, ▶REST, ▶signal transduction, ▶Mad, ▶RAR, ▶nonhomologous end-joining, ▶trichostatin, ▶SAHA, ▶CpG, ▶E1A, ▶NuRD, ▶Sin3/Rpd3, ▶SMRT, ▶N-CoR, ▶DNA methylation, ▶imprinting, ▶lyonization, ▶Xic, ▶Xist, ▶tumor suppressor gene, ▶histone demethylation, ▶topoisomerase, ▶hereditary nonpolyposis cancer; Ahringer J 2000 Trends Genet 16:351; Cress WD, Seto E 2000 J Cell Physiol 184:1; Tanny JC, Moazed D 2001 Proc Natl Acad Sci USA 98:415; Wade PA 2001 Hum Mol Genet 10:6693; Huang X, Kadanaga JT 2001 J Biol Chem 276:12497; Yang W-M et al 2002 J Biol Chem 277:9447.

Histone Demethylation: A lysine-specific demethylase (LSD1), a nuclear homolog amine oxidase removes the methyl group from lysine 3 of the histone H3

N-terminal tail and acts as a transcriptional corepressor. This enzyme cannot demethylate trimethylated lysine 4 of histone 3, the most active form of H3 in transcription. In the process LSD1 generates formaldehyde. The enzyme is present in *Schizosaccharomyces pombe* to humans and apparently plays a general role in gene regulation. Histone H3 lysine 36 demethylation also requires a JHDM1 histone demethylase domain, which in the presence of FeII and α -ketoglutarate demethylates H3-K36 and generates formaldehyde and succinate (Tsukada Y-i et al 2006 Nature [Lond] 439:811). JHDM2A demethylates H3K9 and facilitates transcription activation by the androgen receptor (Yamane K et al 2006 Cell 125:483). JMJD2A (jumoni domain containing) family members demethylate trimethylated and dimethylated lysines of histones (Whetstone JR et al 2006 Cell 125:467). The JMJD2 family protein GASC1 (gene amplified in squamous carcinoma 1) removes tri- and dimethylation of histones and the HP1 protein, and restores function to heterochromatinized DNA and contributes to cancer (Cloos PAC et al 2006 Nature [Lond] 442:307). JMJD2A/JHDM3A demethylates trimethyl H3 histone lysine 9 and lysine 36 and upregulates the expression of human ASCL2 (achaeta-like, 11p15.5) transcription factor involved in trophoblast development (Klose RJ et al 2006 Nature [Lond] 442:312). Human diseases attributed to defects in methylation (colon cancer, leukemias) may have a new therapeutic target. ▶histone deacetylation, ▶histone methyltransferases, ▶epigenesis, ▶COMPASS, ▶androgen, ▶androgen receptor; Shi Y et al 2004 Cell 119:941; Shi Y-J et al 2005 Mol Cell 19:857; Trojer P, Reinberg D 2006 Cell 125:213; crystal structure: Ng SS et al 2007 Nature [Lond] 448:87.

Histone Fold: The core histone octamer is composed of two tetramers (H2A, H2B, H3, H4) which share common motifs of two short α -helices and a long central helix connected by β bridges. Each monomer dimerizes in a head-to-tail arrangement and interacts with the DNA. ▶nucleosome, ▶histones; Selleck W et al 2001 Nature Struct Biol 8[8]:695.

Histone Methyltransferases (HMT): A family of gene-regulatory proteins. They repress gene expression and the cell cycle transition G1→S by chromatin remodeling. Methylation of Histone H3 on lysine 4, 36, and 79 is linked to the activation of genes. Methylation of H3 lysine 9 and 27 and H4 on lysine 20 is found in heterochromatin and in inactive genes in euchromatin (see Fig. H50). In *Arabidopsis*, Histone 3 Lys4 (H3K4me) dimethylation generally marks gene-related sequences and distinguishes them from non-transcribed regions. Trimethylation of H3K4 is a hallmark of the majority of active genes

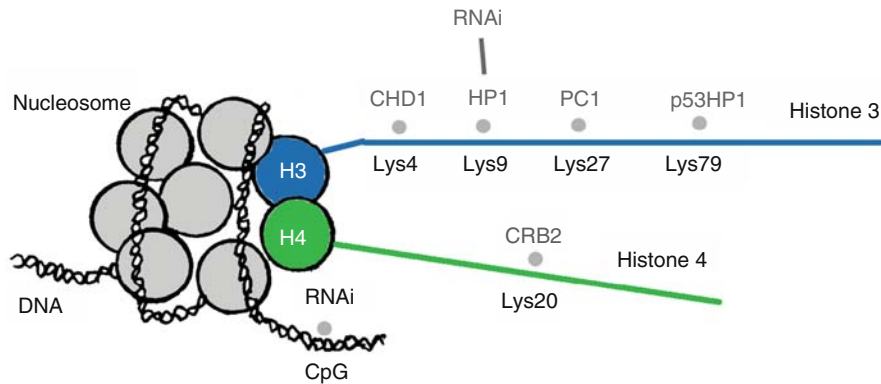


Figure H50. Proteins binding methylated lysine residues in histones 3 and 4 of the nucleosomes. RNAi also affects methylation through HP1. CHD1 (chromodomain helicase DNA-binding protein 1), HP1 (heterochromatin protein 1), and PC (Polycomb protein) bind by chromodomain. P53HP1 (p53-binding protein) and CRB2 (Cut5-repeat-binding protein 2) bind through the Tudor domain, latter to lysine 20 of Histone 4. (Modified after Bannister AJ, Kouzarides T 2005 Nature [Lond] 436:1103)

(Santos-Rosa H et al 2002 Nature [Lond] 419:407). Demethylation of trimethyl-H3K4 is mediated by the Polycomb-like proteins Ring6a/MBLR and JARID1d that are transcribed at the ENGRAILED 2 gene at human chromosome 7q36 (Lee MG et al 2007 Cell 128:877). H3K27me3 is associated with silent genes that are involved in development. NURF nucleosome remodeling protein and ATP-dependent ISWI proteins are involved in the association with the H4K4me3 tails (Wysocka J et al 2006 Nature [Lond] 441:86). A plant homodomain (PHD) finger of human BPTF (bromodomain and PHD transcription factor) interacts with the H3K4me3 through its antiparallel β -sheets at specific amino acid sites (Li H et al 2006 Nature [Lond] 442:91). The ING2 (inhibitor of growth) subunit (a domain of the lipid-signaling PtdIn[5]P) of the repressive mSin3a-histone deacetylase 1 complex also can bind to trimethylated histones and mediate gene repression (Shi X et al 2006 Nature [Lond] 442:96; Pe-a PV et al 2006 Nature [Lond] 442:100). Lys4, Lys9, and Lys27 methylation in the nucleosomes seem to be regulated differently according to genes, tissues, and development (Alvarez-Venegas R, Avramova Z et al 2005 Nucleic Acids Res 33:5199). H3 lysine 9 may be di- and trimethylated in genetically active regions of mammals. H3 trimethylation at lysine 27 is mediated by EZH2 (enhancer of Zeste); Akt-mediated phosphorylation of EZH2 suppresses the process (Cha T-L et al 2005 Science 310:306). The COMPASS complex is involved in mono-, di-, and trimethylation of H3 K4 (Schneider J et al 2005 Mol Cell 19:849). This methylation is progressive during transcription and rapidly removed upon suppression. Thus, methylation is not a permanent epigenetic state but it may be reversed. Heterochromatin protein 1 γ is also

present during the elongation of the transcript by RNAS polymerase II (Vakoc CR et al 2005 Mol Cell 19:381).

SUV39H1 (Xp11.23, 412 amino acids) is homologous to the *Drosophila* Su(var)3-9 that is a suppressor of variegation. Members of this family are ubiquitous in eukaryotes. SUV39H1 methylates Lys9 in histone H3. It is associated with HP1, which is homologous to the two CBX-like proteins of 185 and 191 amino residues, respectively. HP1 targets the methyltransferase complex to the pericentromeric heterochromatin and to the promoters of genes to be silenced. HP1 α , with the cooperation of Histone H2A.Z, mediates the folding of the chromatin fibers (Fan JY et al 2004 Mol Cell 16:655). SUV39H1 generally occurs in a complex with histone deacetylase, required for methylation.

SUV39H deficiency leads to chromosomal instability, increased risk of tumors and male meiotic anomalies in mice. The retinoblastoma protein is also required for the activity of the complex since it controls the expression of translation elongation factor E2F. G9a is a novel mammalian lysine-preferring HMTase. Like SUV39H1, the first identified lysine-preferring mammalian HMTase, G9a transfers methyl groups to the lysine residues 4, 9 and 27 of histone H3 at a 10- to 20-fold higher efficiency than SUV39H1, which only methylates lysine 9. G9a has an enzymatic nature distinct from SUV39H1 and its homologue H2. G9a was also localized in the nucleus but not in the centromeric domain where the SUV39H1 member of the family is found. Histone-4 methyltransferases (PRMT1) methylates Arg 3 and that is followed by acetylation of the protruding H4 tails by p300. CARM1 and PRMT1 methylate H3 arginine 2, 17 and 26 and activate nuclear

receptors. Histone H3 lysine 4 demethylation in the nucleosomes is mediated by the BHC/LSD1 protein complex containing the REST transcription factor (Lee MG et al 2005 *Nature [Lond]* 437:432). Histone methylation may be preceded by monoubiquitination. A high-resolution map of histone methylation in the human genome is available for 20 histone lysines and arginine, for histone variant H2A.Z, RNA polymerase II and insulator-binding protein CTCF. Promoter, insulator, enhancer, and transcribed region methylation were identified. Mono-methylation of H3K27, H3K9, H4K20, H3K79, and H2BK5 were involved in activation whereas trimethylation of H3K27, H3K9, and H3K79 resulted in repression. H2A.Z is associated with regulatory elements. In T cells cancer breakpoints were associated frequently with H3K4 methylation (Barski A et al 2007 *Cell* 129:823). ▶[chromatin remodeling](#), ▶[NURF](#), ▶[ISWI](#), ▶[bromodomain](#), ▶[phosphoinositides](#), ▶[sin3](#), ▶[histone tail](#), ▶[histone variants](#), ▶[p300](#), ▶[retinoblastoma](#), ▶[E2F](#), ▶[position effect](#), ▶[histone code](#), ▶[methylation of proteins](#); Meisetz Nielsen SJ et al 2001 *Nature [Lond]* 412:561; Tachibana M et al 2001 *J Biol Chem* 276:25309; Wang H et al 2001 *Science* 293:853; Peters AHFM et al 2001 *Cell* 107:323; Kouzarides T 2002 *Current Opin Genet Dev* 12:198; Lachner M, Jenuwein T 2002 *Current Opin Cell Biol* 14:286; enzyme structure: Cheng X et al 2005 *Annu Rev Biophys Biomol Struct* 34:267; Shilatifard A 2006 *Annu Rev Biochem* 75:243.

Histone Phosphorylation: Histone phosphorylation has important roles in chromatin remodeling and initiation of transcription. In addition, C-terminal phosphorylation of H2A histone follows exposure to ionizing radiation. H2A and H2B phosphorylation may signal to caspases and apoptosis. H3 phosphorylation (by Ip11, AIR, NIMA) at Ser/Thr begins at the pericentromeric regions and then spreads along the chromosome arms before mitosis. In the latter cases it actually promotes chromosome condensation although for transcription relaxation of coiling is required and that takes place at chromatin remodeling. ▶[chromatin remodeling](#), ▶[histones](#), ▶[TAF_{II}230–250](#), ▶[Ip11](#), ▶[AIR](#), ▶[NIMA](#), ▶[survivin](#); Jenuwein T, Allis CD 2001 *Science* 293:1074; Nowak SJ, Corces VG 2004 *Trends Genet* 20:214.

Histone Tails: Histone tails are the N- and C-terminal amino acid sequences flanking the histone cores and assuring the coherence of the nucleosome octamer. The tail is frequently modified postranslationally and provides means for chromatin alteration and gene expression. The amino-terminal tail of Histone 3 (H3) and Histone 4 (H4) when methylated hinders gene expression. Proline (P) isomerase Fpr4, a member of the FK506 binding protein family, catalyzes proline

isomerization at sites P30 and P38 alters conformation of the protein. Isomerization of P38 inhibits the ability of Set2 (a methyltransferase) to methylate H3 lysine 36 (H3K36) and thus isomerization is another mechanism of regulating gene expression (Nelson CJ et al 2006 *Cell* 126:905). ▶[nucleosome](#), ▶[isomer](#), ▶[FK506](#), ▶[proline](#), ▶[methyltransferases](#), ▶[histone methyltransferases](#)

Histone Variants: Histone variants may involve only minor or major alterations. Histone 2AX (γ -H2AX) can be phosphorylated and has a role in repair of DNA double-strand break, synapsis, apoptosis, and immunoglobulin gene class switching as well as V(D)J recombination (Fernandez-Capetillo O et al 2004 *DNA Repair* 3:959). Checkpoint control gene MDC1 binds to H2AX and regulates responses to DNA double-strand breaks (Stucki M et al 2005 *Cell* 123:1213). Histone H2A.Z has a role in chromatin remodeling and chromosome segregation (Rangasamy D et al 2004 *Nature Struct Mol Biol* 11:650). H2A.Z in yeast is enriched in the intergenic regions and its presence is inversely proportional to the rate of transcription, not by suppression but by the activation of some genes involved in chromatin remodeling (Li B et al 2005 *Proc Natl Acad Sci USA* 102:18385). MacroH2A has developmental regulatory roles in silencing the mammalian X chromosome and other silencing functions (Chow JC, Brown CJ 2003 *Cell Mol Life Sci* 60:2586). H2A-Bbd has a large primary structure difference from the other H2A molecules and it appears to be a negative regulator of transcription (Bao Y et al 2004 *EMBO J* 23:3314). Methylation of H3 and H4 histones controls epigenetic changes (Grewal SIS et al 2004 *Curr Opin Cell Biol* 16:230). The linker histones of the H1 type display substantial variations among different species and in different tissues of the same individual (Vaquero A et al 2004 *Mol Cell* 16:93). In the germ cells, H3.3A and H3.3B replace most of Histone 3 during the development of spermatids from spermatogonia. In the centromere there is a specific CenH3 histone variant that replaces the canonical H3 histone. The H3.3 histone replaces histones displaced by replication and it serves as a marker for transcribed regions (Henikoff S et al 2004 *Trends Genet* 20:320). A single protein chaperone RbAp48 complex containing CenH3 and H4 assists in assembling, modifying, and remodeling of the chromatin. This complex is different from the H3 and H3.3 assembly complex (Furuyama T et al 2006 *Proc Natl Acad Sci USA* 103:6172).

These histones are very similar in amino acid composition although their coding sequence varies (Bramlage B et al 1997 *Differentiation* 62:13). Histone H3 is the only histone with one or two cysteine residues. Histone H3.3 replaces H3 in

transcriptionally active chromatin (Mito Y et al 2005 Nature Genet 37:1090). CENP-A (centromeric protein) is also a variant of H3. TH2B is a testis-specific variant of H2B displaying additional phosphorylation sites and is present in octamers very similarly to somatic histones (Li A et al 2005 Biochemistry 44:2529). H1 has different variants (Kimmins S, Sassone-Corsi P 2005 Nature [Lond] 434:583) that are present during gametogenesis: H1t (in pachytene to elongating spermatids), H1t2 (in round and elongated spermatids), HILS1 (with shorter C terminus in elongated spermatids), and H1Foo (with elongated C terminus in oocytes). Histone B4 occurs in early development of the embryo and changes into H1 later. HB4 makes chromatin more accessible (Saeki H et al 2005 Proc Natl Acad Sci USA 102:5697). ►histones, ►epigenesis, ►transcription, ►double-strand breaks, ►sister chromatid exchange, ►spermiogenesis, ►centromere; He H, Lehming N 2003 Briefings Funct Genom Proteom 2:234; Sarma K, Reinberg D 2005 Nature Rev Mol Cell Biol 6:139; H3 variants and H3 barcode hypothesis: Hake SB, Allis CD 2006 Proc Natl Acad Sci USA 103.

Histones: Histones are five basic (rich in arginine and lysine) DNA-binding proteins. H2A, H2B, H3, and H4 are parts of the nucleosome core and H1 (H5 in birds) is generally a linker between nucleosomes. In mammals H1 has several isoforms, which may regulate gene expression. H1 deficiency may cause changes in the methylation pattern of DNA and developmental alterations in *Arabidopsis* (Wierzbiczki AT, Jerzmanowski A 2005 Genetics 169:997). Reduction of H1 alters chromatin structure but it influences the expression of only a few genes. It primarily affects imprinted and X-chromosomal genes (Fan Y et al 2005 Cell 123:1199). H2AX may be a modified C-terminal phosphorylated histone (γ -H2AX) that may be present in 15% of H2A. H2AX seems to protect chromatin against the consequences of double-strand breaks of the DNA and against cancer, especially in the presence of active p53 (Bassing CH et al 2003 Cell 114:359; Celeste A et al 2003 Cell 114:371). The histone genes were highly conserved during evolution. The N-terminal domains of the core histones and the C-terminal domain of H2A protrude from the nucleosomes and provide means for interacting with other proteins involved in genetic regulation and repair. The macroH2A variant is involved in the inactivation of the inactive X chromosome (lyonization). Phosphorylation of serine and acetylation of lysine residues in the N-terminal domain of core histones (H3, H4) contributes to modulation of transcription by the nucleosomal structure. H3 arginine methylation occurs in active transcription. This process is facilitated by

CARM1/PRMT4 (coactivator-associated arginine methyltransferase). Deimination of arginine by PADI4 (peptidyl arginine deiminase) produces citrulline from arginine and antagonizes transcriptional induction (Cuthbert GL et al 2004 Cell 118:545). Acetylation/deacetylation, phosphorylation, and methylation mediate the modulation. Methylation of tail lysines and arginines may result in activation or repression depending on the residue modified. Lys4 methylation prevents the recruitment of histone deacetylase to the active coding region and protein Set1 protects against the deacetylase (Bernstein BE et al 2002 Proc Natl Acad Sci USA 99:8695). Subsequently, a combination of proteins is attracted to the N end. There are 17 lysine and 7 arginine residues that can potentially be methylated, and considering other sites of methylation the combinatorial chance is about 3×10^{11} (Bannister AJ, Kouzarides T 2005 Nature [Lond] 436:1103). It is assumed that these accessory proteins represent a “histone code” for the regulation of chromatin remodeling and transcription (Turner BM 2002 Cell 111:285). The H2A tail contains a leucine zipper, which may be involved in interaction with the TATA box-associated proteins. The “deviant” histones may associate with the nucleosomal structure and exercise regulatory roles. The centromeric nucleosomes bind specific proteins (CENP-A, CENP-B, CENP-C) that are essential for proper chromosome segregation. The H1 and H5 linker histone in the nucleosomal structure contain a “winged helix”, a bundle of three α -helices attached to a three-stranded antiparallel β -sheet. The absence of H1 may slightly decrease the expression of some yeast genes (Hellauer K et al 2001 J Biol Chem 276:13587). This structure is found in sequence-specific regulator proteins like the catabolite activator protein and the hepatocyte-activating factor HNF3. The HNF3 protein replaces the H1 linker within chromatin containing the serum albumin enhancer. Similarly, H3 may be replaced by CENP-A at the centromere. Histones also regulate telomeric sites and the silent mating type locus. The yeast nucleosomes are compact and may not have H1 although a H1 gene was discovered in chromosome XVI. In *Tetrahymena*, H1 may act as specific positive or negative regulator for some genes but does not have a general regulatory role in transcription although it is believed that H1 stabilizes the higher order of chromatin structure. These pieces of information indicate the special role of histones and nucleosomes in gene regulation through chromatin structure. The histone genes lack introns; their mRNA is not polyadenylated. In the mammalian spermatozoa, protamines and transition proteins replace the somatic histones during maturation. The histone level may be controlled by ubiquitination. Histone2B (but not H2A) is specifically deubiquitinated by the USP7-GMPS complex (van der Knaap J

et al 2005 Mol Cell 17:695). Histone H2A ubiquitination is associated with the E3 ubiquitin ligase complex. The complex is composed of several Polycomb-group proteins (Wang H et al 2004 Nature [Lond] 431:873). ►nucleosome, ►H1TF2, ►HU, ►HiNF, ►CCE, ►chromatin, ►spermiogenesis, ►RPD, ►lyonization, ►histone acetyltransferase, ►histone deacetylase, ►LCR, ►promoter, ►chromatin remodeling, ►CARM1, ►ubiquitin, ►histone variants, ►Polycomb, ►parental histone segregation; Santisteban MS et al 2000 Cell 103:411; Nakayama J-i et al 2001 Science 292:110; Faast R et al 2001 Curr Biol 11:1183; Marmorstein R 2001 Nature Rev Mol Cell Biol 2:422; Jenuwein T, Allis CD 2001 Science 293:1074; Celeste A et al 2002 Science 296:922; Ahmad K, Henikoff S 2002 Mol Cell 9:1191; Nishioka K et al 2002 Mol Cell 9:1201; Peterson CL, Laniel M-A 2004 Current Biol 14:R546; Johnson L et al 2004 Nucleic Acids Res 32:6511; histone modifications and gene expression: Shilatifard A 2006 Annu Rev Biochem 75:243; proteomics approach for the analysis of modification: Macek B et al 2006 Mol Cell Proteomics 5:949; <http://genome.nhgri.nih.gov/histones/>.

Historical Control: The concurrent controls are run along the experimental series. In some instances this is impossible to use (e.g., some epidemiological studies, effects of environmental pollution, etc.) because there are no means to exempt the control from the overall consequences of the factors studied. For example, if we want to assess the effect of a particular compulsive vaccination system there is no contemporaneous non-vaccinated cohort group for the comparison. In such cases, similar data preceding the experiment or control data collected elsewhere under similar conditions are used as standard for the comparisons. ►control, ►concurrent control, ►cohort

Histotope: The site of the MHC molecule recognized by the T cell receptor. ►MHC, ►TCR, ►agretope, ►desetope, ►epitope

Hit and Run Technique: This technique is expected to target the mutation or replacement of only a single nucleotide or a very minute segment of a gene. The causative agent is not permanently required for the altered state. ►targeting genes; Skinner GG 1976 Br J Exp Pathol 57[4]:361.

Hitchhiking: Non-advantageous genes may be maintained in a population because of their close linkage to genes of selective advantage. The effect of hitchhiking is inversely proportional to the frequency of recombination. Directional hitchhiking models assume that linked polymorphism is periodically eliminated from the population, yet it is replenished by mutation and genetic drift. ►linkage drag,

►genetic load, ►Hill-Robertson effect, ►linkage disequilibrium, ►Muller's ratchet, ►evolvability, ►background selection, ►pseudo-hitchhiking, ►H test; Maynard-Smith J, Haigh J 1974 Genet Res 23:23; Barton NH 2000 Philos Trans R Soc London B Biol Sci 355:1553; Fu YX 1997 Genetics 147:915.

Hit Theory: ►target theory

HIV-1, HIV-2: HIV-1 and HIV-2 are lentiviruses and causative agents of acquired immunodeficiency disease which suddenly erupted in the 1950s. These two different yet related viruses evolved from the related Simian viruses (SIV) long present in about 26 African primate species. Generally, in the wild primates SIV infection does not lead to a devastating disease like in humans. The HIV-1 is supposedly originated from chimpanzees while HIV-2 from the sooty mangabeys although the transmission from nonhuman primates to humans has taken place repeatedly from the 1930s on. ►acquired immunodeficiency (AIDS), ►viral vectors, ►lentivirus, ►SIV, Hahn BH et al 2000 Science 287:607; <http://www.hiv.lanl.gov/content/index>; HIV Protein Interaction Database: <http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/index.html>; recombination server: <http://jphmm.gobics.de/>.

Hix: An invertase. ►invertases

HKA: The Hudson, Kreitman & Aguadé test for evolutionary neutrality. ►mutation neutral

H3K9: Lysine⁹ in histone-3; a common target of methylation and silencing of gene expression. ►histone methyltransferases, ►heterochromatin, ►epigenesis

HKR Oncogenes: HKR oncogenes were renamed GLI. ►GLI

HKT (high-affinity kalium transport) A membrane protein conferring the ability of potassium uptake. ►ion channels

HL60: A human granulocyte line. ►granulocyte

HLA: A human leukocyte antigen (see Fig. H51). The H2 gene cluster determines the corresponding functions in mouse. The development of congenic resistant lines in mice permitted, eventually, the determination of histocompatibility by serological tests rather than by tissue transplantation. The genes concerned with the determination of specificity are generally designated as the major histocompatibility complex (MHC). The HLA Class I molecules have two polypeptide sub-units. The 44-kDa highly variable heavy chain is coded within the MHC cluster in the short arm of human chromosome 6p21.31, whereas the invariable ~12-kDa β_2 -microglobulin is

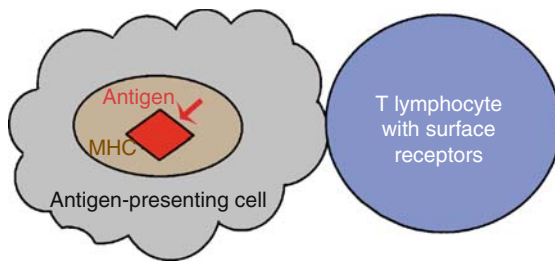


Figure H51. Epitope fragments of about a dozen amino acids are positioned in a cleft of the MHC molecule located on an antigen presenting cell. These fragments are delivered to the T cell receptors and destroyed there by the enzymes secreted by the T cell

H

encoded at another location (15q21-q22) in the genome. Paralogous HLA clusters also appear in human chromosomes 1q21, 9q33-q34, and 19p131-p13.4. The heavy chain has three domains of about 90 amino acids each, and one of them interacts with the β_2 -microglobulin.

These proteins are transmembranic with about 30 amino acids extending within the cell and a larger portion is outside the cell. The heavy chain consists of three domains α_1 , α_2 and α_3 , encoded by genes HLA-A, HLA-B, and HLA-C. The Class I polypeptides were originally designated as transplantation antigens. HLA Class II antigens are heterodimeric composed of a 33- to 34-kDa α chain and a 28- to 29-kDa β chain. The human MHC Class II genes are HLA-DR, HLA-DQ, and HLA-DP. All of the HLA genes are interrupted by several introns. The α_3 and the β_2 -microglobulin of the Class I HLA genes and the β_2 and α_2 polypeptides of the Class II polypeptides are homologous with the heavy chain constant region of immunoglobulin M. The β_2 -microglobulin bears similarity to the V gene of immunoglobulins. Heterozygosity for both Class I and Class II genes can improve protection against some viral infections. The HLA cluster occupies about 3,600 kb in the DNA, including interspersed other genes (total of ~ 224 loci) not shown here:

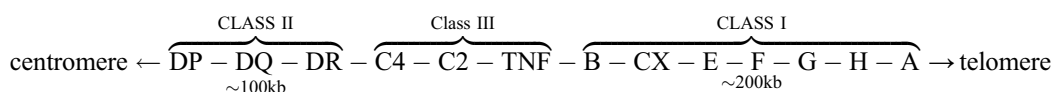
The entire human HLA region has been sequenced and it includes 128 genes and 96 pseudogenes, some of the genes have paralogues in other chromosomes (Nature 401:921 [1999]). Within the Class II region there are about 20 multiple repetitive sequence families (retrotransposons, retrotransposons, human endogenous retroviruses [HERV]) occupying $\sim 20\%$ of the region. Retroelements seem to affect recombination within HLA. A detailed haplotype map of HLA

is available (Walsh EC et al 2003 Am J Hum Genet 73:580). A high-resolution linkage disequilibrium map to all three HLA regions, using single nucleotide polymorphism, facilitates fivefold increase in genotyping MHC linked diseases (Miretti MM et al 2005 Am J Hum Genet 76:634).

The DP cluster contains alternating 2 α and 2 β genes in opposite orientation; DQ also has the same arrangement of the 2 α and 2 β genes; DR has β_1 , β_2 , β_3 in the same left to right sequence and 1 α genes in opposite orientation. Both Class I and Class II genes appear to have pseudogenes. The HLA genes have a large number of alleles and certain alleles of some genes, e.g., A1 and B8, are in linkage disequilibrium, i.e., they are syntenic much more often than expected by random recombination.

The HLA genes display high polymorphism that may be correlated with the specificity of the immune reaction. In the N-termini of the A proteins there may be 7% differences. In exons 2 and 3 of the A genes the base substitutions generally result in amino acid replacements whereas in exon 4 half of the base substitutions are silent at the protein level. The β chains of DP, DQ, and DR are highly polymorphic but the α chains of DR and DP are conserved. The variations were suspected to be the result of gene conversion but some of the variation implicates interallelic recombination.

The amount of HLA gene products varies substantially in different cells. B lymphocytes display more A, B, and somewhat less C antigens whereas in T lymphocytes all three proteins are much less active. Interferons and tumor necrosis factors stimulate the expression of the Class I genes. Class II genes are expressed primarily on B lymphocytes, myelocyte resembling cells, and macrophages. When activated, T lymphocytes as well as skin fibroblasts and some endothelial cells may express them. Class II genes' transcription is induced only by γ interferon. If mouse lymphocytes are transformed with the HLA heavy chain genes of Class I, the heavy chain can function with the murine β_2 -microglobulin. It is detectable by monoclonal antibodies against HLA determinants while in transgenic cells cytotoxic lymphocytes did not attack the HLA determinants consistently. The heavy chain can function with the murine β_2 -microglobulin and it is detectable by monoclonal antibodies against HLA determinants while in transgenic cells cytotoxic lymphocytes did not attack consistently the HLA determinants. Genetically engineered HLA Class I indicated that the first two external regions of the heavy chain (α_1 and α_2) are critical for encoding serological determination. Class



II genes are expressed on the surface of mouse lymphocytes and the mouse cell can provide the invariant antigen chain.

Within the long DNA tract of the HLA cluster, several genes involved in disease susceptibility have been identified. 21-hydroxylase deficiency (in between DR and A) causes congenital adrenal hyperplasia (CAH1), hemochromatosis (HFE, either between B and A or distal to A) causing cirrhosis of the liver, diabetes, dark pigmentation, and heart failure. The gene for juvenile myoclonic epilepsy, JME (proximally to A), causes convulsions limited to certain areas, and is possibly involved in ragweed sensitivity, etc. The tumor necrosis factors TNF-A and TNF-B, cachectin (hormone-like protein product of macrophages) releasing fat and lowering the concentration of fat synthetic and storage enzymes and lymphotoxin (lyses cultured fibroblasts) are also coded within the HLA cluster.

The most important functions of the complex are in immune recognition, defense against bacteria and viruses. They also have a number of other not entirely clarified roles. The glycoproteins encoded by the HLA genes are deposited on the surface of the majority of cells. These surface antigens are the ID cards of the individuals. Their identity is determined by the inheritance of the specificity of the MHC alleles and not processed further as it is the case with the antibody transcripts. The Class I gene products are located on the cytotoxic T cells (CTC) that destroy the cells of the body when infected.

The Class II proteins are on the surface of B-lymphocytes and macrophages that are involved in binding humoral (circulating) antigens. Antigens are separated into polypeptides by cellular proteases and the polypeptides associate with specific compartments of the specific HLA protein molecule.

The CD8 (cluster of differentiation 8 protein, 34 kDa, encoded by a gene in human chromosome 2, product of differential processing of the transcript) becomes part of the T lymphocyte cytotoxic or suppressor molecule in association with Class I HLA proteins recognized by the T lymphocyte receptor (TCR) (see Fig. H51). [The TCR protein is a complex of different polypeptide chains encoded at 14q11.2 (TCR α), at 7q35 (TCR β), at 14q11.2 (TCR δ), at 11q23 (TCR ϵ) and at 7p15-p14 (TCR γ)]. CD4, a 55-kDa protein (encoded in human chromosome 12) is associated with TCR and with Class II HLA proteins on specific T lymphocytes. The CD8 and CD4 proteins also act as signal transducers in association with CD3 antigens (multiple cistrons encoded at 11q23), and the helper T lymphocytes secrete lymphokines that activate B cells to secrete antibodies. In addition, they turn on a protein tyrosine kinase to initiate signal transfers to the cell nucleus.

The human MR1 gene locus (1q25.3), also called HLALS, encodes a polypeptide that has similarities to the Class I major histocompatibility antigens. The human MHC-B and MHC-C duplicated 22.3 Myr ago and Old World monkeys diverged from the human lineages 27–30 Myr ago (Fukami-Kabayashi K et al 2005 Proc Natl Acad Sci USA 102:9230). ▶major histocompatibility complex, ▶H-2, ▶congenic resistant lines, ▶antibody, ▶T cells, ▶TCR, ▶CD8, ▶CD4, ▶CD3, ▶TAP, ▶adrenal hyperplasia, ▶hemochromatosis, ▶myoclonic epilepsy juvenile, ▶ragweed sensitivity, ▶ankylosing spondylitis, ▶Reiter syndrome, ▶lupus erythematosus, ▶psoriasis, ▶microcytotoxicity test, ▶mixed lymphocyte reaction, ▶endogenous virus, ▶RFX, ▶lymphochip; Hill AV 2001 Lancet 357:2037; Shiina T et al 2001 Genome Res 11:789; Hughes AL, Yeager M 1998 Annu Rev Genet 32:415; Ting JP-Y et al 2002 Cell 109[S02]:21; human-chimpanzee Class I region: Anzai T et al 2003 Proc Natl Acad Sci USA 100:7708; Wahl A et al 2006 Expert Rev Proteomics 3:641.

HLH: The amphipathic (both hydrophobic and hydrophilic sides) α -helices of proteins connected by a loop.

HLM Oncogene: A mosaic of various types of retroviral elements found in avian and mammalian viruses. Oncogene HLM2 was assigned to human chromosome 1. ▶retrovirus

HLP: A histone-like protein. ▶histones

HMBA (hexamethylene bisacetamide): HMBA causes genome-wide transient demethylation in mouse erythroleukemia cells while the DNA is not replicating. ▶methylation of DNA

HMCRC: Human-mouse conserved region in the DNA.

HMG: ▶high-mobility group of proteins

HMG Box: A high-mobility group domain of the SRY gene product and other proteins with high affinity DNA-binding but differing sequence specificity. ▶SRY

HMG-CoA Reductase: ▶cholesterol, ▶Niemann-Pick disease

HML and HMR: The left (α) and right (α) mating type gene cassettes, respectively, in chromosome 3 of yeast. These elements are expressed only when transposed to the mating type, MAT site. Both of these loci are flanked by HML-E and HML-I and HME-E and HMR-I silencing elements where binding sites exist for a combination of three proteins: ORC, a protein complex originating replication, Rap1, and Abf. HMR-I has the ORC and Abf binding sites (ACS) but has no Rap1 binding site. Rap1 binds the

silencer proteins Sir3 and Sir4. ORC recruits Sir1. HMR-I has both an origin of replication and a silencing function. ►mating type, ►ORC, ►Rap, ►Abf, ►silencer, ►mating type determination in yeast

hMLH1: A human DNA repair locus in chromosome 3p21 where mutations may lead to colorectal cancer. ►hereditary nonpolyposis colorectal cancer, ►DNA repair

HMM (hidden Markov model): ►Markov chain

HMMgene: A gene prediction program. ►gene prediction; <http://www.cbs.dtu.dk/services/HMMgene/>.

HMS: ►copia

HMSN (hereditary motor and sensory neuropathy): A group of hypomyelination diseases like the Charcot-Marie-Tooth disease, Dejerine-Sottas syndrome, and HNPP. ►hypomyelinopathies

HMS-PCI: High-throughput mass spectrometric protein complex identification. (See Ho Y et al 2002 Nature [Lond] 415:180).

HNF (hepatocyte nuclear factor): HNF proteins are transcription factors of liver-specific genes involved in carcinogenesis, atherosclerosis, hyperlipidemia, insulin resistance, hypertension, blood clotting, etc. HNF-1 α (human chromosome 12q22-t23, mouse chromosome 5) and HNF-4 α ([TCF14] human chromosome 20q12-q13.1) regulate insulin secretion and their defect may lead to non-insulin-dependent diabetes. HNF-3 α (human chromosome 14q12-q13, mouse chromosome 12) is a negative regulator of HNF-1 α and HNF-4 α whereas HNF-3 β has a positive regulatory effect on HNF-1 α , HNF-4 α , and HNF-3 α . HNF-3 α appears to compete for the binding site of HNF-3 β (human chromosome 20p11, mouse 2). HNF-3 γ is in human chromosome 19q13-q13.4 and in mouse chromosome 7. HNF3 may bind to nonacetylated nucleosomes. ►cancer, ►atherosclerosis, ►hyperlipidemia, ►diabetes, ►MODY, ►hypertension, ►blood clotting, ►plasmin, ►hepatocyte growth factor, ►glomerulocystic kidney disease hypoplastic familial, ►transcription factors; Shih DQ et al 2001 Nature Genet 27:375; Odom DT et al 2004 Science 303:1378.

HNGFR: A high molecular nerve growth factor receptor. ►LNGFR

HNPCC (human nonpolyposis colon cancer): A hereditary nonpolyposis colorectal cancer. ►colorectal cancer

HNPP (hereditary neuropathy with liability to pressure palsy, human chromosome 17p11.2): HNPP bears

similarity to hereditary motor and sensory neuropathies (HMSN), represented by the Charcot-Marie-Tooth syndrome and other hypomyelination diseases although it is distinguished from them in several ways. Its onset is during adolescence or shortly after. The hypomyelinated tomacula (sausage-like swellings) are diagnostic criteria. ►palsy, ►neuropathy, ►MLE, ►MITE, ►hypomyelination, ►HMSN, ►Charcot-Marie-Tooth disease

hnRNA: heterogeneous nuclear RNA; all the thousands of diverse species of RNA found in the eukaryotic nucleus, including primary transcripts and pre-mRNA in various stages of processing. The hnRNA includes introns and other transcribed but not translated RNAs. These RNAs may be associated with proteins ranging from 34 kDA to 120 kDA in size. There are about 20 different proteins within the particles. The six most common core proteins, A12, A2, B1, B2, C1, and C2 occur in multiple copies within each globular aggregate. The complex takes a beads-on-string like structure with each globular structure (about 20-nm in diameter) containing 100–800 nucleotides and having a sedimentation coefficient of about 40S. A gene in human chromosome 19q13.3 codes the U1AP protein. The U1-70K snRNP is the major antigen recognized by anti-(U1)RNP sera in autoimmune diseases. It has been estimated that only about 5% of the pre-mRNAs are exported from the nucleus to the cytoplasm. Most of the rest are degraded. ►snRNA, ►hnRNP, ►RNP, ►U1-RNA, ►autoimmune disease, ►KH domain; Roy-choi TS 1999 Crit Rev Eukaryot Gene Expr 9:107; Krecic AM, Swanson MS 1999 Curr Opin Cell Biol 11:363; <http://www.iscid.org/encyclopedia/hnRNA>.

H-NS: A histone-like nucleoid structuring protein abundant in prokaryotes; it participates in nucleoid structure, gene regulation, and silencing. It plays a key role in cell response to changes in temperature and osmolarity. H-NS can decorate DNA molecules at one H-NS dimer per 15–20 bp (Roee A et al 2003 Biophys J 84:2467).

hnRNP: Heterogeneous ribonucleoprotein. These proteins regulate gene expression at post-transcriptional levels. Some of the recognition motifs are RNP1 octamers and RNP2 hexamers, which are embedded in conserved regions of ~80 amino acids and are present in one to four copies. The K homology (KH) domains of about 60 amino acids may be present in up to 15 copies per protein. In the genome of *Arabidopsis*, 196 RNA recognition (RRM) and 26 KH proteins were found. These proteins are more complex in this plant than those found in metazoa. ►hnRNA, ►export adaptors, ►RNA binding proteins; Lorkovic ZJ, Barta A 2002 Nucleic Acids Res 30:623.

hobo: ►hybrid dysgenesis

Hodgkin Disease (HD): A malignant lymphoma with an unknown genetic determination because the familial nature of the condition is not sufficiently clear. WF Bodmer argued in favor of a gene linked with a HLA complex. In a two-marker case (A and A'), the distribution of 1AA:2AA':1A'A' would be expected in the progeny of heterozygotes without linkage. In a survey of 32 afflicted sib pairs, the actual proportions were 16:11:2, which were significantly different from 1:2:1 at the level of 0.005 probability. More recently, linkage to the pseudoautosomal region has been suggested. If it is assumed that the frequency of the gene *a* (Hodgkin) is 0.01 and all *aa* individuals become afflicted and only 0.05 of the *AA* individuals develop the disease and none of the *AA* do, then only about 0.01 of the Hodgkin patients will be homozygotes for *aa*. In a case of 32 two-offspring families with two afflicted children the expected frequency of *aa* was about 2.5×10^{-6} . This also assumed that the two-sib families had *AA* × *AA* parents (about 4×10^{-3}) and the frequency of two-child-afflicted families was about 2.5×10^{-3} . These latter figures thus point to the possibility that in some populations the frequency of the recessive homozygotes may indicate high familial expression of the disease due to drift/founder effect.

►ascertainment test, ►Hardy-Weinberg theorem, ►HLA, ►lymphoma, ►Epstein-Barr virus, ►leukemia, ►anaplastic lymphoma, ►MALT, ►IL-9, ►pseudoautosomal; Staudt LM 2000 J Exp Med 191:207.

Hoechst Stain 33258: The Hoechst stain 33258 is used for banding of AT-rich minor groove DNA sequences in the chromosomes and it is also an antibiotic. ►Harlequin staining of chromosomes, ►sister-chromatid exchange

HOG-1 (high osmolarity): A protein kinase of the MAPK family. ►signal transduction, ►osmosis, ►p38

Hogness Box (-Goldberg): (TATA box): A 7-8 base pair region of conserved homology rich in TA, preceding the transcription initiation of the mRNA by about 19–31 residues in the promoter region of eukaryotic genes:

Exceptionally, some promoter regions lack the TATA box, these are called *TATA-less promoters*

such as U1, U2, U4, and U5 RNA promoters. The TATA box (see Fig. H52) is generally surrounded by GC rich sequences (proximal and distal sequence elements, PSE and DSE). In these U promoters, PSE and DSE are still present. Transcription by RNA polymerase II requires the association of the TATA box with a TATA binding protein (TBP) or additional TATA associated factors (TAF). ►Pribnow box, ►TATA box, ►TBP, ►TAF, ►open promoter complex, ►transcription factors; Hernandez N 2001 J Biol Chem 276:26733.

hok-sok-mok: ►plasmid maintenance

Holandric Gene: The holandric gene is Y-chromosome linked. The mammalian Y chromosome appears largely heterochromatic under the light microscope and it carries few genes. The H-Y antigen gene has been assigned to the proximal region of the long arm of Y and the testis-determining factor, formerly called TDF, now SRF, is proximal to the centromere in the same arm in humans. The long arm also contains the pseudoautosomal region (PAS); this DNA sequence Yp (SMCY) is homologous to a X-chromosomal tract, Xp (SCX), the region where X and Y crossing over can occur. The gene for surface antigen MIC2Y was assigned to the euchromatic region Ypter - q1 of the Y chromosome. The homolog was assigned to a X-chromosomal band between Xp22.3 and Xpter. The azoospermia factor (AZF) Sp3 or HGM9 maps at the site of H-Y and may be identical with it. Genes controlling body height and tooth length were suspected to be in the Y-chromosome. An arginosuccinate and an actin pseudogene were located to the human Y chromosome. A gene for hairy ears was suspected to be in the Y chromosome but its status is not resolved with certainty. No hereditary disease gene is linked to the Y chromosome, although in aneuploids (XYY, XO), it may cause defects. ►Y chromosome, ►sex determination, ►differential segment, ►H-Y antigen, ►SRF, ►pseudoautosomal, ►azoospermia, ►pseudogene, ►actin, ►heterochromatin, ►surface antigen, ►hairy ear, ►imprinting; Jobling MA, Tyler-Smith C 2000 Trends Genet 16:356.

Holandric Inheritance: Genetic transmission (only) through the male. ►imprinting

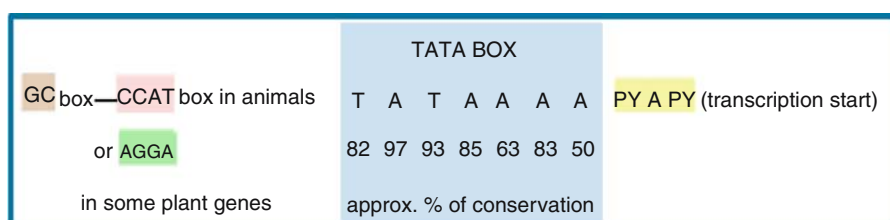


Figure H52. Hogness box

Holin: The protein product of the *t* gene of phages that conducts the lysozyme into the periplasmic space of the bacteria conducive to lysis. ▶lysozyme, ▶periplasma, ▶endolysin, ▶lysis; Wang I-N et al 2000 Annu Rev Microbiol 54:799.

Holism: The view that organisms represent an integrated system of elements and mechanisms and that the integrated system is more than a collection of the parts and therefore cannot properly be understood on the basis of the separated components. ▶organismal genetics

Holliday Junction (Holliday junction): The points where the polynucleotides forming the Holliday structures are exchanged during homologous recombination as well as during phage lambda integrase mediated exchange at the *att* sites. In most eukaryotes and in budding yeast, Holliday junctions take place between homologous chromosomes (see Fig. H53). In contrast, in *Saccharomyces pombe*, single Holliday junctions form between sister chromatids and they are resolved by a specific (Mus81-Eme1) endonuclease (Cromie GA et al 2006 Cell 127:1167).

Peptides WRWYCR and KWWCRW inhibit recombination not just in the events mentioned, but

also in Cre-, Xer-, and Flp mediated processes indicating that inhibitor specificity is not in the amino acid sequence in the recombination proteins, but they are specific for the Holliday junction itself. The peptides interfere with the unwinding of DNA by *E. coli* RecG helicase and with the resolution by the RuvABC complex (see Fig. H54) (Kepple KV et al 2005 Proc Natl Acad Sci USA 102:6867).

This juncture may be bound by Rad1 protein in the presence of Mg^{2+} and cut by this endonuclease. Rad1 appears to be the catalytic subunit of the Rad1/Rad10 endonuclease. Rad54 promotes branch migration in homologous recombination (Bugreev DV et al 2006 Nature [Lond] 442:590).

The Bloom syndrome (BLM) and the Werner syndrome (WNS) helicases are involved in the processing of the junctures regulated by p53. ▶Holliday model, ▶Holliday structure, ▶RAD, ▶recombination molecular mechanism of, ▶integrase, ▶branch migration, ▶CRE, ▶Flp, ▶RecG, ▶RuvABC, ▶Bloom syndrome, ▶Werner syndrome, ▶p53; Bond CS et al 2001 Proc Natl Acad Sci USA 98:5509; Lilley DMJ, White MF 2001 Nature Rev Mol Cell Biol 2:433; Yang Q et al 2002 J Biol Chem 277:31980; McKinney SA et al 2003 Nature Struct Biol 10:93.

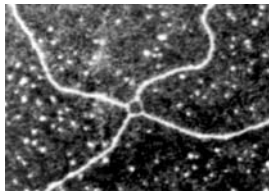


Figure H53. Electronmicrograph of a holliday juncture (Courtesy of Drs. H. Potter & D. Drechsler)

Holliday Model: The Holliday model of general recombination is best explained by Figure H55. (After Potter, H. and Dressler D 1976 Proc Natl Acad Sci USA:73:3000. The model was originally proposed by Holliday R 1974 Genetics 78:273). This is the most widely accepted model of both prokaryotic and eukaryotic recombination. ▶Holliday juncture, ▶Holliday structure, ▶single-end invasion, ▶dissolution; diagram.

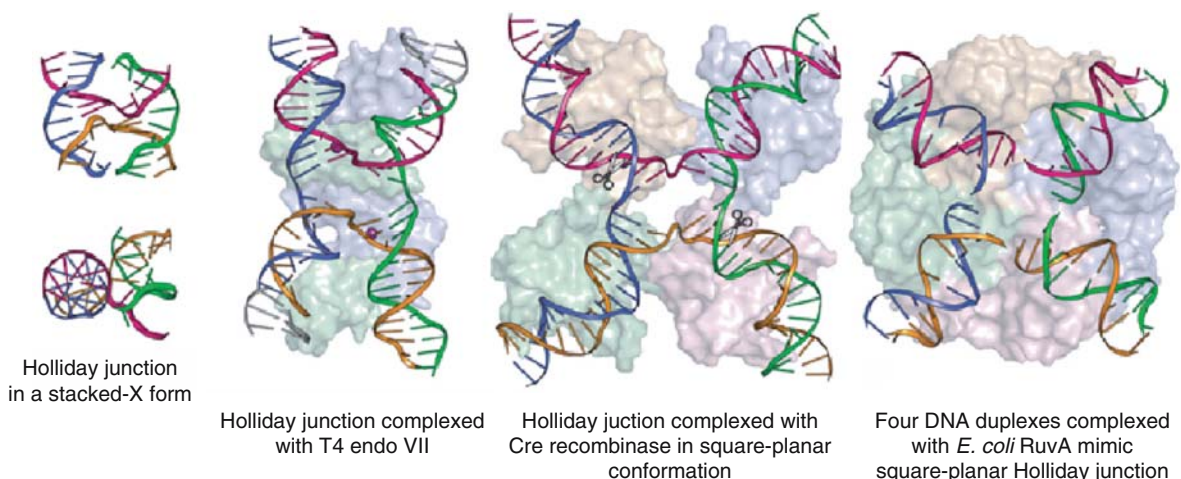


Figure H54. Holliday juncture. (Courtesy of Drs. Wei Wang and Dietrich Suck; see also Biertümpfel et al. 2007 Nature [Lond] 449:616)

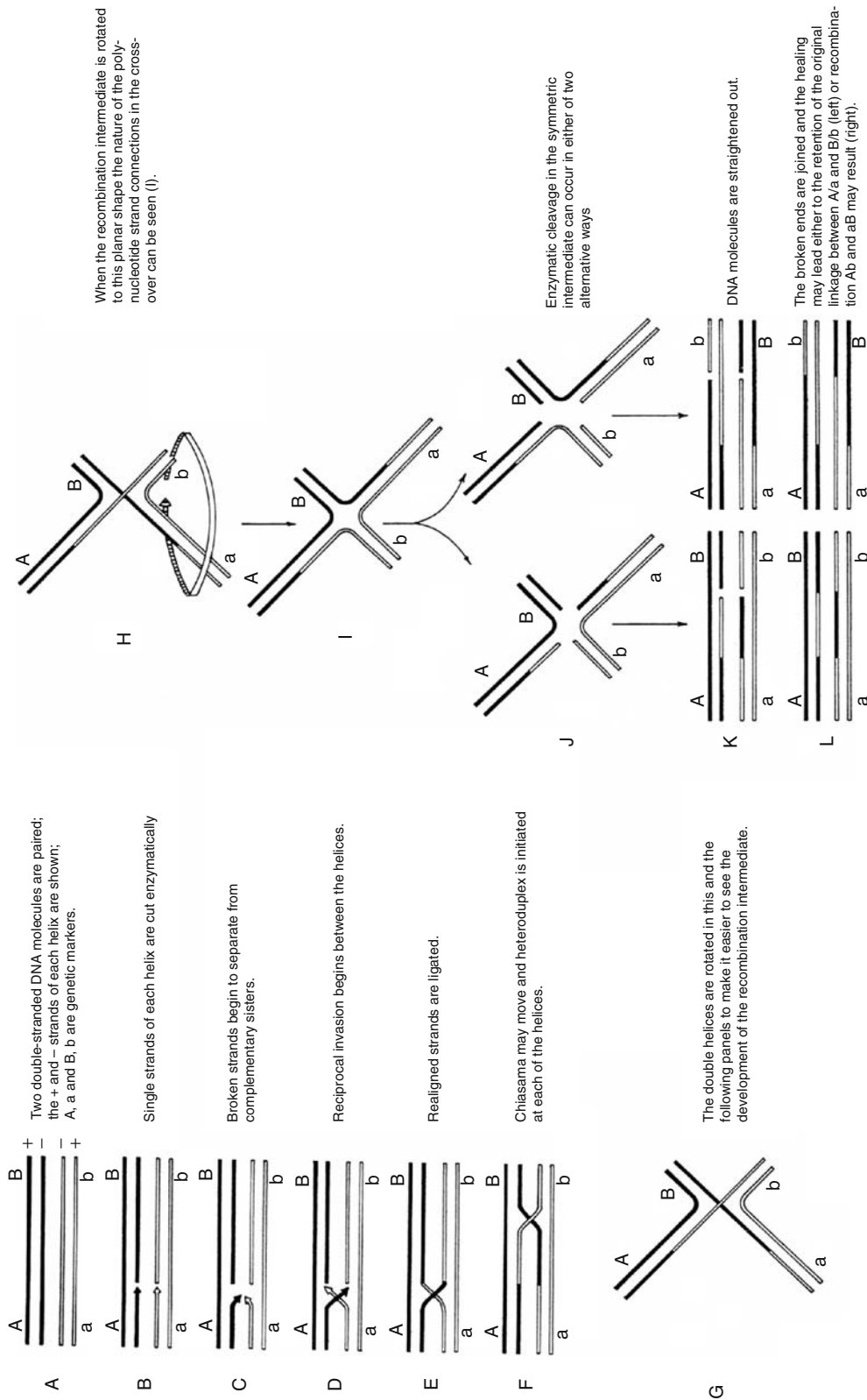


Figure H55. Holliday model of recombination. After Potter H & Dressler D 1976 Proc. Natl Acad. Sci USA 73:3000

Holliday Structure: A recombinational intermediate of DNA displaying a four-strand cruciform arrangement. (See ►[Holliday model](#) step I, Fig. 55). Its resolution requires a specific endonuclease, and depending on the manner, the resolution takes place either by crossing over (flanking marker exchange) or gene conversion (non-crossover), without outside marker exchange results (steps L). ►[model](#), ►[cruciform DNA](#); Allers T, Lichten M 2001 Cell 106:47.

Holocentric: In holocentric chromosomes found in several species of insects (*Lepidoptera*, *Hemiptera*, *Homoptera*), in the nematode *Caenorhabditis*, and in certain plants (*Luzula*) the spindle fiber attachment is not limited to the centromere (kinetochore), but the microtubules can be attached to many points along the chromosome (see Fig. H56), appearing as if the centromere would be diffuse.

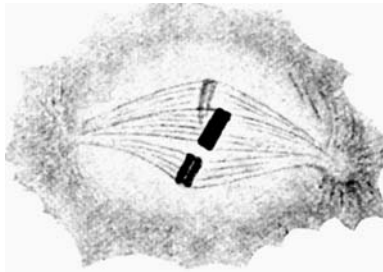


Figure H56. Holocentric chromosome fragments. (From Hughes-Schrader S, Ris H 1941 J Exp Zool 87:429)

In some genotypes of maize and rye, additional spindle fiber attachment sites (neocentromeres) accompany the major centromere. This characteristic may influence the distribution of the chromosomes to the poles (preferential segregation, non-disjunction). Species with holocentric chromosomes may be subjected to high doses of chromosome-breaking agents and still a more or less orderly anaphase distribution may take place. This feature has been exploited for biological control *lepidopteran* of agricultural pests. Heavily irradiated individuals with broken chromosomes may survive and mate, but in their progeny the chromosomal fragments may fuse leading to multiple translocations and lethal offspring. ►[screwworm control](#), ►[genetic sterilization](#), ►[centromere](#), ►[neocentromere](#), ►[centromere activation](#), ►[translocation](#); Dernburg AF 2001 J Cell Biol 153(6):F33.

Holoenzyme: A functionally complete enzyme, including cofactors. ►[apoenzyme](#)

Hologenesis: A view that claims that humans originated at many locations of the globe.

Holography: A three-dimensional photography with the aid of split laser beams.

Holokinetic: Same as holocentric.

Holometabolous Insect: The homometabolous has a larval stage of development and the larvae include imaginal disks, which are the initials of the adult body parts and from which all the appendages emerge according to a determined plan. ►[imaginal disk](#); Yang AS 2001 Evol Dev 3(2):59.

Holoprosencephaly: Dominant with human chromosomal locations 7q36 (sonic hedgehog, SHH), 2p21, 13q32 (ZIC2, a homolog of the *Drosophila* odd-paired, Opa, Zn-finger protein), but possibly other locations affect the expression of this syndrome (21q22.3, 18p11.3 [Niemann-Pick syndrome], 2q35 [Indian hedgehog], 12q13). The anomalies involve cleft lip, cyclopia, hypotelorism (abnormal distance between organs), defective head and face, and mental defects due to neural tube anomalies. The SHH human gene's transmembrane receptors are smoothened (7q32) and patched (9q22.3). The TG-interacting factor (TGIF, 18p11.3) a homeodomain protein, interacts with Smad2, Nodal, and a sonic hedgehog protein, and repress transcription of genes, which control signaling to the neural axis pathway. Its incidence is 1/250 in conceptuses and ~1/16,000 in live-borns. Severely affected newborns usually die within days; the less-affected cases may survive for a few years. No cure is available. ►[head/face/brain defects](#), ►[cleft lip](#), ►[cyclopia](#), ►[sonic hedgehog](#), ►[hedgehog](#), ►[tumor suppressor pathway](#), ►[megalin](#), ►[Smith-Lemli-Opitz syndrome](#), ►[SMAD](#), ►[Nodal](#); Belloni E et al 1996 Nature Genet 14:353; Roessler E et al 1996 Nature Genet 14:357; Cohen MM Jr 2006 Birth Defects Res Clin Mol Teratol 76(9):658.

Holt-Oram Syndrome (HOS): A dominant or sporadic arm, thumb, and heart malformation associated with human chromosome 12q24.1. The defective transcription factor involved is homologous with the *Drosophila* gene *Serrate* and the *Brachyury* mouse gene family of T box. The prevalence of the syndrome is 1×10^{-5} . No evidence has indicated that the type or site of mutation within the TBX5 sequence can predict the severity of the heart or limb malformation, and most of the mutations truncating TBX5 have failed to display defects in these organs (Brassington A-ME et al 2003 Am J Hum Genet 73:74). A newer report indicates, however, that the transcriptional regulator of TBX5, TAZ is potent coactivator, and TBX5-dependent genes are important for cardiac and limb development in the HOS syndrome (Murakami M et al 2005 Proc Natl Acad Sci USA 102:18034). ►[heart disease](#), ►[polydactyly](#), ►[adactyly](#), ►[Brachyury](#), ►[thrombocytopenia](#),

►sporadic, ►Tabatznik syndrome, ►T box; Ghosh TK et al 2001 Hum Mol Genet 10:1983.

Homeoallele: Alleles in the homeologous chromosomes. ►homeologous chromosome

Homeobox: A conserved (183 bp) sequence within homeotic genes. ►homeotic genes

Homeodomain: The part of the protein that is coded for by the homeobox; it contains a DNA-binding helix-turn-helix motif protein domain. The homeodomain contains three α -helices and a flexible N-terminal arm. The third or recognition helix takes position in the major groove of the DNA. The N-terminus keeps contact with several bases in the minor groove of the DNA. The best-conserved part of the homeobox is the TAAT motif.

The homeodomain genes determine the anterior posterior pattern of development and they are usually clustered in the genome. The homeodomain proteins are transcription factors. ►homeotic genes, ►DNA-binding protein domain, ►helix-turn-helix motif, ►homeobox, ►pseudogenes, ►morphogenesis in *Drosophila*, ►anterior, ►posterior; Gehring WJ et al 1994 Annu Rev Biochem 63:487; Banerjee-Basu S, Baxevanis AD 2001 Nucleic Acids Res 29:3258; <http://genome.nih.gov/homeodomain/>.

Homeogene: ►homeotic gene

Homeogenetic Induction: In homeogenetic induction, cells or tissues start on a certain path of development by induced cell(s) and continue producing the same cell types. (See Tiedemann H et al 2001 Dev Growth Differ 43(5):469).

Homeologous: ►homeologous

Homeologous Recombination: Homeologous recombination may take place between DNA (chromosome) strands that are similar but not entirely homologous. Recombination between *E. coli* and *Salmonella* with about 16% non-homology is about 10^{-5} of that of recombination within the species. Mismatches within the species were found to affect recombination to a less dramatic extent. In mouse, 2/232 mismatches reduced recombination to about 5%. Mitotic recombination in budding yeast at a difference of about 17–27% resulted in reduced exchange by a factor of 13–180. Meiotic recombination is also much reduced in higher eukaryotes in case of sequence differences. ►illegitimate recombination, ►homologous recombination

Homeopathy: Administering to a sick person, small doses of a medicine that given in larger doses to a healthy individual would produce the symptoms of

the same disease, which, it intends to cure. Homeopathy's origin can be traced back to Hippocrates (~fourth–fifth century BC) and Paracelsus (sixteenth century AD). Homeopathy was elaborated upon by Hahnemann (1767). An analysis of 110 homeopathy and 110 matching conventional medications indicated that the effects of homeopathy are comparable to that of placebo (Shang A et al 2005 Lancet 366:726). Today in the USA, it is a largely discredited practice although there are some adherents worldwide. (See Barberis L et al 2001 J Altern Complement Med 7(4):337; ►placebo).

Homeosis: Changing a body part into the likeness of another body part. ►homeotic genes

Homeostasis: The property of a system to maintain its composition by a flexible adjustment of the function of its genes (genetic homeostasis), or a physiological, or developmental buffering capacity of cells or developing organisms under a range of conditions. ►logarithmic stability factor, ►stress, ►allostasis

Homeostasis, Genetic: The property of a population to equilibrate its genetic composition and resist mutational changes.

Homeotic Genes: Homeotic genes specify an alternative competence for differentiation of a part of the body, e.g., in *Drosophila*, legs in place of antennae, in plants, petals in place of stamens, (see Fig. H57) etc.; they contain a homeobox. Homeosis (term coined by Bateson in 1894) was recorded by the ancient world (King Midas, seventh century B.C. grew 60-petalled roses). The discovery of homeosis by Calvin Bridges in 1915 stimulated more interest in these genetically determined developmental anomalies. Subsequently, other such developmental genes were discovered both in *Drosophila* and all types of higher organisms. In *Caenorhabditis*, about 10% of the developmental genes contain homeoboxes. In the plant *Arabidopsis*, 35–70 homeogenes were estimated to exist. Homeotic genes are generally large complexes, the *BXC* complex occupies more than



Figure H57. Left: normal drosophila female, middle: antennapedia mutant. Right: homeotic shoot apex of *Arabidopsis* (Courtesy of Dr. K. Németh)

300-kb, and less than 1/10 of it codes for mRNA. They are interspersed with introns and intergenic DNAs required for the developmental regulation of the complex. In *Drosophila melanogaster*, the homeotic genes are basically continuous (only introns are wedged within), in *Drosophila viridis*, the *Ultrabithorax* complex is mapped to two different salivary chromosome bands in chromosome 2. The first molecular analysis conducted (in DS Hogness laboratory, 1983) on the *antennapedia* complex, *ANTC* (3-47.5), revealed that this complex spans 335-kb, and includes several transcription units. All homeotic genes have a 180-bp consensus sequence, the so-called *homeobox* that specifies the *homeodomains* of regulatory proteins. The structural features of the *Ant* gene of *Drosophila* represent the organization of the homeoproteins below (see Fig. H58).

The 7–8 amino acids at the amino termini are rather well conserved across taxonomic groups, except the one represented by (?). The homeodomain of this protein may form three helical units between amino acids 1 (Ser) and 22 (Glu), between 28 (Arg) and 38 (Leu), and between 42 (Glu) and 58 (Lys). The best-conserved amino residues are in bold italic. This homeodomain region has homology to the helix-turn-helix motif of prokaryotic repressor proteins and to the MAT $\alpha 2$ protein with repressor function at the mating type site in yeast. These three helical regions may fold into a helix-turn-helix DNA binding motif.

The homeoprotein may make (unspecific) surface contact with the phosphate backbone of the DNA in the major groove. The homeodomain's conserved residues, preceding the helices, attach to the minor groove of the DNA and for the more specific contacts,

probably helix III is responsible. These homeoproteins regulate processes of differentiation and either point or frameshift mutations may abolish their DNA-binding abilities and alter the pattern of differentiation. Binding can also take place at more than one DNA sequence as long as some basic similarities are shared in the base sequences. Therefore, one homeoprotein may regulate more than a single gene, although at a different degree. Homeoboxes display great similarities in sequence among different organisms. Mammals usually have four homeobox gene clusters, A, B, C, and D. Homeobox *HOX2* of the mouse is in chromosome 11, but its human homolog is in human chromosome 17 (containing in a 180-kb region altogether nine homeobox genes separated by a few units of recombination). *HOX1* of the mouse is in chromosome 6 but its homolog is in human chromosome 7p along with seven other homeoboxes. *HOX1* is also homologous to the *ANTC* homeobox of *Drosophila*. *Hox* genes in the mouse also occur in chromosome 11, 15, and 2. An additional homeobox gene cluster of three subgroups has been discovered in the X chromosome of mouse. The 12 *Rhox* genes (reproductive homeobox X-linked) control the development of the female and male reproductive tissues (MacLean JAH et al 2005 Cell 120:369). Each Hox/Hom contains a cluster of ~9–11 genes with an average length of about 10 kb, and thus the clusters are about 100 kb, each. The genes within the cluster show paralogy and most likely arose by serial duplications during evolution. The genes within a paralogous group also referred to as cognate. Some *trans-paralogous* genes (situated in chromosomes 6 and 2, respectively) of the mouse are

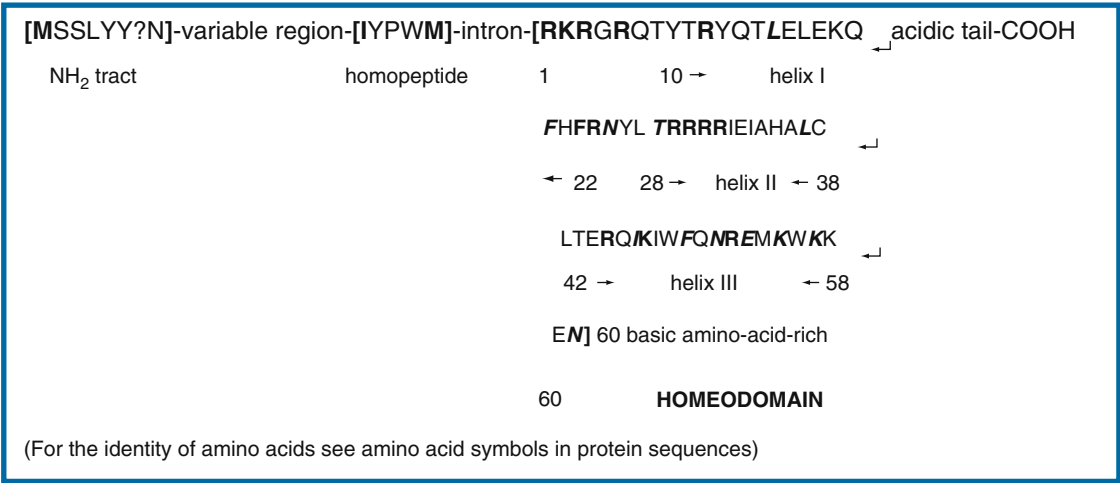


Figure H58. A homeodomain protein structure represented by the *Ant* gene product of *Drosophila*

capable of substituting for each other if one of them is deleted. Some similarities are apparent among the homeotic loci in different organisms and these are called *orthologous* because they appear to have common evolutionary origin. Statistical surveys of *Drosophila*, mouse, *Caenorhabditis*, humans, etc., indicate that the flanking areas of the homeotic gene clusters were conserved during evolution. Homeoboxes are regulated by cis- and trans-acting elements directly or indirectly. ►POU, ►developmental pattern formation, ►helix-turn-helix, ►mating type yeast, ►morphogenesis, ►Wolf-Hirschhorn syndrome, ►syndactyly, ►coordinate regulation, ►operon, ►paralogous loci, ►collinearity, ►heterochronic mutation, ►Polycomb, ►paralogous, ►orthologous, ►parahox genes ►[protohox genes]; Krumlauf R 1994 Cell 78:191; Ferrier DEK, Holland PWH 2001 Nature Rev Genet 2:33; Zákány J et al 2001 Cell 106:207; Galant R, Carrol SB 2002 Nature [Lond] 415:910; Ronshaugen M et al 2002 *ibid*: 914; <http://www.iephb.nw.ru/hoxpro>.

Homer: A 186 amino acid glutamate receptor binding protein with a single PDZ domain. ►PDZ, ►AMPA, ►GABA; Sal C et al 2001 Neuron 31:115.

Homing: Moving of insertion or other mobile elements within or into a genome. ►linotte

Homing Endonucleases: Homing endonucleases are encoded within mitochondrial and nuclear introns and catalyze the movement of introns and inteins. They have recognition sequences of 18 to 40 nucleotide pairs. The best studied representative of these enzymes is I-Sce. It is mitochondrially encoded within the ω^+ yeast factor (21S rRNA). After being spliced out, it is translated into Sce protein. The VDE endonuclease is within the intron of a vacuolar membrane ATP-ase. They are transcribed and translated together and when the protein is processed, the VMA1 ATPase and the VDE endonuclease are produced by evicting VDE and splicing the amino and carboxy-terminal amino acid sequences of VMA1.

The Sce system can be used for site-specific chromosome breakage and repair studies after introduction with appropriate vectors into the cells. The event can be monitored in a *S1neo* construct where the *neo* antibiotic resistance gene is interrupted by a 18 bp I-Sce I sequence and therefore *neo* is not expressed. The I-Sce I sequence is flanked by a CATG duplication: S1neo~~~~CATG~~CATG. After I-Sce I cleavage, two types of *neo* genes are found: (1) *neo*~~~~CATG expressed and *neo*~~~~Δ not expressed because of the Δ deletion. Other types of constructs can also be produced that can restore *neo*

activity by cleavage and repair. I-Sce I can be introduced into the cells also by electroporation and can bring about non-homologous repair. The double-strand breaks generated by the homing endonuclease were found to increase gene targeting up to a 1000-fold. They induce site-specific breaks within the 14-44 base pair recognition sequence. Four families of homing endonucleases are distinguished. These systems—although basically different from the Cre/loxP or FLP/FRT34; can be used for similar purposes. Insertion of *mobE* endonuclease into the *nrdA* gene of *Aeromonas hydrophila* phage Aeh1 creates a unique genes-in-pieces arrangement, where *nrdA* is split into two independent genes, *nrdA-a* and *nrdA-b*, each encoding cysteine residues that correspond to the active-site residues of uninterrupted NrdA proteins. Remarkably, the *mobE* insertion does not inactivate NrdA function, although the insertion is not a self-splicing intron or intein (Friedrich NC et al 2007 Proc Natl Acad Sci USA. 104:6176). ►mitochondrial genetics, ►Cre/loxP, ►FLP/FRT, ►intron homing, ►inteins, ►site-specific recombinases, ►chromosomal rearrangements, ►super-Mendelian inheritance, ►marker exclusion, ►LAGLIDADG; Dujon B et al 1989 Gene 82:115; Jurica MS, Soddard BS 1999 Cell Mol Life Sci 55:1304; Edgell DR, Shub DA 2001 Proc Natl Acad Sci USA 98:7898; Chevalier BS, Stoddard BL 2001 Nucleic Acids Res 29:3757; Wessler SR 2005 Trends Plant Sci 10:54.

Hominidae: The family of humans *Homo sapiens*, *Homo erectus*, *Homo habilis*, and other most closely related, now extinct, genera that are more highly evolved than the closest family of *Pongidae* that includes the orangutan, chimpanzee, gorilla and other great apes. The brain size in modern humans varies, the Australian aborigines have a brain volume over 1,200 cm³ whereas that of *Homo erectus* was over 1,000, *Homo habilis* above 700, *Australopithecus* 400 to 500, gorilla 500, and orangutan and chimpanzee just below 400. (The word australis means southern; pithekos indicates ape in Greek). Apparently, brain size has changed very little in the last 300,000 years. Sequencing 53 intergenic, non-repetitive DNA segments (24,234 bp) from humans, chimpanzees, gorillas, and orangutans revealed a very low average sequence divergence. The divergence for human–chimpanzee is 1.24%, human–gorilla 1.62%, and for chimpanzee–gorilla 1.63%. On the basis of a molecular evolutionary clock, humans separated from chimpanzees 4.6 to 6.2 million years ago (Chen F-C, Li W-H 2001 Am J Hum Genet 68:444). Newer analysis of chromosome human 21 and the corresponding sequences in chimpanzee revealed

very small differences in coding (0.51%), in promoter (0.88%) and exon-intron junctions (0.85%), by sequencing 127 genes (Shi J et al 2003 Proc Natl Acad Sci USA 100:8331).

The taxonomic classification and evolutionary descent of *Primates* is not entirely clear. The majority of anthropologists favor the idea that *Homo sapiens* evolved in Africa (about 1 million years [Myr] ago) and then spread to Asia and Europe in relatively recent time. One incomplete tree of hominid descent is shown below.

There is fossil indication that *H. habilis* and *H. erectus* coexisted for about half a million years and therefore *habilis* did not convert directly into *erectus* and therefore there might not have been a simple direct line of descent as shown in the figure (see Fig. H59) (Spoor F et al 2007 Nature [Lond] 448:688). Human evolution from primates will be revealed by the completion of the genome projects. At this time the actual steps and course of human evolution are not entirely clear because of the scarcity of paleontological remains (Dalton R 2006 Nature [Lond] 440:1100).

It is already known that the DNA base composition of humans and chimpanzees is almost 99% identical. Therefore, morphological and brain differences may be accounted for by different regulation of the basically identical genetic material. The lower human chromosome number appears to be due to chromosome fusion (e.g., human chromosome 2). Pericentric inversions of human chromosome 18 and chromosome 3 show major differences from the corresponding ape chromosomes (Muzny DM et al 2006 Nature [Lond] 440:1194). Rearrangements frequently alter regulation of genes. The human genus (Hominini) has been reclassified on the basis of new criteria and because of the inherent problems of scanty anthropological remains; modifications are likely to be proposed. Mandibular ramus morphology (a projection of the lower jaw) on a recently discovered specimen of *Australopithecus afarensis* closely matches that of gorillas. This

finding was unexpected in the view that chimpanzees are the closest living relatives of humans. Because modern humans, chimpanzees, orangutans, and many other primates share a ramal morphology that differs from that of gorillas, the gorilla anatomy must represent a unique condition, and its appearance in fossil hominins must represent an independently derived morphology. The absence of this morphology in modern humans has cast doubt on the role of *Au. afarensis* as a modern human ancestor (Rak J et al 2007 Proc Natl Acad Sci USA 104:6568).

►hologenesis, ►Primates, ►Eve foremother of molecular mtDNA, ►Y chromosome, ►out-of-Africa, ►genome projects, ►inversion, ►language, ►chimpanzee, ►bonobo, ►*Homo floresiensis*; Wood B, Collard M 1999 Science 284:65; Stone AC et al 2002 Proc Natl Acad Sci USA 99:43; Wood B 2002 Nature [Lond] 418:133; Carroll SB 2003 Nature [Lond] 422:849; White TD et al 2003 Nature [Lond] 423:742; Cela-Conde CJ, Ayala FJ 2003 Proc Natl Acad Sci USA 100:7684; <http://www.mnh.si.edu/anthro/humanorigins>; <http://www.talkorigins.org/faqs/homs>.

Hominins: The various evolutionary ancestors at the separation of human and ape lineages. They include *Homo*, *Australopithecus*, and the more ancient *Paranthropus* and *Ardipithecus*. By some definition hominins include primates up to human lineage and the associated subfamilies of *Pan* and *Gorilla* ►hominidae, ►Pongidae; Underdown S 2006 Nature [Lond] 444:680.

Hominoid: Hominoids includes gibbons, great apes, and hominids (and extinct species). ►primates, ►hominids, ►pongidae, ►great apes

***Homo sapiens* (man):** $2n = 46$. ►hominidae, ►human races, ►primates

***Homo floresiensis*:** An extinct human race that lived in the late Pleistocene period in Indonesia. Its body size

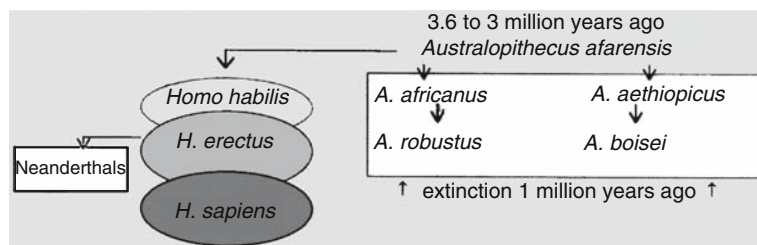


Figure H59. New skeletal mtDNA analysis of Neanderthal remains supports the view that these people represent an evolutionary dead end as shown at left

was comparable to that of the African pygmy. Its brain volume $\sim 380 \text{ cm}^3$ is comparable to the chimpanzee's. The first skeletal remains were discovered in 2003. (See Lieberman DE 2005 Nature [Lond] 437:957).

Homoalanine: $\text{C}_4\text{H}_9\text{NO}_2$.

Homoalleles: Homoalleles differ at the same nucleotide site of a codon, and therefore only four different alleles can be produced, containing at a particular site either A or T, or C or G, and within the nucleotides recombination is impossible. Such an allele can be changed by intracodon (between nucleotides) recombination or base substitution.
▶ [homoeoalleles](#), ▶ [heteroalleles](#)

Homocaryon: ▶ [homokaryon](#)

Homocitrullinuria: ▶ [urea cycle](#)

Homocystinuria: Homocystinuria may occur due to different causes: (i) recessive deficiency of cystathionine synthetase [human chromosome 21q22.3], (ii) defects in vitamin B12 metabolism, (iii) poor intestinal absorption of B12, (iv) deficiency of methylenetetrahydrofolate reductase (1p36.3). Within group (i) different forms were also found; some responded also to vitamin B6 (pyridoxine). The phenotypes may resemble that of the Marfan syndrome. In some instances, deletion of the 145 amino acid carboxy terminal of cystathionine synthase alleviates the metabolic problems. It seems that this segment negatively controls the catalytic activity and it is under regulation by AdoMet. The general symptoms involve dislocation of the eye lens (ectopia lentis), thromboembolism (obstruction of the blood vessels), bone abnormalities, mental retardation in 2/3 of the afflicted, psychological disorders, etc. Prevalence is $\sim 2 \times 10^{-6}$ although in Ireland it is much more common. The diagnostic test to determine elevation of homocysteine (see Fig. H60) and methionine in the urine is carried out by the cyanide-nitroprusside reaction. Prenatal and carrier identification is practical. Types (ii) and (iii) respond favorably to vitamin B12 (hydroxycobalamin), and

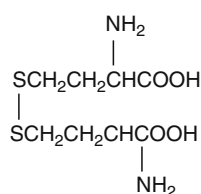


Figure H60. Homocystin

cultured cells require methionine. Type (iv) individuals respond favorably to pyridoxine and folic acid. Defects in methionine synthase reductase (MTRR, 5p15.3-p15.2) may also increase the blood homocystine level. In Down syndrome, the level of cystathionine and cysteine is increased, the level of homocysteine is reduced, folate-dependent methionine synthesis is diminished, and folate deficiency may occur.
▶ [coronary heart disease](#), ▶ [hypertension](#), ▶ [genetic screening](#), ▶ [amino acid metabolism](#), ▶ [cystinuria](#), ▶ [cystinosis](#), ▶ [cystathionuria](#), ▶ [cobalamin](#), ▶ [vitamin B₁₂ deficiency](#), ▶ [methionine biosynthesis](#), ▶ [hyperhomocysteinemia](#), ▶ [AdoMet](#), ▶ [aminoacidurias](#), ▶ [Down syndrome](#), ▶ [Marfan syndrome](#); Janošik M et al 2001 Am J Hum Genet 68:1506; Jakobowski H 2002 J Biol Chem 277:30425.

Homoeoalleles: Evolutionarily and functionally closely related genes in polyploid species. ▶ [homoalleles](#)

Homoeobox: ▶ [homeobox](#), ▶ [homeotic genes](#)

Homoeologous Alleles: Homoeologous alleles occur in the homoeologous chromosomes of allopolyploid species; also called homoeoalleles.

Homoeologous Chromosomes: Nonidentical yet related chromosomes derived from a common ancestor, and despite some evolutionary divergence, show partial homology like the A, B, and D genomes of wheat.
▶ [homologous chromosomes](#), ▶ [nullisomic compensation](#)

Homoeotic: Related by evolutionary descent but modified during the course of evolution; similar but not entirely identical (recent usage is generally homeotic although homoeotic would be the etymologically correct spelling).

Homogametic Sex: (XX) produces only X-chromosome-containing gametes, in contrast to the heterogametic (XY) individual, which can have both X- and Y-chromosome-bearing gametes. The homogametic sex can be either female (XX) or male (ZZ).
▶ [chromosomal sex determination](#), ▶ [heterogametic](#)

Homogamy: Mating between similar types or self-fertilization in plants.
▶ [autogamy](#), ▶ [assortative mating](#), ▶ [heterogamy](#)

Homogeneity Test: The homogeneity test (see Table H2) can be used to determine whether different sets of data are statistically homogeneous enough to be considered a part of the same population, and whether the information is homogeneous enough to permit pooling. This test is basically a chi square procedure but the use of the Yates correction is not allowed. Without testing the homogeneity of separate sets of experiments, the information should not be pooled, even when the combined data fit well to a null

Table H2. Homogeneity test (using pea data of Mendel)

| Family 1 (<i>n</i> = 36) | | | | | Family 3 (<i>n</i> = 97) | | | | | |
|---|-------|-------|------------------|--------------------------|-------------------------------------|-------|-------|------------------|-------|------|
| D | R | df ⊗ | chi ² | | D | R | df ⊗ | chi ² | | |
| (1) observed numbers | 25 | 11 | | (1) observed numbers | 70 | 27 | | | | |
| (2) expected (3:1) | 27 | 9 | | (2) expected (3:1) | 72.25 | 24.25 | | | | |
| (3) difference (1)–(2) | 2 | 2 | | (3) difference (1)–(2) | 2.75 | 2.75 | | | | |
| (4) square of difference | 4 | 4 | | (4) square of difference | 7.563 | 7.563 | | | | |
| (5) divide (4) by (2) | 0.148 | 0.444 | 1 | 0.592 | (5) divide (4) by (2) | 0.105 | 0.312 | 1 | 0.417 | |
| Family 2 (<i>n</i> = 39) | | | | | Families Combined (<i>n</i> = 172) | | | | | |
| D | R | df ⊗ | chi ² | | D | R | df ⊗ | chi ² | | |
| (1) observed numbers | 32 | 7 | | (1) observed numbers | 127 | 45 | | | | |
| (2) expected (3:1) | 29.25 | 9.75 | | (2) expected (3:1) | 129 | 43 | | | | |
| (3) difference (1)–(2) | 2.75 | 2.75 | | (3) difference (1)–(2) | 2 | 2 | | | | |
| (4) square of difference | 7.563 | 7.563 | | (4) square of difference | 4 | 4 | | | | |
| (5) divide (4) by (2) | 0.259 | 0.776 | 1 | 1.035 | (5) divide (4) by (2) | 0.031 | 0.093 | 1 | 0.124 | |
| Homogeneity test | | | | | Probability * | | | | | |
| Total of the 3 families | | | | | 3 | | | | | |
| Combined data | | | | | 1 | | | | | 0.72 |
| HOMOGENEITY (difference of the above lines) | | | | | 2 | | | | | 0.38 |

hypothesis. The use of this test is best explained by the tabulated example shown. ►chi square, ►null hypothesis, ►Yates correction

Homogeneously Stained Region (HSR): Due to amplification in cancer cells, extended chromosomal bands are detectable by light microscopy. ►double minutes

Homogenote: ►endogenote

Homogenotization: The production of homozygosity for knockout, either by targeting both chromosomes in the somatic cells, or culturing the heterozygous knockout cells under highly selective conditions favoring the knockout chromosome. ►knockout, ►targeting genes

Homogentisic Acid: ►alkaptonuria

Homograft: In a homograft, there is no known genetic difference between the transplanted and host tissues.

Homohistont: A non-chimeric tissue derived from a chimera. ►chimera

Homohybrid DNA: The annealed product of two methylated or unmethylated DNA sequences.

Homoio-genetic Induction: Homoio-genetic induction is passed on by cells that have been previously induced. (See Nieuwkoop PD 1999 Int J Dev Biol 43(7):615).

Homokaryon: ►dikaryon

Homolog: Homologs have similar primary and three-dimensional structures (3D) and functions. In homologous proteins, the 3D structure is commonly better preserved during evolution than the amino acid sequence. Thus, they have common motifs. Similarity does not necessarily mean homology. Homology indicates relationship by common evolutionary descent. ►orthologous loci, ►paralogous loci; Homologene database of homologous genes (over 165,491 groups by 2005) of sequenced eukaryotes: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=homologene>).

Homologous Chromosomes: Homologous chromosomes contain the same cytological gene loci, and form bivalents in meiosis. The homology may not be perfect and the difference may be up to several hundred kilobases. The nonhomologous chromosomes may display substantial telomeric homology among several chromosomes. In molecular evolutionary terms, homology may exist among certain chromosomes or chromosomal regions or sites of different taxonomic groups if they carry similar nucleotide sequences. ►homoeologous chromosomes; Mefford HC et al 2001 Hum Mol Genet 10:2363.

HomoloGene: The homologene detects homologs of annotated genes among 18 sequenced eukaryotic organisms. ►homologous genes; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=homologene>.

Homologous Genes: Homologous genes carry out basically the same function, and are descended from common ancestors, yet their primary structure may not be entirely the same. ►analogous genes; <http://www.ncbi.nlm.nih.gov/HomoloGene/>.

Homologous Incompatibility: In homologous incompatibility, the pathogen cannot cause disease because a particular, race-specific gene of the host conveys resistance to it.

Homologous Pathogen: A pathogen that is genetically qualified to cause disease in a particular host.

Homologous Proteins: Homologous proteins occur in different species and display similar structure and function such as the various globins, the majority of metabolic enzymes, etc.

Homologous Recombination: Genetic exchange between essentially identical chromosomes (polynucleotide chains). Homologous recombination can be used for gene disruption and studying the consequence of lack of function of a particular locus (see Fig. H61). For this, a plasmid is constructed that carries in between the flanking sequences of the target gene, other nucleotide sequences such as an antibiotic resistance gene. The flanks permit homologous pairing and recombination and may take place within the boundary of an interrupted DNA stretch (e.g., the target):

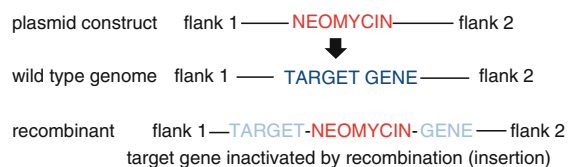


Figure H61. Homologous Recombination

Such a manipulation is useful in animal cell cultures and the resistance to the antibiotics can select the recombinant cells. Extremely rare double crossovers can thus be recovered. Cutting within the target by an appropriate restriction endonuclease can enhance homologous recombination by about 10 fold. The frequency of somatic homologous recombination in mammalian cells may vary within the range of 10^{-8} to 10^{-6} per cell per generation. One may note that this term “homologous recombination” has gained a new meaning because classical genetics recognized recombination as always homologous. In yeast, homologous recombination usually requires

a homology of at least 30 bp. Single-stranded DNA about 30-nucleotides-long may promote recombination by promoting annealing to complementary sequences. *Non-allelic homologous recombination* occurs between duplicated sequences and contributes to genetic variations by nucleotide loss and gain, common in human populations (Hinds DA et al 2006 Nature Genetics 38:82). ►illegitimate recombination, ►recombination, ►crossing over, ►targeting genes, ►Cre/loxP, ►FLP/FRT, ►excision vector, ►recombination molecular mechanisms eukaryotes, ►recombination molecular mechanisms prokaryotes, ►ectopic recombination, ►heterochromosomal recombination, ►deletion, ►I-SceI; Hiom K 2001 Curr Biol 11:R278; Sonoda E et al 2001 Proc Natl Acad Sci USA 98:8388; Bollag RJ et al 1989 Annu Rev Genet 23:199; Court DL et al 2002 Annu Rev Genet 36:361; recombination proteins in yeast: Krogh BO, Symington LS 2004 Annu Rev Genet 38:233; mechanisms: Sung P, Klein H 2006 Nature Rev Mol Cell Biol 7:739.

Homolog-Scanning Mutagenesis: Homolog-scanning mutagenesis is applicable to gene families coding for structurally related proteins. Homologous domains of the proteins (7 to 30 amino acids) are substituted for each other, and in the substituted domain amino acids are replaced by another amino acid, e.g., alanine. Then the binding of the substituted domains to the protein receptor (e.g., growth hormone, protein kinase) is analyzed. Such an analysis may reveal any change in receptor binding and function. A simpler procedure is the “charged-to-alanine scanning mutagenesis” in which blocks of amino acids (4 to 8) are replaced by alanine. ►site-specific mutation, ►oligonucleotide-directed mutagenesis, ►cysteine-scanning mutagenesis, ►Kunkel mutagenesis; Vik SB et al 1988 J Biol Chem 263:6599; Kunkel TA et al 1991 Methods Enzymol 204:125; Griffith KL, Wolf RE Jr 2002 J Mol Biol 322:237.

Homology: Similarity based on nucleotide sequences in the DNA and RNA or amino acid sequences in the protein. It also indicates evolutionary relationship. Information on homology of human and yeast genes can be obtained at <http://www.ncbi.nlm.nih.gov/>

XREFdb. The discovery of homology sometimes appears puzzling. *Saccharomyces* yeast contains a gene homologous to the *NifS* gene of nitrogen fixing *Azotobacter*, although yeast does not fix nitrogen.

Further studies revealed that this gene actually inserts sulfur into metal—sulfur centers of metal-loenzymes using pyridoxal phosphate as cofactor. The reliance on homology for understanding genetic functions is of great importance. Yeast, *Drosophila*, and *Arabidopsis* are relatively simple organisms and can genetically be manipulated by mutation, recombination, transformation, etc (see Table H3).

They can help shed light on the series of gene functions in a genomic context in other organisms, e.g., humans, in whom the application of these laboratory techniques (e.g., controlled mating) is limited or impossible. Evolutionists distinguish between *repetitive homology*, such as the multiplicity of legs in the millipedes, and *non-serial homology*, e.g., the leaves of a plant. Usually, a 25% or higher homology is considered as evidence for common evolutionary relationship. The evolution of homology of morphological traits such as legs of mammals and wings of birds or fins of fishes is not straightforward and it has been suggested that it is based not on particular genes, but rather on “character identity networks” (Wagner GP 2007 Nature Genet 8:473).

The amino acid sequence homology of cytochrome C protein is shown in 35 different organisms (see Fig. H62). The shaded areas indicate complete identity at the alignments. (Courtesy of Margaret Dayhoff, ed. Atlas of Protein Sequence and Structure, 5. Natl. Biomed. Res. Found. Georgetown Univ. Washington, DC). Alignment of nucleotide sequences provides more critical information because the amino acid sequences do not distinguish among synonymous codons. Among bacteria, the homologous genes, except members of operons, are not in identical orders. Apparently, replication may rearrange the gene positions in the various genomes. A conservative estimate of the sequenced human and mouse genomes revealed 3,920 orthologous gene pairs. ►analogy, ►DNA sequence alignment, ►indel, ►orthology, ►paralogy, ►xenology, ►congruence analysis, ►phylogenetic weighting, ►URF, ►illustration

Table H3. Proportion of proteins conserved among three organisms (Data from Constanzo MC et al. 2001 Nucleic Acids Res. 29:75)

| | Unique to | <i>C. elegans</i> | <i>S. pombe</i> | <i>S. cerevisiae</i> | Shared by all |
|----------------------|-----------|-------------------|-----------------|----------------------|---------------|
| <i>C. elegans</i> | 77 % | | 2 % | 3 % | 18 % |
| <i>S. pombe</i> | 29 % | 3 % | | 20 % | 46 % |
| <i>S. cerevisiae</i> | 39 % | 3 % | 20 % | | 38 % |

| AMINO ACID POSITIONS | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116 | 117 | 118 | 119 | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 128 | 129 | 130 | 131 | 132 | 133 | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 | 143 | 144 | 145 | 146 | 147 | 148 | 149 | 150 | 151 | 152 | 153 | 154 | 155 | 156 | 157 | 158 | 159 | 160 | 161 | 162 | 163 | 164 | 165 | 166 | 167 | 168 | 169 | 170 | 171 | 172 | 173 | 174 | 175 | 176 | 177 | 178 | 179 | 180 | 181 | 182 | 183 | 184 | 185 | 186 | 187 | 188 | 189 | 190 | 191 | 192 | 193 | 194 | 195 | 196 | 197 | 198 | 199 | 200 | 201 | 202 | 203 | 204 | 205 | 206 | 207 | 208 | 209 | 210 | 211 | 212 | 213 | 214 | 215 | 216 | 217 | 218 | 219 | 220 | 221 | 222 | 223 | 224 | 225 | 226 | 227 | 228 | 229 | 230 | 231 | 232 | 233 | 234 | 235 | 236 | 237 | 238 | 239 | 240 | 241 | 242 | 243 | 244 | 245 | 246 | 247 | 248 | 249 | 250 | 251 | 252 | 253 | 254 | 255 | 256 | 257 | 258 | 259 | 260 | 261 | 262 | 263 | 264 | 265 | 266 | 267 | 268 | 269 | 270 | 271 | 272 | 273 | 274 | 275 | 276 | 277 | 278 | 279 | 280 | 281 | 282 | 283 | 284 | 285 | 286 | 287 | 288 | 289 | 290 | 291 | 292 | 293 | 294 | 295 | 296 | 297 | 298 | 299 | 300 | 301 | 302 | 303 | 304 | 305 | 306 | 307 | 308 | 309 | 310 | 311 | 312 | 313 | 314 | 315 | 316 | 317 | 318 | 319 | 320 | 321 | 322 | 323 | 324 | 325 | 326 | 327 | 328 | 329 | 330 | 331 | 332 | 333 | 334 | 335 | 336 | 337 | 338 | 339 | 340 | 341 | 342 | 343 | 344 | 345 | 346 | 347 | 348 | 349 | 350 | 351 | 352 | 353 | 354 | 355 | 356 | 357 | 358 | 359 | 360 | 361 | 362 | 363 | 364 | 365 | 366 | 367 | 368 | 369 | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 378 | 379 | 380 | 381 | 382 | 383 | 384 | 385 | 386 | 387 | 388 | 389 | 390 | 391 | 392 | 393 | 394 | 395 | 396 | 397 | 398 | 399 | 400 | 401 | 402 | 403 | 404 | 405 | 406 | 407 | 408 | 409 | 410 | 411 | 412 | 413 | 414 | 415 | 416 | 417 | 418 | 419 | 420 | 421 | 422 | 423 | 424 | 425 | 426 | 427 | 428 | 429 | 430 | 431 | 432 | 433 | 434 | 435 | 436 | 437 | 438 | 439 | 440 | 441 | 442 | 443 | 444 | 445 | 446 | 447 | 448 | 449 | 450 | 451 | 452 | 453 | 454 | 455 | 456 | 457 | 458 | 459 | 460 | 461 | 462 | 463 | 464 | 465 | 466 | 467 | 468 | 469 | 470 | 471 | 472 | 473 | 474 | 475 | 476 | 477 | 478 | 479 | 480 | 481 | 482 | 483 | 484 | 485 | 486 | 487 | 488 | 489 | 490 | 491 | 492 | 493 | 494 | 495 | 496 | 497 | 498 | 499 | 500 | 501 | 502 | 503 | 504 | 505 | 506 | 507 | 508 | 509 | 510 | 511 | 512 | 513 | 514 | 515 | 516 | 517 | 518 | 519 | 520 | 521 | 522 | 523 | 524 | 525 | 526 | 527 | 528 | 529 | 530 | 531 | 532 | 533 | 534 | 535 | 536 | 537 | 538 | 539 | 540 | 541 | 542 | 543 | 544 | 545 | 546 | 547 | 548 | 549 | 550 | 551 | 552 | 553 | 554 | 555 | 556 | 557 | 558 | 559 | 560 | 561 | 562 | 563 | 564 | 565 | 566 | 567 | 568 | 569 | 570 | 571 | 572 | 573 | 574 | 575 | 576 | 577 | 578 | 579 | 580 | 581 | 582 | 583 | 584 | 585 | 586 | 587 | 588 | 589 | 590 | 591 | 592 | 593 | 594 | 595 | 596 | 597 | 598 | 599 | 600 | 601 | 602 | 603 | 604 | 605 | 606 | 607 | 608 | 609 | 610 | 611 | 612 | 613 | 614 | 615 | 616 | 617 | 618 | 619 | 620 | 621 | 622 | 623 | 624 | 625 | 626 | 627 | 628 | 629 | 630 | 631 | 632 | 633 | 634 | 635 | 636 | 637 | 638 | 639 | 640 | 641 | 642 | 643 | 644 | 645 | 646 | 647 | 648 | 649 | 650 | 651 | 652 | 653 | 654 | 655 | 656 | 657 | 658 | 659 | 660 | 661 | 662 | 663 | 664 | 665 | 666 | 667 | 668 | 669 | 670 | 671 | 672 | 673 | 674 | 675 | 676 | 677 | 678 | 679 | 680 | 681 | 682 | 683 | 684 | 685 | 686 | 687 | 688 | 689 | 690 | 691 | 692 | 693 | 694 | 695 | 696 | 697 | 698 | 699 | 700 | 701 | 702 | 703 | 704 | 705 | 706 | 707 | 708 | 709 | 710 | 711 | 712 | 713 | 714 | 715 | 716 | 717 | 718 | 719 | 720 | 721 | 722 | 723 | 724 | 725 | 726 | 727 | 728 | 729 | 730 | 731 | 732 | 733 | 734 | 735 | 736 | 737 | 738 | 739 | 740 | 741 | 742 | 743 | 744 | 745 | 746 | 747 | 748 | 749 | 750 | 751 | 752 | 753 | 754 | 755 | 756 | 757 | 758 | 759 | 760 | 761 | 762 | 763 | 764 | 765 | 766 | 767 | 768 | 769 | 770 | 771 | 772 | 773 | 774 | 775 | 776 | 777 | 778 | 779 | 780 | 781 | 782 | 783 | 784 | 785 | 786 | 787 | 788 | 789 | 790 | 791 | 792 | 793 | 794 | 795 | 796 | 797 | 798 | 799 | 800 | 801 | 802 | 803 | 804 | 805 | 806 | 807 | 808 | 809 | 810 | 811 | 812 | 813 | 814 | 815 | 816 | 817 | 818 | 819 | 820 | 821 | 822 | 823 | 824 | 825 | 826 | 827 | 828 | 829 | 830 | 831 | 832 | 833 | 834 | 835 | 836 | 837 | 838 | 839 | 840 | 841 | 842 | 843 | 844 | 845 | 846 | 847 | 848 | 849 | 850 | 851 | 852 | 853 | 854 | 855 | 856 | 857 | 858 | 859 | 860 | 861 | 862 | 863 | 864 | 865 | 866 | 867 | 868 | 869 | 870 | 871 | 872 | 873 | 874 | 875 | 876 | 877 | 878 | 879 | 880 | 881 | 882 | 883 | 884 | 885 | 886 | 887 | 888 | 889 | 890 | 891 | 892 | 893 | 894 | 895 | 896 | 897 | 898 | 899 | 900 | 901 | 902 | 903 | 904 | 905 | 906 | 907 | 908 | 909 | 910 | 911 | 912 | 913 | 914 | 915 | 916 | 917 | 918 | 919 | 920 | 921 | 922 | 923 | 924 | 925 | 926 | 927 | 928 | 929 | 930 | 931 | 932 | 933 | 934 | 935 | 936 | 937 | 938 | 939 | 940 | 941 | 942 | 943 | 944 | 945 | 946 | 947 | 948 | 949 | 950 | 951 | 952 | 953 | 954 | 955 | 956 | 957 | 958 | 959 | 960 | 961 | 962 | 963 | 964 | 965 | 966 | 967 | 968 | 969 | 970 | 971 | 972 | 973 | 974 | 975 | 976 | 977 | 978 | 979 | 980 | 981 | 982 | 983 | 984 | 985 | 986 | 987 | 988 | 989 | 990 | 991 | 992 | 993 | 994 | 995 | 996 | 997 | 998 | 999 | 1000 | 1001 | 1002 | 1003 | 1004 | 1005 | 1006 | 1007 | 1008 | 1009 | 1010 | 1011 | 1012 | 1013 | 1014 | 1015 | 1016 | 1017 | 1018 | 1019 | 1020 | 1021 | 1022 | 1023 | 1024 | 1025 | 1026 | 1027 | 1028 | 1029 | 1030 | 1031 | 1032 | 1033 | 1034 | 1035 | 1036 | 1037 | 1038 | 1039 | 1040 | 1041 | 1042 | 1043 | 1044 | 1045 | 1046 | 1047 | 1048 | 1049 | 1050 | 1051 | 1052 | 1053 | 1054 | 1055 | 1056 | 1057 | 1058 | 1059 | 1060 | 1061 | 1062 | 1063 | 1064 | 1065 | 1066 | 1067 | 1068 | 1069 | 1070 | 1071 | 1072 | 1073 | 1074 | 1075 | 1076 | 1077 | 1078 | 1079 | 1080 | 1081 | 1082 | 1083 | 1084 | 1085 | 1086 | 1087 | 1088 | 1089 | 1090 | 1091 | 1092 | 1093 | 1094 | 1095 | 1096 | 1097 | 1098 | 1099 | 1100 | 1101 | 1102 | 1103 | 1104 | 1105 | 1106 | 1107 | 1108 | 1109 | 1110 | 1111 | 1112 | 1113 | 1114 | 1115 | 1116 | 1117 | 1118 | 1119 | 1120 | 1121 | 1122 | 1123 | 1124 | 1125 | 1126 | 1127 | 1128 | 1129 | 1130 | 1131 | 1132 | 1133 | 1134 | 1135 | 1136 | 1137 | 1138 | 1139 | 1140 | 1141 | 1142 | 1143 | 1144 | 1145 | 1146 | 1147 | 1148 | 1149 | 1150 | 1151 | 1152 | 1153 | 1154 | 1155 | 1156 | 1157 | 1158 | 1159 | 1160 | 1161 | 1162 | 1163 | 1164 | 1165 | 1166 | 1167 | 1168 | 1169 | 1170 | 1171 | 1172 | 1173 | 1174 | 1175 | 1176 | 1177 | 1178 | 1179 | 1180 | 1181 | 1182 | 1183 | 1184 | 1185 | 1186 | 1187 | 1188 | 1189 | 1190 | 1191 | 1192 | 1193 | 1194 | 1195 | 1196 | 1197 | 1198 | 1199 | 1200 | 1201 | 1202 | 1203 | 1204 | 1205 | 1206 | 1207 | 1208 | 1209 | 1210 | 1211 | 1212 | 1213 | 1214 | 1215 | 1216 | 1217 | 1218 | 1219 | 1220 | 1221 | 1222 | 1223 | 1224 | 1225 | 1226 | 1227 | 1228 | 1229 | 1230 | 1231 | 1232 | 1233 | 1234 | 1235 | 1236 | 1237 | 1238 | 1239 | 1240 | 1241 | 1242 | 1243 | 1244 | 1245 | 1246 | 1247 | 1248 | 1249 | 1250 | 1251 | 1252 | 1253 | 1254 | 1255 | 1256 | 1257 | 1258 | 1259 | 1260 | 1261 | 1262 | 1263 | 1264 | 1265 | 1266 | 1267 | 1268 | 1269 | 1270 | 1271 | 1272 | 1273 | 1274 | 1275 | 1276 | 1277 | 1278 | 1279 | 1280 | 1281 | 1282 | 1283 | 1284 | 1285 | 1286 | 1287 | 1288 | 1289 | 1290 | 1291 | 1292 | 1293 | 1294 | 1295 | 1296 | 1297 | 1298 | 1299 | 1300 | 1301 | 1302 | 1303 | 1304 | 1305 | 1306 | 1307 | 1308 | 1309 | 1310 | 1311 | 1312 | 1313 | 1314 | 1315 | 1316 | 1317 | 1318 | 1319 | 1320 | 1321 | 1322 | 1323 | 1324 | 1325 | 1326 | 1327 | 1328 | 1329 | 1330 | 1331 | 1332 | 1333 | 1334 | 1335 | 1336 | 1337 | 1338 | 1339 | 1340 | 1341 | 1342 | 1343 | 1344 | 1345 | 1346 | 1347 | 1348 | 1349 | 1350 | 1351 | 1352 | 1353 | 1354 | 1355 | 1356 | 1357 | 1358 | 1359 | 1360 | 1361 | 1362 | 1363 | 1364 | 1365 | 1366 | 1367 | 1368 | 1369 | 1370 | 1371 | 1372 | 1373 | 1374 | 1375 | 1376 | 1377 | 1378 | 1379 | 1380 | 1381 | 1382 | 1383 | 1384 | 1385 | 1386 | 1387 | 1388 | 1389 | 1390 | 1391 | 1392 | 1393 | 1394 | 1395 | 1396 | 1397 | 1398 | 1399 | 1400 | 1401 | 1402 | 1403 | 1404 | 1405 | 1406 | 1407 | 1408 | 1409 | 1410 | 1411 | 1412 | 1413 | 1414 | 1415 | 1416 | 1417 | 1418 | 1419 | 1420 | 1421 | 1422 | 1423 | 1424 | 1425 | 1426 | 1427 | 1428 | 1429 | 1430 | 1431 | 1432 | 1433 | 1434 | 1435 | 1436 | 1437 | 1438 | 1439 | 1440 | 1441 | 1442 | 1443 | 1444 | 1445 | 1446 | 1447 | 1448 | 1449 | 1450 | 1451 | 1452 | 1453 | 1454 | 1455 | 1456 | 1457 | 1458 | 1459 | 1460 | 1461 | 1462 | 1463 | 1464 | 1465 | 1466 | 1467 | 1468 | 1469 | 1470 | 1471 | 1472 | 1473 | 1474 | 1475 | 1476 | 1477 | 1478 | 1479 | 1480 | 1481 | 1482 | 1483 | 1484 | 1485 | 1486 | 1487 | 1488 | |
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Homology-Dependent Gene Silencing: ► [co-suppression](#), ► [RIP](#), ► [post-transcriptional gene silencing](#), ► [anti-sense technology](#); Cogoni C 2001 Annu Rev Microbiol 55:381.

Homomeric Protein: Protein built from identical subunits.

Homomultimeric Protein: Protein consisting of more than two identical subunits.

Homonomous: Similar in structure and function; the metameric body parts of insects have developed in a similar homonomous manner in different species. ► [metamerism](#), ► [homeogenes](#), ► [homeobox](#)

Homopeptide: Single amino acid repeats in proteins; they occur in 4.3% of the human proteins. (See database of 13 species: http://repeats.med.monash.edu.au/genetic_analysis/).

Homophila: A database that correlates human disease genes with their *Drosophila* homologues. About 74% of the human genes associated with disease have one or more strong matches with *Drosophila* sequences. (See <http://superfly.ucsd.edu/homophila/>; Chien S et al 2002 Nucleic Acids Res 30:149).

Homoplasmy: In homoplasmy within a cell, tissue, or organism, the organellar genomes (mitochondrial, plastid) do not show genetic differences. Despite the usually large number of organelles per cell and the high rate of mutation, homoplasmy is the most common situation. Low level of heteroplasmy is difficult to detect, however, if the number of organelles is large. In cancer cells, high degree of mutant mtDNA homoplasmy is common. Homoplasmy for mtDNA defects may cause lethality in the offspring of a clinically normal mother who is a carrier. ► [heteroplasmy](#), ► [sorting out](#), ► [heteroplastidy](#), ► [mtDNA](#), ► [mitochondrial diseases in humans](#); Collier HA et al 2001 Nature Genet 28:147; McFarland R et al 2002 Nature Genet 30:145.

Homoplastidic: A cell is homoplastidic if all the plastids/chloroplasts are identical within that cell. ► [heteroplastidy](#), ► [chloroplast genetics](#)

Homoplasy: Parallel evolution (similarity is not based of common ancestry). In other words, two alleles or genes are identical or near-identical in state and/or in function, but they do not share common ancestry. ► [convergent evolution](#), ► [microinversions](#); Collard M, Wood B 2001 J Hum Evol 41(3):167.

Homoploid Speciation: Hybrid speciation without a change in chromosome number.

Homopolymer: A synthetic polynucleotide chain built from only one type of nucleotides, e.g., AAAA or CCCC, etc.

Homopolymeric Amino Acids: Homopolymeric amino acids may occur in proteins due to increased numbers of trinucleotide repeats. The best known among them are the polyglutamine stretches that lead to a variety of diseases. Although rare, polyleucine and polyalanine sequences are even more toxic. ► [trinucleotide repeats](#); Dorsman JC et al 2002 Hum Mol Genet 11:1487.

Homopolysaccharides: Polysaccharides built of one type of sugar subunits.

Homoproline: ► [pipecolic acid](#)

Homoscedasticity: Homogeneity (equality) of the variances in a group of samples.

Homoselection: In small populations, selection may favor homozygotes and this increases the specialization to the unique environmental niche. ► [heteroselection](#), ► [selection](#)

Homoserine: (2-amino-4-hydroxybutyric acid): An analog, antimetabolite of threonine (see Fig. [H63](#)). ► [threonine](#), ► [serine](#)

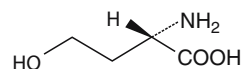


Figure H63. L-Homoserine

Homoserine Lactone: An autoinducer (see Fig. [H64](#)). At the NH site, different molecular groups may join to assure specificity for signaling. ► [autoinduction](#)

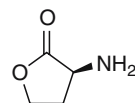


Figure H64. Homoserine lactone

Homosexual: An individual who is attracted to the same sex identifies himself/herself as homosexual, develops sexual fantasies about the same sex, and practices homosexuality. Various studies estimate the prevalence of homosexuality from 2 to 10% in human populations. Homosexual orientation occurs in other mammals also, especially under conditions when the opposite sex is not available.

In some primitive human societies, magical powers are attributed to homosexuals, however, in the majority of societies and religions, homosexuality is disapproved. The ancient Greeks accepted it as an abnormal condition. Base reliefs in the tombs from the Fifth Dynasty of Old Kingdom Egypt discovered in the 1960s depict men in intimate poses expected only in conjugal relations (Reeder G 2000 World of Archeol. 32:193).

Most homosexuals may begin same-sex orientation between age 5 to 30, most commonly by puberty. The bases of homosexuality are not entirely clear.

Homosexuality has been attributed to hormonal, psychological, anthropological, genetic, and moral causes, or to a combination of part or all of these factors. The exact scientific study of homosexuality is difficult because generally a multitude of factors influence the development of all behavioral traits and homosexuality may also have different categories from obligate homosexuality to bisexuality and primarily heterosexuality. Recent anatomical studies attributed brain differences concomitant with homosexual orientation. Many great artists, including the Russian composer Pyotr Tchaikovsky, the painter Leonardo de Vinci, and the famous writer Oscar Wilde and others were homosexuals.

Twin studies suggested higher concordance of this type of sexual orientation between monozygotic twins than between dizygotic ones. One study concluded (on the basis of 4600 individuals) that female relatives of homosexual males have higher fecundity than female maternal relatives of heterosexuals. This information explains why homosexuality does not disappear from the populations (Camperio-Ciani A et al 2004 Proc Roy Soc Lond B Biol Sci 271:2217). The observation that male homosexuals have more homosexual males than lesbian females in their kindred may indicate either that the genetic bases of female homosexuality may not be identical to that of males or may also point to some environmental causes. One study involving 114 families of homosexual index cases found an increase of same-sex orientation among maternal uncles and cousins in comparison to paternal relatives, suggesting the possibility of sex-linked transmission of the gene(s) concerned. Empirical correlation indicates an increased tendency toward homosexuality in younger brothers who were preceded by gestation of their shared mothers. This observation indicates that homosexual tendency in males (but not in females) is affected by prenatal condition(s) rather than postnatal environmental influences (Bogaert AF 2006 Proc Natl Acad Sci USA 103:10771). It has been hypothesized that male histocompatibility antigen (H-Y) of older brothers sensitizes their mother and that increases homosexuality of younger brothers (Blanchard R, Klassen P 1997 J Theor Biol 185:373). This theory does not have, so far, experimental proof.

In 40 families where at least two homosexual males occurred, in approximately 64% of the sib-pairs tested, an apparent linkage was observed to the DNA marker Xq28 with a multipoint lod score of 4, indicating a higher than 99% probability for syntenicity. Another study (Rice G et al 1999 Science 284:665)

failed to confirm linkage to Xq28 by studying 52 gay male siblings. The heritability of male homosexuality was reported to be 0.50, but the inheritance of female homosexuality seems more complex. Researchers debate some of this human information. There is some indication that high fetal androgen levels may favor the development of both male and female adult homosexuality. In *Drosophila*, the *satori* (*sat*) mutants of males do not court or copulate with females but have sexual interest in males. The locus co-maps and is allelic with *fru* at 91B chromosomal band. The *fru^{sat}* flies lack the male-specific Lawrence muscle (MOL). The *fru^{sat}* protein, expressed in some brain cells, is probably a transcription factor with two Zinc-finger domains. The female flies produce two double bonds (dienes) with 27 and 29 carbons and these excite males. The male flies make monoenes (one double bond) of 23 and 25 carbons of the pheromones. The transformer gene (*tra*) regulates these two pheromones. When the *tra* gene is ubiquitously expressed, a mixture of the two pheromones is produced in the males and elicits homosexual courtship by normal males.

Heterosexual men and heterosexual females responded differently to putative pheromones, a testosterone derivative and an estrogen-like odor, respectively. Homosexual men's response resembled that of heterosexual women, rather than that of heterosexual men. Maximum activation in all three groups was observed in the medial preoptic area/anterior hypothalamus. These areas of the brain are involved in sexual behavior of animals (Savic I et al 2005 Proc Natl Acad Sci USA 102:7356). The social status of human homosexuals is an ethical, rather than a biological problem, yet the ethical solution may be facilitated by better biological information. ▶lod score, ▶sibling, ▶twinning, ▶kindred, ▶ethics, ▶behavioral genetics, ▶sex determination, ▶behavior genetics, ▶pheromones, ▶sex reversal; Hammer DH et al 1993 Science 261:321; Hu S et al 1995 Nature Genet 11:248; Yamamoto D, Nakano Y 1999 Cell Mol Life Sci 56(7–8):634.

Homosexual Cross: The mitochondrial genome of yeast appears to have sex-factor-like elements ω^+ and ω^- and the crosses between $\omega^+ \times \omega^-$ are called heterosexual, while the crosses $\omega^+ \times \omega^+$ or $\omega^- \times \omega^-$ are homosexual crosses. ▶mtDNA, ▶mitochondrial genetics

Homothallism: The same individual (thallus) of lower eukaryotes produces both *plus* and *minus* or A and a mating type spores that can fuse into a zygospore. The homothallism bears similarity both to monoecy and autogamy in higher plants. These spores are not necessarily immediate meiotic products. ▶monoecious, ▶dioecious, ▶zygospore, ▶heterothallism, ▶pseudohomothallism

Homotopic Transplantation: Homotopic translation transfers cells or tissue(s) to an identical site but in a different individual.

Homotropic Enzymes: Allosteric enzymes acting on the same substrate and usually regulated by their substrate. ►allostery

Homozygosity in a Randomly Selected Individual: At a locus for an allele, under equilibrium conditions between mutation and genetic drift, homozygosity is approximately $F = \frac{1}{1+4N\mu}$, where N = population size, μ = mutation rate. Homozygosity estimator in a population is obtained by $\frac{2(H_w - H_b)}{1 + H_w - 2H_b}$, where H_w = proportion of homozygosity within an individual and H_b = proportion of homozygosity between individuals. In outbreeding populations of dioecious species, homozygosity for the majority of loci is expected to be low. A study of short tandem repeats in human families in CEPH revealed that on the average more than 10 cM homozygous tracts occur. The longest 77-cM segment included 118 homozygous markers. Apparently, there is a substantial degree of autozygosity or relatedness in these populations. The linkage disequilibrium can be preserved only in the absence of recombination and low mutation rate. Actually, the long homozygous segments also indicate that these families are of relatively recent origin and mutation and selection did not have a chance yet to break up the linkage. ►genetic equilibrium, ►genetic drift, ►autozygosity, ►linkage disequilibrium, ►CEPH; Broman KW, Weber JL 1999 Am J Hum Genet 65:1493.

Homozygosity Mapping: Homozygosity mapping locates autosomal recessive genes in consanguineous families by identity of descent in the pooled records. The information may be collected by determining the restriction fragment length polymorphism (RFLP, Lander ES, Botstein D 1987 Science 236:1567) or on the basis of genome sequence data (Leutenegger A-L et al 2003 Am J Hum Genet 73:516). ►IBD, ►consanguinity, ►mapping, ►autozygosity mapping, ►human genome, ►RFLP; <http://www.broad.mit.edu/ftp/distribution/software/>.

Homozygous: In a homozygous organism, diploid or polyploid, the alleles at a locus are identical, e.g., *aa* or *aaaa* or *AA* or *AAAA*. In a new mutant line, the mutation is generally heterozygous but homozygosity may be obtained if selectable marker(s) are available by screening for rare somatic non-junction.

Honeybee: *Apis mellifera* 2n = female 32, male n = 16, diploid workers and 2n female (queen) and haploid males (drones, 1n) (see Fig. H65). Bees do not have sex chromosomes and sex determination is by

haplodiploidy. The genome of >10,000 genes has been sequenced in 2006 (Nature [Lond] 443:931). The A + T content and the CpG sequences are relatively high. Major transposon families are absent. The difference between workers and queen is developmental, due to difference in nutrition. A complex of pheromones secreted by the mandibular glands and the tergite glands of the queen are required for the many functions to assure the biological order within the colony (Keeling CI et al 2003 Proc Natl Acad Sci USA 100:4486). Homovanillyl alcohol (a dopamine-like compound) (see Fig. H66) is the key component of the queen mandibular pheromone that affects changes in the brain, resulting in specific behavior (Beggs KT et al 2007 Proc Natl Acad Sci USA 104:2460).

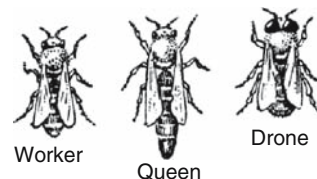


Figure H65. Honey bee

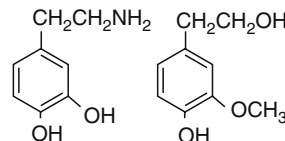


Figure H66. Dopamine (left), homovanillyl alcohol (right)

The workers are generally highly heterozygous because the queen mates with many drones and this conveys an advantage to the colony. The ovaries of the Asian honeybee (*A. florea*) workers are activated after the queen dies and lay eggs from which only drones hatch leading to demise of the colony. These egg-laying workers develop primarily by workers non-natal (nonindigenous) for the colony that are intruders, parasitizing queenless nests and eggs (Nanork P et al 2005 Nature [Lond] 437:829).

Honeybees have rich, map-like organization of spatial memory and that helps them to return to feeder areas (Menzel R et al 2005 Proc Natl Acad Sci USA 102:3040). Communication of the bees is a waggle dance of considerable efficiency for the new recruits that can find the feeder area direction, although in the final stages they depend on odor and visual signs of the target (Riley JR et al 2005 Nature [Lond] 435:2005). The brain of a honeybee is ~1 mm³ and contains 950,000 neurons. ►social insects,

►complementary sex determination, ►haplodiploidy, ►dopamine; <http://www.cyberbee.net>; Michener CD 2000 The Bees of the World, Johns Hopkins Univ. Press, Baltimore, MD, USA; Goodman L 2003 Form and Function in the Honey Bee. Intl Bee Res. Assoc. Cardiff, UK; Oldroyd BP, Wongsiri S 2006 Asian Honey Bees: Biology, Conservation and Human Interactions. Harvard Univ. Press. Cambridge, MA, USA; Menzel R et al 2006 Cell 124:237; origin, evolution and distribution of honeybees: Whittfield CW et al 2006 Science 314:642; neuropeptides: Hummon AB et al 2006 Science 314:647; <http://compbio.dfci.harvard.edu/tgi>; <http://www.ibra.org.uk/>; genome sequence: <http://www.hgsc.bcm.tmc.edu/projects/honeybee/>.

Hoogsteen Pairing: Hoogsteen pairing refers to nucleotide pairs, by an association different from that proposed by Watson and Crick. The A—T pairs have an 80° angle between the glycosylic bonds and a 8.6 Å distance between anomeric carbons (differing in configuration about C). In the *reversed Hoogsteen* pairs, one base is rotated 180° relative to the other. Hoogsteen pairing takes place between nucleotides of a third strand of DNA in the major groove of the duplex. This happens when in the duplex one strand is polypurine and the other is polypyrimidine; the third strand is most commonly polypyrimidine in the triplex DNA. ►Y-family DNA polymerases, ►DNA polymerase, ►Watson and Crick model, ►triple helix formation; see Fig. H67; Soliva R et al 1999 Nucleic Acids Res 27:2248; Aishima J et al 2002 Nucleic Acids Res 30:5244.

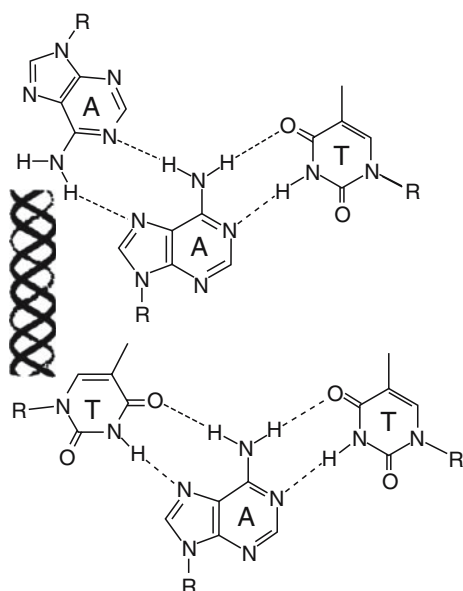


Figure H67. DNA triple helix and Hoogsteen base pairing

Hookworm (*Ancylostoma*): A parasitic nematode posing substantial health hazard to humans and animals. ►AcAP

HOP (*Humulus lupulus*): A climbing dioecious plant (see Fig. H68) with $2n = 20$ chromosomes although forms (*H. japonicus*) with $2n = 16$ females and $2n = 17$ males have also been reported. Its main use is for brewing beer but it may be mixed in bread in some areas of the world. The soft resins and essential oils of the flowers add a typical bitter flavor to the brew and have some preservative effect. It is related to hemp (*Moraceae*). Some extracts have pharmaceutical value.



Figure H68. Hop plant leaf, flower and fruit

Hopeful Monster: Neo-Darwinism assumes that evolutionary changes take place by accumulation of minor mutations that favor fitness of an organism. An alternative suggestion raised the possibility that some major mutations conveyed distinctive alterations to an individual, transcending conventional taxonomic boundaries, and such an individual was called a hopeful monster. ►saltation, ►saltatory replication, ►gradualism; Richards E 1994 Isis 85(3):377.

Hopping: Movement from one location to another by a transposable or insertion element. Hopping also occurs in translation when the peptidyl-tRNA passes further downstream to a similar or same codon. ►transposable elements, ►insertion elements, ►re-coding, ►translational hopping

Hopsigen: Processed pseudogene database. ►pseudo-gene, ►processed pseudogene; <http://pbil.univ-lyon1.fr>; <http://pseudogene.org/human/index.php>; pseudogenes shared by human and mouse: http://pbil.univlyon1.fr/databases/hopsigen_orthologs.html.

Hordeum bulbosum: A wild barley; it exists in diploid and tetraploid forms ($x = 7$). It gained particular attention because when crossed with the common barley (*Hordeum vulgare*, $2n = 14$) or with wheat ($2n = 42$), its chromosomes are eliminated from the zygote and thus haploids are produced at a high frequency. ►haploids, ►chromosome elimination

Hordeum vulgare: Cultivated barley ($2n = 14$). It is used for animal feed, human food, and for the industrial production of malt and beer. The global production of barley is about half of that of maize and about 40% of that of wheat. It evolved probably from the wild *H. spontaneum* ($2n = 14$), a species with which it is readily crossable and forms fertile hybrids. *H. spontaneum* has 2 dominant genes (*Bt* and *Bt₁*) that make the ear brittle. The two-rowed barley develops fertile flowers in the central part of the spikelets, whereas in the six-row barley all three flowers are female-fertile under the control of gene *v*. In the naked barley, the glumes (husks) are not attached to the kernel because of a gene. It is an autogamous species. ▶databases, ▶crop plants, ▶barley

H

hORF: An open reading frame, which has a function identified only by homology. ▶ORF

Horizontal Gaze Palsy, Familial (with progressive scoliosis, 11q23-q25): Rare recessive anomaly of the movement of the external eye muscles (myokymia) associated with abnormal deviation from straightness of the spine, caused by mutation in axon guidance in the brain. ▶ophthalmoplegia, ▶scoliosis; Jen J et al 2002 Neurology 59:432; Jen JC et al 2004 Science 304:1509.

Horizontal Transmission (HGT, horizontal gene transfer): ▶transmission, ▶transfer lateral

Horizontal Resistance: In horizontal resistance, the host is resistant to all races of a pathogen.

Hormesis: Increased growth by irradiation at low doses or by other stress factors. It is a controversial idea that very low doses of radiation make human cells more resistant to subsequent exposure to higher doses. Hormetic U-shape response is characteristic also against some toxic agents. Recent analysis indicates, however, no-threshold (NLT) for potential radiation damage. ▶radiation; Macklis RM, Beresford B 1991 J Nucl Med 32:350; Holzman D 1995 J Nucl Med 36:13n, Calabrese EJ 2002 Rev Mut Res 511:181.

Hormonal Effects on Sex Expression: Although sex-determination is under the control of genes within the sex-chromosomes, the expression of sex characteristics may be influenced by natural hormones or those administered through medical treatment. Human females treated by steroid hormones to prevent miscarriage may give birth to females who may become somewhat masculinized after puberty.

The bovine freemartins also display some virile features, presumably caused by intrauterine exposure to male sex hormones. Genetically determined subnormal production of the pituitary growth hormone

(human gene assigned to chromosome 17q23-q24) may involve recessive sexual anomalies. Castration and ovariectomy lead to intersex phenotype that can be further enhanced by grafting ovaries into male or testes into female chickens (see Fig. H69). The plant hormone gibberellin may affect sex ratio in some species, and can restore fertility in some genetic dwarf plants. ▶hormones, ▶testicular feminization, ▶animal hormones, ▶growth hormones, ▶freemartins, ▶plant hormones, ▶sex determination, ▶gonads

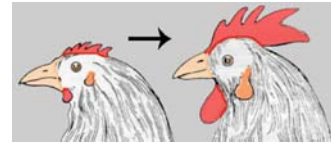
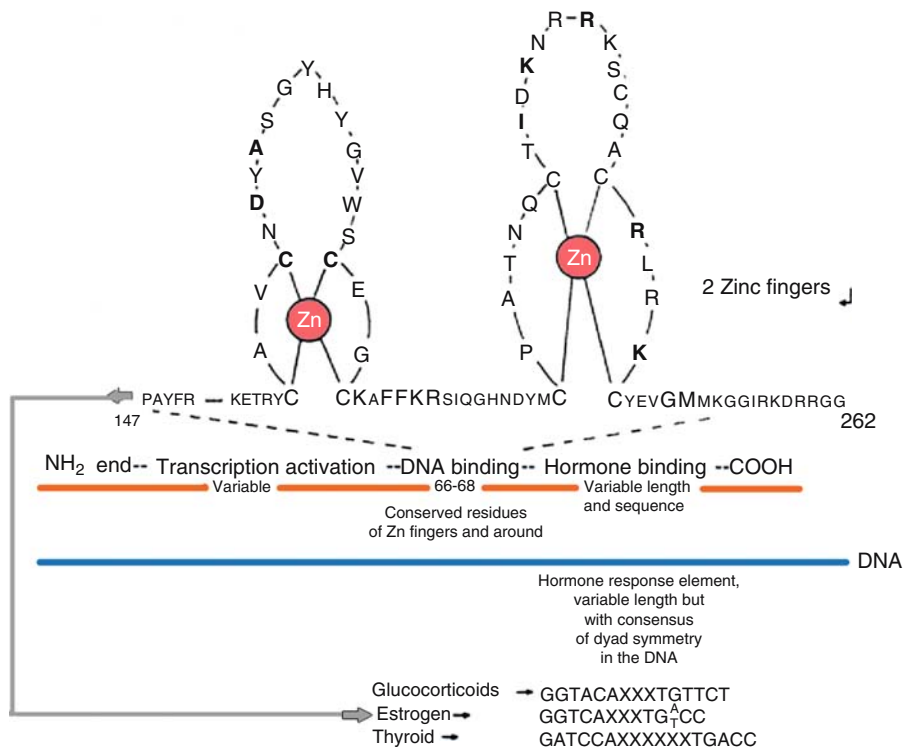


Figure H69. Testosterone-treated hen develops rooster-like features

Hormone Receptors: Hormone receptors are located on the surface or within target cells and transmit their signals to the genes that are set into action when the signals reach them. In *Caenorhabditis elegans*, hormone receptors represent about 1.5% of the coding sequences of the entire genome.

The general structure of the Zn-fingers of the steroid and thyroid (peptide) hormone receptors are shown (see Fig. H70). Steroid hormones are not readily soluble in aqueous media like blood and require special carrier serum proteins to be carried to the plasma membrane. The glucocorticoid receptor is usually situated in the cytoplasm and moves to the nucleus after binding with a ligand. The estrogen and progesterone receptors are mainly in the nucleus and the thyroid receptors are present only in the nucleus. The hormones combine with hormone receptor proteins. These complexes then may bind also to other complexes of hormones and navigate to the hormone response elements (HRE) in the upstream regulatory regions of the genes. The HREs are found in either the promoter or in the enhancer regions where they regulate the transcription of particular genes. These HRE elements vary from hormone to hormone specificities but all have a consensus sequence of dyad symmetry, sometimes palindromic and frequently separated by 3 or more non-conserved bases. The most important functional parts of the hormone receptors are the 66 to 68 conserved and basic amino acid rich tracts that bind to the DNA. The binding may require that a ligand be associated with the receptor or the removal of the ligand-binding domain. The DNA binding region of the hormone receptor forms two Zinc fingers by cross-linked to Zn. The two fingers are coded for by two separate



H

Figure H70. Zinc fingers of the estrogen receptor DNA-binding protein. The most conserved residues are shown in bold. Nuclear localization is specified by the carboxy terminus. The amino acid symbols in protein sequences are given by the single-letter code. Three different hormone response consensus sequences are shown at the lower part of the diagram. The hormone response element is generally about 200 bases upstream from the transcription initiation site

exons, and the entire DNA-binding region is separated by introns from other coding regions of the receptor gene. The structure shown represents the estrogen receptor but it is characteristic for many transcription factors. Thus the hormone receptors are hormone-inducible transcription factors. For the DNA binding, the 3 amino acids following the last Cys residue of the right finger appears most important. The palindrome-like structure of the HRE in the DNA indicates that the hormone receptor protein works as a dimer. The function of the receptor as a transcription factor requires hormone binding. Primarily, the residues near the C terminus determine the hormone binding. This hormone-binding region is critical for specificity. If a chimeric protein is constructed that replaces this binding region with the amino acid sequences of another hormone receptor, then the chimeric protein activates transcription of genes normally receptive to the first segments of the chimera in response to the latter hormone, but not to the hormone that normally activates these genes. The receptor protein does not bind to the HRE unless it is linked to the hormone. Yet, if the hormone-binding domain is deleted, the receptor can bind to the cognate HRE. When the

human estrogen response element (HRE) is transfected into yeast along with a functional estrogen receptor gene, estrogen can promote the expression of yeast genes even if their normal UAP (upstream activating sequence) has been deleted. In some instances, all the components of transcriptional activation by hormones are present, yet no activation is observed because an inhibitor may tie up the system and may prevent, e.g., dimerization of the receptor. These basic molecular genetic studies have found medical applicability. The proliferation of breast cancer depends on a continuous supply of estrogen. The drug tamoxifen can compete for the estrogen-binding site but this complex is not capable of activating transcription. Thus, it may be used as an antineoplastic drug in combination with surgery, irradiation, and chemotherapy if clinical evidence indicates that the tumor has estrogen and progesterone receptors. The steroid analog, RU486, developed in France, is a progesterone analog (antiprogesterone) and can block the implantation of the fertilized ova because of the depletion of normally functional receptors. It is also beneficial for the treatment of endometriosis and leiomyoma. Thus, it is used—in countries where it is approved—as an “after morning

pill” for prevention of pregnancy. The most commonly used birth control pills contain a combination of estrogen and progesterone and their elevated level shuts down the production of the pituitary hormones, thus preventing ovulation. The levonorgestrel pill (Plan B) contains only progestin and interferes with ovulation. It is 80–90% effective if taken within 3 days or less after unprotected sex. None of these drugs protect against sexually transmitted disease. ▶[hormones](#), ▶[transcription factors](#), ▶[signal transduction](#), ▶[breast cancer](#), ▶[testicular feminization](#), ▶[hormone-response elements](#), ▶[hormones](#), ▶[tamoxifen](#), ▶[DNA-binding protein domains](#), ▶[nuclear receptors](#), ▶[RU486](#), ▶[endometriosis](#), ▶[leiomyoma](#); Zhu T et al 2001 Cell Signal 13:599; Chang C, Stadler R 2001 Bioessays 23:619; Robinson-Rechavi M et al 2001 Trends Genet 17:554; pharmacist refusal to dispense contraceptives: Greenberger MD, Vogelstein R 2005 Science 308:1557.

Hormone-Response Elements (HRE): Short DNA sequences flanking genes that respond rapidly to activation by steroid or peptide hormones. Steroid hormones, retinoic acid, thyroid hormone, and vitamin D₃ interact with ligand activated transcription factors (see Fig. H71). The receptors for this steroid/nuclear receptor superfamily are bound to the interspaces of the “half-sites” (n) between the tandem repeats of six base pairs:

These six nucleotide pairs are unchanged but the number of bases (n) between the boxes varies. These are recognized by heterodimers of receptor proteins. The binding domains may include Zn fingers. ▶[glucocorticoid response elements](#), ▶[estrogen response elements](#), ▶[thyroid hormone response elements](#), ▶[RAR](#), ▶[RAX](#), ▶[Zn fingers](#), ▶[regulation of gene activity](#), ▶[ethylene](#), ▶[retinoic acid](#), ▶[nuclear receptors](#); Klinge CM 2001 Nucleic Acids Res 29:2905.

Hormones: Peptides (polypeptides), amino acid-derivatives, and steroids synthesized in a gland of animals and carried by the blood to the site of their action(s) where they control the local function (first messengers). They are not nutrients. Animal hormones are, e.g., somatotropin (growth hormone), corticotropin (in adipose and kidney tissues), thyrotropin (stimulates thyroids), follitropin and lutropin

(in gonads), prolactin and lipotropin (in mammary glands), insulin (regulates sugar metabolism), serotonin (in nervous system), testosterone, estrogen (in most cells), progesterone (in uterus), prostaglandins (in smooth muscles), etc. Plants synthesize five different groups of hormones that are quite different (except the brassinosteroids) in chemical nature from animal hormones. These control primarily cell elongation (auxins), cell divisions (cytokinins), elongation, germination (gibberellins), abscission of leaves and fruits, dormancy, germination (abscisic acid), elongation, ripening, and morphogenesis (ethylene). These plant hormones display numerous types of interactions and are involved in complex manners in signal transduction. ▶[steroid hormones](#), ▶[animal hormones](#), ▶[hormone receptors](#), ▶[hormone-response elements](#), ▶[plant hormones](#), ▶[brassinosteroids](#)

Horotelic Evolution: ▶[bradytelic evolution](#)

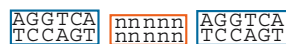
Horse: *Equus caballus*, 2n = 64. The Mongolian wild horse (*Equus przewalskii*) (see Fig. H72) 2n = 66. Mitochondrial DNA evidence indicates that domestication of horses must have occurred in numerous independent events. ▶[hinny](#), ▶[mule](#), ▶[Prezewalsky horse](#); map: Genomics 66:123 [2000]; radiation map: Choudhary BP et al 2002 Mamm Genome 13:89; Y chromosome map: Raudsepp T et al 2004 Proc Natl Acad Sci USA 101:9321; <http://www.uky.edu/Ag/Horsemap/>; horse genome project: <http://www.broad.mit.edu/mammals/horse/>.



Figure H72. Prezewalsky horse



9-CIS retinoic acid receptor site



All-Trans retinoic acid receptor site



Vitamin D₃ receptor site

Figure H71. Hormone response elements

Horse Threadworm: ► *Ascaris*

Horseradish (*Armoracia rusticana*): A perennial pungent condiment; $2n = 4x = 32$. The pungent substance is allyl isothiocyanate (AIT) and may cause pain, inflammation, and extreme sensitivity to heat. The same substance is present in other cruciferous plants that contain mustard oil. AIT depolarizes a subset of the primary sensory neurons and activates ANKTM1, a member of the transient receptor potential ion channel. Capsaicin and Δ^9 -tetrahydrocannabinol (in marijuana) function through the same path. ► [capsaicin](#), ► [cannabinoids](#), ► [ion channels](#); Jordt S-E et al 2004 Nature [Lond] 427:260.

Horsetail Movement: During meiotic prophase of yeast, the nucleus—under the direction of the spindle pole body and with the aid of the microtubules—slowly oscillates in a manner reminiscent of how the horse moves its tail. The telomeres are then clustered and the chromosomes are paired. (Hiraoka Y 1998 Genes Cells 3:405).

Horsetail Stage: In fission yeast (but not in budding yeast), meiosis before intimate pairing the 3 chromosomes aggregate to the spindle pole body (SPB) by their telomeres and are moved back and forth until the homologous regions find each other along the string. This stage bears similarity to the bouquet stage in the majority of eukaryotes. ► [spindle pole body](#), ► [bouquet](#)

HOS1, HOS2, HOS3: Histone 3 and 4 deacetylase enzymes of yeast. ► [histone deacetylation](#)

Hospital-Acquired Infection: Iatrogenic, nosocomial.

Host: An organism that can enter into a particular relationship with another.

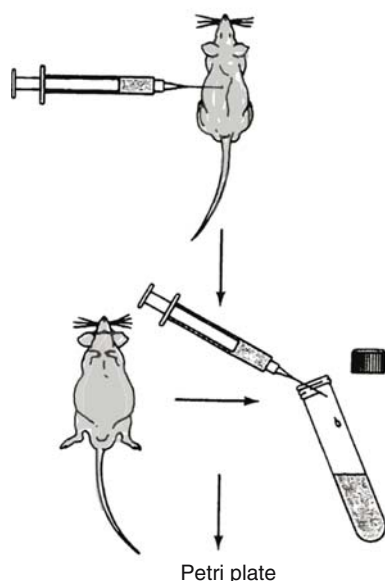
Host Cell Reactivation: DNA repair mechanisms operating in bacterial cells harboring defective bacteriophages. ► [DNA repair](#)

Host-Controlled DNA Modification: ► [restriction modification](#)

Host-Lethal Genes: ► [colicins](#), ► [killer strains](#), ► [killer plasmids](#), ► [pollen killer](#)

Host-Mediated Assay: The host-mediated assay tests whether the host metabolism can convert a compound (a pro-mutagen) into a mutagen, detectable by the cells passed through the host, e.g., yeast, bacterial, or animals cells injected into and then withdrawn from the abdominal cavity of a mouse previously exposed to a potential mutagen. Forward or back-mutation frequency in the cells is assessed after withdrawal from the abdominal cavity of the test animal and then plating the cells onto selective solid media or growing them in liquid media. Such a rapid assay was designed for substituting it to the slow and expensive direct mammalian assays of promutagen. (See Fig. H73); ► [Big Blue](#), ► [Muta Mouse](#), ► [bioassays in genetic toxicology](#)).

Host-Pathogen Relations: Host-pathogen relations are based on susceptibility or tolerance/resistance genes in the host and virulence and avirulence genes in the



Microbial or cultured animal cells are injected intraperitoneally into a mammalian host for proliferation.

After a period of 1 to 3 days a test chemical dissolved in saline or in saline plus a solubilizer is injected subcutaneously once or more into the mouse or rat. The control animals are treated with the solvent solution only. This mutagenic exposure lasts for a few hours or a few days.

A sample of the injected cell population is withdrawn from the abdominal cavity into centrifuge tubes in preparation for assaying the mutagenic effectiveness of the test chemical in comparison with the control.

The recovered cells are plated on Petri dishes or incorporated into soft agar culture tubes to screen the mutants produced withing the host as a consequence of the treatment.

Figure H73. Host-mediated mutagen test (Modified after Fischer GA et al. 1974 Mutation Res. 26:501)

pathogen, respectively. The development of the disease depends on the appropriate genetic determination and expression of genes in the two organisms. In order to display resistance, plants usually carry *R* (dominant gene[s] for resistance) and the microorganism has *avr* (virulence) gene[s]. The several plant disease resistance genes (*R*) interact with RAR1 and the SGT1 complex of SKP1, Cul1 subunits of SCF (Skp1 – Cullin – F box) and have ubiquitin ligase function (Azevedo C et al (2002 Science 295:2073). In *Arabidopsis*, SGT1b has two genetically separable functions in the plant immune system. SGT1b antagonizes RAR1 and negatively regulates R protein accumulation before infection. SGT1b also regulates independently of RAR-1 function apoptosis of cells during infection. The balance between RAR1 and SGT1, also in concert with the chaperone HSP90 (heatshock protein), modulate R protein accumulation and signaling competence (Holt III BF et al 2005 Science 309:929).

Other allelic combinations lead to disease susceptibility. In plant breeding, successful efforts were made to transfer disease resistance genes from wild relatives to the cultivated varieties (e.g., the *Ry* dominant genes of the wild potato, *Solanum stoloniferum*, conveys resistance against the potato Y virus (PVY) or leaf rust (*Puccinia triticina*) from *Aegilops umbellulata* (new name *Triticum umbellulatum*) to the cultivated bread wheat, etc. The leaf-rust-resistance locus (Lr10) of hexaploid wheat has been isolated by map-based cloning (Feuillet C et al 2003 Proc Natl Acad Sci USA 100:15253). A mildew (*Blumeria graminis*) resistant variation in barley (mlo-11) involves a truncated gene regulatory sequence plus a coding sequence of the normal locus. Apparently interference with normal transcription of *Mlo* results in resistance (Piffanelli P et al 2004 Nature [Lond] 430:887).

The classical methods of breeding for resistance have had to overcome problems of linkage of the resistance to agronomically undesirable genes present in some primitive species. Some viral plant pathogens have lines with extra genomic *satellite RNA* and the presence of the latter may suppress the expression of the full-scale disease (*attenuation*). The disease symptoms may be prevented in some cases also by the simultaneous presence of another related plant virus (*cross protection*). It has been shown that 25-nucleotide viral RNA may target a 25-kDa protein involved in viral movement and may generate a posttranscriptional silencing signal and protection against other viruses. This phenomenon, also called *preimmunity*, can be exploited by transferring through transformation into the plant species a coat protein gene of some of the RNA viruses. Another molecular

plant breeding approach is to introduce into the plants antisense mRNA of the viral protein that would prevent the synthesis of viral proteins within the plants. The latter method may be coupled with a ribozyme expression system that would degrade the viral RNA. Plant resistance or tolerance to viral infection may be based also on transcriptional or posttranscriptional silencing bearing similarities to co-suppression by transgenes. In some plants, the silencing may take place also without the presence of transgenes. A transgenic oligopeptide fused to a carrier may interfere with the viral capsid and thus confers resistance to several viruses (Rudolph C et al 2003 Proc Natl Acad Sci USA 100:4429).

Various genetic mechanisms are known to be involved in resistance against bacterial and fungal pathogens. The *hypersensitivity reaction* of the plant tissues restricts infection by death of the surrounding host cells resulting, in addition, in the liberation of antimicrobial cellular substances. A collection of chemically diverse substances, called phytoalexins, regulate the synthesis of plant cellular compounds that are involved in the defense mechanisms or are the consequences of the infection process. Various genes involved in the synthesis of phenol-derivatives may be regulatory targets. The activation or enhancement of the transcription of genes determining cell wall components (polysaccharides, lignin, suberin, saponin, etc.) may provide a barrier to infection. Cinnamoyl-CoA-reductase is an effector of small GTPases in plants and mediates lignin production in response to NADPH oxidase generated hydrogen peroxide and lignin production (Kawasaki T et al 2006 Proc Natl Acad Sci USA 103:230). The activation of plant enzymes (*pathogenesis-related proteins*) such as various glucanases, chitinases, and proteases may lead to continued breakdown of the cell walls of the pathogens, and thus facilitates the escape of potential hosts from microbial infection. Upon infection, the plants may produce reactive oxidative species (ROS), which may damage or destroy the infectious agents. Plants ectopically expressing ferritin may become tolerant to oxidative damage and pathogens (Deák M et al 1999 Nature Biotechnol 17:192). Plants do not have an immune reaction—like that mediated by antibodies of animals—to invading agents yet some type of systemic resistance may be induced by exposure to necrosis-causing microorganisms, with certain chemicals such as nicotinic acid-derivatives, etc. Some microorganisms secrete or contain in their cell walls organic molecules (proteins, glucans, glucosamines, fatty acid-derivatives, etc.) that provoke the defense mechanisms of plants or the plants themselves may produce such molecules upon contact with the pathogens. These compounds are

called *elicitors*. Elicitors come in much different chemical compositions and display substantial specificity for different hosts and pathogens. Many of these substances seem to reach the plant cell nucleus through the various ion channels or the signals are transduced through the membrane systems to activate the appropriate plant cells and functions. Recently several plant genes have been cloned that are involved in the disease-resistance-tolerance mechanisms (*RPS1*, *RPS2*, *Pto*, [*Pseudomonas syringae*], *Cf-9* [*Cladosporium fulvum*], *L⁶* [*Melampsora lini*], *N* [tobacco mosaic virus], *Hm1* [*Cochliobolus carbonum*], etc. It is believed that these genes act by activating the plant defense system through responding to the elicitors of the avirulent pathogens or by producing enzymes that degrade the fungal toxin. *P. syringae* avirulence protein AvrPtoB, when secreted into plant cells, inhibits apoptosis in the plant tissue. This protein has ubiquitin ligase activity whereby it inactivates host defenses (Janjusevic R et al 2006 Science 311:222).

Plants may contain intracellular or plasma membrane-associated proteins RPS2 that behave like an immune receptor to the bacterial pathogen's effector protein (AvrRpt2 in *Pseudomonas syringae*). AvrRpt2, when delivered to the plant cell, is cleaved near the amino terminus and its carboxyl terminus (a putative cysteine protease) then incites the cognate RPS2-dependent defense. The 21 kDa bacterial AvrRpt2 protease causes the disruption of the plant RPS2-RIN4 complex, and RIN4 is eliminated as long as three of this carboxyterminal fragment do not contain mutations at three critical amino acid sites. RIN4 (resistance-interacting negative protein) possess two sequences similar to AvrRpt2. The cleavage of AvrRpt2 requires another plant cofactor, cyclophilin, a single-domain peptidyl-prolyl cis-trans isomerase (Coaker G et al 2005 Science 308:548). Similar mechanisms exist in *Arabidopsis*, tomato, and yeast (Schulze-Lefert P, Bieri S 2005 Science 308:506).

In some instances, inorganic antimicrobial compounds accumulate. *Arabidopsis* roots exude numerous antimicrobials (butanoic acid, *trans*-cinnamic acid, coumaric acids, indolepropanoic acids, ferulic acid, vanilic acid, methyl-*p*-hydroxybenzoate, *p*-hydroxybenzamide, syringic acid) in response to various strains of *Pseudomonas syringae* and the bacterial strains may or may not cause damage to the roots according to their specificities (Bais HP et al 2005 Nature [Lond] 434:217). Green plants emit C6-aldehydes, C6-alcohols, and their acetates, and these so-called green leaf volatiles (GLVs) are biosynthesized via the lipoxygenase/hydroperoxide lyase (HPL) pathway. *Arabidopsis* plants, whose GLV biosynthesis had been modified by the larvae of

the cabbage white butterfly, *Pieris rapae*, and a fungal pathogen, the gray mold *Botrytis cinerea*, develop a defense system. *Cotesia glomerata*, a parasitic wasp that attacks *P. rapae* larvae, was attracted to at least two GLVs, (*E*)-2-hexenal and (*Z*)-3-hexenyl acetate, which were emitted by *Arabidopsis* in response to herbivore damage. Also, GLVs induced several defense genes in *Arabidopsis*, resulting in higher resistance to *B. cinerea* (Shiojiri K et al 2006 Proc Natl Acad Sci USA 103:16672).

In *Theobroma cacao*, cyclooctasulfur accumulation in the xylem walls was observed in *Verticillium dahliae* resistant plants. Salicylic acid is generally considered as an agent for improving plant resistance probably through its stimulating action of hydrogen peroxide release from the cells. *S*-nitrosoglutathione reductase generates nitrosothiol that enhances plant salicylic acid production (Feechan A et al 2005 Proc Natl Acad Sci USA 102:8054). Plant mutants with reduced ability to synthesize salicylic acid or phytoalexins become more susceptible to pathogens. These latter compounds are credited for systemic acquired resistance (SAR). The *Xa21* (*Xanthomonas oryzae*) gene of rice conveys resistance to this plant pathogen. DNA sequence analyses indicate a leucine-rich repeat, characteristic for serine/threonine kinases. It has been suggested that this protein is a signal transducer to alert the plant cell defense system. In some pathogenic bacteria (*Pseudomonas*) the same virulence factors mediate pathogenicity in plants (*Arabidopsis*) and in animals (mouse). It is assumed that a signal transduction path in general mediates plant disease resistance. A pathogen-generated ligand, produced by an avirulence gene, is recognized by an extra- or intracellular receptor, encoded by a plant receptor gene and the recognition sets into motion the process of defense. Different plant species and different resistance reactions indicate the involvement of a leucine-rich repeat (LRR) and leucine zipper binding sites shared by many resistance genes. The majority of isolated disease resistance genes display a nucleotide-binding domain, a common feature of many ATP- and GTP-activated protein families involved in signal transduction. The nucleotide-binding leucine-rich repeat (NB-LRR) resistance genes (R) and pseudogenes are present in multiple (about 150) copies in *Arabidopsis*. They are present in all five chromosomes as singletons or multiple clusters. The R genes may recognize more than a single type of avirulence factors and protect against different types of pathogens, e.g., fungi and viruses or virus and nematode. Great diversity may exist among the different R genes; some have lost the LRR sequences, yet they may be involved in some types of signal transduction.

Plant disease resistance genes may be classified into five structural groups and some of their domains reveal homologies to innate immunity genes of animals (e.g., the Toll-like receptors [TLR]). The criteria for classification of resistance genes involve their location or location of some of their domains, e.g., cytoplasmic or transmembrane or membrane association or the combinations of these features. Salicylic acid, jasmonic acid, and ethylene and similar plant compounds monitor and regulate responses to pathogens. The pathogen surveillance proteins of plants respond to invaders by PAMP-triggered immunity (PTI). [PAMP stands for pathogen-associated molecular patterns]. PAMPs include bacterial lipopolysaccharides and flagellin mediating bacterial movements. Insects present chitin and fungi display ergosterol. Plant receptor-like kinases (RLK) sense also the first 18 amino acids of the bacterial elongation factor EF-Tu. ETI (effector triggered immunity) recognizes the PTI and responds to this effector with some delay after MAP kinase pathway signaling to the nucleus. Te WRKY transcription factors are attracted to the resistance genes. The plant then transcribes genes responsible for reactive oxygen species (ROS) and attempts to prevent further microbial growth by reinforcing cell walls by callose.

Some bacteria can subvert the PAMP-triggered defense by type III secretion system (TTSS)-generated effectors. *Pseudomonas syringae* can secrete 20–30 effectors. The pathogen is protected against the effectors (Chisholm ST et al 2006 Cell 124:803). *P. syringae* subverts the plant immune system by secreting a virulence protein, HopM1 (712 amino acids) and targeting it against the AtMIN7 protein of *Arabidopsis*. The bacterial protein recruits the aid of host proteasomes to destroy immunity (Nomura K et al 2006 Science 313:220). In *Arabidopsis*, microRNAs repressing auxin signaling restrict *Pseudomonas syringae* growth (Navarro L et al 2006 Science 312:436).

The *Pto* serine/threonine protein kinase of tomato and the closely linked *Prf* gene seem to bind directly to the *Pseudomonas syringae* avirulence gene (*AvrPto*), conveying susceptibility to the pathogen. A single amino acid substitution in the plant resistance gene *Pto* may be sufficient to develop resistance to the *Pseudomonas*. Several bacterial species rely on acyl-homoserine lactones (AHL) for quorum sensing and, with its aid, to select a host plant to invade and eventually infect. If AHL can be inactivated by breaking special bonds of the molecule (quorum quenching), the disease symptoms can be prevented (Dong Y-H et al 2001 Nature [Lond] 411:813). Plants can protect themselves by hypertensive reactions but some pathogens learn how to counteract this reaction by special effectors.

Some pathogens develop ubiquitin ligase function to prevent the hypersensitive/apoptotic functions of the host or to alter critical defense proteins by desumoylation. Some fungal effectors include cysteine-rich protease inhibitors for host evasion. Plants may defend themselves against viral RNA by RNAi systems but some plant viruses have already developed effectors against this type of defense (Soosar JL et al 2005 Nature Rev Microbiol 3:789).

Many of the putative resistance genes cloned may lack the stringent criteria to be the principal determinants of resistance to a particular pathogen. Some plant pathogenic fungi (*Helminthosporium victoriae*) can be infected with double-stranded RNA viruses (totivirus) and cause lytic disease to the fungus. Recently in a wild relative of the cultivated beets, a membrane protein was identified that conveys resistance against a nematode (a lower eukaryotic animal). The defense of animals relies on innate and adaptive immunity systems. Posttranscriptional gene silencing may control resistance to viral diseases.

Plant defense gene expression profiles can be monitored by microarray hybridization. The gene expression profile can be evaluated by the LCK (local context finder) procedure (Katagiri F, Glazebrook J 2003 Proc Natl acad. Sci USA 100:10842).

Although insect resistance and herbicide resistance were successfully incorporated into plants by the methods of molecular engineering, disease resistant transgenic plants so far appear to be of less economic success.

In animals, the immune system of the host is the primary defense. In recent years it has become clear that viral pathogens have the potentials of rapid evolution due to their high rate of mutation and short generation time. Thus, the jumping across the species boundaries by HIV and corona viruses are frightening examples (Grenfell BT et al 2004 Science 303:327). Animal and human host transcriptional responses to various pathogens and 5042 genes were summarized by Jenner RG, Young RA. in 2005 (Nature Rev Microbiol 3:281). ▶immune system, ▶infection, ▶infectious diseases, ▶innate immunity, ▶stoma, ▶antisense RNA, ▶RNAi, ▶signal transduction, ▶alien substitution, ▶transformation, ▶Floor's model, ▶ribozyme, ▶hypersensitive reaction, ▶apoptosis, ▶ubiquitin, ▶virulence, ▶avirulence, ▶SAR, ▶biological control, ▶antimicrobial peptides, ▶secondary metabolism, ▶plant defense, ▶guard hypothesis, ▶wound response, ▶chitin, ▶plantibody, ▶2,5-A, ▶salicylic acid, ▶jasmonic acid, ▶ethylene, ▶pathogen-derived resistance, ▶silencer, ▶flagellin, ▶co-suppression, ▶parasitoid, ▶methylation of DNA, ▶post-transcriptional gene silencing, ▶quorum sensing, ▶ROS, ▶oxidative burst, ▶pathogenicity island, ▶octadecanoic acid, ▶PTGS, ▶RdRP, ▶caspase,

►insect resistance in plants, ►secretion machine, ►saponins, ►oleuropein, ►plant pathogenesis, ►phytoplasma, ►RAR, ►SGT, ►SKP, ►VIGS, ►SNAREs, ►Feys, ►selection types, ►co-evolution, ►symbiont, ►acquired immunodeficiency, ►SARS, ►*Piriformospora indica*, Fey BJ, Parker JE 2000 Trends Genet 16:449; Dangle JL, Jones JDG 2001 Nature [Lond] 411:826; Cao H et al 2001 Annu Rev Phytopath 39:259; Hulbert SH et al 2001 Annu Rev Phytopath 39:285; Lengeling A et al 2001 Mamm Genome 12(4):261; Asai T et al 2002 Nature [Lond] 415: 977; Maleck K et al 2002 Genetics 160:1661; Mackey D et al 2002 Cell 108:743; Schneider DS 2002 Cell 109:537; Lellis AD et al 2002 Current Biol 12:1046; Voinnet O 2005 Nature Rev Genet 6:206; type III effector function in plant pathogenesis: Mudgett MB 2005 Annu Rev Plant Biol 56:509; plant pathology guidebook: <http://www.biologie.uni-hamburg.de/b-online/ppigb/text.htm>; <http://www.phi-base.org/>; plant disease signaling: <http://www.drastic.org.uk>; plant pathogenesis: <http://www.pathoplant.de>.

Host-Range: The host-range implies that an infectious agent (virus, bacterium, fungus) can grow in some but not in other individuals depending on genotype of the agent and its target. (See da Silva ACR et al 2002 Nature [Lond] 417:459).

Host-Range Restriction: As per the host-range restriction, the same oncoprotein may not transform different species because the host cellular machinery does not favor its function. Some viruses infect or fail to infect other species. (See Oto T, Kawaoka Y 2000 Vet Microbiol 74(1–2):71).

Host-Resistance Genes: Host-resistance genes in mammals are generally quantitated on the basis of the length of survival after infection by viruses, bacteria, or protozoa or on the basis of the density of the pathogen in the infected foci. The inheritance is assessed on the basis of crosses with recombinant inbred strains in mouse. Most of the resistance genes are linked to the H-2 complex (MHC) but other locations as source of resistance have also been identified. The bacterial pathogen *Listeria monocytogenes* induces a dramatic dephosphorylation of histone H3 as well as a deacetylation of histone H4 during early phases of infection. This effect is mediated by the major listerial toxin listeriolysin O in a pore-forming-independent manner. Strikingly, a similar effect is also observed with other toxins of the same family, such as *Clostridium perfringens* perfringolysin and *Streptococcus pneumoniae* pneumolysin. The histone modifications correlate with a reduced transcriptional activity of a subset of host genes, including key immunity genes (Hamon MA et al 2007 Proc Natl Acad Sci USA 104:13467).

Several resistance genes have been cloned. Comparative analyses assist in the use of the information for human and livestock research. ►host-pathogen relations, ►pathogenicity island, ►*Listeria monocytogenes*, ►*Clostridium perfringens*, ►*Streptococcus pneumoniae*, ►histones; Staskawicz BJ et al 2001 Science 292:2285).

Hot Spot: Highly mutable site within a gene or high-frequency recombination site in chromosomes. Recombinational hot spots are generally expressed as cM/kb (map unit/kilobase). Within the *a'* gene of maize the recombination frequencies varied between 5×10^{-3} to 8×10^{-2} cM/kb, whereas in the 140 kb distance between *a'* and *sh2* 6×10^{-4} cM/kb was observed. Within the pseudoautosomal site (*PAR*) of *Drosophila*, 1 cM/53 kb was found. Within the mammalian histocompatibility locus, recombination frequencies of 1 cM/0.6 kb to 1 cM/400 kb have been reported. The frequency of recombination shows great variation along the length of the chromosomes. In humans, 50% of the recombination occurs in less than 10% of the sequences and the local rate of variation may exceed four orders of magnitude (McVean GAT et al 2004 Science 304:581). Usually, a number of hot spots are recognized and there is no equivalence between genetic and physical length. In the vicinity of minisatellites, recombinational hot spots may be found by molecular analyses. In humans and chimpanzees, the recombination hot spots occurred at different chromosomal locations and indicated rapid evolution of hot spots (Winckler W et al 2005 Science 308:107). In human chromosome 22, recombination is increased between long, tandem GT repeats. ►chi elements, ►cold spot, ►coefficient of crossing over, ►mariner, ►MITE, ►coefficient of crossing over, ►recombination hot spots, ►recombination, ►HLA, ►recombination frequency, ►genotyping, ►mutation rate; Lichten M, Goldman ASH 1995 Annu Rev Genet 29:423; Majewski J, Ott J 2000 Genome Res 10:1108; Gerton JL 2000 Proc Natl Acad Sci USA 97:11383).

Hot-Start PCR: Hot-start PCR is used to detect allele-specific changes in the mtDNA. The reaction begins at relatively high temperature but subsequently the temperature is reduced during the cycling (touch-down PCR) in order to improve the specificity of the amplification. ►polymerase chain reaction, ►PCR allele-specific, ►TULIPS-PCR; Ailenberg M, Silverman M 2000 Biotechniques 29:1018.

Hot-Stop PCR: A method for quantitation of allele ratios. (See Uejima H et al 2000 Nature Genet 25:375).

Housefly: *Musca domestica*, 2n = 12. Genome size bp/n = 9×10^8 . (See anatomy: <http://www.ento.csiro.au/biology/fly/fly.html>).

Housekeeping Genes: Housekeeping genes are functional throughout the life of a cell and in the majority of cells and tissues. In the promoters the TATA and CAAT boxes are not present. Their 5' CpG islands are not methylated. ►asparagine synthetase, ►TATA box, ►CAAT box, ►transcription illegitimate, ►methylation of DNA, ►capping enzymes, ►CpG islands

HOVERGEN (homologous vertebrate genes): A database that facilitates identifying homology between nucleic acid and protein sequences. ►evolution, ►databases; <http://pbil.univ-lyon1.fr/databases/hovergen.html>.

HOWDY: An integrated human genome database. It permits also cytogenetic localization. See <http://www.alis.tokyo.jst.go.jp/HOWDY/>.

H

Hox: Proteins (transcription factors) that control differentiation along different paths in the anterior-posterior axis of the body. Mammalian cells are endowed with 39 HOX genes in four clusters (HoxA to HoxD) that belong to 13 paralogous groups. Truncation of the human HOXA may lead to abnormal development of the central nervous system (Tischfield MA et al 2005 Nature Genet 37:1035) resulting in multiple phenotypic defects (deafness, hypoventilation, cardiac and vascular defects, mental retardation and autism). In *Drosophila*, Hox proteins work in cooperation with two segmentation proteins, Sloppy paired and Engrailed. The two proteins repress the Hox target *Distalless* gene in either anterior or posterior compartments (Gebelein B et al 2004 Nature [Lond] 431:652). The expression of other members of the differentiation proteins downstream is generally activated in 3' → 5' direction within the group. Some of the *Hox* genes influence a series of others in different differentiation processes (Lei H et al 2005 Proc Natl Acad Sci USA 102:2420). ►homeotic genes, ►duplication, ►PAX; Gehring WJ et al 1994 Annu Rev Biochem 63:487; Moconochie M et al 1996 Annu Rev Genet 30:529; Shen W et al 2001 Mol Cell Biol 21:7509; Wellik DM, Capecchi MR 2003 Science 301:363; evolution of Hox gene clusters: Lemons D, McGinnis W 2006 Science 313:1918.

Hox Clock: As per the hox clock, the temporal activation of the homeotic hox gene clusters determines the spatial/axial pattern of differentiation. ►hox, ►homeotic genes; Kmita M, Duboule D 2003 Science 301:331.

HP1 (HP-1): A small protein with an amino-end chromodomain and a C-terminal chromoshadow domain. ►heterochromatin, ►chromodomain, ►chromoshadow

HpaII: is a restriction endonuclease enzyme with recognition site C↓CGG.

HPBP: The human platelet basic protein is a member of a large cytokine family. ►cytokines; Zhang C et al 2001 Blood 98(3):610.

HPFH: ►thalassemia

HPFN: The human plasma fibronectin is a cell adhesion molecule. ►CAM; Poulouin L et al 1999 Protein Extr Purif 17:146.

HPLC (high performance liquid chromatography): HPLC is suitable for the separation (among other molecules) of oligonucleotides up to 20 residues by partitioning them between a stationary phase (such as a chromatography column) and a mobile phase (such as solvents) forming a gradient pumped through a system, carefully monitored. ►sequenator, ►electrophoresis, ►high-performance liquid chromatography

HPRT: The hypoxanthine phosphoribosyl transferase is controlled in humans by a recessive gene (map location Xq26-q27.2, 57 kb). Its deficiency causes the Lesch-Nyhan syndrome involving choreoathetoses (involuntary, uncoordinated movements), spasticity (high muscular tension), mental retardation, tendency to self-mutilation, overproduction of uric acid, renal damage, etc. It can be detected prenatally. The molecular basis of the defect is an interruption of the salvage pathway of nucleotides because the guanosine and hypoxanthosine cannot be phosphorylated. The defects of this enzyme have been extensively exploited for *in vitro* selective isolation of fused mammalian cells and for the isolation of mutations. Prenatal diagnosis and carrier identification of defects is feasible. ►salvage pathway, ►HAT medium, ►Lesch-Nyhan syndrome, ►HGPRT, ►epilepsy

HPV: Human papilloma virus. ►papilloma virus, ►bovine papilloma virus

HR: Hypersensitive reaction. ►hypersensitive reaction, ►host-pathogen relationships

hr: Human recombinant in abbreviation, e.g., hrEGF, human recombinant epidermal growth factor.

hRAS (HRAS): RAS proto-oncogene of humans. ►RAS

HRE: ►hormone-response elements

HRF (homologous restriction factor, synonym (C8bp): ►membrane attack complex

HRI (hemin regulated inhibitor, EIF2AK3, human chromosome 2p12): Hemin apparently interferes with the function of this specific protein serine/threonine kinase involved in translational activation; in the absence of hemin the protein kinase is active and protein synthesis may be shut off leading to cell death. Hemin inactivates it by forming disulphide-linked homodimers. Functionally it is similar to the

yeast GCN2 and the PKR-endoplasmic reticulum elongation factor kinase, PEK/PERK. ►hemin, ►protein kinase, ►GCN2, ►GCN4, ►PKR; Crosby JS et al 1994 Mol Cell Biol 14:3906.

HRP-A: A human homolog of the single-strand binding protein involved in genetic recombination. It is required for in vitro replication of SV40 DNA and growth. ►SV40; Baumann P, West SC 1999 J Mol Biol 291(2):363.

hs: A prefix that stands for *Homo sapiens*, e.g., hsDNA, human DNA or hDNA.

HS Site: ►DNase hypersensitive site

HSA: Human serum albumin.

HSA (human sequence assembly): HSA7 is the assembled nucleotide sequence of human chromosome 7.

Hsc (heat shock cognate): A form of a heat-shock protein in the normal cytosol. ►heatshock protein, ►Hsp70

Hsc66: A 615 amino acid *E. coli* protein, encoded by *hscA*, member of the Hsp70 family. It is induced by cold shock. It lacks the ATP-binding domain of Hsp70. It is co-transcribed with *hscB* (encoding a DnaJ-like protein) and *fdx* (encoding ferredoxin). ►cold shock, ►heat shock, ►DnaK, ►ferredoxin; Silberg JJ et al 2001 J Biol Chem 276:1696.

hsdR: Some mutations in *E. coli* that eliminate restriction function but not the modification in the restriction-modification system. ►restriction enzyme, ►restriction-modification; Doronina VA, Murray NE 2001 Mol Microbiol 39:416.

HSE: Heatshock elements located in the upstream region of eukaryotic heatshock responding genes and recognized by heat-shock protein transcription factors. A typical heatshock element is an about 14 bp palindromic sequence with a GAA core: 5'-CTN-GAANN TTCNAG-3' 3'-GANCTT NNAAGNTC-5' ►heat-shock proteins, ►transcription factors inducible, ►HSTF, ►Hsc

HSF: Heat shock transcription factor, which activates the transcription of heatshock proteins. ►heat-shock proteins, ►HSE

Hsj1a, Hsj1b: Neuron-specific chaperones of the DnaJ family. Alternative splicing of the same RNA transcript produces them. They do not have intrinsic ATPase activity, yet they increase this function of Hsp70. ►chaperone, ►DnaJ

HSP (heat-shock proteins): HSP110 of mammals are similar to the SSE proteins of yeast and they are related to Hsp70. The 40-kDa-mammalian chaperone Hsp40 (J protein) facilitates the folding

of the polypeptides coming off the ribosomes. These are also stress proteins highly inducible by heat, although may be formed constitutively. The sea urchin egg carries a HSP that serves as a receptor for the sperm. Another related protein is Osp94/APG-1 formed in response to heat, high osmotic, and other stresses. The GRP glycoproteins of diverse molecular sizes are also heat-inducible and function in the spleen, lymph nodes, and Peyer's patches in connection with the immune responses. The HSP40 family members are co-chaperones of the Hsp70 family of proteins resembling DnaJ. The HSP40 members interact with nucleic acid and proteins in concert with Hsp70, and occur in the nucleus, mitochondria, endoplasmic reticulum, and on the membrane surfaces mediating chaperon functions (protein folding, translocation, renaturation of proteins of wrong conformation, proteolysis), signal transduction, and formation of macromolecular complexes. The Hsp100 (Clp) family of proteins is generally involved in aggregation and disaggregation of proteins of different sizes. Hsp104 is another stress protein controlling also the Psi^+ prion-like protein of yeast. Hsp47 is the serpin family stress protein of vertebrates, found in the endoplasmic reticulum where it binds to procollagen. Hsp101 is a plant chaperone closely related to Hsp104. Hsp78 is a soluble mitochondrial chaperone of yeast. Hsp26 is a sHsp of yeast with major role in stress and cytoskeletal control. ►heat-shock proteins, ►HSE, ►HSTF, ►Hsc, ►Hsp70, ►Hsp83, ►Hsp90, ►constitutive gene, ►spleen, ►lymph nodes, ►Peyer's patches, ►immune system, ►DnaJ, ►conformation, ►signal transduction, ►chaperones, ►chaperonins, ►Clp, ► PSI^+ , ►sHSP, ►serpin, ►pro-collagen, ►endoplasmic reticulum; J proteins: Sahi C, Craig EA 2007 Proc Natl Acad Sci USA 104:7163.

HSP60 (CPN60, chaperonin 60): ►chaperonins

Hsp70: A heat-shock protein gene (activated by elevated temperature); it is a chaperone. These proteins are widely distributed among diverse species, prokaryotes and eukaryotes, and have been found in various subcellular compartments. The proteins are endowed with multiple functional domains required for peptide and co-factor binding and a weak ATPase activity. Hsp70 functions involve control of protein folding, lytic phage infection of bacteria, un-coating of clathrin-coated vesicles and thereby selective endocytosis, and assist proteases in degradation of abnormal proteins, etc. ATP hydrolysis and polypeptide binding activity of Hsp70 depends on two different domains of the protein. Hsp70 also needs the cooperation of Hsp40 (DnaJ). The human homologs (HSPA) are encoded in chromosomes 6p21.3, 14q22, 14q24.1, 5q31.1,

9q34, 1q, 14q24, and at other locations. Mouse homologs were identified in chromosomes 17, 12, 2 and 18. Male mice lacking Hsp70 homologs are unable to produce spermatids and mature sperm and show dramatic increase of apoptosis of the spermatocytes. Female mice of the same constitution did not show meiotic disturbances or infertility. The four *SSA* genes of yeast are highly homologous (80%) members of this family of proteins (~70-kDa). *SSA2* is essentially constitutive, the others are heat-inducible. The *SSA* gene products negatively regulate their own and each other's synthesis. The *SSA* genes are essential for normal cell viability. The *SSB* gene products of yeast are associated with the ribosomes. The *Ssc* yeast proteins occur in the mitochondrial matrix and envelope, aid the translocation between the cytosol and the mitochondria, and are also involved in general protein folding and lysis in that organelle. *Ssc* proteins are weakly inducible by heat. *Ssh1* protein is encoded in chromosome 12 of yeast and located in the mitochondria where it may be involved with DNA replication and protein processing. *Ssi* (100-kDa) protein controls endoplasmic reticulum traffic, particularly when the *KAR2* gene of yeast is defective. *Kar2* protein (682 amino acids) in the endoplasmic reticulum of yeast mediates translocation and folding of proteins and also nuclear fusion after mating. *BiP* is an essential endoplasmic reticulum chaperone present in fission yeast, several plant species, *Trypanosomas*, and mammals. The *Hsc4* proteins of *Drosophila* are also Hsp70-related. *Hsc3* in *Drosophila* is homologous to *Kar2* and *BiP*. The Mammalian *Prp73* is 73-kDa chaperon recognizing the S-peptide (residues 1-20 of ribonuclease A). *Pbp74* (74-kDa) peptide-binding protein in the mammalian and yeast mitochondria aids peptide import and processing within the mitochondrial matrix. *Stch* chaperone (471 amino acids) is encoded in human chromosome 21q11.1 and the protein is located in the microsomal fraction of the cell and has ATPase activity. ▶[heat-shock proteins](#), ▶[HSE](#), ▶[HSTF](#), ▶[apoptosis](#), ▶[chaperone](#), ▶[clathrin](#), ▶[endocytosis](#), ▶[ATPase](#), ▶[Prp73](#), ▶[HSTF](#); Hartl FU 1996 Nature [Lond] 381:571; Bukau B, Horwich AL 1998 Cell 92:351.

Hsp83: ▶[Hsp90](#)

Hsp90: A chaperone protein family including heat-inducible and constitutive chaperones involved with the signal transduction kinases and steroid receptors. In yeast, a study of the function of 4,700 viability genes revealed 198 putative physical interactions and 451 genetic and chemical-genetic interactions with the Hsp90 chaperone (Zhao R et al 2005 Cell 120:715). Homologs occur in prokaryotes (*HtpG*), *Drosophila* (*Hsp83*), mammals (*Grp94*), yeast, and

plants. Hsp90 and its homolog Hsp83 may cause transmissible epigenetic alterations in plants (Queitsch C et al 2002 Nature 417:618) and in animals (Sollars V et al 2003 Nature Genet 33:70). Hsp90 chaperones are regulators of cell circuits and may mediate protein folding in response to environmental variations. After several generations it may reassort genetic variations and leads to the expression of traits that were cryptic in the progenitors. Fungal drug resistance may develop as a consequence of its action on new or old mutations (Cowen LE, Lindquist S 2005 Science 309:2185). The structure of Hsp90 displays dramatic conformational change dependent on ADP nucleotide association (Shiau AK et al 2006 Cell 127:329). ▶[heat-shock proteins](#), ▶[chaperones](#), ▶[protein folding](#), ▶[Grp94](#); Kumar P et al 2001 Cell Stress Chaperones 6:78; crystal structure of Hsp90 domains in association with ATP and co-chaperones: Pearl LH, Prodromou C 2006 Annu Rev Biochem 75:271.

HSR: ▶[homogeneously stained region](#)

HSSB (human single-strand binding protein): The same as replication protein A; see it there.

HST Oncogene: The HST oncogene was assigned to human chromosome 11q13; originally identified in stomach cancer but it was also found in Kaposi sarcoma. Its product is a heparin-binding protein with homology to the fibroblast growth factor (FGF). It is also called K-FGF. ▶[FGF](#), ▶[oncogenes](#), ▶[growth factors](#), ▶[Kaposi sarcoma](#)

HSTF: The heatshock transcription factor regulates about 20 heatshock genes by binding cooperatively to more than one heat shock element. It is activated by phosphorylation. ▶[HSE](#), ▶[HSP](#); Tanguy RM 1988 Biochem Cell Biol 66(6):584.

Hst1p (homolog of Sir2): The protein involved in mating type determination in yeast. Rusche LN, Rine J 2001 Genes Dev 15(8):955.

HSV (Herpes Simplex Virus): ▶[Herpes](#)

HTC: A database for high-throughput not yet definite genomic sequences.

HTDV (human teratocarcinoma derived virus): An endogenous human retrovirus family occurring in about 25–50 copies per genome. About 10,000 solitary LTRs are also present. They are well expressed in different organs. ▶[retroviruses](#), ▶[solitary LTR](#)

hTERT: The catalytic subunit of human telomerase. ▶[telomerase](#)

HTF Islands: 1–2 kb sequences around the 5' region of genes where the Hpa II restriction endonuclease cleaves Tiny Fragments because the cytidines are not

methyated. At most other regions, because of methylation, only larger fragments are cut. The mammalian genome may display 30,000 HTFs. (See Bird AP 1986 Nature [Lond] 321:209; Zardo G, Caiafa P 1998 J Biol Chem 273:16517).

H1TF2: A histone transcription factor binding to CCAAT box. ▶ [histones](#); Martinelli R, Heintz N 1994 Mol Cell Biol 14:8322.

HTG/HTGS (high throughput-genomic sequences): Division of gene banks permitting the search for unfinished nucleotide sequences. ▶ [databases](#), ▶ [genome projects](#), ▶ [GenBank](#); <http://www.ncbi.nlm.nih.gov/HTGS/>.

HtpG: ▶ [Hsp90](#)

HTLV (human T cell leukemia virus): The retroviral causative agent of some adult leukemias and partial paralysis (HTLV-1-associated myelopathy). The 40 kDa viral TAX protein (trans-acting viral factor) is apparently responsible for its carcinogenicity. In the early years of AIDS, the disease was attributed to HTLV before HIVs were identified. ▶ [AIDS](#), ▶ [HIV](#), ▶ [leukemia](#), ▶ [myelopathy](#); Overbaugh J, Bangham CRM 2001 Science 292:1106; Yoshida M 2001 Annu Rev Immunol 19:475.

HTML (hypertext markup language): HTML permits the display of what an internet (www) address and content look like. This computer program can generate World Wide Web pages (www) and links HTTP (hypertext transfer protocol) to the program to use with the www. ▶ [www](#)

HTS: High-throughput screening.

HU: "Histone-like" prokaryotic protein involved in maintaining the DNA structure and transposon integration. ▶ [histones](#)

HUB: Interacting protein network modules. They may interact simultaneously with most of their partners or the interaction may vary by time. ▶ [networks](#), ▶ [genetic networks](#); Han J-DJ et al 2004 Nature [Lond] 430:88.

hUBF: The human upstream binding factor is a transcription factor. ▶ [transcription complex](#), ▶ [transcription factors](#)

Hudson, Kreitma, Aguadé Method: ▶ [mutation neutral](#)

HuGENet (Human Genome Epidemiology Network): The HuGENet contains collaboratively assembled information on how human genetic variation affects disease and health <http://www.cdc.gov/genomics/hugenet/default.htm>. ▶ [risk](#), ▶ [epidemiology](#); Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]: <http://www.strobe-statement.org/>.

HUGO (Human Genome Organization): The source of mammalian genomic data, available in Macintosh Hypercard disks from HUGO Europe, One Park Square West, London NW1 4IJ, UK, Phone: 44 71 935 8085. Fax: 44 71 706 3272. INTERNET: s.brown@sm.ic.ac.uk; Human Genome Variation Society: <http://www.hgvs.org/>.

Human Artificial Chromosome (HAC): HACs are not yet equivalent to similar constructs in *Saccharomyces* or *Schizosaccharomyces* and their closest counterparts are the minichromosomes that may be less than 1/10 of the size of the chromosome before truncation yet are mitotically quite stable. Human minichromosomes can be generated in vitro by mixing alphoid, telomeric, and carrier DNAs. These structures transfected into human cells are maintained, and segregate and bind centromeric proteins. Current evidence indicates, however, that neither the alphoid DNA nor the CENP-B protein may be required for normal centromeres. Neocentromeres have been analyzed and apparently lack alphoid DNA and are not suitable for the construction of human artificial chromosomes. Despite earlier assumptions that human artificial chromosomes may not function normally if they are introduced into somatic cells because under normal conditions the cells are disomic rather than trisomic although the extra chromosome (HAC) would not carry genes that are already present in one or two doses in the genome. This problem might even further be aggravated if the cell would undergo meiosis. Current evidence indicates, however that the new technology facilitates the overcoming of these difficulties and mammalian artificial chromosomes are useful vectors. They can be transmitted through generations and can have important role in biotechnology and in the pharmaceutical industry (Duncan A, Hardlaczky GY 2007 Curr. Opin Biotechnol. 18:420). In cell culture, human artificial chromosomes have been used as genetic vectors to introduce specific genes and have demonstrated the potentials of complementing deficiencies of hypoxanthine guanine phosphoribosyl transferase. HACs may be exploited also for the transfer of genes from humans to other mammals. Human artificial chromosome vectors equipped with chromosome 17 alphoid DNA generated 32–79% artificial minichromosomes but the alphoid DNA of the Y chromosome generated only 4%. The stability of the minichromosomes decreased when the guanine phosphoribosyl locus (HPRT1) was included. ▶ [minichromosome](#), ▶ [HAC](#), ▶ [YAC](#), ▶ [BAC](#), ▶ [PAC](#), ▶ [alphoid DNA](#), ▶ [α-satellite](#), ▶ [neocentromere](#), ▶ [disomic](#), ▶ [trisomy](#); Harrington JJ et al 1997 Nature Genet 15:345; Ikeno M et al 1998 Nature Biotechnol 16:431; Tyler-Smith C, Floridia G 2000 Cell 102:5; Mejia JE et al 2001 Am J Hum Genet 69:315; Mejia JE et al 2002

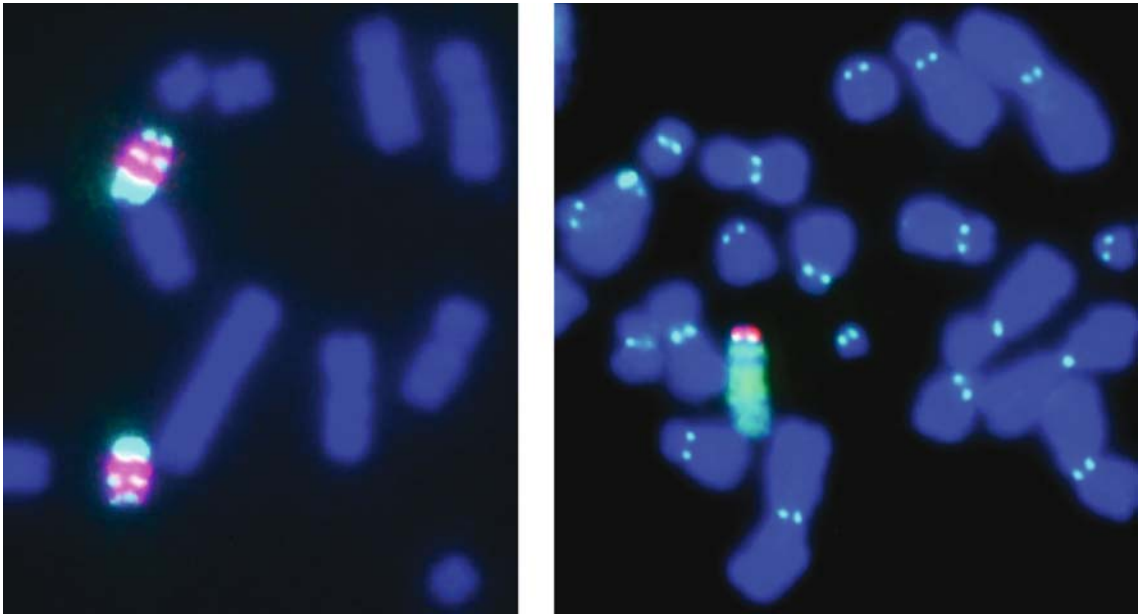


Figure H74. At left: Platform artificial chromosomes in Chinese Hamster cell. FISH image, red signals correspond to the acceptor sites on the platform chromosome, green signals show mouse satellite DNA. Blue DNA counterstaining was made with DAPI (Lindenbaum M et al 2004 Nucleic Acids Res. 32:e1720). At right: Human satellite DNS-based artificial chromosomes are kinetochores immunostained with anti/centromere serum, red FISH signal on SATAC is a human centromere-specific alpha-satellite DNA, green signal human alpha satellite DNA specific to pericentric heterochromatin. Blue DNA counterstaining was made with DAPI (Csonka E et al 2000 J. Cell Sci. 113:3207, Hardlacky GY 2001 Curr. Opin. Mol Therapeutics 3(2):125. 2001). Photomicrographs are the courtesy of Professor Gyula Hadlaczky)

Genomics 79:297; Csonka E et al 2000 J Cell Sci 113:3207; HAC construction: Kotzamanis G et al 2005 Gene 351:29.

Human Chromosome Maps: Linkage and mapping information until the 1960s were obtained mainly by studying family pedigrees. This procedure was very inefficient both because in human populations controlled mating is not feasible and because of the small populations available, crossing over frequencies can not be used the same manner as in, e.g., *Drosophila*. Some of the gene locations were determined by deletion mapping, but until 1956 even the number of human chromosomes was uncertain. In the late 1960s and early 1970s, new chromosomal staining techniques made possible the recognition of chromosome bands, permitting the more precise location of genes relative to these beacons. During the 1960s, the culture of isolated mammalian cells had been improved and in 1960 fusion of somatic cells was accomplished, followed in 1965 by the production of mammalian somatic cell hybrids. It was discovered that in human-mouse somatic cell hybrids, human chromosomes are preferentially lost, facilitating the assignment of particular genes to specific

human chromosomes. Only those human genes were expressed in the cultures that were present and their expression ceased when the critical chromosome was eliminated. By induced breakage, the location of genes could be further specified when it was seen that the retention of particular cross bands was essential for the expression of a particular gene. In 1960, nucleic acid hybridization was discovered and by the mid 1960s, nucleic acid hybridization was used for localizing genes in cultured human HeLa cancer cells. Somatic cell hybridization permitted the chromosomal assignment of three times as many genes within a few years as family analysis accomplished over half a century. By 1970, methods were developed to assign mouse DNA fragments to chromosomal location by in situ hybridization. In situ hybridization also facilitated the location of about twice as many genes than the pedigree analysis. Discovery of restriction endonuclease enzymes in the late 1960s and 1970's opened in genetics a new era of physical mapping and localizing cloned genes or just "anonymous DNA" sequences to chromosomal positions. Isolated DNA sequences could be ordered on the basis of the overlapping fragments by the use of chromosome walking and jumping first employed

in *Drosophila* in 1983. The use of isolated genes from other species (*Drosophila*, mouse, yeast, etc.) as probes permits now the identification of the position of homologous genes and DNA sequences. By the extension of these techniques, individual human genes can be isolated, cloned, and sequenced; thus, the technology is in use for the ultimate mapping of the human genome at the nucleotide level, to recognize the structural bases of functions, regulation, and organization of the genome. The detailed mapping is assisted now by sophisticated computer programs to determine the order of several gene loci on the basis of the maximum likelihood principle. This information, sought by the human genome projects, will contribute to evolutionary information as well to medical applications of gene therapy. The 2002 (Kong A et al Nature Genet 31:241) genetic map includes 5,136 microsatellites (AC/TG) markers based on 1,257 meiotic events. The 'complete' nucleotide sequence of the human genome available by 2000 facilitates the determination of the position of most human genes. By 2004, an almost complete map of the euchromatic sequence was published containing a reevaluated gene number of 20,000–25,000 protein-coding genes (Nature [Lond] 431:931). Although the physical map of the human genome is 'practically' complete (Science 291, 15 Feb. 2001, Nature [Lond] 409, Feb. 15, 2001), the full functional annotations will have to wait.

A compendium of the gene expression pattern of normal human tissues is available (Hsiao LL et al 2001 Physiol Genomics 7:97). The genetic and the nucleotide sequence based physical maps are not entirely consistent because of technical ambiguities (DeWan AT 2002 Am J Hum Genet 70:101). Human chromosome 1 contains 3,141 genes and 991 pseudogenes (Gregory SG et al 2006 Nature 441:315), 2 has about 1,346 protein-coding genes and 1,239 pseudogenes, whereas chromosome 4 has 796 and 778, respectively (Hillier LW et al 2005 Nature [Lond] 434:724). Chromosome 8 has 793 genes and 301 pseudogenes (most of them reprocessed); the average chromosome-8 gene is 3,056 bp with 9.9 exons and 4.1 transcripts. The gene density (5.6/Mb) is almost half of the genome average 10/(Mb). The most distal part of chromosome 8 of humans shows high divergence from chimpanzees and other mammals. This region includes the defensin genes controlling innate immunity and gene MCPH1 (microcephaly) involved in brain development (Nusbaum C et al 2006 Nature [Lond] 438:331). [Microcephaly genes occur also in human chromosomes 19.13.1, 15q15, 9q33, 1q31, 13q12.2]. Chromosome 15 has high number of duplications in the centromere-proximal and -distal regions. It has a total (including putative and gene fragments) of 695

genes and 250 pseudogenes (Zody MC et al 2006 Nature [Lond] 440:671). See Fig. H75; ►draft genome sequence, ►pedigree analysis, ►mapping, ►deletion mapping, ►chromosome banding, ►radiation hybrids, ►somatic cell hybridization, ►nucleic acid hybridization, ►in situ hybridization, ►probes, ►restriction endonucleases, ►RFLP, ►chromosome walking, ►DNA sequencing, ►maximum likelihood, ►gene therapy, ►mouse, ►human genome, ►Gene-Note; Nature [Lond] 402:489; Nature [Lond] 402:311; history of human chromosome counts: Gartler SM 2006 Nature Rev Genet 7:655). human physical map: <http://www.ncbi.nlm.nih.gov/genemap99/>; cytogenetic map of morbid genes:

http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9606 HOWDY; human chromosome variations: <http://projects.tcag.ca/variation/>; assistance in searching new linkage information: <http://bioinfo.cs.technion.ac.il/superlink-online/>.

H

Human Dignity: Human dignity is part of universal human rights of self-determination. From it flows the views on the sanctity of human life, euthanasia, abortion, death penalty, prisoners' rights, torture, political freedom, and various principles concerning the use of biotechnology (cloning, stem cell research), informed consent, sale of human body parts, experimentation with human subjects, prostitution, gene patenting, social equality, lack of discrimination, etc. For some of these concepts there is complete or nearly universal support in all enlightened, free societies, while for others there is no consensus. (See also Caulfield T, Brownsword R 2006 Nature Rev Genet 7:72).

Human Evolution: The study of human evolution has gained in recent years important tools by the application of molecular markers of mtDNA (of skeletal remains) and mtDNA and Y chromosomes to the survey of dead and living populations, respectively. These methods permit the separation of the gene flow also by the sexes. Commonly in migrating populations, mixtures of immigrant men's and native women's gene pools seem to prevail because the invading men eliminated or reduced the number of the native men but begot offspring with the women and among the immigrants females were not always represented equally to males. The information may be biased by the size of the admixing populations. The entire human species has essentially the same amount of DNA, the same number of genes in the same order in the chromosomes. Yet, differences among human races are also obvious. These differences seem to be based on a few minor deletions or additions to the genome. The spread of infectious diseases may contribute to human evolution. Malaria and HIV infections and high mortality may select for tolerance

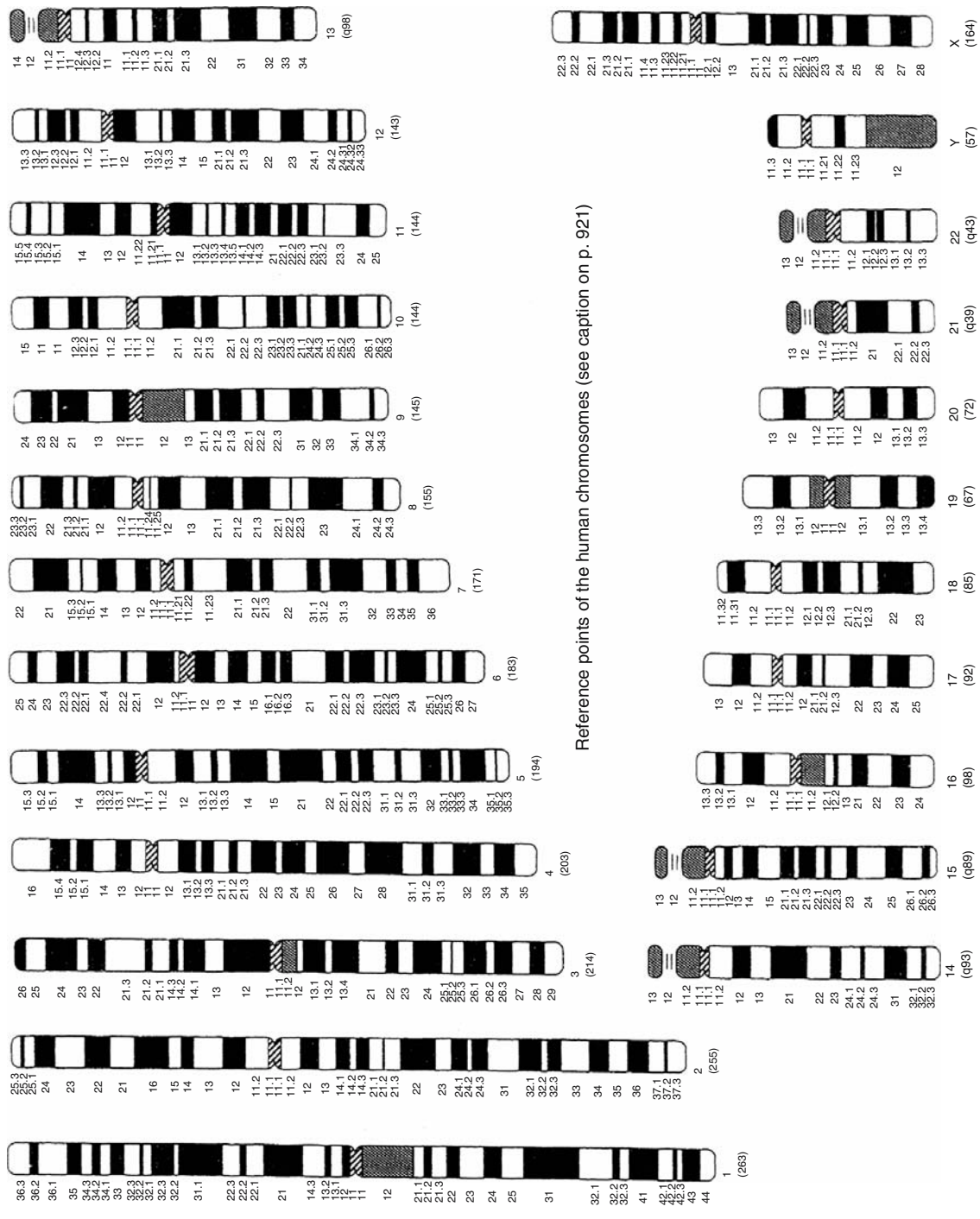


Figure H75. Continued

Figure H75. REFERENCE POINTS FOR MAPPING GENES OR DNA SEQUENCES TO HUMAN CHROMOSOMES

(above) Each chromosome is numbered; 1 is the longest by cytological evidence. Since the metaphase length is somewhat ambiguous because the condensation, due to genetic and other causes, may vary and length is not an absolutely consistent feature of the karyotype. The approximate minimal DNA content (Mb) of each chromosome is shown in parenthesis under each diagram. The centromere is represented by constrictions and the pericentromeric region is diagonally hatched. The short arms (shown above the centromere) are designated by p (for petit) and the long arms are designated by q. Each arm has cross-bands corresponding to observations by Giemsa, q and c banding techniques. The fine hatching indicates heterochromatic regions. Each chromosome, starting at the centromere, is divided into domains and subdomains designated by numbers. if we see that the location of TNFR-2 (encoding tumor necrosis factor 2, a 75-KDA protein) is at 1p36.3-p36.2, we know that it is in the terminal region of chromosome 1, either in the first black band or above. The telomeric region is usually designated by ter. Acrocentric chromosomes (13, 14, 15, 21, 22) and their heterochromatic areas and satellites are finely cross-hatched. The large number of genes is impossible to represent on a single page. the location of the physical markers occupied, by 1996 (Nature 380, suppl.), about 138 pages in fine print. (Illustration is based partly on the New Haven Human Gene Mapping Library Chromosome Plots. Number 4. HGM9.5, constructed by Spence MA and Spurr NK) by 2001 after the completion of the finished the human genome (Nature [Lond] 431:932, 2004) the length of the individual chromosomes required revision compared to the data seen in this illustration. Thus the latest length in Mbp of the euchromatic sequences of the chromosomes is: **1 223.9, 2240.0, 3 199.3, 4 188.4, 5 177.7, 6 170.0, 7 155.6, 8 145.6, 9 120.4, 10 133.0, 11 134.5, 12 132, 13 96.3, 14 88.3, 15 82.1, 16 78.9, 17 78.8, 18 76.12, 19 60.1, 20 60.7, 21 34.2, 22 35.2 X 151.8, Y 26.7** These figures ignore the unsequenced gaps and heterochromatin.. The total euchromatic length is about 2.88 billion bp out of the total of ~3.08 billion. (For publicly available genome data see Nature [Lond] 409:860 (2001). Physical maps of the human chromosomes can be found in some details in Nature [Lond] 409:942–958 (2001), Nature [Lond] 431:931 (2004). The cytogenetic map shown here is still used but one must remember that its resolution is not sufficient for the precise location of the large number of protein-coding genes, estimated to about 20,000–25,000 in the euchromatic sequences. Therefore the same cytogenetic map sites often accommodate several functionally different genes.

or resistance because of the differential survival to reproductive age. A refined map of human chromosome 17q21.31 displays a 900-kb inversion in two different orientations, H1 and H2. The H2 lineage is rare in Africans, almost absent in East Asians but is represented in 20% among Europeans. These two structural rearrangements did not recombine. In Icelandic populations, the H2 lineage seems to have positive selective value as indicated by the higher number of children of the carrier females and higher genetic recombination than the non-carriers (Stefansson H et al 2005 Nature Genet 37:129). ▶mtDNA, ▶Y chromosome, ▶hominidae, ▶chimpanzee, ▶language, ▶Eve foremother of mitochondrial DNA, ▶Y chromosome; Jones S, Martin R, Pilbeam D eds 1992 Human Evolution, Cambridge Univ. Press, New York; Cavalli-Sforza LL, Feldman MW 2003 Nature Genet 33(Suppl.):266; <http://www.becominghuman.org>.

Human Experimentation: Human experimentation must be limited to cases where other methods or means of study are not available. The subject(s) of the study should consent and be fully informed of the implications of the experiments. No experiment should be conducted which, by existing knowledge, is likely to involve injury, death, or unnecessary suffering. The experimenter must have the highest qualification. The experiments must be terminated any stage when

the subject so desires or when the experimenter expects harm. ▶ethics, ▶informed consent, ▶privacy rules, ▶genetic privacy; Foster C 2001 The Ethics of Medical Research, Cambridge Univ. Press, New York.

Human Gene Index: Human gene sequences, annotations, etc. <http://www.tigr.org/tigr-scripts/tgi/Tindex.cgi?species=human>.

Human Gene Mutation Database: <http://www.hgmd.org/>.

Human Gene Transfer: In human gene transfer, the vectors can be replication-deficient retroviral or adenoviral vectors. The retroviral vectors may integrate 9-kb passenger DNAs into the chromosomes and may destroy tumor suppressor genes or activate oncogenes if inserted nearby, and thus may permanently alter the genome either favorably by inserting the desired genes or undesirably as mentioned above. Adenoviral vectors have a carrying capacity of about 7.5-kb DNA. These enter the cells by special receptors. Adenoviral vectors do not integrate into the chromosomes and do not replicate indefinitely but have to be reapplied after a few weeks or months. They are well suited for in vivo use because they may be efficient in replicating and non-replicating cells and may have high titer (10^{13} virion/mL). The adenoviral vectors may involve inflammation of the tissues and may encounter antivector

cellular immunity. New vectors are continuously developed for greater efficiency.

Plasmid-liposome carriers also have been explored under in vivo conditions. Human gene transfer may be used to insert selectable markers into T cells, stem cells, tumor-infiltrating lymphocytes, neoplastic cells in hematopoietic lines, and sarcoma cells, etc. Gene transfer may have also therapeutic goals. Most of the human gene transfer experiments were plagued with inconsistent results and the expectations based on animal model experiments were not entirely fulfilled. The vectors need further improvement regarding "homing-specificity" (targeting), side effects (inflammation), elimination of the possibility of insertional mutations, and eliminating possible immunological reactions against the vectors. ►transformation genetic, ►vectors, ►gene therapy, ►cancer gene therapy, ►adenovirus, ►liposomes; Factor PH ed 2001 Gene Therapy for Acute and Acquired Diseases. Kluwer, Boston.

Human Genetics: Basic genetics using human (cells or individuals) as the subject of study. The human genome contains approximately 30,000 to 25,000 genes and their physical mapping and sequencing is near completion. In general, the function of several physically identified gene is discovered weekly. Human genetics is relying more and more on the methods of reversed genetics and bioinformatics (Botstein D, Risch N 2003 Nature Genet 33 [Suppl.]:228). ►BodyMap, ►clinical genetics, ►medical genetics, ►pharmacogenetics, ►OMIM, ►HGMD; Hawly RS, Mori CA 1999 The Human Genome: A User's Guide. Acad. Press, San Diego, CA, Jenssen TK et al 2001 Nature Genet 28:21; Badano JL, Katsanis N 2002 Nature Rev Genet 3:779; genetic testing: <http://www.ncbi.nlm.nih.gov/>; <http://hum-molgen.de/>; <http://www.ncbi.nlm.nih.gov/genome/guide/human>; <http://www.sanger.ac.uk/>; allele frequencies: <http://alfred.med.yale.edu/>; human gene mutation database: <http://www.hgmd.org/>; hereditary disease frequency: <http://www.findbase.org/>; newsletter of the American Society of Human Genetics: <http://www.ashg.org/genetics/ashg/snpit/>; locus specific database: <http://www.hgvs.org/entry.html>; locus specific mutation database: <http://www.hgvs.org/dblist/glsdb.html>; disease central mutation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/disease.html>; mutation and SNP database: <http://www.genomic.unimelb.edu.au/mdi/dblist/ccent.html>; ethnic variation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/deth.html>; dysmorphology: http://www.lmdatabases.com/about_lmd.html; miscellaneous human mutation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/other.html>; screening: [\[hrsa.gov/screening/\]\(http://hrsa.gov/screening/\); human, mouse zebrafish genomic data: <http://www.ensembl.org/index.html>; nomenclature information and rules: <http://www.gene.ucl.ac.uk/nomenclature/>; human sequence variation nomenclature for DNA, RNA and protein: <http://www.hgvs.org/mutnomen/>; DNA mutation software: <http://www.ebi.ac.uk/cgi-bin/mutations/check.cgi>; wide range of genetic/genomic/chromosomal/molecular resource: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>; mitochondrial mutation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/mito.html>; chromosomal variation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/chromo.html>; American College of Medical Genetics standards for clinical laboratories: \[http://www.acmg.net/Pages/ACMG_Activities/stds-2002/stdsmenu-n.htm\]\(http://www.acmg.net/Pages/ACMG_Activities/stds-2002/stdsmenu-n.htm\); Clinical Molecular Genetics Society guidelines for DNA sequencing and interpretation: \[http://www.cmgs.org/BPGs/Sequencing_new.htm\]\(http://www.cmgs.org/BPGs/Sequencing_new.htm\).](http://mchb.</p>
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Human Genome: About 90% of the genome, 2.91 billion bp of the euchromatic portion was sequenced by the whole-genome shotgun approach using the DNA of five individuals of different ethnicity, and published by the Celera group on Feb. 16, 2001 and on Feb. 15 by the Human Genome Sequencing Consortium. 25% of the genome is in scaffolds of over 10 million basepairs and 90% is in assemblies of 100,000 bp or more. Celera found 25,588 protein coding transcripts and computational analysis and mouse information indicated the presence of ~12,000 additional genes. The Consortium estimated ~31,000 protein-coding genes. The definitive number of genes is still uncertain; the best current estimates are ~25,000. About 75% of the DNA is intergenic. About 740 genes are transcribed into RNA but not translated into protein. Only 1.1% is in exons and 24% is in introns. On the average, there was found 1 bp variation per 1250 bp among genomes, and less than 1% of the SNPs were found to alter the amino acid sequences in the proteins. Mate pairs using BAC clones arraigned the megabase size sequences. The high throughput automation and computational technology made possible rapid progress beyond expectation. The gene density of the chromosomes varies, and generally the genes are not distributed uniformly along the length of the DNA. There are more genes in the GC-rich tracts than in the AT-rich sequences. Chromosomes 11, 17, 19, and 22 are relatively gene-rich whereas X, 4, 18, 13, and Y are poor. The highest numbers of genes are in chromosomes 1, 2, 19, and 11, in this order. Recombination frequencies per Mb are higher in the telomeric region and also higher in females than in males. The first coding exons appear to have high CpG proportions. There is a high proportion of processed

pseudogenes, especially for ribosomal proteins (67%), lamin receptors (10%), and to smaller extent in others. 107 blocks contain repeated genes, 781 of them five or more. Duplications are extensive over the entire genome, especially in chromosome 2 and 14. The latter is duplicated in over 70%. Some of the genes responsible for diseases (bleeding disorders, developmental regulation, and cardiovascular conduction) are in paralogs of duplicated segments. Interestingly, these duplications are similar to those in mice, indicating that their origin predated the evolutionary divergence. The nucleotide diversity based on SNIPs for the autosomes was found to be 8.94×10^{-4} and for the X chromosome 6.54×10^{-4} . The transition: transversion rate varied from 1.59:1 to 2.07:1, depending of the analytical methods. The distribution of SNIPs deviates from the Poisson expectation. In the coding sequences, the missense nucleotide substitutions are relatively rare (0.12–0.17%), indicating that conservatism for the integrity of the proteins is favored by selective evolution. The intergenic and intron regions harbor most of the SNIPs. About 40% of genes had no identified function by 2001. The annotation remains of central interest (Hubbard T 2002 Bioinformatics Suppl. 2: S140). Some inconsistencies and errors turned up on reexamination of the draft completed by 2000. The largest categories are nuclei acid metabolism (7.5%); transcription factors (6%), hydrolases (proteases), signal transduction (G proteins), receptors, kinases, phosphatases, transporters, cytoskeletal proteins, ion channels, motor proteins, cell adhesion molecules are common. Human-*Drosophila* orthologs were 2,758, and the human-*Caenorhabditis* orthologs appeared to be 1,523. The nucleic acid metabolic enzymes, polymerases, helicases, ligases, nucleases, and ribosomal proteins were best preserved during evolution. The lower animal genomes (*Drosophila*) are devoid of the human genes mediating acquired immunity. The human nervous system is controlled by a much larger number of genes than the similar functions in *Caenorhabditis* or *Drosophila*. Intracellular signaling, hemostasis, apoptosis, translation, and ribonucleoprotein genes are substantially expanded in humans compared to other, lower organisms. The number of genes is about only twice that of *Caenorhabditis* because with the more elaborate regulatory system in humans the higher complexity of functional needs can be taken care of. ▶draft genome sequence, ▶shotgun sequencing, ▶scaffolds in genome sequencing, ▶clone-based mapping, ▶exon, ▶intron, ▶mate pairs, ▶BAC, ▶fingerprinting, ▶acquired immunity, ▶paralogous loci, ▶gene number, ▶SNIPs, ▶diversity, ▶polymorphism, ▶Poisson distribution, ▶missense mutation, ▶transposition, ▶transversion, ▶rough draft, ▶gene,

▶ENCODE, ▶annotation of the genome; combined linkage-physical map of human genome of 14,759 sites: Kong X et al 2004 Am J Hum Genet 75:1143; Venter JC et al 2001 Science 291:1304; Lander ES et al 2001 Nature [Lond] 409:86034; Errata in Nature 412:565–566; Katsanis N et al 2001 Nature Genet 29:88; sequence and annotation of chromosome 7: Scherer SW et al. 2003 Science 300:767; sequence and annotation of chromosome 11: Taylor TD et al 2006 Nature [Lond] 440:497; chromosome 12: Scherer SE et al 2006 Nature [Lond] 440:346; recombination map: Kong A et al 2002 Nature Genet 31:241; inconsistencies in assemblies: Rouchka EC et al 2002 Nucleic Acids Res 30:5004; quality assessment: Schmutz J et al 2004 Nature [Lond] 429:365; <http://www.alis.tokyo.jst.go.jp/HOWDY/>; human genome variations [HGVbase]: <http://hgvdbase.cgb.ki.se>; Bermuda Standards, sequence fidelity standards: <http://www.genome.gov/10001812>; mammalian gene collection database: <http://mgc.nci.nih.gov/>; human [and some other] genome resources: <http://www.ncbi.nlm.nih.gov/genome/guide/human/>; human protein database: <http://www.genprot.org/>; genome annotation: http://vega.sanger.ac.uk/Homo_sapiens/index.html; <http://www.jbirc.jbic.or.jp/hinv/ahg-db/index.jsp>; human invitational database: <http://www.h-invitational.jp>; Genomic variants per chromosome: <http://projects.tcag.ca/variation>.

Human Genome Diversity Project (HGDP): The HGDP studies 52 populations including African, Europeans, Western Asians, Southern Asian, Eastern Asians, Oceanians and Native Americans. It contained (in 2004) 1064 cell lines and provided free samples to 56 laboratories and collected the largest, diverse DNA samples of the species. Its goal includes information on world-wide distribution of human genetic disease genes. It provides information also on the origin of human populations. ▶MAPMAP, ▶human evolution; Cavalli-Sforza LL 2005 Nature Rev Genet 6:333.

Human Genome News: Monthly publication on the human genome project by the National Institute of Health and the U.S. Department of Energy. Information: Human Genome Management Information System, Betty K. Mansfield, Oak Ridge National Laboratory, 1060 Commerce Park, MS-6480, Oak Ridge, TN 37831, USA. Phone: 615-576-6669. Fax: 615-574-9888. bkq@ornl.gov; <http://www.ornl.gov/hgmis/>; <http://www.doegenomes.org/>.

Human Immunodeficiency Virus (HIV): ▶acquired immunodeficiency syndrome

Human Intelligence (IQ): Human intelligence is not a simple qualitative trait but is generally defined as

the composite index of a variety of scores each of which is expected to have different genetic determination. The intelligent quotients (IQ) also vary, depending on the variety of test batteries used for the analysis, such as cognitive, verbal, mathematical, logical, performances, among others. Since intelligence is such a complex trait, it must be under the control of many genes. All polygenic traits have genetic and environmental components, so does intelligence. As a consequence it is impossible to separate clearly ability from achievement, and the tests involve generally the latter. Nevertheless, it is obvious that all traits are expressed on the basis of a genetic blueprint in the DNA, and “intelligence” cannot be an exception. Shortly before the end of the nineteenth century, Francis Galton, the father of statistical genetics, came to the conclusion that the apparent mental abilities of parents and children are correlated. Galton found that 36% of the sons of the 100 most distinguished men were still eminent but only 9.5% of their grandsons and 1.5% of their great grandsons were such. Also, 23% of the brothers of eminent men were also eminent. Since then several studies confirmed the existence of such general correlations. These correlations may be biased to a great degree because the environmental conditions of parental and offspring population is also highly correlated. Before World War I, intelligence quotients were introduced for standardized quantitative measurements of intelligence. The Binet test had been widely used for determining scholastic performance and predictions. According to these quotients, children scoring according to the average of their age group were classified with a score of 100 and whose performance corresponded to two years behind or two years ahead of their peers were assigned IQ values 80 or 120, respectively. Within similar socio-economic and educational groups, these figures were meaningful. Comparisons between mono- and dizygotic twins reared together and apart, as well as those between adopted children and foster and birth parents were studied for the inheritance of IQ.

These studies have proven by objective measures the existence of a significant hereditary component of the IQ indexes. Some studies attribute great influence to maternal effects through the womb environment. The IQ values should be very cautiously considered if different ethnic or socio-economic groups are compared. Also, the developmental rate of individuals may vary a great deal. Some of the children are early or late “bloomers” and this condition limits the predictive value of the indexes. There can be no question that certain genes, concerned with the nervous system, are responsible for mental retardation. The IQ indexes should not be used, however, for ethnic or social group-discrimination because the

statistical ranges of individual IQ values are highly overlapping in human populations, e.g., of blacks and whites in the USA. Although the averages of the two groups displayed a 15% difference, such information does not serve any useful purpose (see Fig. H76, drawn on the basis of data by AR Jensen 1998 The 3 g Factor. Praeger, Westport, CN). Racial gaps in

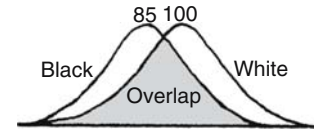


Figure H76. IQ distribution according to AR Jensen

achievement can be substantially reduced by appropriate social-psychological intervention involved in boosting self-confidence (Cohen GL et al 2006 Science 313:1307). Also, humans can be judged only individually. Furthermore, diverse individual values of athletes, business people, laborers, physicians, geneticists, theoretical physicists, etc., are all important for the good functioning of human societies. Anyhow, IQ data are statistical and do not have rational neurobiological bases. Sex differences in mental test scores have been examined repeatedly in large representative populations. Although the overall differences between the sexes appear small, the males' abilities in mathematical and mechanical performance appeared higher whereas in associative memory, reading comprehension, and perceptual speed the females were at advantage. The genetic meaning of these data is not clear. Males and females share the same chromosomal complement, except the Y-chromosome, which by current knowledge contains minimal information beyond what is located in the pseudoautosomal segment and the genes related to sex determination and male fertility. Fragile sites in several human chromosomes are associated with trinucleotide repeats. The C residues of these variable-length repeats may be methylated to a variable extent and the increase of methylation is correlated with a decrease of intellectual abilities of the individuals. The range of IQ of dull individuals is 20–84, of the feeble-minded is 50–70, the imbecile is 20–50, and the idiot is < 20. These three lower types combined represent 2–3% of the general population, but are substantially higher in consanguineous sibships, especially when one or both of the parents are subnormal. IQ represents a good example of regression. Children of higher IQ people (IQ 140) display values about 121, whereas the IQ of low IQ (85) people's offspring may exceed (92) the parent's. Although various IQ tests have been widely used for psychological and clinical studies, general cognitive abilities can be better assessed by Spearman's *factor*

analysis based on the *g* test (general factor test) developed at about the same time as the Binet test. The *g* test uses correlation matrices of various abilities, e.g., study of classics, modern languages, mathematics, pitch, music, etc. The basic idea is that one single ability is expected to be correlated with diverse other abilities and the *g* score can express it all in a single numerical manner (*factor loading*). The *g* test generates a composite index that weighs the separate tests by the overall correlation with all other component tests. Since the 1910s, Cyril Burt proposed the more complex *group factor* approach as a refinement of the *g* test. The IQ tests are also numerical but the final score is derived from the summation of the average individual scores (e.g., reading, memory, judgement, etc.). Recently, the availability of methods for the study of quantitative gene loci and multivariate genetic analyses permit the study of genetic correlation among numerous genes. Also, the heritability of cognitive abilities can be assessed with much better resolution. The progress in neurobiology (neuroimaging) sheds also some light on the spatial organization and cooperation of the sites of these separate cognitive centers in the brain. The availability of chromosome and genome sequence information along with microarray hybridization techniques is expected to further reveal how the cognitive index of *g* is controlled by molecular factors. Since in a human population the individual genes may be represented by different alleles, the fine differences may be revealed by single nucleotide polymorphism (SNIP). With the progress of the proteome analysis, eventually better treatment may be feasible for the mentally retarded or those who are afflicted by affective disorders. The molecular genomics of behavior will certainly raise many ethical problems. The progress in biology and genetics must go ahead even in some of the delicate areas. Application of the new technology requires, however, different types of moral and ethical decisions. One must keep in mind the lack of a generally agreed upon definition of what constitutes intelligence. ►polygenes, ►heritability, ►behavior genetics, ►behavior in humans, ►genius, ►mental retardation, ►microcephaly, ►cognitive abilities, ►euteleogenesis, ►myopia, ►fragile sites, ►FMR1 mutation, ►trinucleotide repeats, ►autism, ►dyslexia, ►QTL, ►multivariate analysis, ►heritability, ►microarray hybridization, ►DNA chips, ►SNIP, ►mental retardation, ►affective disorders, ►proteome, ►Spearman rank-correlation test, ►brain human, ►covariance, ►behavior genetics, ►imaging, ►admixture in populations, ►chimpanzee; Macphail EM, Bolhuis JJ 2001 Biol Rev Camb Philos Soc 76(3):341; Dickens WT, Flynn JR 2001 Psychol Rev 108:346; Plomin R, Craig I 2001 Br J

Psychiatry Suppl. 40:s41; Bartels M et al 2002 Behavior Genet 32:232.

Human Mutagenic Assays: Humans cannot be subjected to mutagenic treatments and a mutagenic risk to human populations is determined largely by indirect means, using microbial, and animal and plant bioassays of genetic toxicology. Other methods may involve epidemiological efforts involving dominant mutations, survey of chromosomal aberrations in blood samples, testing cell cultures for mutability, and biochemical and molecular methods to assay genetic repair in cell culture, monitoring changes in DNA by restriction fragment polymorphism using appropriate probes, SNIPs, etc. Increase in recessive mutations are difficult to detect because the human mating system does not favor homozygosis. Although the populations of Hiroshima and Nagasaki were exposed to very high doses of ionizing radiation as a consequence of the atomic explosion during World War II, no statistically significant increase in gene mutation could be detected. Developmental defects and incidence of neoplasia, however, increased. Similarly, although the meltdown of a nuclear reactor in Chernobyl in 1986 caused a significant increase in birth defects and cancer, it is too early to tell whether these were only teratological effects or genetic causes are also involved. More recent data seems to indicate that genetic alterations were also caused. ►atomic radiations, ►bioassays in genetic toxicology, ►host-mediated assays, ►substitution mutation, ►mutation detection, ►mutation rate in humans, ►SNIP; human mutation database: <http://www.hgmd.cf.ac.uk/ac/index.php>.

Human Origins: Anthropologists and paleontologists are not in agreement about how *Homo sapiens* populated the world. The earliest human relics—based on $^{40}\text{Ar}/^{39}\text{Ar}$ dating—in Africa appear to be $195 \pm \text{kyr}$, substantially older than the earlier estimate (McDougall I et al 2005 Nature [Lond] 433:733). Some scientists claim that Europe was invaded from Africa 40,000–50,000 years ago during the Paleolithic period. Others favor the demic-diffusion hypothesis according to which during the Neolithic period (10,000 years ago) humans migrated to Europe from the Near East bringing with them early agricultural practices. Others postulate that agriculture moved to Europe without actual migration of people. According to some views, these waves of immigrants failed to interbreed with the earlier settlers. According to others, the origin was not supposed to be multiple but multiregional (Wolpoff MH et al 2000 Am J Phys Anthropol 112:129), yet *Homo erectus* continuously interbred with the different geographically dispersed populations of *H. sapiens*. These different concepts are based on fossil, skeletal morphology, mtDNA, and

Y chromosome and classic gene frequencies. Ancient migration from Africa via Southeast Asia might have taken place southward to Australia and northward to China and Japan. Indians and Eskimos populated the Americas about 10,000 years ago through a land bridge across the Behring Strait from North Asia. The ancestral size of the original human population (about 10,000) was inferred from DNA sequence variations using statistical methods (Yang Z 2002 *Genetics* 162:1811). ▶hominoids, ▶radiocarbon dating, ▶argon dating, ▶Out-of-Africa, ▶Y chromosome, ▶Eve foremother; Lell JT, Wallace DC 2000 *Am J Hum Genet* 67:1367; Tishkoff SA, Verelli BC 2003 *Annu Rev Genomics hum Genet* 4:293.

H

Human Population Growth (Modified after Biraben JN 1980 *Population* 4:1): Some calculations indicate a 2/3 probability that the world's population will not double during the twenty-first century (see Table H4). Probabilistic forecast indicates 85% chance that the world population will cease growing by the end of the twenty-first century and the probability is 60% that it will not exceed 10 billion by the end of this century. After that there is a 15% chance for decline. The United Nations currently predicts 8.9 billion by 2050. ▶age-specific birth and death rates, ▶human origins; Lutz W et al 2001 *Nature [Lond]* 412:543; tragedy of the common: <http://www.un.org/popin/data.html>.

Table H4. Human Population Growth

| Years | 400 | 1 | 500 | 1000 | 1500 | 2000 |
|--------------------|-----|-----|-----|------|------|-------|
| Millions of people | 160 | 250 | 200 | 250 | 460 | ≈6000 |

Human Protein Atlas (www.proteinatlas.org/): Expression, localization and classification of proteins (antibodies) in human tissues and cancers. It displays the encoding genes according to chromosomes, homologies with other species, references, etc.

Human Races: Human races are distinguished by anthropologists on the basis of anthropometric traits. Geneticists delineate the races on the basis of *gene frequencies* shared within the group and as different from other “racial” populations. The classification of “races” is compounded by social and cultural factors. The main human races are Caucasoid, Mongoloids (including Chinese, Japanese, Koreans, and American Indians, etc.), and Negroid. Khoisanoids or Capoids (Bushmen and Hottentots) and Pacific races (Australian aborigines, Polynesians, Melanesians, and Indonesians) may also be distinguished. Many other subgroups within the larger ethnic groups may be classified. There is no genetic incompatibility among the various human races and there is no

well-founded scientific evidence that interracial marriage would lead to the disruption of co-adapted gene blocks resulting in biological or mental deterioration in the offspring. The three major human races are genetically closely related as indicated by determination of evolutionary genetic distance. There is a controversy in the biomedical community as to what extent race would have any meaning for therapy. Different alleles are represented by different frequencies among ethnic groups and there may be differences in response to medication and a different need for social services. The human race is extremely closely related on the basis of DNA sequences to primates, primarily to chimpanzees, yet the genetic isolation is complete. ▶allelic frequencies, ▶evolutionary distance, ▶genetic isolation, ▶racism, ▶SNIPs, ▶miscegenation, ▶interracial human hybrids, ▶primates, ▶*Homo sapiens*, ▶human evolution; Barbuji G et al 1997 *Proc Natl Acad Sci USA* 94:4516; Roychoudhury AK, Nei M 1988 *Human Polymorphic Genes: World Distribution*. Oxford Univ. Press, New York; Sankar P 2003 *Nature Genet* 34:119; Kittles RA, Wiss KM 2003 *Annu Rev Genomics Hum Genet* 4:33.

Human Subjects of Experimentation: ▶bioethics; <http://www.bioethics.gov/>; USA federal regulations: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>; compliance report to USA Congress: <http://www.fas.org/sgp/crs/misc/RL32909.pdf>; ▶GWA

Human Transcripts: <http://www.hgsc.bcm.tmc.edu/HTDB/>.

Humanics: Combination of genetics and social sciences.

Humanin: A short polypeptide that prevents neuronal death in Alzheimer disease. ▶Alzheimer diseases; Hashimoto Y et al 2001 *Proc Natl Acad Sci USA* 98:6336.

Humanized Antibody: A chimeric molecule with the variable region of the mouse fused to the constant region of the human antibody. This molecular chimera retains its binding specificity and some characteristics of the human antibody. Some humanized antibodies have been tried as immunosuppressors of lymphatic, breast, and other tumors. Hyperchimerization and civilization are synonyms of humanized antibody. Humanized mouse antibodies (mAb) reduce allergic response. Making alteration in the Ab amino acids can also mask mouse epitopes. For therapeutic mAb it is important that it be effective in cytotoxicity. The Fc in mouse may make this effector function insufficient. The humanized form produced in non-human cells may alter the expected glycosylation pattern and may make it less effective. If mAb is produced in human B-lymphocytes, the

immunogenic risk can be reduced. Either human B cells are immunized *ex vivo* in the presence of human antigens and then immortalized by cell fusion, or donors are selected with high immunoreactivity to the specific antigen. By such procedures mAbs are generated with specificity for human mesothelin and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are now in preclinical trial (Li J et al 2006 Proc Natl Acad Sci USA 103:3557). ▶antibody, ▶immune system, ▶HAMA, ▶veneering of antibody, ▶epitope, ▶monoclonal antibody, ▶GM-CSF, ▶mesothelin; Vaswani SK, Hamilton SG 1998 Ann Allergy Asthma Immunol 81(2):105.

Humor: Body fluid, like the serum. It contains important solutes.

Humoral Antibody: The humoral antibody is made by the B lymphocytes and circulates in the bloodstream rather than being attached to the surface of T lymphocytes. ▶immune system, ▶antibody

Humoral Antigen: The humoral antigen is secreted into the bloodstream. ▶B cell, ▶T cell, ▶immune system

Humunculus: A seventeenth–eighteenth century preformationist figment that either in the human egg or sperm a miniature version of a human adult resides that eventually develops into a human embryo. ▶preformation

Humus: Decaying organic matter in soil.

Hunter Syndrome: ▶mucopolysaccharidosis (MPS II)

Hunter-Thompson Chondrodysplasia: ▶chondrodysplasia

Huntingtin: ▶Huntington's chorea

Huntington's Chorea (Huntington's disease, HD): A dominant, gain-of-function, genetic disorder (chromosome 4p16.3) with a prevalence of 4 to 9×10^{-5} live births of Western European descent. The deletion of this chromosomal area leads to the Wolf-Hirschhorn disease. It is a progressive degeneration of the basal ganglia (spinal cord) and the brain cortex causing uncoordinated (choreic) movements and loss of mental abilities (dementia). It exists in the juvenile (akinetetic/rigid) form with an onset in the teen years or with the late onset at age 30 to 50. Expectancy of survival, after the first symptoms appear, is about 20 years. Motor disorders (jerkiness) in the carriers may be observed years before the onset of the disease. The late onset form is generally inherited through the mother and the early onset through the father. Although this difference of the gene with a near-perfect penetrance was attributed initially to a mitochondrial co-factor, it appears to be determined by differential methylation (imprinting). Repression of

PGC-1 α by huntingtin leads to mitochondrial dysfunction and neurodegeneration (Cui L et al 2006 Cell 127:59).

Prenatal testing is feasible because of a very closely linked DNA marker, D4S10 (G8). Because the onset is frequently delayed beyond the reproductive period, early analysis of risk on the basis of linkage to this tight molecular marker is desirable. Various biochemical alterations (GABA, glutamic acid decarboxylase, choline acetylase deficiency) may be associated with the disease. Among Huntington patients 322 mRNAs showed significant alterations in expression. On this basis—by microarray hybridization—presymptomatic individuals were distinguished from healthy individuals and Huntington patients. Alterations in mRNA correlated with the progression of the disease (Boroveczki F et al 2005 Proc Natl Acad Sci USA 102:11023). In mice, HD is frequently associated with diabetes because of deficiency of pancreatic β -cell mass and reduction in the number of insulin-containing secretory vesicles (Björkvist M et al 2005 Hum Mol Genet 14:565). It has been shown that the 'huntingtin' protein (≈ 350 -kDa) in the basal ganglia and cerebral cortex displays 37 to 121 glutamines (CAG) repeats vs. the normal protein, which have only 6–34 repeats. Amino-terminal mutant fragments accumulating in the striatal neurons are the principal cause of neuropathy. Huntingtin cleavage at the caspase-6 site mediates neuronal dysfunction (Graham RK et al 2006 Cell 125:1179).

SUMOylation of *Drosophila* huntingtin exacerbates neurodegeneration, whereas ubiquitination abrogates the process. Both SUMO and ubiquitin bind to identical lysine residues (Steffan JS et al 2004 Science 304:100). PKR binds preferentially to CAG repeats in mutant huntingtin RNA and this may be important in pathogenesis. When the mismatch repair enzyme MSH2 is deficient, the trinucleotide instability increases. Glucocorticoid receptor (GR) localizes the repeat into the nucleus. Deletion or mutation in the C-terminal of GR was found to suppress aggregation and nuclear localization. Surprisingly, mutation in the DNA-binding N-terminal domain increased aggregation and nuclear localization by GR. The chemical disruption of the aggregation may alleviate the disease (Apostol BL et al 2003 Proc Natl Acad Sci USA 100: 5950). The genetic transmission of the normal range of the repeats is stable whereas in the abnormal it is unstable. The longer repeats hasten onset and increase severity of the condition. Homozygosity may result in embryonic lethality. The polyglutamine aggregates compromise cellular viability. When in a mouse model the HD gene was turned off during development by an antibiotic in the drinking water of 18-weeks-old puppies, the extranuclear polyglutamine aggregates

were gradually reduced or disappeared and concomitantly the neurological motor disorder was alleviated. The huntingtin protein resembles neuronal nitric oxide synthase. It has been assumed that it is a transcription factor. The mutant huntingtin and atrophin-1 seem to interfere with transcription through CREB-binding protein CBP. Increased histone deacetylase activity may play a role in the accumulation of the polyglutamine tracts and the neurodegeneration. The ~10-kb normal Huntington gene is transcribed into two mRNAs of 13.5- and 10.5-kb and it is essential for embryo survival. Huntingtin binds to dynein and acts in a complex along with dynactin and huntingtin-associated protein-1 to facilitate vesicular transport (Caviston JP et al 2007 Proc Natl Acad Sci USA 104:10045). The presence of the wild type huntingtin is required for the normal production of the brain-derived neurotrophic factor (BDNF), a requisite for the survival of striatal neurons in the brain. By neural transplantation, both the cognitive and the motor system deficits may be alleviated. Mice mutant for the huntingtin gene can be normalized by introduction of the wild type HD transgene. The huntingtin-interacting protein (HIP14) is a palmitoyl transferase that controls neuron function by palmitoylation of multiple neuronal proteins (Huang K et al 2004 Neuron 44:977). The polyglutamine-induced cell death is dramatically decreased in *Drosophila* lacking the Dark/Apaf-1 protein, which regulates caspases/apoptosis (Sang T-K et al 2005 Hum Mol Genet 14:357). In *Drosophila*, single-chain Fv antibodies that bind huntingtin intrabodies reduce cellular aggregation and toxicity (Wolfgang WJ et al 2005 Proc Natl Acad Sci USA 102:11563). RNAi is a potential means for controlling HD abnormalities (Harper SQ et al 2005 Proc Natl Acad Sci USA 102:5820). Yeast has genes that appear homologous to that in humans. In a yeast test, 28 deletions suppressed toxicity of a mutant huntingtin fragment. The suppressors apparently affected vesicle transport, vacuolar degradation, transcription, and prion-like aggregations. The globular aggregates of different sizes may be the major cause of the Huntington disease (Mukai H et al 2005 Proc Natl Acad Sci USA 102:10887; ►inclusion body). One of the most potent suppressors involved kynurenine 3-monooxygenase, an enzyme mediating tryptophan degradation and reactive oxygen species (ROS), and this finding suggests a new type of therapeutic intervention in Huntington disease (Georgini F et al 2005 Nature Genet 37:526). In vitro analysis of huntingtin-mediated transcriptional repression indicates multiple transcription factor targets, particularly TFIID, TFII (Zhai W et al 2005 Cell 123:1241). ►genetic screening, ►DNA marker, ►inclusion body, ►mental retardation, ►epilepsy,

►fragile sites, ►nitric oxide, ►trinucleotide repeats, ►mismatch repair, ►atrophin-1, ►kynurenine, ►ROS, ►Wolf-Hirschhorn syndrome, ►CREB, ►PKR, ►junctophilin, ►SUMO, ►PGC1, ►ubiquitin, ►Apaf, ►apoptosis, ►caspase, ►RNAi, ►antibody; Leavitt BR et al 2001 Am J Hum Genet 68:313; Peel AL et al 2001 Hum Mol Genet 10:1531; Zuccato C et al 2001 Science 293:493; Steffan JS et al 2001 Nature [Lond] 413:739; Dunah AW et al 2002 Science 296:2238; history of the recognition: Bates GP 2005 Nature Rev Genet 6:766.

HUPO: Human Proteome Organization. ►HUGO, ►proteome; <http://www.hupo.org>.

HuR: Group of AU-rich element-binding proteins of the ELAV family. (►AU-rich elements, ►ELAV).

Hurler Syndrome (mucopolysaccharidosis I, MPS I, 4p16.3): Also called Scheie syndrome or Hurler-Scheie phenotype. It is due to the deficiency of α -L-iduronidase. The symptoms range from severe mental retardation, enlargement of the liver and spleen (hepatosplenomegaly, bone diseases (dysostosis multiplex), opacity of the cornea, hearing loss, and heart problems, but there is usually normal intelligence and life span. Aminoglycoside antibiotics, (geneticin, gentamycin) by suppression of nonsense mutation, may alleviate the symptoms. ►mucopolysaccharidosis, ►mucopolidosis, ►Hunter syndrome, ►hypertrichosis, ►iduronic acid, ►aminoglycosides; Keeling KM et al 2001 Hum Mol Genet 10:291.

hut Operon: Histidine utilization genes. Histidine is synthesized from three precursors ATP and phosphoribosyl-pyrophosphate (PRPP) and glutamine, and it is involved in the regulation of other amino acids by yielding both glutamate and ammonia. The operon includes five structural genes, *hutH*, *hutU*, *hutI*, *hutG* and *hutM*, and *hutP*, and regulates histidine utilization and degradation. *hutP* is just downstream of the promoter and an overlapping nucleotide sequence controls antitermination/termination of transcription. Antitermination requires L-histidine and Mg^{2+} . ►histidine operon, ►antitermination; Zalieckas JM et al 1999 J Bacteriol 181:2883, *hutP* crystal structure: Kumarevel T et al 2005 Nature [Lond] 434:183.

Hutchinson-Gilford Syndrome (progeria, HGPS): A rare very precocious aging of either recessive or dominant inheritance (human chromosome 1q) leading to heart defects and death by the second decade of life. The disease is usually accompanied by multiple heat-labile protein defects. The basic defect seems to be in lamin A. In 80% of the cases, at G608 there is a GGC→GGT transition in exon 11 of lamin A (McClintock D et al 2006 Proc Natl Acad Sci USA

103:2154). A mouse model is available for the study the progressive defect of the vascular smooth muscles (Varga R et al 2006 Proc Natl Acad Sci USA 103:3250). Lamin A precursor, prelamin, terminates with C-terminal motif CaaX (where *C* stands for cysteine, *a* for aliphatic amino acids, and *X* for a variety of amino acids). Prelamin normally is farnesylated at the C residue and the three terminal amino acids are removed by endoproteolytic cleavage. The farnesylated cysteine is carboxy-methylated. During biogenesis by a second proteolytic event, a zinc metalloprotease (Zmpste 24) removes the terminal 15 amino acids, including farnesyl and the carboxymethylated CaaX modifications. As a consequence of lamin defect, the nuclear membrane is deformed. The progeria seems to be associated with mutation of the CaaX motif (SaaX; S being serine) and abnormal farnesylation due to alteration at the cleavage site and the internal deletion near the C terminus. It appears that farnesyltransferase inhibition (see Fig. H77) may alleviate or remove some of the lamin-related progeroid symptoms (Toth JI et al 2005 Proc Natl Acad Sci USA 102:12873; Mallampalli MP et al 2005 Proc Natl Acad Sci USA 102:14416). In the great majority of cases, “Progeria of Childhood” a single nucleotide mutation (1824 C→T) in the *LMNA* gene, which encodes lamin A and C, nuclear intermediate filaments that are important components of the nuclear lamina is responsible for the anomaly. Short hairpin RNA (shRNA) constructs were designed to target by lentivirus vector the 1824 C→T mutations in pre-spliced or mature *LMNA* mRNAs. One of the shRNAs targeted to the mutated mRNA reduced the expression levels of Δ50 lamin A to 26% or lower and improved the disease symptoms including senescence of cells (Huang S et al 2005 Human Genet 118:444).

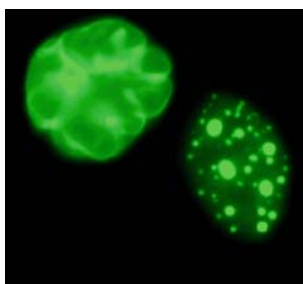


Figure H77. Progeria. Left: farnesyltransferase-inhibitor reversed nuclear damage. Right: untreated cells. (Courtesy Dr. Brian C. Capell, NHGRI)

In HGPS patients with a mutant lamin, loss of facultative heterochromatin was observed. This loss was associated with loss of histone H3 trimethylated lysine (H3k27) in the inactive X chromosomes of

human females. In constitutive pericentric heterochromatin, trimethylation of histone 3 lysine 9 (H3K9) and levels of heterochromatin protein HP1α and the CREST antigen were also reduced. The reduction was accompanied by an increase of trimethylation in H3K20, a biomarker for constitutive heterochromatin. These epigenetic alterations seem to be the molecular bases of the rapid aging caused by the disease (Shumaker DK et al 2006 Proc Natl Acad Sci USA 103:8703). ▶aging, ▶lamins, ▶CREST, ▶histones, ▶epigenesis, ▶heterochromatin; Eriksson A et al 2003 Nature [Lond] 423:293; Goldman RD et al 2004 Proc Natl Acad Sci 101:8963.

HUVEC: Human umbilical vein endothelial cells.

HVEM (herpes virus entry mediator): HVEM may block the entry of herpes virus into T cells but not into other cells. The 283-276 residue protein participates together with its receptor, LIGHT, in TNF function. ▶LIGHT, ▶TNF

HVR: Hypervariable regions in the DNA. ▶DNA fingerprinting, ▶somatic hypermutation

H-Y Antigen (6p23-q12, structural gene): A histocompatibility antigen controlled by another gene on the X chromosome (Xp22.3, HYR), the H-Y regulator. The HYA histocompatibility Y antigen is located in the long arm of the Y chromosome (Yq). It was recognized by rejection of skin grafts of male donors by female recipients, but the male recipients did not reject the grafts donated by females. The mice involved in these studies were inbred for many generations and were supposed to be isogenic, except for factors in the Y-chromosome. Therefore, the rejection was attributed to a male-specific antigen. Thereupon it was hypothesized that the H-Y male-specific cell surface antigen is also a male (testes) determining factor. Another gene, SMC, encoding an H-Y epitope on both the X and the Y chromosomes was located near the centromere in the long arm of the Y-chromosome encoding an 11-peptide residue of the SMCY protein of 1539 amino acids. The X-chromosome has a homolog SMCX with about 200 amino acid site differences scattered along the entire length, except in the 11 residue H-Y antigen where there is only a single amino acid difference between the SMCY and SMCX. In the mouse, the H-Y controlling gene (*Hya*) in the short arm of the Y chromosome and the epitope is defined by the octamer Thr-Glu-Asn-Ser-Gly-Lys-Asp-Ile. Exceptional individuals with XY chromosomal constitution displayed female phenotype and cytological analyses revealed a deletion at the tip of the short arm of the Y-chromosome. Also, chromosomally XX exceptional males carried a translocated terminal segment of the short arm of the Y-chromosome in one

of the X-chromosomes. This terminal segment was thus identified as the testis-determining factor (TDF) and thus the H-Y antigen has a true histocompatibility role, but it is apparently not responsible for testis differentiation. The H-Y antigen is the product of several genes. The current name of *TDF* is *SRY* (sex-determining region Y). ▶chromosomal sex determination, ▶sex determination, ▶sex reversal, ▶SRY, ▶gonadal dysgenesis, ▶azoospermia, ▶testicular feminization, ▶freemartins, ▶pseudohermaphroditism; Wolf U 1998 Cytogenet Cell Genet 80:232.

Hyacinth (*Hyacinthus orientalis*): Bulbous, monocot, fragrant spring flower (see Fig. H78), $2n = 16$.



Figure H78. Hyacinth

Hyaline: A transparent membrane and cartilage protein.

Hyalinosis, Infantile Sistematic: ▶fibromatosis

Hyaloplasm: The very finely granulated part of the cytoplasm. ▶cytoplasm

Hyalurodinase Deficiency (3p21.3-p21.2): A recessive hyaluronic acid (see Fig. H79) storage disease. Short stature and excess hyaluronate occur in the fluid of the joints. ▶mucopolysaccharidosis, ▶glucuronic acid, ▶glucosamine

Hybrid: Progeny of two genetically not identical parents. ▶F₁

Hybrid Antibody: Hybrid antibodies have more than one epitope-binding site because they are produced by genetic or chemical modification. ▶hybrid hybridoma, ▶humanized antibody, ▶antibody; Chintalacheruvu KR et al 2001 Clin Immunol 101:21.

Hybrid Arrested Translation (HART): When a mRNA is hybridized with a cDNA, only those sequences can be translated in vitro that are not base-paired. The pairing prevents translation of the paired sequences. On this basis the coding sequence for a particular polypeptide can be identified. Hybridization of mRNA by antisense RNA also prevents translation. ▶antisense RNA, ▶cascade hybridization, ▶hybrid-released translation; Paterson BM et al 1977 Proc Nat Acad Sci USA 74:4370; Nagy E et al 1987 Virology 158:211.

Hybrid, Asymmetric: After somatic cell fusion some chromosomes of one of the “parental” cells were eliminated. ▶alien addition, ▶cell fusion, ▶somatic cell genetics

Hybrid Breakdown: Reduced viability of the F₂ generation compared to the F₁. The most likely cause is homozygosity of deleterious recessive genes or negative recessive epistasis. ▶epistasis

Hybrid Capture: A commercial (Digene Corp. Silver-spring MD) DNA solution hybridization method for testing viral cancer risks. (See Clavel C et al 1999 Br J Cancer 80:1306; Lörincz AT 1996 J Obstet Gynecol Res 22:629).

Hybrid Depletion: Hybrid deletion identifies any cDNA that encodes a subunit of a multimeric protein. It is managed by preparing an mRNA pool coding for the protein of interest. The mRNA is hybridized to a cDNA cloned in a single-stranded vector, and the hybrids are fractionated by CsCl equilibrium centrifugation providing at the bottom of the centrifuge tube the unhybridized, i.e., the antisense RNA. When it is injected into *Xenopus* oocytes along with the coding mRNA of the original pool, it may block the translation of the complementary mRNA. ▶mRNA, ▶density gradient centrifugation, ▶antisense technology

Hybrid DNA: A heteroduplex. ▶heteroduplex

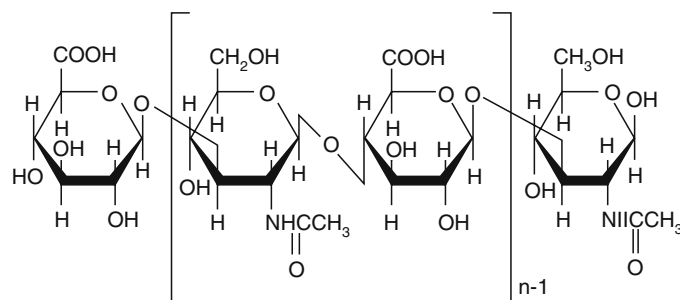


Figure H79. Hyaluronic acid has alternating units of D-glucuronic acid and acetyl glucosamine

Hybrid Dysgenesis: A historical term for various genetic phenomena caused by transposable elements in *Drosophila*. It entails mutations and chromosomal rearrangements in hybrids of two genetic stocks. *P-M* system: The *P*-strains carry a transposable element and a suppressor of transposition. In the other strains (*M*), there is a genetic factor that derepresses the transposase and thus the hybrid becomes genetically unstable, while both the parental forms are stable. (The *P* and *M* originally indicate paternal and maternal conditions, respectively.). In *Drosophila*, over 30 different hybrid dysgenesis systems have been identified. The best known among them is the *P-M* system. The physical structure of a complete *P* element is shown in the diagram (see Fig. H80).

Some *P* elements have internal deletions, duplications, and substitutions (such as $\pi 2$, $Pc[ry]$). The *P* element can be *autonomous* (transpose by their own power) and *nonautonomous* (requires a more complete [helper] element to move it). The autonomy of an element has been successfully tested by introduction through transformation of an in vitro engineered *P* element ($Pc[ry]$) carried on a plasmid along with the *rosy* gene (*rosy* is the structural gene for xanthine dehydrogenase [map position 3–52] and mutants have rosy eyes). The wild type allele introduced into *ry*[−] homozygotes have normal eyes and are capable of moving into the *sn* (*singed*, map location 1–21, responsible for bristle [microchaetae] deformations), and this fact can easily be monitored.

The movement of *P* is controlled by the transposase function that is encoded by the four exons that extend to almost the entire length of the element (see diagram). The transposase begins transcription at

base 85 and terminates at 2696, thus the transcript includes about 2.5 kb. The transposase enzyme is an 86.8-kDa protein. The *P* element can excise almost completely and leave behind the original genomic sequence or it may delete internal sequences, sometimes including even flanking nucleotides, involving genes with a total length rarely exceeding 7 kb. The imprecise excisions generate the defective elements. The frequencies of these excisions vary, ranging from 0.4 to nearly 2% per generation of the dysgenic flies. The mutability at the *sn* locus varies from 20 to 60%, but may reach up to 90% when two reverse oriented *P* elements (*double P*) are present at the target site. The targets for insertion are not distributed at random and *P* is inserted by several orders of magnitude more frequently in the *sn* locus than into the alcohol dehydrogenase (*Adh*) gene. Also, there is a tendency for *P* elements to become clustered. For insertion, the non-translated upstream regions of genes are favored compared to the coding regions. Insertion into euchromatic sites is favored over heterochromatin. Interbands appear more likely targets over chromosomal bands. *P* elements integrate with preference for 5'-end of the genes. The integration does not seem to have base-specificity, rather some structural properties of DNA are the basis of choice for insertion. The 8-bp target site duplication created by the *P* insertion is situated within a 14-bp palindromic sequence. Also, transposition in the germline is much more frequent than in the somatic cells. The suppression of transposition of the *P* chromosomes may only partially be relieved in the strains designated as *M'*. These transposable elements induce a variety of genetic events, including

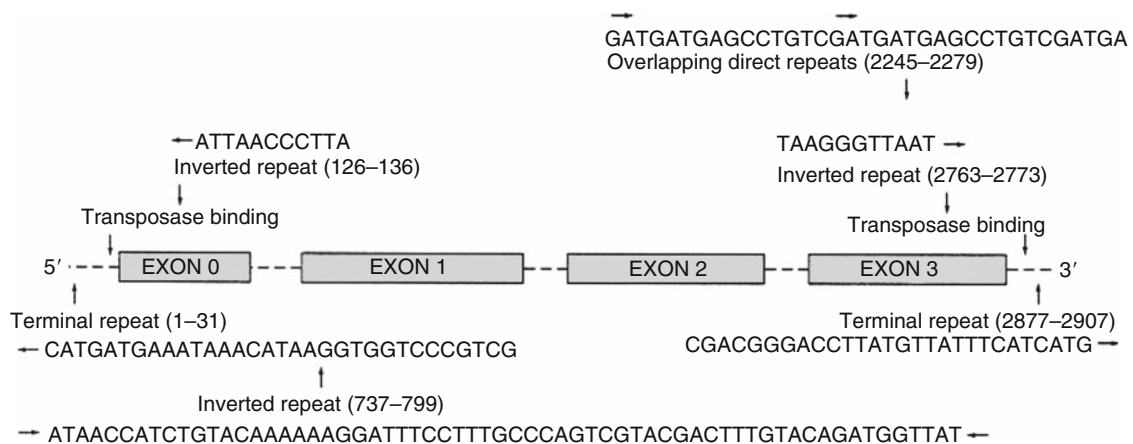


Figure H80. The structure of a complete *P* element of *Drosophila* (2,907) flanked in the genomic DNA target site by 8 bp direct repeats. The numbers in parenthesis indicate the nucleotide positions (beginning with the 5' end). The horizontal arrows indicate the direction of the repeats; the vertical arrows point toward the positions in the linear sequence of the *P* element. (After Engels WR 1989. *Mobile DNA*, Berg DE & Howe MM, eds., pp. 437–484. American Society of Microbiology, Washington, DC.)

recombination in the male *Drosophila*, mutation, and chromosomal rearrangements. P elements carrying visible markers or the molecularly defined insertions can be used for chromosome mapping (Zhai RG et al 2003 Proc Natl Acad Sci USA 100:10860). The *P-M* system slightly boosts the effect of other mutagens. The frequency of X-chromosomal rearrangements was estimated to be 10% per generation and the second breakpoint tends to stay within the same chromosome. The active transposable elements also cause segregation distortion because the transmission of the *P* chromosomes is reduced compared to the *M* chromosomes. The transposons are also associated with gonadal abnormality and (GD) sterility at temperatures particularly above 27° C. The cytological sites and cis-effects too may affect the activity of the *P* elements. Various mutations induced by *P* are subject to suppressors. This transposon, similar to others, can be used for gene tagging and isolation, particularly its special constructs carrying selectable markers such as neomycin resistance so they can be screened efficiently (smart ammunition). The element *pogo* (about 2.2-kb) is somewhat similar to *P*, and it has either 23-bp inverted terminal repeats and no target site duplication, or a 21-bp inverted terminal repeat flanked by duplication of TA. The transposable element *hobo* (variable up to 3-kb) with up to 50 copies and 8-bp targets site duplication. Some (H) *hobo* elements are located in euchromatic regions and others are empty (E) sites. Reciprocal crosses do not activate *Hobo* but its presence is associated with high degree of instabilities. “*HB*” is a small (1.6-kb) element with 20 copies and 8-bp target site duplication. *HB* contains one reading frame of 444 bp that shares 25% homology with the amino acids of the *Tc* element of *Caenorhabditis elegans*.

The other best-studied transposable system of *Drosophila* causing hybrid dysgenesis is the *I-R* system. The complete *I* element is 5.4-kb (5–15 copies/genome scattered among the chromosomes) and has many features of a retrotransposon (its transposition is via an RNA intermediate), but it does not have long terminal repeats. Thus, it is structurally quite different from *P*, yet some of its functions warrant its description. The counterpart of the *M* cytotype of the *P-M* system is the *R* (responsive) cytotype. Hybrid dysgenesis is observed in the crosses of *R* females with *I* males. These sterile/semisterile females are called SF (stérilité femelle) whereas the reciprocal non-dysgenic ones are RSF. The female sterility of *I-R* does not involve gonadal anomalies (in contrast to GD in *P-M*) but hatching of the eggs is reduced. Eventually, the *R* strains may be converted to *I* by “chromosome contamination”, i.e., accumulation of chromosomes derived from an *I* strain by crossing and segregation. *I* factor activity

involves mutations (recessive and dominant) that are frequently clustered, indicating their occurrence shortly before or at meiosis. The frequency of mutation varies at different loci and does not follow the same pattern as with *P*. The molecular structure of the complete *I* element of 5,371 bp is known. It does not have terminal repeats, however, four TAA reiterations are near the 3'-end of one strand and in the genomic DNA there are 12-bp duplications at the target site. One of the strands of *I* has open reading frames (ORF) I (1,278-bp) and II (3,258-bp), separated by 471 bases. There is probably another ORF of 228-bp. The base sequences in ORF II are similar to viral and virus-like transposases and reverse transcriptases. There are apparent coding sequences at the COOH-end for RNase H (ribonuclease digesting RNA in RNA-DNA hybrid molecules as required in reverse transcription). Elements similar to *I* have been detected in the mammalian *L1*, *Drosophila* non-viral retrotransposable elements (*F* family), *R2* ribosomal insertions in silk worm, *Cin4* element in maize, and in the *ingi* elements of *Trypanosoma brucei*. Near the 3' end of ORF II and the longest ORFs of *L1* and *Cin4* code the amino acid sequence: Cys-Pro-Phe-Cys-Gln-Gly-Asp-Ile-Ser-Leu-Asn-His-Ile-Phe-Asn-Ser-Cys that resembles the metal-binding domain of general transcription factor TFIID. ORF I has a sequence with some homology to the DNA-binding viral *gag* polypeptides (group-specific antigen). The *I* elements are most common near the centromeric regions. Mutations induced by *I* are stable and do not revert (unlike to *P*). Many of the *I* elements are truncated and show internal deletions and rearrangement. The *R* factor is quite complex, and it is determined by both nuclear and cytoplasmic regulatory components. Its role is to release the *I* elements' expression. The *FB* family of transposable elements is complex ca. 6.5-kb, or smaller size transposons cause a variety of genetic effects. They seem widespread in *Drosophila* but are present in small copy number. They cause chromosomal rearrangement in 1/1,000 chromosomes. ▶transposable elements, ▶retroposons, ▶copia, ▶HEI; Engels WR 1996 Curr Top Microbiol Immunol 204:103; Simmons MJ et al 2002 Proc Natl Acad Sci USA 99:9306; Rio DC 2002 In Craig NL et al eds Mobile DNA II. Am. Soc. Microbiol. Press, Washington, DC, USA, p 484.

Hybrid Element Insertion: In meiotic recombination induced by a P element of *Drosophila* at the site of recombination, a hybrid P element is retained, most commonly with either a deletion or a duplication. The 5' and the 3' ends two elements join into a single transposon to form a hybrid element and may jointly transpose to other positions. Recombination then

generates deletions. Subsequent recombination events contribute to additional variability. ▶ [insertion elements](#), ▶ [hybrid dysgenesis](#); Gray YH et al 1996 Genetics 144:1601.

Hybrid Histocompatibility Phenomenon: ▶ [allogeneic inhibition](#)

Hybrid Hybridoma (quadroma): Fusion of two different hybridomas. ▶ [hybridoma](#), ▶ [heterohybridoma](#); Withoff S et al 2001 Br J Cancer 84:1115.

Hybrid Inviability: A post-mating or zygotic mechanism of sexual isolation. The hybrids die either before sexual maturity or the offspring is sterile. In a case of *Drosophila* species, hybrid inviability is based on epistatic interactions of the products of genes involved in the control of the nuclear pore complex (Presgraves DC et al 2003 Nature [Lond] 423:715). ▶ [hybrid lethality](#), ▶ [hybrid sterility](#), ▶ [zygotic lethal](#), ▶ [speciation](#), ▶ [Haldane's rule](#), ▶ [embryo culture](#); Burke JM, Arnold ML 2001 Annu Rev Genet 35:31.

Hybrid Lethality: The parental forms are normal yet hybrid embryos are aborted; this phenomenon is not uncommon when different species (with different chromosome numbers) are crossed. Functionally diverged genes in the parental species can be a contributing factor of lethality in the hybrids (Brideau NJ et al 2006 Science 314:1292). ▶ [hybrid inviability](#), ▶ [hybrid sterility](#), ▶ [zygotic lethal](#), ▶ [Haldane's rule](#)

Hybrid Nucleic Acid: Double-stranded structure from two strands of different origin. ▶ [DNA](#), ▶ [DNA hybridization](#), ▶ [heteroduplex](#)

Hybrid PCR Products: Hybrid PCR products can occur when the amplified sample is heterozygous or when related sequences are amplified with the same primer. ▶ [PCR](#)

Hybrid Released Translation (HRT): In HRT, cloned DNA is attached to a membrane filter and annealed with mRNAs. Then after melting the hybridized mRNA is eluted and then translated in an in vitro system (wheat germ or rabbit reticulocytes). The labeled polypeptides are then analyzed by electrophoresis. ▶ [hybrid arrested translation](#); Conlan RS et al 1995 Plant Mol Biol 28(3):369.

Hybrid Resistance: ▶ [allogeneic inhibition](#)

Hybrid Specific Amplification (HAS): A procedure for the isolation of common fractions of two DNA samples, avoiding the repeated sequence background. The principle of the procedure is basically the same as that of subtractive suppression hybridization. ▶ [subtractive suppression hybridization](#); Lecerf F et al 2001 Nucleic Acids Res 29:e87.

Hybrid Sterility: In hybrid sterility, the hybrid gonads or gametes are abnormal and incapable of normal sexual union. Usually, this phenomenon is based on malfunction of numerous genes. More commonly, the sterility affects the males or the male gametes and the females may be successfully backcrossed with normal males. ▶ [hybrid dysgenesis](#), ▶ [hybrid inviability](#), ▶ [hybrid lethality](#), ▶ [sterility](#), ▶ [zygotic lethal](#), ▶ [male sterility](#), ▶ [Haldane's rule](#); Orr HA, Turelli M 2001 Evolution Int J Org Evolution 55:1085; Barbash DA, Ashburner M 2003 Genetics 163:217.

Hybrid Swarms: Hybrid swarms arise when the habitats of two related species are adjacent and mass outcrossing takes place. In such cases, the parental and the hybrid forms may not be easily recognized in the zone.

Hybrid Vigor: The superior performance (growth, fitness) of hybrids has been observed for centuries before the birth of modern genetics. In its simplest case, hybrid vigor may be attributed to the presence of *complementary dominant* genes. If one parent is *AAbb* and the other is *aaBB*, their offspring is *AaBb*, which has now the favorable dominant alleles at both loci (*dominance theory of hybrid vigor*). Geneticists measure vigor by reproductive advantage, fitness. The fitness of a homozygous recessive (R) class may be $w_{aa} = 1 - s$, where s is the coefficient of selection. The frequency of the homozygous recessives in a population may be determined by the rate of mutation (μ) from allele *A* to allele *a*. The average proportion of the recessive class is expected to be: $\hat{p}^2 = \mu/s$ and the average frequency of recessive alleles is expected to be $\hat{q} = \sqrt{\mu/s}$. The average fitness of the population then becomes $\hat{w} = 1 - s\hat{q} = 1 - s\sqrt{\mu/s} = 1 - \sqrt{s^2\mu/s} = 1 - \sqrt{s\mu}$.

If each of the n alleles contributes equally to the performance of the individual (additive effect), the average reduction of fitness caused by homozygosity of the recessive alleles in the populations is $n\sqrt{s\mu}$. For example, assuming that an organism has 10,000 gene loci and an average mutation rate of 10^{-5} , the selection coefficient against the recessive alleles is 0.01. After substitution we obtain $n\sqrt{s\mu} = 10,000 \sqrt{0.01 \times 0.00001} \cong 3.16$. This indicates that inbreeding may reduce fitness of the population by a factor of about three compared to the situation when each locus has at least one dominant allele at all loci of a diploid organism.

On the average, this hypothetical example is in agreement with experimental observations on inbred and hybrid populations and lends support to the dominance theory of hybrid vigor (heterosis). If the mid-parent value, $m = 0.5(P_1 + P_2)$ and $0.5(P_1 - P_2) = d$ and $h = F_1 - m$, it is possible to predict—in case of

perfect additivity of all genes and the F_1 displays hybrid vigor—the best performance to be expected by accumulating all the favorable alleles in the inbreds. $P_{\text{mx}} = m + \frac{h}{\sqrt{H/D}}$ where H are the heterozygotes and D = the homozygous dominants.

Increased vigor of hybrids may be caused also by *overdominance* (superdominance), i.e., the heterozygote Aa surpasses both AA and aa . Let us assume that the selection coefficient of each of the two classes of homozygotes (AA and aa) is -0.05 . In such a case, the three genotypic classes (according to the Hardy-Weinberg theorem) would occur in one generation of reproduction: AA (95): Aa (200): aa (95). If the population is mating at random, the allelic frequencies are equal (0.5) and the fitness of both types of homozygotes is also equal. Since the size of the population (the three classes combined) is 390 rather than 400 as expected without selection, the proportion of the surviving zygotes is $390/400 = 0.975$, indicating 2.5% (10/400) reduction by a single cycle of reproduction. This reduction may not be significant for the majority of species that produce more offspring than the population that the habitat can maintain. The reduction in size may become, however, quite serious if overdominance occurs at not only one but also at several or many loci (see Table H5). The table indicates that for most populations even a 0.5% disadvantage of the homozygotes at larger number of loci may have very serious adverse consequences and would be hardly acceptable in herds of domesticated animals or in crop plants. The contribution of overdominance at single loci may be large enough to be of selective advantage in feral conditions or improve the performance of agricultural species. ▶inbreeding, ▶selection coefficient, ▶superdominance, ▶overdominance; Barton NH 2001 Mol Ecol 10:551.

Hybrid Zone: At the geographical boundary of two races natural hybrids occur and as a result speciation may ensue. ▶speciation; Perry WL et al 2001 Evolution 55:1153.

Table H5. Reduction in population size at three different percentages of disadvantages of the homozygotes

| Number of overdominant loci | 5% | 1% | 0.5% |
|-----------------------------|------------------------|---------|---------|
| 10 | 0.77633 | 0.95111 | 0.97528 |
| 100 | 0.07952 | 0.60577 | 0.77856 |
| 1000 | 1.01×10^{-11} | 0.00665 | 0.08183 |

Hybridization: Crossing (mating) of genetically different individuals. Also, annealing DNA single strands with RNA or a single-stranded DNA of different origin (probe). The two nucleic acid strands must bear some homology to anneal. ▶Mendelian laws, ▶ c_0t curve, ▶Southern hybridization, ▶Northern hybridization, ▶Western hybridization, ▶South-Western method, ▶in situ hybridization, ▶dot blot

Hybridization Arrest: Antisense oligonucleotides selectively interfere with the function of a particular part of the genetic material by virtue of Watson—Crick or Hoogsteen base pairing. ▶antisense technologies, ▶Watson and Crick model, ▶Hoogsteen pairing

Hybridization Probe: A radioactively or by fluorochrome (e.g., biotin) labeled nucleotide sequence that hybridizes with the complementary nucleotide sequences and identifies the homologous tract(s), either on an extracted DNA or in situ in a chromosome. ▶probe, ▶radioactive label, ▶biotinylation

Hybridogenetic: A species hybrid containing, say, the A and B genomes and that normally mates with one of the parental species (say B), but its gametes transmit only one of its genomes (say A), thus the A genome is reproduced clonally while the B genome is added newly by each mating. ▶hemiclonal, Marescalchi O, Scali V 2001 Mol Reprod Dev 60(2):270.

Hybridoma: A myeloma (cancer) cell fused with a spleen B lymphocyte, producing monoclonal (identical by origin) antibodies. The cancer cell assures rapid proliferation and indefinite growth, while the other component determines the specificity. Hybridomas have many applications in basic research and are very useful for the production of monoclonal antibodies and for the generation of lymphokines. An alternative to hybridomas—which may be unstable—may be splenocytes derived from mice transgenic for temperature-sensitive SV40 large tumor antigens, driven by a mouse major histocompatibility promoter. Such a system produces monoclonal antibodies under permissive conditions (Pasqualini R, Arap W 2004 Proc Natl Acad Sci USA 101:257). ▶senescence, ▶immortalization, ▶monoclonal antibody, ▶lymphokines, ▶magic bullet, ▶lymphocytes, ▶heterohybridoma, ▶hybrid hybridoma; Springer TA ed 1985 Hybridoma Technology in the Biosciences and Medicine, Plenum, New York; European database: http://www.cabri.org/CABRI/srs-doc/ecacc_hybrid.info.html.

Hybridoma Growth Factor (HGF): ▶interferon β -2

Hydatidiform Mole (19q13.3-q13.4, 6q24): A human hyperplasia resulting from an abnormal fertilization when the epithelial layer of the ovum is induced to proliferate into a tuft of cysts resembling a bunch of

grapes. No embryo is formed. The karyotype of such a structure is 46 (XX) and all the chromosomes are derived from a diploidized sperm of 23 (X) constitution. In the familial biparental hydatidiform mole (gene NALP7, 19q13.4), the maternal complement lacks the imprinting factor but otherwise resembles the androgenetic form of the disease. In several families exon 3, exon 5, or exon 7 splice junction base substitution mutations were found. NALP7 is a maternal effect negative regulator of IL-1 β and it is involved in inflammatory responses, apoptosis, spontaneous abortion, and stillbirth (Murdoch S et al 2006 Nature Genet 38:300). ►[androgenesis](#), ►[demethylation](#), ►[imprinting](#), ►[mole](#), ►[Muckle-Wells syndrome](#); <http://orca.gen.kyushu-u.ac.jp>.

Hydra: An about 25–30 mm freshwater animal of about 100,000 cells. The freshwater hydra (*Hydra vulgaris attenuata*) (see Fig. H81) is $2n = 32$. It propagates mainly by budding; clonal offspring are produced every 1.5 to 2 days. Sexual reproduction plays a minor role; the production of a few eggs—predominantly by hermaphroditic means—takes a few weeks. It produces a variety of cell types (including a nerve system) and a differentiated body under the control of morphogens similar to those in more complex animals. Some hydras are green because of symbiosis with algae and thus in the past were mistaken as plants. They have excellent abilities for regeneration. The image shows the green fluorescent protein-labeled endodermal epithelial stem cells in transgenic *Hydra*. The procedure used permits the tracking of stem cells during morphogenesis. The photograph is the courtesy of Professor CG Bosch. ►[regeneration](#); Lohmann JU, Bosch TC 2000 Genes Dev 14:2771; Wittlieb J et al 2006 Proc Natl Acad Sci USA 103:6208; <http://www.ucihs.uci.edu/biochem/steele/default.html>; www.hydrabase.org.



Figure H81. *Hydra vulgaris*

Hydrocarbons: Organic compounds containing only hydrogen and carbon; can be aliphatic (alkanes

[paraffin], alkenes, alkynes, cyclic aliphatic) or aromatic. Although some of them are chemically rather inert (paraffin), the complex polynuclear hydrocarbons (benzo-a-pyrene, benzantracenes, methylcholantrenes) are highly toxic, carcinogenic, and mutagenic. They are present in combustion products. ►[environmental mutagens](#), ►[cigarette smoke](#)

Hydrocephalus (Xq28): A disease of cerebrospinal fluid accumulation in the brain as a result of defect in its secretion and absorption. It can be the symptom of physiological or mechanical lesions and may be due to several autosomal recessive (Dandy-Walker syndrome) occlusions of the openings of the fourth ventricle of the brain, the symptoms of Albers-Schönberg osteopetrosis [extreme bone density and bone proliferation]). Autosomal dominant (achondroplasia, osteogenesis imperfecta congenital Type II, defects in bone formation), X-linked recessive (narrowing of a brain fluid channel following inflammation or bleeding), and X-linked dominant (orofacial-digital syndrome I, involving oral, digital and mental abnormalities) genetic causes are involved. Its prevalence is 0.01 to 1×10^{-3} births. It may be entirely sporadic, or the recurrence risk when it is hereditary may vary from 15 to 50% within families, depending on the type of inheritance involved. Prenatal diagnosis may be feasible using ultrasound detection or brain tomography or magnetic resonance imaging. ►[prenatal diagnosis](#), ►[mental retardation](#), ►[Walker-Wagner syndrome](#), ►[Arnold-Chiari malformation](#), ►[orofacial-digital syndrome](#), ►[Dandy-Walker syndrome](#), ►[osteopetrosis](#), ►[sonography](#), ►[anencephaly](#)

Hydrocortisone: A glucocorticoid hormone, an anti-inflammatory drug. It can be biosynthesized in yeast with the cooperation of eight mammalian proteins. ►[cortisone](#); Szczebara FM et al 2003 Nature Biotechnol 21:143.

Hydrogel: Synthetic extracellular matrix for in situ genetic engineering. It may assist tissue morphogenesis and tissue remodeling and regeneration by cell adhesion, growth factors, and cell-associated proteases. (Pratt AB et al 2004 Biotechnol Bioeng 86:27).

Hydrogen Bond: A weak bond between one electronegative atom and a hydrogen atom that is covalently linked to another electronegative atom C or N. Hydrogen bonds tie together the polynucleotide chains of a DNA double helix ($A = T$ and $G \equiv C$), and also affect conformation of proteins. ►[hydrogen pairing](#), ►[base analogs](#), ►[Watson and Crick model](#), ►[protein structure](#); Pauling L 1960 The Nature of the Chemical Bond, Cornell Univ. Press, Ithaca, NY; Luscombe NM et al 2001 Nucleic Acids Res 29:2860.

Hydrogen Hypothesis: ►endosymbiont theory

Hydrogen Pairing: Hydrogen pairing secures the double-stranded form of DNA or RNA by establishing hydrogen bonds between the O atom attached to the C atom at position 4 (or position 6, depending upon whether the American or the Beilstein numbering system is used for the pyrimidine ring) of thymine (uracil) and the NH₂ group at the C of position 6 in

adenine. The second hydrogen bond is formed between the hydrogen attached to the N at position 3 (or according to the Beilstein system 1) of the pyrimidine ring of thymine. Cytosine pairs with three hydrogen bonds with guanine between positions 4-6, 3-1 and 2-2 as shown in the figure (see Fig. H82). Cytosine and adenine cannot form hydrogen bonds, unless a tautomeric shift occurs. Similarly, the pairing of thymine (or analogs) with guanine requires another

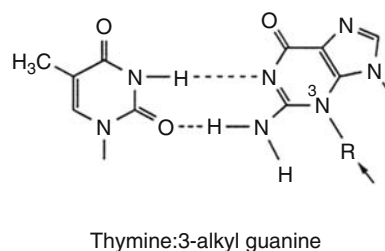
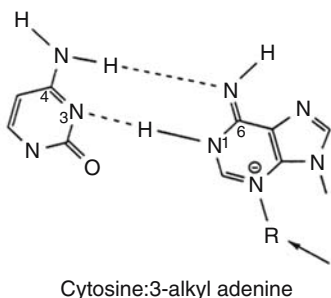
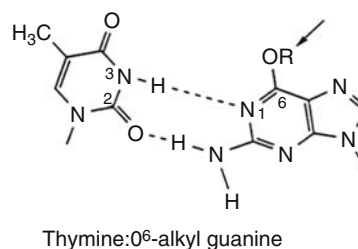
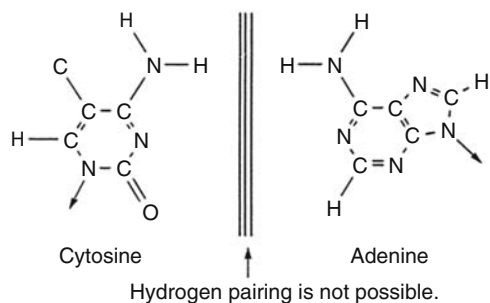
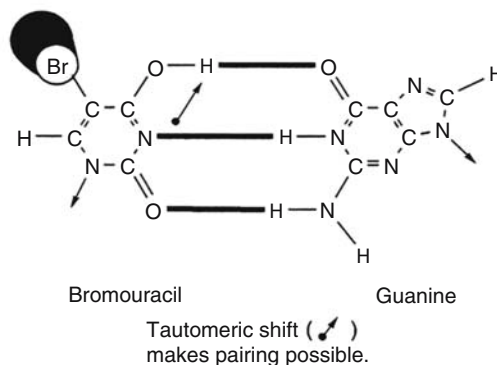
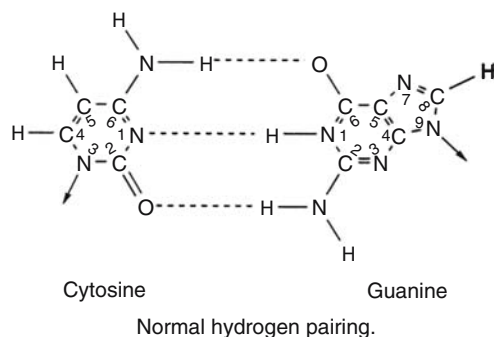
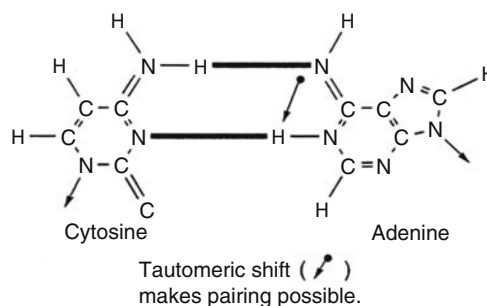
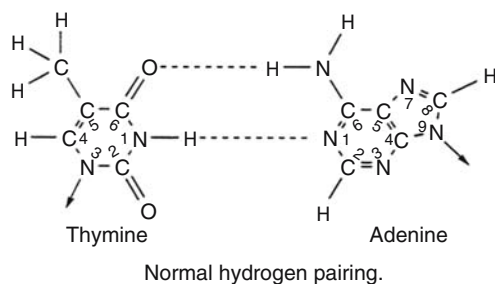


Figure H82. Keto–enol transformations. Hydrogen bonding between DNA bases. Normal bonds are dashed lines. After tautomeric shift, the hydrogen bonds are formed as represented by the heavy lines.

tautomeric shift. The tautomeric shift is an isomerization of the bases, changing the position of a hydrogen atom from position 3N to position O⁴ on the thymidine molecule, or moving one hydrogen from N⁶ position to 1N position in adenine. As the formula shows, the bases may undergo keto–enol transformations. Although hydrogen bonding assures the great specificity of DNA replication the deoxythymine and the deoxyadenine analogs difluorotoluene deoxynucleoside and 9-(*aza*-4-methyl-benzylimidazolyl)-1'-β-2'-deoxyribose, which are very similar in shape to the normal nucleosides are incapable of hydrogen pairing. Nevertheless these analogs are capable of directing the *in vivo* incorporation of thymine and adenine, respectively with high fidelity (Delaney JC et al 2003 Proc Natl Acad USA 100:4469). This fact indicates that the base shape alone may be sufficient to determine the fidelity during the transfer of the genetic information. ▶DNA, ▶base substitution, ▶point mutation, ▶base analogs, ▶tautomeric shift, ▶imino transformation, ▶steric-exclusion model, ▶metallo-base pairing; see Fig. H83; Kool ET 2001 Annu Rev Biophys Biomol Struct 30:1; chemically redesigned bonds: Brenner SA 2004 Science 306:625.

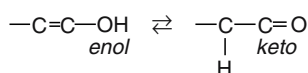


Figure H83. Enol keto interconversion

Hydrogen Peroxide (H₂O₂): H₂O₂ may act as an intracellular messenger in both plant and animal tissues. In plants, salicylic acid inactivates catalase and that may be a factor in the activation of plant defense mechanisms against pathogens. In animal tissues, it may be involved in the activation of NF-κB transcription factor, the regulation of the immune reaction, and immunosuppression. H₂O₂ may initiate apoptosis. When cells are stimulated by cytokines, phorbol esters and growth factors, H₂O₂ may be released into the extracellular space. ▶NF-κB, ▶host-pathogen relationship, ▶immunosuppression, ▶glucocorticoids, ▶granulomatous disease, ▶super-oxide dismutase, ▶ROS, ▶OH[•]

Hydrogen Pump: ▶proton pump

Hydrogenosomes: Mitochondria-like organelles in *Trichomonads* that seem to be evolutionarily precursors of mitochondria (Boxma, B. et al. Nature [Lond] 434:74). They are surrounded by double membrane and produce ATP from pyruvate and hydrogen or other molecules, but have no DNA. In the ciliate *Nyctotherus ovalis*, living in the intestinal tract of

cockroaches, hydrogenosomes were found that contain a minimal DNA genome, but the hydrogenase gene of the ciliate resides in the nucleus and the protein encoded by it is imported into this organelle. In the hydrogenosome of the parasite, *Trichomonas vaginalis*, DNA could not be found (Clemens DL, Johnson PJ 2000 Mol Biochem Parasitol 106:307). ▶mitochondria, ▶mitochondria cryptic, ▶mitosome, ▶endosymbiont theory; Dyall SD, Johnson PJ 2000 Curr Opin Microbiol 3(4):404; Sutak R et al 2004 Proc Natl Acad Sci USA 101:10368.

Hydrolases: Enzymes carrying out hydrolysis reactions. ▶hydrolysis

Hydrolethalus Syndrome: Recessive 11q23-q25 hydrocephalus, polydactyly, and other developmental defects, which have a prevalence ~2 ↔ 10⁻⁴ in Finland.

Hydrolysis: Splitting a molecule by inserting a molecule of water; one of the parts of the former will obtain OH, and the other H, from the H₂O.

Hydropathy Index: The hydropathy index indicates the relative hydrophilic and hydrophobic properties of chemicals.

Hydropathy Plot: The hydropathy plot is used to determine the hydrophobic amino acid tracts in (membrane) proteins on the basis of the energy requirement for transfer into water from a nonpolar solvent. ▶membrane proteins; Jayasinghe S et al 2001 J Mol Biol 312:927.

Hydrophilic: A hydrophilic substance is readily miscible with water; it has polar groups.

Hydrophobic: A hydrophobic substance is insoluble in water, or poorly (if at all) soluble in water; it lacks polar groups. Also, the (unjustified) fear of (drinking) water, such as occurs in the viral disease *rabies*, is called hydrophobia.

Hydrophobic Vacuum Cleaner: The mechanism of action of multidrug resistance transporters. ▶multiple drug resistance; Sharom FJ et al 2001 Semin Cell Dev Biol 12(3):257.

Hydrophobin: A hydrophobic membrane material on the surface of aerial hyphae and on dikaryons of fungi. ▶hypha, ▶dikaryon; Wosten HA 2001 Annu Rev Microbiol 55:625.

Hydroponic Culture: Growing plants in salt solutions, rather than in soil, under semi-axenic conditions. (See Hill WA et al 1992 Adv Space Res 12(5):125).

Hydrops: An edema (accumulation of fluids) may occur in kidney diseases or in erythroblastosis fetalis and in many other diseases. ▶erythroblastosis fetalis

Hydrops-Ectopic

Motheaten Skeletal Dysplasia (HEM, Greenberg dysplasia, 1q42.1): A short-limbed dwarfism with ectopic and unusual ossifications. Cholesterol synthetic enzyme or lamin B receptor defects may be involved. ▶ [laminopathies](#), ▶ [cholesterol](#); Chitayat D et al 1993 Am J Med Genet 47:2723.

Calcification–

Hydrops Fetalis: Prenatal anemia accompanied by fluid accumulation in the fetal body, caused by failure to synthesize the α chain of hemoglobin (an extreme form of thalassemia major), or by destruction of hemoglobin in other hemolytic anemias (rh). The idiopathic form is of spontaneous origin and others are caused by certain immunological conditions. ▶ [thalassemia](#), ▶ [hemoglobin](#), ▶ [Rh](#), ▶ [erythroblastosis fetalis](#), ▶ [adrenomedullin](#)

Hydroxyapatite: Calcium phosphate hydroxide (may contain also silica gel). The phosphate residues of nucleic acids bind to calcium and thus double-stranded DNA binds to it more strongly than it does to single-stranded molecules. On this basis, by adsorption chromatography, the two types of DNA can be separated from each other and DNA-RNA hybrids can be separated from RNA. The single-stranded molecules come off the columns by low molarity buffer, and at higher molarity the double-stranded molecules can be eluted. Hydroxyapatite also participates in calcification of the extracellular matrix and in bone formation. Calcification of the arteries may lead to aortic failure and death.

Hydroxyguanine: One of the products of oxidative damage to the DNA that is generally repaired by base excision. ▶ [DNA repair](#); Tuo J et al 2001 J Biol Chem 276:45772.

Hydroxyl Radical ($-\text{OH}^\cdot$): The hydroxyl radical is widespread in biological molecules; it can be formed from hydrogen peroxide in the presence of transition metals and may cause damage to macromolecules. A relational database, ORChID (OH Radical Cleavage Intensity Database), contains extensive hydroxyl radical cleavage data produced from two DNA libraries (Greenbaum JA et al 2007 Genome Res 17:947). ▶ [hydrogen peroxide](#), ▶ [transition state](#), ▶ [ROS](#), ▶ [SOD](#)

Hydroxylamine (NH_2OH): An antagonist of pyridoxal-phosphate (PLP)-requiring enzymes, cleaves Asp-Gly linkages at high pH, blocks oxidation of H_2O , but permits electron transfer through photosystems I and II from artificial donors. Its poisonous effect (α effect) may be based also on its high nucleophilic reactivity. For genetics, it is important that hydroxylamine react with carbonyl groups ($\text{C}=\text{O}$) of pyrimidines, target specifically cytosine residues in nucleic acids,

generate hydroxylaminocytosine (a thymine analog), and cause the transition of a $\text{G} \equiv \text{C}$ base pair into a $\text{T} = \text{A}$ pair, resulting in base-specific mutations. It is however, a weak mutagen, effective in prokaryotes, but without much effect in higher eukaryotes. ▶ [transition mutation](#), ▶ [base analog](#), ▶ [base substitution](#), ▶ [hydrogen pairing](#); Freese E 1971 In: Hollaender A (ed) Chemical Mutagens, Plenum, New York, p 1.

21-Hydroxylase Deficiency: ▶ [adrenal hyperplasia](#)

5-Hydroxymethyl Cytosine: The most common form of cytosine in T-even phage DNA. ▶ [DNA methylation](#), ▶ [5-azacytidine](#), ▶ [DNA base composition](#)

3-Hydroxy-3-Methylglutaryl CoA Lyase Deficiency: Leucine is degraded in six enzymatic steps into acetoacetic acid and in the process acetyl-CoA is generated. The last enzyme in this path is 3-hydroxy-3-methylglutaryl CoA lyase. Deficiency of this enzyme causes acidosis (accumulation of acids) and reduction of sugar in the blood (hypoglycemia). This potentially fatal disease is controlled by autosomal recessive mutation. ▶ [isoleucine-valine metabolic pathway](#), ▶ [isovalericacidemia](#), ▶ [methylcrotonylglycinemia](#), ▶ [methylglutaconicaciduria](#), ▶ [amino acid metabolism](#)

Hydroxytryptamine: ▶ [serotonin](#)

Hydroxyurea (NH_2CONHOH): An inhibitor of ribonucleoside reductases; thereby it prevents the formation of deoxyribonucleotides from ribonucleotides. Consequently, it blocks DNA synthesis in the S-phase of the cell cycle and thus, is also an antineoplastic agent and a strong poison. ▶ [neoplasia](#), ▶ [S phase](#), ▶ [DM \[doubleminute\] chromosome](#)

Hyena: *Crocuta crocuta*, $2n = 40$; *Hyena brunnea*, $2n = 40$. ▶ [behavior genetics](#)

Hygromycin B (Hyg, {5-deoxy-5-[[3-[4-[(6-deoxy- β -D-arabino-hexofuranos-5-ulos-1-yl)oxy]-3-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-1-2-O-methylene-D-neoinositol}): An antibiotic, commonly used for screening transformed plant and animal cells by the expression of hygromycin phosphotransferase gene (*hph*) as a selectable marker (confering resistance). Hyg inhibits ribosomal ATPase. It is also an antihelminthic drug. ▶ [antibiotics](#); Ganoza MC, Kiel MC 2001 Antimicrob Agents Chemother 45:2813.

Hylandra suecica (formerly *Arabidopsis suecica*): a putative amphidiploid ($2n = 26$) of *Arabidopsis thaliana* ($2n = 10$) and *Cardaminopsis arenosa* ($2n = 32$). The photograph (see Fig. H84) is of laboratory specimens of *Cardaminopsis* ($2n = 32$) and *Arabidopsis* ($2n = 20$) and the hybrid is an amphidiploid ($2n = 16 + 10$); (Rédei, unpublished). (See Löve Å 1961 Svensk Bot Tidskr 55:211).

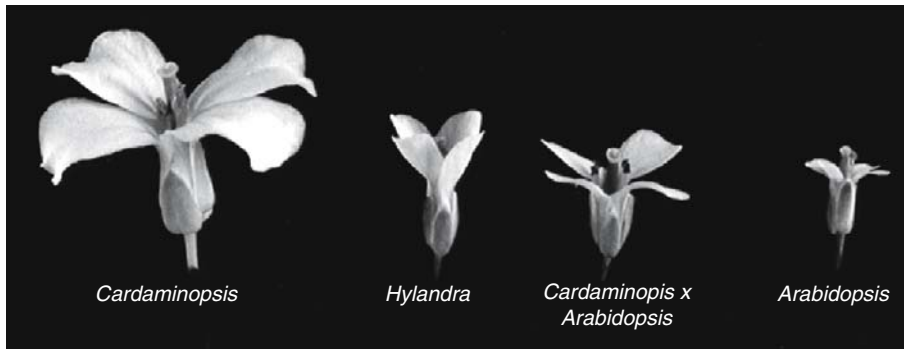


Figure H84. Hylandra is a putative hybrid of *Cardaminopsis* and *Arabidopsis*

Hymenium: A fruitingbody-forming tissue in fungi.

Hyoscyamine: An anticholinergic alkaloid that blocks neurotransmission through the parasympathetic system (originating in the brain and controlling the heart, head, neck, chest, abdomen, and pelvic organs). It is an alkaloid of the solanaceous species of plants *Hyoscyamus*, *Datura*, and *Atropa*. ▶alkaloids

Hyoscyamus: ▶henbane

Hyperactivity: ▶attention deficit-hyperactivity

Hyperacute Reaction (HAR): In the hyperacute reaction, in xenotransplantation of organs to immunologically competent human tissues, the circulating natural antibodies immediately recognize the Gal α 1-3Gal antigens on the endothelial lining of the graft vascular tissues and this activates the recipient's complement. As a result, the transplant is destroyed within minutes to hours. ▶xenotransplantation, ▶xenograft, ▶complement, ▶antibody, ▶grafting in medicine; Dawson JR et al 2001 Immunol Res 22 (2–3):165.

Hyperammonemia: ▶carbamoylphosphate synthetase deficiency, ▶ornithine transcarbamylase deficiency, ▶ornithine aminotransferase deficiency, ▶urea cycle, ▶glutamate dehydrogenase, ▶acetylglutamate synthetase deficiency

Hyperargininemia: ▶argininemia

Hyperbetalipoproteinemia: ▶hyperlipoproteinemia

Hyperbilirubinemia: Excessive amounts of bilirubin in the blood causing jaundice, common symptom of several diseases involving destruction of red blood cells. It may be involved in indirect epistasis. ▶Dubin-Johnson syndrome, ▶Criggler-Najjar syndrome, ▶Gilbert syndrome, ▶bilirubin, ▶epistasis

Hyperbranched Strand Displacement Amplification: By hyperbranching, hundreds of DNA copies are generated within a few hours. The procedure permits

identification of gene losses or dosage imbalance in tumor cell lines. Comparative genomic hybridization is applicable to the samples. ▶comparative genomic hybridization; Lage JM et al 2003 Genome Res 13:294.

Hypercalciuric Hypercalcemia: There are two forms of hypercalciuric hypercalcemia: the homozygous dominant primary severe neonatal, the hyperparathyroidism (NSHPT) at chromosome 3q13.3-q21, and the heterozygous (recessive) hypocalciuric hypercalcemia (HHC1) at the same 3q13.3-q21 chromosomal location. The basic defect is attributed to G-protein receptors and the connected Ca²⁺ sensors that are involved in parathyroid hormone release from the cell. ▶hypercalcemia-hypercalciuria, ▶G-proteins, ▶parathormone

Hyperchimerization: Hyperchimerization indicates the production of humanized antibodies by transfer of the CDR. ▶humanized antibody, ▶CDR, ▶civilization

Hypercholanemia, Familial: Familial hypercholanemia involves elevated serum bile acid level, fat malabsorption, and itching. The basic defect is in the tight junction protein-2 (TJP2, 9q12-q13) that binds the cytoplasmic C termini of the proteins to the cytoskeletal actin. Defects in glycine *N*-choloyltransferase (BAAT, 9q22.3) also disrupt bile acid transport and circulation. Thus, a complex inheritance is displayed. (Carlton VEH et al 2003 Nature Genet 34:91).

Hypercholesterolemia: ▶familial hypercholesterolemia

Hyperchromicity: As per hyperchromicity, single-stranded nucleic acids have increased UV absorption relative to the double-stranded molecules. ▶DNA, ▶DNA denaturation, ▶DNA thermal stability

Hyperferritinemia with Cataracts: An iron storage disease encoded at 19q13.3-q13.4. ▶ferritin

Hypergeometric Distribution: In hypergeometric distribution, when a collection or population is sampled

(selected) without replacement, the probabilities will change, unlike in the binomial or multinomial distributions where the basic probabilities are assumed to remain constant. The distribution can be characterized by the formula shown. Where T = the finite number of elements, k = the exclusive and exhaustive classes of T , N = the number of observations = $n_1 + n_2 + \dots + n_k$, $T = T_1 + T_2 + \dots + T_k$. ▶distributions, ▶Fisher's exact test; McDonald JW et al 1999 Biometrics 55:620.

$$\frac{\begin{bmatrix} T_1 \\ n_1 \end{bmatrix} \begin{bmatrix} T_2 \\ n_2 \end{bmatrix} \dots \begin{bmatrix} T_k \\ n_k \end{bmatrix}}{\begin{bmatrix} T \\ N \end{bmatrix}}$$

H

Hyperglycemia: The increase in blood glucose level.

Hyperglycerolemia: ▶glycerol kinase deficiency

Hyperglycinemia (hyperglycinuria, 13q32): Hyperglycinemia may be the result of a deficiency of propionyl-CoA carboxylase I. It may cause protein intolerance, retarded development, swollen face, lethargy, frequent vomiting, low platelet counts, and other blood diseases. ▶thrombocytopenia, ▶glycinemia ketotic, ▶glycine biosynthesis, ▶iminoglycinuria

Hyperhaploid: Gametes with more than the full basic chromosome number. ▶disomic

Hyperhomocysteinemia (MTHFR, 1p36.3): MTHFR is caused by mutation in the 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme, and homozygotes for the condition have increased levels of homocysteine, an increased risk of cerebrovascular (brain), and peripheral (vein) and coronary heart disease. Mutations in methionine synthase (1p43) may be responsible for both hyperhomocysteinemia and hypermethioninemia (Watkins D et al 2002 Am J Hum Genet 71:143). Homocysteinemia may be caused also by other metabolic defects. ▶homocystinuria, ▶cobalamin, ▶vitamin B12 defects, ▶tetrahydrofolate; Chen Z et al 2001 Hum Mol Genet 10:433.

Hyper-IgE Syndrome (Job syndrome): An immunodeficiency with high IgE, recurrent skin abscesses, and pneumonia, located in the short arm of human chromosome 4.

Hyper-IgM Syndrome: ▶immunodeficiency

Hyper-IgM Syndrome (HIGM, HIM, X-linked immunodeficiency with hyper IgM): HIGM is located to chromosomal position Xq26. Although initially a defect in the B cells was suspected, recent evidence indicates a defect involving a ligand of CD40 in the helper T cells. Other symptoms (neutropenia, inflammations, etc.) have also been described. Usually, the

production of IgG, IgA, and IgE is reduced, but IgM and IgE are not affected. The clinical symptoms are respiratory infections, lymphoid hyperplasia, oral ulcers, autoimmunity, etc. ▶CD40, ▶CD-40 ligand, ▶immunoglobulins, ▶class switching, ▶ectodermal dysplasia; Weller S et al 2001 Proc Natl Acad Sci USA 98:1166.

Hyperimmunoglobulinemia D (HIDS): A human chromosome 12q24 disease with strong resemblance to mevalonic aciduria, periodic fever, rash, diarrhea, swollen lymphnodes (adenopathy), and arthralgia (pain in joints). HIDS seems to be involved with a deficiency of mevalonate kinase. ▶mevalonic aciduria

Hyperinsulinemia: ▶hypoglycemia

Hyperinsulinism: ▶hypoglycemia

Hyperkalemic Paralysis: A group of dominant periodic paralysis diseases induced by high level of potassium caused by human chromosome 17q23-q25 defects. ▶periodic paralysis

Hyperlexia: Precocious reading ability. The posterior superior temporal cortex of the brain is hyperactivated. The same area is hypoactivated in dyslexia. ▶dyslexia

Hyperlipidemia: The autosomal dominant condition has similarities to familial hypercholesterolemia, but in this case hypercholesterolemia is not found in the offspring. Familial combined hyperlipidemia (FCHL) has a prevalence of 0.01 to 0.02, and is responsible for 10–20% of the early onset coronary heart disease. One gene responsible for hyperlipidemia has been located to human chromosome 1q21-q23 in the area of the apolipoprotein A-II locus (APOA2). Generally, very low and low-density lipoproteins accumulate. Early onset is relatively rare and results in hypertriglyceridemia. Its incidence exceeds by five times that of hypercholesterolemia. ▶coronary heart disease, ▶cholesterol, ▶lipid, ▶apolipoprotein, ▶familial hypercholesterolemia, ▶familial triglyceridemia, ▶sterol, ▶HLP, ▶hypertension, ▶CD36; Allayee H et al 1998 Am J Hum Genet 63:577.

Hyperlipoproteinemia: Hyperlipoproteinemia is caused by a dominant gene in human chromosome 19q13.2, coding normally for apolipoprotein E-d, a 299-amino acid polypeptide. A defect in this protein involves the accumulation of chylomicron (a small lipoprotein which normally transports dietary cholesterol and triacylglycerides [triglycerides] from the intestines to the blood stream). As a consequence of the defect, the conditions for coronary heart disease may develop. Several forms of this disease are usually distinguished. Some types (IV) are induced by high carbohydrate diet, alcohol, uremia, glycogen storage

diseases, and steroid contraceptives. Recessive form of the Type I disease is associated with human chromosome 8p22. The latter type involves large amounts of chylomicron accumulation even on normal diet, but disappears on a fat-free diet. It may not lead to early atherosclerosis. Lipoprotein lipase activity is deficient in this recessive form. The lipase gene encodes a 475 amino acid protein, including a 27-residue leader peptide. ▶coronary heart disease, ▶lipoprotein, ▶triacylglyceride, ▶cholesterol, ▶sex hormones, ▶chylomicron, ▶atherosclerosis, ▶lipase, ▶apolipoprotein, ▶abetalipoproteinemia, ▶beta-lipoprotein

Hyperlysinemia (7q31.3): An autosomal recessive phenotype caused by a defect in the enzyme lysine- α -ketoglutarate reductase. This enzyme is a bifunctional complex also of saccharopine dehydrogenase, controlling a step subsequent to α -ketoglutarate reduction in lysine degradation. The complex is also called α -aminoacidipic semialdehyde synthase. The defect in this enzyme causes the accumulation of lysine in the blood, resulting in physical and mental retardation. Hyperlysinemia may also occur if the transport of lysine into the mitochondria fails. Dibasic aminoaciduria also involves excessive urinary excretion of lysine. ▶dibasicaminoaciduria, ▶lysine biosynthesis, ▶amino acid metabolism; Sacksteder KA et al 2000 *Am J Hum Genet* 66:1736.

Hypermethylation: In many types of cancers, dozens of genes (tumor suppressors) are silenced by hypermethylation in the promoter regions within CpG islands. The oncogenes—in contrast—are hypomethylated and thus expressed at a higher rate than in normal cell. ▶methylation of DNA, ▶hypomethylation, ▶tumor suppressor gene, ▶CpG island, ▶oncogene

Hypermorphic Mutant: A hypermorphic mutant over-expresses a particular trait. ▶hypomorphic, ▶gain-of-function mutation

Hypermutation (somatic hypermutation): A common phenomenon in the variable (V) region-coding sequences of immunoglobulin (Ig) genes. If a κ chain promoter is inserted upstream of the constant region (C), it may cause mutational events also in the C and V regions, indicating that transcription may be required for somatic hypermutation. Some other genes (e.g., BCL-6) may also undergo hypermutation if an Ig enhancer is introduced in B cells. The rate of mutation has been estimated to be six orders of magnitude higher than the average somatic rate of mutation in other genes. DNA polymerase ι (iota) seems responsible for somatic hypermutation of immunoglobulins, although the repair DNA polymerases (η , κ and rev1) are also error-prone (Faili A

et al 2002 *Nature (Lond)* 419:944). If the variable κ immunoglobulin gene segment was replaced by heterologous sequences (prokaryotic *neo*, *gpt*, or β -globin), the rate of hypermutations did not decrease. Although many of the hypermutational event appear to be point mutations, a substantial fraction of the mutations involve double-strand breaks in the B cells that have completed the cell cycle. ▶AIDS, ▶antibody, ▶affinity maturation, ▶immune response, ▶immunoglobulins, ▶junctional diversification, ▶somatic hypermutation, ▶transposon, ▶transposable elements, ▶antibody gene switching BCL, ▶enhancer, ▶neomycin, ▶DNA polymerases; Muramatsu M et al 2000 *Cell* 102:553; Kinoshita K, Honjo T 2001 *Nature Rev Mol Cell Biol* 2:493; Rattray AJ, Strathern JN 2003 *Annu Rev Genet* 37:31.

Hypermutation, Germinal: Germinal hypermutation may occur in the germinal centers under stress. This mechanism may generate random mutations, including adaptationally (evolutionarily) beneficial ones, at high frequencies. ▶directed mutation, ▶germinal center; Toellner KM et al 2002 *J Exp Med* 195:383.

Hypernephroma (adenocarcinoma of kidney): Hypernephroma, most commonly, involves rearrangement (translocations) of the short arm of human chromosome 3 or loss of 3p14.2. Trisomy or tetrasomy 7 may also be associated with kidney carcinomas. ▶renal cell carcinoma, ▶von Hippel-Lindau syndrome

Hyperornithinaemia: ▶urea cycle

Hyperoxauria: ▶oxalosis

Hyperparathyroidism (HRPT1, 1q25-q31, MEN1, 11q13): Dominant adenoma of the parathyroid gland. The condition is caused by a defect in the thyrotropin receptor A, G-protein receptor. Another dominant form is characterized by multiple bone tumors on the jaws. An autosomal recessive form affecting newborns is also known. Mutations in the calcium-sensing receptor (Casr) may upset parathyroid hormone production and may cause familial hypocalcemia or hypocalciuric hypercalcemia. The parathyroid hormone receptor is at 3p22-p21.1. ▶adenoma, ▶goiter, ▶G-protein, ▶parathormone, ▶hypocalcemia, ▶multiple endocrine neoplasia

Hyperphagia (overeating): An important cause of obesity, caused by mutation in the melanocortin receptor MC4R. ▶obesity, ▶melanocortin

Hyperphenylalaninemia: An autosomal recessive condition attributed to reduced phenylalanine hydroxylase activity or dihydropteridine reductase deficiency. Hyperphenylalaninemia is caused also by deficiency of pterin-4- α -carbinolamine dehydratase (10q22).

►phenylketonuria, ►phenylalanine, ►pteridines, ►GTP cyclohydrolase I deficiency

Hyperplasia: Abnormal increase of normal cells in a normal tissue. ►neoplasia

Hyperploid: A hyperploid contains extra chromosome(s) beyond the normal number.

Hyperpolarization: A negative shift in the electric potential in a cell membrane. ► I_h

Hyperprolinemia: Type II (1p36) is caused by autosomal deficiency of the enzyme Δ^2 -pyrroline carboxylate dehydrogenase and consequently by accumulation of proline and also glycine in the blood (the mechanism is unclear). The patients generally show some degree of mental retardation and convulsions. In Type I (22q11.2) disease, proline oxidase is deficient and renal problems occur with or without mental defects. ►proline biosynthesis, ►amino acid metabolism, ►iminoglycinuria

Hypersensitive Reaction (HR): In a hypersensitive reaction, at the place of infection by fungi, bacteria, and viruses, plant cells may suddenly die in a limited area and thus stop the spread of the infection and convey resistance to the host (see Fig. H85). This is considered to be an autophagy, an innate plant immune system. Several genes play a role in this programmed cell death (Liu Y et al 2005 Cell 121:567). The hypersensitivity reaction in case of fungi is elicited by hyphal cell membrane and in particular by the fatty acids eicosapentaenoic (EPA) and arachidonic (AA) acids, and it is inhibited by β -1,3 and β -1,6-glucans. The availability of EPA and AA is determined by lipoxygenase activity. Peroxides or other reactive oxygen intermediates (ROI) may also have a role in the development of HR and may be signal transducers. Bursts of ROI can be generated by NADPH oxidases. Mutation in the oxidase eliminates ROI but not significantly, cell death; however, in the presence of salicylic acid cell death occurs (Torres MA et al 2005 Nature genet 37:1130). In mammalian macrophages, ROI is usually aided by nitric oxide (NO) to attack invading bacteria. In plants, the HR seems to be activated by an oxidative burst and

increase in NO. In addition, NO may initiate a signaling pathway through phenylalanine ammonia lyase and salicylic acid leading to the activation of different disease resistance genes. The development of the HR may also be the cause or consequence of the alteration of ion channel functions. In bacteria, *hrp* (hypersensitivity and pathogenesis) genes and mutants were identified and these interact with various plant products, e.g., the plant flavonoids (acetosyringone) initiates the activation of the virulence cascade of *Agrobacterium*, although these bacteria do not produce a typical HR and an early report could not be generally confirmed. The hairpin 44-kDa regulatory protein has been implicated in the HR expression. The bacterial avirulence (*avr*) genes may suppress the HR, depending on particular host species. In animals, the hypersensitivity is usually called allergy. In the *immediate response*, the allergens bind to the surface of IgE and the following degranulation causes the release of histamines and interleukins resulting in inflammation. In the late-phase (4–24 h) inflammation response, leukotrienes and platelet-activating factors are secreted. The hypersensitive reaction is functionally comparable to apoptosis in animals, although it programs cell death by somewhat different mechanisms, by a vacuolar protease rather than by caspases, which do not occur in plants (Hatsugai N et al 2004 Science 305:855). Similar to animal apoptosis, the mitochondria of plants also control cell death. The pro-apoptotic Bax protein promotes plant cell death. BAX-inhibitor like proteins has also been found in plants. Plants also have caspase-like enzymes but their role in HR is not clear compared to the critical role of caspases in animals. The inner mitochondrial membrane enzyme called alternative oxidase (AOX) is absent from animal mitochondria, but present in plants. Its suppression by antimycin results in hypersensitivity and cell death. In contrast, activation of AOX may reduce the size of the necrotic spots. Some plastid proteins may also mediate HR. In plants, the MAPK pathway is activated during the hypersensitive reaction with the concomitant generation of hydrogen peroxide. ►host-pathogen relation, ►hydrogen peroxide, ►MAPK, ►allergy, ►phenylalanine ammonia lyase, ►nitric oxide, ►salicylic acid, ►histamine, ►interleukins, ►leukotrienes, ►platelet activating factor, ►apoptosis, ►porin, ►ROS; Lam E et al 2001 Nature [Lond] 411:848; Ren D et al 2002 J Biol Chem 277:559.

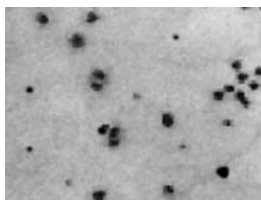


Figure H85. Hypersensitive reaction

Hypersensitive Site: A hypersensitive site includes nucleotide sequences, which are readily cut by endonuclease because these tracts are (relatively) free of chromosomal proteins. These sites are generally found in front of transcribed genes and it

is supposed that these facilitate the attachment of the transcriptase enzyme. ►[regulation of gene activity](#)

Hypersensitivity: A term used in mutagen (carcinogen) testing, indicating the percentage of compounds classified as carcinogens (mutagens) among all compounds tested by a system. Also, it designates atopic (hereditary) allergy manifested within minutes after exposure to an allergen. ►[allergy](#), ►[DTH](#); Kleinjan DA et al 2001 Hum Mol Genet 10:2049.

Hypertelorism: Abnormally long distance between two organs or organ parts in the body (see Fig. [H86](#)).



Figure H86. Hypertelorism

Hypertension: Hypertension is probably under the control of a few or several (~50) genes. In humans, the heritability of essential hypertension is about 30–35%. In rats, genetic analysis identified at least two genes with major effects BP/SP-1 and BP/SP-2 (blood pressure/sodium pump) in rat chromosome 10 (human chromosome 17q23). BP/SP-1 is probably linked closely to gene ACE1 (angiotensin converting enzyme). Hypertension has also an important physiological component associated with the lithium-sodium countertransport and thus depends on environmental (dietary) factors. A RHO-associated, Ca^{2+} -sensitive protein kinase seems to have a regulatory role. Hypertension occurs in about of a third of the human populations and is frequently evoked by kidney diseases. Hypertension is the most common cause of heart disease, especially among US blacks (33% vs. whites 25%). ►[coronary heart disease](#), ►[cardiovascular disease](#). Various familial disorders are frequently associated with hypertension: coarctation of the aorta, polycystic kidney disease, Alport syndrome, pheochromocytoma, neurofibromatosis, aldosteronism, hypoadosteronism, hyperthyroidism, homocystinuria, Wilms tumor, familial hypertriglyceridemia, hyperlipidemia, and hydroxysteroid dehydrogenase deficiency (11 β HSD). Blood pressure may vary from 80 mm (Hg) or less at the diastole (expansion of the heart ventricles) to the very high 200 mm at systole (contraction of the ventricles). The average normal blood pressure in adults is 80 at diastole and 120 at systole. In children it is lower, in older people it is usually higher. Elevated salt diet is normally

conducive to hypertension as the heart releases an atrial natriuretic peptide. The formation of this peptide is regulated by a guanyl cyclase A receptor (GC-A). Disruption of the GC-A gene in mice results in high blood pressure irrespective of the amount of salt in the diet. Mutations in the 11- β -hydroxysteroid dehydrogenase (16q22) may lead to hypertension. A mice mutation for Emilin1, a cysteine-rich secreted glycoprotein increases blood pressure and reduces blood vessel size. Emilin binds specifically to pro-TGF- β and inhibits its maturation by furin convertase. Inactivation of a single TGF- β allele restores blood pressure to normal level (Zacchigna L et al 2006 Cell 124:929). In patients with *essential hypertension* who typically lack sufficient RAS activation, ACE inhibitors (angiotensin converting enzyme) and angiotensin receptor blockers (ARBs) effectively reduce blood pressure and ameliorate cardiovascular complications suggesting that dysregulation of the RAS contributes to their elevated blood pressure. AT1 angiotensin receptors expressed in the kidney are the primary determinants of hypertension and end-organ damage in Angiotensin II-dependent hypertension (Crowley SD et al 2006 Proc Natl Acad Sci USA 103:17985).

A possible and promising gene therapy approach uses in an adenoviral helper vector system the gene of the atrial natriuretic peptide under the control of the mifepristone promoter. The level of the expression can be regulated according to the dosage of mifepristone. Such a system in a rodent model increased urinary cGMP output, significantly reduced systolic blood pressure and heart weight. The major advantage of this gene therapy system is its regulatable nature compared with the external supply of the peptide (Schillinger KJ et al 2005 Proc Natl Acad Sci USA 102:23789). ►[aldosteronism](#), ►[mineral corticoid syndrome](#), ►[Liddle syndrome](#), ►[Gitelman syndrome](#), ►[Gordon syndrome](#), ►[pseudohypoadosteronism](#), ►[brachydactyly](#), ►[hypotension](#), ►[angiotensin](#), ►[LDL](#), ►[nitric oxide](#), ►[stroke](#), ►[debrisoquine](#), ►[RHO](#), ►[hyperlipidemia](#), ►[hypercholesterolemia](#), ►[PPAR](#), ►[pulmonary hypertension](#), ►[DC36](#), ►[gene therapy](#), ►[adenovirus](#), ►[cGMP](#), ►[mifepristone](#), ►[TGF](#), ►[furin](#); Garbers DL, Dubois SK 1999 Annu Rev Biochem 68:127; Lifton RP et al 2001 Cell 104:545; genetic bases: Cowley AW Jr 2006 Nature Rev Genet 7:829.

Hyperthermia (malignant hyperthermia, MHS): MHS may involve only an increase of the skin temperature, or a general elevation of the body temperature (hyperpyrexia) may occur after anesthesia. The susceptibility is under dominant control in humans but it is recessive in the light-skinned pigs. Gene MHS1 is in human chromosome 19q13.1, encoding also a ryanodine receptor (RYR1), MHS2 is at

17q11.2-q24, MHS3 encodes a subunit of a voltage-dependent Ca^{+} channel at 7q21-q22, MHS4 is at 3q13.1, MHS5 at 1q32, and MHS6 is in 5p. Several other genes also play various roles in hyperthermia. ▶temperature-sensitive mutation, ▶cold hypersensitivity, ▶halothane gene, ▶ion channels, ▶ryanodine; Robinson RL et al 2000 Ann Hum Genet 64:307.

Hyperthyroidism: An autosomal dominant defect may be caused by inadequate response of the thyrotropin secreting cells to the pituitary thyroid-stimulating hormone (TSH). As a consequence, high levels thyroid hormones appear and goiter, increased pulse rate, fatigue, nervousness, sweating, heat intolerance, and other symptoms develop. In a recessive form (human chromosome 14), a deficiency of the TSH receptor is caused by an insert of a 8-amino acid sequence near the NH_2 end of the protein. A human chromosomal site (22q11-q13) codes for a thyroid autoantigen but that is not the receptor as once assumed. ▶thyroid hormone response element, ▶TRE, ▶hormones, ▶cardiovascular disease, ▶goiter

Hypertonia: Excessive tension of the muscles, hard to stretch. It seems that hypertonia in the central nervous system of the mouse is due to mutation to reduced γ -aminobutyric acid type A receptor. ▶GABA; Gilbert SL et al 2006 Nature Genet 38:245.

Hypertonic: The salt concentration of this type of solutes is high enough to draw out water from a cell. ▶isotonic, ▶hypotonic

Hypertranscription: A mechanism of dosage compensation in the male *Drosophila* by upregulation of transcription of the genes in the single X chromosome, thus making the phenotypes in males (XY) akin to females (XX). It is mediated by the MSL proteins, which seem to be required for the accumulation of histone H4, acetylated at lysine 16 in the X of the male. Apparently, MLE and MSE proteins direct an acetyltransferase to the X-chromosomal histone. ▶dosage compensation; Gorman M, Baker BS 1994 Trends Genet 10:376; Ruiz MF et al 2000 Genetics 156:1853.

Hypertrichosis: Excessive hairiness. In the autosomal dominant hypertrichosis universalis, hair covers abundantly the entire body until the end of infancy, in another form gum disease was also present. In an autosomal recessive form, the excessive hairiness was accompanied by nerve disease (neuropathy). An Xq24-q27.1-linked hypertrichosis affects the males more than the females where lyonization causes patchy appearance of hair. The condition is very rare; only about 50 cases have been so far described. Excessive hairiness does occur, however, as part of several syndromes such as the Hurler

syndrome, de Lange syndrome, Coffin-Sirius syndrome, Lawrence-Seip syndrome, Schinzel-Geidion syndrome, Gorlin-Chaudhary-Moss syndrome. ▶hair, ▶hirsute, ▶atavism, ▶lyonization; and the syndromes listed above.

Hypertriglyceridemia: An increase in the hepatic very-low density lipoprotein secretion. Carnitin appears to regulate hypertriglyceridemia. ▶hyperlipidemia, ▶carnitin

Hypertrophic Cardiomyopathy: Autosomal dominant heart defect in the β -myosin heavy chain or the myosin light chain, or troponin. ▶heart diseases, ▶myosin, ▶troponin, ▶cardiomyopathy dilated, ▶cardiomyopathy hypertrophic familial

Hypertrophy: An overgrowth generally with larger than normal cells.

Hyperuricemia: Abnormal amount of uric acid in the blood and may cause gout. ▶gout, ▶uric acid, ▶allopurinol

Hypervalinemia (valinemia): Accumulation of valine in the urine and blood plasma because of a defect in the enzyme valine transaminase, caused by an autosomal recessive factor. Symptoms include drowsiness and vomiting. Prenatal diagnosis is feasible. ▶isoleucine-valine biosynthetic pathway

Hypervariable Loci: Hypervariable loci are involved in cell surface proteins of pathogenic organisms and facilitate the evasion of the host defense system. Huntington's chorea and the fragile X syndrome in humans involve hypervariable chromosomal sites. ▶phase variation, ▶mutator genes, ▶Huntington's chorea, ▶fragile X, ▶trinucleotide repeat; Verstrepen KJ et al 2005 Nature Genet 37:986.

Hypervariable Sites: In the light and heavy chains of antibody molecules, hypervariable sites are responsible for their high specificity in recognizing different antigens. They are short polypeptide loops and called also the complementarity determining regions (CDRs). ▶antibody

Hyperzincemia: Hyperzincemia causes dwarfism, anemia, hypogonadism, etc. due to abnormally high level of Zn in the blood. ▶acrodermatitis enteropathica

Hypha (plural hyphae): Fungal filaments, cylindrical structural units of the mycelia. They are surrounded by a wall and filled with cytoplasm unless they are vacuolated. They elongate by growing at the tips (apex). When branching hyphae aggregate, they may form an erect mycelium, called *coremium*, or horizontal strands may form *rhizomorphs*. The spherical or irregular aggregates functioning as enduring (dormant) bodies are *sclerotia*. Hyphae aggregating in

pseudoparenchyma tissue are the *stroma*. Hyphae may be involved in plasmogamy and activity in some sort of sexual function (*somatogamy*), although they may not be sexually specialized. ▶ [fungal life cycles](#), ▶ [heterokaryon incompatibility](#); Xiang Q et al 2002 Genetics 160:169.

Hypoaldosteronism (adrenal hyperplasia): The two genes responsible for the recessive 11-β-hydroxylase deficiency have been located to human chromosome 8q21, and a defect of these is responsible for the accumulation of 11-deoxycorticosterone and consequently for hypertension, and other hormonal defects. The same enzymes are involved also in the hydroxylation of 18-hydroxysteroids and 17-hydroxysteroids. These genes are members of the P450 (cytochrome) enzyme coding family. Affected females show masculinization and the males show precocious puberty because of the accumulation of steroids. Some of the aldosterone deficiency mutations are allelic to the aldosterone-overproducing defect (aldosteronism) indicating the presence of a multifunctional protein. The *pseudohypoaldosteronism*, which is caused not by aldosterone deficiency but by the recessive deficiency of the mineral corticoid receptor, encoded at human chromosome 4q31.1 or q31.2. This condition is characterized by salt wasting in the urine, and responds favorably to salt administration. The hypoaldosteronism defects appear quite common among oriental (Persian) Jews. Pseudohypoaldosteronism type I may be due either to a defect in an epithelial sodium channel (ENaC) resulting in hyperkalaemic (high in potassium) acidosis and salt wasting. The α subunit of the channel is encoded in human chromosome 12p13.1-ter, whereas the β and γ subunits are coded by chromosome 16p12.2-p13.11. The most common basis of pseudohypoaldosteronism is, however, mutation in the mineral corticoid receptor gene (MRL). ▶ [aldosteronism](#), ▶ [P-450](#), ▶ [Jews and disease](#), ▶ [Liddle syndrome](#), ▶ [Bartter syndrome](#), ▶ [Gitelman syndrome](#), ▶ [mineral corticoid syndrome](#), ▶ [cardiovascular diseases](#), ▶ [ion channels](#), ▶ [pseudohypoaldosteronism](#)

Hypo-α-Lipoproteinemia (11q23.3, 9q22-q31): One of the several lipid metabolism disorders contributing to coronary heart disease. ▶ [Tangier disease](#), ▶ [lipoproteins](#), ▶ [cardiovascular diseases](#); Kort EN et al 2000 Am J Hum Genet 66:1845.

Hypoascorbemia: ▶ [ascorbic acid](#)

Hypobetalipoproteinemia (hypo-β-lipoproteinemia, 2p23, 3p21-p22): Hypobetalipoproteinemia involves dominant, reduced levels of apolipoprotein B that may result in increased levels of blood cholesterol and atherosclerosis, yet individuals with this anomaly may

have prolonged lifespan. ▶ [apolipoproteins](#), ▶ [atherosclerosis](#), ▶ [hyperlipoproteinemia](#), ▶ [abetalipoproteinemia](#), ▶ [cardiovascular diseases](#), ▶ [beta-lipoprotein](#)

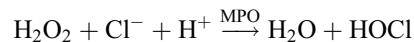
Hypoblast: The precursor of the mesoderm and endoderm. ▶ [mesoderm](#), ▶ [endoderm](#)

Hypocalcemia: Reduced amount of calcium in the blood in several diseases involving defects in ion channels. Autosomal dominant hypocalcemia (CASR, 3q13.3-q21) is mutation in the calcium-sensing receptor of the parathyroid gene (PTH, 11p15.3-p15.1) or in PTH itself. ▶ [ion channels](#), ▶ [parathormone](#), ▶ [hypocalciuric hypercalcemia](#)

Hypocalciuric Hypercalcemia (HHC2, 19p13.3): The calcium level in the blood and urine is elevated. In some cases, it involves bone and blood vessel disorders. The basic defect seems to be in a G-protein receptor. The phenotype is very similar to that of hypercalciuric/hypocalciuric hypercalcemia at 3q13.3. ▶ [G-proteins](#), ▶ [hypercalciuric hypercalcemia](#)

Hypochlorate (Ca[ClO]₂): Calcium and sodium hypochlorites (hypo) are among the oldest and most effective oxidative sterilizing agents. The former does not leave alkalic residues after washing and it is more useful as an antiseptic for live tissues. ▶ [sterilization](#)

Hypochlorous Acid (HOCl): HOCl is generated in neutrophils and catalyzed by myeloperoxidase (MPO) as a highly reactive defense mechanism:



Hypochondriasis: A type of affective disorder when illness is imagined on the basis of irrelevant signs. ▶ [affective disorders](#)

Hypochondrogenesis: A connective tissue disorder caused by mutation in collagen.

Hypochondroplasia: This autosomal phenotype is reminiscent of achondroplasia, but the tibia (shin-bone) and the head are rather normal. The fingers are short but the hand is not three-pronged. This gene appears to be allelic to that responsible for achondroplasia. It may be caused by a defect in the function of fibroblast growth factor receptor 3, FGFR3 at human chromosome 4p16.3. ▶ [stature in humans](#), ▶ [achondroplasia](#), ▶ [achondrogenesis](#), ▶ [dwarfism](#), ▶ [fibroblast growth factor](#), ▶ [dwarfism](#), ▶ [receptor tyrosine kinase](#)

Hypochromicity of Nucleic Acids: In double-stranded molecules, the free rotation of the bases is hindered, resulting in reduced optical density in UV light compared to single-stranded molecules (hyperchromicity). ▶ [DNA](#), ▶ [hyperchromicity](#)

Hypocotyl: The section of a plant embryo or plant situated between the cotyledon attachment point and the radical or root, respectively.

Hypocretin: ►orexin

Hypodontia (adontia): Autosomal dominant condition of lack or underdevelopment of up to six teeth (see Fig. H87). PAX9 gene (14q21) encoding 342 amino acids is defective. ►teeth, ►dental non-eruption, ►dentinogenesis imperfecta, ►dental ankylosis, ►tooth agenesis, ►olygodentia, ►PAX



Figure H87. Hypodontia. (Form Bergsma D ed 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

Hypogammaglobulinemia/

Common Variable Immunodeficiency (CVID): Complex immunodeficiency with uncertain familial determination. Defects in tumor necrosis factor-like receptor TNFRSF138 gene product, TAC1 (transmembrane activator), are involved with the condition, resulting in IgA deficiency in a complex manner (Salzer E et al 2005 Nature Genet 37:820; Castigli E et al 2005 Nature Genet 37:829). ►gammaglobulinemia, ►immunodeficiency, ►Epstein-Barr virus, ►Hirschsprung disease

Hypoglossia/Aglossia (Hanhart syndrome): Small tongue and very small mandibles, generally with short fingers. It is sporadic or autosomal recessive.

Hypoglycemia: Hypoglycemia involves lower than normal blood sugar content and may result in shaking, cold sweat, low body temperature, headache, irritability, and eventually even coma. An autosomal recessive gene may cause it by a deficiency of glycogen synthetase in the liver. Another recessive gene in human chromosome 1p31 may cause acyl-coenzyme A-dehydrogenase deficiency and hypoglycemia. Mutations in the sulfonylurea receptor gene may cause hyper-insulinemia (human chromosome 11p14-p15.1) and consequently hypoglycemia. Hypoglycemia may result indirectly from a large number of different ailments. ►epilepsy, ►ion channels, ►sulfonylurea

Hypogonadism: less than normal function of the gonads (ovary and testes); it is frequently associated with retardation in growth and mental abilities. Mutation in the DAX-1 human gene may result in adrenal defects such as adrenal hypoplasia and hypogonadotropic hypogonadism (deficiency in the hormone gonadotropin and gonadal hypofunction). Mutation in the gonadotropin-releasing hormone receptor (4q13.1-q21.1) may also be responsible. It may involve obesity. ►adrenal hypoplasia, ►Kallmann syndrome; Pitteloud N et al 2006 Proc Natl Acad Sci USA 103:6281.

Hypogonadotropic Hypogonadism (19p13.3, 9q34.3): A genetically heterogeneous defect in pubertal maturation caused mainly by deficiency of the gonadotropin-releasing hormone (GNRH1) and G-protein-coupled receptor (GPR54), receptor of the KiSS-1 peptide regulating the onset of puberty (Kaiser UB, Kuohung W 2005 Endocrine 26:277). ►Kallmann syndrome, ►luteinizing hormone-releasing, ►Marinesco-Sjögren syndrome

Hypohidrosis: Reduced ability to sweat caused by autosomal recessive defect of the sweat glands.

Hypokalemia: Autosomal recessive (16q13) low potassium and magnesium level in the body causing neuromuscular abnormalities. ►periodic paralysis, ►hypoadosteronism, ►pseudoaldosteronism, ►Gitelman syndrome, ►Bartter syndrome

Hypolactasia: ►disaccharide intolerance, ►lactose intolerance

Hypomagnesemia (11q23): A dominant renal defect involving wasting of Mg^{2+} and frequently involving Ca^{2+} excretion, due to mutation in the Na^+ , K^+ -ATPase γ subunit.

Hypomelanosis of ITO: Pale skin spots in whorls or patches of tan associated with other, diverse anomalies, indicating that this syndrome is a mixed bag, often associated with breakage of different chromosomes. ►incontinentia pigmenti, ►pigmentation defects, ►skin diseases

Hypomethylation of DNA: Hypomethylation of DNA may cause chromosomal instability and cancer. ►methylation of DNA; Eden A et al 2003 Science 300:455; Gaudet F et al 2003 Science 300:489.

Hypomorphic: The product of the gene is below the level of that of the wild type. ►leaky mutant

Hypomyelination: ►hypomyelinopathies

Hypomyelinopathies: Hypomyelinopathies involve defects in the myelin coat of the nerves, such as congenital hypomyelinating neuropathy. ►Charcot-Marie-Tooth type 1 disease, ►neuropathy, ►sensory neuropathy, ►Egr, ►Dejerine-Sottas syndrome, ►HMSN, ►HNPP

Hyponasty: ►epinasty

Hypoparathyroidism: The activity of the parathyroid gland is reduced, resulting in hypocalcemia and hyperphosphatemia. The patients suffer from neuromuscular problems including even seizures. Vitamin D may alleviate the problems. The anomaly is controlled at several autosomal locations with dominant or recessive alleles. One rare form is linked to Xq26-q27.

Hypophosphatasia: Either a *dominant* mutation expressed in adults as a deficiency of the liver (general) alkaline phosphatase gene in human chromosome 1p36.1-p34, or the *recessive* mutation in the same locus appears as the infantile hypophosphatasia. The adult phenotype involves early loss of teeth and bowed legs, like in rickets. The level of intestinal alkaline phosphatase is normal. In some forms the stature is somewhat shorter. The infantile type is manifested already before birth, and involves severe skeletal anomalies, increased levels of phosphoethanolamine, inorganic pyrophosphate in the urine, and in the serum higher levels of pyridoxal phosphate. Death may occur within a year. In some instances, infusion of normal blood plasma resulted in prolonged normalization. It was suggested that a cofactor of the enzyme is missing. ►stature in humans, ►dwarfism, ►hypophosphatemia, ►rickets

Hypophosphatemia: A dominant bone disease coded in human chromosome Xp22 region resulting in low level of phosphate in the blood, and no or minimal response to vitamin D. The defect may involve abnormal phosphate absorption too. Its prevalence is 2×10^{-4} . *Autosomal dominant hypophosphatemic rickets* (ADHR, 12p13.3) is due to mutation in gene FGF23; it is resistant to vitamin D. The *autosomal recessive gene* ARHP has been mapped to 4q21 where it encodes dentin matrix protein 1, which appears to be a regulator of FGF23, an osteomalacia (insufficient mineralization of the spongy bone, rickets) inducing protein (Lorenz-Depiereux B et al Nature Genet 2006 38:1246). The X-linked PHEX gene encodes a neutral endopeptidase and is responsible for the *hypophosphatemic rickets* (XLH, Xp22.2-p22.1). The heterogeneous *autosomal hypophosphatemic bone disease* (HBD) and the autosomal recessive *hereditary hypophosphatemic rickets with hypercalciuria* (HHRH) both respond to vitamin D. ►hypophosphatasia, ►exostosis, ►spermine, ►FGF, ►rickets; Sabbagh Y et al 2001 Hum Mol Genet 10:1539; Sabbagh Y et al 2005 Proc Natl Acad Sci USA 102:9637.

Hypoplasia: Underdevelopment of an organ. ►aplasia

Hypoploid: A hypoploid contains less than the full set of chromosomes. ►autopolyploid, ►nullisomic

Hypoproconvertinemia: A recessive bleeding disease caused by deficiency of blood clotting factor VII encoded in human chromosome 13q34-qter. The afflicted individuals may be deficient also in antihemophilic factor X. ►antihemophilic factors, ►proconvertin

Hypospadias: The urethra opens at the lower part of the penis; it has autosomal dominant and recessive transmission. Prevalence is close to 0.3%, with a heritability of about 0.57 and may accompany several syndromes, e.g., hypertelorism (22q11.2), steroid α -reductase 2 type pseudohermaphroditism (2p23), androgen receptor defects (Xq11-q12), Wilms tumor (11p13), mutation in the HOXA13 gene (7p15-p14.2), McKusick-Kaufman syndrome (20p12), etc. Hypospadias were attributed to mutation in CXorf6 (human chromosome Xq28) in Japanese populations (Fukami M et al 2006 Nature Genet 38:1369). ►penis, ►steroid dehydrogenase, ►named individual entries

Hypostasis: A condition when another gene, the epistatic one, masks the expression of a gene. ►epistasis

Hypotension: Hypotension, in contrast to hypertension, involves low blood pressure. Some of the cases may be determined only by different alleles of identical loci. The autosomal dominant orthostatic form (*Shy-Drager syndrome*) is characterized by incontinence, anhidrosis (absence of sweating), ataxia, tremor, and low norepinephrine level in the plasma. The *pseudo-hypoaldosteronism* (*PHA-I*) is autosomal dominant and involves serious dehydration, salt wasting, high level of potassium, and a form of hyperaldosteronism. The mutation seems to affect the genes controlling the same ion channel as in the Liddle syndrome. The *Gitelman syndrome* is a human chromosome 16 recessive that involves a defect in the Na-Cl cotransporter and consequently, salt wasting. ►hypertension, ►adrenergic receptors, ►Liddle syndrome, ►aldosteronism, ►mineral cortical syndrome; Zuscik MJ et al 2001 J Biol Chem 276:13738.

Hypothalamus (forebrain): The part of the brain where the vision, visceral activities, water balance, temperature, sleep, etc. control centers are located. ►brain human

Hypothesis: A supposition or multiple alternative suppositions (hypotheses) are used to explain certain experimental data and generally statistical approaches are used to decide which of the alternatives have the greatest probability to be true. One must keep in mind that the statistical methods do not prove cause-effect relationships or mechanisms, only the degree of chance or likelihood is indicated. Karl Popper, the philosopher, stated, "Our belief in some hypotheses can have no stronger basis than our repeated

unsuccessful critical attempts to refute it” (The Logic of Scientific Discovery). The refutability, of course, depends also on the precision of the factual basis of the hypothesis. The trust in the validity of a hypothesis is increased greatly if it is supported by replication under somewhat different circumstances or by different procedures, rather than under exactly identical conditions, which may be loaded by the same bias each time. The *working hypothesis* is used as guidance to design experimental procedures to test the most likely mechanism involved. In experimental science, such as genetics, only the testable hypotheses have any value. ▶ [null hypothesis](#), ▶ [probability](#), ▶ [likelihood](#), ▶ [maximum likelihood](#), ▶ [chi square](#), ▶ [genetic risk](#); Page GP et al 2003 Am J Hum Genet 73:711; Lipton P 2005 Science 307:219.

H

Hypothyroidism: ▶ [goiter](#)

Hypotonia: Weak muscle tension. It is a typical feature of the Down syndrome, Prader-Willi syndrome, cri-du-chat syndrome, and various other chromosomal anomalies and trisomies.

Hypotonic: The concentration of salts in this type of media is lower than the osmolality of the cell, therefore water from the cells may be drawn out into the medium. ▶ [hypertonic](#), ▶ [hypotonic](#), ▶ [osmolality](#), ▶ [osmotic pressure](#)

Hypotrichosis: Rare autosomal recessive reduction of hair on the face and absence of pubic hairs even after puberty. Baby hair is shed shortly before or after birth. Congenital atrichia (baldness) or hypotrichosis of Marie Unna was mapped to 8p22-p21, but the latter does not seem identical with congenital atrichia. Hypotrichosis simplex (HSS), a rare dominant baldness affecting both sexes early on, was mapped to 6p21.3. The gene encodes corneodesmosin, a glycoprotein expressed in the epidermis and the inner root sheath of the hair follicles (Levy-Nissenbaum E et al 2003 Nature Genet 34:151). The recessive hypotrichosis associated with juvenile macular dystrophy encodes P-cadherin at 16q22.1. ▶ [hair](#), ▶ [hypertrichosis](#), ▶ [alopecia](#), ▶ [cadherin](#), ▶ [macular corneal dystrophy](#), ▶ [lymphedema](#); Sprecher E et al 2001 Nature Genet 29:134.

Hypotrophy: Less than normal growth of a tissue or organ caused by inadequate nourishment.

Hypouricemia: A type of nephrolithiasis. In the Dalmation coachhund type, the kidneys do not reabsorb urate. In other cases, the decrease of urate in the urine is accompanied by excessive excretion of calcium. ▶ [nephrolithiasis](#), ▶ [kidney diseases](#)

Hypoventilation: Hypoventilation may be controlled at several human loci (20q13.2, 11p13, 5p131 and 4p12. The congenital central hypoventilation syndrome (CCHS) is an abnormal respiration without

lung disease, neuromuscular, or brain defects. Its most important cause appears to be a defective PHOX2B homeobox gene at 4p12 (Amiel J et al 2003 Nature Genet 33:459). Some of the factors involved in Hirschsprung disease are also responsible for hypoventilation. ▶ [Hirschsprung disease](#)

Hypoviruses: Hypoviruses are persistent and hard to transmit infectious agents in fungi and cause no symptoms. However, the synthetic transcripts of such viruses when introduced into the chestnut blight fungus (*Cryphonectria parasitica*) by electroporation can reduce the virulence of the fungus and thus indicates a means of biological control. ▶ [symbionts hereditary](#)

Hypoxanthine: A purine base very similar to guanine, except that from the C2 position in hypoxanthine, NH₂ is removed (see Fig. H88). It can be formed also by deamination at the 6 position of adenine. Its nucleoside is (confusingly) inosine and its nucleotide is called inosinic acid. It may occur in some anticodons of tRNA. Insine (I) is a “universal base” because it can pair with various bases in this order with decreasing thermal stability I•C > I•A > I•T ≈ I•G > I•I. Therefore, it can be used in degenerate PCR primers

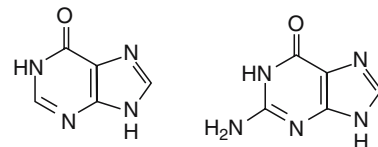


Figure H88. Hypoxanthine (left), Guanine (right)

and for degenerate microarray probes (Watkins NE et al 2005 Nucleic Acids Res 33:6258). When guanine is deaminated into hypoxanthine through chemical mutagens (nitrous acid), lethal mutation occurs because hypoxanthine cannot support nucleic acid replication. The enzyme hypoxanthine-guanine phosphoribosyl transferase (deficient in the Lesch-Nyhan syndrome) can phosphorylate both of these purines in the salvage pathway of nucleic acid. ▶ [HPRT](#), ▶ [salvage pathway](#), ▶ [HAT medium](#), ▶ [nitrous acid mutagenesis](#), ▶ [inosine](#), ▶ [wobble](#), ▶ [ADA](#)

Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT): The enzyme that donates the ribose phosphate moiety to the purine bases hypoxanthine and guanine from 5'-phosphoribosyl-1-pyrophosphate and thus forms the corresponding nucleotides. Another enzyme, adenosine phosphoribosyl transferase, synthesizes adenylic acid from adenine. HGPRT is the key enzyme in the salvage pathway of nucleic acid synthesis. ▶ [salvage pathway](#), ▶ [HAT medium](#), ▶ [Lesch-Nyhan syndrome](#)

Hypoxia: Low oxygen concentration in the environment of cells or tissues. The effectiveness of ionizing radiation in induction of mutation or chromosome breakage is reduced under low oxygen concentration. Hypoxia may trigger the formation of double minutes and chromosomal instability. Hypoxia promotes the binding of hypoxia-inducible factors (HIF) to the hypoxia-response element in the vascular endothelial growth factor promoter and it so stimulates angiogenesis. Deletion of the hypoxia-response element may cause motor neuron degeneration that resembles the anomaly of amyotrophic lateral sclerosis. Hypoxia is a factor in tumorigenesis. Hypoxia inhibits the translation of mRNA by suppressing key regulators such as eIF-2A, eEF-2, and TOR among other factors resulting in energy conservation under low oxygen level (Liu L et al 2006 Mol Cell 21:521). *Normoxia* is normal oxygen tension in the environment. ►oxygen effect, ►HIF, ►eIF, ►eEF, ►TOR, ►animation, ►double minutes, ►fragile sites, ►angiogeneses, ►VEGF; von Hippel-Lindau syndrome; Jiang H et al 2001 Proc Natl Acad Sci USA 98:7916; Harris AL 2002 Nature Rev Cancer 2:38.

Hypoxic Genes: Hypoxic genes are expressed primarily under anoxia. ►anoxia, ►amyotrophic lateral sclerosis

Hysterectomy: The surgical removal of the uterus. ►uterus

Hysteresis: A time lag between two processes. Also, hysteresis refers to the lowering of the point of freezing without lowering the temperature required for melting; antifreeze proteins may regulate it. Hysteresis is a common mechanism of regulation of gene expression networks. Networks of positive feedback may control hysteretic or bistable switches. Bistable expression system can throw OFF and ON the threshold-dependent toggles. Hysteretic systems require bigger signals for OFF and ON switching by interfacing historical and current input signals. Epigenetic toggle switches may involve two rather stable expression states. The response may be based on a graded dose input. Synthetic hysteretic system may have great potentials for gene therapy in as much as the transgene expression may reflect the needs of the metabolic system of the recipient rather than responding to a single, fixed dose. A tetracycline responsive positive feedback loop may communicate with a constitutive macrolide-dependent transrepressor expression unit and impinges on transcription modulation of the transgene. At macrolide concentrations around the switching dose, the network shows hysteresis and represents “artificial memory” imprinted on the expression of the transgene (Kramer BP, Fussenegger M 2005 Proc Natl Acad Sci USA 102:9517). ►antifreeze proteins, ►temperature-sensitive mutation, ►epigenesis, ►macrolide, ►tetracycline, ►gene therapy, ►genetic networks

Historical vignettes

On May 8 1900 William Bateson wrote in the J Roy. Hort. Soc. (Lond) 25:54

“An exact determination of the laws of heredity will probably work more changes in man’s outlook on the world, and in his power over nature, than any other advance in natural knowledge that can be foreseen.

There is no doubt whatever that these laws can be determined. In comparison with the labour that has been needed for other great discoveries it is even likely that the necessary effort will be small.”

Boyce Rensberger (science journalist) in Science 289:61 (2000)

“Without a grasp of scientific ways of thinking, the average person cannot tell the difference between science based on real data and something that resembles science—at least in their eyes—but is based on uncontrolled experiments, anecdotal evidence, and passionate assertions.”

I Blood Group (Ii system): I and i are universal erythrocyte antigens that exhibit alteration during development but minimal polymorphism. The synthesis of I/i antigens results from the cooperation of glycosyltransferases on common substrates and there is not a single diagnostic immunodeterminant sugar specific for the blood type. It may be associated with autoimmune hemolytic anemias. ▶blood types, ▶ABO blood type, ▶hemolytic disease, ▶hemolytic anemia

I Element: ▶non-viral retrotransposable elements, ▶retroposon, ▶retrotransposon

I.U: International unit is a quantity of various vitamins, hormones, enzymes, etc. that bring about a standard response as determined by the International Conference for Unification of Formulas.

IAA: Denotes indole acetic acid. ▶plant hormones. (see Fig. I1).

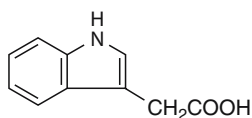


Figure I1. Indole-3-acetic acid

IAM: ▶infinite allele mutation model, ▶microsatellite, ▶minisatellite, ▶SMM model

IAP: ▶chloroplast import

IAP (intracisternal [within closed compartments] A particles): These are retroviral elements in the mouse genome capable of transposition. They are normally not active but demethylation of their long terminal repeats increases their transcription 50–100 fold. Male germ cells are demethylated shortly before the formation of the spermatogonia. Female germs are demethylated slightly later but only during the period between the primordial germ cells and growing oocytes. The spermatogonia and the oocytes are heavily methylated. The IAP elements are not found in humans. ▶Prader-Willi syndrome, ▶dyskeratosis; Vogler C et al 2001 *Pediatr Res* 49(3):342.

IAP (inhibitor of apoptosis): Controls apoptosis by binding or in other ways interfering with caspase or pro-caspase activation. At its N-terminus it contains one or more BIR motifs and its C-terminus has a RING finger domain for recruiting caspase. The

IAPs are involved in ubiquitin ligase activity and may autoregulate their degradation by proteasomes. The expression of a construct containing the RING domain of X-linked IAP causes its ubiquitylation and degradation by the proteasome. This results in apoptosis and markedly reduced melanoma proliferation following the administration of cisplatin (Silke J et al 2005 *Proc Natl Acad Sci USA* 102:16182). The Smac/DIABLO protein binds to the IAP and promotes caspase activity. Binding proteins REAPER, HID and/or GRIM promote caspase activity presumably by neutralizing the IAP. ▶apoptosis, ▶BIR, ▶caspase, ▶RING finger, ▶ubiquitin, ▶proteasome, ▶Smac, ▶DIABLO, ▶melanoma, ▶cisplatin; Verhagen AM et al 2001 *Genome Biol* 2: reviews 3009; Sharief MK, Semra YK 2001 *J Neuroimmunol* 119:350.

IARC: The International Agency for Research on Cancer, Lyon, France, publishes reviews on carcinogens as scientific publications of the IARC. ▶cancer, ▶environmental mutagens, ▶databases; <http://www.iarc.fr/>.

Iatrogenic: (adjective) Refers to the adverse effect(s) resulting from or concomitant to medical treatment, hospital-acquired infections. ▶nosocomial

IBD: Identical by descent refers to an allele inherited from an ancestor that is exactly the same as that of the particular ancestor and not the result of a new mutation identical by state (IBS). IBD-APM means identical by descent for affected-pedigree-member. More information can be obtained by combining conventional linkage tests with high-resolution single nucleotide polymorphism scans (Burdick JT et al 2006 *Nature Genet* 38:1002). ▶inbreeding coefficient, ▶SNIP

ibid: An abbreviated form of the Latin adverb *ibidem* means the same place; it is sometimes used in citations when another paper appears at the same place, i.e., in the same journal.

IBIDS: ▶ichthyosis

IbpA, IbpB (Inclusion Body Proteins): These are small heatshock protein chaperones of prokaryotes. ▶sHSP; Kitagawa M et al 2000 *FEMS Microbiol Lett* 184(2):165.

IBS: ▶IBD, ▶identity of state

IC₅₀: Refers to median inhibitory concentration (of a drug or other chemical compound).

ICAD (inhibitor of CAD): ▶CAD, ▶caspase, ▶AIF; Sakahira H et al 1999 *J Biol Chem* 274:15740.

ICAM (CD54, intercellular adhesion molecule, 19p13.3-p13.2): These proteins bind together

(epithelial) cells through integrins. The concentration of ICAM-2 in uropod projections, rather than being evenly distributed, is a special target for cytotoxic lymphocytes (CTL). The targeting is assisted by the cytoskeletal - membrane linker protein ezrin. ICAM-1 protects against allograft rejection. ►N-CAM, ►cadherin, ►integrin, ►DC-SIGN, ►CD proteins, ►dengue fever, ►LFA, ►uropod, ►T cell; Springer TA 1990 Nature [Lond] 346:425; Sultan P et al 1997 Nature Biotechnol 15:759; crystal structure: Song G et al 2005 Proc Natl Acad Sci USA 102:3366.

ICAT (isotope-coded affinity tag): This is a protein analytical procedure that may be substituted for the two-dimensional gel electrophoresis. The cells are grown under two different conditions and a biotin-linked isotope is used to label the cysteine residues of the proteins. The extracted protein is digested and the labeled peptides are subjected to affinity chromatography and the peptides are further analyzed by high-performance liquid chromatography/mass spectrometry. Differences in the expression of genes are demonstrated by differences at the level of the isotope. ►gel electrophoresis, ►two-dimensional gel electrophoresis, ►MALDI/TOF/MS, ►proteomics; Smolka MB et al 2001 Anal Biochem 297:25; Han DK et al 2001 Nature Biotechnol 19:946; Turecek F 2002 J Mass Spectrom 37:1.

Iccosomes: Dendritic cells package antigen: antibody complexes into budding structures that shed from their surface. ►dendritic cell; Terashima K et al 1992 Semin Immunol 4(4):267.

ICE (interleukin-1 β converting enzyme, caspase 1 in human chromosome 11q22): A cysteine protease which is activated during Fas-mediated apoptosis. Its family includes CPP32 and Ich-1 proteases. The ICE is a mammalian homolog of *ced-3*. ►Fas, ►apoptosis, ►interleukins, ►CPP32, ►granzyme B, ►RNKP-1, ►IL-1, ►caspase; Druilhe A et al 2001 Cell Death Differ 8(6):649.

Ice Man (Ötzi): A frozen mummy was discovered in 1991 in the Tyrolean Alps, its age was estimated to be 5,100 to 5,300 years. Some claims have been made that it may be a scientific hoax but detailed analysis has negated this possibility. Also, 10-genome equivalent quantity of DNA per gram of its tissue, comprising only redundant sequences, has been recovered. One DNA sequence of the hypervariable region of the mitochondrial DNA indicated close similarities to central and north European populations. The cause of his death as revealed by an X-ray was an arrow flint. DNA analysis revealed four different types of blood on his clothing leading to the conclusion that he was involved in bloody fighting with others. ►mtDNA, ►ancient DNA, ►mummies;

Williams AC et al 1995 Biochim Biophys Acta 1246:98; Bortenschlager S, Oegg K eds. 2000 The Iceman and His Natural Environment. Springer, Wien, Austria.

Iceland: The Icelandic population has been considered one of the genetically most homogeneous populations in the world in terms of blood group, allozyme data and mitochondrial DNA (Helgason A et al 2000 Am J Hum Genet 66:999). However, a re-examination of the mitochondrial DNA diversity does not confirm the validity of this view (Árnason E 2003 Ann Hum Genet. 67:5). The latter view has been questioned, as it is thought to be based on inappropriate comparisons (Helgason A, Stefánsson K 2003 Am J Hum Genet 73:947).

I-Cell Disease: ►mucopolysaccharidosis

ICER (inhibitor of CRE): A basic leucine zipper domain protein of the CREB family lacking the C-terminal transactivation domain. It is inducible by FSH. ►CRE, ►CREB, ►FSH, ►leucine zipper; Trocme C et al 2001 J Neurosci Res 65(2):91.

ICF: ►immunodeficiency, ►methylation of DNA

ICH1: This is a protease implicated in apoptosis. Its N-terminus is homologous to caspase 2. ►apoptosis, ►caspase; Zeng Q et al 2000 J Comp Neurol 2000 424:640.

Ichthyosis: This non-inflammatory keratosis of the skin appearing in different forms under different genetic controls is often associated with various syndromes (see Fig. 12). In the *autosomal dominant* (with poor penetrance) ichthyosis vulgaris (1q21), the scaling of palms and soles appears during the first three months after birth and it may be caused by keratohyalin deficiency, a precursor of filaggrin, an element of keratin fibers (Smith FJD et al 2006 Nature Rev Genet 38:337). Sequencing of this large, highly repetitive gene has revealed 15 variants, including seven that are prevalent. All the variants are either nonsense or frameshift mutations that, in representative cases, result in loss of filaggrin production in the epidermis and manifest childhood eczema (Sandilands A et al 2007 Nature Genet 39:650). There are a number of variations of the dominant types. Its incidence among schoolchildren in England was ~1/250. The *autosomal recessive* lamellar (14q11.2, keratinocyte transglutaminase, TGM1) form has many variations involving redness of the skin, brittle hair, blisters, liver disease, physical and mental retardation, etc. There are other recessive lamellar ichthyosis genes in human chromosome 2 (LI2, 2q33-35) and LI3 is located at 19p12-q12. The recessive forms are generally more serious than the dominant ones. The harlequin type (2q34; so named

because the diamond-shaped 4–5 cm diameter scaly, horny spots resemble the diamond-patterned costume of a harlequin) may cause death within the first week after birth. The defect is in the ABC transporter A12. Some recessive forms involve hair loss, progressive neural defects, enlarged liver and kidney defects. In the Sjögren-Larsson syndrome (17p11.2) the frequency of the recessive gene responsible for the disease in a county of Sweden was 0.01 and that of carriers was 0.02 while the prevalence was 8.3×10^{-5} . Fatty aldehyde dehydrogenase deficiency, neurological disorders and keratosis characterize this latter form of ichthyosis. Another form of recessive ichthyosis is related to triglyceride storage anomalies. In the autosomal recessive ichthyosis (14q11) the activity of keratinocyte transglutaminase activity is considerably reduced. X-linked ichthyosis (Xp22.32) based steroid sulfatase deficiency may produce asymmetric malformations of the lung, thyroid, several nerves, etc. and hypoplasia on the same side as the ichthyosis. Another X-linked (distal part of Xp) group reveals deficiency of placental steroid sulfatase. This is also called IBIDS. ▶keratosis, ▶skin disease, ▶collagen, ▶lyonization, ▶trichothiodystrophy, ▶collodion fetus, ▶filaggrin, ▶Chanarin-Dorfman disease, ▶erythroderma, ▶eczema



Figure 12. Ichthyosis

ICOS (inducible co-stimulator, a human homolog of CD28): This is a homodimeric protein (M_r 55–60K) which enhances T cell proliferation, lymphokine secretion, upregulates cell-to-cell interaction, antibody production by B cells and the production of IL-10 (but not IL-2) in response to foreign antigens. The B7 related protein (B7RP) expressed on B cells and ICOS without interacting with the B7—CD28 system, stimulates adaptive immune response. ICOS^{-/-} mice are deficient in immunoglobulin class switching and germinal center formation. CD40 and its ligand may compensate for the ICOS defects. The ICOS may influence T_H-1 and T_H-2 lymphocytes and may be partly responsible for graft rejection and autoimmune disease. ▶CD28, ▶B7 protein, ▶CTLA, ▶IL-10, ▶IL-2, ▶T cell receptor, ▶immunoglobulin, ▶germinal center, ▶CD40, ▶autoimmune disease; McAdam AJ et al 2001 Nature 409:102; Özkaynak E et al 2001 Nature Immunol 2:591 and following articles.

Icosahedral: This is a body with 20 facets like the capsids of some viruses. ▶isometric phage

ICR: Compounds synthesized by the International Cancer Research Institute, Philadelphia, are acridines with alkylating side chains and cause frameshift mutations. ▶mutagens

ICR: Refers to the internal control regions through the zona pellucida. ▶A box

ICR (insulator control region): ▶enhancer competition, ▶insulator

ICSI (intracytoplasmic sperm injection): Spermatozoa in some humans and animals are unable to penetrate the egg. In such cases the spermatozoon may be injected mechanically into the ooplasm. This technology can also be used for genetic transformation. However, there are some risks of mechanical or chemical (in the delivery fluid) injury to the egg. The genetic risk is that the spermatozoon injected is not competing and a less viable or defective one may fertilize. This method enables men with a very low sperm count to father children. Unfortunately, the genetically determined low sperm count is transmitted to the offspring. Mouse and human spermatozoa have small acrosomes compared to bulls, boars and hamster and the inclusion of the acrosome during ICSI can be very harmful to the oocytes in as much as lysis and deformation can occur (Morozumi K, Yanagimachi R 2005 Proc Natl Acad Sci USA 102:14209). The removal of both the plasma membrane and acrosome from the mouse spermatozoa before the ICSI not only accelerates the onset of oocyte activation, but also results in improved embryonic development (Morozumi K et al 2006 Proc Natl Acad Sci USA 103:17661). ▶ART, ▶in vitro fertilization, ▶acrosome; Ma S et al 2001 Fertility & Sterility 75:1095; Faddy MJ et al 2001 Nature Genet 29:131; Cox GF et al 2002 Am J Hum Genet 71:162.

Icterus: A technical term for jaundice. ▶kernicterus, ▶hyperbilirubinemia

ID: ▶idant

ID (integrating database): This is formed in the GenBank containing information on accession number, ASN.1, gi, Bioseq. ▶GenBank, ▶accession number, ▶ASN.1, ▶gi, ▶Bioseq

ID₅₀: Refers to the dose of an infectious agent that infects 50% of the cells exposed to it.

ID Proteins: These interfere with differentiation by blocking the access of basic helix-loop-helix transcription factors to the E box in the DNA. In mice there are four *Id* genes and knocking out all of them is

lethal, but when at least one allele is functional premature withdrawal of the neuroblasts from the cell cycle and failure of the normal angiogenesis and vascularization occur. Overexpression of Id2 is due to the activation of the transcription of the Myc family of oncoproteins. For the progression of the cell cycle induced by Myc requires the inactivation of Rb (retinoblastoma) protein by the dominant-negative Id2. Id1 opposes the effect of p16^{INK4a} in senescence. The degradation of Id2 by the anaphase-promoting complex (APC-CDH1) and D box motifs promotes axonal growth (Lasorella A et al 2006 Nature [Lond] 442:471). ▶E box, ▶D box, ▶anaphase promoting complex, ▶Cdh1, ▶angiogenesis, ▶helix-loop-helix, ▶retinoblastoma, ▶Myc, ▶p16^{INK4a}, ▶senescence; Alani RM et al 2001 Proc Natl Acad Sci USA 98:7812.

Idant: A higher hierarchical genetic structure as conceived during the early/middle nineteenth century. Biophores (~alleles) aggregated into ids (~loci) and ids formed idants (~chromosomes).

Idaxozan: ▶clonidine

IDC (Idiopathic Dilated Cardiomyopathy): ▶cardiomyopathy dilated

IDDM: Denotes insulin-dependent diabetes mellitus. ▶diabetes mellitus

Identical By Descent: ▶IBD

Identical By State: ▶IBD

Identical Twins: ▶twinning

Identifier: Sequences within introns or non-coding 3' regions are involved in genetic regulation. The identifier sequences are transcribed by RNA polymerase III and may define chromatin regions and facilitate the transcription by RNA polymerase II as promoters are made more accessible to soluble transacting molecules. ▶introns, ▶regulation of gene activity, ▶RNA polymerase, ▶transacting element; Mellon SH et al 1988 Nucleic Acids Res 16:3963.

Identifier Syntax: In the BLAST search program this indicates the source of the information, e.g., GenBank, EMBL and Swiss-Prot. ▶gi

Identity By Descent (IBD): The shared gene(s) in a pedigree is derived from a common ancestor and is not due to an identical mutation (identity by state).

Identity Gene: This controls developmental specifications for an organ. (Science 2002 296:297–316)

Identity Index: ▶evolutionary distance

Identity of State: When the coefficient of inbreeding is determined, the identity of an allele must be specified as *identity by descent* (i.e., passed on by a common

ancestor) not by coincidentally occurring mutation. Mutation may generate only *identity by state*. ▶coefficient of inbreeding, ▶consanguinity

Idiogram: This is a diagram of the chromosome set, including all essential morphological features of chromosomes, such as arm ratio, satellites and banding pattern (see Fig. I3).

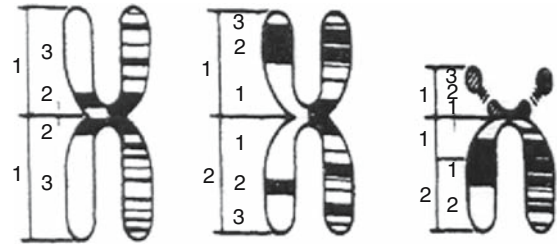


Figure I3. Idiogram

Idiomorphs: Refer to the opposite mating type-determining gene loci in fungi. Typically, they occupy the same location in various haplotypes but have a different sequence (Arie T et al 2000 Mol Plant Microbe Interact 13:1330).

Idiopathic: This means spontaneous, i.e., the cause or origin is unknown.

Idiopathic Hypogonadotropic Hypogonadism: ▶hypogonadotropic hypogonadism

Idiopathic Torsion Dystonia (ITD, DYT1, Torsin A): This is a dominant (human chromosome 9q34) neurological disorder (~30% penetrance) with onset before the late 20s, it first affects the limb muscles and the effects may later spread. Its incidence ($1.6-5 \times 10^{-4}$) is higher among Ashkenazy Jews compared to other populations. Torsin A is a protein of the ATPase family. ▶dystonia; Clarimon J et al 2005 Ann Neurol 57:765.

Idiopathic Ventricular Fibrillation (IVF): This is a common cause of fatal heart disease involving arrhythmia. Missense or splice-donor mutations in cardiac sodium channel gene SCN5A may increase the risk of developing this condition.

Idioplasm: A nineteenth century hypothetical concept about the physical basis of heredity.

Idiotope: Refers to the determinant of antigenic specificity. ▶antigen, ▶antibody

Idiotype: The term was originally coined in 1884 for identifying the entire complex of genetic determinants in a cell but it is no longer used in that sense. In modern immunogenetics it refers to idiotopes that distinguish one group of antibody producing cells

from other groups of immunoglobulin producing cells. Thus, the idiotype represents the specificity of all the idiotopes because the antigens bind within or at the idiotopes to the variable region of the antibody. The recurrent (also called public, major or cross-reactive) idiotypes regularly appear during the immune response but the private (or minor) idiotypes may or may not appear even in genetically identical individuals. ▶epitope, ▶paratope, ▶allotype, ▶isotype, ▶antibody, ▶immunoglobulins, ▶HLA, ▶anti-idiotypic, ▶internal image immunoglobulin; Jerne NK 1985 Science 229:1057.

Idiotypic Exclusion: In a family of genes only one gene product is expressed. ▶allelic exclusion, ▶locus exclusion

Idling Reaction: In amino acid starved cells synthetic activity is reduced ▶stringent control., and the ribosomes are uncharged with aminoacylated tRNAs. Under such conditions uncharged tRNAs may be attached to the ribosomes and block any residual protein synthetic activity as the idling reaction. ▶protein synthesis; Bilgin N et al 1992 J Mol Biol 224:1911.

iDNA (initiator DNA): At the onset of DNA replication the polymerase α /primase synthesizes it before polymerase δ takes over the chain elongation. ▶replication fork, ▶DNA replication; Law A et al 1998 Nucleic Acids Res 26:919.

Iduronic Acid: This is an epimer (a diastereomer [stereoisomers without being mirror images]) of glucuronic acid and dermatan sulfate, heparan sulfate and heparin. ▶mucopolysaccharidosis, ▶Hurler's syndrome, ▶glucuronic acid, ▶heparin

IES: ▶internally eliminated sequences

IEX (immediate early expressed protein): This may block apoptosis induced by FAS and TNF. Its function is mediated by NF- κ B. ▶apoptosis, ▶NF- κ B, ▶TNF, ▶FAS; Segev DL et al 2001 J Biol Chem 276:26799.

IF-1, IF-2, IF-3: These are protein synthesis initiation factors in prokaryotes and eukaryotic organelles. IF-1 is a ribosome dissociation factor and it cooperates with IF-2 and IF-3. IF2-1 and IF2-2 facilitate the binding of the tRNA^{fMet} to the AUG translation initiation codon on the 30S ribosomal subunit. In *E. coli* IF2-1 is a 97.3-kDa single polypeptide with a GTP binding domain in its center. IF2-2 is 79.7 kDa? IF-3 (20.7 kDa) is a ribosome subunit anti-association factor and a facilitator of tRNA^{fMet} and initiator codon interaction. In the eukaryote *Saccharomyces* there is a (*FUN1* gene product yIF2) homolog to the IF2. The eukaryotic eIF2 is a three

subunit functionally similar but structurally different protein. The yIF2 is present in an evolutionarily similar form from *Archaeobacteria* to eukaryotes. ▶protein synthesis, ▶eIF, ▶alarmone, ▶Shine-Dalgarno sequence; Carter AP et al 2001 Science 291:498.

IGT (irradiation and fusion gene transfer): Human chromosomes are fragmented by irradiation (~3 Krad) and then allowed to hybridize somatically with rodent chromosomes. From such a cell culture the majority of human chromosomes and fragments are eliminated but those fragments that recombine with the chromosome are retained. The co-retention of human markers sheds light on their physical proximity within the human chromosomes. ▶somatic cell hybrids, ▶chromosome assignment, ▶radiation hybrid; Walter MA, Goodfellow PN 1995 Mol Biotechnol 3(2):117.

IFN: ▶interferons, ▶IFR

IFN-Gamma: This is the same as MAF, a lymphokine.

IFR (interferon regulatory factor): This is a negative regulator of interferon and when it binds to CCE it activates histone 4 transcription, involved in the progression from the G1 to the S phase of the cell cycle. ▶histones, ▶interferons, ▶HiNF, ▶CCE, ▶cell cycle; Nakaya T et al 2001 Biochem Biophys Res Commun 283:1150.

Ig: This means immunoglobulin (with additional letters to identify various types). ▶antibody, ▶immunoglobulins, ▶immune system

Ig and Ig β : These are immunoglobulin-associated proteins that form disulfide linked heterodimers (Ig α —Ig β). They belong to a large family of antigen receptor-associated signal transducers and include a tyrosine-containing cytoplasmic motif. B cell activation requires this dimer for triggering the Src and Sky family kinases for receptor phosphorylation. These proteins play an additional regulatory role. The heterodimer is essential for the differentiation of B cells. ▶lymphocytes, ▶immunoglobulins, ▶Src, ▶Sky, ▶CD40; Rudolph AK et al 1981 Eur J Immunol 11(6):527.

IGCs: ▶speckles intranuclear

IGF: ▶insulin-like growth factor

IGI (integrated gene index): This is a list of all genes revealed in a genome. ▶IPI

IGM (inheritable genetic modification [of humans]): ▶GMO

IgNAR: This is an atypical immunoglobulin heavy chain (in cartilaginous fishes) which does not associate with

a light chain. Each heavy chain has one variable and five constant domains. ►immunoglobulins, ►antibody; Stanfield RL et al 2004 Science 305:1770.

Ignorant DNA: This molecular by-product of coincidental amplification may be slightly harmful but may also be beneficial under certain circumstances, e.g., rRNA and satellite sequences. ►selfish DNA, ►junk DNA, ►satellite; Epplen JT 1988 J Hered 79(6):409.

IGS: ►intergenic spacer

IgSF (immunoglobulin superfamily): The cell adhesion molecules (CAM) commonly contain immunoglobulin domains. These domains have a core with two face-to-face arranged β -sheets and highly variable other regions. ►immunoglobulins, ►CAM, ►protein structure

IGTC: International Gene Trap Consortium: <http://www.genetrap.org/>; ►trapping promoters

I_h (I_f): Refers to hyperpolarization-activated cation channels (HAC) in the cell membrane activated by cAMP and cGMP controlled Na⁺/K⁺ ion. Such a process determines the pacemaker activity of active neurons and heart cells. The three cloned HACs contain 863, 910 and 779 amino acids, respectively. ►hyperpolarization, ►ion channels

IHF (integration host factor): A heterodimeric host protein that is required for site-specific recombination. It may also have some function in transcription and replication. It is a member of the high mobility group proteins and its function may bear some similarity to that of histones in eukaryotes. ►high mobility group proteins, ►site-specific recombination, ►recombination, ►intasome; Holbrook JA et al 2001 J Mol Biol 310:379.

iHOP (information hyperlinked over proteins): This contains 12 million sentences over 80,000 genes for more than 1,500 organisms, including humans, mice, *Drosophila*, *Caenorhabditis*, zebrafish, *Arabidopsis* yeast, *E. coli* and others. <http://www.pdg.cnb.uam.es/UniPub/iHOP>

Ii Genes: ►ABO blood group

Ii: This is an invariant chain of the major histocompatibility complex involved in the assembly of class II molecules in the endoplasmic reticulum. This chain is subsequently degraded by lysosomal proteinases and amino acids 81–104 are retained as CLIP (class II-associated Ii peptide) before the foreign antigen is loaded on to the T lymphocytes and it is removed by chaperone H-2M. ►major histocompatibility complex, ►HLA; Frauwirth K, Shastri N 2001 Cell Immunol 209(2):97.

iIF-3P: Refers to the translation elongation factor stimulating the preinitiation complex on the 40S ribosomal subunit. ►protein synthesis, ►eIF, ►PIC

IIH: This is shorthand for TFIIH. ►transcription factors

I_{KAch}: Inwardly rectifying acetylcholine regulated K⁺ channel, activated by G_i protein, inhibits the opening of the voltage-gated Ca²⁺ channels and thus regulates nerve and muscle functions. ►ion channels, ►G_i protein

Ikaros: A transcriptional regulator of lymphocytes which is associated with pericentromeric heterochromatin. The gene is alternately spliced to generate multiple zinc finger proteins involved in gene regulation and chromatin remodeling. ►heterochromatin, ►lymphocytes; Trinh LA 2001 Genes Dev 15:1817; Lopez R A et al 2002 Proc Natl Acad Sci USA 99:602.

I κ B (inhibitor of NF- κ B): This regulatory protein binding to transcription factor NF- κ B retains it in the cytoplasm until it is degraded by proteolysis after being phosphorylated, and then it releases the transcriptional activator NF- κ B to migrate into the nucleus. The inactivation of I κ B usually requires stress signals or a pathogenic attack. Ankyrin repeats characterize the various types of I κ B and are also present in several morphogenetic factors of *Drosophila* (e.g., *cactus*). The Epstein-Barr virus nuclear antigen contains glycine-alanine (GA) repeats, which are inhibitory to cis MHC class I restricted antigen presentation. Thus, it prevents the activation of cytotoxic T cells (CTL) and the virus may evade immune recognition. The insertion of GA repeats into the I κ B α chain protects it from ubiquitination and thereby the activation of the NF- κ B transcription factor (see Fig. 14). Phosphorylation and proteolytic cleavage are key instruments in the separation of I κ B from the NF- κ B complex and it gives the two NF- κ B subunits a chance to migrate into the nucleus and serve as transcription factors. The phosphorylation of I κ B is carried out by the morphogenesis factor and cytokine-activated kinases IKK- α and - β isozymes (M_r 70–90 K), respectively. IKK is part of a large complex which also includes an associated scaffold protein (IKAP, 150 K M_r). I κ B is modified by the ubiquitin-carrier protein SUMO-1 and it is therefore not ubiquitinated and protected from degradation by proteasomes. While ubiquitination is favored by phosphorylation, SUMO-1 is inhibited by phosphorylation. I κ B ζ is an inducible protein which regulates the expression of the Toll/IL-1 receptor and associated genes (Yamamoto M et al 2004 Nature [Lond] 430:218).

I κ B-Ras1 and 2 proteins degrade the I κ B β subunit at a lower rate than the α subunit.

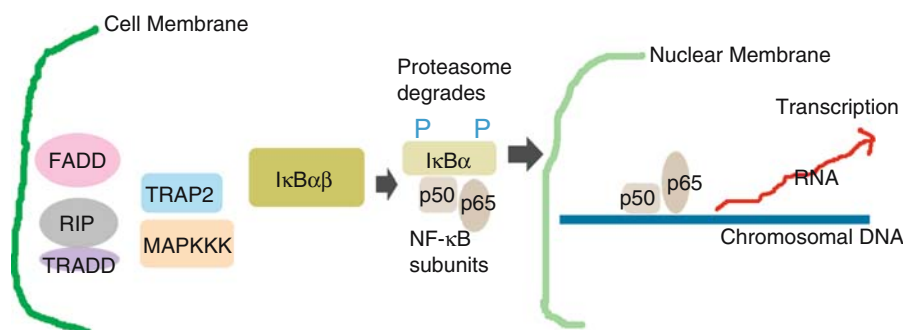


Figure 14. The action path of IκB (Modified after T. Mariatis 1997 Science 278:818)

►signal transduction, ►regulation of gene activity, ►NF-κB, ►FADD, ►RIP, ►TRADD, ►MAPKKK, ►PEST, ►TNF, ►glucocorticoid, ►immunosuppression, ►ankyrin, ►morphogenesis in *Drosophila*, ►ubiquitin, ►antigen presenting cell, ►PIC, ►IKK, ►NIK, ►RAS; Imbert V et al 1996 Cell 86:787; Pahl HL 1999 Oncogene 18:6853; Bottero V et al 2001 J Biol Chem 276:21317; Ruefli-Basse AA et al 2003 Science 302:1581.

IKK: Denotes IκB protein serine kinases. IKKα (IKK1) responds to morphogenetic signals in the activation of NF-κB whereas IKKβ responds to proinflammatory cytokines and controls NF-κB, which in turn regulates inflammation and apoptosis. IKKα phosphorylates histone H3 and thus mediates cytokine-induced gene expression of NF-κB-dependent genes (Yamamoto Y et al 2003 Nature [Lond] 423:655). IKKγ (NEMO) is a modulatory subunit of NF-κB. Aspirin inhibits IKKβ. ►IκB, ►NAK, ►NF-κB, ►NEMO, ►aspirin, ►cyclooxygenase, ►Akt, ►ectodermal dysplasia, ►prostate cancer; Senftleben U et al 2001 Science 293:1495.

IL: Refers to interleukin. (See O'Neill LAJ, Bowie A eds. 2001 Interleukin Protocols, Humana Press, Totowa, NJ, USA).

IL-1: This is a lymphocyte-activating factor. The IL-1α (17-kDa) and β (also about 17-kDa) chains are encoded in human chromosome 2q13 at very close linkage. IL-1ra is a cytokine receptor antagonist of IL-1. The IL-1 receptors (IL-1R) are encoded close by in human chromosome 2. IL-1 mediates Ser/Thr phosphorylation of various proteins (cytoskeleton) and Hsp27. The IL-1 activated Ser/Thr kinase is IRAK and the specific transduced molecule is TRAF6. These molecules are elements of the NF-κB cascade. The IL-1 system is involved with the hematopoietic cells, the neuroendocrine and the central nervous systems. It generally cooperates with TNF. IL-1 has clinical implications for inflammations, blood coagulation, osteoporosis, metastasis, neurodegenerative

and autoimmune diseases. ►interleukins, ►IL-17, ►prostaglandin, ►Toll, ►mental retardation, ►dendritic cell, ►ICE, ►NF-κB, ►IRAK, ►TNF, ►hepcidin; Bomford R, Henderson B eds. 1990 Interleukin-1, Elsevier, New York.

IL-2: Refers to the T-cell growth factor, TCGF, a ~15.5-kDa glycoprotein, encoded at 4q26-q27. It promotes the proliferation and differentiation of lymphocytes. The discovery of IL-2 has made possible the long time culture of T cells. The IL-2Rβ and the IL-2Rγ chain subunits are members of the cytokine receptor superfamily. The IL-2Rβ (human chromosome 22q11.2-12) and γ (Xq13) chains are shared by the other IL receptors. The human IL2Rα (chromosome 10p14-p15) has only 13 amino acids in its cytoplasmic domain and it may not have a significant role in signal transduction. The IL-R receptor complex has a prominent role in various signal transduction pathways. Mice with the IL-2 receptor chain β (IL-Rβ) show excessive differentiation of B cells into plasma cells and excessive amounts of immunoglobulins G1 and E and the production of autoantibodies resulting in hemolytic anemia. Defects in the widely shared IL-2Rγ cause severe combined immunodeficiency (SCID) in humans. It is synthesized primarily by CD4⁺-T_H lymphocytes. The IL-2 gene is activated by a Jun kinase at the 5'-untranslated region and also modulated at the 3'-untranslated sequences. IL-2 may serve as an adjuvant in genetic immunization. ►interleukins, ►B cells, ►T cells, ►immunoglobulins, ►autoantibody, ►anemia, ►SCID, ►cytokines, ►NF-AT, ►AP-1, ►Oct-1, ►NF-κB, ►RAP1, ►JUN, ►ICOS, ►cytokines, ►memory immunological, ►immunization genetic; Lotzova E, Herberman RB eds. 1990 Interleukin-2 and Killer Cells in Cancer, CRC Press, Boca Raton, FL; structure of IL-2 and its α receptor: Rickert M et al 2005 Science 308:1477.

IL-3: This haematopoietic growth factor is a 28-kDa glycoprotein secreted by CD4⁺ lymphocytes, encoded in human chromosome 5q31. IL-3 is within a

gene cluster IL-3—CSF2—IL-13—IL-4—IL-5→ centromere. IL-3 plays an important role in the development of immunity to parasites by stimulating the formation of hematopoietic effector cells. Together with IL-13 they inhibit inflammation and boost humoral immunity and IgE responses. ►interleukins, ►hematopoiesis, ►IL-13, ►CIS, ►allergy; Craddock BL et al 2001 J Biol Chem 276:24274.

IL-4: B-cell growth factor, ~18-kDa glycoprotein, encoded at human chromosome 5q31.1. It stimulates the formation of immunoglobulins G and IgE. Its receptor is encoded at 16p12.1-p11.2. The activation of gene expression by IL-4 requires phosphorylation of tyrosine, homodimerization and nuclear translocation of STAT6. IFN- β and - γ inhibit IL-4 induced activation of STAT6 and STAT6 induced genes partly by inducing SOCS-1. IL-4 and IL-13 are implicated in asthma and allergic reactions. ►interleukins, ►immunoglobulins, ►IL-13, ►IL-3, ►STAT, ►IFN, ►SOCS, ►asthma; Spitz H 1992 IL-4: Structure and Function, CRC Press, Boca Raton, FL; Kelly-Welch AE et al 2003 Science 300:1527; IL-4 antagonist structure: LaPorte SL et al 2005 Proc Natl Acad Sci USA 102:1889.

IL-5 (eosinophil differentiation factor): This is encoded at human chromosome 5q31. IL-5R α is expressed on B lymphocytes, eosinophilic and basophilic granulocytes. It is involved in the differentiation of B cells by being associated with the syntenin protein that binds transcription factor Sox4. ►IL-3, ►lymphocytes, ►syntenin, ►allergy, ►Sox; Geijsen N et al 2001 Science 293:1136.

IL-6 (IFN- β 2/BSF-2): An interleukin group of proteins (21–28-kDa), encoded in human chromosome 7p21, it binds to upstream DNA sequences in some genes. Its receptor, IL-6R, is a transmembrane protein. IL-6 formation is induced by infection and primarily mediates humoral immune reactions. The IL-6 promoter contains GRE, AP-1, SRE and other transcription factor-binding sites. The IL-6 receptor (IL-6R) is trimeric and includes gp130 (918 amino acids, encoded at 5q21), IL-6R α chain (80-kDa, encoded at 1q21) and IL-6. Its level is correlated with total body fat; IL-6 and IL-1 deficiency together causes hyperphagia and obesity in mice (Chida D et al 2006 Diabetes 55:971). ►interleukins, ►GRE, ►AP-1, ►SRE, ►CRE, ►gp130, ►hepcidin; Marsch J et al eds. 1992 Polyfunctional Cytokines: IL-6 and Lf, Wiley, New York; MacKiewicz A et al eds. 1995 Interleukin-6-Type Cytokines, Annals of the New York Academy of Science vol. 762.

IL-7 (lymphopoietin, ~25-kDa): Stimulates lymphocyte precursors in the bone marrow. It is indispensable for normal proliferation of T cells. If the α -chain

of the IL-7 receptor is defective in mice, D-J joining is normal in immature B cells but recombination of the distantly situated heavy chain V gene segments is progressively impaired in proportion to their distance from D-J. The IL-7 receptor ligands seem to signal for the recombination by regulating the access of the recombinase to the DNA. IL-7 promotes embryonic neurons. It regulates antiviral CD4⁺ T cell memory (Lenz DC et al 2004 Proc Natl Acad Sci USA 101:9357). ►immunoglobulins, ►B cell, ►T cell, ►TNF, ►osteoporosis; Tan JT et al 2001 Proc Natl Acad Sci USA 98:8732.

IL-8: This activates neutrophils, cell migration, adhesion, inflammation. ►SDF, ►melanoma growth-stimulatory factor; Xie K 2001 Cytokine Growth Factor Rev 12(4):375.

IL-9 (32–39-kDa glycoprotein): An erythroid colony stimulating factor that promotes (mast) cell proliferation and differentiation. The IL-9 receptor (522 amino acids) is encoded in the pseudoautosomal region of Xq28. But pseudogenes are found at 9p34, 10p15, 16p13.3 and 18p11.3 as well in the X and Y chromosomes. IL-9R appears to be constitutively expressed in Hodgkin's disease and seems to be involved in asthma. IL-9 appears to stimulate myeloid leukemia. ►pseudoautosomal, ►Hodgkin's disease, ►pseudogene, ►mast cells, ►asthma, ►T cell regulatory, ►leukemia; Demoulin JB et al 2001 Cell Growth Diff 12(3):169.

IL-10 (CSIF): This 18.5-kDa protein encoded at 1q31-q32 is produced primarily by T_H cells and acts as a cytokine synthesis inhibitor, yet it may stimulate the growth of mast cells and CD8⁺ T cells. IL-10 is involved in autoimmune diseases, protozoan, fungal and bacterial infections and various carcinomas. Its receptor (hIL-10R, 90–110-kDa) is similar to the interferon receptors and is encoded at 11q23.3. A second receptor gene is in human chromosome 21. IL-10 signals through the Jak-STAT and Tyk2 pathways. Gene therapy used for the alleviation of inflammation seems promising. ►mast cell, ►T cell, ►ICOS, ►signal transduction, ►osteopontin, ►Tyk2; Moore KW et al 2001 Annu Rev Immunol 19:683; Xing Z, Wang J 2000 Curr Pharm Des 6:599.

IL-11 (23-kDa, encoded at 19q13.3): This controls hematopoiesis in the bone marrow. Many of its functions overlap with those of IL-6. The ~43 kDa IL-11 receptor, IL-11R α 1 chain is encoded at 9p13 close to IL-11R α 2. They recruit gp130 and gp190 glycoproteins and activate the Jak/Tyk cytoplasmic tyrosine kinases. ►hematopoiesis, ►gp130, ►gp190; Kaye JA 1996 Stem Cells 14 Suppl 1:274.

IL-12 (interleukin-12): A heterodimeric cytokine that is, one of the most potent stimulators of T helper cells (T_H), natural killer cells (NK) and B lymphocytes, it increases the production of interferon γ (IFN- γ). It is produced by macrophages, neutrophils, dendritic cells and B lymphocytes. The light chain (p35) is encoded at human chromosome 3p12-q132 and the heavy chain (p40) is at 5q31-q33.1. IL-12 receptor (IL12R) deficiency causes susceptibility to infections. Microbial lipoproteins stimulate IL-12 production by macrophages and the process is mediated by Toll-like receptors. Nitric oxide synthase (NOS2) is important in mediating signaling to IL-12. IL-12 is a very promising tool in controlling HIV, Leishmaniasis, malaria, tuberculosis, schistosomiasis and other infectious diseases although some of its side effects (toxic shock syndrome, atherosclerosis) may limit its application. separate entries, ►osteopontine; Lotze MT et al eds. 1996 Interleukin 12, Annals of the New York Academy Science Volume 795; Picard C et al 2002 Am J Hum Genet 70:336.

IL-13: The 131 or 132 amino acid protein is encoded at human chromosome 5q31. It is a monocyte and B lymphocyte regulator, synergistic with IL-2. It is functionally related to IL-4 although the homology between the two is about ~20%. Unlike IL-4, IL-13 is not a T cell proliferation factor. IL-13 receptor $\alpha 1$ subunit is encoded at Xq13. ►IL-3, ►IL-4, ►asthma; Chiaramonte MG et al 1999 J Immunol 162:920.

IL-14: This is produced by activated T cells and B cell lymphoma. ►T cell, ►lymphoma; Ford R et al 1995 Blood 86:283.

IL-15: A ~114 amino acid T- cell growth factor, encoded at human chromosome 4q13, is produced by monocytes and epithelial cells. IL-15 induces the proliferation of activated T cells and B cells. Along with IL-2 it boosts the production of IFN γ and TNF α . ►T cell, ►monocyte, ►IFN, ►TNF, ►memory immunological, ►chymase; Perera LP 2000 Arch Immunol Ther Exp 48(6):457.

IL-16 (LCF, lymphocyte chemoattractant): This 130 amino acid lymphokine (M_r 13,500) is secreted by activated CD8 $^+$ cells, it binds to T cells by the CD4 receptor and suppresses HIV and SIV. ►HIV, ►SIV, ►T cell; Cruikshank WW et al 2000 J Leukoc Biol 67(6):757.

IL-17 (CTLA-8): An interleukin with homology to ORF13 of Herpes Virus Samiri (HVS). The human IL-17 is a 20 to 30-kDa homodimeric protein. It regulates cytokine and (leukemia) oncogene mRNA stability. Along with IL-1, it is involved in the activation of T cells and thus plays a role in autoimmune arthritis (Nakae S et al 2003 Proc Natl

Acad Sci USA 100:5986). IL-17 producing CD4 T cells form a separate lineage from the T_H1 and T_H2 helper cells and play a central role in inflammatory responses (Harrington LE et al 2005 Nature Immunol 6:11213; Park H et al 2005 Nature Immunol 6:1133). ROR γ t orphan receptor directs the differentiation of proinflammatory IL-17 $^+$ TH cells (Ivanov II et al 2006 Cell 126:1121). ►CTLA, ►IL-1, ►IL-25, ►arthritis, ►inflammation, ►T cells, ►T H , ►ROR; Shi Y et al 2000 J Biol Chem 275:19167.

IL-18 (IGIF, interferon γ inducing factor): This is produced by peripheral blood mononuclear cells, dendritic cells, intestinal epithelial cells, osteoblastic stroma cells and upon stimulation by monocytes, macrophages (Kupffer cells). It has two different immunoglobulin receptors. IL-18 enhances inflammatory responses but in cooperation with IL-12 it is antiallergic. IL-18 activates natural killer lymphocytes, T_H cells and the production of interferon γ . It is a defense molecule against bacteria, viruses, some fungal pathogens and protozoa. Along with IL-12 and INF γ it may cause tumor regression. Its therapeutic use, however, is hampered because of the toxicity of cytokines and also because it leads to inflammatory and autoimmune reactions. ►monocytes, ►killer cell, ►T H , ►interferons, ►cytokines, ►Kupffer cell, ►autoimmune disease; Nakanishi K et al 2001 Annu Rev Immunol 19:423.

IL-20: A 176 amino acid homolog of IL-10, its overexpression in transgenic mice is lethal. IL-20 binding activates STAT3 in keratinocytes. It is upregulated in psoriasis. ►psoriasis, ►STAT, ►keratin; Rich BE, Kupper TS 2001 Curr Biol 11:R531; Blumberg H et al 2001 Cell 104:9.

IL-21: Along with its receptor (IL21R) IL-21 regulates the clonal expansion of natural killer lymphocytes and the production of immunoglobulins. ►autoimmune disease; Parrish-Novak J et al 2000 Nature [Lond] 408:57; Ozaki K et al 2002 Science 298:1630.

IL-22 (12q15): A cytokine of epithelial tissues which mediates epithelial innate immunity when activated by CD4 $^+$ T cells and T_H cells.

IL-23 (human chromosome 12): This is a heterodimeric cytokine which shares a p40 subunit with IL-12. It stimulates IL-17 and is critical for the inflammation response of the brain and other tissues. IL-23 is increased in tumors and upregulates matrix metalloprotease MMP9, it increases angiogenesis and reduces infiltration (tumor surveillance) by CD8 T cells. In contrast IL-12 promotes tumor surveillance as well as the cytotoxic effect of T cells (Langowski JL et al 2006 Nature 442:461). ►IL-12, ►IL-17, ►immunological surveillance, ►T cell, ►acanthosis,

►**metalloproteinases**; Aggarwal SW et al 2003 J Biol Chem 278:1910; Cua DJ et al 2003 Nature [Lond] 421:744.

IL-24: ►**mda-7**

IL-25: This is a suppressor of inflammatory responses (Kleinschek MA et al 2007 J Exp Med 204:161).
►**IL-17**

IL-32: An inducer of tumor necrosis factor α , IL-1, IL-6 and IL-8, it appears to be involved in the inflammatory pathway, including rheumatoid arthritis. ►**TNF**, ►**IL-1**, ►**IL-6**, ►**IL-8**, ►**rheumatoid fever**; Kim S-H et al 2005 Immunity 22:131; Joosten LAB et al 2006 Proc Natl Acad Sci USA 103:3298.

IL-33: This is an IL-1 like interleukin; its receptor is ST2 and it activates NF- κ B and MAP kinases. In vivo, it induces the expression of IL-4, IL-5 and IL-13 (Schmitz J et al 2005 Immunity 23:479). ►**IL-1**, ►**IL-4**, ►**IL-5**, ►**IL-13**, ►**NF- κ B**, ►**MAP kinases**

ILK (integrin-linked protein kinase): It phosphorylates protein kinaseB, Akt and cyclins. ►**protein kinases**, ►**Akt**, ►**integrin**, ►**cyclins**; Yamaji S et al 2001 J Cell Biol 153:1251.

Illegitimate Child: Such a child is sired by a male other than the legal father. This status can be ascertained by DNA fingerprinting. The mother is always certain. Illegitimacy, contrary to some myths, does not endow the “love baby” with better abilities, despite some famous examples (Leonardo da Vinci, Francis Bacon, etc.). The out-of-wedlock children generally suffer physical and emotional stress. Illegitimate offspring in old pedigrees may confound recombination frequencies, especially at tight linkage, it may cause problems in prenatal diagnosis of some disorders, and may frustrate genetic counseling. ►**DNA fingerprinting**, ►**prenatal diagnosis**, ►**genetic counseling**

Illegitimate Insertion: Insertion elements may be incorporated into the genome by a process that does not require complete or even substantial homology unlike general recombination events that usually have the requisite of homology between the sites of recombination. Restriction enzymes may facilitate integration when it is non-homologous but do not promote homologous insertion. ►**illegitimate recombination**; Manivasakam P et al 2001 Nucleic Acids Res 29:4826.

Illegitimate Pairing: Refers to the synapsis between not entirely identical strands, which may lead to aberrant crossover products. ►**oblique crossing over**, ►**unequal crossing over**

Illegitimate Recombination: Refers to recombination when the synaptic strands are not or not entirely

homologous (microhomology). Insertion and transposable elements are integrated by non-homologous recombination and their target site shows minimal homology. ►**homologous combination**, ►**non-homologous recombination**, ►**non-homologous end-joining**, ►**recombination**, ►**ectopic recombination**, ►**Ku**, ►**DNA ligases**, ►**synapsis**, ►**RecA-independent recombination**, ►**insertion element**, ►**transposable elements**; Ehrlich SD et al 1993 Gene 135:161; Hanada K et al 2001 J Bacteriol 183:4964.

Illumination: Various types of units of measurement are in use. The most common unit is Lux = 1 standard new candela from 1 m distance per 1 m^{-2} or it is measured in watt or joule units. ►**joule**, ►**watt**, ►**candela**

ILTs (LIR, MIR, CD85, human chromosome 19q): These are surface receptors on monocytes, macrophages, dendritic cells and B lymphocytes containing immunoglobulin-like domains and most of them carry ITIM sequences in the cytoplasmic side. ILT1 and ILT7 lack ITIM and are associated with ITAM containing Fc ϵ RI γ membrane adaptor protein. ►**ITAM**, ►**ITIM**, ►**Fc ϵ RI γ** ; Volz A et al 2001 Immunol Rev 181:39.

Image Analyzer (image processor): This technique uses video cameras with high light sensitivity, attached to the microscope. The camera is connected to a computer that can further enhance the image recorded by the camera. Thus it can electronically enhance (by digitalization) and process the image and can detect details that cannot be perceived by directly viewing through the microscope. The electronic system may show the picture in “false colors”, i.e., selected by the operator rather than the natural color of the object. The use of such devices can rid the image of background “noise” and greatly enhance its clarity. In addition, the operator’s eyes are not stressed. The tissue-specific distribution and expression of the bacterial luciferase transgene can be monitored by the microchannel plate enhanced photon counting analyzers. This set-up consists of a microscope, an image processor, a TV monitor and a computer. The heart of the equipment can be outlined as:

MICROSCOPE → photocathode
→ microchannel plates
→ phosphor screen → DISCRIMINATING
VIDICON

This system can resolve a single photon. By comparison a single native bacterial cell releases about 10,000 photons. Image analyzer (e.g., VAX Station II/GP4) is also used for scanning DNA fingerprint autoradiograms. ►**microscopy**, ►**luciferase**

Image Clones: These are gridded sequences verified (Research Genetics: <http://www.resgen.com/>) or not sequence verified human and other gene clones, gene clusters, suitable for microarray hybridization. ▶ **Uni-Gene**, ▶ **microarray hybridization**

Image Processing: ▶ **image analyzer**

Imaginal Disks: After fertilization of the *Drosophila* egg, the zygote nucleus begins to divide within a common cytoplasm and forms a syncytium (a multinucleate protoplasm) without actual separation by cell membranes. After about 2 h and almost 13 divisions the cellular blastoderm stage is reached (around 6,000 cells). Then the cells move to the periphery of the embryo and the yolk occupies the central space. Within less than 24 h the larva is hatched and this developmental stage (3 instar steps) lasts for about 4 days. Inside the larva some groups of cells, distinguishable by location, shape and size, the *imaginal disks* (50,000 cells) are set aside for serving as initials for the various organs and structures of the adult organism. The larva does not use the imaginal disks and removal of these disks does not kill the organism. As the larva is metamorphosed into pupa most of the larval tissues disintegrate to support the development of the differentiation from the disks. During pupation, from these “prefabricated elements”, the imago is assembled by cell and tissue fusions. From the anterior (front) part the head, from the middle region the thorax and from the posterior (hind) part the abdomen develop. If the imaginal disks are removed from their original position after the 3rd instar stage (about 5 days) and grafted into a new location of another larva, these disks develop into an extra eye, a wing, a leg or other structures, depending on which imaginal disk has been chosen for the surgery and not on the host tissue. Thus, in the imaginal disks developmental determination is completed much before the onset of morphological and functional differentiation. For correct differentiation it is necessary that the transplant is done in a larva and not in an adult. In the abdomen of an adult the disks only proliferate. After a series of transfers through adults, the original determination of the disks may change, and when the proliferated disk tissue is transplanted into a larva, an antennal disk may lead to the development of a leg instead. This altered course of differentiation is called *transdetermination*. The path of transdetermination is not accidental or random. For example, a genital disk may develop into a proboscis (mouthpart) or may pass through some indirect steps in a certain order such as genitalia → proboscis → antenna → leg. A wing from the genital disk cannot be formed directly but may develop through an antenna or a leg. The process of transdetermination is only a change in competence for

differentiation without a mutational change whereas in homeotic mutants one structure is replaced or altered after a change in the DNA. ▶ *Drosophila*, ▶ **morphogenesis**, ▶ **homeotic genes**, ▶ **development**, ▶ **fate maps**, ▶ **determination**, ▶ **proboscis**, ▶ **antenna**, ▶ **blastoderm**, ▶ **homeotic mutants**; Ramirez-Weber F-A, Kornberg TB 2000 Cell 103:189.

Imaging: New technologies (fMRI, tomography, endoscopic confocal microscopy) permit scanning of the whole body to monitor the turning on of genes and follow metabolic processes (including activities in the brain), stages of cancer and its metastasis, without sacrificing the animals or invasive examination of humans. The use of [^{18}F] fluorodeoxyglucose is selectively done by cells of high glucose metabolism (cancer) and facilitates the identification of malignancy when used with tomography (FDG-PET). Vascular cell adhesion molecule (VCAM) can be used to reveal increased angiogenesis in cancer. Radio-labelled Annexin V and TRAIL can reveal apoptosis. The anti-tumor efficacy of epothilones (spindle-fiber poisons) can be detected. ▶ **nuclear magnetic resonance spectroscopy**, ▶ **microscopy**, ▶ **image analyzer**, ▶ **tomography**, ▶ **angiogenesis**, ▶ **annexin**, ▶ **TRAIL**, ▶ **VCAM**, ▶ **epothilone**; Swedlow JR et al 2003 Science 300:100; Weissleder R 2006 Science 312:1168.

Imago: Refers to the adult form of an insect either male or female (see Fig. 15). ▶ *Drosophila*, ▶ **imaginal disk**

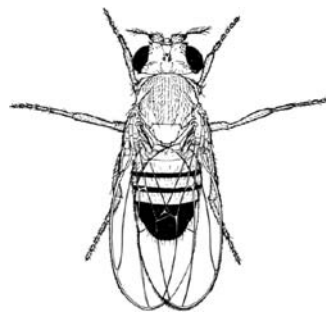


Figure 15. Imago

Imatinib: ▶ **Gleevec**, ▶ **Desatinib**

Imbibition: Refers to the absorption of water or other liquids.

IMC: Denotes intramolecular chaperone. ▶ **chaperone**

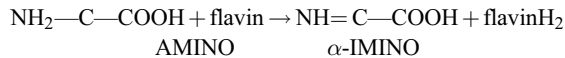
Imerslund–Grasbeck Syndrome: This refers to megaloblastic anemia (MGA1).

Imidazole: This is present in many organic molecules and may mediate tautomerism. ▶ **Src**, ▶ **tautomeric shift** (see Fig. 16).



Figure I6. Imidazole

Imino Form: Refers to a type of an amino acid that arises from an amino form according to the following reaction:



Similar transformation can take place in nucleotides and can facilitate unusual hydrogen pairing between bromouracil and guanine or cytosine and adenine. ▶[hydrogen pairing](#)

Iminoaciduria: Proline and hydroxyproline use the semi-recessive renal glycine reabsorption mechanism and when it fails these amino acids accumulate in the urine. ▶[aminoacidurias](#)

Iminoglycinuria: In this condition excessive proline and hydroxyproline are present in the urine. This is probably due to heterozygosity of hyperglycinuria. ▶[hyperglycinemia](#)

Imitatory Epigenotype: This theory assumes that the functional units of the phenotype are genetically modular and integrated within the group and relatively independent of the rest of the phenotype. It can be studied by the statistical methods used for QTL. ▶[QTL](#); Mezey JG et al 2000 Genetics 156:305.

Immediate Early Genes: These early genes of a virus are first turned on after infection without any requirement for synthesizing virally encoded proteins. ▶[delayed early genes](#), ▶[late genes](#)

Immobiline: Precast gel strips for first-dimensional run in two-dimensional gel-electrophoresis.

Immortalization: Denotes that a cell in a culture will not senesce but will proliferate indefinitely. Normally, cultured cells die but cancerous transformation or by fusing normal cells with a cancer cell makes them “immortal”. Immortalization and tumorous growth are, however, under separate genetic control. Cells of the germ line are also practically immortal because of their transmission from generation to generation until the extinction of the strain. ▶[hybridoma](#), ▶[cancer](#), ▶[telomeres](#), ▶[p16^{INK}](#); Tevethia MJ, Ozer HL 2001 Methods Mol Biol 165:185.

Immune Clearance: Refers to the destruction of infecting foreign cells by the phagocytotic activity of various special lymphocytes. Its major sites are in the liver, and to a lesser degree in the spleen but other

tissues with phagocytotic activity may also perform this function. The C3 complement and its receptors, C5b-9 and IgG, are important factors. ▶[complement](#), ▶[immunoglobulins](#)

Immune Deviation: In non-atopics postnatal exposure to inhalant allergens may redirect the fetal immune response toward the T_H1-like cytokine pattern. ▶[atopy](#), ▶[allergen](#), ▶[allergy](#), ▶[asthma](#)

Immune Evasion (immune escape): Some viruses may inactivate the MHC class I antigen presentation system and thus escape the attention of the cytotoxic T lymphocytes (CTL). Nevertheless, the killer cells (NK) may destroy the invader. Herpes simplex viruses may inactivate or interfere with the TAP transporters and various subunits of the proteasomes. In HIV-infected human cells the peptide epitopes of the virus may mutate and rather than being a ligand they may serve as T cell receptor antagonists resulting in the inactivation of the HIV-specific T cells. Some adenoviral glycoproteins immobilize the MHC class I molecules to the endoplasmic reticulum. Some cytomegaloviruses (CMVs) make proteins that bind to the MHC class I molecules and “dislocate” the heavy chains into the cytosol (from the endoplasmic reticulum) and thus the proteasomes destroy them. Another trick of some viruses to mediate the internalization and thus inactivation of the MHC I proteins. CMVs may produce their own MHC class I homolog proteins (UL18, m144) that help evade natural killer cell attacks on the virus. These protein homologs may regulate the immune system in various other ways as well. CMV may also down regulate the synthesis of the MHC II type molecules involved in the B lymphocyte defense system. An IL-10 homolog encoded by the Epstein-Barr Virus (EBV) may interfere with T cell function. The inhibition of the mRNA translation of the virus-encoded antigen limits antigen presentation on the MHC class I molecules to CTL (Yin Y et al 2003 Science 301:1371). Viral IL-10 homologs may subvert the IL-12-regulated interferon, cytokine and TAP production. Some viruses may interfere with the process of apoptosis, used by the organ to pathogen infected cells before the maturing infective viral particles could be released. *Staphylococcus* bacteria secrete poly- γ -DL-glutamic acid (PGA) to facilitate growth and survival in human hosts. PGA shelters *S. epidermidis* – an opportunistic hospital-acquired pathogen—against host antimicrobial peptides and neutrophil phagocytosis (Kocianova S et al 2005 J Clin Invest 115:688). Some bacteria and viruses modulate the surface structures (inhibit the complement of the host or display antigenic variations) in order to avoid recognition. The pathogens may activate or interfere with the Toll-like receptor

(TLC) signaling pathway. Host receptors may be degraded, antigen presentation may be inhibited, cell surface molecules may be modulated, etc. ▶ [immune system](#), ▶ [antigen presenting cell](#), ▶ [epitope](#), ▶ [anti-microbial peptides](#), ▶ [neutrophil](#), ▶ [MHC](#); T cell; MICA; Kavanagh DG et al 2001 J Exp Med 194:967; Groh V et al 2002 Nature [Lond] 419:734; common and specific principles of immune evasion by viruses and bacteria: Finlay BB, McFadden G 2006 Cell 124:767.

Immune Homeostasis: After an immune reaction the immune system is reset to the pre-immunization state and can then respond to a new antigen. ▶ [immune system](#)

Immune Privilege: Grafts to certain sites (eyes, testes, brain) may be protected from rejection caused by the constitutive expression of the Fas ligand (FasL). Other factors may be blood tissue barriers, direct secretion of the tissue fluid into the blood, absence of efferent lymphatics, potent immunosuppressive environment (TGF β), reduced expression or induction of MHC, neuropeptides, α -melanocyte-stimulating hormone, vasoactive intestinal peptide, calcitonin gene-related peptide [CGRP], and membrane-bound inhibitors of the complement activation and fixation. Immune privilege may be necessary for pregnancy, for avoiding certain diseases and graft rejection, etc. ▶ [TGF](#), ▶ [Fas](#), ▶ [MHC](#), ▶ [calcitonin](#), ▶ [complement](#); Rall GF et al 1995 J Exp Med 182:1201; O'Connell J et al 2001 Nature Med 7:321.

Immune Response: The response is mounted by the body against foreign invaders. It may be triggered by sensing some surface architectural elements of the invader (*stranger hypothesis*) or by stress signals emanating from the cells/tissues in the stressed body (*danger hypothesis*). Such signals may be conveyed by uric acid crystals, which are degradation products of nucleic acids. The dendritic cells then present the foreign antigen to the CD8⁺ T lymphocytes. The dendritic cells can also recognize the infectious agents by their Toll-like receptors and migrate to the lymphoid organs and secrete interleukin-12 (IL-12). Here they encounter CD4 T cells which can develop into either Th₁ or Th₂ helper T cells. The Th₁ lymphocytes secrete interferon- γ and mediate immunity against viruses or bacteria. The Th₂ effector cells use interleukin-4 (IL-4) to protect against multicellular pathogens or allergens. Correct recognition is important because inappropriate reaction may result not only in lack of protection, but also in autoimmune disease or allergy. In the activation of the Th₁ cells the four Notch receptors and their five ligands play a key role under the influence of the RBPJ κ transcription factor (a mammalian homolog of the *Drosophila*

Suppressor of Hairless [*Su(H)*]). If RBPJ κ is reduced or absent (in mouse cells) Th₂ development is favored. ▶ [MHC](#), ▶ [immune system](#), ▶ [glycans](#); Heath WR, Carbone FR 2003 Nature [Lond] 425:

460; Shi Y et al 2003 Nature [Lond] 425:516; Amsen D et al 2004 Cell 117:515; Tanigaki K et al 2004 Immunity 20:611.

Immune Selection: Refers to the process by which pathogens are capable of evading or resisting the host immune system.

Immune Suppression: Refers to the removal or inactivation of the antigen. This can be achieved by destroying the target cells by CTL, B cells, macrophages or killer cells or by cytokines and other immunosuppressive agents. An immunosuppressive drug reduces the body's ability to mount an immune response and defend against foreign antigens. Contradiction prevents suppression and allows for the development of immunity. ▶ [immune tolerance](#), ▶ [CTL](#), ▶ [killer cell](#), ▶ [veto cell](#); Takemoto SK 2000 Clin Transpl 481.

Immune Surveillance: ▶ [immunological surveillance](#)

Immune Synapse: On the surface of natural killer T cells (NK) inhibitory immunoglobulin-like receptors (KIR1, KIR2) occur that cause clustering of HLA-C molecules at the surface of the target cells. At the target and the NK cells HLA—KIR forms rings around the intercellular cell adhesion molecules and lymphocyte-associated antigen-1 for about 20 minutes. Multiple such synapses may occur as the T cells invade the selected target. Synapse formation requires the reorganization of the cytoskeleton of the T cells and the antigen-presenting cells. ▶ [killer cell](#), ▶ [KIR](#), ▶ [HLA](#), ▶ [antigen](#), ▶ [agrin](#), ▶ [cytoskeleton](#), ▶ [antigen-presenting cell](#); Khan AA et al 2001 Science 292:1681; Dustin ML, Coper JA 2000 Nature Immunol 1:23; van der Merwe PA, Davis SJ 2002 Science 295:1479.

Immune System: Refers to a complex defense organization of vertebrate animals. The main cellular components of the immune system are the lymphocytes and macrophages. B lymphocytes synthesize the antibodies that react and destroy the foreign antigens. T lymphocytes generate the antigen receptor-MHC protein complex that specifically recognizes individual antibodies and is involved in the destruction of foreign antigens (see Fig. 17). Lower animals may use phagocytosis as defense. Plants do not have an immune system like animals yet they also have pathogen-associated molecular mechanisms for recognition by the so-called elicitors. Some of the elicitors are peptides. A 23-amino acid peptide of *Arabidopsis* (*AtPep1*) activates the transcription of the defending

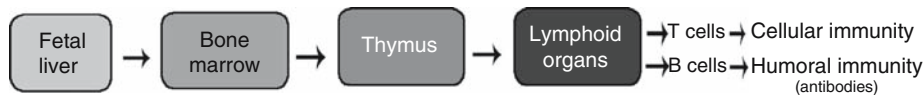


Figure 17. Development of the immune system and major components

gene (*PDF1.2*) and the synthesis of H_2O_2 . The precursor of the peptide (92 amino acids) can be induced by wounding, methyl jasmonate and ethylene. There are 6 paralogs of *PDF1.2* in *Arabidopsis* and orthologs occur in other plant species (Huffaker A et al 2006 Proc Natl Acad Sci USA 103:10098). The *AtPep1* receptor also functions in transgenic tobacco plants (Yamaguchi Y et al 2006 Proc Natl Acad Sci USA 103:10104).

The immune system protects the body from microbial infections and also from non-infectious foreign macromolecules such as proteins, polysaccharides and tissue grafts.

Smaller foreign molecules (*haptens*) may also trigger the immune system primarily when associated with proteins. The molecules that elicit the immune response are called antigens. Antigens stimulate the formation of antibodies which are the actual defense molecules. The immune reaction is extremely specific and minute differences between antigens, such as single amino acid substitutions or isomers may be particularly recognized. The immune system distinguishes the body's own antigens from those of extraneous origin. The absence of an immune response to the body's self antigens is known as *acquired immunological tolerance*. The tolerance, i.e., distinguishing self from foreign molecules develops in the thymocytes by negative selection of self-reacting T cells. The T cell antigen receptor controls the activation and subcellular localization of Ras and MAPK signaling intermediates and by a subtle margin and thus develops self-tolerance (Daniels MA et al 2006 Nature [Lond] 444:724).

The immature immune system may learn to ignore even a foreign antigen if exposed to it at a very early stage. Immunological tolerance may be produced in the later stages of development with immunosuppressive drugs, by very high or repeated exposure to extremely low amounts of the foreign antigen. Also, altering the so-called *antigen-presenting cells* may affect tolerance. These antigen-presenting cells bind, process and combine foreign antigens with Class I and II proteins of the HLA complex (MHC). T lymphocytes can be made tolerant to foreign antigens more readily than the B cells. In some rare *autoimmune diseases* even self-discrimination may break down with very serious consequences for the individual because the defense system of the body may destroy its own tissue. The key players in mounting an immune response are approximately two

trillion lymphocytes (white blood cells) of the human body. *B lymphocytes* are involved in the *humoral* (circulating in the blood) immune response. B cells produce antibodies. These are called B cells because they are produced in the bursa of Fabricius (intestinal pouches) in birds. In humans, B cells originate from the stem cells of the fetal yolk sac, then in the liver and finally in the bone marrow (humans do not have a bursa). The pre-B cells appear in the fetal liver by the 8th week of gestation and contain μ immunoglobulin chains in their cytoplasm but not on their surface. About 2 weeks later B cells appear. By the 13th week B cells have μ immunoglobulin on their surface. By the 12th week B cell production shifts to the bone marrow. IgD (immunoglobulin δ) appears by the 14th week in the spleen, lymph nodes and blood. After the 14th week HLA antigens begin to appear. As the antibody gene rearrangements proceed all other immunoglobulin genes may be expressed (see Fig. 18). The proliferation and differentiation of B cells requires the presence of antigens on their surface and some soluble factors obtained from the T cells. The T_H (helper) and T_S (suppressor) cells regulate the development of B cells. The activation of helper T cells requires the presence of APC cells (*antigen-presenting cells*), HLA Class I and II proteins and interleukin-1. The T_H cells secrete some mediators (e. g., lymphokines).

The activated lymphocytes and mediators then induce the formation of receptors that is followed by the proliferation and differentiation of both T and B lymphocytes. The suppressor lymphocytes may prevent the induction of the immune response by exposure to a wide variety of molecules. Important representatives of the immune system are *T lymphocytes* (shaped in the thymus), their primordia develop by the 5th-6th week of human gestation and the first mature T cells appear by the 9th-10th week (see Fig. 19). T cells are involved in the *cell-mediated* immune response, i.e., they react with antigens bound to their surface. As the maturation of the T cell precedes the CD antigens (CD1, Cd2, CD4, etc.) appear on their surface and identify T cell subsets. By the 16th-20th week the spectrum of subsets reaches that of adults. T cells usually respond to antigens in association of the HLA complex (MHC, major histocompatibility complex). T cells with CD8 antigens respond to Class I proteins of the HLA complex whereas CD4 T cells are limited to HLA Class II proteins (DP, DQ, DR). This phenomenon is called

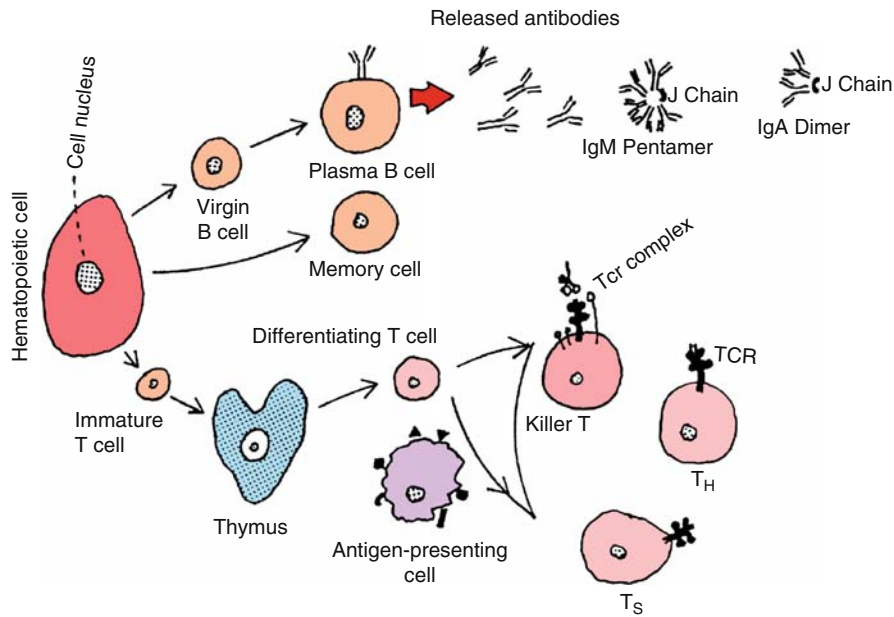


Figure 18. Development of the immune system and its major components. The B and T lymphocytes in mature individuals are generated by the hematopoietic cells in the bone marrow. The virgin B cells become either plasma cells or memory cells upon the encounter of a foreign antigen and lymphokines. As a response the plasma cells manufacture antibodies that are first embedded in the plasma membrane of the B cells, and when the membrane is “saturated”, they are released as circulating antibodies. Antibody IgM polymerizes into a pentamer and joins A J peptide chain. The IgA antibody forms a dimer and A J polypeptide chain also braces it. The memory cells do not become active until follow-up exposure to the particular antigen. Each of the antibody-producing cells makes one single type of antibody and its clonal progeny also makes the same antibody. Different antibodies are made by different B cell clones. The immature T cells differentiate into T cells within the thymus. The thymus is a bilobate organ that develops in the embryo and it reaches its maximal function during puberty and then begins a gradual, slow decline, accompanied by a decrease of T lymphocyte production and a weakened immune response. The mature T cells are of three main types: *killer cells* (cytotoxic T lymphocytes, CTL), *helper T cells* (T_H) and *suppressor T cells* (T_S). The specificity of the T cell function depends on the surface antigens carried by the antigen-presenting cells. The TCR (T cell receptor) has substantial structural and functional homology with the immunoglobulin proteins. The TCR complex is formed by the participation of the MHC protein, encoded by the HLA complex and a series of cell membrane proteins. The killer cells destroy the membranes of the invading cells, followed by lysis of their content

MHC restriction. Maternal IgG may cross the placenta after the 16th week and provides early immune protection for the fetus. Fetuses and newborns may not respond much to foreign cells because lymphocyte development may be arrested when contacted by antigens and anti-idiotypic antibodies. IgM and IgA are normally (in the absence of infection) not present in substantial amounts in newborns. Although after birth the maternal IgG tends to be eliminated, it is gradually replaced by the infant’s own antibodies. By the age of 3, IgG levels become sufficient. Before the end of the first year IgM levels reach those of adults but IgA levels rise very slowly, reaching adult levels only by 9–12 years of age. The appearance of the immune reaction is the result of a developmental process. The *virgin T cells* (that have never been exposed earlier to a specific antigen) become *effector cells*, i.e., they begin to proliferate and

produce either the cell-mediated (T cell) or the humoral (B cell) response. Some other lymphocytes are also induced to proliferation and differentiation. This time they do not participate in the immune response but become *memory cells* that will “remember” the same antigen by virtue of their differentiation, and assume the effector cell role later on similar exposure (*clonal mechanism of secondary immune response*).

The immune response is mounted relatively slowly (in days or weeks) when exposed to a particular antigen for the first time (*primary immune response*) but on subsequent exposures the response is faster because of the availability of memory cells. This phenomenon forms the basis of immunization (vaccination) as it is used in medicine. In order to generate an immune response the lymphocyte receptors must be exposed to an antigen. This is

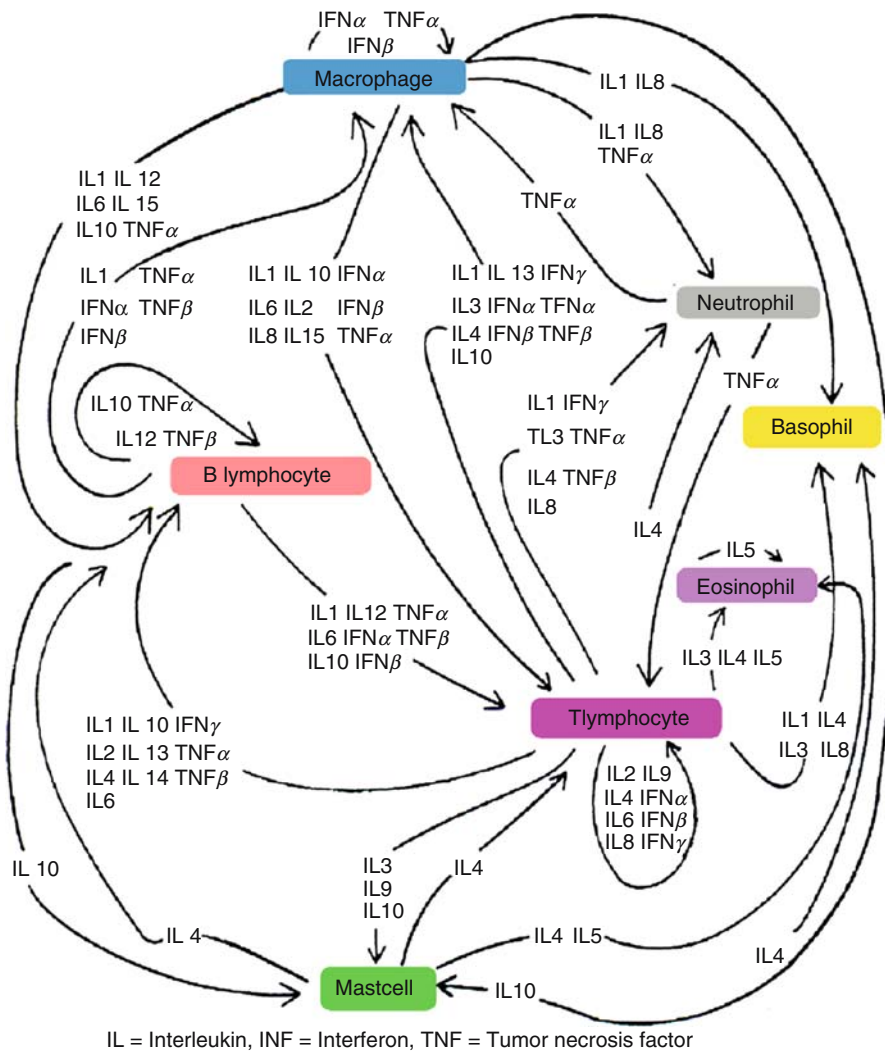


Figure 19. Some types of communication in the immune system

usually followed by the signals of cytokines and other co-stimulator molecules (CD40, CD80, CD86 on the antigen-presenting cells) resulting in the clonal proliferation of specific lymphocytes and memory cells. Contact of CD28 and CD80, CD86 initiates the immune response and the CTLA-4 receptor with CD80, CD86 terminates the T cell immune reactions. CD28 also stimulates the synthesis of the Bcl anti-apoptosis proteins or B cells. The C3d component of the complement in association with the CD21 complement receptor is the co-stimulator. In case the antigen cannot reach the lymphocytes or the co-stimulatory response is defective there will be no immune response. The immune system is largely associated with lymph nodes and the spleen and as such represents systemic responses. Some of the immune reactions are, however, localized to specific tissues such as the gut epithelia or intraepithelial lymphocytes.

In insects, different types of peptides such as cecropin (35–39 amino acids), defensin, attacin, diptericin (82 amino acids), drosopcin, metnikowin, drosomycin, andropin and lysozyme mediate the humoral defense system. In addition, cellular response (phagocytosis) may also be available. A genome-wide survey of the *Drosophila* genome (13,197 genes tested) using microarray analysis revealed that microbial infection induced 230 genes and repressed 170. A different defense system occurs in plants. The molecules (virulence factors) of the invading pathogens act as elicitors for the production of host proteins. These proteins may cause basic changes in the plant metabolism. In extreme cases the hypersensitive reaction kills the infected plant cells to prevent the spread of the disease throughout the entire plant body (Nimchuk Z et al 2003 Annu Rev Genet 37:579). ▶antibody, ▶immune response,

►immunoglobulins, ►HLA, ►T cells, ►TCR, ►surrogate chains, ►B cells, ►autoimmune disease, ►complement, ►lymphokines, ►phagocytosis, ►hapten, ►antigen, ►MHC, ►antigen-presenting cell, ►blood cells, ►lymphocyte, ►lymphocyte homing, ►interleukin, ►immune system diseases, ►innate immunity, ►memory immunological, ►CD80, ►CD40, ►CD28, ►complement, ►CD21, ►apoptosis, ►immune evasion, ►immune tolerance, ►leukalexins, ►host-pathogen relations, ►xeno-transplantation, ►molecular mimics, ►bystander activation, ►allergy, ►asthma; Abbas AK Janeway CA 2000, Cell 100:129; Janeway CA Jr 2001 Proc Natl Acad Sci USA 98:7461; Germain RN 2001 Science 293:240; Di Gregorio E et al 2001 Proc Natl Acad Sci USA 98:12590; plant immune system: Jones JDG, Dangl JL 2006 Nature [Lond] 444:323; killer cells; immunoglobulin receptors; MHC; alloantigens: <http://www.ebi.ac.uk/ipd>.

Immune System Diseases: ►agammaglobulinemia, ►DiGeorge syndrome, ►Wiskott-Aldrich syndrome, ►Reiter syndrome, ►arthritis, ►lupus erythematosus, ►celiac disease, ►immunodeficiency, ►Sjögren syndrome, ►autoimmune diseases

Immune Tolerance: Refers to the failure of the immune system to respond to antigen(s) by supposedly suppressing the alloreactive T cells. The earlier belief was that neonates were supposed to exhibit immune tolerance, however, recent research has indicated that their immune response may be different. Immune tolerance is regulated either by anergy or by suppression. Suppression may be mediated by low oral doses of antigens or by clonal anergy when high doses of the antigen are provided. Oral tolerance may extend to tolerance of the gut immune system and may thus exhibit a systemic immune reaction to ingested proteins. The brain-blood barrier prevents lymphocytes from entering the central nervous system. The peripheral immune tolerance may include T cell-activated repression by the secretion of TGF- β . Both CD4 and CD8 regulatory T cells control and can transfer donor-specific tolerance for allografts (Sho M et al 2005 Proc Natl Acad Sci USAS 102:13230). It is somewhat baffling why allogeneic fetuses are not rejected by the maternal immune system. The mother's body may reject organ transplants from the child because of the paternal genes of the offspring. Notwithstanding, the same mother can carry to term the child. It has been hypothesized that either physical separation or antigenic immaturity of the fetus or some sort of immunological inertness of the mother toward the conceptus may be responsible. It appears that the maternal T cells specific for paternal MHC class I alloantigens are reduced during pregnancy. The

observation that the concentration of tryptophan is lower in the maternal-fetal interface tissues led to the experimentally supported assumption that tryptophan may be required for T cell proliferation. The level of tryptophan is reduced by indoleamine 2,3-dioxygenase (IDO). The inhibition of IDO by higher doses of tryptophan analog 1-methyltryptophan reduced the maintenance of allogeneic concepti in mice apparently by curtailing the chances for T cell mediated rejection. The loss of autoimmunity may occur after infection by pathogens due to molecular mimicry, epitope spreading or bystander activation. B cell tolerance may be lost after removal of the self-antigen or when T cell help is provided at the initial exposure but not if the T cell is available after the exposure to the self-antigen. In tissue or organ transplantation generally immunosuppressive drugs are used. However, these drugs themselves present health risks. Research is underway to find ways of minimizing the immune reaction to foreign proteins (Waldmann H, Cobbold S 2004 Science 305:209). Some tumors avoid destruction by induction of T cell tolerance (Willimsky G, Blankenstein T 2005 Nature [Lond] 437:141). ►antigen, ►anergy, ►mast cell, ►immunoediting, ►TGF, ►mucosal vaccines, ►T cell, ►T cell receptor, ►T cell regulatory, ►thymus, ►immune system, ►self-tolerance, ►immunosuppression, ►alloreactive, ►immunity, ►Rh blood group, ►incompatibility, ►conceptus, ►bystander activation, ►epitope, ►molecular mimics, ►transplantation in utero; Krensky AM 2001 Pediatr Nephrol 16:675; Godnow CC 2001 Lancet 357:2115; Robertson SA, Sharkey DJ 2001 Semin Immunol 13(4):243; Moffett-King A 2002 Nature Rev Immunol 2:656.

Immunity: Refers to a protected state against biological (microbial) or other agents. *Natural immunity* is the readily emerging incompatibility between donor and recipient tissues. The xenoreactive natural (human) antibodies (XNA) react with the Gala1–3Gal terminal antigens present on the endothelial lining of blood vessels of the xenografts of the majority of mammals (except humans and some primates). This binding then activates the human complement system. The graft *complement decay accelerating factor* (DAF), *membrane cofactor proteins* (MCP) and CD59 cannot neutralize the host natural immunity reaction and thus rejection may be initiated. Further injury to the graft is inflicted by the natural killer cells of the host. Although NK cells normally carry *inhibitory receptors* that usually prevent an attack on MHC class I molecules but this system may also fail with the MHC system of the graft. *Acquired immunity* develops as a reaction of the immune system of the organism. The transfer of antibodies or activated

lymphocytes from another body conveys *passive immunity*. *Natural immunity* means that the cells are not susceptible to a particular organism, e.g., humans are not infected by wheat rust. *Genetic or familial immunity* indicates that a group of individuals is resistant to or free of a particular type of infection. In *maternal or intrauterine immunity* humoral antibodies pass through the placenta into the fetus. *Cell mediated immunity* is the result of T lymphocyte activation by adoptive transfer (adoptive immunization) of an immune donor to syngeneic recipients. *Humoral immunity* is provided by the antibodies secreted by B lymphocytes. In *neonate immunity* IgG immunoglobulins are secreted by the mother's milk with the assistance of the FcRn receptor. At the newborn stage monocytes and macrophages have limited activity resulting in the reduction of the MHC class II proteins, co-stimulatory molecules, antigen processing and cytokines. Natural killer cells are present but not very active. *Phage immunity* describes the condition where a lysogenic bacterium cannot be superinfected by another bacteriophage. ▶immune response, ▶antibody, ▶humoral antibody, ▶MHC, ▶FcRn, ▶lymphocyte, ▶superinfection, ▶mucosal immunity, ▶syngeneic, ▶xenotransplantation, ▶complement, ▶killer cells, ▶immune tolerance, ▶MHC, ▶cytokines, ▶antigen-presenting cell, ▶killer cells

Immunization: Refers to the induction of immunity. It can be *active immunization* by introducing specific antigens into the body to promote the formation of a specific antibody or *passive immunization* by introducing antibodies into the body that may provide temporary immunity. Vaccination involves the introduction of live (attenuated) or killed microbes into the body either through the bloodstream or by oral means. The bonding subunit of *E. coli* heat-labile enterotoxin (LT-B) is a very effective immunogen. Bacterial polysaccharide vaccines are not effective in infants before 18–24 months of age although protein conjugates may be effective in few weeks old neonates. At this stage attenuated live viral or bacterial vaccines are usually not advisable. The results of DNA immunization at the early stages of life are still debated.

Transgenic plants encoding LT-B, express the foreign peptides, and are able to bind the natural ligand after oligomerization. Mice fed by antigens produced by transgenic plants can be orally immunized. Also, tobacco plants transgenic for murine antibody κ chain, hybrid immunoglobulin A - G heavy chain, an immunoglobulin J chain and a rabbit secretory component, respectively, after intercrossing produced segregating progeny that simultaneously expressed all four polypeptides. The polypeptide

chains were successfully assembled within the transgenic hybrid into a functional high molecular weight secretory immunoglobulin that could recognize streptococcal surface adhesion molecules. Interestingly, in plants this process can take place in a single cell whereas in animals it requires two cell types. The results indicate the possibility of using immunoglobulins manufactured by plants for oral vaccination. In "reactive immunization" the antigen is so highly reactive that a chemical reaction takes place at the site of the combining antibody. This mechanism may enhance catalytic antibody chemistry. The common type of immunization does not result in covalent interaction between the antigen and the antibody. Although sharks can synthesize a variety of immunoglobulins (somewhat different from higher mammals) they cannot be immunized. ▶antibody, ▶immunoglobulins, ▶immunization genetic, ▶vaccines, ▶transformation genetic [transformation of plants], ▶intercellular immunization, ▶intracellular immunization, ▶immunization in vitro, ▶memory immunological

Immunization, Genetic (DNA vaccination): Involves introducing into an animal (or into a specific animal tissue) a gene or expression gene library encoding a particular antigenic protein(s) by biolistic transformation or plasmid vectors resulting in antibody production. The transgene is introduced into muscle tissue or into the skin. The latter, especially when associated with lymphoid tissues, is more suitable because it harbors a greater number of antigen-presenting cells. This method does not involve the risk of live or attenuated pathogen vaccines. Targeting antigen-ligand (L-selectin or CTLA-4) constructs to the lymph nodes or to antigen-presenting cells (dendritic cells, macrophages and lymphocytes) enhances the effectiveness of DNA immunization 100 to 1000 fold. They may elicit Th1 or CD4⁺ and CD8⁺ T cell responses. The presence of special DNA sequences (IL-2) may serve as *adjuvants* and substantially magnify the reaction. Poly G:C or poly I:C or palindromic (5'-GACGTC, 5'-ADCGCT, 5'-AACGTT) sequences may effectively induce the production of interferons and interleukins, potent stimulants of the killer effects of lymphocytes. Co-injection of vectors containing mutant caspases stimulates T and B lymphocyte responses. DNA vaccination appears to be effective for infectious diseases, malaria, autoimmune diseases, cancer and also for proteomic research. DNA-based vaccines, encoding syngeneic or allogenic, lectin-like natural killer cell ligands (NKG2D) along with survivin or carcinoembryonic antigen activate both innate and adaptive antitumor responses (Zhou H et al 2005 Proc Natl Acad Sci USA 102:10846). The goal of this

procedure in the case of cancer is not prevention but the cure of tumors already present in the body. A potential advantage of DNA vaccination versus protein vaccines is the continuous expression of the antigen. DNA vaccines are expected to be processed for immune recognition by the cell's special protein degradation system, have high temperature-stability, and the cost may be low. A possible slight risk is that the transgenic products may have adverse side effects such as inducing autoimmune reaction or immune tolerance. DNA immunization appears to be substantially less effective as aging progresses. In a rat model, using orally administered adeno-associated virus vaccine containing the NR1 subunit of the NMDA receptor generated strong anti-epileptic and neuroprotective effects. ▶ **immunization**, ▶ **antibody**, ▶ **biolistic transformation**, ▶ **viral vectors**, ▶ **library**, ▶ **selectins**, ▶ **CTLA-4**, ▶ **T cell**, ▶ **gene therapy**, ▶ **IL-2**, ▶ **monoclonal antibody**, ▶ **malaria**, ▶ **auto-immune diseases**, ▶ **cancer**, ▶ **IFN**, ▶ **IL**, ▶ **immune tolerance**, ▶ **polynucleotide vaccination**, ▶ **NMDA receptor**, ▶ **adeno-associated virus**, ▶ **epilepsy**, ▶ **vaccine**, ▶ **surviving**, ▶ **carcinoembryonic antigen**; Xu M et al 2000 Trends Biotechnol 18:167; Maloy KJ et al 2001 Proc Natl Acad Sci USA 98:3299; Schadendorf D 2002 Semin Oncol 29:503; Chambers RS, Johnston SA 2003 Nature Biotechnol 21:1088, <http://www.natx.com/DNAVaccines.html>; DNA vaccine design server: <http://miracle.igib.res.in/dynavac/>.

Immunization, Intracellular: This is the same as immunization genetic.

Immunization In Vitro: B lymphocytes are cultured in vitro in the presence of cytokines and growth factor complexes in order to produce antibodies. It has somewhat limited significance; nevertheless, it may be particularly useful when antibody production is elicited against hazardous antigens. ▶ **immunization**

Immunoadsorption: Describes the process of binding a cognate antibody to an antigen in order to facilitate the separation of a specific type of antigen or antibody from a mixture. In *extracorporeal immunoadsorption* the blood is pumped out of the body and allowed to react with an affinity column and then may be pumped back into the body after this clearance, e.g., removal of radioactively labeled antibody. ▶ **immunofiltration**

Immunoassay: This is based on the recognition of an antigen by an antibody. ▶ **radioimmunoassay**, ▶ **Western blot**, ▶ **immunoblot**, ▶ **conformation-dependent immunoassay**

Immunoblotting: Refers to the separation of proteins by gel electrophoresis and identification of an appropriate component by the specific monoclonal antibody

labeled by fluorochrome or radioactivity. ▶ **Western blotting**, ▶ **electrophoresis**

Immunocontraceptive: The vaccination of animals with zonula pellucida proteins and adjuvants prevents fertilization to a substantial extent. Immunization with eppin is a reversible contraceptive measure used in male primates. ▶ **contraceptives**; eppin; O'Rand MG et al 2004 Science 306:1189.

Immunocytochemistry: Locates antigens in the cell with the aid of labeled antibodies through microscopic examination. ▶ **immunolabeling**

Immunodeficiency: This condition may be due to several different (~80) causes. Some of them have milder effects whereas others are lethal. Immunodeficiency is frequently caused by defects in the lymphocyte differentiation system (thymus). Some of the immunodeficiencies are parts of other syndromes such as Down's syndrome, sickle-cell anemia, ataxia telangiectasia, glycoprotein deficiency, glucose-6-phosphate dehydrogenase deficiency, immunoglobulin imbalance [deficiency of IgA and IgG but increased IgM], defects of the HLA histocompatibility system and some are caused by non-genetic events, such as infection [HIV] or drugs and various allergies that may have a genetic component. Xq13.1-linked immunodeficiency with hyperimmunoglobulin M (IgM) but absence of IgG, IGA and IgE is caused by a defect in the interleukin receptor IL-2R γ c chain and interaction between CD40 and CD 40L and accounts for nearly half of all the cases. As a consequence T cells and B cells do not differentiate normally. The ICF syndrome (human chromosome 20q11.2, immunodeficiency, centromere instability [centromere areas 1, 9 and 16]) and facial anomalies involve a defect in DNA methyltransferase 3B. Methylation at specific sites in the heterochromatin is essential for the maintenance of chromosome integrity (Hansen RS et al 2000 Hum Mol Genet 9:2575). Several immunodeficiencies are the consequence of medical treatment, e.g., cancer therapy or the use of immunosuppressive drugs in tissue transplantation. Jak-3 deficiency causes lymphocyte problems. ADA (adenosine deaminase) recessive defects are responsible for about 15–25% cases of severe immunodeficiency. RAG1/RAG2 (recombination activating genes) interfere with the generation of immunoglobulins and lead to impaired lymphocyte receptors. Recessive mutation in ZAP 70 gene (2q12) is detrimental to the development of T cell receptors. Recessive mutations at 11q23 (CD3 ϵ /CD3 γ) also cause immunodeficiency due to problems with immunoglobulins. Mutations in the MHC class I (6p21.3) and class II peptides adversely affect T and B lymphocytes. ▶ **agammaglobulinemia**, ▶ **hypoglobulinemia**, ▶ **hypogammaglobulinemia**, ▶ **severe**

combined immunodeficiency [SCID], ▶bare lymphocyte syndrome, ▶Nezelof syndrome, ▶DiGeorge syndrome, ▶chronic granulomatous disease, ▶Duncan syndrome, ▶Wiskott-Aldrich syndrome, ▶Epstein-Barr Virus, ▶hyper-IgM syndrome, ▶HLA, ▶CD40 ligand, ▶RAG1/RAG2, ▶ZAP-70, ▶CD3, ▶ADA, ▶RFX, ▶methylation of DNA, ▶lymphoproliferative diseases, ▶acquired immunodeficiency; Fischer A 2004 Nature Immunol 5:23; <http://bioinf.uta.fi/idr/>.

Immunodeficiency, Viral: ▶acquired immunodeficiency (AIDS)

Immunodominance: Of the many possible epitopes of the antigen, cytotoxic lymphocytes (CTL) recognize only one or a few. ▶epitope; CTL; Brehm MA et al 2002 Nature Immunol 3:627.

Immunoediting: This proposes that tumors that evoke strong immune response by T cells develop a survival mechanism by down regulating or eliminating the molecules to which the immune system reacted. ▶immune tolerance, ▶immunological surveillance

Immuno-Electronmicroscopy: Fluorescent antibodies label cell constituents and thus the location of proteins can be identified with electronmicroscopic resolution. ▶histochemistry, ▶microscopy; Yamazaki K, Eyden BP 1998 J Submicroscopic Cytol Pathol 30:217.

Immuno-electrophoresis: This can be carried out by different procedures. In *diffusion*, over the electrophoretically separated proteins, antisera (antibody or antibodies) are placed in a trough. The protein bands are permitted to diffuse in a radial manner from their original position in the gel while the antibody diffuses vertically and at their position of reaction with each other an elliptical arc of precipitation is formed. In *rocket electrophoresis* the antigen is placed in the wells of the gel that contain the antibody. After switching on the electric current the antigen moves and forms a rocket-shaped trail of precipitation as it reacts with the antibody. The length of the rocket indicates the amount of antigen applied to a well. ▶ELISA, ▶rocket electrophoresis

Immunofluorescence: Refers to the identification of a protein (antigen) by *direct* adsorption to a specific antibody that has an attached fluorochrome. Alternatively, to the first (unlabeled) antibody a second cognate, fluorochrome-labeled antibody is added for the sake of immunostaining (*indirect* method). ▶fluorochromes, ▶antigen, ▶antibody

Immunogen: This is a substance which elicits an immune response. ▶immune system

Immunogenetics: This is concerned with the hereditary and molecular aspects of antigen and antibody systems and the immune response. <http://imgt.cines.fr:8104/home.html>.

Immunoglobulins: These are the structural units of antibody molecules. Each antibody is a heterotetramer consisting of two identical light immunoglobulin chains (either of two λ κ) and two identical heavy chains (see Fig. 110). The five heavy chains of humans and mice exhibit considerable variations but the light chains are fairly constant. There are five classes (*isotypes*) of immunoglobulins IgM, IgG, IgA, IgD and IgE, identified according to the heavy chain subunits: μ , γ , α , δ and ϵ . The Ig heavy chains are glycoproteins containing about 15, 4, 10, 18, 18% sugars in a molecular mass of 70, 50, 55, 62 and 70 (kDa) for μ , γ , α , δ , and ϵ , respectively. IgM is a pentamer containing five μ heavy chains and five light chains and one J chain; its molecular mass is around 900 kDa.

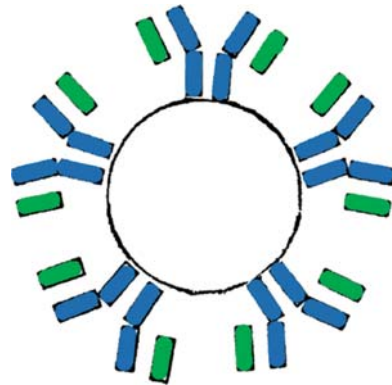


Figure 110. The pentameric structure of immunoglobulin M (IgM), joined by J chain in the center. Note the absence of hinges. ▶antibody

The J polypeptide (ca. 20-kDa), synthesized within IgM secreting cells, is covalently attached between two Fc domains antibody, and it is supposed to initiate oligomerization. (The J polypeptide is not the product of the J genes located between the variable and constant gene clusters). The IgA antibody is a monomer or a dimer or a trimer with molecular weights 153, 325 and 580, respectively, and may have a J chain. Besides the J polypeptide IgA may also have a secretory component (SC) of 558 amino acids. The SC is picked up by the secretory IgA dimers from the surface of epithelial cells and it braces the IgA dimers and protects them from proteolysis.

The SC is part of the transport receptor and mediates the translocation of Ig and IgM into glandular secretions. The IgG, IgD and IgE antibody

monomers are of 150, 180 and 190-kDa, respectively. IgD and IgE are of minor significance although the latter mediates allergic reactions and its level is elevated hundreds of fold in chronic infections. Each of the five major types of heavy chains can be associated with either one of the light chains.

The five classes of antibodies play somewhat specialized roles. IgG is the humoral, circulating antibody and it is the major class. It can cross the placenta and enter extravascular areas. IgE manages the allergic reactions and IgA has a major role in defense against microbial infections. IgM and IgA have two subclasses, IgG and the λ chains have four, designated as e.g., IgM1 and IgM2. Some of the IgG subclasses can cross the placenta. IgM is secreted in low amounts by B lymphocytes but this is the first immunoglobulin produced by newborns which readily activates the complement cascade, and thus represents one of the first lines of defense. IgA is produced mainly in the gastrointestinal system and plays a major role in mucosal immunity. Within these subclasses *allotypes* are distinguished, 25 for human IgG, 2 for IgA and 3 for the kappa (κ) chain. These allotypes represent antigenic markers on the immunoglobulin chains and are designated as e.g., Gm1, Gm2... Am1... Km1... for IgG, IgA and κ chain markers, respectively. The allotype variants represent amino acid substitutions at one or more sites. The characteristic series of allotype markers are inherited as gene blocs and are called *haplotypes*.

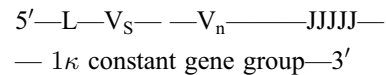
The genes encoding immunoglobulins are clustered in three supergene families. The heavy chain genes are clustered at human chromosomal location 14q32.33. The κ genes are in human chromosome 2p12, whereas the λ gene family is in human chromosome 22q11.12.

Within the approximately 7,000-kb heavy chain region in the long arm of chromosome 14 the genes L encode the signal that leads the polypeptide to the endoplasmic reticulum. V_H (variable heavy), D (diversity), J (juncture) and the various constant heavy chain genes C_μ to C_α , are arranged in groups. The groups are separated by long base sequences (~~) and spacers (ζ) with switch signals (S) in front of the constant heavy chain genes. The general organization of immunoglobulin genes is very similar in all mammals although they are located in different chromosomes:

(ψ indicates pseudogenes). Up front of this sequence, the basal promoter of the Ig heavy chains contains non-translated regulatory transcriptional elements, such as the dispensable *heptamer* consensus: (5'-CTCATGA-3') and 10 to 40 bp downstream the indispensable *octamer* consensus: (5'-ATGCAAAT-3'). The latter is 30 to 60 bp upstream from the TATA box, that is

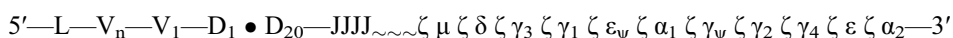
followed within about 20 to 30 bp the transcriptional initiation site for the LVDJ and the constant heavy chain sequences, μ to α_2 . (The orientation of the octamer is opposite to the direction of transcription). Between the LVDJ region and the constant heavy chain genes, there are enhancer elements of the 5'-CAGGTGGC-3' motif and three core repeats of multiple GC sequences.

The κ cluster is similarly organized in human chromosome 2:



The λ genes are in human chromosome 22. The variable genes occur in six groups. Here the J genes are not clustered separately but situated in front of the six constant λ gene groups. Some of the λ genes are outside the clusters and may not be functional. The individual λ segments are quite variable in size. The V_S , one of the switching sequences, is explained here.

The base promoter of the κ light chain contains at about 100 bp upstream from the transcription initiation site a pentanucleotide consensus, and within -90 to -60 bp the octamer consensus (oriented in the direction of the transcription) follows. This does not have the heptamer shown at the heavy genes. The TATA box is at about the same distance from the transcription initiation site as in the heavy chains. There are enhancer elements, designated as κB (5'-GGAAAGTCCCC-3') and Ek1 to Ek3 (variants of the enhancer motif shown at the heavy chains), between the LVJ genes and the constant κ gene group. The strongest enhancer is the κB . Both the heavy and light gene enhancers act preferentially in B lymphocytes. The heavy chain enhancers seem to be constitutive whereas the light gene enhancers become active after the rearrangement of the genes. Besides the enhancers, the immunoglobulin genes appear to have silencers of expression for non-lymphocyte chromosomes. Turning on the promoters requires transcription factors, one of them is 60-kDa OTF-2 which has specificity for the immunoglobulin enhancer consensus 5'-CAGGTGGC-3'. The 90-kDa OTF-1a general mammalian transcription factor is also present in the lymphocytes. The DNA-binding domains of these two factors are very similar but their other domains are different. These enhancers also bind other types of proteins and the only lymphocyte-specific enhancer appears to be the octamer. The light chain specific transcription factor is protein NF- κB that binds to the 5'-GGGPu(C/T)TPyPy(C/T)C-3' motif. After the immunoglobulin light chain has undergone rearrangement, preparatory to transcription, the pattern of the *nuclease-sensitive sites* in the promoter region is altered.



5' Promoter-Enhancers--V_n...V₁---D₂₀...D₁-J_n...J₁--S-μ--S-δ-S-γ--Sε-S-α 3' DNA

virgin B cell ... V₂---D₅-J₅---μ-----δ · **PRIMARY RNA TRANSCRIPTS**

processing ... V₂ D₅ J₅ μ polyA and V₂ D₅ δ polyA **two mRNAs**

translation V₂ D₅ J₅ μ and **IgM and IgD POLYPEPTIDES**

heptamers (7mers) at the ends of the two coding units and this leads to the elimination of the interjacent segment with the *signal ends*. The ends of the coding sequences are the *coding ends*. The signal ends may be joined to form a circular DNA structure and this circularization, followed by elimination, is apparently a major source of rearrangements. In some instances there is an inversion of the V gene relative to the J gene. In such a case the intervening material may not be deleted although the V gene may be inactivated. Some of the rearrangements are *non-productive* because they occur at random and are in the wrong register. Since codons are triplets, two-thirds of the rearrangements may result in garbled sequences. Some nucleotides may be lost at the coding ends and some may be added (*N nucleotides*) by the enzyme deoxynucleotidyl transferase. At the coding ends, the 5' terminus of one of the DNA strands may covalently fuse with the 3' terminus of its complementary strand. When the resulting hairpin structure breaks, a protruding end of nucleotides may be formed that can serve as a template to generate an inverted terminal repeat of a few nucleotides (*P nucleotides*). The 96th codon at the end of the V_H gene is actually generated by a fusion between the V and J genes. This is a critical point because the 96th amino acid is part of the antigen-binding region as well as the connection of the light and heavy chains. Both deletions and additions increase the variability of the antibody genes. The V_H regions can combine with any of the five constant heavy chains (μ, δ, γ, ε, α and their subclasses, *isotypes*) and this is a source of another variation.

The expression of the immunoglobulin genes requires that the promoter be transposed to the vicinity of an enhancer base promoter structure. The enhancer becomes normally active only in the B lymphocytes. Before any antigen is encountered, IgM and IgD class antibody production starts. In such virgin B cells, both immunoglobulins have identical variable regions but they may differ in the constant regions of the μ and the δ chains. Since B cells are diploid, genes in only one of the two homologous chromosomes can be expressed at a time and only one type of rearrangement can function in a cell, this is known as *allelic exclusion*.

The virgin B cells can then differentiate either into *plasma cells* or into *memory cells* upon exposure to an antigen. The former become an immediate producer

of an antibody, the latter would be activated into plasma cells only upon subsequent exposure to the same antigen. The differentiation is aided by *lymphokines* (a variety of growth regulating proteins), and various T lymphocytes (T_H, T_S) and macrophages. The association of the virgin lymphocytes with an antigen triggers the mechanism of *isotype switching*. Isotype switching brings about the selection of the proper heavy chain constant region by a process of transcription although DNA deletions may also be involved. In the undifferentiated B lymphocyte transcription begins at the heavy chain gene leader sequence upstream and continues through the variable and diversity regions to the end of the δ gene, passing through exons and introns. Polyadenylation signal follows the last exon of the transcribed constant region of the μ and δ genes:

Two types of μ chains exist at the early stage of the B lymphocyte. The μ_m chain (with a hydrophobic C terminus and an alternative processing event) and μΣ. The former is included in the lymphocyte membrane as a monomeric IgM antibody (2 light-2 μ chains) whereas the secreted IgM becomes pentameric and also adopts a ca. 20 kDa J peptide with the composition of (μ₂λ₂)₅J (the J is synthesized in the B lymphocyte but not coded in the constant heavy chain cluster). After recombination and deletion occur at one of the S switch points, in the non-coding ca. 2-kb upstream tracts, at the (GAGCT)_nGGGGT motifs, of the constant heavy chain genes, the rearranged gene are transcribed. The introns are eliminated and the transcript is processed into polyadenylated mRNA. The mRNA is translated into the individual heavy chain monomers:

switching at γ

V₂---D₅-J₅-----γ PRIMARY TRANSCRIPT
↓
IgG 50 kDa polypeptide

switching at α

V₂---D₅-J₅-----α PRIMARY TRANSCRIPT
↓
IgA 55 kDa polypeptide

In the examples given here the same VD and J genes are shown, actually any of the VDJ genes can be selected before switching. Additional variation is

generated by somatic mutation during the proliferation of the lymphocyte clones. The frequency of these mutational events (about 10^{-3} per base) appears to be higher than the usual mutation rate of other types of genes. After the heavy chain is completed it may combine with any of the two light chain polypeptides. IgG and IgA are further polymerized to form the final antibody. The activity of B cells is terminated partly by binding the antigen to the secreted antibody. This prevents the binding of the antigens to the B lymphocyte receptors and thus the stimulation of immunoglobulin synthesis ceases. Some birds (ducks, geese, swans) produce immunoglobulin Y (IgY), which does not occur in mammals or in some other avian species but it bears similarities to IgG and IgE. IgY is produced in larger and smaller forms; the latter is deficient in the crystalline fragment.

The completed polypeptide chains are modified glycosylation (using covalently D-galactose, N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, L-fucose, D-mannose and acetylneuraminic acid) that affects their structure and function. IgG has only 3% carbohydrates whereas other chains may have 3–4 times as much. The glycans are mainly at the constant regions of the heavy chains although the number and location of the glycosylation sites vary. Glycosylation affects the activation of the complement, their stability in relation to proteolysis, the number of antigen binding sites available (avidity), etc. In certain diseases (rheumatoid arthritis, tuberculosis, Crohn's disease, Sjögren syndrome, scleroderma and some autoimmune conditions) the IgG molecules lose their galactose. The agalactosyl IgG molecules decrease during pregnancy and their level is lower during the first 25 years of life thereafter it increases again.

In humans and pigs the proportion of κ : λ chains is about 6:4 whereas in rodents κ chains are about 19 times more common than the λ chains. Chickens have only λ light chains, and in many other animals (bovines, horses) the λ chain is preponderant. All vertebrates synthesize immunoglobulins yet the antibodies of the lower animals (fishes, amphibians, reptiles, birds) are somewhat different from those of higher forms. In mammals usually five types of immunoglobulins are produced. There are exceptions, however. Rabbits lack IgD while mice and rats have all five types. In cattle, sheep, pigs and horses IgM, IgG, IgA and IgE occur. In cats IgG, IgM, IgA and IgE and several subclasses are found while dogs have all five types. In camels and llamas the IgG molecules are built of heavy and light chains whereas other immunoglobulins have only heavy chains and the variable domain of the light chain is missing. Transgenic mice containing camelid heavy chain antibody (HCab) loci rearrange properly, result in allelic exclusion, efficiently rescue B cell

development, and undergo class switch recombination and affinity maturation. They generate functional HCabs subsequent to antigenic challenge, providing a new way of producing human HCab when the llama variable heavy chain (VHH) regions are replaced with soluble human VH (Janssens R et al 2006 Proc Natl Acad Sci USA 103:15130).

In invertebrates there are some immune defense molecules. In the *Drosophila*, the *Amalgam* (*ama*, 1–47.5) encoded cell adhesion proteins display some bear immunoglobulin-like domains. The fasciclin II glycoproteins involved in neuronal recognition of grasshoppers have five immunoglobulin-like domains. It is conceivable that the PapD prokaryotic protein involved in pilus assembly has some evolutionary relation to immunoglobulins. The similarity is not in the amino acid sequence but in the overall structure of the domains.

Extremely large phage antibody libraries can be generated in bacteria with the aid of two non-homologous *Lox* sites in a phagemid vector. The exchange among variable heavy and variable light chain genes creates functional recombinants with a diversity of $\sim 3 \times 10^{11}$. Gene conversion generates additional diversity. ►antibody, ►surrogate chains, ►IgNAR, ►immune system, ►immunization, ►lymphocytes, ►complement, ►HLA, ►TCR, ►T cell, ►T cell receptors, ►B cell, ►DNA-PK, ►RAG, ►RSS, ►V(J)D recombinase, ►antibody gene switching, ►class switching, ►AID, ►SCID, ►terminal nucleotidyl transferase, ►repertoire shift, ►affinity maturation, ►CDR, ►somatic hypermutation, ►hypermutation, ►accessibility, ►translin, ►monoclonal antibody, ►hybridoma, ►multiple myeloma, ►macroglobulinemia, ►ELISA, ►tail-piece secretory, ►membrane segment, ►transposons [Tn3, ►Tn5, ►Tn7, ►Tn10], ►hemolin, named diseases under separate entries, ►*Cre/LoxP*; Bross L et al 2000 Immunity 13:589; Arakawa H et al 2002 Science 295:1301; immunoglobulin diversification paths: Maizels N 2005 Annu Rev Genet 39:23; immunoglobulins and T cell receptors: <http://imgt.cines.fr>; variable genes: <http://www.vbase2.org/>.

Immunoglobulins in the Human Serum: (mg/mL), IgG1, 146 kDa [γ 1]: ~ 9 ; IgG2, 146 kDa [γ 2]: ~ 3 ; IgG3, 170 kDa [γ 3]: ~ 1 ; IgG4, 146 kDa [γ 4]: ~ 0.5 ; IgM, 970 kDa [μ]: ~ 1.5 ; IgA1, 160 kDa [α 1]: ~ 3 ; IgA2, 160 kDa [α 2]: ~ 0.5 ; IgD, 200 kDa [δ]: ~ 0.03 ; IgE, 200 kDa [ϵ]: ~ 0.0001 . Immunoglobulins also occur in milk, tears, genitourinary and lung secretions.

Immunohistochemistry: ►immunocytochemistry

Immunolabeling: ►immunostaining, ►ELISA, ►immunofluorescence, ►RIA, ►immuno-scintigraphy, ►monoclonal antibody, ►immunocytochemistry, ►immunosensor, ►fluorochromes

Immuno-Liposome: Refers to a liposome that is coated with target-specific antibodies to deliver, e.g., therapeutic agents to cancer cells. ►cancer gene therapy, ►liposome, ►bispecific antibody

Immunological Learning: The quality of the antibody improves as clonal selection progresses. ►clonal selection

Immunological Memory: Survivors of a cell (individual) that mounted an immune response are more effectively protected in the event of a subsequent infection. The mechanism of this protection may be based on the maintenance of specific T or B cells even in the absence of the antigen or some types of lymphocytes have the ability to remember the antigen. Recurrent low levels of infection may maintain some lymphocytes or some regulatory networks of cytokines respond in case of subsequent infection. ►immune system, ►lymphocytes, ►T cell, ►B cells; Utzny C, Burroughs NJ 2001 J Theor Biol 211:393; HU H et al 2001 Nature Immunol 2:705.

Immunological Privilege: At some tissue sites (such as the central nervous system, maternal—fetal interface, adrenal cortex, testis, ovary, hair follicles, liver) the immunological reaction is not elicited either by acquiring tolerance or by failure of the antigens to communicate effectively with the other sites.

Immunological Surveillance: This is one of the defense mechanisms against cancerous body cells. The surface antigens of the transformed (cancer) cells are different from their normal counterparts. The immune system continuously monitors the body for invading microorganisms and other foreign antigenic material (macromolecules, grafts, etc.) and also recognizes the cancer cells at an incipient stage and with the aid of the immune system (Rousseau Merck MF et al 1996 J Exp Med 183:725) gets rid of them. Experimental data in support of this idea indicated that antibodies produced against mammary cancer preferentially recognized the metastatic cells without reacting with the normal cells. The CCR7 chemokine receptor is an organizer of the immune response (see Fig. 111). Cancerous transformation may be initiated by a single mutation although for the development of neoplasias additional events are required. Mutation rates per cell are in the range of 10^{-9} , because the human body may have 4 to 5 times more cells, cancer mutations may affect each person numerous times during his lifetime. Nevertheless, the incidence of death due to cancer is about 0.2 of all deaths. If no biological protection was available, all individuals would have had cancerous transformation(s). The general validity of immunological surveillance for protection against cancer has been questioned because several types of cancers occurred at the

same frequency in immune-compromised or genetically weak immune system animals as in normal individuals. In a nude mouse with a defective immune system the incidence of cancer did not increase. When naive $CD4^+$ T cells specific for an antigen expressed by tumor cells were transferred into tumor-bearing mice transient clonal expansion occurred early after transfer, accompanied by phenotypic changes associated with antigen recognition (Stavely-O'Carroll K et al Proc 1998 Natl Acad Sci USA 95:1178). In recent years immunosurveillance has attracted renewed attention (Dunn GP et al 2004 Immunity 21:137).

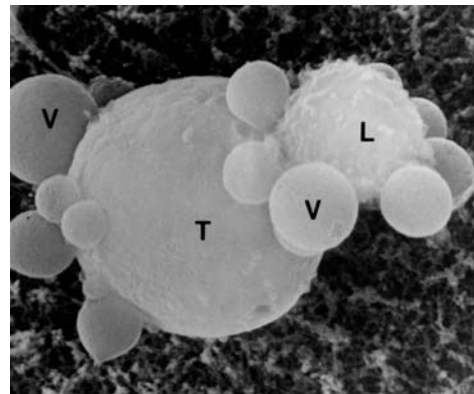


Figure 111. The small lymphocyte (L) is attacking a large tumor cell (T). As the cancer cell begins to lyse, first the microvilli dilate, then surface vesicles (V) appear and eventually it shows blebbing before destruction. (Courtesy of Dr. A. Lepins. See also Lepins A et al 1978 Cell Immunol 36:331)

In transgenic mice where T lymphocytes and tumor-associated antigens could be monitored in some tumors a degree of immune tolerance developed. Recent information (Ochsenbein AF et al 2001 Nature [Lond] 411:10558) has revealed that (i) tumor-specific induction of protective cytotoxic T cells (CTLs) is contingent on how many tumor cells reach the secondary lymphatic organs early and stay there long enough; (ii) diffusely invading systemic tumors can eliminate CTLs; (iii) tumor cells which are either located outside the lymphatic organs or are not within the reach of T cells stay on; and (iv) the major histocompatibility class I molecules may not be protective. Killer cells, $CD8^+$ T cells and activated macrophages express the stimulatory NKG2D lectin-like receptors and this may also contribute to the rejection of tumor cells.

In BALB/c mouse ascites-injected animals may exhibit complete resistance to different types of cancer determined by a dominant factor. Advanced cancer cells are destroyed by innate leukocytes without damaging the normal cells (Cui Z et al

2003 Proc Natl Acad Sci USA 100:6682). ▶immune system, ▶cancer, ▶chromosome breakage, ▶genetic tumors, ▶cancer prevention, ▶CCR, ▶cancer therapy, ▶T cell, ▶MHC, ▶tumor suppressor factors; Diefenbach A et al 2001 Nature [Lond] 413: 165; Shastri N et al 2002 Annu Rev Immunol 20:463; Dunn GP et al 2002 Nature Immunol 3:991.

Immunological Synapse: Refers to the TCR engagement with the antigen-presenting cells with the aid of integrin family adhesion molecules. ▶TCR, ▶antigen-presenting cell, ▶integrin

Immunological Tests: These tests are extremely sensitive for the detection of the presence of a particular protein or other molecules, which can form cross-reacting material (crm) with specific antibodies. Frequently, if the quantity of the material is very low and standard biochemical assays are not sensitive enough for identification, immunoprobes are used for testing. ▶antibody preparation, ▶immunoprobe, ▶immunoscreening, ▶immunofluorescence, ▶pathogen identification

Immunological Tolerance: ▶immune system

Immunomicelles: These are polyethylene glycol-phosphatidylethanolamine conjugate tumor targeting vehicles for the delivery of poorly soluble drugs (e.g., taxol). To the micelle mouse an anti-tumor antibody (mAb2C5) is attached for specific recognition of the target. ▶liposome; Torchilin VP et al 2003 Proc Natl Acad Sci USA 100:6039.

Immunomodulators: Refers to viral encoded proteins regulating antigen presentation, regulators of cytokines, cytokine antagonists, inhibitors of apoptosis and interfering with the functions of the complement. ▶antigen-presenting cell, ▶cytokines, ▶apoptosis, ▶complement

Immunopanning: This is a cell separation technique used in neurobiology. (Gard AL et al 1993 Neuroprotocols 2:209).

Immuno-PCR: This is a polymerase chain reaction version resembling Capture-PCR. It detects specific antibody-DNA conjugates with high sensitivity. ▶Capture-PCR, ▶polymerase chain reaction; Sano T et al 1992 Science 258:120.

Immunophilins: These two classes of proteins bind immunosuppressants such as either rapamycin and FK506 (FKBP) or cyclosporin. All known immunophilins display rotamase (peptidyl-prolyl *cis-trans* isomerase) activity in vitro. The 59-kDa member of the FKBP family is a component of the inactive glucocorticoid receptor. Immunophilins apparently interact with protein kinases of the signal transducing paths and with the heatshock protein 90,

a chaperone. Immunophilins FKBP12 bind to the GS domain of the TGF β receptors and stabilize them in an inactive form. Activation occurs upon phosphorylation. The implantation of blastocysts into the uterus requires estrogen and progesterin and immunophilin FKBP52 serves as a co-chaperone for the steroid nuclear receptors in this process (Daikoku T et al 2005 Proc Natl Acad Sci USA 102:14326). ▶FK506, ▶cyclosporin, ▶rapamycin, ▶cyclophilin, ▶T cell, ▶immunosuppressants, ▶estrogen, ▶progesterin, ▶implantation nuclear receptors, ▶photosystems; Ivery MT 2000 Med Res Rev 20:452.

Immunopolymorphism: Denotes variation in T cell receptors, major histocompatibility system and antigens. <http://www.ebi.ac.uk/ipd/>.

Immunoprecipitation: The reaction of an antigen with a cognate antibody may lead to blood coagulation or to the selective precipitation of a protein. From a mixture of proteins the interactive molecules (enzyme-substrate, proteins of signaling pathways, etc.) may be co-precipitated. Chromatin immunoprecipitation (ChIP) can identify the protein components of the transcriptional machinery (Zhou Q-P et al 2004 Nucleic Acids Res 32:884). Co-immunoprecipitation occurs when two cross-reactive molecules are isolated together. ▶affinity chromatography, ▶ChIP, ▶ChIP-chip, chromatin transcription factor immunoprecipitation detection method: <http://chip.dfci.harvard.edu/~wli/MAT>, ▶Western blotting, ▶microcalorimetry, ▶gel retardation assay, ▶protein complexes, ▶pull-down assay, ▶paired-end ditag

Immunoprobe: This is also known as immunoblot. Bacterial colonies are immobilized on a filter and a specific antibody is added. This antibody can bind the epitope of a second antibody or an antibody plus protein A that may be labeled by a radioactive isotope (I^{135}) or a biotinylated molecule. The complex can then be detected by autoradiography on the dot blot or separated in SDS-polyacrylamide gel and the labeling identifies the substance of interest. ▶Western blotting, ▶colony hybridization, ▶protein A, ▶probe, ▶DNA probe

Immunoproliferative Disease, X-Linked: ▶Epstein-Barr Virus

Immunoprophylaxis: Refers to the use of vaccines or antisera for the prevention of infection (disease).

Immunoproteasomes: These are used for degradation of foreign antigens by cytotoxic T cells. The proteins are ubiquitinated and partially degraded by immunoproteasomes. In these proteasomes some of the subunits of the constitutive proteasomes are replaced by other polypeptides induced via interferon γ (IFN γ). Thus, immunoproteasomes are different from

the constitutive ones in structure and also in stability because after the disappearance of the foreign antigens and IFN γ the cells return to the constitutive state. This cytokine also induces the proteasome activator PA29, which facilitates antigen presentation through a more open proteasome structure. IFN γ induces the formation of proteasome maturation protein (POMP) and the proteasomal $\beta 5i$ subunit low-molecular weight protein 7 (LMP7) and $\beta 2i$ multicatalytic endopeptidase-like 1 protein (MECL1). These subunits replace the constitutive proteasome homologs $\beta 1$, $\beta 2$ and $\beta 5$. LMP7 activation leads to degradation of POMP and a decrease of proteasome activity, reduction of the MHC class I surface expression and induction of apoptosis (Heink S et al 2005 Proc Natl AcadSci USA 102:9241). Immuno-proteasomes have a strong influence on the repertoire of T cells in antigen-specific immune response (Osterloh P et al 2006 Proc Natl Acad Sci USA 103:5042). ▶T cells, ▶antigen processing and presentation, ▶proteasome, ▶interferon; Klotzel P-M 2001 Nature Rev Mol Cell Biol 2:179.

Immunoscintigraphy: By using a scintillation camera (capable of detecting the flashes emitted by radioactive isotopes) radioactively labeled monoclonal antibodies can be localized in the body or tissues by even a three-dimensional image.

Immunoscreening: The product of a gene is identified on the basis of a cognate antibody.

Immunosensor: This is a solid-state apparatus capable of detecting antigen-antibody binding, based on changes in mass or electrochemical or optical properties. It may be employed in clinical, environmental or food analysis.

Immunostaining: Purified antibodies can be labeled by fluorochromes and their specific recognition sites can be visualized in situ with the aid of fluorescence light microscopy. Also, antibodies labeled by colloidal gold permits their analysis by electronmicroscopy.

Immunostimulatory DNA (ISS): This contains within short stretches of plasmid vehicles CpG dinucleotides: 5'-GACGTC-3', 5'-AGCGCT-3' or 5'-AACG% %'-3'. Such sequences promote the production of interferon- α and - β and interleukin-12. The significance of this finding for gene replacement therapy is that ISS may cause the production of proinflammatory cytokines and thereby down regulate gene expression. Immunostimulatory gene expression boosts immunological surveillance and also facilitates cancer therapy. It may be achieved by the use of IL-2, with a tumor-specific antigen, or an anti-erbB-2 single chain antibody. ▶therapy, ▶cytokines, ▶T cells, ▶erbB, ▶single-chain Fv fragment, ▶cancer gene therapy;

Uchijima M et al 2001 Biochem Biophys Res Commun 286:688.

Immunosuppressant: Blocks or reduces the immune response by irradiation, specific antimetabolites or specific antibodies. ▶cyclosporin, ▶cannabinoids, ▶calcineurin, ▶immunophilins

Immunosuppression: The activation of the immune system generally involves the activation of cytokines and cell adhesion. In tumor cells the immune system is suppressed and this suppression is suspected to involve the inhibition of lymphocytes (CTL, NK, B cells) by IL-2, IL-10, TGF- β , etc. Repression of this process calls for the inhibition of the transcription factors required to develop the key elements of the immune system (see Fig. 112). Glucocorticoids, prednisone (also a glucocorticoid), the fungal cyclic oligopeptides, e.g., cyclosporin, mycophenolic acid (C₁₇H₂₀O₆), acidcyclophosphamide (carcinogen), azathioprine (an arthritis drug), cytarabin (cytosine analog), mercaptopurine (a purine analog), methotrexate (a folic acid antagonist), muromonab-CD3 (a murine monoclonal antibody [IgG_{2a}] targeted to the lymphocyte membranes), etc. are used. The new suppressants may prevent stimulation of the T cell receptors (TCR) or the co-stimulatory responses or down regulate the amplification of the specific antigen-responding T cells.

Specific Janus kinase-3 inhibitors (CP-352.664, CP-690.550) may also prevent allograft rejection. Janus kinase signals to several cytokines (Changelian PS et al 2003 Science 302:875). ▶glucocorticoids, ▶cyclosporin, ▶cyclophosphamide, ▶methotrexate, ▶immune tolerance, ▶immune system, ▶hyperacute reaction, ▶Gal α 1-3Gal, ▶IL-2, ▶IL-10, ▶TGF, ▶CTL, ▶killer cell, ▶Jak kinase, ▶transplantation in utero; Kahan BD, Koch SM 2001 Curr Opin Crit Care 7(4):242.

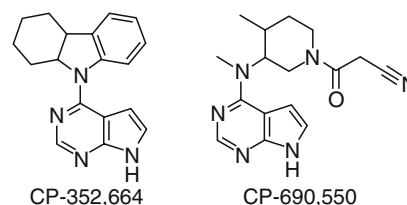


Figure 112. Immunosuppressor molecules

Immunotherapy: This includes immunization, the use of immunopotentiators, immunosuppressants, hyposensitization to allergens, monoclonal antibodies and transplantation of bone marrow or thymus. In rats heatshock proteins prepared from the same cancer (but not from others) retarded the progression of the primary cancer, reduced metastasis and prolonged

life. Another possibility is to fuse antigen-presenting dendritic cells with carcinoma cells and the cell hybrids are used for immunization of syngeneic animals. When surgically removed cancer cells (surface antigens) were delivered to the same animal the mouse body immuno- rejected the cancer. In some instances both CD4⁺ and CD8⁺ T cells responded favorably and the primary tumors as well as the metastatic cells were rejected. Immunotherapy of cancer may use IL-2, IL-4, IL-5, IL-6, IL-1 receptor antagonists, interferon, tumor necrosis factor (TNF α), granulocyte-macrophage colony stimulating factor (GM-CSF) or interferon (IFN γ) to boost the host effectors and the MHC class I and II molecules or apply tumor-specific antigens in order to activate cytotoxic T cells against the cancer cells. GM-CSF appears to be particularly effective. When it is difficult for the antibody to access sensitive tissues in the tumor, a novel approach is to target the blood vessel internal epithelium with the immunoglobulins through intravenous injection (Oh P et al 2004 Nature [Lond] 429:629). In humans TNF (tumor necrosis factor) and $\alpha_4\beta_1$ integrin are the most successful targets for the treatment of several autoimmune diseases. mentioned concepts as separate entries, ►[bacillus Calmette-Guerin](#), ►[vaccinia virus](#), ►[SER-EX](#), ►[statins](#), ►[cancer gene therapy](#), ►[adoptive cellular therapy](#), ►[autoimmune diseases](#), ►[plantibody](#); Chen ZN et al 2001 Cell Biol Int 25:1013; McLaughlin PM et al 2001 Crit Rev Oncol Hematol 40:53; Blattman JN, Greenberg PD 2004 Science 305:200.

Immunotherapy, Active Specific: This therapy boosts the immunogenic response by immunization with endogenous antigenic determinants of the cells. This is expected to result in immunological memory and thus have a long-lasting effect. ►[immune response](#), ►[memory immunological](#); Pol S et al 2001 J Hepatol 34:917.

Immunotherapy, Adoptive (passive): Ex vivo-selected allogeneic transgenic donor lymphocytes are employed against viral infection or leukemia. After reintroduction it may become necessary to select against the introduced lymphocytes in case host—graft incompatibility occurs. The negative selection requires the activation of a special suicide gene. ►[ex vivo](#), ►[allogeneic](#), ►[leukemia](#), ►[suicide vector](#); Bathe OF et al 2001 J Immunol 167:4511.

Immunotherapy, Passive: If a patient does not have an active immune system, preformed specific antibodies may be employed.

Immunotoxin: This may be an antitoxin or a specific antibody equipped with a bacterial, fungal or plant toxin. The monoclonal antibody (Fab domains, Fv) provides the means of homing on the special target cell(s) of cancer (lymphoma, melanoma, breast and colorectal carcinomas) or graft rejection (bone marrow transplant) or T cells responsible for autoimmune disease (arthritis, lupus or HIV infected T cells). In addition it may carry cytokine and soluble receptors to assist targeting. The toxin (*Pseudomonas* exotoxin, diphtheria toxin, ricin, abrin, α -sarcin) then specifically destroys the target by inhibiting local protein synthesis without affecting the other cells. Lysosome targeting (lysosomotropic) amines (NH₄Cl), chloroquine and carboxylic ionophores (monesin) protect the cells from some immunotoxins (e.g., diphtheria toxin) but make them more sensitive to others (e.g., ricin). The clinical applicability of this therapy is still very limited. The toxins may damage to some extent other cell types too. ►[magic bullet](#), ►[antitoxin](#), ►[monoclonal antibody](#), ►[antibody engineering](#); Knechtle SJ 2001 Philos Trans R Soc Lond B Biol Sci 356:681; Manzke O et al 2001 Med Pediatr Oncol 36:185.

Impact Factor: This is a scientometric index monitoring the citation frequency of “average articles” in particular journals within a specific period of time (Garfield E. 1972 Science 178:471). It is calculated by dividing the number of cited articles in a journal by the number of articles published in that journal during a period of two years. The information is available in the Journal Citation Reports (Science Citation Index) in alphabetical order and by grouped fields. It is commonly used for the evaluation of the performance of individuals or departments because it indicates the impact of the publications. It is a useful tool of evaluation within a discipline although papers describing methods are cited more frequently than those dealing with data and theory. It is not entirely suitable for comparison across different disciplines because “glamorous” journals are commonly cited more frequently than the traditional ones. The Institute of Scientific Information carrying out the tallying may also be affected by some human errors (Nature [Lond] 2002 vol. 415:101, *ibid.* 726, *ibid.* 731). Nevertheless, it is probably the most objective tool for rating the prestige of a journal. The Citation Index is also used to assess the impact of the authors of the scientific papers. Another proposed factor for the evaluation of scientific output is the *h* index, which considers the number of papers with higher *h* value and ignores those which are below; i.e. it considers the number of publications that received a certain number of citations. For example, eight

journal research papers of the author of this book received (995) an average of 124 citations since his retirement. It was suggested that such an index permitted realistic comparisons across scientific disciplines (Hirsch JE 2005 Proc Natl Acad Sci USA 102:16569). The latter approach has obvious merits relative to counting only the number of publications irrespective of their impact that may yield only a *trash index*. Obviously large numbers of publications which are not useful to the scientific community are definitely harmful because the reader may not be able to judge their merit before reading them and wastes his valuable time that could be spent on meritorious publications. There are increasing problems, however, in determining the number of citations because there are too many scientists with the same name. Also, older papers even if they continue to be very useful may not be included in the bibliographies just because of the date of publication. Mendel's Versuche paper is rarely cited today and Watson and Crick's epoch-making 1953 paper in Nature is infrequently mentioned in current research publications. Books and review papers may be of great value to scientists yet the Citation Index does not adequately cover these contributions. Some papers may be cited because of factual errors or they may be even fabrications but the Index does not reveal these details. There is no index for papers withdrawn by journals or authors. Recently, Google's PageRank index (PR) as well as a combination with the Impact Factor (IF) such as $PR \times IF = Y\text{-factor}$ have been proposed (Ball P 2006 Nature [Lond] 439:770). Google's PageRank can be found at <http://www.iprcom.com/papers/pagerank/>. There is no perfect criterion for the impact of a scientist's contribution and the impact may also vary with time. ▶ [citation index](#); Butler L 2002 Nature (Lond) 419:877; Lehmann S et al 2006 Nature [Lond] 444:1003, <http://scientific.thomson.com/products/wos/>.

Impala (*Aepyceros melampus melampus*): $2n = 60$.

Impaternalate: Refers to offspring originated by parthenogenetic reproduction. ▶ [parthenogenesis](#)

IMPDH (inosine-5'-monophosphate dehydrogenase): This is involved in lymphocyte replication. Mycophenolic acid (MPA), an approved immunosuppressive drug, is its potent inhibitor (Desmoucelles C et al 2002 J Biol Chem 277:27036).

Imperfect Flower: This has either male or female sexual apparatus, it is monoecious or dioecious but not hermaphroditic. ▶ [flower differentiation](#); ▶ [hermaphrodite](#); ▶ [monoecious](#); ▶ [dioecious](#) (see Fig. I13).

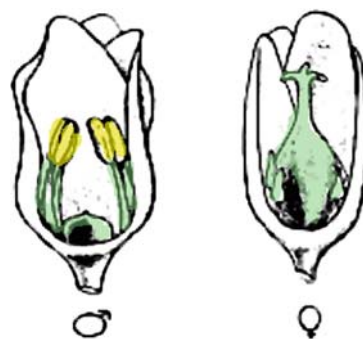


Figure I13. Asparagus flowers (After J.A. Huyskes & J. Sneep)

Imperfect Fungi: These do not have a known sexual mechanism of reproduction. ▶ [fungal life cycles](#)

Impetigo: This is a pus-forming skin infection caused by the plasmid-carrying *Staphylococcus aureus* bacteria.

Implant: Denotes a grafted addition to the body or an inserted artificial object or an implanted zygote.

Implantation: Refers to the attachment of the blastocyst to the lining of the uterus after about a week of fertilization and embedding it into the endometrium (in humans). In mice lysophosphatidic acid receptor (LPA3) and cyclooxygenase 2 (COX2) are involved in the control of implantation and prostaglandin biosynthesis (Ye X et al 2005 Nature [Lond] 435:104). ▶ [blastocyst](#), ▶ [uterus](#), ▶ [prostaglandin](#), ▶ [cyclooxygenase](#), ▶ [lysophosphatidic acid](#), ▶ [Sta](#), ▶ [immunophilins](#), ▶ [steroids](#); Paria BC et al 2002 Science 296:2185.

Importin and β : These are protein factors mediating the passage through the nuclear pore by binding the α subunit to a nuclear localization sequence of a protein, Ran-GTP. Importin β has a positive regulatory role in nuclear import and as a motor adaptor to move molecules along the microtubules; it has negative roles in mitotic spindle assembly, centrosome dynamics, formation of the nuclear membrane, and nuclear pore assembly (Harel A, Forbes DJ 2004 Mol Cell 16:319). ▶ [nuclear pore](#), ▶ [nuclear localization sequence](#), ▶ [karyopherin](#), ▶ [transportin](#), ▶ [RNA export](#), ▶ [Ran](#), ▶ [GTP](#), ▶ [NuMA](#), ▶ [TPX2](#); Mingot J-M et al 2001 EMBO J 20:3685; Gruss OJ et al 2001 Cell 104:83; structure: Matsuura Y, Stewart M 2004 Nature [Lond] 432:872.

Impotence: This is the inability to initiate or maintain erection of the penis due to organic or psychological factors. nitric oxide, phosphodiesterase; Renaud RC, Xuareb H 2002 Nature Rev Drug Discovery 1:663.

Imprecise Alignment of DNA Strands: There is only limited homology between the strands.

Imprinting: The expression of behavioral or other traits may be influenced by the parental source of chromosomes, i.e., the paternal and maternal genomes may have a different effect (imprinting) on the developing offspring because of the modification of an allele by a cis-element or different methylation of the sequence (Kaneda M et al 2004 Nature [Lond] 429:900). More than 150 mammalian genes are subject to imprinting. Methylation also affects the organization of the chromatin. The generation of antisense transcript may be a means of imprinting (Runte M et al 2001 Hum Mol Genet 10:2687). In mice, the insulin-like growth factor gene (*IGF-2*) transmitted through females is not transcribed (imprinted, turned off) in most of the tissues and only the one transmitted through the male is active. In colorectal cancer there is ~30% loss of imprinting (biallelic expression) whereas in healthy individuals this is only ~10% (Cui H et al 2003 Science 299:1679). If the offspring receives a mutant copy of the gene through the male and a normal copy through the female, the heterozygote is crippled. The choroid plexus (the brain tissue secreting the cerebrospinal fluid) and the leptomeninges (the innermost of the three membranes covering the brain and the spinal cord) were not subject to *IGF-2* gene imprinting in mice. The *IGF-2* is a single chain polypeptide and an autocrine regulator of hormone response and growth. The deletion of a silencer element from the mouse *Igf2* involves loss of imprinting (LOI) and increases the chances of multiple intestinal neoplasias in mice (Sakatani T et al 2005 Science 307:1976). It appears that methylation takes place in CG-rich islands of 200 to 1,500 base pairs and notably, several of the imprinted genes are either in chromosome 11p or 15q in humans, or in mouse chromosome 7. At the telomeric end of mouse chromosome 7 there is a differentially methylated CpG island (KvDMR) that is responsible for imprinting several maternal genes. Intron 10 in this island (Kcnq1) of KvDMR contains the paternally expressed, non-coding antisense transcript, Kcnq1ot1. When 244 base pair is deleted from there the silenced genes are derepressed (Mancini-DiNardo D et al 2006 Genes & Development 20:1268). The maternally expressed gene, MEG3 is in human chromosome 14q. In mouse chromosome 17, in *IGF-2* gene a 113-bp methylation imprinting box has been identified. In mice imprinted genes are located at nine regions in six autosomes. In human chromosome 15q11-q13 an *imprinting center* (IC) has been found, involved in epigenetic resetting of this 2-Mb domain. The IC is part of the promoter and the first exon of the

small nuclear ribonucleoprotein peptide N (SNRPN) gene. When the untranslated *H19* mouse gene was disrupted, *Ins-2* and *Igf-2* genes —100-kb upstream of *H19*—were transmitted by the female. It has been suggested (but not verified) that the chromosomal choice of imprinting is determined by a competition for a nearby enhancer. The actual *H19* regulator, *Afr1* affects the fetoprotein- α transcription as well. *Igf* is preferentially expressed in the male because a germ line-inherited methylation silences the promoter of the *H19* gene. The 5' upstream region of *H19* contains an imprinting methylation signal (mark) in the male rodent. This ~42 bp element is conserved by evolution. In the offspring, 27% higher weight was observed compared to animals that received the same chromosome from their father. In mouse chromosome 11 *mash-2* encodes a helix-loop-helix protein and it is maternally expressed only in the placenta. If this gene is deleted maternal lethality results but there is no consequence if transmitted through the male. Placenta-specific mouse genes are imprinted but in humans their expression is biallelic due to the absence of dimethylation of H3 histone lysine 9 and lysine 27 (Monk D et al 2006 Proc Natl Acad Sci USA 103:6623). If the mouse conceptus receives two paternal or two maternal chromosomes 12, intrauterine death results. Uniparental conceptuses are also inviable. Normally, *Ins-2* (insulin) is expressed paternally in the embryo yolk but biparentally in the pancreas. The tissue-specificity of imprinting of the insulin-like growth factor is determined by which of the four promoters of the gene was used. The human gene, *GNAS1* (chromosome 20q13.2-q13.3) displays biallelic inheritance as well as imprinting in both paternal and maternal directions, depending on the promoter used and alternative splicing (Hayward B. E. et al., 1998 Proc. Natl. Acad. Sci. USA 95:15475). The upstream *Nesp* and *Nesp/Gnasxl* promoters are methylated maternally and paternally. The downstream G protein α -subunit is unmethylated with rare exception. Upstream of $G_s\alpha$ there is an imprint mark where methylation is established in oogenesis; thus this imprinting is tissue-specific (Liu J et al 2005 Proc Natl Acad Sci USA 102:5513).

Several paternally inherited X chromosomal genes are inactive in early embryonic tissues. Although differential inactivation is a common property of X chromosomal genes, asynchronous replication has been observed between homologous autosomes in mice (Singh N et al 2003 Nature Genet 33:339). An exception is the *Xist* gene, which is expressed only from the paternally derived X chromosome. In some cases the demonstration of true imprinting is difficult because in human diseases the penetrance and expressivity of the genes may vary widely. Imprinted genes frequently carry special repeats, display

unusual sex-specific rates of recombination and the size of their introns are relatively short. Parthenogenesis may cause embryonic lethality in mouse if the imprinted paternal genes are not expressed. During tumorigenesis both the paternal and maternal copies of the IGF-2 gene are expressed. Imprinted genes usually replicate asynchronously from the rest of the gene pool. Although it appears that expressed genes replicate early, this rule does not hold for imprinting because early replicating paternal genes may be still silent. Imprinting appears mainly in mammals, however imprinting-like phenomena have been observed in the plant *Arabidopsis* (Choi Y et al 2002 Cell 110:33). Imprinting of the late-flowering epimutation in the *FWA* gene of *Arabidopsis* is limited to the endosperm and its activation depends on the DNA glycosylase gene (*DME*) *DEMETER* (Kinoshita T et al 2004 Science 303:521). Gene *MEDEA* (*MEA*) is imprinted in the *Arabidopsis* endosperm and it is activated by hypomethylation of the maternal allele by the *DME*. *METHYLTRANSFERASE* (*MET1*) maintains CG methylation of the *MEA*. The active *MEA* Polycomb-like complex (*MEA* + *FIE* + *PcG*) in the endosperm silences the paternal *MEA* allele by methylation (Gehring M et al 2006 Cell 124:495).

In mammals 0.1–1% of the genes may show some degree of imprinting; in mice and humans only about three dozen imprinted genes had been identified by 2000 (see Verona RI et al 2003 Annu Rev Cell Dev Biol 19:237).

There is no generally valid interpretation of the evolutionary utility of imprinting. It has been hypothesized the imprinting has a *dosage compensation* purpose. Loss of imprinting may predispose to sporadic colorectal cancer. Also, imprinting may permit the expression of an oncogenic allele. Alternatively, the *conflict/kinship theory* has been proposed. According to this theory, if the female produces offspring by more than one male during her period of fertility, the more vigorous pregnancy places greater demands on the female and thus weakens the mother and thereby potentially harms the future offspring sired by other male(s). To resolve this conflict the mother activates on growth promoting genes. The male silences genes that suppress growth. Some of the facts seem to support this conflict theory, others do not. According to the conflict hypothesis, there should be no imprinting in monogamous species. However, this expectation is not realized in the monogamous *Peromyscus polionotus* rodents. Imprinted genes, because of monoallelic expression, may be at a higher risk to contribute to tumorigenesis because a single recessive mutation may trigger the process. ▶methylation of DNA regulation of gene activity, ▶Xist (Tsix), ▶IGF, ▶Angelman's

syndrome, ▶Prader-Willi syndrome, ▶Beckwith-Weidemann syndrome, ▶Wilms' tumor, ▶Albright hereditary osteodystrophy, ▶Russel-Silver syndrome, ▶insulin-like growth factor, ▶myotonic dystrophy, ▶ataxia, ▶MYF-3, ▶KIP2, ▶polar overdominance, ▶*VENTURE*, ▶diabetes mellitus, ▶lyonization, ▶parthenogenesis, ▶co-suppression, ▶snRNP, ▶dosage compensation, ▶enhancer competition, ▶CTCF, ▶imprinting box, ▶parent-of-origin effect, ▶uniparental disomy, ▶hydatidiform mole, ▶obesity, ▶fetoprotein- α , ▶histones, ▶epigenesis; Bartolomei MS, Tilghman SM 1997 Annu Rev Genet 31:493; Pfeifer K 2000 Am J Hum Genet 67:777; Nakagawa H et al 2001 Proc Natl Acad Sci USA 98:591; for linkage analysis: Strauch K et al 2000 Am J Hum Genet 66:1945; Spencer HG 2000 Annu Rev Genet 34:457; Reik W, Walter J 2001 Nature Reviews Genet 2:21; Mann JR 2001 Stem Cells 19:287; Ferguson-Smith AC, Surani MA 2001 Science 293:1086; Bourchis D et al 2001 Science 294:2536; Sleutels F et al 2002 Nature [Lond] 415:810; Wilkins JF, Haig D 2003 Nature Rev Genet 4:359; de la Casa-Espérón E, Sapienza C 2003 Annu Rev Genet 37:349; Haig D 2004 Annu Rev Genet 38:553; Jiang Y-h et al 2004 Annu Rev Genomics Hum Genet 5:479, <http://www.mgu.har.mrc.ac.uk/research/imprinting/>; catalog of imprinted genes: <http://igc.otago.ac.nz/home.html>; <http://www.geneimprint.com>; imprinted human gene catalog: <http://www.otago.ac.nz/IGC>.

Imprinting, Behavioral: A response learned during the early phase of life has a lasting effect on the behavior of an animal throughout its life.

Imprinting Box: This is responsible for imprinting of genes situated in the region 15q11-q13 of the human chromosome (and in the homologous chromosome 7 segment of the mouse). The human imprinting box extends to ~200 bp of the promoter/exon 1 site of the small ribonucleoprotein peptide N (SNRPN, 15q12) gene and a 1-kb sequence about 35 kb upstream including the short regions of overlap (SRO) of Angelman's syndrome (AS-SRO) and Prader-Willi syndrome SRO (PWS-SRO). The insulin-like growth factor receptor gene (IGF2R) can act alone as a methylation initiating imprinting box. ▶Angelman's syndrome, ▶Prader-Willi syndrome, ▶insulin-like growth factor, ▶imprinting; Shemer R et al 2000 Nature Genet 26:440.

Imprinting, Molecular: Biological molecules are coated by polymers that preserve their three-dimensional structure (imprint) in order to facilitate their manipulation (breaking up at selective locations, fractionation from complex mixtures).

Imputation: Refers to estimation of the missing values in a set of data using the information available. For this purpose multiple regression may be used.
▶regression

In Silico Biology: Describes the identification of genes in databases with the aid of bioinformatics. (Harris SB 2002 Embo Rep 3:511).

In Situ Hybridization (ISH): The DNA double strands within the cells (chromosomes) are separated (denaturation) in cytological preparations on microscope slides and labeled (radioactively or by fluorochromes or by immunoprobes) and complementary DNA or RNA strands (probes) are annealed (see Fig. I14). The cells are then visualized by microscopy as usual for cytological microtechniques and can either be autoradiographed or viewed through fluorescence microscopy to ascertain the position of the hybridized ↑ probe. Thus, the chromosomal location of molecular markers can be determined. ▶DNA hybridization, ▶somatic cell hybrids, ▶probes, ▶fluorochromes, ▶chromosome painting, ▶FISH, ▶immunoprobe, ▶nick translation, ▶in situ PCR, ▶PRINS, ▶GISH, ▶MFISH; Pardue ML 1973 Cold Spring Harbor Symp Quant Biol 38:475; Carpenter NJ 2001 Semin Pediatr Neurol 8(3):135.

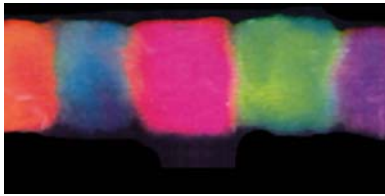


Figure I14. In situ hybridization

In Situ PCR: PCR technology is used within single cells. The DNA is amplified followed by in situ hybridization. By treating the cells with reverse transcriptase before PCR enhances its utility. Such a procedure permits the detection of cellular genic activity, viral infection and the expression of just introduced transgenes for gene therapy. ▶PCR, ▶RT-PCR, ▶PRINS, ▶FISH; Kher R, Baccalao R 2001 Am J Physiol Cell Physiol 281:C726.

In Vitro: The reaction or culture is carried out in a “glass” vessel rather than in an intact cell or in natural culture conditions, respectively such as in vitro culture, in vitro fertilization or in vitro enzyme assay.
▶ART, ▶cell genetics

In Vitro Fertilization (IVF): Extracted mammalian eggs can be fertilized by competent sperms (AID or AIH) outside the body and then surgically implanted into

the uterus. Such a procedure may have over 40% chance of success and helps to overcome sterility in many women with infertility problems caused by factors other than the ova. In vitro fertilization produces normal babies but the chance of having non-identical twins is greatly increased if the gynecologist implants more than a single fertilized egg to assure a reasonable degree of success. When single blastocysts stage (5 days old, in 175 individuals) and cleavage stage (3 days old, in 176 individuals) embryos were used for in vitro fertilization in women under 36 years of age, the blastocysts stage implantation resulted in higher pregnancy (32%) than in at the cleavage stage (21.6%). In the latter group there were two cases of monozygotic twins (Papanikolaou EG et al 2006 New Engl J Med 354:1139). IVF of women above 35 years of age had disappointingly low success (~37%). The low rate was attributed to increasing aneuploidy in older eggs. Preimplantation elimination of chromosomally defective eggs resulted in even lower frequency (25%) of fertilization presumably because the removal of single blastomeres for cytological tests harmed the embryos (Mastenbroek S et al 2007 New England J Med 357:9).

Concerns have been expressed about a slight increase in genetic defects among the offspring produced with the aid of these techniques, particularly the ICSI (Powell K 2003 Nature [Lond] 422:656; Gicquel C et al 2003 Am J Hum Genet 72:1338). IVF has applied significance in animal breeding. For example, from the ovaries of cows eggs can be retrieved in slaughterhouses and after in vitro fertilization can be re-implanted into any (even some sterile) cows. Through this procedure more beef can be produced. There is an opportunity to obtain more offspring from genetically superior individuals of domestic animals by the use of surrogate mothers. It has applications in wildlife preservation of endangered species (in zoos) or in species with an unsatisfactory natural rate of reproduction. ▶twinning, ▶artificial insemination, ▶insemination by donor, ▶preimplantation genetic, ▶GnRFA, ▶ART, ▶ICSI, ▶test tube baby; Elder K, Dale B 2000 In Vitro Fertilization, Cambridge Univ. Press, New York; Ozturk O et al 2001 Hum Repr 16:1319.

In Vitro Mutagenesis: Mutation is produced in isolated DNA sequences that is then re-introduced into the cells by transformation. ▶localized mutagenesis, ▶site-specific mutagenesis, ▶gene replacement TAB mutagenesis, ▶transformation genetic, ▶cas-sette mutagenesis, ▶Kunkel mutagenesis, ▶PCR-based mutagenesis, ▶doping nucleotides; Lehoux DE et al 2001 Curr Opin Microbiol 4:515.

In Vitro Packaging: Recombinant DNA equipped with the phage λ *cos* sites and genes required for packaging (*origin* of replication and other sequences of about 4–6 kb at both *cos* neighborhoods) can accept inserts so that the total length remains in the range of 37–52 kb, can be packaged into phage capsids that may infect *E. coli* and yeast cells and bring about transformation. Similar procedures are applicable to other systems. ▶cosmid vector, ▶lambda phage; Okimoto T et al 2001 Mol Ther 4(3):232.

In Vitro Protein Synthesis: ▶in vitro translation systems

In Vitro Translation: ▶rabbit reticulocyte translation assay, ▶wheat germ translation, ▶translation in vitro, ▶oocyte translation

In Vivo: The process takes place in intact cells or in the tissues of a living organism or cell. ▶in vitro, ▶ex vivo

Inactive-X Hypothesis: ▶Lyon's hypothesis

Inborn Error of Metabolism: This is a historical term for biochemical genetic defects. Generally mutation in single genes blocks or changes the metabolic pathways at a single specific step. The photograph shows the response of an auxotrophic mutant of *Arabidopsis* unable to synthesize the pyrimidine moiety of thiamine. On basal medium it germinates but fails to grow; its growth is fully restored on the appropriate pyrimidine, PY and thiamine, TH. A slight growth is also seen on the thiazole moiety of thiamine TZ (Rédei, 1965 unpublished). The consequences of the mutation may be alleviated either by providing the missing compound or by avoiding the supply of the accumulated precursors that cannot be further processed because of the defect in the enzymatic step. Although a single enzymatic step is often involved, the lack or overproduction of a metabolite can affect more than a single metabolic process in complex diseases (see Fig. 115). Inborn errors of metabolism include defects in quantitative genes and other intrauterine lesions and infections. In plants auxotrophic mutations are very rare; the number of identified metabolic defects due to genetic causes (mutation, deletion, insertion, rearrangement) is increasing in humans. Defects in humans may be caused by the absence or decrease of a metabolite, the adverse effect of accumulated precursor(s), overproduction, faulty regulation of a pathway and/or adverse effects on more than one pathway in a metabolic network. The defect can be cell autonomous, i.e., affects only a particular cell or it may be non-autonomous and its consequence spreads to other tissues either by diffusion or secretion and active

transport. The presence of a metabolic defect can be discovered by simple means; Garrod identified alkaptonuria by the brown spots on the diapers of newborns. The nature of the defect can be identified by chemical analysis, the use of isotope or fluorochrome labeled metabolic tracers, enzymes assays of body fluids or tissues, by microarray hybridization, two-dimensional electrophoresis or mass spectrometry, nuclear magnetic resonance spectrometry (NMR) and other tools of proteomics. The treatment of the disease varies according to its nature. Phenylketonuria or fructose intolerance requires metabolic restrictions, in Wilson disease avoidance of copper helps. In other cases dietary supplements can help, e.g., consuming starch in glycogen storage diseases or taking biotin in biotinidase deficiency or avoiding fasting in some forms of fatty acid metabolism disorders. In Gaucher disease enzyme replacement, in Hurler's syndrome enzyme replacement and bone marrow transplantation are used. For several diseases somatic gene therapy is available. The implantation of embryonic stem cells may be helpful for a range of human lesions and disease. Avoidance of several diseases is possible by genetic counseling, screening for carriers and neonatal screening. Screening newborns for inborn metabolic errors by tandem mass spectrometry revealed a frequency of 1.57×10^{-4} (Wilcken B et al 2003 New England J Med 348:2304). ▶auxotrophy, ▶one gene — one enzyme theorem, ▶biochemical genetics; Garrod AE 1902 Lancet 2:1616; see individual entries for diseases and other terms; excellent review: Lanpher B et al 2006 Nature Rev Genet 7:449.

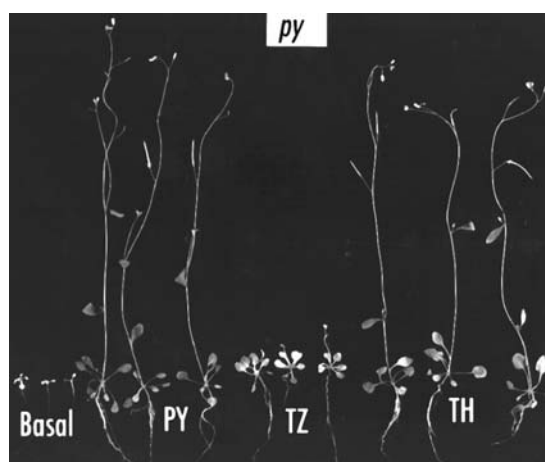


Figure 115. *Arabidopsis py* mutants respond only to the pyrimidine moiety of the thiamine or to thiamine

Inbred: Denotes a line developed by continued inbreeding until the majority of the genes become

homozygous. In mice usually 20 generations of brother × sister (or parent × offspring) mating is done to produce such lines. In species where self-fertilization is feasible (e.g., plants) ten generations of inbreeding results in more than 0.999% homozygosity ($1 - 0.5^{10}$), unless the genes are very tightly linked in repulsion. ▶coefficient of inbreeding, ▶coisogenic, ▶congenic, ▶substrain, ▶subline, ▶linkage disequilibrium

Inbreeding: Refers to mating among biological relatives, including self-fertilization, brother-sister mating and mating with ancestors or offspring. ▶coefficient of inbreeding, ▶inbreeding in autopolyploids, ▶inbreeding and death rates, ▶inbreeding and population size, ▶inbreeding progress; Fisher RA 1949 *The Theory of Inbreeding*, Oliver & Boyd, Edinburgh.

Inbreeding and Death Rates: Inbreeding results in homozygosity of deleterious and lethal genes which in turn increase spontaneous abortions, infant mortality and the frequency of hereditary diseases (see Table 11). The frequency of the adverse consequences depends upon the frequency of these undesirable genes in the population concerned and the degree of inbreeding. When infant mortality in first cousin marriages and that in the general population marriages is compared the frequency in the former is

Table 11 Infant mortality and inbreeding

| Ethnicity | First-cousin marriages % | General population % |
|-----------|--------------------------|----------------------|
| Canadian | 8.8 | 4.1 |
| French | 9.4 | 4.4 |
| Japanese | 6.2 | 3.9 |
| Swedish | 8.5 | 4.0 |

(After Fraser, F. C. & Biddle, C. J. 1976. *Am. J. Hum. Genet.* 28:522.)

Table 12 Arriving at homozygosity after backcrossing as a function of recombination frequency

| Recombination | Number of Backcrosses → | 2 | 3 | 6 | 9 | 12 |
|---------------|-------------------------|-------|-------|-------|-------|-------|
| 0.5 | | 0.500 | 0.750 | 0.969 | 0.996 | 0.999 |
| 0.3 | | 0.300 | 0.510 | 0.832 | 0.942 | 0.980 |
| 0.1 | | 0.100 | 0.190 | 0.409 | 0.569 | 0.686 |

(After Klein, J. 1975. *Biology of the Mouse Histocompatibility-2 Complex*. Springer, Berlin.)

almost double. Some of the variation within columns may also be due to random statistical error:

In a recent analysis the excess death rate — up to age 10 — of the progeny of first cousin marriages in Japan, Pakistan, India and Brazil combined appeared to be 4.4%. ▶coefficient of coancestry, ▶inbreeding coefficient, ▶inbreeding depression, ▶incest, ▶genetic load, ▶lethal equivalent

Inbreeding and Linkage: The probability of homozygosity after backcrossing to an inbred line varies according to the intensity of linkage and the number of backcrosses performed (see Table 12).

Inbreeding and Population Size: Inbreeding increases more in smaller populations than in large ones. The increase can be reduced by controlled mating, i.e., when the mating pairs are selected from different families or if an equal number of mates is selected from each family of the herd. The rate of inbreeding (Δ_F) = $1/2N_e$. If the actual size of the population is say 10, then $\Delta_F = 1/(2 \times 10) = 0.05$. In case the effective population size is only 0.75 of the total population then $\Delta_F = 1/2N_e = 1/(2 \times 10 \times 0.75) = 1/15 = 0.066$. The coefficient of inbreeding becomes $F_g = 1 - (1 - \Delta_F)^g$ where F_g is the inbreeding coefficient of the g^{th} generation and Δ_F is the rate of inbreeding. ▶inbreeding coefficient, ▶inbreeding depression, ▶inbreeding rate, ▶population size effective

Inbreeding Autopolyploids: Since autopolyploids have more alleles present per locus, homozygosity at a locus is achieved only after a larger number or several generations. Many of the autopolyploid species reproduce by self-fertilization and the deleterious consequences of inbreeding have been eliminated by natural selection. Since many of the crop plants are polyploid, plant breeders rely on crossing for improvement. In allopolyploids the consequences of inbreeding may vary according to the species. A comparison of the proportion of homozygotes in diploids and tetraploids of the initial genetic constitutions *Aa*, *Aaaa* and *AAaa*, respectively, after five generations of self-fertilization is presented in the table (see Table 13).

Table I3 Progress of inbreeding in autotetraploids compared to diploids

| Generation | Aa (diploid) | Aaaa Chrom. segr. ¹ | Aaaa Max. equat. ² | AAaa Chrom. segr. ¹ | AAaa Max. equat. ² |
|----------------|--------------|--------------------------------|-------------------------------|--------------------------------|-------------------------------|
| F ₂ | 0.500 | 0.250 | 0.295 | 0.050 | 0.099 |
| F ₃ | 0.750 | 0.380 | 0.460 | 0.194 | 0.285 |
| F ₄ | 0.875 | 0.493 | 0.581 | 0.326 | 0.442 |
| F ₅ | 0.938 | 0.558 | 0.674 | 0.438 | 0.566 |
| F ₆ | 0.969 | 0.648 | 0.747 | 0.531 | 0.662 |

(After Burnham, C. R. 1962. *Discussions in Cytogenetics*. Burgess, MN.)

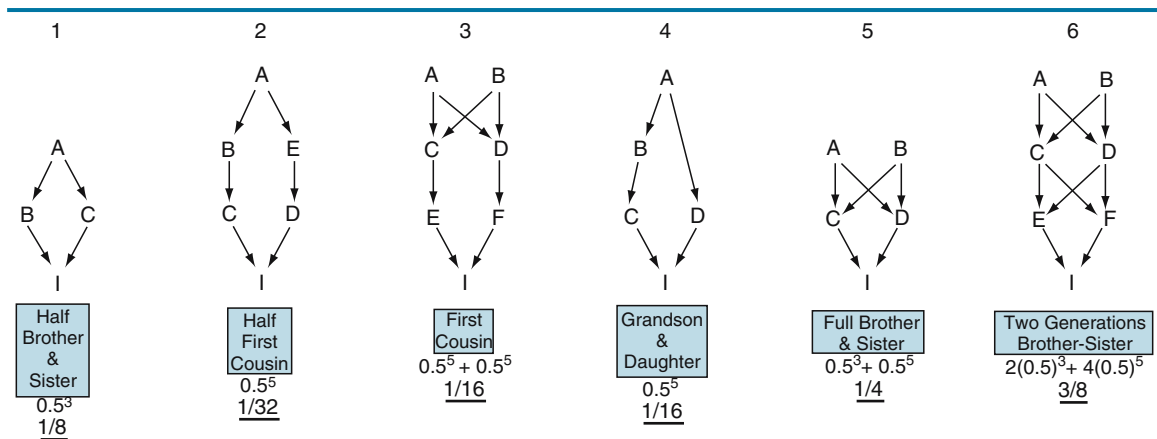
¹Chromosome segregation indicates that the gene is absolutely linked to the centromere.

²Maximal equational segregation occurs when the gene segregates independently from the centromere.

Inbreeding Coefficient: Denotes the probability that *two alleles at a locus in an individual* are identical by descent from a common ancestor, i.e., the chance that an individual is homozygous for an ancestral allele by inheritance (not by mutation). The inbreeding coefficient for second cousins is 1/64 and for third cousins it is 1/256. In case only one of the parents is common at the starting generation the inbreeding coefficient of half-sibs at uncle-niece or aunt-nephew marriage is 1/16, for first cousins 1/32, for second cousins 1/128, and for third cousins 1/512.

Consanguinity (coancestry) is a similar concept but the coefficient of coancestry indicates the chances that *one allele in two individuals* would be identical by descent. F symbolizes the coefficient of inbreeding. The calculation of F is based on the fact that in a diploid at each locus there are two alleles and only one is contained in any gamete (either one in a particular egg or sperm). Thus, each individual has 0.5 chance for passing on a particular allele to a particular offspring. To illustrate the method of calculation examples will be discussed (see Fig. I16).

Brother (X) and sister (Y) have two common parents (W) and (V). An offspring of the mating (X) × (Y) → (X)→(I) or (W)→(Y)→(I), therefore his chances for homozygosity for one allele derived from (W) is $0.5^2 = 0.25$. In other words, in F₂ the chance is 1/4 for homozygosity for any allele according to the Mendelian law. In a half-brother and half-sister progeny grandparent (A) can transmit a particular allele to (I) either through (B) or (C) parents and the inbreeding coefficient of (I) is $0.5^3 = 1/8$ because three individuals are involved in the transmission route (A), (B) and (C). Similarly, the inbreeding coefficient of other types of matings can be calculated as indicated in the chart. In half first cousin mating individuals (C), (B), (A), (E) and (D) are involved in the transmission path, each with a 0.5 chance thus the coefficient of inbreeding becomes $0.5^5 = 0.03125 = 1/32$. In two generations of brother-sister matings (see scheme 6), the transmission of alleles may follow the routes [E-C-F, F-D-E], {E-C-A-D-F, F-D-B-C-E, E-D-A-C-F and F-C-B-D-E}, i.e., [2] and {4} paths of $[0.5]^3$ and $\{0.5\}^5$, respectively. The coefficient of

**Figure I16.** Calculation of the coefficient of inbreeding on the basis of the paths of allele transmission

inbreeding is $2[0.5]^3 + 4\{0.5\}^5 = 0.375 = 3/8$. If there are multiple paths through the same ancestor, all the paths through the shared ancestors must be included in the calculation with the precaution that the same ancestor must be counted only once in the same path. The method can be illustrated by another example where (Z) and (U) are the common ancestors and again the inbreeding coefficient of individual (I) is sought. There are two routes through (Z): T-Z-L-K and T-Z-M-K and also two paths through (U): K-M-U-T and K-L-U-T. Each of these four paths involves four ancestors contributing genes to (I). Therefore, the coefficient of inbreeding of (I) is $4(0.5)^4 = 0.25 = 1/4$. Under practical conditions of breeding far more complicated schemes may be encountered yet their solution can be sought in terms of these simple examples. It is easier to determine the loops of gamete contribution by working backwards from the critical individual, (I) in this case. It is conceivable that the common ancestors are not completely unrelated, contrary to the assumption in the calculations here, but they may have some degree of relatedness and their inbreeding coefficient, F_A (ancestral coefficient of inbreeding) must also be taken into account. Therefore, the general formula for the coefficient of inbreeding is $F = \Sigma[(0.5)^n(1 + F_A)]$ where Σ is the sum of the paths through which an individual can derive identical alleles from his ancestors and n = the number of individuals in the paths. $1 + F_A$ is the correction factor for the inbreeding coefficient of the common ancestor in the path. Calculating the coefficient of inbreeding may not only be very important in a breeding project, but it may also be relevant to human families. It is assumed that the frequency of a recessive genetic disorder is $q^2 = 1 \times 10^{-6}$ and if the population is in a genetic equilibrium the frequency of that allele is $q = \sqrt{q^2} = \sqrt{0.000001}$. Then the risk related parents face of having an afflicted child is: $q^2(1 - F) + q(F)$. Since the inbreeding coefficient of the offspring of first cousins is $F = 1/16 = 0.0625$ (see Figs. I17 and I18), after substitutions one obtains: $0.000001 \times 0.9375 + (0.001 \times 0.0625) \approx 0.000063$. Since 0.000063 is ~63 fold higher than 0.000001 (the frequency of individuals with this affliction in the general population), first cousin parents are at a >63 fold greater risk than unrelated parents to have an offspring afflicted with a hereditary disease that has a gene frequency of 0.001. In some cases inbreeding may be detected by DNA fingerprinting or by nucleotide sequence of the genome. ▶F, ▶coefficient of coancestry, ▶consanguinity, ▶relatedness degree, ▶inbreeding progress, ▶inbreeding rate, ▶fixation index, ▶genetic load, ▶homozygosity mapping, ▶DNA fingerprinting, ▶inbreeding depression; Fisher RA 1965 The Theory of Inbreeding, Academic Press, New York.

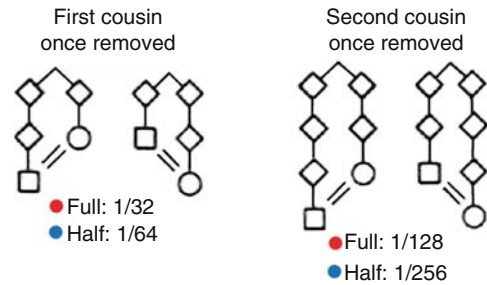


Figure I17. Coefficient of inbreeding among cousins

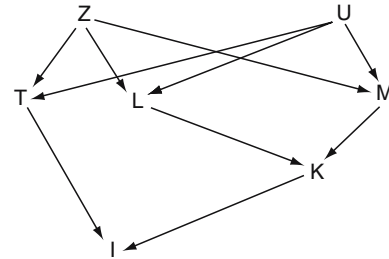


Figure I18. Multiple paths of allele transmission

Inbreeding Depression: When inbreeding and the deleterious recessive genes become homozygous, the viability, vigor and fitness of the individuals and the population decline in normally outcrossing or dioecious or monoecious species. The degree of depression varies according to the species and traits affected. Some degree of inbreeding takes place in human populations. Inbreeding is common (~50%) in parts of Pakistan and India where uncle-niece or first cousin marriages are often seen (see Fig. I19). In Japan and South America inbreeding varies between 1% and 10% whereas in Europe and North America consanguinity is about 1% except in some isolated religious groups. The major religions (Christianity, Judaism, Buddhism and Zoroastrian) approve first cousin marriages with some restrictions. In Sweden even half-sibs can legally marry if the government approves of such a union. In eight states of the US first cousin marriage is considered criminal whereas in 22 states it is illegal. In ancient Egypt the pharaoh frequently married his sister; this probably explains the relatively large number of mummies of infants at the burial places. Consanguineous marriages increase homozygosis and the frequency of inborn errors of metabolism, malformations and other physical or mental genetic load. In many societies consanguineous marriages are preferred to ensure that the family estate remains intact. As industrialization and urbanization advance the frequency of consanguineous marriages declines. In animal husbandry inbreeding is used with the purpose of fixation of desirable traits. In plant breeding, maximal hybrid vigor of some

crops (heterosis) is achieved by using inbred lines.
 ►inbreeding progress, ►inbreeding coefficient,
 ►inbreeding and death rates, ►heterosis, ►controlled mating, ►Marfan syndrome; geographic distribution of human consanguinity: Bittles AH 2001 *Clinical Genet* 60(2):89.



Figure I19. Pharaoh and wife, close relatives (Courtesy of C.S. Gowans)

Inbreeding, Progress of: The proportion of homozygosity of any selfed or inbred generation for any number of allelic pairs can be computed by the formula (see Fig. I20):

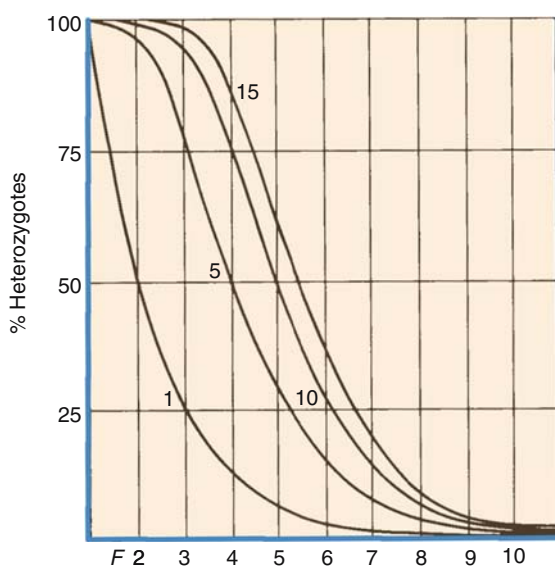


Figure I20. Consequences of repeated inbreeding (selfing) on the frequency of heterozygotes for 1, 5, 10 and 15 allelic pairs. (Redrawn after Jones, D.F. 1925 *Genetics in Plant and Animal Improvement*. Wiley, New York)

$[1 + (2^g - 1)]^n$ where g is the number of generations selfed (note: e.g., by F_5 there are 4 selfings because F_1 is the result of crossing) and n is the allelic pairs involved. An example of expansion of the binomial in case of 3 pairs of alleles in F_5 :

$$[1 + (2^4 - 1)]^3 = [1 + (16 - 1)]^3 = 1^3 + 3(1)^2(15) + 3(1)(15)^2 + 1(15)^3 \text{ or rewritten as } 1^3(15)^0 + 3(1)^2(15)^1 + 3(1)^1(15)^2 + (1)^0(15)^3$$

where the first exponent in each term indicates the number of heterozygous genes and the second exponent denotes the number of homozygous genes in each class of individuals. In this example 1 is heterozygous for all 3 loci and homozygous for none (3×15). Further, 45 is heterozygous for 2 loci and homozygous for 1 (3×15^2), i.e., 675 is heterozygous for 1 locus and homozygous for 2. 1×15^3 , i.e., 3375 is heterozygous for none of the 3 loci but is homozygous for all 3 in a total population of 4096 ($1 + 45 + 675 + 3375 = 4096$). ►heterozygote proportions, ►binomial, ►coefficient of inbreeding, ►fixation index

Inbreeding Rate: This is determined as $\Delta_F = 1/(2N_e)$, where N_e = effective population size. If the actual size of a population is 10 then $\Delta_F = 1/(2 \times 10) = 0.05$. In this computation the effective population number is considered to be equal to the total number. Under practical circumstances this is rarely the case. If it is assumed that the effective size is only 3/4 of the actual number then $\Delta_F = 1/(20 \times 0.75) \cong 0.066$, a higher fraction. The coefficient of inbreeding can also be calculated as: $F_g = 1 - (1 - \Delta_F)^g$ where g = the number of generations of inbreeding and F = inbreeding coefficient.

Accordingly, after 25 generations, $F_{25} = 1 - (1 - 0.066)^{25} \approx 1 - (0.934)^{25} \approx 0.819$ whereas if 10 is the effective size, $F_{25} = 0.723$ in this hypothetical case.

►effective population size, ►inbreeding progress, ►inbreeding coefficient, ►fixation index

INCENP: ►sister chromatid cohesion

INCEST: Refers to legally prohibited sexual intercourse between close (biological) relatives. Incest is primarily a legal, ethical and moral concept. From the viewpoint of genetics, the consanguinity of the parents is considered and legal restrictions may not be adequate to avoid the deleterious consequences of such matings for the offspring. In ancient Egypt the pharaohs frequently (and legally) married their sisters and this may explain the large number of mummies of children at the burial places. Relatively scarce data are available on children of first-degree relatives (parent \times child, brother \times sister) yet it is clear that nearly 40% of them have more or less severe physical and/or mental defects. Interestingly, in populations where uncle–niece and cousin marriages have been practiced for centuries the number of birth defects is not as high as would be expected. Apparently, the inbreeding continued for many generations purged the gene pool of the most deleterious alleles that are maintained at random mate selection. ►coefficient of coancestry, ►coefficient of inbreeding, ►genetic load

Inchworm Model: During transcription the RNA polymerase is flexibly connected to the template. The front-end domain is tightly associated with the DNA (~10 bases) and that is followed by a loose association (~15–20 bases), including the catalytic domain, which in turn is followed by another tight association (~10 bases) to the transcript. Thus, the movement of the polymerase displays a variable discontinuous pattern. A somewhat similar mechanism is seen in an *end-to-end template switching*. When the nucleotide supply is low the polymerase can jump from a single-strand template to 7–9 bases of another linear double-stranded DNA. The upstream electrostatic interaction involves the C-end of the β subunit whereas the downstream interaction involves the N-end of the β subunit of the polymerase. The polymerase ternary complex may also move backward and the catalytic site may be involved in the cleavage of the RNA strand. Kinesin may move either by inchworming or by the hand-over-hand mode. ▶RNA polymerase, ▶transcription, ▶transcript elongation, ▶protein synthesis, ▶promoter clearance, ▶TCF, ▶kinesin; Uptain SM et al 1997 Annu Rev Biochem 66:117.

Incidence: This is the frequency of occurrence of a genetic alteration or disease in a population. ▶prevalence, incidence and prevalence database: <http://library.dialog.com/bluesheets/html/bl0465.html>.

Incipient Species: Refers to a group of organisms in the process of speciation. ▶speciation, ▶evolution

Inclusion Body (IB): This is a protein aggregate in *E. coli* cells expressing at a high rate some foreign gene(s), in the presence of amino acid analogs or antibiotics. They appear to be the products of processing of proteins and degradation of defective polypeptides. These proteins can be examined by a phase contrast microscope and can be concentrated by the centrifugation of lysed or sonicated cells. Some RNA viruses replicate within cytoplasmic inclusion bodies. Inclusion bodies are formed by the aggregation of huntingtin and other proteins in Huntington's chorea. In this disease, the role of inclusion bodies has been controversial in as much as both deleterious and beneficial effects have been reported. Recent evidence has indicated that IB formation reduces the level of huntingtin and the risk of neuronal death (Arrasata M et al 2004 Nature [Lond] 431:805). In mice shortstop inclusions themselves may not be pathogenic as such but they may enhance excitotoxicity (caused by neurotoxic glutamate-like substances) and thus mediate neurodegeneration (Slow EJ et al 2005 Proc Natl Acad Sci USA 102:11402). ▶phase contrast microscope, ▶sonicator, ▶Ibp, ▶Huntington's chorea; Rattenholl A et al 2001 Eur J Biochem 268:3296.

Inclusion Body Myopathy (cytoplasmic body myopathy):

This is a late-onset non-progressive muscle weakness. The muscle fibers contain microscopically visible inclusions in the cytoplasm. Both autosomal dominant and recessive inheritance have been reported. Dominant inclusion body myopathy 3 (IBM3, 17p13.1) displays rimmed vacuoles and ophthalmoplegia. The recessive IBM2 (9p12-p13) shows amyloid-like inclusions. The latter is relatively frequent among Jews of Kurdish and Iranian origin. This disease is caused by mutation in the UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase. ▶amyloid, ▶ophthalmoplegia, ▶Lewy body; Eisenberg I et al 2001 Nature Genet 29:83.

Inclusive Fitness: This is a type of altruistic behavior.

Parents defend their children—at their own risk—for the sake of maintenance of their genes, which the offspring shares with them. This altruistic behavior is positively correlated with the degree of relationship. According to Hamilton's rule the closer the genetic relationship, the greater is the degree of altruism. R.A. Fisher and J.B.S. Haldane discussed this phenomenon earlier. Siblings—on the average—are expected to share half of their genes and fitness whereas cousins share only 1/4. Hamiltonian medicine shows that infection caused by multiple microbial strains may either increase or decrease virulence. In some instances large colonies are formed which because of kin selection (i.e., altruistic behavior among relatives) increase the harm to the host. In other instances the different microbes turn against each other and reduce the risk to the host (Foster KR 2005 Science 308:1269). While brushing teeth different bacteria are mixed on the gums which reduces the extent of dental corrosion. ▶fitness, ▶altruistic behavior, ▶kin selection, ▶inbreeding coefficient, ▶microbiome; Sundstrom L, Boomsma JJ 2001 Heredity 86(pt 5):515; Griffin AS, West SA 2003 Science 302:634.

Incompatibility: See for plants ▶S alleles, ▶incompatibility alleles for mammals. ▶ABO blood group, ▶Rh blood group, ▶erythroblastoma, ▶immune tolerance, ▶histocompatibility [in tissue and organ transplantation], ▶plasmid incompatibility, ▶fungal incompatibility, ▶heterokaryon incompatibility, ▶cytoplasmic incompatibility, ▶maternal tolerance, ▶eclampsia; incompatibility mechanisms among plants: Bomblies K, Weigel D 2007 Nature Rev Genet 8:382.

Incompatibility Alleles: Self-incompatibility in a large number of plant species (tobacco, clover, crucifer, fescue, beet, cherry, etc.) may prevent self-fertilization or formation. The number of different incompatibility alleles may run into hundreds in some species. A plant pollen carrying a particular incompatibility allele may not successfully develop a pollen

tube in the stylar tissue of the same genetic constitution but may successfully fertilize another plant of a different allelic constitution (see Fig. I21). A sperm with a S1 allele is incompatible with a stylus of S1S1 type but may fertilize a S2 egg. In a S1S2 heterozygote neither a S1 nor a S2 sperm may be successful but they have no barriers in S3S3 plants. In some species compatibility may be determined by the sporophytic tissue; in a S1S2 stylus, if the S2 allele is dominant, the S1 pollen may be successful and produce a S1S1 seed. In some cases the S1S2 pollen of a tetraploid plant may be compatible with a S1S1 egg if the S2 allele is dominant. In the *Brassicaceae* the S alleles extend to several hundred kb and include several closely linked transcriptional units, often referred to as the S haplotype.

Incompatibility may also be based on different timing of pollen release and receptivity of the stigma. Compatible combinations may arise through induced mutations. Heterostyl (different height of the stylus and stamen) may also prevent self-fertilization. S-specific glycoproteins and ribonuclease enzymes cause self-incompatibility. In the *Brassicaceae* two tightly linked genes, mediating incompatibility, encode the S locus receptor serine/threonine protein kinase (SRK) and the secreted glycoprotein (SLG, 431 amino residues). It is assumed that a pollen-borne ligand ties SLR and SLG into a signaling complex that prevents germination or the growth of the pollen tube on the stigma or in the style. An interesting observation is that a SRK incompatibility protein provides protection against *Pseudomonas syringae* infection. In the *Solanaceae* the S locus encodes another type of glycoprotein with ribonuclease

activity (S-RNase) and this ribonuclease may inhibit the growth of the incompatible pollen tubes. In wild poppy (*Papaver rhoeas*) Ca^{2+} signaling inhibits incompatible pollen tip growth and actin depolymerization and apoptosis follow (Thomas SG et al 2006 J Cell Biol 174:221).

The *Hmr* (hybrid male rescue) gene determines hybrid incompatibility among the sibling species of *Drosophila melanogaster* (Barbash DA et al 2003 Proc Natl Acad Sci USA 100:5302). It encodes a MYB-related DNA-binding transcriptional regulator protein. The gene evolved by base substitutions, deletions and insertions especially in the DNA-binding domain may be a main factor of sexual isolation and speciation. ►mentor pollen effect, ►male sterility, ►apomixis, ►gametophyte, ►genetic load, ►fungal incompatibility, ►Rh blood group, ►ABO blood group, ►self-incompatibility, ►MYB oncogene, ►actin; Wang X et al 2001 Plant Physiol 125:1012.

Incompatibility Load: ►genetic load

Incompatibility, Mother–Fetus: During gestation the paternal alloantigens of the fetus should not permit an immune reaction by the mother to ensure the survival of the fetus. Several mechanisms are believed to be involved in this. It has been observed that HLA-G, Fas–FasL or TRAIL–TRAILR control apoptosis of maternal leukocytes during pregnancy. Indolamine 2,3-dioxygenase, a tryptophan-catabolizing enzyme, suppresses maternal T cell activity and rejection of allogeneic fetus (Munn DH et al 1998 Science 281:1191). The complement regulator decay accelerating factor protein, Crry in the placenta controls tolerance in mice and humans (Xu C et al 2000 Science 287:498). The inhibitory co-stimulatory programmed cell death (PD1) protein and its ligands (PL1, PDL2) are also critically involved (Guleria I et al 2005 J Exp Med 202:231).

Incompatibility is genetically determined in erythroblastosis fetalis in the case of wrong Rh allele combinations or to some extent in other blood groups. Incompatibility may be mediated by the activation of the complement. Decay accelerating factor (DAF) inactivates the C3 complement component convertase protein that activates C3. Membrane cofactor protein (MCP) is required for degradation of the activated C3 and C4. In murines a regulatory protein suppresses C3 deposition but if it becomes homozygous for an inactive mutation fetal loss may ensue. ►erythroblastosis fetalis, ►genetic load, ►killer cells, ►complement, ►decay accelerating factor, ►MCP, ►incompatibility, ►Rh blood group, ►eclampsia, ►HLA, ►Fas, ►TRAIL, ►apoptosis, ►allogeneic

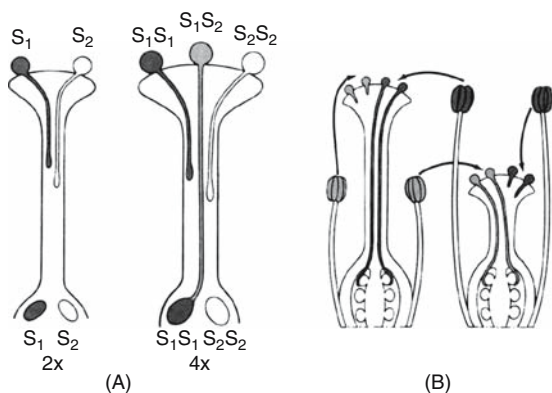


Figure I21. (A) The compatibility of the diploid pollen in a duplex tetraploid plant. (B) Incompatibility associated with dimorphism of style and stamen length. (After Linskens HF, Kroh M 1967. Encyclopedia of Plant Physiology. Vol. 18. Springer. Berlin, Germany)

Incompatibility Plasmids: These utilize the same system of replication and cannot co-exist. When they are introduced into the bacterial cell they have to compete with each other and consequently one is eliminated. Plasmids (phages) that carry the same replicon belong to the same incompatibility group. RNA I, RNA II and the Rop protein determine incompatibility. There are more than 30 plasmid compatibility groups. ▶RNA I; Miller CA, Cohen SN 1993 Mol Microbiol 9:695.

Incompatibility, Vegetative (somatic incompatibility): Refers to the blocking of hyphal fusion and the formation of heterokaryons. ▶hypha, ▶heterokaryon, ▶fungal incompatibility

Incomplete Digestion: The reaction with restriction enzymes is terminated before all potential cleavage sites are cut. A greater variety and a few large fragments are cut because some neighboring sequences are not cleaved apart. ▶restriction enzymes

Incomplete Dominance: This is also known as semi-dominance and it is observed when the expression of the gene does not entirely mask or prevent the expression of the recessive allele at the same locus in a hybrid. ▶dominance, ▶epistasis

Incomplete Linkage: Recombination takes place between or among the syntenic genes in question. ▶recombination, ▶crossing over, ▶synteny, ▶linkage

Incongruence: This may be construed as evidence of horizontal gene transfer because the variation at certain loci is higher than that of the flanking regions. ▶transfer lateral; Farris JS et al 1995 Cladistics 10:315.

Incontinentia Pigmenti (Bloch-Sulzberger syndrome, IP1): Human X-linked (Xp11) dominant “marble-cake-like” dark pigmentation on the skin of the trunk is generally preceded by an inflammation. It may begin soon after birth and may fade by the age of 20. The condition may be associated with eye, tooth, bone and heart anomalies. Most of IP2 cases are apparently due to mutation/chromosomal breakage at the gene NEMO (NF-κB essential modulator)/IKKγ (IκB kinase-γ) closely linked to antihemophilia factor VIII at Xq28. Mutation/chromosome breakage in both IP1 and IP2 is lethal in the case of males before or around birth whereas in the heterozygous females survive to adulthood and the severity of the symptoms varies. Some of the rare cases of males with IP1 may be mosaics or of XXY constitution. ▶hypomelanosis of Ito, ▶pigmentation defects, ▶erythrokeratoderma variabilis, ▶antihemophilic factors, ▶NF-κB, ▶ectodermal dysplasia, ▶NEMO; Aradhya S et al 2001 Hum Mol Genet 10:2171.

Incorporation Error: This is a mechanism of mutation when a nucleic acid base analog or a wrong base is inserted into nucleic acid during replication. As a consequence one base pair replaces another. The meaning of the codon may change and it appears as a visible mutation if the codon change leads to an amino acid substitution at a critical site in the protein. For example: during replication a 5-bromouracil is inserted into the DNA at a C site resulting in a BrU—G base pair. During the next replication the BrU—A pair is formed and during a subsequent replication a T=A pair is substituted at a site where originally a C=G pair existed. ▶replication error, ▶base substitution mutations, ▶hydrogen pairing; Freese E 1963 in Molecular Genetics, p. 207, Taylor JH ed. Acad. Press, New York.

Incremental Truncation for the Creation of Hybrid Enzymes (ITCHY): ▶iterative truncation

Incross: Refers to hybridization between two strains that have the same genetic background.

Indel: An insertion or deletion in the DNA nucleotide sequences can be illustrated by the simple example below the alignment score (see Fig. 122). $Pr = p^3 q^2 r^1$ where p is the probability of identity (match), q is the probability of substitution (mismatch) and r is the probability of an indel. The alignment score can be derived as follows:

$S' + \log Pr = 3(\log p) + 2(\log q) + (1(\log r))$ and $S = S' - \log s = S' - 6(\log s)$ S' = a constant satisfying $\log(p/s) = 1$). And $S = 3 - 2\mu - 1\delta$ where $\mu = \log(q/s)$, $\delta = \log(r/s)$ and S = number of identities - μ number of substitutions - δ number of indels. Computer programs based on high level mathematics that cannot be presented here can resolve the problem.

```

AAGTTC
| | | Match
A  GCCC
  ^ Mismatch
Indel

```

Figure 122. Indel

The average size of indels among taxonomically diverse species was found to be about 36 nucleotides but some indels extended to 10 kb. The frequency of unpaired nucleotides due to indels was almost three times more than those caused by base substitutions (Britten RJ et al 2003 Proc Natl Acad Sci USA 100:4661). Comparison of the DNA sequences between the corresponding human chromosome 21 and chimpanzee chromosome 22 revealed that the single nucleotide mismatches represented only 1.44% of the sequence whereas 68,000 small or large

stretches of indels were found. The initial map of human indels contains 415,436 unique polymorphisms within the range of 1 to 9989 base pairs. On an average, there was 1 indel/7.2 kb human DNA. Further, 148,000 indels were found within genes and 5542 of these were within promoters or exons where they had the maximal effects on function (Mills RE et al 2006 *Genome Res* 16:1182). (See Waterman MS, Joyce J, Eggert M 1991 *Phylogenetic Analysis of DNA Sequences*, pp 59–89; Miyamoto MM, Cracraft J eds. Oxford University Press, New York; ►DNA sequence information, ►databases, indel scanning: <http://indelscan.genomics.sinica.edu.tw/IndelScan/>.

Independence: Two events are independent when the occurrence of one does not affect the chance of occurrence of the other. Genes at a distance of 50 map units or more segregate independently, the sex of the first child is (normally) independent of the sex of the next one, if two pennies are tossed they can land on their head or their tail independently from each other unless they are defective or biased.

Independence Test: ►association test (contingency chi square).

Independent Assortment: Alleles of different loci (non-allelic genes) may re-assort freely in the gametes and therefore segregate independently in zygotes in the absence of a linkage. The independent assortment of alleles is one of the most essential discoveries of Mendel and it is frequently called Mendel's third law. ►Mendelian laws

Independent Events: These events do not affect or influence each other.

Indeterminate Inflorescence (raceme): The main axis can elongate indefinitely but the branches terminate in a flower bud. ►raceme

Index: Refers to an alphabetical or other ordered set of files or symbols or numbers distinguishing particular things in an array. For example: allele a^1 , "1" distinguishes this allele among all other a alleles, or *NK3* homeobox 3 of *Drosophila* or *adp^{fs}* an *adipose* allele conveying female sterility, or the second asymmetric leaf locus as_2 (*AS-2*) of *Arabidopsis*.

Index Case: ►proband (propositus, proposita).

Index Locus: ►polymorphism information content (PIC)

Index Value: This is a concept used for selection in animal breeding. A score weights each trait and these scores are summed in an index value. The use of this index acts as a safeguard against the possibility of selecting one particular trait only and thus

jeopardizing the overall success of the program because disease susceptibility or low fertility, etc. frequently accompany high performance. ►gain, ►selection; Falconer DS 1960 *Introduction to Quantitative Genetics*, Ronald, New York.

Indexers: This is an amplification system for specific DNA fragments from whole genome digests without the need for cloning. It uses restriction enzymes class-IIIs. The non-identical cohesive ends can be selectively modified by ligation to synthetic oligodeoxy-ribonucleotides with the corresponding complementary ends. This permits the introduction of PCR and sequencing primer sites and labels into small fragments of the genomic digest. An advantage over cloning is that fragment losses, rearrangements can be avoided without cloning, probes or libraries. The procedure is applicable to small prokaryotic and large eukaryotic genomes for analyzing sequence tagged sites, restriction mapping, RFLP, sequencing and DNA diagnostics. ►restriction enzymes class-IIIs, ►PCR, ►sequence tagged site; RFLP; Unrau P, Deugau KV 1994 *Gene* 145:163; Guilfoyle RA et al 1997 *Nucleic Acids Res* 25:1854; SibsonDR, Gibbs FEM 2001 *Nucleic Acids Res* 29(19):e95.

Indians: ►Native Americans

Indicator Mice: This is transgenic for a recombinase (*Cre* or *Flp*). When it is crossed to another transgenic line carrying a construct with a FRT sequence in front of the structural gene *LacZ*, on Xgal medium develops blue color only when the recombinase flipped out the FRT stop codon. The test indicates the functionality of the recombinase and its utility for targeting. ►targeting genes, ►Cre/LoxP, ►Flp/FRT, ►Xgal

Indirect Diagnosis: Denotes identification of a gene by linkage rather than by direct evidence.

Indirect End-Labeling: Determines the distance of a DNase hypersensitive site from a restriction enzyme cleavage site. The chromatin is first digested by a Klenow fragment of DNAase I and then it is isolated and treated with a restriction endonuclease. The double digest is subsequently separated by electrophoresis and probed with a sequence adjacent to the restriction site. The size of the fragment generated by the double cuts indicates the distance of the DNase hypersensitive site from the site of restriction. This procedure can localize in the DNA the sites where transcription may be initiated because hypersensitive sites are correlated with the position of transcriptionally active genes. ►DNase hypersensitive site, ►Klenow fragment, ►restriction endonuclease; Li S et al *Methods* 2000 22(2):170.

Indirect Suppression: Some suppressor mutations do not correct the primary change in the gene rather they modify the translation process and thereby suppress the expression of the mutation. ▶ [suppressor mutation](#)

Indole: This is a heterocyclic compound present in many organic associations in biological materials (see Fig. I23). When excited by ultraviolet light, it displays a characteristic fluorescence spectrum that facilitates its rapid detection. Among other roles it is a precursor of tryptophan synthesis: anthranilate → indole + serine → tryptophan.

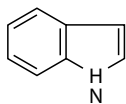


Figure I23. Indole

Indole Acetic Acid (IAA): This is a plant hormone synthesized from tryptophan via the pathway Trp→indole-3-acetaldoxime→indole acetonitrile →IAA or Trp→ indolepyruvic acid→indole-3-acetaldehyde→IAA. (See formula at ▶[IAA](#)).

Indophenoloxidase: See under the new name ▶[super-oxide oxidase](#)

Induced Fit: This fit of enzymes (proteins, ribozymes) occurs when the conformation is so modified that the activity improves; this may be caused by binding to a ligand or substrate. Both the substrate and ligand may change conformation for the fit. The crystal structure of the encounter complex on the pathway of ligand binding by IgE antibody SPE7 is formed by a wide range of ligands that initially bind with identical affinity. Non-specific ligands rapidly dissociate, whereupon the antibody isomerizes to a nonbinding isomer. Specific ligand complexes, however, slowly isomerize to give a high-affinity complex (James LC, Tawfik DS 2005 Proc Natl Acad Sci USA 102:12730). ▶[ligand](#), ▶[key-lock](#), ▶[DNA binding proteins](#), ▶[Lac operon](#)

Induced Helical Fork: After the binding protein contacts a few bases of the DNA, it keeps apart the double helix. ▶[Watson and Crick model](#), ▶[binding proteins](#)

Induced Mutation: This is obtained by exposure to a mutagen and is presumably generated by the mutagen itself rather than by an incidental spontaneous event. ▶[spontaneous mutation](#), ▶[mutation](#)

Induced Replicosome Reactivation: ▶[replication-restart](#)

Inducer: A substrate or an analog of a substrate of an enzyme prevents a repressor protein from attaching to

the promoter (operator) of a gene and thus facilitates its expression. ▶[induction](#), ▶[gratuitous inducer](#), ▶[repression](#), ▶[activator proteins](#), ▶[inducible gene expression](#)

Inducible Enzyme: The presence of a substrate or a substrate analog is required for their synthesis. ▶[Lac operon](#), ▶[Ara operon](#); Monod J, Audureau A 1946 Ann Inst Pasteur 72:868.

Inducible Gene Expression: This is required in many instances to stimulate the expression of a particular gene (transgene) in a specific tissue or cells. Inducible promoters are useful tools in biotechnology as they can be employed for turning on/off genes in response to special, physiological or developmental factors. ▶[metallothionein](#), ▶[transcriptional activators](#), ▶[transactivator](#), ▶[VP16](#), ▶[two-hybrid hybrid method](#), ▶[split-hybrid system](#), ▶[three-hybrid system](#), ▶[tetra-cycline](#)

Induction: This term has several meanings. Phage induction refers to the facilitation of the transition from the prophage stage to the lytic phase. The induction of enzymes set into motion the catalytic activity. The assembly of the pre-initiation complex of transcription induces gene expression. Embryonic development is induced by the transmission of various exogenous and endogenous signals. In *reciprocal induction* in development an inducer may be positively affected by the tissue that is formed by its inducing action. ▶[prophage](#), ▶[enzyme induction](#), ▶[regulation of gene activity](#), ▶[transcription](#), ▶[signal transduction morphogenesis in Drosophila](#), ▶[organizer](#), ▶[photomorphogenesis](#)

Induction, Developmental: The fate of a cell or tissue is affected by the interaction of the embryonic cell or tissue with its neighbors. ▶[embryonic induction](#)

Induction of a Lysogenic Bacterium: This is the process of liberating phage particles by first inducing a change from a prophage to a vegetative state of the phage. ▶[zygotic induction](#), ▶[prophage](#)

Induction of an Enzyme: This initiates the synthesis of new enzyme molecules by the presence of an inducer that may be the substrate or an analog of the substrate of that enzyme. ▶[derepression](#), ▶[gratuitous inducer](#)

Indusium: This is a membrane-type layer over the sorus (sporangial cluster) of ferns.

Industrial Melanism: As industrialization (coal-burning pollution) advanced (in Britain) the dark variants (dominant) of the black peppered moth (*Biston betularia*) increased as a selective trend to camouflage the insect on soot covered tree barks. ▶[natural selection](#), ▶[adaptation](#); *Biston betularia*; Kettlewell HBD 1961 Annu Rev Entomol 6:245.

Infantile Amaurotic Idiocy: ▶Tay-Sachs disease

Infarction: Refers to blood vessel necrosis caused by coagulation (thrombus) obstructing proper circulation. ▶necrosis, ▶thrombosis

Infection: Denotes invasion of a host by a virus or another organism. The invader may establish a mutually beneficial or neutral relation with the host (symbiosis). Many bacterial species regularly inhabit the host without causing any harm. In the infected host different sets of host genes are either activated or repressed than in the uninfected controls (Falkow S 2006 Cell 124:699). Infection by some bacteria frequently results in pathogenic consequences. The microbial agent generally subverts the host defense system on the surface and adheres to the special receptors. They engage the cytoskeleton to facilitate penetration and disable the phagocytotic mechanisms of the host cell. In order to maintain itself the infective agent must overcome the immune system of the host. After the invasion the pathogen may redirect the host metabolism to its own interest and produces disease symptoms. If the host quickly succumbs to the disease a frequency-dependent selection may eventually work against the invader or over time the host may develop resistance. In *Listeria* the transcription of the virulence factor is controlled by the activator PrfA that is thermoregulated by a 5' secondary structure of PrfA. It blocks its ribosome binding at a temperature below (37°C) that of the host (Johansson J et al 2002 Cell 110:541).

In *latent infection* the virus remains in a few copies and a few viral proteins are expressed so that the host defense is not evoked temporarily. At an opportune moment the virus may enter a lytic stage. In *chronic infection* the pathogen invades the host repeatedly or the infection persists for a prolonged period. Latent agents *cause opportunistic infection* when the immune system is compromised.

For epidemic spread the basic reproductive number, R^0 is used to define the mean number of infections caused by an infected individual in a susceptible population. However, there are large individual differences in the infectiousness and several mathematical procedures have been developed for the prediction of disease spread (Lloyd-Smith JO et al 2005 Nature [Lond] 438:355). ▶host-pathogen relationship, ▶epidemiology, ▶frequency-dependent selection; Knodler LA et al 2001 Nature Rev Mol Cell Biol 2:578; Hill AVS 2001 Annu Rev Genomics Hum Genet 2:373; Kazmierczak BI et al 2001 Annu Rev Microbiol 55:407; Gruenheid S, Finlay BB 2003 Nature [Lond] 422:775; virus entry into animal cell: Smith AE, Helenius A 2004 Science 304:237; bacterial invasion: Cossart P, Sansonetti PJ 2004 Science 304:242; bacterial invasion machinery: Pizarro-Cerdá J,

Cossart P 2006 Cell 124:715; parasite invasion: Sibley LD 2004 Science 304:248; reviews of viral infection mechanisms: Marsh MS Helenius A 2006 Cell 124:729; Greber UF, Way M 2006 Cell 124:741.

Infectious Center: This is a spot from where infectious phage or bacteria can be produced.

Infectious Diseases: These diseases are not hereditary as was assumed before the emergence of genetics yet susceptibility may be genetically determined. Infectious agents, however, undergo evolutionary changes and new diseases emerge and re-emerge. They are the major cause of human mortality worldwide. In 2002, ~57 million deaths were caused by infectious agents, especially among people under age of 50 years. Three-quarters of the infections emerge from animals and adapt to humans by new mutations. Pathogens acquire the means to evade the human immune system and develop resistance to antibiotics, medication and vaccines. ▶host-pathogen relation, ▶matrix diseases; Cooke GS, Hill AV 2001 Nature Rev Genet 2:967; Morens DM et al 2004 Nature [Lond] 430:242; Merrell DS, Falkow S 2004 Nature [Lond] 430:250; Boes M, Ploegh HL 2004 Nature [Lond] 430:264; host and pathogen models of plants and animals: Pradekl E, Ewbank JJ 2004 Annu Rev Genet 38:347; http://databases.biomedcentral.com/browsesubject/?sub_id=2011.

Infectious Drug Resistance: Drug-resistant genes are carried on the conjugative plasmids of bacteria. ▶conjugation bacterial, ▶plasmid

Infectious Heredity: ▶symbionts hereditary, ▶Wolbachia, ▶segregation distorter, ▶plasmid, ▶prions

Infectious Nucleic Acid: This may be a purified viral DNA or RNA that may propagate in the host cell and code subsequently for viral particles.

Infectious Protein: ▶prion, ▶encephalopathies, ▶kuru

Inference, Statistical: Refers to conclusion(s) drawn about a population on the basis of a random sample of the population. The conclusions are generally based on statistical tests such as significance and likelihood. Inference in general means reasoning; prediction of an unknown on the basis of known or assumed facts. ▶significance level, ▶confidence intervals, ▶likelihood, ▶Bayes' theorem, ▶Bernoulli process

Infertility: This may be due to various causes such as anatomical abnormalities of the sexual organs (hermaphroditism, dysgenesis, testicular feminization and polycystic ovary disease). Infectious diseases, hormonal abnormalities, malfunction of CREM, psychological factors, organic diseases, medications, alcoholism or other substance abuse, malnutrition and chromosomal defects (trisomy, translocations,

inversions, deletion, duplications and aneuploidy) may also lead to infertility. Hereditary abnormalities (cystic fibrosis, mental retardation, Kallman's syndrome, Kartagener syndrome and myotonic dystrophy) may involve infertility. In the US nearly 15% of couples are involuntarily infertile. In about 20–50% of human infertility cases males are involved; 70–90% of them have defects in spermatogenesis or spermiogenesis. After the age of 50, semen volume and sperm concentration gradually decrease (in some cases increase), sperm motility is reduced and fertility rate is lower. Male infertility may be due to the absence of a 10 repeat CAG microsatellite within the mitochondrial DNA polymerase γ gene (Rovio AT et al 2001 Nature Genet 29:261).

Spermatozoa with large heads, a variable number of tails and an increased chromosome number is a common cause of sterility in men. A genome-wide microsatellite scan of 10 infertile men with this phenotype revealed that they were homozygous for single nucleotide deletion in a common region harboring the aurora kinase C gene (*AURKC*, 19q13.3). This founder mutation results in premature termination of translation, yielding a truncated protein that lacks the kinase domain (Dietrich K et al 2007 Nature Genet 39:661).

About 38% women may be infertile. The consequences of the long-term use of fertility drugs on the incidence of ovarian cancer may not be entirely clear (Parazzini F et al 2001 Hum Repr 16:1372). Women who smoke have an early menopause that may be due to exposure to the polycyclic aromatic hydrocarbons (PAH) in the smoke. PAH binds to its receptor (AHR) in the promoter of the BAX gene and promotes apoptosis of the egg, leading to infertility (Matikainen T et al 2001 Nature Genet 28:355). By tissue transplantation between two sterile male mouse lines, fertility may be restored because of complementation. ▶fertility, ▶fertilization, ▶sex hormones, ▶ART, ▶fecundity, ▶gametogenesis, ▶spermiogenesis, ▶PN-1, ▶sterility, ▶azoospermia, ▶cell cycle, ▶CBAVD, ▶CREM, ▶asthenozoospermia, ▶smoking, ▶claudin-11, ▶miscarriage, ▶microsatellite, and the other entries; Aurora Ogawa T et al 2000 Nature Med 6:29; Moore FL, Reijo-Pera RA 2000 Am J Hum Genet 67:543; Kidd S et al 2001 Fertility & Sterility 25:237; Cooke HJ, Saunders PTK 2002 Nature Rev Genet 3:790.

Infiltration: This means the introduction of various substances into the biological tissues by diffusion, frequently facilitated by evacuation (under negative pressure).

Infinite Allele Mutation Model (IAM): Among the practically infinite number of genetic variations of nucleotide sequences each mutation creates a new

allele that did not exist earlier in the genome. It predicts that evolutionary alterations in (microsatellite) DNA occur either by addition or deletion of one copy (of tandem repeats) in a novel fashion. ▶stepwise mutation model, ▶microsatellite; Kimura M, Crow JF 1964 Genetics 49:725.

Infinitesimal Model: When a linkage is sought between quantitative trait loci (QTL) and other genetic markers, the analysis is conducted on the basis of a null hypothesis that a particular chromosome or chromosome segment segregates independently from a QTL. ▶QTL, ▶interval mapping, ▶null hypothesis, ▶adaptation

Inflammasome: This is a protein complex activating inflammation reactions (Mariathasan S et al 2004 Nature [Lond] 430:213). Essential components of the complex in response to bacterial RNA are cryopyrin (encoded by the CIASI/NALP3 gene, 1q44), caspases-1 (a cysteine protease [ASC] encoded at 11q22.2-q22.3), interleukin-1 β [IL-1 β , 2q14] and IL-18 [11q22.2-q22.3], Toll-like receptor [4q32] and ATP. Caspase-1 activation promotes cell survival in case of infection by bacteria, which produce pores on the cell wall with the aid of secreted toxins (Gurcel L et al 2006 Cell 126:1135). Macrophages deficient in cryopyrin can activate caspases-1 and secrete IL-1 β and IL-18 when infected with gram-negative *Salmonella typhimurium* and *Francisella tularensis*. Macrophages exposed to gram-negative *Staphylococcus aureus* and *Listeria monocytogenes* require both cryopyrin and ASC to secrete IL-1 β (Mariathasan S et al 2006 Nature [Lond] 440:228; Kanneganti T-D et al 2006 Nature [Lond] 440:233). ▶caspases, ▶IL-1, ▶IL-18, ▶Toll, ▶macrophage, ▶gram negative, ▶Salmonella, ▶tularemia, ▶Listeria, ▶Staphylococcus, ▶Muckle-Wells syndrome, ▶gout, minireview: Ogura Y et al 2006 Cell 126:659.

Inflammation: This is a physiological response to infection by pathogens or to adverse environmental chemical or physical agents. Immunoglobulin G (IgG) mediates proinflammatory responses. Sialylation of the Fc (fragment crystalline) of IgG switches the response to an anti-inflammatory mode (Kaneko Y et al 2006 Science 313:670). Despite being an initial healing response, inflammation may eventually lead to a chronic state such as observed in autoimmune diseases and cancer. In nearly 20% of sporadic cancer inflammation plays a role and NF- κ B promotes it (Pokarsky E et al 2004 Nature [Lond] 431:461). Soluble epoxide hydrolase inhibitors (e.g., AUDA-BE = 12-(adamantan-1-yl-ureido)-dodecanoic butylester) (see Fig. 124) reduce lipopolysaccharide-induced mortality, systemic hypotension and tissue injuries without any adverse

side effects (Schmelzer KR et al 2005 Proc Natl Acad Sci USA 102:9772). Systemic inflammatory response is a life threatening condition caused by an increase of proinflammatory cytokines such as IL-1 and TNF- α (without microbial infection). Toll-like receptors are involved in gene-specific chromatin modifications and are associated with transient silencing of one class of genes, which includes proinflammatory mediators, and priming of the second class, which includes antimicrobial effectors (Foster SL et al 2007 Nature [Lond] 447:972). ▶NF- κ B, ▶cancer, ▶nitric oxide, ▶cyclooxygenase, ▶immunoglobulins, ▶antibody, ▶Toll, ▶sialic acid; Nature [Lond] 420:846–891[2002]; <http://pstiing.licr.org/>.

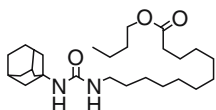


Figure I24. AUDA-BE

Inflammatory Bowel Disease: ▶Crohn disease, ▶ulcerative colitis; review: Xavier RJ, Podolsky DK 2007 Nature [Lond] 448:427.

Inflorescence: This is a cluster of flowers, characteristic for the taxonomic classification of plants. Inflorescence branching in maize is under the control of trehalose enzymes (see Fig. I25) (Sato-Nagasawa N et al 2006 Nature [Lond] 441:227). ▶trehalose; Vollbrecht E et al 2005 Nature [Lond] 436:1119; evolution of inflorescence: Prusinkiewicz P et al 2007 Science 316:1452.

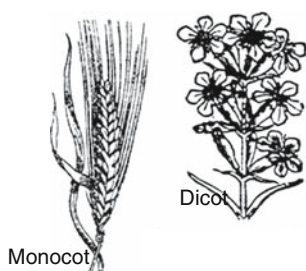


Figure I25. Inflorescences

Influenza Virus: This is a group of commonly spherical (120-nm) single-stranded RNA (12900–14600-nucleotides) viruses. The genome of the A strain is segmented and consists of eight molecules, a central one surrounded by seven others. When its density becomes high, defective interfering particles, containing deletions, may slow down viral multiplication (see Figs. I26 and I27).

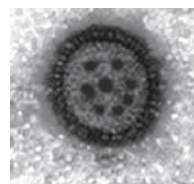


Figure I26. Influenza

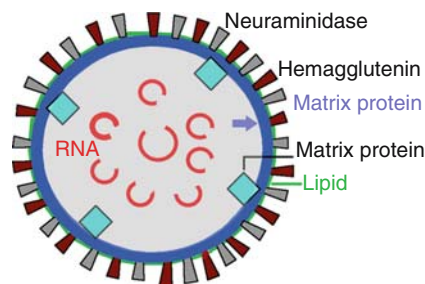


Figure I27. Structure of the influenza virus

Their major surface glycoprotein is hemagglutinin (560 amino acids), which is usually modified by mutation (Plotkin JB, Dushoff J 2003 Proc Natl Acad Sci USA 100:7152). Hemagglutinin, after cleavage by the host proteases, mediates the attachment of the virus to the cell and the transfer of the ribonucleoprotein into the cell. The other common surface glycoprotein is neuraminidase (460 amino acids) which is anchored to the lipid membrane by its amino end. The virus is classified/typed into subtypes according to the hemagglutinin (H) and neuroaminidase (N). In humans, H1N1, H2N2, H3N2 and H5N1 subtypes were so far commonly responsible for epidemics. The H5N1 virus caused the bird influenza outbreak in Vietnam in 2003–2004. The transmission of the avian virus from birds to pigs and humans has been verified but no human to human transmission has been found although the potential human-to-human infection is possible (Hien TT et al 2004 New England J Med 350:1179) (see Fig. I28). Mouse is infected with the influenza virus but it is not a suitable model for the study of transmission. Guinea pigs can spread the virus by droplets to other animals (Lowen AC et al 2006 Proc Natl Acad Sci USA 103:9988). The avian and the human strains differ in the anatomical distribution of the preferred binding molecules sialic acid linked to galactose: SA α 2,3Gal and SA α 2,6Gal. The latter is dominant on the epithelial cells in the nasal mucosa but SA α 2,3Gal is rare there. In the paranasal sinus epithelium, pharynx and bronchi mostly express SA α 2,6Gal. The human-derived H5N1 recognizes preferentially SA α 2,6Gal bound extensively to bronchial epithelium and less to alveolar cells. In contrast avian

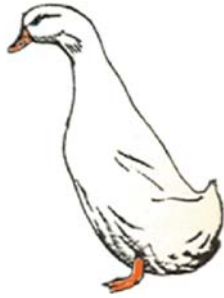


Figure 128. Peking duck source of the famous roast and flu

viruses bind extensively to alveolar SA α 2,3Gal. This difference may be the basis of the relatively inefficient human-to-human transmission of H5N1 (Shinya. K. et al. 2006 Nature [Lond] 440:435). Hemagglutinin receptor mutations at amino acids 182 and 192 independently convert hemagglutinin of H5N1, the avian virus into the human-recognizing form and the human form still recognizes the avian host (Yamada S et al 2006 Nature [Lond] 444:378). Two amino acid changes in the HA receptor may abolish transmission in ferrets (Tumpey TM et al 2007 Science 315:655).

The H7 type is extremely pathogenic to poultry and can jump over to humans (Webby RJ, Webster RG 2003 Science 302:1510). Equine influenza virus (H3N8) can jump to dogs (Crawford PC et al 2005 Science 310:482). Migratory birds may pose a great risk for the rapid spread of diseases. The evolution of the virus depends primarily on the antigenic variations. That is not exactly the same as the nucleotide replacements in the genetic material because some of the mutations do not involve amino acid replacements and some amino acids have disproportionately large antigenic effects (Smith DJ et al 2004 Science 305:371). All the major human influenza pandemics seem to have originated by mutation from avian viruses (Taubenberger JK et al 2005 Nature [Lond] 437:889). The reconstructed virus causing the lethal worldwide epidemic of 1918 owed its virulence – compared to the current influenza viruses (H1N1) – to a few mutations, its ability to replicate in the absence of trypsin, caused death in mice and embryonated chicken eggs and increased growth in human bronchial epithelial cells. The RNA for the 8 viral genes were preserved and isolated from in formalin fixed lung autopsy samples and from unfixed, frozen samples of a corpse buried in permafrost in 1918 (Tumpey TM et al 2005 Science 310:77).

The C type flu virus has another single surface glycoprotein, HEF that destroys the cellular receptor by neuraminatase-O-acetylase. The viral M1 protein (M_r ~28K) controls the nuclear traffic of the

virus. The virus has several types, designated by place of origin such as Spanish, Hong Kong and Russian strains or as Type A (most common and reoccurring in 2–3 year cycles), Type B (causes epidemics in 4–5 year cycles), and Type C (a sporadically occurring one). In Type A virus the hemagglutinin HA1 plays an important role for infectivity. The nucleotide substitution in this domain is high (5.7×10^{-3} per site). At least 18 amino acids are critical for evading the host immune response. The expected mutation rate at these sites has predictive value for the pharmaceutical industry for the production of inoculation for the following year. The Spanish Flu of 1918 was particularly devastating as it killed 675,000 Americans and reduced the average life expectancy by 10 years. Influenza virus A encodes and translates, by an alternative reading frame, an 81-residue protein PB1-F2, which promotes apoptosis. It appears that upon infection this mitochondrially-localized protein kills the host immune cells (Chen W et al 2001 Nature Med 7:1306). Birds, horses, swines and cats also have influenza-type infections by different viruses.

The bird influenza virus posed a threat to human populations only in 1997. The highly virulent flu strains usually develop from reassorted viruses of the human and avian types sometimes via the pig flu virus. The nucleotide sequences of 169 H5N1 strains, including 2,196 genes, have been reported (Obenauer JC et al 2006 Science 311:1576). The avian flu spreads to various species of birds, including migratory birds, which may carry it to long distances, and it infects humans but at present time (by 2008) there is no firm evidence that infected humans would transmit this avian virus to other human beings. Swans are particularly susceptible to H5N1 and among the domestic poultry ducks are probably less susceptible than chickens. Viral infection of the respiratory tract occurs with possible secondary infection by *Streptococcus*, *Staphylococcus* and *Haemophilus* bacteria. Vaccination against the influenza virus may be effective. However, there are problems because of the annual variations in the subtypes and the best methods of manufacturing effective vaccines against the variations in the prevailing types. Also, a few unprotected individual birds can reignite the epidemics (Saville NJ et al 2006 Nature [Lond] 442:757). Because of the frequent variations the industry must produce a new type of vaccine every year that provides limited protection when the virus changes. Amino acid changes in hemagglutinin by converting at site Serine 223 to Asparagine improved the hemagglutinin titer and effectiveness of the H5N1 vaccine (Hoffmann E. et al. 2005 Proc. Natl. Acad. Sci. USA 102:12915). The prevention of virus transmission is of major importance. Targeted prophylaxis, quarantine and

pre-vaccination may effectively contain a pandemic (Longini IM et al 2005 Science 209:1083). Several vaccines may elicit adverse reactions in some individuals because of host genetic factors. Antiviral drugs have not been widely exploited. Neuraminidase inhibitors such as Zanamivir, Ralenza, Oseltamivir and Tamiflu may restrict all types of influenza viruses (Laver G 2005 Nature [Lond] 434:821; Matrosovich MN et al 2004 J Virol 78:12665). These drugs are effective in prevention and generally do not have any serious side effects except in cases of cirrhosis of the liver or poor general health (Kaji M et al 2005 J Infect Chemother 11:41). Recent findings have revealed around 10% increase in psychoneurotic side effects following the use of Tamiflu in Japan. Mutation to Oseltamivir had been observed in humans (Mai Le Q et al 2005 Nature [Lond] 437:1108; Moscona A 2005 New England J Med 353:2633). X-ray crystallography has revealed a cavity adjacent to the active site of neuraminidase 1 that closes on ligand binding. This observation has brought to light a new potential target for antiviral drug development (Russell RJ et al 2006 Nature [Lond] 433:45). ▶reassortant, ▶hemagglutinin, ▶neuraminidase deficiency, ▶Newcastle virus, ▶prophylaxis, ▶quarantine; Gibbs MJ et al 2001 Science 293:1842; Bae S-H et al 2001 Proc Natl Acad Sci USA 98:10602; Steinhauer DA, Skehel JJ 2002 Annu Rev Genet 36:305; Ferguson NM et al 2003 Nature [Lond] 422:428; Palese P 2004 Nature Medicine 10:S82; large-scale sequence variation in the human A virus: Ghedin E et al 2005 Nature [Lond] 437:1162; Fauci AS 2006 Cell 124:665; evolution of influenza virus: Nelson MI, Holmes EC 2007 Nature Rev Genet 8:196; Influenza virus problems: Science 2006 312:379; influenza virus resource: <http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html>; <http://influenza.genomics.org.cn>; virus A genotyping: <http://www.flugenome.org/>, annotation of virus A and B: <http://www.ncbi.nlm.nih.gov/genomes/FLU/Database/annotation.cgi>.

Informatics: This is a system of databases and electronic retrieval. ▶bioinformatics, ▶databases

Information: It is obvious that the more the information that is available about a population the easier and more reliable is the decision of the geneticist about a parameter of that population(s). Statistically, the information $I_p = \frac{1}{V_p}$ indicating that the total amount of information is inversely proportional to the variance (V) of the statistic employed. The calculation of the information for a particular set of data can be carried out by:

$$I = \sum \left(\frac{1}{m} \left[\frac{dm}{d\theta} \right]^2 \right)$$

where m is the expectation in terms of parameter θ , and Σ is the sum of all classes. R.A. Fisher pointed out that

maximizing the likelihood function provides an estimate of T , which has the limiting value of $1/nV_T = I$. The reciprocal of the variance of the maximum likelihood estimate permits assessing the value of other estimates. If the variances obtained by other methods are not $1/nI$, they do not provide the complete possible information and are therefore inferior to the maximum likelihood statistics. ▶maximum likelihood, ▶variance; Mather K 1957 The Measurement of Linkage in Heredity, Methuen, London.

Information (in statistics): It is sometimes called “support” or “lod-score”. ▶lod score

Information Retrieval: Refers to the procedures to obtain information from a set of stored data, such as a specific nucleotide sequence in the database. ▶databases; Yandell MD, Majoros WH 2002 Nature Rev Genet 3:601.

Information Theory: <http://www.lecb.ncifcrf.gov/~toms/paper/primer>.

Informational Macromolecules: Denote DNA, RNA, proteins that can convey genetic, developmental, biochemical and evolutionary instructions to a cell or organism.

Informative Mating: This reveals the inheritance or linkage relationship of a gene or an allele.

Informativeness: Refers to the usefulness of a test for making a distinction between/among alternative hypotheses. ▶robustness

Informed Consent: A genetic counselor may face a dilemma regarding the information he/she may wish to withhold from the counselee because of the psychological impact. Legally, all the dangers associated with the professional evaluation should be shared with the individual, and within the legal limits of confidentiality. Action to be pursued requires informed consent. Organ donation for direct use for human treatment involves different ethical considerations and informed consent for organ donation for medical or basic biological research. Both may involve risk for the donor and in the latter case (e.g., oocytes donation for stem cell research) the beneficial effects for society may not be seen for years or ever (Magnus, D. & Cho, M.K. 2005 Science 308:1747). ▶counseling genetic, ▶genetic privacy, ▶confidentiality, ▶bioethics, ▶gene therapy, ▶cancer gene therapy, ▶public opinion, ▶morality, ▶biopiracy; US Office for Protection from Research Risks (OPRR) 1993, Dept. of Health and Human Services, Washington DC; Greely HT 2001 Annu Rev Genet 35:785.

Informosome (masked RNP): Refers to mRNA complexed with protein and thus having a very low

turnover rate and stability. (Spirin AS 1994 Mol Reprod Dev 38:107).

INGI: ►p53

ingi: ►hybrid dysgenesis, ►I-R

Ingression: This is the movement of cells from the surface into the inner region. ►gastrulation

INH: A protein complex that contains at least six species, isolated from oocytes. It inhibits the activation of pre-MPF. ►maturation protein factor

INHAT: Refers to an inhibitor of histone acetyltransferases CBP and PCAF. ►CBP, ►PCAF

Inherency: Genes that are important for organogenesis in higher evolutionary forms usually have some comparable representatives in more primitive forms.

Inheritance: This is the process of receiving genes from one's ancestors and passing them on to one's offspring. DNA codes these genes in eukaryotes and prokaryotes; in some viruses the transmitted genetic material is RNA. The genetic material may be located in the nucleus (nuclear inheritance) or carried by the nucleoid in prokaryotes. The genetic material in mitochondria and chloroplasts mediates extranuclear inheritance. Prokaryotes and cytoplasmic organelles may also have plasmid vehicles of heredity. Colloquially people may say that a certain trait of the children is inherited from one or the other parent. Actually, traits are not inherited, only the genes, which determine them, are transmitted. Epigenetic modification of histone proteins may, however temporarily be maintained in the offspring. ►genotype, ►phenotype, ►heredity, ►genetics, ►reverse genetics, ►DNA, ►RNA, ►prions, ►genealogy, ►pedigree, ►acquired characters inheritance, ►epigenetics, ►dauermodification

Inheritance, Cortical: ►cortical inheritance

Inheritance, Cultural: This refers to information transfer by non-biological means such as customs, traditions and behavior. Cultural inheritance plays a significant

role in the phenotype but the genes of the organism determine its genetic significance. The genes involved may have different selective values. ►fitness

Inheritance, Delayed: ►delayed inheritance

Inhibin: This is an antagonist of activin. Inhibins are glycoproteins (A and B) in the seminal and follicular fluids and inhibit the production of follicle-stimulating hormone and regulate gameto-genesis, embryonic and fetal development as well as blood formation (hematopoiesis). ►activin, ►FSH

Inhibition: ►inhibitor

Inhibition of Transcription: Any inhibitor of the RNA polymerase protein can block transcription. Bis ([1,10]-phenanthroline) cuprous chelate ($[OP]_2Cu^+$) is one such inhibitor. On its own it is not gene-specific, however, it can cut oxidatively single-stranded DNA templates and is suitable for mapping transcription initiation sites (see Fig. I29). Gene-specific inhibition of transcription can be accomplished by antisense RNA, triple-helix formation and DNA-binding polyamides. Gene-specific inhibition is feasible by targeting $[OP]_2Cu^+$ to the promoter in an open transcription complex with the aid of template-specific oligonucleotides with $[OP]_2Cu^+$ attached to the oligonucleotides at various positions at either ends or interstitially. The template strand is then interrupted by the $[OP]_2Cu^+$ position, e.g., OP-5'-GUGGA-3', 5'-GUGGA-3'-OP or 5'-GU[OP]GGA-3'. The inhibition is most efficient with 5 nucleotides representing one-half turn of A or B DNA-type double helix. The preferred cleavage site is 2–3 nucleotide from the OP linkage toward the 3' end. 2'-aminouridine appears to increase the specificity of the intercalation. The presence of the RNA polymerase is essential for the binding. ►antisense RNA, ►TFO, ►triple helix formation, ►polyamides, ►transcriptional repression, ►transcription corepressor, ►RNAi, ►DNA types; Milne L et al 2000 Proc Natl Acad Sci USA 97:3136.

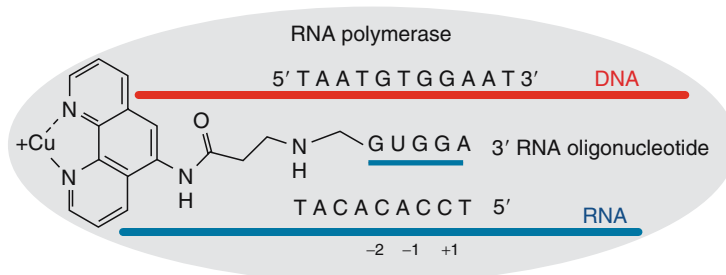


Figure I29. Inhibition of transcription

Inhibitor: This is a substance that interferes with the *activity* of an enzyme versus a repressor that prevents the *synthesis* of the enzyme. ►[regulation of enzyme activity](#)

IN1 (integrase interacting protein): This tethers the retroviral (HIV) integrase enzyme and facilitates the integration at or near the DNase hypersensitive site of the eukaryotic chromosome. ►[integrase](#), ►[DNase hypersensitive site](#), ►[Cre/loxP](#), ►[FLP](#), ►[resolvase](#), ►[retroviruses](#), ►[HIV](#)

Initial Sequence Contig: Refers to the assembly of overlapping sequences from a single clone.

Initiation Codon: This is the first translated codon. In prokaryotes it is commonly AUG (90%) translated into formylmethionine but GUG (8%) and UUG (1%) can also be used. AUU is rarely employed because IF3 discriminates against this *non-canonical* codon versus the above three *canonical* codons. In prokaryotes the non-formyl AUG is prevented from initiation by the secondary structure in the mRNA and the interaction between mRNA and ribosomal RNA. In eukaryotes AUG does not code for formylmethionine but for methionine. In some rare cases in mammals the initiation codon is CUG or GUG (Tailor, C.S. et al. 2001 J. Biol. Chem. 276:27221, Schwab, S.R. et al. 2003 Science 301:1367). In some insect viruses the initiator codon is CAA (glutamine) and an initiator tRNA is not required. The initiation codon is charged to a specific initiator tRNA. ►[aminoacyl-tRNA synthetase](#), ►[elongation factors](#), ►[Shine-Dalgarno sequence](#), ►[ribosome scanning](#), ►[translation initiation](#), ►[transcript elongation](#), ►[modified bases](#), ►[genetic code](#)

Initiation Complex: This contains the small subunit of the ribosome with associated mRNA, aminoacylated tRNA and the various initiation protein factors and energy donor nucleotide triphosphates. In prokaryotes the initiation complex, comprising three single polypeptide chains proteins, has a mass of ~150 kDa. In eukaryotes about 10 initiation factors comprising >25 polypeptide chains has an aggregate mass of ~1,200 kDa. Although both types of systems require the ternary complex of Ifs (initiation factors)•GTP•tRNA, several differences exist in the details of executing the functions. In eukaryotes the ternary complex usually binds the 40S ribosomal subunit before the mRNA binding although the reverse sequence of events is possible. In prokaryotes there is a near equal chance of selection of either of these possible routes of binding the 30S subunit. In eukaryotes the 40S ribosomal subunit recruits to the 5' cap of the mRNA, the initiation factors eIF3 and eIF2-GTP and the initiator tRNA. EIF3 then interacts with the cap-binding complex eIF4F and the 40S

subunits scan for the appropriate start codon in the mRNA. Factor eIF5 releases eIF2 and in the presence of eIF5B-GTP both 40S and 60S ribosomal subunits are assembled into the 80S ribosome. Then the start codon Met-tRNA₁ instead of the ribosomal P site eIF5B is released from GTP to proceed with peptide extension. The Cricket Paralysis Virus can initiate translation without this complete machinery by the placement of the IRES (internal ribosomal entry site) at the A site of the ribosome. Other insect viruses, however, require most of the regular initiation factors and Met-tRNA₁ (Jan, E. et al. 2003 Proc. Natl. Acad. Sci. USA 100:15410). ►[protein synthesis](#), ►[preinitiation complex](#), ►[initiation factors](#); Kimball SR 2001 Progr Mol Subcell Biol 26:155.

Initiation Factor for Transcription: ►[initiation complex](#), ►[IF](#), ►[eIF](#)

Initiation Factors of Protein Synthesis: These are involved in initiation of translation. ►[eIF](#), ►[IF](#) and ►[iIF](#); Sonenberg N et al eds. 2000 Translational Control of Gene Expression, Cold Spring Harbor Lab. Press, Cold Spring Harbor, New York.

Initiator (Inr): ►[promoter](#), ►[core promoter](#)

Initiator Codon: This is the starting site of translation in the mRNA; it is generally 5'-AUG-3' but sometimes it can be 5'-GAG-3', 5'-GUG-3' or 5'-GUA-3'. ►[protein synthesis](#), ►[translation](#)

Initiator tRNA: This carries formylmethionine (prokaryotes) and initiation methionine (eukaryotes) to the P site of the ribosome to begin translation. The structure of this tRNA can be distinguished from the rest of the transfer RNAs. This rRNA in bacteria, besides the AUG, may recognize GUG and UUG as a formylmethionine codon. Not all proteins begin with a methionine because of processing. Mutation in the anticodon of tRNA^{fMet} may start translation with amino acids other than formylmethionine or methionine. The eIF2 initiation protein distinguishes between the initiator and the elongation tRNA^{Met} on the basis of several criteria: the A1:72 base pair at the bottom of the amino acid acceptor stem, three G:C pairs in the anticodon stem, initiators do not have the TψC in the T arm and A54 rather than T54 is in the T arm and within the T loop A60 replaces pyrimidine-60. In plants and fungi, at position 64 a phosphoribosyl group is attached to the 2'-OH of the ribose. Additional variations may exist in some species. ►[protein synthesis](#), ►[ribosome](#), ►[transfer RNA](#), ►[IRES](#), ►[initiation codon](#), ►[eIF2](#), ►[pseudoknot](#); O'Connor M et al 2001 RNA 7:969.

Injectisome: This is an apparatus of pathogenic bacteria for delivering type III secretions into the host (see Fig. 130). The tip of a long injection needle of *Yersinia*

composed of several proteins is diagramed after Mueller (Mueller CA et al 2005 Science 310:674).



Figure I30. Injecting needle tip

INK (p^{INK}): Polypeptide inhibitors of cyclin-dependent kinases involve and cause cell cycle G1 phase arrest. The INK family includes proteins p15, p16, p18 and p19 bind Cyclin D/CDK4. ▶cancer, ▶cell cycle, ▶CDK, ▶p15, ▶p16, ▶p18, ▶p19

Innate: This means inherited, congenital. ▶congenital

Innate Immunity (natural immunity): This is based on cell surface receptors (pattern recognition receptors, PRR) and other protein molecules encoded by the germline. The Toll-like receptors (TLR) through their TLR/IL-1 receptor domains (TIR) recognize extra-cellular or membrane-enclosed foreign organisms. The NOD-like (nucleotide-binding oligomerization proteins, NLR) include different families of proteins. NOD1 and NOD2 recognize bacterial peptidoglycans. The NALP3 “inflammasomes” control proinflammatory cytokines IL-1 β and IL-18. They respond to PAMPs (pathogen-associated molecular pattern recognition proteins) and DAMPs (danger-associated molecular pattern). Viruses are recognized RIG-like helicases. (See details of function reviewed by Meylan E et al 2006 Nature [Lond] 442:39).

These systems generally recognize carbohydrate structures and then stimulate the synthesis of various molecules such cytokines, interleukins and tumor necrosis factor. Some natural killer cells (neutrophils, macrophages) recognize inimical cells by lectin-like membrane receptors. This innate immunity is a rather fixed, rigid system in comparison to the acquired immunity mediated by immunoglobulins which are greatly adaptable and variable. Innate immunity can shape the development of the acquired immunity by interacting with it. The protein fragments cut up by the macrophages may be presented to the adaptive immune system represented by the B and T cells. It may guide the selection of antigens by lymphocytes and the secretion of cytokines by the helper T lymphocytes. Innate immunity is the first line of defense by initiation of inflammation through recruiting phagocytic and bactericidal neutrophils and macrophages. The innate immune system recognizes foreign bodies with the aid of pattern-recognition

receptors. In mouse double-strand RNA viruses are recognized by retinoic-acid-inducible protein I (RIG-I) and by the melanoma-differentiation-associated gene 5 (MDA5) that encodes another antiviral protein. RIG-I responds to dsRNA by the production of interferon whereas MDA5 is specific for polyinosinic-polycytidylic acid. RIG-I responds to paramyxoviruses, influenza virus and Japanese encephalitis virus. MDA5 is critical for picornaviruses (Kato H et al 2006 Nature [Lond] 441:101).

The complement is part of innate immunity but it also cooperates with the acquired immunity system. Innate immunity is also present in insects (*Drosophila*) although they lack the adaptive immunity system found in vertebrates. The innate defense system of bacteria recognizes non-methylated DNA and cleaves the foreign DNA by restriction endonucleases. Mammals possess relatively few CG pairs and the C is commonly methylated within the PuPuCGPyPy sequence. The unmethylated bacterial, fungal and insect CG pairs then activate macrophages, dendritic and B cells without normally attacking the self-DNA. Through the mediation of the MEK signal transduction pathway and NF- κ B the genes of the acquired immune system are turned on. The specificity of the discrimination is attributed to the different Toll-like receptors, which recognize bacterial lipopolysaccharides, glycolipids, flagellin, etc. Another signaling route is through DNA-PK. These two pathways may anastomose. The defense system in *Drosophila* relies on phagocytosis, proteolytic cascades, melanin formation, opsonization and the synthesis of antimicrobial peptides. ▶immune system, ▶natural antibody, ▶complement, ▶acquired immunity, ▶vaccine, ▶lymphocytes, ▶antibody, ▶interferon, ▶opsonins, ▶antimicrobial peptides, ▶Toll, ▶siderophore, ▶flagellin, ▶signal transduction, ▶NF- κ B, ▶DNA-PK, ▶CD14, ▶host-pathogen relationship, ▶T-bet; Aderem A, Ulevitch RJ 2000 Nature [Lond] 407:782; Aderem A, Hume DA 2000 Cell 103:993; Kimbrell DA, Beutler B 2001 Nature Rev Genet 2:256; Roger T et al 2001 Nature [Lond] 414:920; Janeway CA Jr, Medzhitov R 2002 Annu Rev Immunol 20:197; relationship between innate and adaptive immunity: Hoebe K et al 2004 Nature Immunol 5:971.

Innervation: Refers to the development of the nervous system in an organ or tissue.

Innexins: These are invertebrate gap-junction proteins which are functionally similar to connexins in vertebrates. ▶gap junction, ▶connexins

INO80: This is a chromatin remodeling complex participating in the DNA double-strand break repair. (Morrison AJ et al 2004 Cell 119:767; DN repair).

Inoculum: Usually a small microbial cell sample is used for starting a culture (see Fig. I31).



Figure I31. Inoculation loop

INOH: This is a biochemical pathway database (<http://www.inoh.org/>).

Inorganic Pyrophosphatase: This cleaves off 2 molecules of phosphates from molecules.

Inosine: ►hypoxanthine (see Fig. I32).

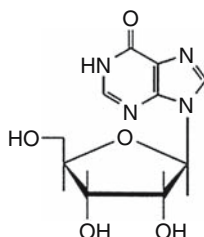


Figure I32. Inosine

Inosinic Acid: ►hypoxanthine

Inositides: ►phosphoinositides

Inositol: This occurs in cells as myoinositol as part of the vitamin B-complex. It is formed through cyclization from glucose-6-phosphate (see Fig. I33). It is an indispensable constituent of some lipids (phosphoinositides). In some forms of diabetes it may accumulate in the urine. ►signal transduction, ►diabetes

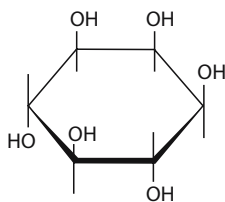


Figure I33. Inositol

Inositol Triphosphate: ►phosphoinositides

Inparalog: This is a gene(s) evolved through more recent duplications. Gene comparisons between species are identified by INPARANOID algorithm (Remm, M. et al. 2001 J Mol Biol 314:1041). ►paralogous loci, ►outparalog

In-Planta Transformation: ►transformation genetic

Input Trait: In genetic engineering of plants the goal of research is to facilitate the culture of plants (e.g., increase resistance to herbicides, pathogens, parasites, cold, etc.). The *output traits* include higher nutrient content, modified plant products (e.g., lipids, fatty acids) manufacturing special proteins (e.g., antibodies) and synthesizing special industrial raw materials (e.g., silk fibroin, plastics). ►genetic engineering

Inr: ►promoter

INSDC (International Nucleotide Sequence Database Collaboration): <http://www.insdc.org/>; ►XML

Insect Control, Genetic: ►genetic sterilization, ►holo-centric chromosomes

Insect Control, Physiological: This uses chemicals as well as biological agents such as viruses, bacteria, fungi, protozoa and natural parasites. Chemicals include alkylating agents (e.g., methyl bromide) that alter the DNA, organophosphates and carbamates that inhibit choline esterases and thus the nerve function, nicotine and derivatives act similarly as acetylcholine mimics. Arsenics inhibit glycolysis, cyanides poison the respiratory system. DDT, pyrethrins activate sodium channels, growth regulators may inhibit chitin synthesis, hormone synthesis, etc. However, the effectiveness of many compounds may be diminished over time because of mutation to resistance. (Wimmer EA 2003 Nature Rev Genet 4:225; biological insect control: <http://www.ent.iastate.edu/list/directory/108>).

Insect Resistance in Plants: Some plant species contain genes for insect tolerance and these are being incorporated into plant breeding material by conventional techniques. The most successful insect resistance gene, the *Bacillus thuringiensis* toxin gene, has been transformed into several species of dicots and provides almost complete defense when it is expressed under the control of efficient promoters. Pea plants transgenic for α -amylase inhibitor 1 and 2 are protected from the pea weevil (*Bruchus pisorum*). α Al-1 causes larval mortality at the 1st and 2nd instar stages whereas α Al-2 is responsible for blocking the maturation of the larvae. Maize plants defend themselves against the armyworm (*Spodoptera exigua*) caterpillars by releasing a sesquiterpene and indole. These volatile compounds encoded by the *stc1* and *Igl* genes, attract parasitic wasps, which deposit their eggs and eventually destroy the caterpillars. Some of these volatile defense compounds (cis-3-hexen-1-ol, linalool, cis- α -bergamotene) perform multiple tasks, e.g., repel herbivorous invaders, decrease their rate of oviposition and recruit their natural predators (Schnee, C et al 2006 Proc. Natl.

Acad. Sci. USA 103:1129). Another species of fall armyworm (*Spodoptera frugiperda*) is perceived by the cowpea (*Vigna unguiculata*). Upon attack the insect secretes a disulfide-bridged peptide ($^+ICDINGVCVDAS^-$) called inceptin, that promotes ethylene production in the plant and triggers the production of phytohormones salicylic acid and jasmonic acid that have a defense function. Inceptins are proteolytic fragments of the γ subunit of chloroplast ATP synthase. Only insects that earlier fed on cowpeas produce inceptin in sufficient quantity to defend against the herbivore (Schmelz, EA et al. 2006 Proc. Natl. Acad. Sci. USA 103:8894).

Spidermite-infected plants may release terpenoids (β -ocimene) that may stimulate defense-related genes in uninfected lima bean plants. Plants transgenic for the cyanogenic glucoside, dhurrin (see Fig. I34) become resistant to the flea beetle *Phyllotreta nemorum*. Host plant specialization of pea aphids may be affected by an endosymbiotic bacterium (Tsuchida, T. et al. 2004 Science 303:1989). *Arabidopsis* plants transgenic for sesquiterpene synthase targeted to the mitochondria use cytochrome oxidase subunit IV (CoxIV)-linalool/nerolidol synthase construct emitted nerolidol and its derivative 4,8-dimethyl-1,3(E),7-nonatriene ([E]-DMNT) against insects (see Fig. I35).

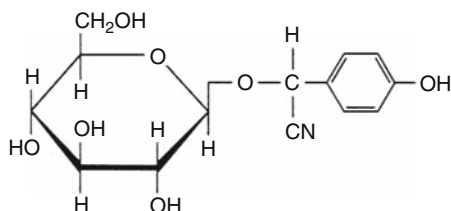


Figure I34. Dhurrin

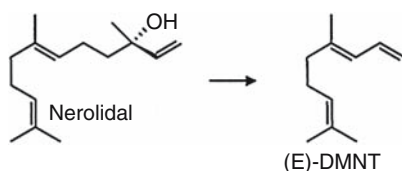


Figure I35. Insect resistance substances in plants

These compounds attract the carnivorous predatory mites (*Phytoseiulus persimilis*) to the plants and provide defense against herbivorous insects (Kappers IF et al 2005 Science 309:2070). Maize (corn) earworm (*Helicoverpa zea*) is a pest of maize and several solanaceous plants (tomato, potato). The host plants produce a carboxypeptidase inhibitor to prevent the pest from feeding on the plant tissues but the pest can adapt by producing an inhibitor-resistant protease. The crystal structure of the *H. zea*

B-type metallocarboxypeptidase has been revealed that has shed light on its properties (Bayés A et al 2005 Proc Natl Acad Sci USA 102:16602). The β -subunit of SnRK1 (SNF-related kinase) protein kinase, GAL83, transcripts rapidly down regulate sugars in the leaves of tobacco upon attack by herbivores and move them to the roots. This defense increases the root reserves and prolongs life and facilitates survival (Schwachtje J et al 2006 Proc Natl Acad Sci USA 103:12935). Secreted proteins encoded by parasitism genes expressed in esophageal gland cells mediate infection and parasitism of plants by root knot nematodes. The ingestion of *16D10* dsRNA in vitro silenced the target parasitism gene in root knot nematode and resulted in reduced infectivity in *Arabidopsis* (Huang G et al 2006 Proc Natl Acad Sci USA 103:14302). Insect have chemosensors for the detection of their animal or plant targets (van der Goes van Naters W, Carlson JR 2006 Nature [Lond] 444:302). [▶*Bacillus thuringiensis*](#), [▶chitin](#), [▶wound response](#), [▶host–pathogen relations](#), [▶selection types](#), [▶high-dose/refuge strategy](#), [▶lotaustalin](#), [▶herbivore](#), [▶jasmonic acid](#); De Moraes CM et al 2001 Nature [Lond] 410:577; Farmer EE 2001 Nature [Lond] 411:854; Palumbi SR 2001 Science 293:1786; Tattersall DB et al 2001 Science 293:1826; Schriber JM 2001 Proc Natl Acad Sci USA 98:12328; Kessler A, Baldwin IT 2002 Annu Rev Plant Biol 53:299; Kennedy GG 2003 Annu Rev Entomol 48:51; insect genomes: Heckel DG 2002 Annu Rev Entomol 48:235; grasshopper elicitor: Alborn HT et al 2007 Proc Natl Acad Sci USA 104:12976.

Insect Viruses: These viruses are of diverse types. The enveloped Baculoviridae and the Poxviridae have double-stranded DNA. The mosquito iridescent virus has non-enveloped dsDNA. The genetic material of the Parvoviridae is non-enveloped single-stranded DNA. The Reoviridae carry non-enveloped double-stranded RNA. The Flaviviridae are single-stranded, enveloped RNA viruses. The *Drosophila C* virus is a non-enveloped ssRNA virus. The Baculoviruses are important for engineering genetic vectors. [▶baculoviruses](#); Friesen PD, Miller LK 2001 p. 443 in Fundamental Virology, Knipe DM, Howley PM eds. Lippincott Williams & Wilkins, Philadelphia, PA.

Insecticide Decay: Insecticides, pesticides and herbicides may decompose spontaneously in soil at different rates; 1,2-dichloroethane in 72 years, paraoxon in 13 months, atrazine (herbicide) in 5 months and aziridine (synonym ethylenimine, carcinogen) in 52 h. The nematocide 1,3-dichloropene is converted into transchloro-3-chloroacrylic acid in $\sim 10,000$ years at 25°C. However, when it is exposed to the enzyme 3-chloroacrylate dehalogenase of *Pseudomonas*

pavonaceae hydrolytic dechlorination proceeds at a half-time of 0.18 s, an increase of about 10^{12} (Horvat CM, Wolfenden R V 2005 Proc Natl Acad Sci USA 102:16199)

Insecticide Resistance: Such resistance usually develops rapidly in various populations of pests as a response to detoxification of the pesticides. In several insects mutations in one (*Cyp6g1*) of the P-450 cytochrome genes (90 in *Drosophila*) is responsible for resistance to DDT as well as other chemicals (organophosphates, neonicotinoids, benzoylphenylureas). In mosquitos amplification of the detoxifying carboxylesterase may occur. Point mutations in the genes encoding γ -aminobutyric acid-gated chloride channel nerve membrane convey resistance to cyclodienes. ▶DDT, ▶organophosphates, ▶cholinesterase, ▶pyrethrin, ▶nicotine; Denholm I et al 2002 Science 297:2222.

Insemination by Donor (DI): This is a therapeutic process to secure offspring in the case of male infertility. In the USA, this method accounts for ~30,000 birth/year. Generally, cryo-preserved semen of sperm banks is utilized. To avoid potential consanguinity and the transmission of hereditary diseases it is advisable to limit the number of inseminations to less than 10 per donor. If the donors are genetically screened the incidence of genetic abnormalities may decline from 2–5% to about half of that in the general population where DI is not used. ▶ART, ▶sperm bank, ▶in vitro fertilization; Kuller JA et al 2001 Hum Reprod 16:1553.

Insert Restriction Site into Plasmid: In this process the restriction endonuclease gene is amplified by the PCR and then the plasmid is opened up by the restriction enzyme. After the primers are removed the target DNA is inserted into the plasmid and ligated to circularize the plasmid.

Insertion Elements: DNA sequences generally shorter than 2000 bases, which can insert into any part of a genome transposons are common in all organisms from prokaryotes to eukaryotes (see Table 14). Some of the bacterial insertion elements have the following characteristics.

They do not carry any genetic information beyond that needed for insertion. Viruses can act as insertion elements in cells. Insertion elements are the major factors of “spontaneous” mutability. According to some estimates, 5–15% of the spontaneous mutations in bacteria are caused by *IS* elements. The presence of *IS1* may increase deletion frequency of the *gal* operon 30 to 2,000 times. *IS* elements also cause chromosomal rearrangements. Many *IS* elements have a large number of potential target sites, others exhibit clear preferences. The mechanism of transposition is either

Table 14. A few insertion elements

| Name | Size (bp) | Inverted Repeats (bp) | Terminal (bp) | Target Duplication |
|-------------|-----------|-----------------------|--------------------------------------|--------------------|
| <i>IS1</i> | 768 | 18/23 | (<i>E. coli</i>) | 8–11 |
| <i>IS2</i> | 1,324 | 32/41 | (<i>E. coli</i>) | 5 |
| <i>IS3</i> | 1,258 | 29/40 | (<i>E. coli</i>) | 3 |
| <i>IS5</i> | 1,250 | 16 | (<i>E. coli</i>) | 4 |
| <i>IS10</i> | 1,329 | 17/22 | (<i>Tn10</i>) | 9 |
| <i>IS66</i> | 2,548 | 18/20 | (<i>Agrobacterium tumefaciens</i>) | 8 |

dependent on replication and the new copy is transposed or it simply involves a relocation of the existing element. The movement of the *IS* elements is affected by host genetic factors (DNA polymerase, gyrase, histone-like proteins, dam methylase, DnaA protein and proteins mediating recombination).

The presence of *IS* elements may alter not just mutation, but also gene expression by their presence in the control regions of genes. In *Drosophila melanogaster* the average insertion density (average number of large insertions/kb/chromosome) is about 0.004 and the average frequency of their movement is 0.023. Some of the historical insertions have been modified and have become permanent regulatory elements of the genes. ▶hybrid dysgenesis, ▶copia elements, ▶retrotransposons, ▶Ti plasmids, ▶LIN, ▶Tn, ▶transposable elements, ▶illegitimate recombination, ▶Ty, ▶pathogenicity islands, ▶RNA insertion element, ▶DD(35)E, ▶site-specific recombination, ▶*Francisella*; Chandler M, Mahillon J 2000 p. 306 in Mobile DNA II, Craig N et al eds. American Society of Microbiology Washington, DC; Mahillon J et al 1999 Res Microbiol 150:675; bacterial insertion elements: <http://www-is.biotoul.fr/>.

Insertion Vectors: These have selectable marker(s) and restriction enzyme site(s) on the vector and chromosome where the foreign DNA can be inserted. The insertion involves a single reciprocal recombination and may generate duplication because the insert has homology to the target. However, the homology does not have to be complete.

Insertional Inactivation: The insertion of any type of DNA into an antibiotic resistance or other gene may inactivate the function (e.g., becomes antibiotic sensitive) because of the disruption of the gene's continuity. ▶insertional mutation, ▶pBR322; McClintock B 1951 Cold Spring Harbor Symp Quant Biol 16:13; Koncz C et al 1992 Plant Mol Biol 20:963.

Insertional Mutation: The insertion of a transposable genetic element within a gene disrupts its function and as a consequence, leads to lethal effects or altered functions (see Fig. I36). The insertion may modify the expression of the target genes by overexpression, suppression of the mutant phenotype or alter it. It has been recently demonstrated that many of the insertions do not lead to an observable change in the expression of the genes or their effect is minimal and only sequencing of the target loci reveals their presence. Labeled probes for the insert can selectively isolate the gene carrying the insertion. Although it was initially believed that the insertions occur at random sites, it has now been documented that the target sites upstream of the promoters or other locations where no essential functions are disrupted are preferred.



Figure I36. Insertional mutation of *Arabidopsis* knocked out the stem but fertility of the fruits is retained. (Rédei, unpublished)

The target selection is mediated by integrase or transposase functions. In some cases only DNA elements are involved in the insertions but retro-transposons sever the target DNA and the free 3'-OH end primes the reverse transcription of the template RNA element and the DNA is then inserted. Generally, there is no homology-dependent pairing requisite for recombination except for the type 2 introns. The insertion also requires protein co-factors such as IHF, HU, MuA and MuB (an ATP-dependent activator of Mu phage protein MuB). The IS10/Tn10 bacterial and the TC1/TC3 *Caenorhabditis* elements interact specifically with a target site consensus. TC transposase recognizes and is inserted at TA dinucleotides. In IS10 the interaction with the target catalyzes the excision of the element from the original location.

Retroviral as well as some other elements preferentially choose nucleosomal sites where the DNA is bent. Tn7 preferentially inserted to a conserved attachment site in *E. coli*, located outside the boundary of the *glmS* gene (glucosaminophosphate isomerase, map position 83). The yeast element Ty3 has high specificity for the promoters of RNA pol III-transcribed genes whereas Ty1 and Ty5 express less stringent specificities (although not exclusively) within the same region. Ty1 also prefers insertion when transcription is (potentially) active whereas Ty5 selects transcriptionally inactive sequences. Therefore, Ty1 is well suited for the induction of insertional mutations. Transposition is generally targeted to sites outside the transposon yet it may occur within the elements and often results in its destruction but it may lead to the evolution of a new element. The maize transposable elements and the *Drosophila* P element move preferentially to nearby sites although they may jump to other chromosomes. Agrobacterial vectors can also produce insertional mutations in plants. The position of insertions can be defined by various polymerase chain reaction techniques. By the use of microarray hybridization insertion libraries can be screened with the aid of capture PCR (Mahalingam R, Fedoroff N 2001 Proc Natl Acad Sci USA 58:7420) and on the basis of homologies to expressed sequence tags. ▶insertion elements, ▶transposons, ▶scanning insertion mutagenesis, ▶GAMBIT, ▶T-DNA, ▶gene isolation, ▶REMI, ▶MICER, ▶integrase, ▶transposase, ▶introns, ▶IHF, ▶HU, ▶Tn7 Tn10, ▶*Caenorhabditis*, ▶DNA bending, ▶Ty, ▶Ac-Ds, ▶hybrid dysgenesis, ▶transposition immunity, ▶Alu family, ▶LINE, ▶EST, ▶microarray hybridization, ▶capture PCR, ▶gene therapy, ▶cancer gene therapy, ▶*Agrobacterium*; Vidan S, Snider M 2001 Curr Opin Biotechnol 12:96; insertion mutagenesis in mouse: Carlson CM, Largaespada DA 2005 Nature Rev Genet 6:568; TRIPLES.

Inside-Out-Signaling: Signals emanating from within the cell control the affinity of ligands and the ligands in turn affect the physiological processes in the cell (outside-in signaling). ▶signal transduction; ligand; Takagi J et al 2002 Cell 110:599.

Insigs (insulin introduced gene): Refers to encoded enzymes regulating cholesterol homeostasis by stimulation through insulin. ▶cholesterol, ▶SREBP; Le JN et al 2006 Proc Natl Acad Sci USA 103:4958.

Insomnia: ▶fatal familial insomnia

InsP₂ (inositol-1,4-diphosphate): Phosphoinositides (see Fig. I37).

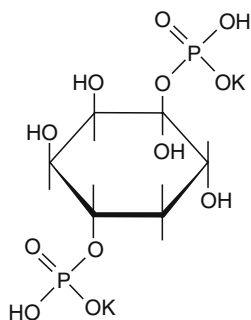


Figure I37. InsP₂

InsP₃ (inositol-1,4,5-trisphosphate): This is a global signaling molecule which liberates Ca²⁺ in the cytoplasm. ►IP³, ►phosphoinositides (see Fig. I38).

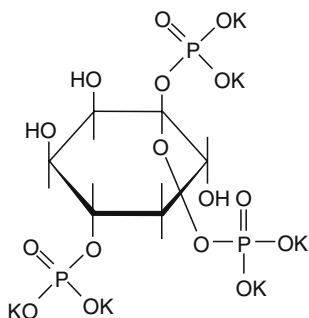


Figure I38. InsP₃

Inspection Bias: This denotes a bias toward biological interest.

Instability, Genetic: This is caused by high rate of mutation, defects in genetic repair, recombination among repeated sequences (trinucleotide repeats, inverted repeats), palindromes, the presence of transposable elements, illegitimate recombination and double-strand breaks. Exonucleases may degrade misaligned tandem repeats and thus favor DNA stability (Feschenko VV et al 2003 Proc Nat Acad Sci USA 100:1134). ►mutator genes, ►mutagens, ►chromosome breakage, ►chromosomal aberration, ►DNA repair, ►trinucleotide repeats, ►repeats inverted, ►at-risk-motif, ►transposable element, ►cancer, ►stress; Myung K et al 2001 Nature [Lond] 411:1073.

Instar: In this phase the insect larvae are between the processes of molting (shedding the outer cover layer). In *Drosophila* three moltings take place after hatching and before pupation. The first and second instars last for ~ one day each, whereas the third instar lasts for ~ two days. ►*Drosophila*

Instincts: A variety of innate behavioral patterns that develop without learning although learning may reinforce them, e.g., motherly love, nursing, fearing for life, conforming to some standards. ►behavior genetics, ►ethics, ►ethology, ►aggression

Institutional Biosafety Committee: This committee must approve genetic engineering projects in terms of (1) the source of the DNA used, (2) the nature of the inserted DNA, (3) the hosts and vectors contemplated, (4) the protein products expected, (5) the nature of the containment facilities and compliance with the regulations of the National Institutes of Health. ►recombinant DNA, ►recombinant DNA and biohazards

Instructive Signal: This is receptor-mediated and involves a signal transduction cascade. ►signal transduction

Insulator: DNA element(s) of 0.5 to 3 kbp that prevent(s) interactions between enhancers and the target promoter but it (they) may/may not permit the expression of stably integrated transgenes. The chicken hypersensitive site 4 DNA is an insulator that protects X-linked mouse gene from repression but not from X chromosome inactivation (Ciavatta D et al 2006 Proc Natl Acad Sci USA 103:9958).

Transcriptional activators may suppress transgene silencing as chromatin insulators (Sutter NB et al 2003 Proc Natl Acad Sci USA 100:1105). However, they must be located between the enhancer and the promoter to be able act. When there is a spacer DNA between the enhancer and the promoter the structural gene is expressed as illustrated by the light bulb switched on. When the spacer is replaced by an insulator element the expression of the structural gene is markedly reduced or eliminated. The insulator may affect the organization of the chromatin or it may act as a regulator of transcription. Such elements are Fab-7 and Fab-8 or the HMR and HML elements controlling sex determination in yeast.

An insulator may prevent position effect. Insulators may show some sort of position effect and two cis insulators may facilitate transcription rather than blocking it. The boundary between heterochromatin and euchromatin reveals a distinct pattern of methylation of histone H3. The gypsy retrotransposon can serve as an insulator by the use of two zinc finger proteins (Su[Hw] and Mod[mdg4]) as well as the centrosomal protein CP190 (Pai C-Y et al 2004 Mol Cell 16:737). The TFIIC transcription factor complex recruited to tRNA genes (located in the pericentric heterochromatin) checks heterochromatin from spreading into the euchromatin. The same transcription factor is also localized between divergent promoters. The TFIIC complex seems to tether

heterochromatin to the nuclear periphery where transcription is limited (Noma K-i et al 2006 Cell 125:859). ▶promoter, ▶enhancer, ▶silencer, ▶boundary element, ▶sex determination in yeast, ▶CTCF, ▶position effect, ▶enhancer competition, ▶histones, ▶epigenesis, ▶transcription factors, ▶transcription factories, ▶chromosome territories; Sun F-L, Elgin SCR 1999 Cell 99:459; Bell A et al 1998 Cold Spring Harbor Symp Quant Biol 63:509; Bell AC, Felsenfeld G 1999 Curr Opin Genet Dev 9:191; Bell AC et al 2001 Science 291:447; Noma K-I et al 2001 Science 293:1150; Gerasimova TI, Corces VG 2001 Annu Rev Genet 35:193; Oki M, Kamakaka RT 2002 Current Opin Cell Biol 14:299; West AG et al 2002 Genes Dev 16:271; mechanisms: Gaszner M, Felsenfeld G 2006 Nature Rev Genet 7:703; chromatin insulators: Valenzuela L, Kamakaka RT 2006 Annu Rev Genet 40:107; see Fig. I39.

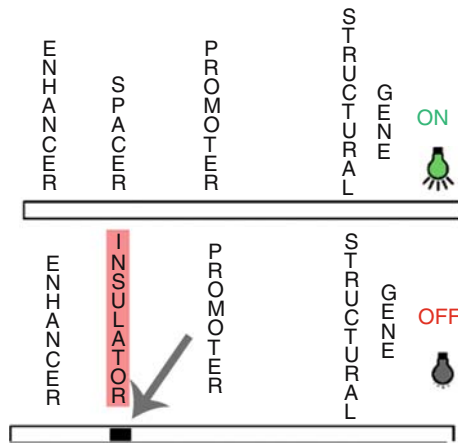


Figure I39. Insulator effect

Insulin: This is one of the most important peptide hormones (MW \approx 5,700) in the body and it is synthesized in the pancreas. The pancreas is a large gland behind the stomach. The islets of Langerhans produce and secrete this hormone into the blood. Insulin regulates glucose uptake into the muscles by glucose transporters, and into the liver by glucokinase. With the assistance of glycogen synthase, glycogen is made in the muscles and the liver. The breakdown of glycogen is mediated by the insulin-regulated glycogen phosphorylase. Glycolysis and acetyl coenzyme A synthesis is boosted by insulin through the enzyme phosphofructokinase and the pyruvate dehydrogenase complex. Fatty acid synthesis in the liver is promoted by acetyl-CoA carboxylase and neutral fat (triacylglycerol) is stimulated by insulin with the aid of lipoprotein lipase. Insulin deficiency leads to the hereditary diabetes mellitus.

Diabetes is a very complicated disease which is controlled by several genes involved either in the differentiation of the islets of Langerhans or at various stages in the synthesis and regulation of the hormones. About 5 to 10% of the population in western countries suffers from one or another form of this disease. Of these cases, however, only 1/10 is insulin-dependent. Insulin-dependent diabetes (IDDM) is largely familial and occurs early in life. The non-insulin-dependent form of the disease (NIDDM) generally affects those who become diabetic after the age of 40. The latter has a relatively small hereditary component and it is most common among obese individuals in the age group of 50 to 60 years. One of the most important clinical manifestations of the disease is hyperglycemia (excessive amount of sugar in the blood), but there are many other complex characteristics. Symptoms of diabetes are manifested in nearly 60 known human diseases. A well-controlled diet and a continuous supply of insulin can effectively manage the early onset diabetes. The treatment of the other forms (NIDDM) varies according to the causative metabolic defect.

The primary structure of insulin was first determined by the two-time Nobel laureate, F. Sanger in 1953, the same year as the Watson - Crick model of DNA was published. These two events signaled the beginning of molecular biology. Insulin is synthesized as a pre-proinsulin equipped with a "signal sequence" that directs the molecules into the secretory vesicles. After the removal of this signal peptide, proinsulin is formed that is stored in the β cells. When the glucose level in the blood increases insulin-specific peptidases process the protein into the functional final form. The A chain of bovine insulin contains 21 amino acids and the B chain has 30, the two chains are joined by disulfide bridges between A7 and B7 as well as A20 and B19 residues and a third disulfide bridge is formed within the A chain between residues 6 and 11 protein structure. The A chain is identical in humans, dogs, pigs and rabbits, and the bovine B chain is identical to that of pigs, goats, dogs and horses. The function of insulin requires the presence of a receptor.

The insulin receptor protein is made of two α and two β chains. The identical α chains bind insulin above the surface of the plasma membrane, whereas the two β chains reach inside the cell through the membrane with their carboxy termini. Upon binding of insulin, the β chains become a specific protein tyrosine kinase that first autophosphorylates and then phosphorylates other proteins in a cascading series of events. As a consequence a number of enzyme activities are altered by the phosphorylation of tyrosine and serine residues. These multiple reactions explain why diabetes occurs in many forms and is

part of numerous other syndromes under the control of a variety of genes and manifested in aneuploids (Turner's syndrome, Klinefelter's syndrome and Down's syndrome). Insulin receptor substrate-1 tends to the integrin family of surface receptors and in this way integrin and growth factor signaling are connected (White MF 2003 Science 302:1710).

The various forms may be under the control of autosomal dominant genes (diabetes insipidus nephrogenic Type II, diabetes mellitus juvenile with early onset). The latter was attributed, in one case, to a substitution of serine for phenylalanine at the 24th position of the β chain. Only a single locus seems to encode the human insulin structural gene in chromosome 11p15.5. The human *INS* and the mouse *Ins* (chromosome 7) are expressed only from paternal allele at some stages of development (imprinting). In rats and mice two distinct loci are involved. Some mutations interfere with the proteolytic processing of proinsulin, resulting in its accumulation (hyperproinsulinemia) without any symptoms of diabetes.

Non-insulin-dependent diabetes was observed to be associated with a mutation of the glucose transporter-4 protein at residue 383 (Val [GTC]→Ile [ATC]) in some cases but not in others. Vasopressin and oxytocin deficiency may also be involved in diabetes. These two octapeptides regulate muscle contraction and renal secretion. Diabetes is generally associated with abnormalities of kidney functions.

Autosomal recessive inheritance appears to account for the juvenile-onset diabetes mellitus Type I and this locus is assigned to human chromosome 6 in close proximity to the HLA Class II genes. This locus is probably a regulatory one, determining insulin susceptibility with a penetrance of 71% for the homozygotes and 6.5% for the heterozygotes. It was reported that if at position 57 of the HLA DQ- β chain has Asp, then most probably diabetes was absent whereas there was a high chance that this 57th residue was non-Asp in diabetics. Other studies have indicated that HLA genes DR3 and DR4 and HLA-DQ have predisposing effects on the expression of diabetes. Apparently HLA-DQw1.2 allele was protective but HLA-DQw8 increased the chances of developing insulin-dependent diabetes. Population genetic studies have also confirmed that having a non-polar amino acid at position 57, the chances of developing diabetes may increase by a factor of about 30.

X chromosomal linkage was observed for nephrogenic diabetes insipidus Type I, and it was proposed that this form of the disease was associated with a defect in the vasopressin 2(V2) receptor.

Till recently, insulin for therapeutic purposes was obtained exclusively from animal pancreas collected at the slaughterhouses. By the use of recombinant

DNA human insulin can be industrially produced with the aid of bacterial cultures and further processing. The industrial production of human insulin by genetic engineering is more successful than that of other proteins because it does not require glycosylation. In yeast, proinsulin mRNA is normally produced but the translation of the message is very inefficient. Human insulin has a definite advantage as some patients may be allergic to the slightly different animal protein. Lower than normal insulin resistance is frequently associated with infections, diabetes, obesity and some forms of cancer. In obese individuals, adipose tissues release increased amounts of non-esterified fatty acids, glycerol, hormones, inflammatory cytokines and other factors that lead to insulin resistance and Type 2 diabetes (Kahn SE et al 2006 Nature [Lond] 444:840). Obesity and diet-induced insulin resistance may be reversed by salicylate or disruption of IKK β (Yuan M et al 2001 Science 293:1673). Insulin resistance is mediated by tumor necrosis factor α and it decreases tyrosine kinase activity in the insulin receptor by activating serine phosphorylation (Kahn BB, Flier JS 2000 J Clin Invest 106:473). White adipocytes transcribe a 750-residue mRNA encoding the protein resistin (resistance to insulin). Neutralization of resistin enhances insulin-stimulated glucose uptake and active resistin reduces the uptake. An increased level of ROS can trigger insulin resistance (Houstis N et al 2006 Nature [Lond] 440:944). Insulin is degraded by an evolutionarily well-conserved Zn²⁺-metalloprotease (Shen Y et al 2006 Nature [Lond] 443:870). ►diabetes, ►HLA, ►TNF, ►IKK, ►obesity, ►insulin-like growth factor, ►insulin-receptor substrates, ►resistin, ►S6 kinase, ►ROS, ►thiazolidinedione, ►p110 α ; Bell GI et al 1980 Nature [Lond] 284:26; Steiner DF et al 1985 Annu Rev Genet 19:463; Lizcano JM, Alessi DR 2002 Current Biol 12:R236; historical: http://www.coreynahman.com/Information_On_Insulin.html.

Insulin-Like Growth Factors (IGF-1, IGF-2): These are required for the passage of the cell cycle from G1 to S phase; they promote cell maintenance, metabolism and cell division. A duplication of the *Igf-1* gene resulted in the development of "mighty mouse", animals with excessive muscle growth and some potential health problems. The human genes for IGF-1 and IGF-2 are located in chromosome 11p15-p11, separated by about 12–13 kbp. The human IGF-2 gene is expressed only from the paternal chromosome. In mice, the IGF genes (chromosome 7) display tissue-specific imprinting and are also expressed from the paternal chromosome. Somatomedin, a mammalian second messenger, has insulin-like functions in regulating bone and muscle growth in conjunction

with the pituitary hormone receptor. A minor 4.8-kb mRNA generates the prepro-IGF2 whereas the major 6-kb mRNA encodes a post-transcriptionally regulated IGF. The insulin-like growth factor receptor (IGF-1R) and the insulin receptor belong to the tyrosine kinase receptor family and regulate both normal and malignant cell proliferation. The paternally expressed IGF2 seems to control—like a QTL—muscle mass and fat deposition in pigs. Mice with deletion of insulin and insulin-like growth factor have normal pancreatic β cell number yet develop diabetes (Ueki K et al 2006 *Nature Genet* 38:583). ▶[signal transduction](#), ▶[insulin](#), ▶[insulin receptor](#), ▶[imprinting](#), ▶[growth factors](#), ▶[pituitary dwarfism](#), ▶[achondroplasia](#), ▶[somatomedin](#), ▶[mannose-6-phosphate receptor](#), ▶[myostatin](#), ▶[pancreas](#), ▶[dog](#), ▶[Simpson-Golabi-Behmel syndrome](#), ▶[prostate cancer](#), ▶[QTL](#); LeRoith D et al 1992 *Ann Intern Med* 116:854; Jiang F et al 2001 *Dev Biol* 232:414; structure of insulin-like growth factor receptor: Ward CW et al 2001 *Mol Pathol* 54:125.

Insulinoma: A relatively benign pancreatic cancer leading to excessive secretion of insulin.

Insulin-Receptor Protein (IR): This heterotetrameric membrane protein is a tyrosine kinase (related to the epidermal growth factor [EGFR] family); its deficiency leads to Donohue syndrome. The enzyme protein tyrosine phosphatase (PTP-1B) dephosphorylates IR and as a consequence in diabetes type II disease, although the cells can make insulin, they are unable to respond to this hormone because of the expression of PTP-1B. The Rabson-Mendenhall disease (INSR, 19p13.2) is due to deficiency of IR. ▶[insulin](#), ▶[diabetes](#), ▶[obesity](#), ▶[Donohue syndrome](#), ▶[Rabson-Mendenhall disease](#), ▶[insulin-like growth factor](#), ▶[GLUTs](#); structure: McKern NM et al 2006 *Nature [Lond]* 443:218.

Insulin-Receptor Substrates (IRS1, IRS2, IRS3, IRS4): After multiple site tyrosine phosphorylation they bind to and activate phosphatidylinositol-3'-OH kinase and other proteins with SH2 domains. Defects in IRS2 may be responsible for insulin-independent diabetes. IRS1 and IRS2 are essential for normal embryonic and post-natal growth. The IRS^{-/-} individuals by 30 days reach less than 1/4 of the wild type weight and the reproductive capability—especially of females—is impaired. ▶[insulin](#), ▶[insulin-like growth factor](#), ▶[SH2](#), ▶[diabetes](#)

Insulinitis: This is an autoimmune inflammation caused by infiltration of the islets of Langerhans by T lymphocytes. ▶[autoimmune disease](#), ▶[Langerhans islets](#), ▶[T cell](#), ▶[lymphocytes](#), ▶[diabetes mellitus](#)

INT Oncogene: INT1 is assigned to human chromosome 12q13 and to mouse chromosome 15. The product of *Drosophila* gene *wingless* (*wg*) is a homolog and therefore the gene is sometimes referred to as WNT. INT4 (human chromosome 17q21-q22, mouse chromosome 11) is also homologous to the *Drosophila* *wg* gene. In mammary carcinomas INT1 is frequently the target site for insertion and inactivation. INT2 is a mammary tumor gene assigned to human chromosome 11q13 and its only relation to INT1 is its presence in mammary tumors. INT2 product shows some relationship to fibroblast growth factor 6. INT3, another mammary tumor gene, encodes a transmembrane protein. ▶[oncogenes](#), ▶[FGF](#), ▶[transmembrane proteins](#), ▶[morphogenesis in *Drosophila*](#), ▶[WNT1](#)

Intasome: A bacterial nucleoprotein complex, including a negative supercoiled phage DNA, wrapped around by several copies of the phage-encoded integrase and the bacterial integration host factor protein (IHF). DNA bending by Xis regulatory proteins promotes the formation of the excisive intasome, but antagonizes the formation of an integrative intasome. Xis stabilizes the synaptic complex by directly interacting with Int bound to the arms of the phage. Xis recognizes a single binding site. Three Xis monomers work in concert to substantially bend the DNA by forming a micronucleoprotein filament (Abbani MA et al 2007 *Proc Natl Acad Sci USA* 104:2109). ▶[integrase](#), ▶[IHF](#); Chen H et al 1999 *J Biol Chem* 274:17358; Esposito D et al 2001 *Nucleic Acids Res* 29:3955.

Integr8: genome and proteome browser: <http://www.ebi.ac.uk/>.

Integral Membrane Protein: Refers to a protein in the membrane without covalent linkage to it and it is bound there by about two dozen uncharged and/or hydrophobic amino acids. The majority of the integral transmembrane proteins contain tightly packed α -helices and they are called helix-bundle class. These membrane proteins insert co-translationally and fold in the endoplasmic reticulum. In eukaryotes insertion is mediated mainly by the Sec61 translocon. ▶[translocon](#), ▶[transmembrane proteins](#)

Integrase: A protein that specifically recognizes transposon or phage (*att*) or yeast integration sites and opens them up for insertion to take place. The integrase makes a staggered cut in the DNA and the enzyme is covalently bound to the DNA via a catalytic tyrosine (Tyr³⁴²). A Holliday intermediate is formed and after a second exchange (and removal of the 40-kDa protein) the recombination product is generated. There is tremendous structural variation among more than 60 integrases yet a four-residue catalytic

unit is highly conserved. The position of the integrase (IN) in the Ty/gypsy group of transposons is 5'-LTR-gag-protease-reverse transcriptase-RNaseH-IN-LTR-3' and among the Ty1/copia-like elements 5'-LTR-IN-reverse transcriptase-RNaseH-LTR-3'. The same enzyme may catalyze both integration and excision as determined by the recombination directionality factors (RDF). Integrases can be used for the insertion of genes in specific locations as a means to gene therapy. ▶ [integration](#), ▶ [Cre](#), ▶ [Flp](#), ▶ [aspartate protease](#), ▶ [att sites](#), ▶ [transposable elements](#), ▶ [lambda phage \[site 27815\]](#), ▶ [IN1](#), ▶ [IHF](#), ▶ [intosome](#), ▶ [Holliday structure](#), ▶ [Holliday model](#), ▶ [integron](#), ▶ [Ty](#), ▶ [copia](#), ▶ [retroviruses](#), ▶ [RAG1](#), ▶ [disintegration](#), ▶ [FRET](#); Hindmarsh P, Leis J 1999 Microbiol Mol Biol Rev 63:836; Craigie R 2001 J Biol Chem 276:23213; Lewis JA, Hatfull GF 2001 Nucleic Acids Res 29:2205; Campbell A et al 2002 Gene 300:13; Radman-Livaja M et al 2005 Proc Natl Acad Sci USA 102:3913; structure and allosteric control: Biswas T et al 2005 Nature [Lond] 435:1059.

Integrated Circuit (chip): This is an electronic circuit within a single piece of semiconducting material. ▶ [semiconductors](#)

Integrated Map: This is based on the combined information on genetic linkage and physical mapping. ▶ [mapping genetic](#), ▶ [physical map](#), ▶ [skeletal map](#), ▶ [unified genetic map](#)

Integrating Vector: ▶ [yeast integrating vector](#)

Integration: A DNA sequence is inserted at both termini by covalent linkage into the host DNA. The DNA structure (bends) affects the site of integration. HIV integrates non-randomly either into purified naked DNA or preferentially into CpG stretches modified by cytosine methylation and within distorted nucleosomal DNA. The murine leukemia virus (MLV) integrates non-randomly, preferably into the major groove of the nucleosomal DNA. Retroviruses most commonly select DNase hypersensitive sites and stretches involved in active transcription. Agrobacterial vectors are usually integrated into the non-translated regions of potentially expressed genes and similar predilections have been observed in the bacterial transposons. The different yeast Ty elements also exhibit preferences. The transfer of foreign DNA into mammalian genomes either by infection or transformation may result in genome-wide methylation at sites remote from that of the integration and may alter the pattern of expression of genes in the recipient genomes. The integration of the DNA into the human genome may be mediated by protein Metnase, which methylates histone H3 lysine 4 and lysine 36, required for opening the chromatin. Metnase increases non-homologous end-joining

repair of double-strand breaks. This protein has a SET domain as well as transposase and nuclease domains required for the uptake of exogenous DNA into chromosomes (Lee S-H et al 2005 Proc Natl Acad Sci USA 102:18075). ▶ [Ty](#), ▶ [T-DNA](#), ▶ [DNase hypersensitive sites](#), ▶ [MLV](#), ▶ [HIV](#), ▶ [transposons](#), ▶ [RIP](#), ▶ [MIP](#), ▶ [methylation of DNA](#), ▶ [transformation](#), ▶ [SET motif](#), ▶ [histones](#), ▶ [non-homologous end-joining](#); Müller K et al 2001 J Biol Chem 276:14271.

Integration: In mathematics, this is the finding of a function of which the integrand is a derivative or finding an equation among finite variables that is the equivalent of the differential equation integrated. $F(x) = \int f(x)dx$ and $\frac{dF(x)}{dx} = f(x)$. ▶ [derivative](#)

Integration Host Factor: ▶ [IHF](#)

Integration Plasmid: This has homologous sequences to the chromosome and after transformation, by recombination, it may be inserted in multiple copies into the yeast chromosome. Linearization of the plasmid may increase its efficiency of integration 10–1000 fold.

Integrative Circuits in Signal Transduction: Multiple kinases initiate a common response. ▶ [signal transduction](#)

Integrative Physiology: This monitors the total function of organs in a non-invasive manner.

Integrative Suppression: Refers to the elimination of the manifestation of a genetic defect by insertion of a normal copy of the gene. (See Brasch MA, Meyer RJ 1988 Mol Gen Genet 215:139).

Integrator: This is a 12 subunit attachment to RNA polymerase II. Two of the subunits are similar to the RNA transcript cleavage and polyadenylation factor complex. The integrator is recruited to the U1 and U2 small nuclear RNA genes and mediates the processing of the 3' end of snRNA and interacts with the C terminal domain of the polymerase. (See Baillat D et al 2005 Cell 123:265).

Integrator Gene: A hypothetical regulator and coordinator of eukaryotic genes. (See Wadgaonkar R et al 1999 J Biol Chem 274:1879).

Integrins (ITG): These are a part of the heterodimeric family of integral membrane proteins that stretch out to the intercellular space and form the extracellular matrix. In connection with fibronectin, other ligands and ICAM integrins control cell adhesion and cell shape, the development of *Drosophila* halteres, legs and wings, signaling, intracellular Ca^{2+} , inositol and lipid metabolism (see Fig. 140). Leukocytes contain a variety of integrins that are involved in inflammatory and immune responses. Integrins have α and β

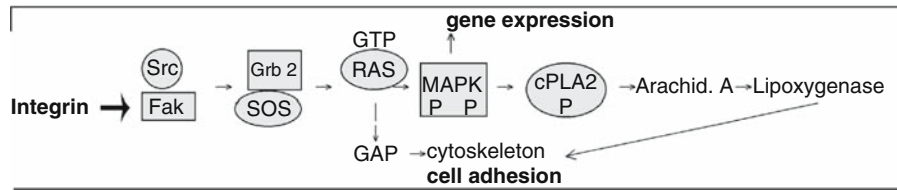


Figure I40. The integrin-mediated signal transduction pathway. (For symbols see individual entries, Arachid. A = arachidonic acid) After Clark EA and Burggie JS 1995 Science 268:233

subunits that are translated separately and their association is not by covalent linkage. Some of the integrin α and β subunit genes have been assigned to human chromosome 2, whereas β -7 integrin appears to be in chromosome 12. The α -6 integrin forms 991-residue extracellular, 23-amino transmembrane and a 36-amino acid intracellular domain. Integrin is associated in the cells with a 59K-serine/threonine protein kinase, containing four ankyrin-like repeats. This integrin-linked kinase (ILK) possibly regulates integrin-mediated signal transduction. Integrins, by binding to ligands, may control substratum adhesiveness and therefore cell migration (see Fig. I41). Integrins integrate the extracellular signal systems with the cytoskeleton. Focal adhesion complexes, containing β 1 integrin, talin, actin and vinculin, are formed upon activation by the extracellular matrix.

The integrin-mediated signal transduction pathway is shown in the Fig. I41. This complex is attached to the cytoskeleton and localized signal transducing molecules. Pre-existing mRNAs are targeted to cytoskeletal micro-compartments where integrin controls their translation in the vicinity of the signal receptor sites. Integrins appear to be involved in fertilization by binding fertilin molecules. They are involved in the control of the cell cycle and apoptosis. In the absence of integrins β 3 or β 3/ β 5 or selectins mice are susceptible to enhanced tumor growth (Taverna D et al 2004 Proc Natl Acad Sci USA 101:763). They signal to the RAS

and the ERK systems. \blacktriangleright fibronectin, \blacktriangleright cadherin, \blacktriangleright talin, \blacktriangleright CAM, \blacktriangleright SOS, \blacktriangleright ICAM, \blacktriangleright FAK, \blacktriangleright Src, \blacktriangleright Grb2, \blacktriangleright RAS, \blacktriangleright MAPK, \blacktriangleright ERK1, \blacktriangleright GAP, \blacktriangleright cPLA₂, \blacktriangleright ankyrin, \blacktriangleright signal transduction, \blacktriangleright angiogenesis, \blacktriangleright epidermolysis, \blacktriangleright lipoxygenase, \blacktriangleright atresia, \blacktriangleright cell migration, \blacktriangleright CD98, \blacktriangleright calreticulin, \blacktriangleright talin, \blacktriangleright actin, \blacktriangleright vinculin, \blacktriangleright caveolin, \blacktriangleright myopathy, \blacktriangleright metastasis, \blacktriangleright fertilin, \blacktriangleright T cell receptor, \blacktriangleright invasin; Clegg DO 2000 Mol Cell Biol Res Comm 3:1; Calderwood DA et al 2000 J Biol Chem 275:22607; Hynes RO 2002 Cell 110:673; structure: Xiao T et al 2004 Nature [Lond] 432:59; <http://www.geocities.com/CapeCanaveral/9629>.

Integron: This is a mobile DNA element, a transposon with a cassette, flanked by a 5' and a 3' conserved sequence. The internal cassette can accommodate antibiotic resistance genes by site-specific recombinase (integrase, *intI*) located in the 5' element and a closely linked *attI* (attachment) site. It contains several rightward (P2, P2, P4 and P5) and one leftward (P3) promoter sites and a ribosome-binding site. The 3' element includes a conserved sulfonamide resistance gene. Sulfonamide resistance stems from a lack of sensitivity of dihydropteroate synthase to sulfonamide inhibition. Its origin, however, is unclear since sulfonamides are synthetic antibiotics. Dihydropteroate is a precursor of folic acid. The integron is the vehicle of antibiotic resistance genes among various types of bacteria. Integrases bear 43–58% homology to similar sequences of bacteriophages. Super-integrations carry several cassettes and can accommodate multiple antibiotic resistance genes and therefore make fighting disease very difficult. Integrations are an important means of generating genomic diversity in prokaryotes. Determining the crystal structure of integrons has revealed that DNA target site recognition and synaptic assembly do not depend on the canonical DNA sequence rather two flipped-out bases interact in *cis* and *trans* with the integrase (MacDonald D et al 2006 Nature [Lond] 440:1157). \blacktriangleright gene cassette, \blacktriangleright integrase, \blacktriangleright folic acid, \blacktriangleright transposon, \blacktriangleright R plasmid, \blacktriangleright shoufflons, \blacktriangleright pathogenicity island; Rowe-Magnus DA et al 2001 Proc Natl Acad Sci USA 98:652; Gillings MR et al 2005 Proc Natl Acad Sci USA 102:4419.

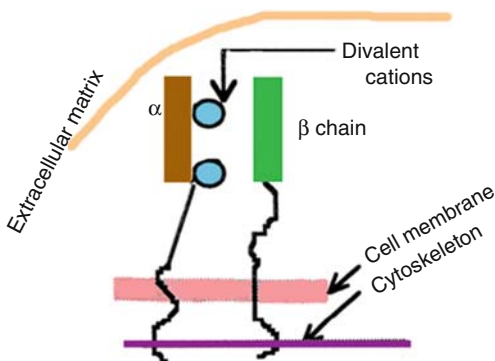


Figure I41. Integrin on the cell surface

Integument: Refers to the maternal somatic tissue layers that surround the ovule of plants and give rise to the seed coat. Thus, the integument may show delayed inheritance. ▶ [megagametophyte development](#), ▶ [delayed inheritance](#)

Inteins: These are elements that are inserted into proteins before the completion of its sequence and removed thereafter; they are protein-splicing elements. They are spliced out post-translationally by autocatalytic proteolysis and ligation. The intein system can be used for genetic engineering. Part of a herbicide resistance gene-intein fusion was transformed into the nucleus and the other part of the same gene, equipped with a carboxy-terminal intein, was introduced into the chloroplast genome. The nuclearly encoded herbicide protein-intein fragment migrates to the chloroplasts and reconstitutes the full length herbicide resistance. Since the chloroplast located fragment is not transmitted by out-pollination to plants in the environment there is no effective spread of herbicide resistance (Chin HG et al 2003 Proc Natl Acad Sci USA 100:4510). Some inteins are site-specific endonucleases. They may also function as transposons and insert their coding sequences into intein-less genes. Inteins have different structures and are found in prokaryotes, algal chloroplasts and other lower eukaryotes. Inteins may provide evidence of horizontal transmission of nucleotide tracts during evolution. ▶ [intron](#), ▶ [transmission](#), ▶ [extein](#), ▶ [herbicides](#), ▶ [semi-synthesis](#), ▶ [protein engineering](#), ▶ [homing endonucleases](#); Paulus H 2000 Annu Rev Biochem 69:447; Liu X-Q 2000 Annu Rev Genet 34:61; Gogarten JP et al 2002 Annu Rev Microbiol 56:263; Perler FB et al 1994 Nucleic Acids Res 22:1125; Evans TC et al 2005 Annu Rev Plant Biol 56:375; <http://www.neb.com/neb/inteins.html>.

Intellectual Property: ▶ [copyright](#), ▶ [patent](#)

Intelligence Quotient (IQ): ▶ [human intelligence](#)

Intelligent Design: This theory of organic evolution does not accept either Darwinism or creationism in its entirety and postulates that the evolution/development of the complexity of biochemical structures requires an intelligent design. Genetics can deal only with experimental facts that can be tested with scientific procedures without subjective assumptions or faith. ▶ [evolution](#), ▶ [Darwinism](#), ▶ [creationism](#), ▶ [scopes trial](#)

Intensifier: Refers to an animal or plant gene that intensifies (darkens) color.

Interaction, Molecular: Such interaction generally requires physical contacts between/among the components such as hydrogen bonding and van der Waals forces. There is another type of interaction, interaction without direct contact, governed by linkage

thermodynamics. Macromolecules and biopolymers share a common milieu within the cell conformations. The equilibria are also modulated by the solute solvent interactions. The response of hemoglobin to CO₂ changes the blood pH is one example of through-solution communication. It demonstrates a response in one type of tissue to a metabolic state in another through the shared solution. Such mechanisms seem to play a significant role in cellular regulation. ▶ [ligands](#), ▶ [hydrogen bond](#), ▶ [van der Waals forces](#); Völker J, Breslauer KJ 2005 Annu Rev Biophys Biomol Struct 34:21.

Interaction Trap: This procedure is basically similar to the two-hybrid method where the interaction of two or more molecules permits a biological or physical observation. ▶ [two-hybrid method](#); Toby GG, Golemis EA 2001 Methods 24:201.

Interaction Variance: This is due to epistasis between quantitative traits and the effect of the environment on gene expression. ▶ [analysis of variance](#), ▶ [epistasis](#)

Interactome: Refers to the system in the proteome where proteins interact and cooperatively determine function(s). Using binary protein-protein interactions, mainly yeast, two-hybrid system large-scale interactions can be developed. These interactions of thousand of genes can shed light on interacting proteins in the human genome, including genes responsible for disease. ▶ [proteome](#), ▶ [protein interactions](#), ▶ [gene product interaction](#), ▶ [protein complexes](#), ▶ [genetic networks](#), ▶ [gateway cloning](#), ▶ [protein-nucleic acid interactions](#), ▶ [ORFeome](#), ▶ [E-map](#); Ito T et al 2001 Proc Natl Acad Sci USA 98:4569; Ge H et al 2001 Nature Genet 29:482; Rual J-F et al 2005 Nature [Lond] 437:1173, atlas of yeast interactome: Collins SR et al 2007 Mol Cell Proteomics 6:439; <http://dip.doe-mbi.ucla.edu/>; protein, nucleic acids interactions: <http://biozon.org/>; human interactome: <http://www.mdc-berlin.de/unihi>.

Interactor: In the evolutionary context, this is an individual(s) who interacts with the biotic and abiotic environment and through the interaction his trait(s) imparts reproductive success and the hereditary material is transmitted to the progeny.

Interalign: This is a multiple sequence alignment program for proteins. ▶ [CLUSTAL W](#), ▶ [MAFFT-5](#); Pible O et al 2005 Bioinformatics 21:3166.

Interallelic Complementation: ▶ [allelic complementation](#)

Interband Region: In polytenic chromosomes the relatively lighter stained space between the characteristic darkly stained bands is known as the interband region (see Fig. 142).



Figure I42. Band and interband regions

Interbreeding: Refers to a process where individuals of different genotypes in a population may mate.

►random mating, ►mating systems

Intercalating Mutagens (such as acridines and some nitrogen mustards): These can insert within nucleotide sequences and cause frameshift mutations, short insertions and deletions. Intercalation also leads to the separation of the base pairs, lengthening and untwisting of the double helix. ►acridine dye, ►nitrogen mustards, ►frameshift mutation

Intercellular: Denotes located between cells. ►intra-cellular

Intercellular Immunization: The antibody production is ectopic and their secretion depends on cells other than lymphocytes. The expression of the immunoglobulin genes can be directed to specific cells by employing cell type specific promoters and enhancers in transformation. Such manipulations may block the expression of genes by the antibodies and may reveal the consequences for their function, for development or disorder and possibly for therapy targeted with high specificity. Besides the transgenic approach, grafting specific cells on to an appropriate tissue may be employed. ►ectopic, ►lymphocytes, ►immunization, ►neuroantibody, ►ablation, ►genetic engineering, ►intracellular immunization

Intercept: ►correlation [in a linear regression $a = Y - bx$].

Interchange: This refers to the reciprocal translocation of chromosomes. ►translocations

Interchange Trisomic: ►trisomic tertiary, ►trisomic analysis

Interchromosomal Interactions: Interferon gamma (IFN- γ , 12q14) defines the development T_h1 helper cells and interleukin-4 (IL4, 5q31) defines the development of T_h2 helper cells, which play different roles in the immune system. The locus control region of the T_h2 gene coordinately regulates the cytokine genes *Il4*, *Il5* and *Il13* although these sites are spread over 120 kb region within the same chromosome (intrachromosomal interaction). These elements are closely juxtaposed in the conformational state of the chromatin. In the nucleus each chromosome has its own particular territory, in the mouse the IFN- γ gene in chromosome 10 and the regulatory cytokine region of the T_h2 gene in chromosome 11 also interact despite being in different chromosomes. Such interchromosomal interactions may have general significance for the development of disease.

►interferon, ►interleukin, ►looping of DNA; Spilianakis CG et al 2005 Nature [Lond] 435:637.

Interchromosome Domain Compartment: The space between chromosome territories may be the area of transcription and RNA processing. ►chromosome territory

Intercistronic Region: Refers to the number of nucleotides between the end of one gene and the beginning of the next one. ►cistron

Intercross: Refers to mating between individuals (siblings) of the same parentage.

Interest: This is the rate to be paid for the use of funds.

Interest = (total amount of funds \times interest rate \times years)/100. Compound interest is the total amount of interest due on both the principal investment and the accumulated interest over time. For example: at 5% interest in 20 years \$100 investment will increase in value to $(1.05)^{20} \times 100 = \265.33 . The interest rate is normally compounded monthly or quarterly and more elaborate formulae are used for precise calculations.

In case money is borrowed it is necessary to know the cost. For this purpose a very simple constant ratio formula is: $i = \frac{2mI}{P(n+1)}$ where m = number of payment periods within one year, I = the discharge rate, P = principal amount, n = the total number of payment periods. If \$100 is borrowed and is supposed to be repaid in 12 equal monthly payments at a charge of 6% discount, the effective interest rate is: $i = \frac{2 \times 12 \times 6}{94(12+1)} = \frac{144}{1222} = 0.1178$, i.e., ~11.8%. Financial institutions use a more accurate formula leading to a slightly different outcome.

Interfacial Enzymology: The enzymes act on substrates located on a surface and hence their activity is regulated by the concentration of the substrate on the surface. Such enzymes may be found within or on cellular membranes.

Interference, Bacterial: One strain excludes the others from infection or colonization sites. The interference is usually mediated by the inhibition of the synthesis of virulence factors or surface receptors. ►RNA interference

Interference, Chromatid: ►chromatid interference

Interference, Chromosome: One crossing over may either reduce (positive interference) or increase (negative interference) the occurrence of additional ones. The availability of complete nucleotide sequences of the chromosomes permits a detailed analysis of the molecular basis of the phenomenon. Interference may proceed along one or two pathways according to the organisms. In yeast, the *MSH4* mutations (involved in mismatch repair) eliminate interference although they reduce crossing over by

only 50–70%. The *MSH4* homolog *HIM-14* in *Caenorhabditis* completely prevents crossing over. In the case of humans, there is statistical evidence for the two-pathway model which has implications for the precision of genotyping (Housworth EA, Stahl FW 2003 *Am J Hum Genet* 73:188). ▶coincidence, ▶coefficient of coincidence, ▶mapping function, ▶chromatid interference, ▶mismatch repair; Zhao H et al 1995 *Genetics* 139:1045; Browman KW, Weber JL 2000 *Am J Hum Genet* 66:1911; Tapper WJ et al 2002 *Ann Hum Genet* 66:75.

Interference, Dominant: The interference changes a transcriptional activator into a repressor. ▶activator protein, ▶repressor

Interference, Negative: ▶coincidence

Interference RNA: ▶RNAi, ▶RNA interference

Interferon: Refers to specific cellular glycoproteins that develop after a viral infection or as a reaction to RNA or other compounds, and they show antiviral activity and possibly anti-tumor activity. Double-stranded RNA (dsRNA) and siRNA can activate interferon genes in mammals through the dsRNA-dependent protein kinase (PKR) and through the Jak-STAT signal transduction route (Sledz CA, Williams BR 2004 *Biochem Soc Trans* 32:952). When associated with all-trans retinoic acid IFN is particularly effective in inhibition, including cancer cell growth inhibition. Interferons have three major forms, IFN- α , - β and - γ . Interferons can be produced following transformation in a variety of cells (yeast, silkworm, mouse, hamster, etc.). Interferons produced by leukocytes contain predominantly the α type. Lymphoblastoid cells (lymphocytes stimulated by an antigen) have 90% α and 10% β interferons. Induced fibroblasts mostly contain the β chain. The γ interferon is produced by antigen- or mitogen-stimulated T lymphocytes. Interferon-induced protein genes have been traced to human chromosomes 21, 10, 4, and 1. Interferons may interfere with protein synthesis by causing phosphorylation of eukaryotic peptide chain initiation factor eIF-2.

Interferon α (leukocytic interferon, IFNA1) genes (up to 30) have been located in human chromosome 9p21-p13. One of these genes, activated by the double-stranded viral replication intermediate, is 2'-5'-oligoadenylate synthetase, which in turn activates the latent ribonuclease L. RNase L degrades single-stranded RNA, the viral genome. Another induced enzyme is the dsRNA-activated protein kinase R (PKR). PKR may mediate apoptosis and may assist in establishing persistent infections by several viruses. An *interferon α receptor* (antiviral protein, AVP) has been assigned to human chromosome 21q22. Translocations of the INFA have been identified in leukemia patients. It has been claimed that intranasal

use of interferon α may prevent common cold. Natural IFN-producing cells (dendritic cell precursors) that express CD4 and major histocompatibility class II synthesize IFNA.

Interferon β -1 (fibroblast interferon/IFB1, human chromosome 9p21-pter) is structurally homologous to α interferon. In patients suffering from acute monocytic leukemia, translocations of IFB1 to chromosome 21 were observed and the break point was within this gene at about 17-cM from the site of the ETS-2 oncogene (chromosome 21q22.1-q22.3). Chromosome 9 contains several interferon genes. *Interferon β -2* (IFNB2 (human chromosome 7p21-p15) is induced by the tumor necrosis factor (TNF) and interleukin (IL-1) when interferon β -1 (IFNB1) is not induced. It is identical to the B-cell differentiation factor (BSF2) and hybridoma growth factor. Interferon β -3 (IFNB3) is in human chromosome 8.

Interferon γ (IFNG, human chromosome 12q14) induces the expression of HLA class II genes. The induction is modulated by a factor in human chromosome 16 (probably a receptor) and by another factor in chromosome 21 that may control the transduction of the γ interferon signal. In RAG (recombination activating) cells a human chromosome 6 factor is also required in human-rodent cell hybrids. IFNG induces the production of a 98-residue polypeptide (IP-10, chromosome 4q21) and other activating polypeptides. Hereditary interferon γ receptor deficiency increases the susceptibility to mycobacteria and *Salmonella* infections. The interferon regulatory factor (IRF) family includes the interferon consensus sequence binding protein (ICSBP, expressed constitutively in B lymphocytes) and other transcription factors (IRFs). Their N-terminal region binds to the DNA (IFN-stimulated responsive element, ISRE) and the C-terminal contains the regulatory sequences. ▶lymphokines, ▶leukemia, ▶interferon response element, ▶B cell, ▶hybridoma, ▶modulation, ▶signal transduction, ▶receptor protein, ▶IRF, ▶interleukin, ▶CD4, ▶MHC, ▶dendrocyte, ▶mycobacterium, ▶allergy, ▶PKR, ▶Jak-STAT, ▶granulocyte, ▶killer cell, ▶RNAi; Stark G R et al 1998 *Annu Rev Biochem* 67:227; Taniguchi T, Takaoka A 2001 *Nature Rev Mol Cell Biol* 2:378; Sen GC 2001 *Annu Rev Microbiol* 55:255; interferons in virus-host relationship: Garcia-Sastre A, Biron CA 2006 *Science* 312:879.

Interferon Receptors: IFN α and β share the same 63.5-kDa receptor. The IFN γ , IFN β and IFN receptors are located in the same cluster (21q-q22.1). The IFN γ receptor binds the ligand at the 245-amino acid extracellular domain whereas the 222-amino acid intracellular domain is involved in signal transduction. ▶interferon, ▶interferon regulatory factors, ▶signal transduction Jak-STAT

Interferon Regulatory Factors (IRF): These bind to the upstream regions of both α and β interferon genes and serve as a transcription activator (IRF-1) or (IRF-2) have an antagonistic effect. There are several additional IRFs. IRF1 binds to two regulatory elements (PRDI and II) in the IFN β gene's promoter. These elements respond to Jun and NK- κ B, which bind to the nearby PRDII and IV. They compete for the same cis element. Both factors have been assigned to human chromosome 5q23-q31. The IRF-2 protein is identical to HiNF. The IRF-E DNA-binding site has the consensus G(A)AAA(G/C)(T/C)GAAA(G/C)(T/C). Some IFRs (IURF-4, vIRF) are elevated in certain cancers. ►interferon, ►upstream, ►cis-acting element, ►leukemia, ►macrophage, ►cytokines, ►transcription factors, ►CCE, ►histones, ►HiNF, ►Jun, ►NK- κ B; Taniguchi T et al 2001 Annu Rev Immunol 19:623.

Interferon Sequence Response Element (ISRE): AGTTTCNNTTTCN[C/T]. ►GAS, ►signal transduction Jak-STAT, ►interferon, ►interferon receptors

Interferon-Induced Proteins: Located in different human chromosomes 1, 2, 4, 10, 12, 21. Interferon-inducible cytokine IP-10 (human chromosome 4q21) is located close to the break point associated with monocytic leukemia. (Monocytes are phagocytic mononuclear leukocytes that develop into macrophages in the lung and the liver). IP-10 has substantial homology to several activating peptides and it may control inflammatory responses. ►cytokines, ►leukemia, ►macrophage

Intergenic Complementation: This provides evidence that the two genes are not allelic but belong to separate loci. ►allelic complementation, ►allelism test

Intergenic Regions: These regions represent the bulk of the DNA, which contains in higher eukaryotes only a small percentage of coding sequences. Recent estimates have revealed that in *Drosophila* 15.6% of intergenic transcribed regions function as missed or alternative transcription start sites used by 11.4% of the expressed protein-coding genes. At least 85% of the fly genome is transcribed and processed into mature transcripts (Manak JR et al 2006 Nature Genet 38:1151). The distinction between genic and intergenic regions is becoming blurred because of overlapping transcripts and human genes frequently coalesce into larger genomic domains.

In yeast the histone deacetylase Rpd3, which exists in two forms, RpdC(S) and RpdC(L), are recruited to promoters to repress transcription. Chromatin immunoprecipitation indicates that the Eaf3 subunit of RpdC(S) is recruited to Histone3 lysine 36, which is methylated by a SET domain of RNA polymerase II

resulting in deacetylation. This process subsequently erases transcription elongation-associated acetylation and suppresses intragenic transcription initiation (Carrozza MJ et al 2005 Cell 123:581; Keogh M-C et al 2005 Cell 123:593).

The transcripts of non-coding intergenic sequences seem to play regulatory roles (Schmitt S et al 2005 Genes Dev 19:697). Alternative promoters specify some of the intergenic transcripts to tissues. Nearly half of the differences between humans and chimpanzees are due to intergenic transcription (Khaitovich P et al 2006 PLoS Genet 2(10):e171). A large fraction includes mobile elements with evolutionary significance. ►introns, ►SET domain, ►histone acetyltransferases, ►transposable elements, ►selfish DNA, ►ENCODE; Kondrashov AS, Shabalina SA 2002 Hum Mol Genet 11:669; Cliften P et al 2003 Science 300:71.

Intergenic Spacers (IGS): Sequences between rRNA genes, which have very short transcripts (appear like feathers) but may contribute to initiation of transcription (see Fig. 143). ►ITS, ►tRNA, ►pol III

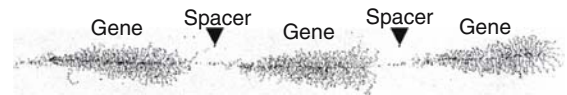


Figure 143. Intergenic spacers. Image courtesy of Spring et al 1976 J Microsc Biol 25:107

Intergenic Suppressor: One mutation suppresses the expression of another situated in a different locus. The suppressor normally encodes a mutant tRNA. ►suppression

Intergenic Transcript: This contains sequences from two separate genes. The mRNA of a large protein transcribed from 20 exons of chromosome 14 contains the intercalated 188 nucleotides exactly matching a part of chromosome 1. The chromosome 1 sequence has no reading frame and does not code for a protein from its transcript (except from the 188 base within chromosome 14 mRNA). ►gene fusion; Claverie JM 2005 Science 309:1529.

Interkinesis: ►interphase

Interleukins: Proteins secreted by white blood cells, phagocytes, B lymphocytes and are involved in stimulating growth and differentiation of lymphocytes concerned with the natural defense system of the body. ►lymphokines, ►IL-1, ►IL-2, ►IL-3, ►IL-4, ►IL-16, etc.; <http://www.gene.ucl.ac.uk/nomenclature/genefamily/interleukins.html>.

Interlocking Bivalents: When another chromosome passes through the terminalizing chiasmata (ring

bivalents), the non-homologous chromosomes may be trapped (interlocked) within the ring (see Fig. I44).
 ▶ring bivalent Rasmussen; SW 1976 Chromosoma 54:245.

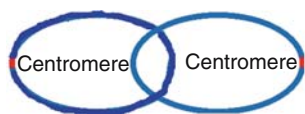


Figure I44. Interlocking bivalent

Interlogs: Refers to the potential interactions of protein based interactome models. ▶interactome, ▶protein interactions

Intermediary Metabolism: In this process, enzymes within the cells produce energy from nutrients and use it to synthesize other compounds or organize cellular components.

"5,0,1,0,105pt,105pt,0,0">Intermediate Filaments: These are ubiquitous 10 nm protein filaments abundant in eukaryotic cells and are encoded by at least 50 genes. They are composed of keratin, desmin, vimentin, neurofilament proteins, glial fibrillary acidic protein (GFAP), lamin, etc. Their anomalies may result in epidermolysis, keratosis and possibly other skin diseases. ▶filament, ▶keratin, ▶keratosis, ▶epidermolysis, ▶desmosome, ▶vimentin, ▶lamins, ▶skin diseases; Kreplak LK, Fudge D 2007 Bioassays 29:26; human intermediate filament database: <http://www.interfil.org/>.

Intermedin: A melanocyte stimulating protein factor.
 ▶melanocyte

Internal Control Regions (ICR): ▶A box

Internal Image Antibody: An anti-idiotypic antibody which binds to the antigen binding site of the complementarity determining region of an antibody rather than to the antigen. ▶anti-idiotypic antibody, ▶immunoglobulin, ▶antibody, ▶complementarity-determining region, ▶antigen

Internal Membrane: Refers to membranes within the cell excluding the plasma membrane.

Internal Promoter: ▶promoter

Internal Transcribed Spacers: ▶ITS, ▶ETS, ▶tRNA

Internalins: These are proteins mediating the bacterial uptake by eukaryotic cells. The internalization requires co-factors such as cadherin, catenin, actin, PI-3 kinase and the reorganization of the cytoskeleton. ▶cytoskeleton, ▶phosphoinositides, ▶cadherin, ▶catenin, ▶actin; Schubert WD et al 2001 J Mol Biol 312:7387.

Internally Eliminated Sequences (IES): During the formation of the macronuclei of *Ciliates* chromosome diminution and fragmentation occurs. The DNA deleted involves repetitive sequences but the IES are not a part of the repetitive sequences, and may even include functional genes. There is a variation in the location and sequences of the IES in different related species. ▶chromosome diminution, ▶Paramecia, ▶Ascaris, ▶macronucleus; Garnier O et al 2004 Mol Cell Biol 24:7370; Huvos PE 2007 J Eukaryot Microbiol 54:73.

International Prognostic Index (IPI): Marks an attempt by the European Society for Medical Oncology to predict the risk/survival of some cancers under standard conditions of treatment. (See Lopez-Guillermo A et al 1994 J Clin Oncol 12:1343).

International Protein Index (IPI): This is an integrated database for proteomics. ▶proteomics; Kersey PJ et al 2004 Proteomics 4:1985; <http://www.ebi.ac.uk/IPI>.

Internet: Refers to a complex system of interconnected electronic communication networks.

Internet2: This is a consortium of more than 200 universities in partnership with industry and government for advanced telecommunications. ▶ABILENE, ▶BIRN; <http://www.internet2.edu/>.

Internode: Refers to a segment of a plant stem between nodes (leaves) (see Fig. I45).

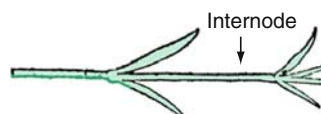


Figure I45. Internode

Interlogs: These are conserved protein-protein interactions facilitating the identification of protein networks. ▶genetic networks; Matthews RL et al 2001 Genomes Res 11:2120.

Interoperability: Refers to different computer programs through which computers can communicate with each other.

Iterons: Denotes the initiator binding sites of the replication origin. ▶iDNA

Interorganismal Genetics: ▶Flor's model

Interphase: This refers to the phase of the cell cycle when mitosis is not in progress. During the interphase between mitoses the cells are actively synthesizing DNA (S phase) and during the G phases other molecules are produced and the cellular organelles are dividing (see Fig. I46). In meiotic divisions the DNA synthesis is limited to repair and all DNA is

produced during the interphase preceding meiosis. According to the traditional view, during interphase the chromosomes are more relaxed and stretched. A high-resolution multicolor FISH banding analysis of human chromosome 5 indicates that in both lymphocytic and HeLa cells the length of interphase chromosomes is about the same as in the metaphase although they display bending and folding (Lemke J et al 2002 Am J Hum Genet 71:1051). Recent data attribute the increased length observed by classical microtechniques to an artifact caused by the fixatives and staining. ►cell cycle, ►mitosis, ►meiosis, ►FISH



Figure I46. Interphase

Interpolation, Linear: See the procedure described under ►*F₂ linkage estimation*

Interpro: This is a database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences. <http://www.ebi.ac.uk/interpro/>.

Interracial Human Hybrids: The genetic distance based on gene frequencies is relatively short ►*evolutionary distance*. among the various human races and despite the theoretical expectation of the deleterious effects of breaking up co-adapted genetic sequences, interracial hybrids suffer no physical harm. Problems may arise, however, in cultural adaptation because the hybrids are normally classified socially with the minority race (whatever the majority is) and discrimination against minorities is not uncommon in all racial, ethnic and cultural groups. Despite the great similarities of the genetic structure of all primates, no hybrids between humans and other primates have been verified. Somatic cells of all types of eukaryotes—including those of humans—can, however, be hybridized but cannot be regenerated into hybrid organisms. ►human races, ►somatic cell hybrids

Interrogation, Genetic: This is an in depth study of the function of a gene or a group of genes.

Interrupted Mating: Bacterial conjugation is halted at definite intervals (by stirring the culture) in order to determine the order of gene transfer and establish the map position on the basis of minutes required for the transfer of a particular gene(s) from the donor to the recipient. The interruption stops the transfer. ►conjugation mapping

Intersectin: An endocytosis protein. ►endocytosis

Intersex: The true intersex types have both male and female gonads which is a very rare condition. More common types are those who have either female or male gonads and chromosomal constitution but they express, to varying degrees, the secondary sexual characteristics normally unexpected for their chromosomal constitution. The intersex phenotype is determined by autosomal genes and in species where the sex chromosome:autosome ratio determines sexuality, the aneuploids appear as intersex types. In *Drosophila* the *tra* (*transformer*, chromosome 3–45) homozygotes of XX chromosomal constitution are sterile males. The *tra2* (chromosome 2–70) mutation in XX background has similar effects as *tra*; in XY background the males look normal and behave in a normal manner yet their sperm is not motile. The *dsx* (*doublesex*, 3–48.1) locus has numerous alleles. The homozygotes for their null alleles (in either XX or XY background) and the heterozygotes for the dominant alleles (in XX background only) are intersexes. The *ix* gene (*intersex*, 2–60.5) makes females intersex with reduced male and irregular female external genitalia. The *ix/ix* males appear to be normal but they are mostly homosexual and the *ix/+* heterozygotes court females and young males but not adult males. The *tra* and *dsx* genes regulate sex expression by alternative splicing of the RNA transcript involved in normal sexuality. In some insects, like the Gypsy moth (*Lymantria dispar*) the sex-determining genes have “strong” and “weak” alleles in some populations and the crosses regularly yield intersex individuals. The crosses between head lice (*Pediculus capitis*) and body lice (*P. vestimenti*) produce intersexes in *F₂* and *F₃*. Further, 98 to 96% of angiosperm plants are hermaphroditic and among 2 to 4% dioecious species intersexes occur, depending on the number of each of the sex chromosomes they carry. In *Melandrium*, for instance, the XXY and XXXY males produce occasionally intersex flowers but the XXXXY individuals are hermaphroditic. ►hermaphroditism, ►pseudo-hermaphroditism, ►sex determination, ►introns, ►gynandromorphs, ►homosexuality, ►relative sexuality, ►gonads, ►anti-Müllerian hormone, ►*Lymantria* for photo, Vaiman D, Pailhoux E 2000 Trends Genet 16:488.

Interspersed Repetitious DNA: Describes nearly 35% of the human genome, including various types of active or inactive transposable elements. ►SINE, ►LINE, ►redundancy

Inter-SS PCR: ►cancer

Interstitial Segment: Refers to the chromosomal region between the centromere and the translocation break point. ► [translocation](#)

$$\text{ELOD} = \left(\frac{1 - 2\theta}{1 - \theta} \right) \frac{n}{2} \log \left(\frac{1}{1 - p} \right)$$

Interval Mapping: Considers pairs of adjacent markers and maximizing the likelihood of quantitatively expressed gene loci (QTL) being in between. ELOD is the expected lod score, θ = recombination fraction, p = the proportion of variance contributed by QTL, n = sample size. The calculation may be difficult under practical conditions because there may be more than one QTL per linkage group. An interval mapping based on the least squares method may be better. ► [QTL](#), ► [lod score](#), ► [least squares](#), ► [ASP analysis](#); Ott J 2001 *Advances Genet* 42:125.

Intervarietal Substitution: This is basically similar to alien substitution except the chromosomes belong to different varieties of the same species. ► [alien substitution](#)

Intervening Sequence (IVS): ► [intron](#)

Intimate Pairing (synapsis): Refers to the very close apposition of the chromosomes at the meiotic prophase that makes possible crossing over (gene conversion) and recombination. ► [recombination mechanisms eukaryotes](#), ► [recombination molecular mechanisms prokaryotes](#), ► [recombination models](#), ► [synapsis](#)

Intimin: An enterobacterial protein that mediates the attachment of the bacterium to the epithelial cells of the intestine and causes erosion facilitating the transport of proteins and intestinal inflammation as a consequence of the infection.

Intine: Refers to the inner layer of the wall of the pollen grain.

Intrabody: An antibody expressed by intracellular immunization in the target cells. ► [intracellular immunization](#), ► [gene therapy](#), ► [tumor vaccination](#); Duff RJ et al 2000 *Methods Enzymol* 313:297. ► [inradiabody](#)

Intracellular: This means located within a cell(s).

Intracellular Clock: The differentiation of particular cells into a particular type of tissue during embryonal development is controlled by the timing of the signal received for differentiation. For example, an animal epithelium excised at the gastrula stage grafted on to the eye disc of an embryo may differentiate into a neural tube but if the same tissue is grafted on to the same position a few hours later it may differentiate into an eye lens.

Intracellular Immunization: This involves the targeting of the antibody to a specific cellular compartment. This can be accomplished by signal peptide sequences specific for, say, the endoplasmic reticulum, mitochondria, the cell nucleus, cytoplasm in general, specific membranes, etc. The function of proteins at the target sites may be modulated leading to alteration of susceptibility to viral infection and replication, modifying cells' surface receptors, altering light receptors, affecting mitosis, etc. ► [differentiation](#), ► [biotechnology](#), ► [intrabody](#), Chames P, Baty D 2000 *FEMS Microbiol Lett* 189:1.

Intrachromosomal Gene Locus Association: ► [inter-chromosomal interaction](#)

Intrachromosomal Recombination: May be responsible for deletions and duplications. ► [sister chromatid exchange](#), ► [transposition](#), ► [ectopic recombination](#), ► [recombination intrachromosomal](#)

Intraclass Correlation: A form of analysis of variance used for the estimation of heritability on the basis of variances between and within classes, e.g., in the progeny of a larger number of different males mated to a smaller number of females, each of which has several offspring (see Table 15). Thus, the degree of variance within the litter of a male mated (sired) to the same female (within "sires") can be compared to the variance among the total offspring of individual males mated to different females (between "sires"). The intraclass correlation of the sires is 1/4 of the heritability for the trait considered because each male contributes half of the genetic material to the offspring quantitatively analyzed, and these again contribute only half of their chromosomes through their haploid sperm. The procedure of calculation is illustrated by the hypothetical example given here.

ANALYSIS OF VARIANCE

| | df | SS | MS |
|--------------------------|----|------|-------|
| Between Males (SS_S) | 3 | 6.5 | 2.17 |
| Within Males (SS_P) | 20 | 21.5 | 1.075 |

$\hat{\sigma}^2_S = \frac{MSS - MSP}{n_i} = \frac{2.17 - 1.075}{6} = 0.1825$ (the male's variance component) $\hat{\sigma}^2_P = MSP = 1.075$ (the progeny variance component)

The Males Intraclass Correlation (r_1), $\hat{\sigma}^2_S / (\hat{\sigma}^2_S + \hat{\sigma}^2_P)$ is equal to 1/4 of the heritability, hence $h^2 = 4\hat{\sigma}^2_S / (\hat{\sigma}^2_S + \hat{\sigma}^2_P) = 4[0.1825 / (0.1825 + 1.075)] = 0.58$.

► [correlation](#), ► [heritability](#), ► [variance](#), ► [variance analysis](#). (Heritability is denoted by h^2 for historical reasons but it is not the second power of an entity). (See Hill WG, Nicholas FW 1974 *Biometrics* 30[3]:447).

Table 15. Procedure for calculating heritability based on intraclass correlation. The mean scores of the offspring are represented in the body of the table. (Y stands for individual or group measurements)

| Males → | A | | B | | C | | D | |
|--|----------------------------|-----------|--|-----------|-------|-----------|-------|-----------|
| Females ↓ | Y_i | $(Y_i)^2$ | Y_i | $(Y_i)^2$ | Y_i | $(Y_i)^2$ | Y_i | $(Y_i)^2$ |
| E | 2 | (4) | 3 | (9) | 3 | (9) | 4 | (16) |
| F | 3 | (9) | 2 | (4) | 4 | (16) | 3 | (9) |
| G | 3 | (9) | 3 | (9) | 4 | (16) | 2 | (4) |
| H | 4 | (16) | 2 | (16) | 3 | (9) | 4 | (16) |
| I | 3 | (9) | 4 | (16) | 4 | (16) | 6 | (36) |
| J | 5 | (25) | 2 | (4) | 5 | (25) | 5 | (25) |
| Sum Y_i | 20 | | 16 | | 23 | | 24 | |
| Sum Y_i^2 | | 72 | | 46 | | 91 | | 106 |
| Sum (Σ) all | Sum ($\Sigma\Sigma$) all | | n (all measurements) = 24, | | | | | |
| $Y_i = Y \dots = 83$, | $Y_i^2 = 315$, | | n_i (no. of families of females) = 6 | | | | | |
| Correction factor (C) = $Y^2 \dots / n = 83^2/24 = 6889/24 = 287$ | | | | | | | | |
| Uncorrected Sum of Squares ($\Sigma Y_i^2/n_i$) | | | | | | | | |
| $= (20^2 + 16^2 + 23^2 + 24^2)/6 = 1761/6 = 293.5$ | | | | | | | | |
| Sum of Squares “Between Males” = $SS_S = (\Sigma Y_i^2) - C$ | | | | | | | | |
| $= 293.5 - 287 = 6.5$ | | | | | | | | |
| Sum of Squares “Within Males” = $SS_P = \Sigma\Sigma Y_i - (\Sigma Y_i^2/n_i)$ | | | | | | | | |
| $= 21.5$ | | | | | | | | |
| Mean Square (MS) is SS/df | | | | | | | | |

(The lower index S stands for "sires"; the lower index P is for progenies)

Intracytoplasmic Sperm Injection: ►ICSI

Intradiabody: This is an intrabody with dual specificity, i.e., targeting two receptors within a pathway such the VEGF receptor and the Tie-2 receptor, and it leads to increased anti-tumor effect (Jendreyko N et al 2005 Proc Natl Acad Sci USA 102:829). ►intrabody, ►VEGF

Intrafallopian Transfer: This transfer of gametes (GIFT) or zygotes (ZIFT) is involved in infertility treatment procedures whereby the spermatozoa and the mature oocytes or in vitro generated zygotes, respectively are surgically inserted into the fallopian tube of the female where fertilization and/or segmentation may proceed. These procedures have a higher rate of success for conception than in vitro fertilization but they often lead to twinning if more than a single egg or zygote is used. ►ART, ►in vitro fertilization, ►TET, ►PROST; Klonoff-Cohen H et al 2001 Fertil Steril 76:675.

Intragenic Recombination: This is rare because alleles of a locus are very close to each other. Intragenic reciprocal recombination is expected to yield wild type and double mutant recombinants that can be verified only if flanking non-allelic markers are available. These outside markers — ideally — should not be more than 5–10 map units at both sides of the locus. The mutant alleles are m^1 , m^2 and m^3 , respectively, p, t and an are outside markers. The + sign indicates non-mutant (see Fig. 147). The following crosses are required to determine the linear order of the m alleles in a simple case:

Among the recombinants, the m phenotype indicates double recessive alleles in the same strand whereas the m^+ phenotype is an indication of recombination between two recessive alleles present in the heterozygous parent, which is testcrossed. According to these results the order of the mutant alleles and the markers must be $p - \underline{m^3} - m^1 - m^2 - t - a$ and none of the recombinant classes are supposed to be contaminants because the markers are consistent with the recombination events suggested. The double

| Test crosses | Reciprocal recombinant phenotypes |
|--|-----------------------------------|
| $\frac{p m^1 t^+ a}{p^+ m^2 t a^+} \times \frac{p m t a}{p m t a}$ | $p m t a^+$ and $p^+ m^+ t^+ a$ |
| $\frac{p^+ m^2 t a^+}{p^+ m^3 t^+ a} \times \frac{p m t a}{p m t a}$ | $p^+ m^+ t^+ a$ and $p m t a^+$ |
| $\frac{p m^1 t^+ a}{p^+ m^3 t a^+} \times \frac{p m t a}{p m t a}$ | $p m^+ t a^+$ and $p^+ m t^+ a$ |

Figure 147. Intragenic recombination test

mutant recombinants may be further tested by recombination to yield the two mutant classes. Intragenic recombination is a rare event (~ 0.02 to 0.000001 or less), close to the range of mutation frequency. Intragenic recombination is more likely to preserve protein function than random mutation (Drummond DA et al 2005 Proc Natl Acad Sci USA 102:5380). (See Whittinghill M 1950 Science 111:377).

Intragenic Suppressor: ▶suppressor gene

Intrasteric Regulation: The internal sequences of protein, resembling substrate tracts (pseudosubstrate) act directly at the active site in contrast to the allosteric effects when the allosteric molecule bears no similarity to the substrate and attaches to the protein at a site different from the active site. Intrasteric control is a means of autoregulation. ▶allosteric control, ▶autoregulation; Kobe B et al 1997 Adv Second Messenger Phosphoprotein Res 31:29.

Intrauterine Fertilization (IUI): In this process the sperm is deposited directly into the uterus, bypassing the cervix (the anterior part of the uterus, which may form a barrier to the passage of the sperm). This type of medical intervention may be undertaken to treat infertility in humans. ▶ART

Intravasation: Refers to the entrance of an extraneous substance into the blood vessels. Metalloproteinases, receptor urokinase plasminogen activator (uPA) and their inhibitors may affect the process. Metastasis of cancer cells may depend on intravasation. ▶extravasation, ▶metastasis, ▶metalloproteinases, ▶urokinase

Intrinsic: This adjective defines the basic, essential attribute of a phenomenon. ▶extrinsic

Intrinsic Disorder: Proteins have multiple conformations. They may play a regulatory role by optimizing allosteric couplings with different ligands (Hilser VJ, Thompson EB 2007 Proc Natl Acad Sci USA 104:8311). ▶allostery

Intrinsic Rate of Natural Increase: ▶age-specific birth and death rates

Intrinsic Terminators: These terminators of transcription in prokaryotes do not require co-factors (are rho-independent) for the termination of transcription. ▶transcription termination in prokaryotes

Introgression: Refers to the transfer of genes from one group of species to another. The two populations may inhabit the same area (sympatric) or they may have only occasional contact because of being in different areas (allopatric). After the initial crossing the mating continues largely within the group and therefore only a few of the “borrowed” genes are maintained. *Marker-assisted introgression* uses molecular tools to monitor the transfer/presence of the desired genetic regions, especially for quantitative trait loci. In human populations mitochondrial DNA analysis and Y chromosomal haplotyping are especially useful for tracing the ethnic origins. ▶QTL, ▶marker-assisted selection, ▶speciation, ▶co-evolution; Anderson E 1949 Introgressive Hybridization, Wiley, New York, Saetre GP et al 2001 Mol Ecol 10:737.

Introgressive Hybridization: This accomplishes introgression. ▶introgression

Intron Homing (retrohoming): Refers to the process of insertion of an intron at a particular site within an intron-less cognate sequence. Accordingly, some introns of yeast mitochondria serve as mobile genetic elements besides performing a ribozyme function. The homing introns, mitochondrial or nuclear, are endonucleases with similarities to restriction enzymes but their recognition sequence is much longer. Intron homing may utilize either (i) the double-strand-break repair pathway common in genetic recombination and yielding reciprocal crossover and non-crossover products, or (ii) a synthesis-dependent strand annealing process that does not produce flanking crossing over. ▶introns, ▶ribozyme, ▶homing endonuclease, ▶mtDNA; Mohr G et al 2000 Genes, Development 14:559; Belfort M et al 2002 in Mobile DNA II, ASM Press, Washington, DC p. 761.

Intron Retention: Refers to a failure of splicing out an intron. ▶introns, ▶splicing, ▶alternative splicing

Intron Sliding: This is an alternative type of splicing used by cryptic splice sites generally caused by the presence of SINE elements. ▶splicing, ▶alternative splicing, ▶SINE, ▶introns; Rogozin IB et al 2000 Trends Genet 16(10):430.

Intron Slippage (intron sliding): The position of introns (intron—exon boundary) may vary among homologous genes of evolutionarily related species by one or a dozen or more nucleotides. ▶ [introns](#), ▶ [alternative splicing](#); Wistow GJ, Piatigorsky J 1990 Gene 96:263.

Intronless Paralog: These are genes inserted into the genome by retrotransposition of processed mRNA. ▶ [retrotransposon](#), ▶ [processed gene](#); Schimenti JC 1999 Mamm Genome 10(10):969.

Introns: These are nucleotide sequences within a gene that are not represented in the mature mRNA transcripts of that gene (intervening sequences, IV). Introns are transcribed but not translated into protein that would be part of the products of the exon-coded genes or will not be included into the final RNA encoded by the gene. Introns separate the coding sequences of the exons (see Fig. 148). Introns are seen in the majority of the eukaryotic genes, including genes of mitochondria and chloroplasts and also in viruses of eukaryotes but they are exceptional in prokaryotic genes. In land plant plastid DNA ca. 20 introns are present and their size varies from 400 to over 1000 bp. The average size of an intron in mice is around $1,800 \pm 300$ and in humans about $3,000 \pm 550$. In the X chromosome the intron size is substantially longer. In imprinted genes the intron number, and particularly its size, is smaller. The RNA maturases in mammals are actually intron sequences within protein genes and assist the splicing of the pre-mRNA transcripts. In algae the cpDNA introns are quite variable in number and size; in *Euglena* 149 introns have been detected. In the red alga *Porphyra* no introns in the cpDNA have been observed. In *Chlamydomonas* the insertion site of an intron

corresponds to an *E. coli* rRNA domain. Introns may appear as latecomers to the eukaryotic organelle genes since in multiple evolutionary lines they are non-homologous either by sequence or location. However, the thymidylate synthetase gene of T4 bacteriophage has an intron, and the archaeobacterial tRNA^{Leu} as well as the large ribosomal subunit genes have introns. One of the largest introns (64-kb) has been found in the human thyroglobulin gene which is involved in the regulation of energy metabolism and in the various forms of goiter. The overall profile of a gene can be represented as: 5'- Enhancer-promoter - transcription initiation site - leader - exon ♦ **intron** ♦ exon-termination signal - 3'.

The origin of introns is unclear. Some arguments favor their ancient evolutionary presence, preceding the divergence of eukaryotes from prokaryotes (Fedorov A et al 2003 Genome Res 13:2236). Some introns may be located at critical regions of the gene, dividing it into functional domains or separating α -helices from β -sheets. It has been suggested that increased replication rate is inversely proportional to the number of introns. Indeed, introns are rare in prokaryotes and fewer in yeast.

Introns may regulate genes controlling complex developmental pathways (Juneau K et al 2006 Genetics 174:511). The large homeotic genes of *Drosophila* seem to contain more introns than other simple genes. The greater density of introns within genes may be promoted by sexual reproduction that enables them to propagate in a selfish manner through gametes of both parents. Introns can protect against the deleterious consequences of recombination because if this occurs within introns rather than within exons, no harm can be caused to the coding capacity. Recombination frequency is negatively

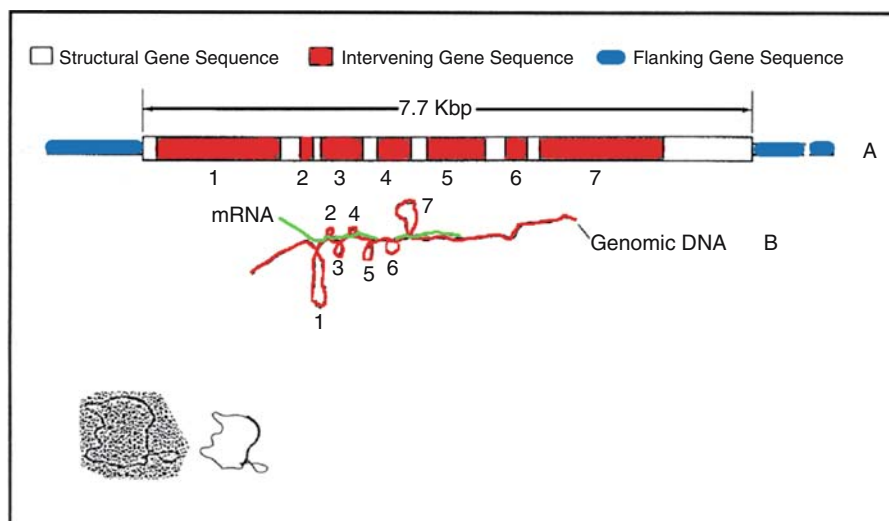


Figure 148. (Photomicrograph is by Batosin, L., Laub, O. Horouritz, M. & Y. Aloni. Courtesy of Professor Aloni.)

correlated with intron length. Introns can also protect against illegitimate recombination by interrupting homologous tracts at random sites. Although these problems have not yet been resolved, the mechanics of transactions concerning introns has made substantial progress.

The number of introns varies greatly (Llopart A et al 2002 Proc Natl Acad Sci USA 99:8121). Some genes, e.g., the histone, human α and β interferon genes have no introns, whereas the γ interferon gene has several. The large (~2-Mbp) human dystrophin gene contains over 60 introns. (Dystrophin is a muscle protein, deficient in muscular dystrophy). The average size of an intron generally varies between 75 and 2,000 bp but some introns are several times as long or no more than about a dozen nucleotides. There are no introns in the 5S, 5.8S, U RNA, 7SL and 7SK RNA genes. In organisms with compact genomes like *Drosophila* and budding yeast the number of introns is usually small but fission yeast contains a large number. Introns comprise nearly 24% of the human genome. The average number of introns/gene in humans is about 7. Interestingly, the mitochondrial genes of budding yeast have relatively more introns than the nuclear genes.

Introns are removed from the primary transcripts of the genes during processing. The removal of introns is essential for the expression of genes. Group II introns have six domains; domain 1 (D1) and D5 are essential for splicing. Thus, the mRNA becomes shorter than the primary transcript. When the mRNA is hybridized to the genomic coding strand of DNA, the latter reveals loops at those positions in the mRNA from where the introns were removed. The chicken ovalbumin gene contains seven introns and loops corresponding to their location and length can be detected by electron microscopy (see map

by Dugaiczky et al Stadler Symp. 11:57, and interpretative drawing by Rédei, 1982). Alternative mRNAs can be obtained from the same DNA sequence by controlling the length, number or pattern of exons used, depending on (i) the site of initiation of transcription, or (ii) the alternative sites of polyadenylation signals, or (iii) the selective retention of particular exons in the mRNA. By using these mechanisms the products of single genes can be diversified during development or differentiation. Alternative splicing may be accomplished by using more than a single promoter, resulting in alternative long or short transcripts, depending on the site of transcription initiation. Alternative polyadenylation signals, at more than a single location downstream, may truncate the transcript at the 3' end. An example of mechanism (see Fig. 149) (i), alternative promoters the exons are bracketed, introns are in bold numbers and parenthesis. Alternative splicing occurs in various eukaryotic genes and various viruses of eukaryotes. In the small genomes of the latter systems a single transcript may permit the production of several proteins. In the determination of correct splicing both cis- and transacting proteins cooperate. When the introns are removed the exons are *spliced* together and the continuity of the mRNA is restored. There are two splice sites, the *upstream donor site* and the *downstream acceptor site*. When the invariant bases (shown in bold numbers in the example) are altered, splicing generally fails. Other neighboring bases may also affect the efficiency of splicing. In animal nuclear genes, an A residue in the vicinity of the splice site is required but its position does not have to be absolutely fixed relative to the splice site. In yeast, there is an absolute requirement for a conserved UACUAAC tract within 6 to 59 nucleotides upstream from the 3' splice signal. Some

TATA1--[1]--(1)--TATA2--[2]--(2)--[3]--(3)--[4]--(4)--[5]--(5)--[6] DNA

Example of splicing mechanism (i):

mRNA 1: --[1]--[4]--[5]--[6]-- alternative transcripts **mRNA 2:** --[2]--[3]--[4]--[5]--[6]--

Example for alternative truncation (mechanism ii):

TATA--[1]--(1)--[2]--(2)--[3]--(3)--[4]--(4)--poly A signal I--[5]--[6]--(6)--poly A signal II--DNA

mRNA 1: -- [1]--[2]--[3]--[4]--AAAAA or **mRNA 2:** - [1]--[2]--[3]--[5]--[6]--AAAAA

Example for mechanism (iii), alternative splicing between identical promoter and polyA signal:

TATA 1--[1]--(1)--[2]--(2)--[3]--(3)--[4]--(4)--[5]--(5)--[6]--(6)--- DNA

mRNAs: --[1]--[2]--[3]--[4]--[6]--AAA,--[1]--[3]--[4]--[5]--[6]--AAA,--[1]--[2]--[4]--[5]--[6]--AAA
 ↑ ↑ ↑ ↑ ↑ ↑

Figure 149. Splicing mechanisms

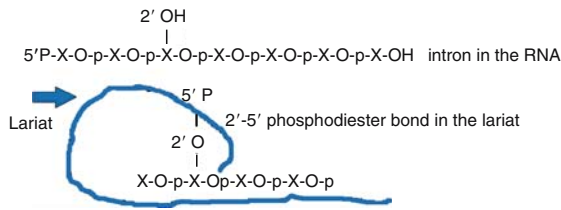


Figure I50. Lariat formation

genes have more than one splice site pairs which facilitate alternative splicing and the assembly of different mRNAs. Although originally introns were regarded as junk DNA, it is now known that some introns are translated but have independent functions from the exons; some have a role in the processing of the transcript shared by the neighboring exons whereas others perform regulatory functions (see Figs. I50 and I51).

On the basis of structural information about the splice sites, some special introns have been classified into group I and group II (see Table I6). The principal characteristics of group I introns are (i) their splicing does not always require a protein enzyme, rather (ii) a short internal sequence facilitates their folding and splicing that is initiated by (iii) an extraneous guanosine or a phosphorylated form of it (see Fig. I52).

Group II introns do not have conserved internal sequences yet they are capable of foldback pairing and the splicing requires an intrinsic signal rather than an extraneous guanine. The spliced group II introns form a *lariat* (similar to that of a tethering rope), the 5' P end forms a phosphodiester bond with the 2'-OH group of a nucleotide within the chain at some distance. The loop itself may have three nucleotides (GpApA).

The splicing of group I introns requires *transesterification* (phosphodiester linkage ex-changes). Transesterification takes place without severing the bonds first. The self-splicing is mediated by ribozymes, RNAs that have enzyme-like catalytic functions.

Ribozymes facilitate the formation of the proper configuration of the RNA transcript and may function like endonucleases. The aI2 ribonucleoprotein of the *COX1* yeast mitochondrial gene catalyzes the cleavage of the DNA target, recognized by complementarity of the sequences within the intron RNA. After cleaving the DNA the aI2 protein reverse transcribes the intron RNA using the 3' end of the DNA as a primer. The aI2 RNA cleaves the sense strand of the DNA whereas the aI2 protein cuts the antisense strand and the latter also boosts the activity of the aI2 ribozyme. The intron assumes a complex secondary

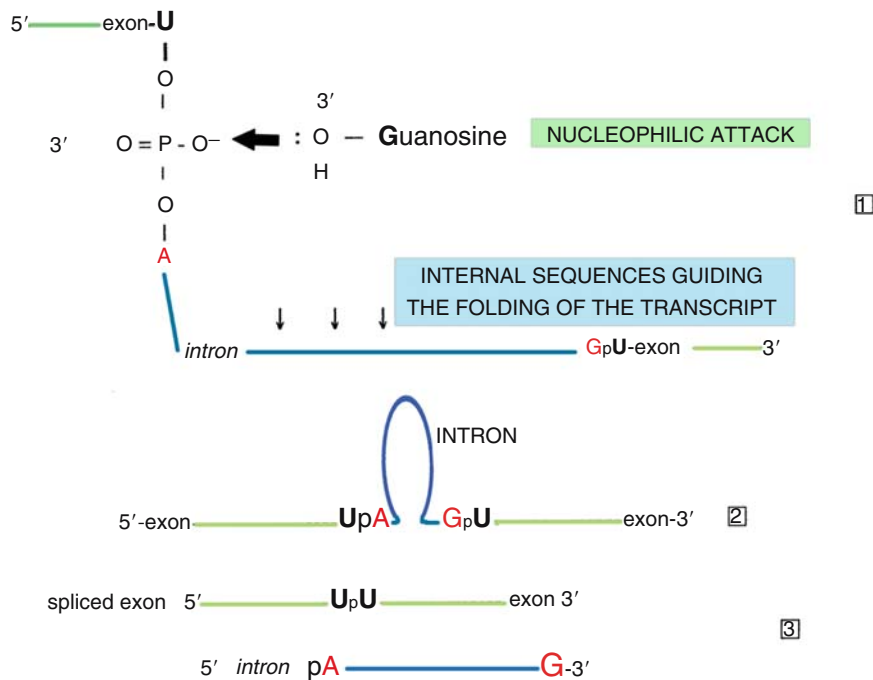


Figure I51. Self-splicing steps. Self-splicing of a group I intron (1) a guanosine (or guanylic acid) conducts a nucleophilic attack against a phosphate group near the point of juncture, and transesterification follows later at both 5' and 3' junctions. this is accompanied by the recognition of internal sequences ↓↓↓ that guide the folding. (2) exon termini in bold and the ends of the intron is in outline letters. (3) spliced exon and intron are displayed

Table I6. The intron - exon border sequences are conserved within groups of different classes of rna transcripts (after cech, cell 44: 207) the bold letters indicate constant bases, the ↓ indicates splice sites, py stands for any pyrimidine and pu for any purine and x means any base

| INTRON | 5' SPICE JUNCTION | 3' SPICE JUNCTION |
|-------------------------------|---|--|
| Common nuclear pre-mRNA | CPuG ↓ GU _G ^U AGU | (PY) _n AG ↓ X |
| Yeast nuclear pre-mRNA | ↓ GUAUGU | (PY) _n AG ↓ X |
| tRNA | X ↓ X | X ↓ X |
| ¹ Introns Group I | U ↓ | G ↓ |
| ² Introns Group II | ↓ GUGCG | (Py) _n AU ↓ |
| <i>Euglena</i> plastid mRNA | ↓ GUG _U ^C G | (Py) _n Ac ^U ↓ |

¹ Nuclear rRNA genes of in some lower eukaryotes, mitochondrial and plastid rRNA genes

² Yeast mitochondrial genes for cytochrome oxidase and cytochrome b

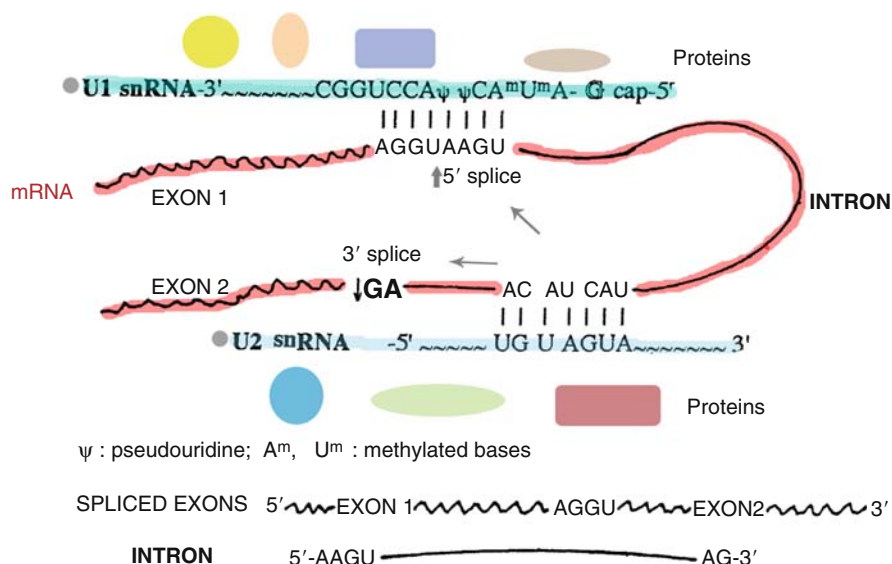


Figure I52. The U1 and U2 snRNAs facilitate the proper configuration of the folding of the transcript and thus identify the correct splicing sites. The A-2'OH nucleotide leads the nucleophilic attack, which is followed by transesterification and ligation of the exon

structure by base pairing of some complementary sequences separated by non-pairing tracts. The extraneous guanosine launches a nucleophilic attack (an electron-rich molecule reacts with an electron poor one that is willing to accept electrons) at the exon-intron boundaries resulting in a nucleotide chain breakage at the site and an exclusion of the intron. Not all group I introns are able to self-splice without the help of *maturase* proteins encoded by introns within some yeast mitochondrial genes. The self-splicing of group II introns is somewhat similar to that of group I. In group II there is no involvement

of guanine. The 2'-OH group of an adenine within the intron initiates the nucleophilic attack. After appropriate folding to bring the 5' and 3' junctures in proximity to each other, the exon is spliced by transesterification and the intron is released as a lariat. The primary RNA transcript of nuclear pre-mRNAs is capped. Cleavage takes place at the 5' end of the intron upstream of a ↓pGU pair as indicated by the arrow. The free 3' end of the intron forms a lariat with an internal A residue and then the intron with the lariat is released and the 3' end of the first exon is ligated to the 5' end of the next exon. The outcome is

the same as discussed earlier. The splicing of the nuclear pre-mRNAs requires, however, a more complex machinery involving spliceosomes.

The spliceosomes are assembled from short U-rich RNAs, ranging in size from 65 (U7) to 217 (U3) nucleotides and a set of different proteins. The most common U RNAs in the mammalian nucleus are U1, U2, U4 and U6. The U3 RNA is involved in RNA processing in the nucleolus. The U7 RNA assists in the formation of the 3' end of the histone mRNAs that have no introns. The corresponding U RNAs are highly homologous even among taxonomically different organisms such as humans and dinoflagellates. The homologous U RNAs among vertebrates are almost identical (ca. 95% similarity). The spliceosomes contain a common set of seven proteins (generally designated by capital letters [B, A', etc.] or by molecular weight [e.g., 59K, 25K]) and may also contain a few specific proteins. About 1% or less of the introns uses AU and AC (rather than the more common GU and AG) as terminal nucleotides. In plants (crucifers) especially AU-AA introns may occur. Some of these introns also use the U12 snRNA for processing. The intron-encoded U22 small nucleolar RNA facilitates the processing of the 18S ribosomal RNA in *Xenopus* oocytes. The U1 snRNA specifically binds to the 5' splice site of the intron and protects this region from RNase attack but it does not cleave at the splice site. The U2 snRNA complex performs the same function near the 3' end of the intron around the adenosine residue whose 2'-OH is involved in the formation of the lariat. The spliceosomes are ellipsoid complexes (about $25 \times 50\text{-}\mu\text{m}$ in size) that actually bring together the splicing sites to make the *cut and paste* process possible. These bindings generally require some degree of complementarity but that is not complete. Besides these two spliceosomes, others (U2, U4, U6) and a number of binding proteins may be involved in facilitating and stabilizing the binding.

The position of *introns* in *tRNA* genes is located next to the third (3') base of the anticodon triplet, with a single base in between. Yeast has about 40

nuclear-coded tRNAs and 10% of them have a single intron containing between 14 and 46 bases. This regular location is somewhat enigmatic because tRNA^{Tyr} genes of yeast with deleted intron sequences are still transcribed, processed normally and function. In the primary transcript, the intron has a triplet that is complementary to the anticodon. For correct splicing, the various loops and arms of the tRNA cloverleaf are important. The first step in splicing of tRNA transcripts is a cleavage by an endonuclease at the ends of the intron. In yeast the 5' terminus of the exon is then represented by an OH group and the 3' terminus by a 2',3'-cyclic phosphate. The cyclic phosphodiesterase then breaks the ring and generates a 3'-OH and a 2'-O-(PO₃) terminus. The 5'-OH end is phosphorylated by a kinase, requiring ATP. Thus, the termini are ready for joining by an *RNA ligase* enzyme. Essentially similar reactions are observed in splicing nuclear tRNAs in mammals and plants.

The splicing mechanisms shown and discussed earlier involve splicing exons within the same primary RNA transcripts. In some instances exons originally located in different transcripts, even in different chromosomes, may be spliced by *transsplicing* (see Fig. 153). Transsplicing can generate.

mRNAs from leader sequences remote to the exons. Transsplicing is common in the protozoa, *Trypanosomes* where different exons can be joined to a single 35-bp leader sequence. (The exons are scattered among approximately 100 chromosomes). The 3' end of the leader and the 5' end of the coding exons can be joined. Since the 5' end of the intron carries the generally conserved 5'-GU sequence, the remote other intron, preceding the remotely transcribed coding exon, terminates at 3' with the conserved AG bases and also has an adenosine nucleophile somewhere in the vicinity of its 5' terminus. The two originally remote introns can be brought together by a 5' to 2' bond as a branched molecule, and subsequently both introns are eliminated and the leader is joined to the coding exon as outlined in the Fig. 153. Transsplicing also occurs in other eukaryotes, e.g., in the nematode *Caenorhabditis*

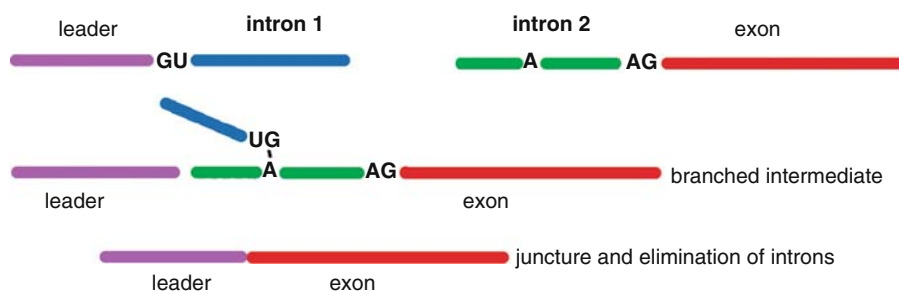


Figure 153. Transsplicing

elegans and in the chloroplast genes of plants. The open reading frames of class II introns have sequences reminding to reverse transcriptases of the type of retroposons. There is no evidence, however, that these would function as reverse transcriptases. Introns and spliceosome sites show evolutionary variations and are suitable for tracing phylogenetic relationships (Roy SW, Gilbert W 2006 *Nature Rev Genet* 7:211). The map position of introns in animals, plants and fungi shows considerable alignment and indicates that the ancestral introns predate the evolutionary divergence of these taxonomic categories (Fedorov A et al 2002 *Proc Natl Acad Sci USA* 99:16128). Among 10,020 intron positions in human–mouse comparisons, five cases of intron loss were detected in the mouse evolutionary lineage but not in humans; moreover no gain was observed in either lineage (Roy SW et al 2003 *Proc Natl Acad Sci USA* 100:7158). Intron loss is attributed to recombination of reverse transcriptase products of spliced mRNA, processed genes (Roy SW, Gilbert W 2005 *Proc Natl Acad Sci USA* 102: 713). In seven diverse eukaryotic groups intron loss varied from $\sim 2 \times 10^{-9}$ to 2×10^{-10} per year during evolution and the rates of gain were between 6×10^{-13} and 4×10^{-12} . These figures indicate that the early ancestors of eukaryotes were intron-rich rather than introns being of more recent origin because the gain was much less frequent than the loss (Roy SW, Gilbert W 2005 *Proc Natl Acad Sci USA* 102:5773). Single introns in the majority of species tend toward the 5' end; *Arabidopsis* is an exception (Sakurai A et al 2002 *Gene* 300:89). Group II introns can be targeted for insertion into a ~ 14 -nucleotide region of target DNA of prokaryotes. Introns inserted in the antisense orientation cannot splice and disrupt the gene. Introns inserted in the sense orientation may serve for selective regulation of gene expression when linked to inducible promoters.

A comparison with the orthologous regions in the mouse and the chimpanzee reveals that human introns with the most similar boundaries are younger. Human introns are alternatively spliced with exceptionally high frequency. Genomic duplication has been an important mode of intron gain in mammals. The alternative splicing of transcripts containing these intron-breeding repeats may provide the plasticity required for the rapid evolution of new human proteins (Zhuo D et al 2007 *Proc Natl Acad Sci USA* 104:882).

►transcription, ►ribozymes, ►endonuclease, ►ligase, ►branch point sequence, ►intron group III, ►mtDNA, ►RNA maturase, ►speckles intranuclear, ►spliceosome, ►exon junction complex, ►spliceosomal intron, ►SR motif, ►*Neurospora* mitochondrial plasmids, ►intein, ►snoRNA, ►deadbox proteins, ►DEAH box proteins, ►splicing, ►gene, ►alternative splicing, ►TAP, ►processed gene,

►homing endonucleases; Bassi GS et al 2002 *Proc Natl Acad Sci USA* 99:128; Clark F, Thanaraj TA 2002 *Hum Mol Genet* 11:451; origin and evolution of introns: Roy SW, Gilbert W 2005 *Proc Natl Acad Sci USA* 102:1986, self-splicing ribozyme-like introns: Nielsen H et al 2005 *Science* 309:1584; <http://hsc.utoledo.edu/bioinfo/eid/index.html>, spliceosomal introns: <http://genome.imim.es/cgi-bin/u12db/u12db.cgi>.

Introns Group I: These self-splicing introns in some ribosomal genes use mechanisms different from the pre-mRNA or the majority of tRNA genes. ►introns for characterization, ►mitochondrial genetics for introns as mobile elements and plasmids, ►spliceosomal introns, structure: Adams PL et al 2004 *Nature [Lond]* 430:45.

Introns Group II: These introns are large ribozymes in a few mitochondrial, chloroplast, fungal and bacterial genes and differ in structure and splicing mechanisms from the common introns (Type I) of eukaryotes. Mobile group II introns are retroelements with reverse transcriptase activity. They are also self-splicing and are capable of intron homing. Group II introns can cause insertional mutations. Both group I and group II introns require deadbox proteins as RNA chaperones (Huang H-R et al 2005 *Proc Natl Acad Sci USA* 102:163). ►introns, ►intron homing, ►mitochondrial genetics, ►spliceosomal introns, ►deadbox proteins, ►chaperone, ►intron group III, Lambowitz AM, Zimmerly S 2004 *Annu Rev Genet* 38:1.

Introns Group III (twintron): These are relatively short, group III introns inserted within the boundary of group II introns in the cpDNA of *Euglena*. Some bacteria also have twintrons in intergenic regions. ►ctDNA

Intussusception: Refers to the insertion of interstitial tissue into the lumen of existing vessels.

Inulin (fructan): This denotes one of the many types of polymers of (~ 30 –40) fructose units in plants (see Fig. 154).

Invader: This refers to a molecular procedure for DNA and RNA quantification. It is suitable for highly sensitive discrimination between mutant and wild type forms and SNPs. The modified invader assay is suitable for the detection of microRNA precursor and microRNA in unfractionated detergent lysate using fluorescence analysis on microtiter plates (Allawi HT et al 2004 *RNA* 10:1153). (See Kwiatkowski RW et al 1999 *Mol Diagn* 4:353; Olivier M et al *Nucleic Acids Res* 30[12] e53)

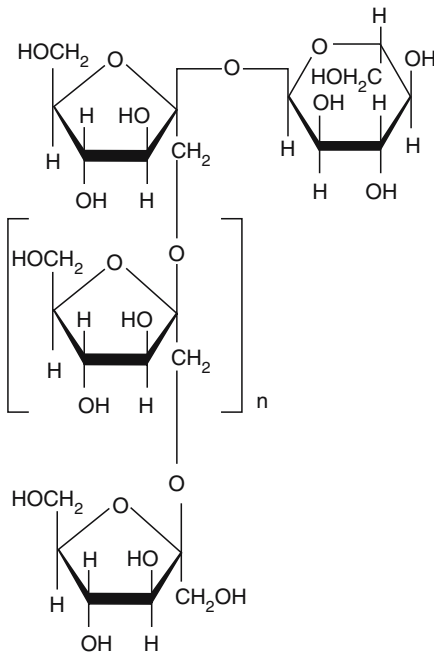


Figure I54. Inulin

Invagination: Refers to folding inward (see Fig. I55).



Figure I55. Invagination

Invariance: This is the reciprocal value of the variance.
▶variance

Invasin: This is the integrin-binding protein of *Yersinia* bacteria assisting infection. ▶integrins, ▶*Yersinia*

Invasion of DNA Strands: ▶branch migration, ▶Holliday model

Invasive: Refers to the penetration of cells commonly leading to their destruction. Can also indicate migration of cancer cells. ▶metastasis, ▶RAGE

Invasive Growth: Yeast cells do not stay on the surface of the culture medium but penetrate it in search of nutrients.

Inverse PCR: ▶inverse polymerase chain reaction

Inverse Polymerase Chain Reaction: This process can be used for molecular analysis of flanking regions of a target (see Figs. I56 and I57).



Figure I56. Restriction fragment including flanks and target

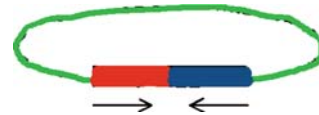


Figure I57. Head to tail association of the flanks in inverse polymerase chain

The fragment shown here is circularized by its cohesive ends and cut with a restriction enzyme within the target. As a consequence a head-to-tail association of the flanks is produced:

This head-to-tail sequence of the flanks is amplified by PCR for nucleotide sequencing. The two flanks may be separated if an appropriate restriction endonuclease site is known at or near their boundary.
▶PCR, ▶target, ▶tail-PCR, ▶capture PCR [CPCR]

Inversion: A chromosomal segment is turned around by 180°(•); centromere (see Fig. I58).

Such chromosomal rearrangements require two breaks, both of them in one chromosome arm in the case of *paracentric inversions*, and one in each arm across the centromere in the case of *pericentric inversions*. Pericentric inversion may alter the arm ratio of the affected chromosome as discussed earlier. Within a single chromosome there may be more than one inversion. These multiple inversions may be independent or may be overlapping or a shorter inversion may be included within a longer one.

If the chromosomes are well suited for cytological analysis, the various types can be identified using a light microscope (see Fig. I59).

Inversions as such may not have much phenotypic consequence, unless they cause “position effect”, influence the expression of the gene because they interrupt either the coding or the non-translated regulatory sequences. These effects may be serious in the relatively rare inversion homozygotes. During

Thus if the **NORMAL ARRANGEMENT** of the genes is: A B C D E • F G H
after **PARACENTRIC INVERSION** the order becomes: A D C B E • F G H
after **PERICENTRIC INVERSION** the sequence is: A B G F • E D C H

Figure I58. Paracentric and pericentric inversion



Figure I59. Two-strand paracentric inversion heterozygote displays double chromatid bridge and two chromatid fragments because of the chromatid tie keeps the crossover chromatids in the middle of the cell, they fail to be incorporated into the egg and thus prevent female sterility. (Courtesy of A.H. Sparrow)

the early years of genetics, inversions were thought to be “C factors”, crossing over inhibitors. Inversions inhibit crossing over in inversion heterozygotes only in the vicinity of the breakage points where the rearrangement prevents intimate pairing of the chromatids. Crossovers are not observed primarily because the strands involved in recombination are usually not transmitted through the paracentric inversion females thus they do not produce defective gametes (see Fig. I60). The consequences for the sperms are not the same for paracentric inversion heterozygotes because the microspore tetrad is not linear and the crossover chromatids are not tied by the inversion-bridge in such a way that they would not be included in any microspore. Therefore in males all four products of meiosis could potentially be transmitted, however 50% of the gametes are still defective. In pericentric inversion heterozygotes duplication-deficiency gametes are formed (without a bridge) in both females and males if crossing over takes place within the inverted segments during meiosis. Thus, crossing over may occur but the crossover gametes or zygotes may not be viable. In animals the consequence of duplication-deficiencies may be different from that in plants. In plants the defective gametes are usually prevented from fertilization because of inviability, whereas in animals the defective sperm may be capable of fertilization but the offspring resulting from such a mating may not survive. The cytological consequences of crossing over within inverted chromosome segments are diagrammed and shown by a photomicrograph. Crossing over within pericentric inversions has the same

genetic consequence as that seen in paracentric inversions, namely 50% of the gametes formed by meiocytes, which have suffered recombination are duplication-deficient. In other words, some of the genes are present in the same strand twice and others are entirely absent, and are therefore generally inviable. Inviability may be gametic or zygotic. In the gametophytes of plants the former is seen whereas in animals the latter is prevalent. Crossing over in pericentric inversion heterozygotes cytologically differs from that in paracentric inversions (see Fig. I61).

In the former, dicentric chromosomes and acentric fragments are not generated by recombination. Double crossing over within the same inverted paracentric segment, involving two homologous chromatids does not produce defective gametes (see Fig. I62). Three-strand double crossing overs yield both acentric fragments and dicentric chromosomes besides the two parental ones. Four-strand double crossing over results in the formation of two acentric fragments and two dicentric chromosomes and generally all gametes become defective. Paracentric inversions may play an important role in speciation because they may cause hybrid male sterility and hence partial sexual isolation. W.S. Stone has estimated that during the evolution of approximately 2,000 species of *Drosophila*, about 350 million paracentric inversions might have occurred, and from these tens of thousands have been permanently fixed, and the fate of another similar number is still undecided. Pericentric inversion may also play a role in speciation because of the complete sexual isolation, and the preservation of the inverted segment as supergenes, refractory to recombination. The descendance of inverted chromosomes in natural populations can be determined on the basis of banded chromosomes or restriction fragment patterns (RFLP). It was found that in *Drosophila subobscura* populations global climate warming increased the frequency of inversions (Balayá J et al 2006 Science 313:1773).

The frequency of inversions in human populations is less than 1% per birth. The actual rate of occurrence may be much higher because many of the afflicted fetuses are spontaneously aborted. Inversions have been added to various mutation tester strains of *Drosophila* so that new mutations could be identified within a particular chromosome without confounding the results by recombination because inversions eliminate the crossovers. Short inverted nucleotide repeats are found at the termini of insertion/transposable elements. Inverted duplication of nucleotide sequences form palindromes and facilitate the formation of double-stranded sequences in single-stranded nucleic acid chains and have determining

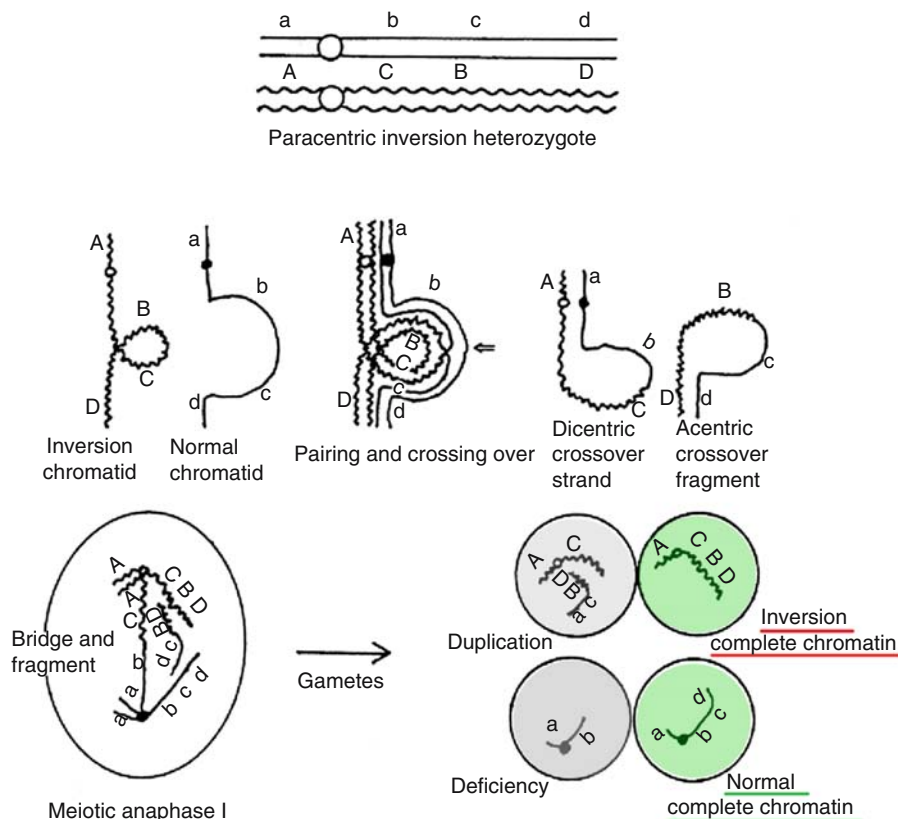


Figure 160. Consequences of recombination. Paracentric inversion heterozygotes produce 50% defective gametes when crossing over takes place within the inverted chromosomal segment. since the frequency of crossing over depends on the length of the segment inverted frequency of the defective gametes varies from 0 to 50%. At the top, an inverted and a normal chromosome are shown. such chromosomes can pair only if the inverted strands form a loop and thus gene-by-gene alignment becomes possible. The configuration of one inverted and one normal strand is shown on the second line at left. in the center of that line the pairing and crossing over (\rightleftharpoons) are diagrammed. As a result of recombination, one of the crossover strands becomes dicentric and deficient for marker (*D*) and duplicated for marker (*A/a*). The other crossover strand becomes acentric and deficient for *A/a* and duplicated for *D/d*. At meiotic anaphase I, the crossing over results in a chromatid bridge because the chromatids are tied together even when anaphase separation proceeds. The tie may either hold together the crossover chromatids and they cannot reach either pole, rather they remain in the middle of the metaphase plane or if the tie breaks, depending on the site of the breakage, additional duplication and simultaneous deficiency may occur. In animals and plants, after recombination of paracentric inversion heterozygotes only a viable (normal or inverted) chromosome enters the egg and thus female sterility is usually not observed. In males (where polarity does not occur during gametogenesis), if recombination takes place within the inversion, 25% of the gametes contain only normal chromosomes, 25% carry inverted chromosomes containing complete chromatin. In the remaining 50% duplication-deficiency or deficiency of the genes is observed, and such gametes are generally sterile or result in embryo lethality. Recombination in pericentric inversion heterozygotes does not result in dicentric bridge but half of both male and female gametes may become defective.

roles in conformation of the molecules, such as in tRNAs. Evidence obtained from *Drosophila buzzatii* indicated that inversions may arise by recombination either within the target site duplications or between two copies of the *hobo* transposable element. Chromosomal (DNA) inversions would be expected to produce “retro-proteins” with an altered three-dimensional structure. The stability of these

retro-proteins may or may not differ from the natural sequence and may or may not affect the function of the proteins. In case a *foldback-like* transposon *Kepler* is inserted at inversion break points in *Drosophila buzzatii* it leads to a substantial reduction in gene expression supposedly due to the antisense RNA effect (Puig M et al 2004 Proc Natl Acad Sci USA 101:913).

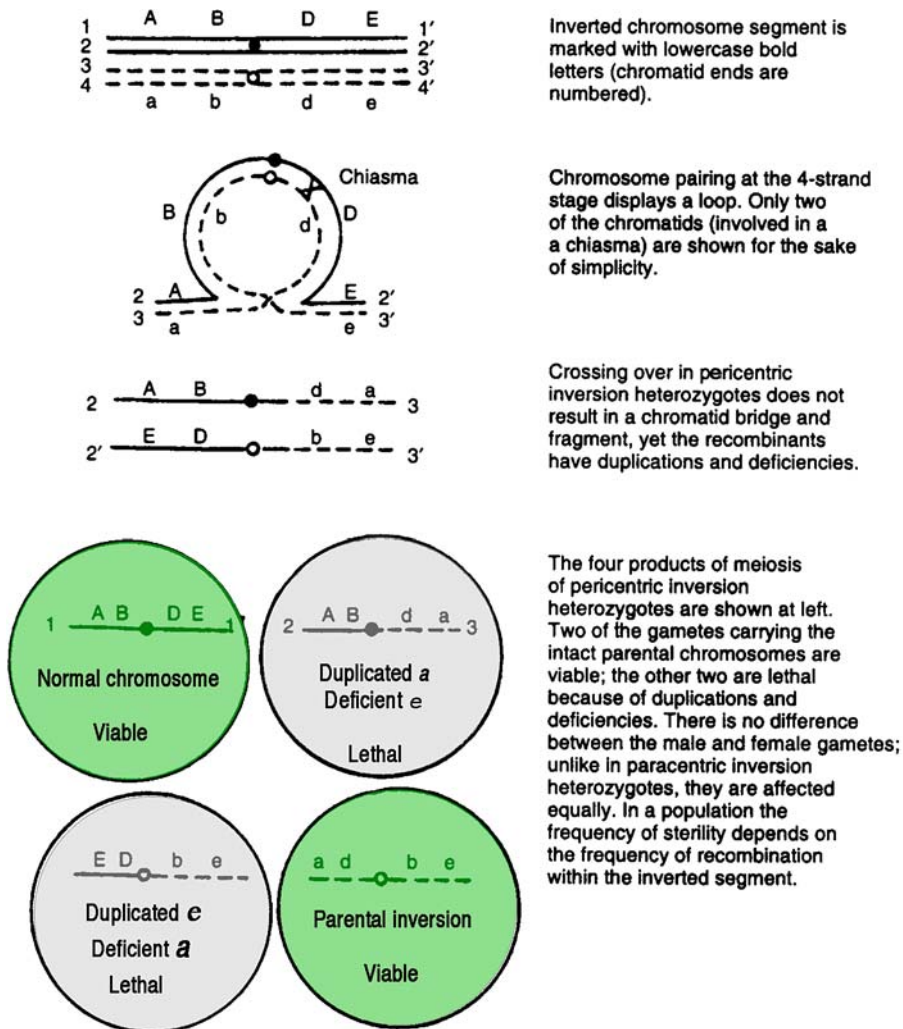


Figure I61. Pericentric inversion heterozygotes and crossing over

A 900 bp inversion in human chromosome 17q121.31 displays two main variations, H1 and H2. The H2 variant is very rare in Africa or East Asia but its frequency in Europe is 20%. In the Icelandic population it undergoes positive selection because both female and male carriers have more children than non-carriers and the recombination frequency is higher in females (Stefansson H et al 2005 Nature Genet 37:129). ▶recessive lethal tests in *Drosophila*, ▶speciation, ▶mutation chromosomal, ▶unbalanced chromosomal constitution, ▶palindrome, ▶conformation, ▶hybrid dysgenesis, ▶antisense RNA, ▶transposon; Ranz JM et al 2001 Genome Res 11:230.

Inversion Loop: ▶inversion

Inversion of Oligonucleotides: The linkages are 3'/5' or 5'/5' and have inverted polarity within the normal

nucleotide tract. They are extremely resistant to exonucleases and have a longer half-life than normal oligonucleotides yet they may not disturb the Watson-Crick structure. These may be used for oligonucleotide therapy.

Inversion, Paracentric: This involves only one arm of a chromosome. ▶inversion

Inversion, Pericentric: The inversion spans across the centromere. ▶inversion

Inversions in Phages and Bacteria: One group of enzymes is invertases (transposases) mediating inversions between the inverted terminal repeats of transposable elements. The other group comprises integrases. The inversion may affect an invertible promoter or the entire gene. The invertase of phage MU (*gin*) is positioned outside the invertible 3000-bp G region flanked by 34-bp inverted repeats. In one

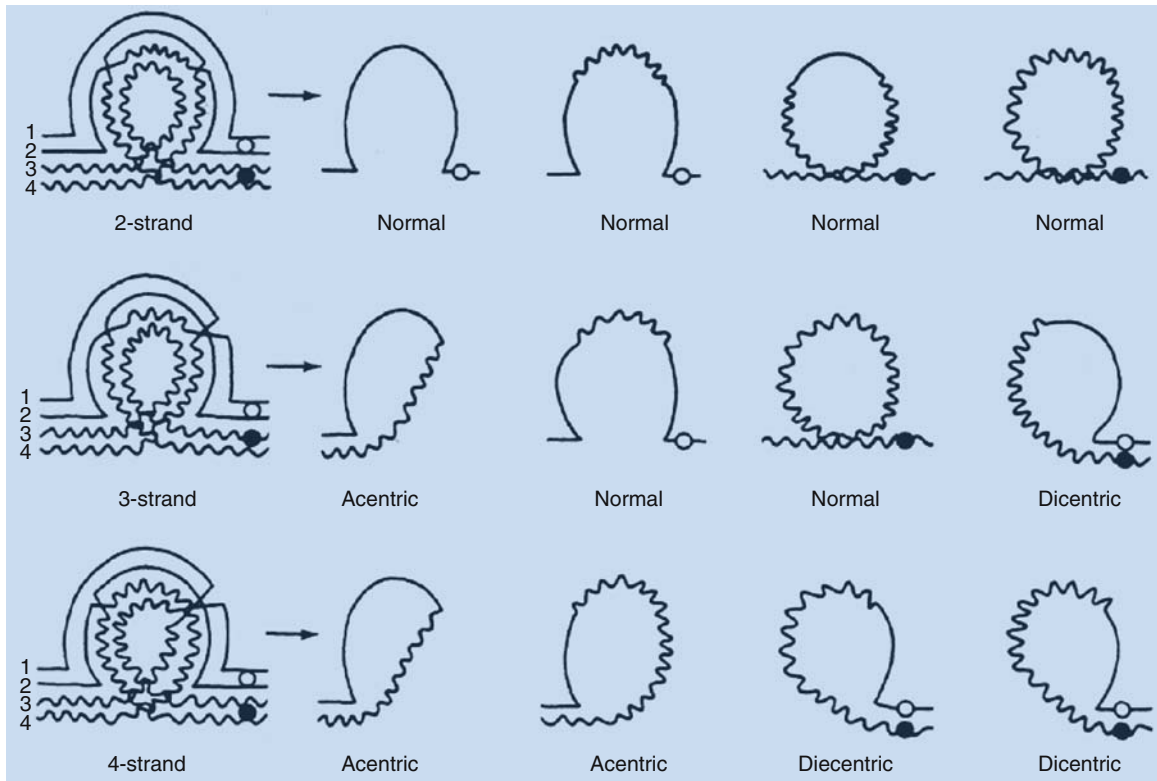


Figure 162. Double crossing over within paracentric inversions. Only 2-strand double crossing over results in two complete chromosomes. Pericentric inversion heterozygotes do not yield dicentric strands yet the overall genetic consequences of double recombination are the same as in pericentric inversion heterozygotes

orientation the host specificity genes *Sv* and *U* (→) permit the attachment of *Mu* to *E. coli* and when inversion (←) takes place the phage can be adsorbed to other host bacteria. A similar system has been observed in the phase variation of *Salmonella*. ▶ *phase variation*, ▶ *transposase*, ▶ *resolvase*; Roth JR, Schmid MB 1981 Stadler Symp 13:53; Johnson RC 2002 In: Craig NL et al (eds) *Mobile DNA II*. Amer Soc. Microbiol. Press, Washington, DC pp 230.

Invertases: These are proteins (*Cin*, *Hin*, *Gin*) involved in viral transposition and bear extensive homology with the N-terminal domains of the resolvases of transposons. In biochemistry the enzyme sucrase which hydrolyzes sucrose to fructose and glucose is also called invertase. ▶ *Cin*, ▶ *Tn*, ▶ *resolvase*

Invertebrates: These are animals without a spinal column. ▶ *genome size*: <http://www.genomesize.com/statistics.php?stats=inverts>.

Inverted Repeat: ▶ *repeat inverted*, ▶ *direct repeat*

Invertrons: These are linear mobile elements in plasmids and mitochondrial DNA. It seems that

5'-linked proteins encode DNA and RNA replication and integration functions. ▶ *Agrobacterium*, ▶ *transformation genetic*, Hermanns J, Osiewacz H D 1992 *Curr Genet* 22(6)491.

Involucre: Refers to a whorl of bracts around an inflorescence. ▶ *bract*

Involution: Denotes a degenerative type of development that is marked by a return to a more primitive or inactive state.

Iodine Stain: For coloring starch (amylose) blue-black is used, while amylopectin (dextrin) is colored reddish-brown (iodine 120 mg and potassium iodide 400 mg in 100 mL water).

lojap(ij): Refers to nuclear mutations in maize located in chromosomes 3L-90 (*ij1*) and 1L (*ij2*), respectively, causing leaf striping because of defects in the development of plastids. The *ij* gene appears to be a specific mutator of extranuclear DNA and displays normal Mendelian inheritance whereas the striping itself is maternally transmitted. Defects in plastid RNA polymerase have been implicated in this

variegation. (See Silhavy D, Maliga P 1998 *Curr Genet* 33[5]340)

Ion: This is a positively (cation) or negatively (anion) charged atom or radical. ►[electrolyte](#)

Ion Channels: Refers to pores with special passage specificity, e.g., a membrane protein when bound to acetylcholine permits the influx of sodium (sodium channel); a variety of ion channels exist (mechanically gated, voltage-gated, ligand-gated, cAMP-gated, etc.). The ion channels may have two or more subunits like the staves of a barrel. The pores may be open or closed and different loops may be associated with them (see Figs. 163 and 164). The pore loop, which is a common component of many types of ion channels, determines which ion can penetrate the pore. The anion-gated ion channels appear to be structurally different from most of the cationic channels inasmuch as they may have different subunit associations creating double or triple pores. Cis–trans isomerization at a proline opens the pore of a neurotransmitter-gated ion channel (Lummis SCR et al 2005 *Nature [Lond]* 438:248). Thousands of different odors activate in the nose the trimeric G protein, G_{olf} , which in turn activates adenylate cyclase and the cAMP-gated cation channels open and transmit the signal to the brain. Some olfactory receptors utilize the IP_3 -gated ion channels. Cyclic guanosine monophosphate (cGMP)-gated channels mediate visual perception. Light rapidly induces the formation of guanylate cyclase, generating cGMP and it is degraded by cGMP phosphodiesterase. The photoreceptors (rhodopsin pigment) are in the retina of the eye. Voltage-gated Ca^{2+} ion channels regulate the influx of calcium through the plasma membrane. The mechanosensitive ion channels sense forces from the lipid bilayer without proteins (Kung C 2005 *Nature [Lond]* 436:647). Mechanical stimuli may affect Ca^{2+} and other ion channels. The L-type ion channels of the neurons may be shut off when the intracellular level of calcium increases beyond a point. The Ca^{2+} ions then serve as widespread intracellular messengers and regulate many diverse cellular functions, particularly the secretion of neurotransmitters. Their modulation is due to the $\beta\gamma$ subunits of the trimeric G protein. The glutamate receptors, permeable to Na^+ , K^+ , and Ca^{2+} , are gated by glutamate in eukaryotes and prokaryotes. The autosomal dominant human disease, *periodic paralysis*, appears to be caused by an amino acid substitution in the α subunit of a sodium channel transmembrane protein. Mutation in sodium channel SCN5A may slow down myocardial conduction and may lead to life-threatening cardiac arrhythmias. Cystic fibrosis is due to a defect in the transmembrane conductance regulator protein kinase A and

ATP-regulated chloride ion channel. In pancreatic β cells ATP-dependent K^+ channels are important for glucose-induced insulin secretion and are targets of sulfonylureas which is used for oral treatment of non-insulin-dependent diabetes (NIDDM). Truncation of the sulfonylurea receptor (SUR) causes persistent hyperinsulinemic hypoglycemia of infancy and unregulation of insulin secretion in severe hypoglycemia. Nearly 60 human diseases are channelopathies, i.e., diseases due to defects in ion channels. The human genome contains 340 putative ion channel genes. Over 400 genes in the human genome are involved with ion channels. Channels can be inward or outward rectifying, depending on the predominant direction of the flow of the ions. The rectification is not always an intrinsic property of the channel protein but may be controlled by accessory substances, spermidine, spermine and other polyamines. Glucocorticoid stress hormones may also regulate the K channels. Ion channels regulate the expression of many genes. ►[signal transduction](#), ►[SOC](#), ►[TRP](#), ►[G proteins](#), ►[neurotransmitters](#), ►[calmodulin](#), ►[rhodopsin](#), ►[periodic paralysis](#), ►[cystic fibrosis](#), ►[IP₃](#), ►[dihydropyridine receptor](#), ►[ryanodine](#), ►[diabetes](#), ►[hypoglycemia](#), ►[sulfonylurea](#), ►[pyrethrin](#), ►[LQT](#), ►[HERG](#), ►[Andersen syndrome](#), ►[Jervell and Lange-Nielson syndrome](#), ►[Ward-Romano syndrome](#), ►[myokymia](#), ►[periodic paralysis](#), ►[hyperkalemic periodic paralysis](#), ►[hypokalemia](#), ►[convulsions](#), ►[epilepsy](#), ►[migraine](#), ►[color blindness](#), ►[glucocorticoid](#), ►[Bartter syndrome](#), ►[ataxia](#), ►[myotonia](#), ►[paramyotonia](#), ►[hyperthermia](#), ►[salt-tolerance](#), ►[patch clamp](#); Doyle JL, Stubbs L 1998 *Trends Genet* 14:92; Apse MP et al 1999 *Science* 285:1256; Hübner CA, Jentsch TJ 2002 *Hum Mol Genet* 11:2435; K^+ channel structure: Jiang X et al 2003 *Nature [Lond]* 423:33, K^+ ion selectivity: Yu S et al 2004 *Nature [Lond]* 431: 830; review of diseases: Gargus JJ 2003 *Am J Hum Genet* 72:785; channelopathy mechanisms – channel functions:

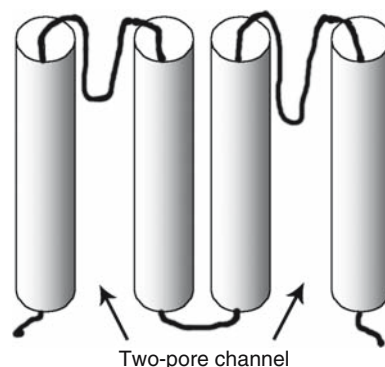


Figure 163. Two-pore channel

Ashcroft FN 2006 *Nature* [Lond] 440:440; crystal structure of voltage-dependent potassium channel: Long SB et al 2005 *Science* 209:897, potassium conductance channel crystal structure: Albright RA et al 2006 *Cell* 126:1147; Ye S et al 2006 *Cell* 126:1161, ion channel – disease reviews: *Nature* [Lond] 2006, vol. 440:439–489; <http://www.neuro.wustl.edu/neuromuscular/mother/chan.html>, ligand-gated ion channels: <http://www.ebi.ac.uk/compneur-srv/LGICdb/LGICdb.php>.

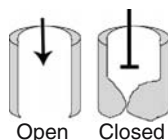


Figure I64. Open and closed ion channels

Ion-Exchange Resins: These can be cation or anion exchangers, their cross linkage determines their use for the separation of molecules of different sizes. There is a variety of ion exchange resins; they are produced by the copolymerization of styrene and divinylbenzene and various other substances and are combined to produce phosphocelluloses, diethylaminoethyl-cellulose (DEAE), carboxymethylcellulose (CMC), etc. They can be used for the separation and purification of monovalent ions or polyelectrolytes of high molecular weight.

Ion Exchangers, Cell Membrane: ► [ion channels](#)

Ion Pumps: These mediate ion transport through membranes by the use of energy (ATP). They ensure osmotic balance and convert ATP energy into electrochemical gradients that are utilized by metabolic pathways. ► [proton pump](#), ► [ion channels](#), ► [uptake selective](#); Dunbar LA, Caplan MJ 2001 *J Biol Chem* 276:29617; Gouaux E, MacKinnon R 2005 *Science* 310:1461.

Ion Trap Mass Analyzer (IT): This is used in connection with mass spectrometry. It analyzes trapped and accumulated ions in high throughput equipment. IT is fast and sensitive but may not be very accurate. ► [linear ion trap](#), ► [mass spectrum](#), ► [proteomics](#)

Ionic Bond: Refers to a non-covalent attachment between a positively and a negatively charged atom.

Ionization: This is a process for the separation of molecules into ions. ► [ion](#)

Ionization Chamber: This equipment measures the radioactivity of gases by the ionizations generated through molecular collisions. Electrodes collect the ions and the current (amplified and registered) is

proportional to the radioactivity. ► [scintillation counter](#), ► [Geiger counter](#), ► [radiation measurement](#)

Ionizing Radiation: Refers to high energy electromagnetic radiation causing intramolecular alterations (ion pairs) in organic material, thereby capable of inducing mutation and cancerous transformation in living cells. Low energy (<2eV) radiation can also cause damage to the DNA and guanine residues absorb more electrons than the other bases, especially in single-stranded DNA (Ray SG et al 2005 *Proc Natl Acad Sci USA* 102:15).

The maximum legal permissible occupational limits for human exposure during a lifetime should not exceed 0.5 mSv per year; the legal limit actually should be 0.2 mSv. 1 Sv (Sievert) = 100 rem (röntgen equivalent man); 1 rem = 1 rad of 250 kVp X-rays.

► [radiation effects](#), ► [radiation measurement](#), ► [radiation hazard assessment](#), ► [cosmic radiation](#), ► [physical mutagens](#), ► [Gray units](#), ► [radiation protection](#), ► [electromagnetic radiation](#)

Ionophores: These hydrophobic molecules are involved in ion transport through cell membranes.

Ionotropic Receptors: These receptors mediate the control of ion channels after binding the appropriate ligand. Together with metabotropic receptors they play an important role in nerve synapses. ► [metabotropic receptor](#), ► [synapse](#)

IP₃ (inositol 1,4,5-trisphosphate): This is derived from inositol phospholipid PIP₂. In response to external signals it releases Ca²⁺ from the endoplasmic reticulum. IP₃R2 and IP₃R3 receptors mediate exocrine secretion, energy metabolism and animal growth (Futatsugi A et al 2005 *Science* 309:2232). ► [phosphoinositides](#), ► [InsP](#), ► [olfactogenetics](#), ► [exocrine](#), ► [Ipk1](#), ► [Ipk2](#), ► [BCL](#)

IP₅, IP₆: These are IP₃-derived signaling molecules; IP₆ along with other phosphoinositides and nuclear pore associated proteins are required for mRNA export from the nucleus. ► [RNA export](#), ► [InsP](#), ► [nuclear pore](#), ► [Ipk1](#), ► [Ipk2](#), ► [ADAR](#)

IPCR: ► [inverse polymerase chain reaction](#)

IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked): This is caused by mutation in the region of human chromosome Xp21-Xq13.3 and encodes the FOXP3 protein involved in the regulation of transcription or RNA splicing. ► [FKH](#), ► [autoimmune disease](#); Sakaguchi S 2004 *Annu Rev Immunol* 22:531.

IPI (integrated protein index): This is an inventory of all the revealed proteins encoded by a genome. ► [IGI](#)

Ipl1: Denotes a yeast mitotic histone kinase

Ipk1 (inositol polyphosphate kinase): This converts inositol-1,3,4,5,6-pentakisphosphate (IP₅) into hexakisphosphate (IP₆). IP₆ is probably a regulator mRNA export from the nucleus and it modulates the function of synaptic vesicles by interacting with synaptogamin. ►phosphoinositides, ►Ipk2, ►RNA export, ►synaptogamins

Ipk2 (inositol polyphosphate kinase): This converts inositol 1,4,5-trisphosphate (IP₃) into inositol-1,4,5,6-tetrakisphosphate (IP₄) and inositol-1,3,4,5,6-pentakisphosphate (IP₅). It is likely that Ipk2 is the same yeast enzyme that was earlier known as Arg82, a pleiotropic kinase regulating sporulation, mating, stress, arginine metabolism and transcription. IP₄ and IP₅ may be effectors for the processes. Ipk2p may also stabilize MCM1p that is probably required for Ipk2 function. ►phosphoinositides, ►Ipk1, ►MCM

IPMDH (isopropylmalate dehydrogenase): α -isopropylmalate is a precursor of leucine and it is derived from α -ketoisobutyrate.

Ipomoea (morning glory): This is an ornamental plant with a relatively short life cycle (4 months); it has many genetic variations. (See Clegg MT, Durbin ML 2003 Nature Rev Genet 4:206)

Ipsilateral: Denotes affecting only one side. ►contralateral

IPTG: Isopropyl- β -D-thiogalactoside is a gratuitous inducer analog of the *Lac* operon. β -galactosidase; ►Lac operon, ►gratuitous inducer

IQ: ►human intelligence

I - R: ►hybrid dysgenesis

Ir: HLA genes were previously known as the immune-response genes that encode the MHC complex. ►HLA

IRA1, IRA2: These are negative regulators of RAS in yeast, antagonistic to CDC25; they are structurally related to GAP. ►RAS, ►GAP; Mitts MR et al 1991 Mol Cell Biol 11:4591.

IRAK (IL-1 activated serine/threonine kinase): A Pelle-like interleukin receptor-associated serine/threonine kinase and adaptor of the MyD88 signaling pathway. IRAK-4 protein deficiency results in lack of activation of NF- κ B and MAPK and susceptibility to infection by pyogenic bacteria. IRAK-4 is involved in the crosstalk between the innate and adaptive immune systems (Suzuki N et al 2006 Science 311:1927). ►NK- κ B, ►MAPK, ►interleukins, ►pyogenic, ►MyD88, ►Pelle, ►Toll, ►IL-1; Jensen LE, Whitehead AS 2001 J Biol Chem

276:29037; Kobayashi K et al 2002 Cell 110:191; Picard C et al 2003 Science 299:2076.

IRB (institutional review board): The board oversees professional and research activities involving primarily human objects.

IRE (iron responsive element): This is a 28-nucleotide 5'-UTR sequence in the ferritin mRNA, it is necessary for iron regulation. IRE sequences in the 3'UTR of the transferrin receptor mRNA protect the mRNA from degradation if the iron level is low. Iron is an essential element for many biological functions but beyond a certain level it may be very toxic because it reacts with oxygen to form hydroxyl radicals and damages the macromolecules. In iron deficiency the cellular metabolism is reprogrammed and some mRNAs are destroyed in order to cope with the deficient Fe level (Puig S et al 2005 Cell 120:99). The quantitative effect of *Ireb-2* iron-regulatory protein on brain degeneration has been debated (Galy B et al 2006 Nature Genet 38:967). ►ferritin, ►transferrin, ►aconitase, ►UTR, ►ROS, ►hemochromatosis, ►anemia; Andrews NC 2000 Annu Rev Genomics Hum Genet 1:175, dual structure of IRE as mRNA complex and aconitase: Walden WE et al Science 2006 314:1903.

Ire: This yeast protein kinase and endoribonuclease is functionally homologous to mammalian JNK and SAPK. Ire1 is a transmembrane protein bound in the cytoplasm to TRAF2, an adaptor protein in signal transduction. Ire signals the stress in the endoplasmic reticulum (ER) when the proteins inside are not folded properly and activation of the chaperones is needed. ER stress is monitored by PERK. ►ribonuclease L, ►JNK, ►SAPK, ►chaperone, ►PERK

IRES (internal ribosome entry site, also called RLP): This may be present in circular viral RNAs (picornaviruses) and can be translated on eukaryotic ribosomes. These viral RNAs (300–450 nucleotides) are not capped at the 5'-untranslated region and carry several AUG codons, and show specific sequences serving as ribosome landing pads. IRES alone can initiate translation and can replace the 1000-kD initiation factor complex. The 5S ribosomal protein interacts with the IRES. By contacting the ribosomes it changes the structure of both the 40S and 60S subunits. The crystal structure of one single viral IRES has been revealed (Pfingsten JS et al 2006 Science 314:1450). The interaction with ribosomes requires the cellular eIF-4F eukaryotic translation initiation factor. Recently, IRES-type elements have been found in other viruses and in eukaryotes. Many of the IRES-mediated translation products of eukaryotes are involved in important cellular processes (development, cell cycle, apoptosis). The IRES

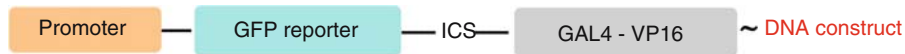


Figure I65. Positive feedback vector. It contains two cistrons; the first with an enhanced green fluorescent reporter and the second is the GA14 enhancer with viral protein V16. In between the two cistrons (ICS) are IRES elements. (Modified of Zhou, W. et al. 2005 Proc. Natl. Acad. Sci. USA 102:6273)

containing non-coding regions (5'NCR) is generally longer than the regular 5'-UTRs. The presence of IRES elements (9 or double of 9 nucleotides) permits the dicistronic transcription of genes and facilitates gene targeting, homologous recombination and modification of gene expression. The use of promoterless vector constructs positions the IRES carrying sequences within the transcribed regions rather than into the non-translated regions of the genome. The IRES elements are frequently borrowed from the encephalomyocarditis virus (EMCV) family. The advantage of this system is that it does not interfere with the regular Cap-mediated ribosome scanning. In hepatitis C virus, the IRES mediates the assembly of the translation initiation complex (Otto GA, Puglisi JD 2004 Cell 119:369). In dicistronic vectors, genes placed downstream of the IRES are transcribed more efficiently than those positioned in front of it.

The IRES elements can enhance translation and therefore their identification may help modify gene expression. The vector outlined here assists in the identification of the IRES elements (see Fig. I65). The first cistron reveals their presence by the reporter and the second cistron binds to the Gal4 upstream activating sequences and with the aid of VP16 herpes virus activator facilitates the screening and identification of the IRES elements. The *Drosophila* insulin-like receptor (dINR) pathway incorporates 4E-BP resistant cellular internal ribosome entry site (IRES) containing mRNAs, to functionally couple transcriptional activation with differential translational control in a cell that is otherwise translationally repressed by eIF-4E binding protein (4E-BP). Integrated transcriptional and translational response mechanism specifically dependent on cellular IRES coordinates an essential physiological signal responsible for monitoring nutrient and cell growth conditions (Marr MT et al 2007 Genes, Dev 21:175). ▶ [ribosome scanning](#), ▶ [dicistronic transcription](#), ▶ [targeting genes](#), ▶ [gene fusion](#), ▶ [eIF4F](#), ▶ [eIF4G](#), ▶ [picornaviruses](#), ▶ [translation initiation](#), ▶ [RLP](#), ▶ [apoptosis](#), ▶ [capping enzymes](#), ▶ [GFP](#), ▶ [GAL4](#), ▶ [VP16](#), ▶ [shunting](#); Holcik M et al 2000 Trends Genet 16:469; Pinkstaff JK et al 2001 Proc Natl Acad Sci USA 98:2770; Fukushi S et al 2001 J Biol Chem 276:20824; Hellen CU, Sarnow P 2001 Genes, Dev 15:1593; Zhou W et al 2003 Proc Natl Acad Sci USA 100:4457;

Hundsdoerfer P et al 2005 Proc Natl Acad Sci USA 102:23421; <http://www.iresite.org/>.

Iressa (Gefitinib): This is a potential inhibitor of EGFR and an anti-cancer drug. On the basis of a large-scale study in 2004 it was concluded that this drug did not provide any survival benefits for non-small cell lung cancer and it was subsequently withdrawn from the market. However, it may be beneficial for certain genetic constitutions. Humanized anti-hEGFR antibody (Cetuximab) and small molecule inhibitors of EGFR (Erlotinib or HKI-272) can lead to dramatic regression of lung tumorigenesis (Ji H et al 2006 Cancer Cell 9:485). ▶ [EGFR](#)

IRF: This is an interferon-regulatory transcription factor, a homolog of c25 rat factor. ▶ [c25](#), ▶ [p53](#), ▶ [interferon](#)

IRF4: ▶ [LSIRF](#)

IRIS: This is the circular pigmented membrane in front of the lens of the eye with the pupil in its center. The retina lines the inner surface of the eyeball (see Fig. I66). It contains capillary veins and it is connected to the optical nerve bundle (not shown in the Fig. I66). The black spot of the retina (not the actual color) may be impaired in macular degeneration. ▶ [macular degeneration](#)

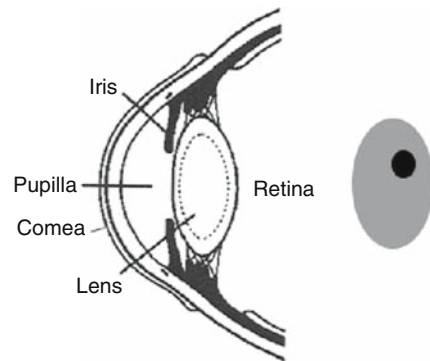


Figure I66. Retina with macula

IRIS: This is the monocot genus of perennial flowers (see Fig. I67) ($2n = 44$, *Iris germanica*).

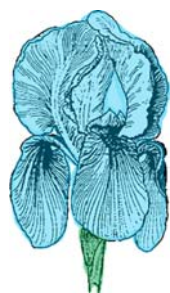


Figure I67. *Iris germanica* flower

Iris Pattern: The iris of the eye with potentially 266 distinguishable physical features provides a pattern suitable for individual identification when a computer analyzes the image recorded by a video camera (see Fig. I68). According to some scholars, this procedure is superior to any other personal identification method, including fingerprinting and DNA fingerprinting. Retinal scans can also determine identity to some degree by the pattern of the vasculature; it has been used in forensics mainly as a post-mortem test to ascertain the cause of death, such as strangulation, shaking, and some poisonous substances. ▶fingerprints, ▶fingerprinting of macromolecules; Daugman J, Downing C 2001 Proc R Soc Lond B Biol Sci 268:1737.

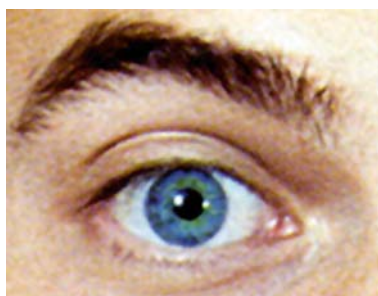


Figure I68. Iris pattern

IRM (interference-reflection microscopy): This is used to study the cell membrane and protein associations (e.g., in immunological synapse). ▶immunological synapse

IRMA (immunoradiometric assay): This uses radiolabeled antibody to quantitate a particular antigen. In the *two-site IRMA* two antibodies are used that bind different epitopes. ▶epitope, ▶ELISA, ▶radioimmunoassay; Frystyk J et al 2001 Growth Horm IGF Res 11(2):117.

Iron Age: This is a prehistoric period dating to the third or fourth millennium; it marks the beginning of recorded history.

Iron Metabolism: Several human diseases involve anomalies in iron metabolism. ▶IRE, ▶hemochromatosis, ▶transferrin, ▶Friedreich ataxia, ▶sideroblastic anemia, ▶aceruloplasminemia, ▶Hallervorden-Spatz disease, ▶ferritin, ▶porphyria, ▶anemia, Roy CN, Andrews NC 2001 Hum Mol Genet 10:2181.

Irradiation: ▶radiation

IRS: Refers to the interferon-response factor. ▶interferon

IRS: ▶insulin receptor substrate

IRS-PCR: (interspersed repetitive sequence—polymerase chain reaction): This is used with radiation hybrids as a rapid test for identifying the nature of the putative hybrid cells and also the PCR product is hybridized as a probe to a normal chromosomal complement and compare it to the previously established map. The IRS-PCR can also be used to screen cosmid and artificial chromosome libraries. ▶radiation hybrid, ▶PCR; Himmelbauer H et al 2000 Nucleic Acids Res 28[2]:e7.

IS: ▶insertion elements

Isadora: This is an 8.3 kb transposable element of *Drosophila*, generally present in 8 copies.

Ischemia: This condition is characterized by restriction of the blood vessels. It may be a major cause of stroke. For gene therapy, the introduction of anti-apoptotic genes, interleukin-1 receptor antagonists, angiogenesis activating vascular endothelial growth factor, superoxide dismutase, etc. have been considered. Among the genetic vectors, injecting adenovirus and herpes virus into the brain or into spinal artery has yielded promising results. ▶stroke, ▶apoptosis, ▶interleukin, ▶VEGF, ▶adenovirus, ▶herpes, ▶superoxide dismutase, ▶alcohol, ▶cardiac diseases

I-Sce1: This is an unusual restriction endonuclease, encoded by yeast mitochondrial introns. It recognizes 18 bp sequences, in the mouse genome it cuts only once per 7×10^{10} bp, i.e., less than once in ten times the size of the total mouse genome. In a modified form it is useful for studying the consequences of double-strand breaks and the mechanism of homologous recombination. ▶restriction endonuclease, ▶double-strand break, ▶homologous recombination; Rouet P et al 1994 Proc Natl Acad Sci USA 91:6064.

ISCNT: Refers to the interspecies somatic cell nuclear transfer technique. ▶nuclear transplantation

ISGF-3: ▶APRF

Isgylation (interferon modulated gene): This plays a ubiquitin-like role in various cellular processes.

►ubiquitin, ►interferon; Malakhova OA et al 2003 *Genes, Development* 17:455.

ISIS (isotype-specific inhibitory sequence): Various types of antisense constructs are effective in reducing or eliminating gene translation. ►antisense technologies, ►isotype

Island Model of Populations: A group of subdivided populations exchanges m alleles with each other regularly and also has a chance to receive alleles at a constant $m - 1$ rate from an earlier population. The situation resembles that of a drift in a single population under migration pressure. The model assumes that each subpopulation has the same size and is equidistant from each other. The continuous model version considers equal density at any point and the discontinuous version assumes that the subpopulations are clustered at nodal points of a lattice. Each of these distributions may be one- or two-dimensional. The discontinuous model is also known as the stepping-stone model and it may be three-dimensional. All variations of the basic model have been criticized because most of the basic stipulations may not be met under natural conditions. (See the theoretical details in Cavalli-Sforza LL, Bodmer WF 1971 *The Genetics of Human Populations*, pp 423 ff.)

Isoacceptor tRNAs: This group of different tRNAs accepts the same amino acid. The identity of a specific isoaccepting tRNA is determined by particular nucleotide sites within the group. The anticodon may serve as an identity site, however the six serine tRNAs do not share a common anticodon base. The nucleotide 73 is a discriminator base and the first base pairs within the acceptor stem. The long variable arm of the tRNA^{Ser}, the extra G1:C73 bp in tRNA^{His}, and the G3:U70 bp in tRNA^{Ala} can characterize *E. coli* tRNAs. In other species identity may be differently determined. The anticodon-flanking nucleosides may play an important discriminating role. ►tRNA, ►aminoacyl-tRNA synthetase, ►wobble, ►protein synthesis, ►transcript; Heyman T et al 1994 *FEBS Lett* 347[2–3]:143; Chaley MB et al 1999 *J Mol Evol* 48[2]:168; Crain PF et al 2002 *RNA* 8:752; Agris P 2004 *Nucleic Acids Res.* 32:223.

Isoalleles: These are wild type alleles which can be distinguished only by special techniques. ►allele, Harris MJ, Juriloff DM 1989 *J Hered* 80[2]:127; King JL 1974 *Genetics* 76:607.

Isoallotype: Refers to variable antigens of one immunoglobulin (IgG) molecule subclass which are invariant on the molecules of another subclass or subclasses. ►allotype; Delacroix DL et al 1986 *Mol Immunol* 23[4]:367.

Isoantigen: This is an allelic variant of an antigen within the species. ►alloantigen

Isobrachial: This means that the two arms of a chromosome are identical (see Fig. 169). ►isochromosome, ►chromosome arm, ►chromosome morphology



Figure 169. Isobrachial chromosome

Isochores: Refers to segments (generally larger than 200 kb) of the DNA of higher eukaryotes having rather homogeneous GC or AT content. Usually one light and two or three different heavy components can be separated by buoyant density centrifugation in the presence of certain ligands, e.g., silver ions (Ag^+). In the mammalian genome the GC-poor isochores represent about 62% and the GC-rich and GC-very rich isochores constitute 22% and 3–4% of the genome. Genes within isochores have base content characteristic of isochores. In high GC isochores the gene concentration is much higher than in the AT-rich areas. Isochores may affect codon usage and replication pattern. The cytologically identifiable Giemsa-stained bands are low in GC, the T bands are high and the R bands occupy a position in between. Because of the high GC content of the T bands, their codon usage is biased. R bands and G/R borders are characterized by a higher frequency of chromosomal exchanges (breakage and chiasmata). Viral and transposon integration sites are correlated with the base composition of the elements; sequences similar to their own are the preferred targets. The origin of isochores has been attributed to natural selection or variation in mutational bias. Recent evidence supports the latter view. ►CpG islands, ►chromosome banding, ►codon usage, ►transposons; Bernardi G 2000 *Gene* 241:3; Galtier N et al 2001 *Genetics* 159:907; Vinogradov AS 2005 *Nucleic Acids Res* 33:559.

Isochromatid Breaks: Refers to damage simultaneously inflicted to both chromatids of a single chromosome (see Fig. 170). ►radiation effects

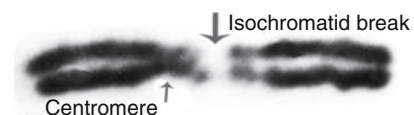


Figure 170. (Courtesy of B.R. Brinkley)

Isochromosome: This has two identical arms and is normally produced by a misdivision of a telocentric

chromosome. ▶ **misdivision**, ▶ **trisomic secondary**, ▶ **isobrachial**

Isodiametric: Its diameters (lines passing through it center) are the same in all directions.

Isodisomy: ▶ **uniparental disomy**

Isoelectric Focusing: This is an electrophoretic separation technique based on the isoelectric point of the molecules to be separated. The isoelectric point is at a pH where a solute has no electric charge and thus does not move in the electric field. For example, when, denatured protein mixture is placed in an electrophoretic gel that contains a pH gradient established by different buffers, the polypeptides migrate to their isoelectric zones. ▶ **electrophoresis**, ▶ **two-dimensional electrophoresis**

Isoelectric Point (pI): This is a point when a charged molecule in a solution—because of the pH—shows no net electric potential and consequently does not move in an electric field. ▶ **isoelectric focusing**

Isoenzymes (isozyme): These are multiple, distinguishable forms (by primary structure [electrophoretic mobility], substrate affinity, reaction velocity and/or regulation) of enzymes that catalyze the same reaction. *Sorting isozymes* are targeted to specific subcellular compartments, e.g., mitochondria, chloroplast or to different organs (see Fig. 171). ▶ **isozyme**

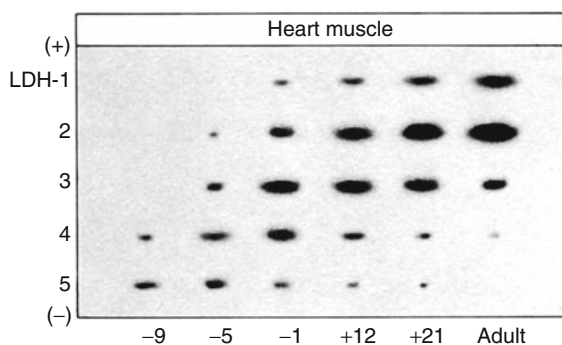


Figure 171. Lactate dehydrogenase isoenzyme profile in the heart muscles in the mouse shows dramatic changes during development. Nine days before birth, isozyme LDH-5 is predominant, and LDH-1, LDH-2 OR LDH-3 are not detectable. In the adult animal almost the opposite is true. LDH is a key enzyme in the pathway of converting sugars into amino acids, lipids, etc. The numbers at the bottom indicate days before (-) or after (+) birth. (From Markerts CL., Ursprung U 1971 Developmental Genetics. Prentice-Hall, Englewood Cliffs, NJ.)

Isorefemale: Refers to a line descended from the same female ancestor which was originally infected by a

cytoplasmically infected bacterium, e.g., in *Drosophila* by *Wolbachia*. ▶ **Wolbachia**

Isoflavones: ▶ **phytoestrogens**

Isoform: Due to differences in amino acid composition, caused by mutation or alternative splicing of the RNA transcript, RNA editing, use of alternative promoters and post-transcriptional or post-translational processing essentially the same protein is somewhat altered. Polypeptides in the cellular organelles may basically have a similar catalytic function as those residing in the cytosol or organ- or tissue-specific forms of enzymes. The human WT1 (Wilms tumor) has 24 isoforms and they all share four C-terminal C₂H₂ Zinc fingers and an N-terminal Pro/Gln-rich regulatory domain. ▶ **alternative splicing**, ▶ **splicing**, ▶ **Wilms tumor**; Hastie ND 2001 Cell 106:391.

Isogamy: Similar gametes are involved in a sexual union, e.g., in protozoa. ▶ **anisogamy**, ▶ **heterogametic**, ▶ **homogametic**

Isogenic Stocks: Their genes are represented by the same alleles at all loci. For practical purposes, isogenicity in rodents is tested by skin grafts. Grafts within inbred lines are believed to be successful but not those in between different inbred lines. Grafts from parents to F₁ are supposed to be successful but not in the opposite direction. ▶ **congenic**

Isograft: In this the genotype of the donor and recipient tissues matches. ▶ **allograft**, ▶ **heterograft**, ▶ **grafting in medicine**

Isoguanine (guanopterin, oxyadenine): This purine analog can pair with thymidine and can cause infidelity of PCR (see Fig. 172). Using 2-thiothymidine triphosphate most of the problems can be prevented because thymidine does not pair well with this purine analog although it can form three hydrogen bonds with isoguanine. Isoguanine can also form three hydrogen bonds with isocytidine. In expanding the bases to 6 – in addition to A, T, G, C – fidelity per round of PCR amplification was about 98%. Such a 6-letter alphabet although not entirely palatable to DNA polymerases, is a system capable of Darwinian evolution (Sismour AM, Benner SA 2005 Nucleic Acids Res 33:5640). ▶ **thiouracil**, ▶ **PCR**, ▶ **base analogs**

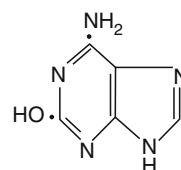


Figure 172. Isoguanine

Isolabeling: Refers to ^3H label (or other) in both daughter chromatids after one replication in ^3H -thymidine medium (or other labeling medium) at a certain tract(s) as a consequence of sister chromatid exchange (see Fig. I73). ▶ [sister chromatid exchange](#)



Figure I73. Isolabeling

Isolation Genetic: This may be determined by the presence of inversions in the population that in the case of recombination yield defective gametes. Also, since recombination within inverted segments produces defective gametes, advantageous gene blocks may be preserved as “supergenes”. Genetic isolation may be the first step in speciation. ▶ [incompatibility](#)

Isoleucine-Valine Biosynthetic Pathway : Steps 1 and 2 are controlled by identical enzymes in both pathways in several organisms and therefore genetic defects in either may generate nutritional requirement for valine [$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{COOH}$] as well as isoleucine [$\text{CH}_3\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}(\text{NH}_2)\text{COOH}$] or the accumulation of the intermediates (see Fig. I74). The *maple syrup urine disease* (MSUD) is manifested in different forms in humans and other mammals and it is caused by a block in the degradation, the decarboxylation (step 2) and accumulation of leucine, isoleucine and valine. The keto-methylvalerate accumulation then causes the characteristic maple syrup odor of the urine. One of the genes (MSUD II) has been assigned to human chromosome 1p31 and a pseudogene to chromosome 3q24. The more serious aspects of the disease are physical and mental retardation, potential coma and death. The disease is also controlled by non-allelic recessive genes, (BCKDHA [branched chain keto acid decarboxylase and dehydrogenase] locus is at 19q13.1-q13.2, BCKDHB is at 6p22-p21). Gene A is responsible for the biosynthesis of the α chain of the enzyme (BCKDHA) and locus B for the β chain (BCKDHB). In one form of the A type disease the administration of thiamin (10 mg/day) reduced hyperaminoacidemia without dietary limitations. The larger subunit (M_r 46,500) of the enzyme is part of a mitochondrial protein complex. The enzyme complex also contains

component E2 (M_r 52,000) that transfers the acyl group of the keto acid from the E1 component (protein A) to coenzyme A. The disease may be due to a single base pair change resulting in a tyrosine substitution at asparagine site 394 of protein A or to deletions of several nucleotides. The defect is detectable prenatally but carriers cannot be identified because of recessivity. The prevalence varies greatly from 3×10^{-5} to 6×10^{-3} in different ethnic groups. Defects in the transaminase reaction (step 3) may also be controlled by a common glutamic-branched-chain-amino acid transaminase. In humans, however, hypervalinemia (valinemia) is caused by a defect in a specific transaminase, resulting in the lack of ability to catabolize valine into keto-isovalerate without affecting the level of leucine and isoleucine in the blood.

MSUD III (7q31-q32) is caused by dihydrolipoamide dehydrogenase deficiency. Methyl-crotonyl-CoA carboxylase deficiency (3q25-q27) is a recessive defect in leucine catabolism without acidosis. Spinal defects result in muscular hypotony and atrophy. Isovaleric acid CoA dehydrogenase deficiency (15q14-q15) is a ketoacidosis with isovaleric academia and is similar to MSUD; the clinical symptoms include retarded psychomotor activity, vomiting and protein aversion. In the Mediterranean (North Africa) region, the disease is known as Fenugreek Tea disease because the odor of the urine is reminiscent of the extract of *Trigonella foenum graecum* L. A nitrosourea-induced mutation in mice blocks the mitochondrial pathway of branched-chain amino acids and can be used as an animal model (Wu J-Y et al 2004 J Clin Invest 113:434). ▶ [genetic screening](#), ▶ [hypervalinemia](#), ▶ [3-hydroxy-3-methyl-glutaryl CoA lyase deficiency](#), ▶ [leucine metabolism](#), ▶ [methylcrotonylglycinemia](#), ▶ [methylglutaconicaciduria](#), ▶ [hydroxymethylglutaricaciduria](#), ▶ [methacrylaciduria](#), ▶ [methylacetoaceticaciduria](#), ▶ [2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency](#); Nellis MM, Danner DJ 2001 Am J Hum Genet 68:232.

Isolocus: Refers to paralogous locus that originates from duplication of the genome. ▶ [paralogous loci](#)

Isomerase: This is an enzyme that interconverts enantiomorphs. ▶ [enantiomorph](#), ▶ [chirality](#)

Isomerism: This is a developmental anomaly displaying single organs, present normally asymmetrically in the body, in a position symmetrical on the two sides of

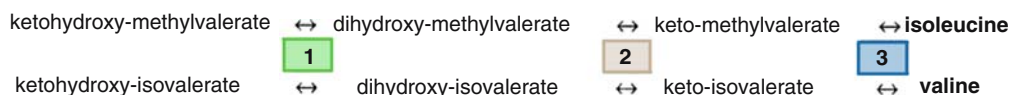


Figure I74. Isoleucine–valine biosynthetic pathway

the body axis. ▶heterotaxy, ▶situs inversus viscerum, ▶left-right asymmetry

Isomerization of Strands: One crossed over DNA strand changes into a two-strand crossover through the rotation of molecules. Isomerization occurs in a triplex formation, such as when RNA is transcribed on the DNA template (Cannon WV et al 2000 Nature Struct Biol 7:594). ▶Meselson-Radding model of recombination, ▶Hoogsteen pairing

Isomers: These are different compounds that have the same molecular formula but their structure varies. Their differences may be relatively subtle (D- and L-glucose) or may be as large as that between ethyl alcohol and methyl ether.

Isometric Phage: This is enclosed in an icosahedral or similar multifaceted globe-shape capsid. Many icosahedral viruses contain a protruding structure outside the icosahedral that serves as a packaging and injection portal (see Fig. 175). (Jiang W et al 2006 Nature [Lond] 439:612).



Figure 175. Icosahedron

Isonymy: There is a probability of kinship between individuals with the same family name. According to some scholars, the frequency of isonymous couples multiplied by a factor of 1/4 may provide information on the coefficient of inbreeding in the population. One-fourth of the married pairs have identical family names before marriage because of the inheritance of the grandfather's name through two sibs and the remaining three-quarters have different surnames. The probability of isonymy is 1/4 for first cousins, 1/16 for second cousins and 1/64 for third cousins. When multiplied by 1/4 these fractions provide the coefficient of inbreeding, i.e., $(1/4 \times 1/4) = 1/16$, $(1/16 \times 1/4) = 1/64$, and $(1/64 \times 1/4) = 1/256$ for the three types of matings, respectively. One study found that 24% of Englishmen sharing the same family name also shared the Y chromosome (King TE et al 2006 Current Biol 16:384). (See Lasker GW, Mascie-Taylor CG 2001 Ann Hum Biol 28:546)

Isopentenyladenine (6-[γ,γ -dimethylallylamino]purine): A post-transcriptionally modified base in tRNA; it is also a cytokinin plant hormone. ▶tRNA, ▶plant

hormones; Takei K et al 2001 J Biol Chem 276:26405.

Isopeptidases: These are de-ubiquitinating enzymes. ▶ubiquitin, ▶UBP

Isoprene: 2-methyl-1,3 butadiene unit of terpenoids, fragrances, rubber, etc. Isoprenylated proteins are anchored to the cell membranes (see Fig. 176). The role of the oncogene product, RAS, functions in carcinogenesis and signal transduction in isoprenylated form, attached to a farnesyl pyrophosphate. ▶RAS, ▶signal transduction, ▶membrane proteins, ▶prenylation, ▶plastoquinone; Lichtenthaler HK 1999 Annu Rev Plant Physiol Plant Mol Biol 50:47.

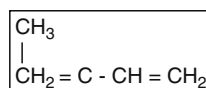


Figure 176. Isoprene

Isoprenoids: These include > 23,000 diverse compounds in viruses to mammals such as cholesterol, steroid hormones, bile acids, retinoids, isopentenyl-tRNA, sphingomyelins, ecdysone, gibberellic acid, abscisic acid, brassinosteroids, carotenoids, rubber, etc. They may function as regulators of transcription, developmental processes involving the hedgehog family of proteins, meiosis, apoptosis, etc. (See Niemann-Pick disease, SF-1, hedgehog, apoptosis, Edwards PA, Ericsson J 1999 Annu Rev Biochem 68:157; Sharkey TD, Yeh S 2001 Annu Rev Plant Physiol Plant Mol Biol 52:407)

Isopropyl Thiogalactoside: ▶IPTG

Isopticnic: These are molecules with equal density. ▶buoyant density

Isopticnotic Chromosome: This does not display the heterochromatic regions. ▶heterochromatin

Isoschizomers: These restriction endonucleases have very similar recognition sites; their cleaved ends being identical (cohesive) they are capable of joining each other, e.g.,

| | | |
|--------|----|--------------|
| Bgl II | 5' | A↓pGpApTpCpT |
| | 3' | TpCpTpApGp↑A |
| Bam HI | 5' | G↓pGpApTpCpC |
| | 3' | CpCpTpApGp↑G |

Their termini after ligation are:

GGATCT
CCTAGA

However, this juncture is no longer recognized by either of the two enzymes because the bases at the left and right ends are incompatible with both Bgl II or Bam HI.

Other isoschizomers are Hpa II 5' C↓CGG 3' does not cut when C is methylated

Msp I 5' C↓CGG 3' is indifferent to methylation

Isoschizomers SmaI (CCC↓GGG) and Xma I (C↓CCGGG) recognize the same sequence but cut it (↓) at different position. ▶restriction enzymes, ▶restriction-modification

Isosteres: These have a similar electron arrangement but different chemical structures and are used for substrate analog designs.

Isothermal: Denotes being at identical temperature.

Isotonic: The active salt concentration of this medium is the same as in the cell. A NaCl solution of 0.9% is isotonic with the human blood and can be used to maintain temporarily good osmotic conditions after substantial bleeding by injecting sterile *sol. natr.-chlor. isotonica* into the (blood vessels) venae. ▶hypotonic, ▶isotonic

Isotope Discrimination: The heavier atoms may be used less effectively than the lighter ones. ▶isotopes

Isotope-Coded Affinity Tags (ICAT): Two chemicals with biotin affinity and a thiol group are labeled with a heavy or light isotope, respectively. The experimental and the control proteins are reduced and derivatized with either the heavy or the light forms. The mixed samples are digested to obtain peptide fingerprints. The tagged fragments are analyzed by mass spectrometry after purification. Only the double peaks with 8 Da difference (i.e., the difference between the light and heavy labels) are further characterized (Gygi SP et al 1999 Nature Biotechnol 17:994). Non-isotopic labeling techniques have also been developed. ▶mass spectrometer [MALDI/TOF/MS], ▶non-isotopic labeling, ▶proteomics

Isotopes: Two or more nuclides having the same atomic number are the same elements but differ either in mass (stable isotopes, such as Hydrogen and Deuterium) or radioactive isotopes (atom) that disintegrate by emission of corpuscular or electromagnetic radiation (α , β γ rays). The latter ones are particularly useful in biology as radioactive tracers of minute amounts of labeled (H^3 , C^{14} , P^{32}) nucleotides or (C^{14} , S^{35} , I^{125}) proteins. Stable isotopes (N^{15} , C^{13} , H^2) can also be used as density labels for distinguishing old and newly synthesized molecules. The types of radiations and energies in million electron volts are H^3 : β , 0.017–0.019, C^{14} : β 0.155, P^{32} : β 1.71, S^{35} : β 0.167, I^{131} : β 0.605, 0.250, and γ 0.164, 0.177, 0.284, 0.364, 0.625, I^{125} : 0.0355, Y^{90} : β 2.24, K^{42} : β 3.6, 2.4 and γ 1.5, Cs^{137} : β 0.518, 1.17 and γ 0.663, Co^{60} : β 1.56, γ 2.33, U^{238} : α 4.180, γ 0.045, Ra^{226} is generally understood to be radium; it has a long half-life (1,620 years) and is quite stable.

It primarily emits α radiation (helium nuclei) 4.750 MeV and γ electromagnetic radiation (0.188 MeV). Radium is converted into a number of other isotopes. Among these radon, the commonly present gas diffusing from rocky soils, has a short half-life (3.825 days) yet it is usually replenished from the source. It emits α radiation and may pose an environmental health hazard if its concentration levels increase. Radium is no longer used for medical or to a very limited extent for industrial purposes because of the hazards involved in handling. Luminous watch dials are made now from fluorochromes. ▶Curie, ▶ μC , ▶fluorochromes, ▶biotin, ▶non-isotopic labeling, ▶half-life, ▶radiocarbon dating, ▶argon dating

Isotopic Graft: A group of cells or a piece of tissue is transplanted to the equivalent position of another animal.

Isotype: Refers to closely similar immunoglobulins with differences in the constant region. Sometimes the word is used in a broader sense to imply similar in constitution or sequence. ▶immunoglobulins, ▶allotype, ▶idiotype

Isotype Switching: Refers to a process of immunoglobulin gene rearrangement. ▶immunoglobulins

Isotypic Exclusion: Either only λ or κ light chains are used with any of the heavy chains for the formation of a particular antibody (both light chains cannot be used simultaneously). ▶antibody, ▶immunoglobulins

Isovaleric Acidemia (IVD): This disorder is controlled by a recessive gene in human chromosome 15q14-q15. It is characterized by sweaty feet-like odor (butyric and hexanoic acid) of the urine, dislike of protein, vomiting, anemia, ketoacidosis, high isovaleric acid content of the blood leading to injury of the nervous system. The biochemical lesion is in isovaleric acid CoA dehydrogenase deficiency. Several types of mRNAs of this gene have been identified on the basis of differences in transcription and different mutations or deletions. ▶amino acid metabolism, ▶isoleucine-valine biosynthetic pathway, ▶Jamaican vomiting sickness, ▶acetyl-CoA dehydrogenase deficiency

Isozyme: (see Fig. 177) ▶isoenzymes

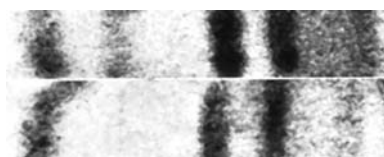


Figure 177. Fructose-1,6-diphosphate aldolase isozymes

Isozygotic: This means homozygous for all genes.

ISP45: ►mitochondrial import

ISPCR: Denotes in situ polymerase chain reaction.
►in situ PCR

ISRE (interferon sequence response element): ►signal transduction [Jak-STAT]

ISSR (inter-simple sequence repeats): Refers to repeats between non-repeated sequences of chromosomes.

IST: Denotes interaction sequence tag.

ISTR (inverse sequence-tagged repeat): This technique is used for physical mapping of genomes. (See Rohde W J 1996 J Genet Breed 50:249)

ISWI: This is the ATPase subunit of NURF and other chromatin remodeling proteins. ►nucleosome, ►nuclear receptors, ►chromatin remodeling; Nurf, Langst G, Becker PB 2001 J Cell Sci 114:2561; Xiao H et al 2001 Mol Cell 8:531; Clapier CR et al 2002 Nucleic Acids Res 30:649.

ITAM (immune receptor tyrosine-based activation motif): ►lymphocytes, ►ZAP-70, ►T cell receptor, ►BLK, ►ITIM, ►killer cell, ►osteoclast, (see Fig. I78).

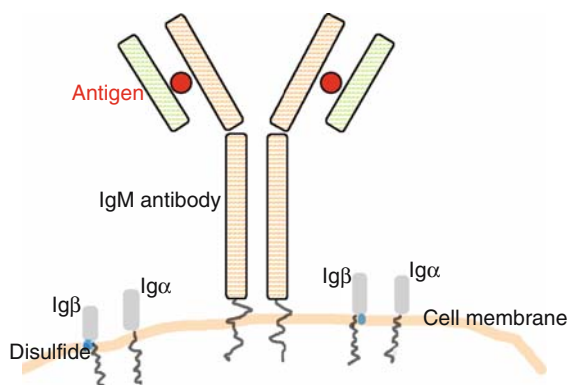


Figure I78. ITAMs are phosphorylated by Lck, Blk, Fln, Lyn and recognized by Syk. Phosphorylation and activation may be initiated by cross-linking antigen of IgM molecules

ITCH: This is E3 type ligase, its activity is promoted by phosphorylation. It plays an important role in the differentiation of lymphocytes (Gallagher E et al 2006 Proc Natl Acad Sci USA 103:1717). ►ubiquitin

ITD: ►idiopathic torsion dystonia

Iteration: This refers to repetitions; a commonly used form is the iterated integral when an individual differentiates first with respect to one of the variables while holding the other constant and then

differentiates the result with respect to the other variable. For biological experiments the distribution may be fitted to a negative binomial, requiring a similar procedure in the calculation of the maximum likelihood of values. For complex numerical iterations computer programs may be required. ►negative binomial, ►maximum likelihood

Iterative Crosses: These are used in breeding programs such as three-way and double-crosses employed for the testing or production of hybrid maize. ►heterosis

Iterative Truncation (ITCHY, incremental truncation for the creation of hybrid enzymes): This method is used to generate hybrid enzymes by fusing truncated N- or C-terminal fragment libraries. The technique of creation enhanced cross over between non-homologous proteins has been termed SCRATCHY (Kawarasaki Y et al 2003 Nucleic Acids Res 31(21):e126). The DNA coding sequences are progressively reduced with the assistance of exonuclease III before ligating the “single-crossover” hybrid library. The new coding sequence may be the same length as the “parental” ones except that parental contribution to the hybrid may vary. The components of the newly created protein may be as different as prokaryotic and eukaryotic. ►protein engineering, ►DNA shuffling; Ostermeier M et al 1999 Proc Natl Acad Sci USA 96:3562; Lutz S et al 2001 Proc Natl Acad Sci USA 98:11248; Griswold KE et al 2005 Proc Natl Acad Sci USA 102:10082., see Fig. I79)



Figure I79. Iterative truncation

Iterons: These multiple, short DNA repeats may bind to the plasmid replication protein and may either initiate or inhibit replication. (See Chatteraj DK 2000 Mol Microbiol 37[3]:467)

Iteroparity: Reproduction takes place on more than a single occasion.

ITG: ►integrin

ITIM (immunoreceptor tyrosine-based inhibitory motif): Typically, the cytoplasmic domain of these molecules contains six amino acids Ile/Val/Leu/Ser)-X-Tyr-X-X-(Leu, Val) where X can be any amino acid. A

balance between activation (ITAM) and inhibition motifs determines the development of the immune system (NK). Clustering of these receptor sites is induced by ligands and a Src type kinase phosphorylates the tyrosine residue. Such an event facilitates the recruitment of SH2 domain phosphatases such as SHP-1 and SHIP. PIR-B attenuates B cell receptor activation in cooperation with SHP-1. Other targets are Sky, BLNK, BASH, phospholipase C, FcγR, etc. ▶killer cells, ▶ITAM, ▶SH2, ▶SHP-1, ▶SHIP, ▶PIR, ▶Sky, ▶BLNK, ▶B lymphocyte receptor, ▶BASH, ▶phospholipases, ▶FcγR, ▶KIR, ▶DAP; Ravetch JV, Lanier LL 2000 Science 290:84.

ITK: This is a non-receptor tyrosine kinase of the Tec family; it signals to TCR. ▶TCR, ▶Tec

ITP: Denotes inosine triphosphate. ▶hypoxanthine, ▶inosine

ITR: Refers to inverted terminal repetition such as observed in human adenovirus DNA. ▶adenovirus

ITS: Internal transcribed spacers are short sequences within eukaryotic pre-tRNA transcription units (5' 18S - ITS - 5.8S - ITS - 28S 3'), and these clusters are separated by external tran-scribed spacers. Their analysis facilitates identification of different strains. ▶ETS, ▶tRNA; Fujita SI et al 2001 J Clin Microbiol 39:3617; ITS2 database: http://darwin.uvigo.es/software/modeltest_server.html.

IU: ▶IU

IUCD (intrauterine contraceptive device): This method prevents implantation of the egg. Although it is an effective method of birth control, it may lead to infection and may cause some discomfort.

IUGT (in utero gene transfer): Used to correct genetic defects of somatic cells by transfer of gene(s) into the unborn fetus. Its advantage is that it can be applied early during embryonic development before irreversible damage occurs, e.g., in various neurological diseases (Tay-Sachs, Niemann-Pick, Lesh-Nyhan, Sandhoff, Leigh, leukodystrophies, gangliosidoses, immunological disorders, thalassemias, osteopetrosis). It is less likely that IUGT involves vector or cell rejection. The treatment of hematopoietic stem cells may be more successful. Animal experiments have yielded encouraging results. Its drawbacks are the potential risk to the mother and the fetus. Also, the vector DNA may cause undesirable insertions or mutations in the germline. ▶ART, ▶gene therapy, Heikkila A et al 2001 Gene Ther 8:784.

IUI: ▶intrauterine fertilization, ▶ART

Ivemark Syndrome: ▶asplenia

Ivermectin: An antibiotic used to treat parasitic infections.

IVET (in vivo expression technology): This technology selects specifically induced bacterial genes that are expressed when bacteria are committed to infection or passage through a host.

IVIG (intravenous immunoglobulin gamma): Its administration provides polyclonal anti-inflammatory effectiveness against autoimmune cytopenias, Guillain-Barré syndrome, myasthenia gravis, anti-Factor VIII autoimmune disease, dermatomyositis, vasculitis (inflammation of the blood vessels) and uveitis (eye inflammation). ▶cytopenia, ▶Guillain-Barré syndrome, ▶myasthenia, ▶anti hemophilic factors, ▶polyomyositis

IVF: ▶in vitro fertilization, ▶ART

IVS: Refers to intervening sequences, they are the same as introns. ▶introns

Ixodoidea (ticks): Group of insects, that are common carriers of *Borrelia* infection, causing Lyme disease and viral infections resulting in encephalitis (see Fig. I80). The insects' saliva contains anticoagulant proteins (e.g., Salp 14) that facilitate their feeding on the host and transmission of the tick-borne pathogens. ▶*Borrelia*, Narasimhan S et al 2004 Proc Natl Acad Sci USA 101:1141.



Figure I80. Tick

Izumo: An immunoglobulin-like sperm protein that mediates sperm fusion with the oocytes.

Historical vignettes

Professor TH Morgan in *The American Naturalist* 60, p. 490 (1926)

“...except for the rare cases of plastid inheritance, the inheritance of all known characters can be sufficiently accounted for by the presence of genes in the chromosomes. In a word the cytoplasm may be ignored genetically.”

In his *A History of Genetics* (Harper & Row, New York, 1965) AH Sturtevant comments on the significance of Walter S. Sutton's papers (Biol. Bull. 4:24 [1902] and *ibid.* 231 [1903]) on the correlation between chromosomal segregation and the Mendelian laws:

“With this paper, this phase of the history is finished. The conclusions were not at once generally accepted, but they could not be disregarded and stand today as essentially correct. At last, cytology and genetics were brought into intimate relation, and results in each field began to have strong effects on the other”.

(It may be worth noting that Sutton, a student of the great EB Wilson, never completed his graduate studies at Columbia University and without a Ph.D. he went on to become a MD and a distinguished practicing surgeon. He also had special engineering talents but quit cytology and genetics where he made such a lasting impact. Sutton died at the age of 39. [See Crow EW & Crow JF 2002 *Genetics* 160:1])

J

J Base (β -D-glycosylhydroxymethyluracil): This occurs in the repetitive DNAs of protozoa and its presence is correlated with a J-binding protein and with the epigenetic silencing of telomeric surface glycoprotein genes (see Fig. J1). These surface glycoproteins mediate antigenic variations of *Trypanosomas* and other related parasites. ▶pyrimidine, ▶antigenic variation, ▶*Trypanosomas*; Sabatini R et al 2002 J Biol Chem 277:958; Yu Z et al 2007 Nucleic Acids Res 35:2107.

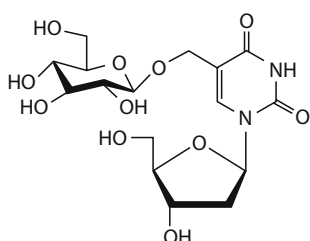


Figure J1. J base

J Chain: A 15-kDa polypeptide that is involved in the formation of antibody molecules. ▶immunoglobulins

J Chromosome: A J-shaped chromosome moving toward the pole (see Fig. J2).



Figure J2. J chromosome

J Gene: ▶immunoglobulins, ▶J chain

J Protein: ▶HSP

JAB (Jun activation-domain-binding protein): A co-activator of AP1 transcription factor functioning by transactivating c-Jun and JunD. It interacts with the $\beta 2$ subunit of LFA-1. It may switch off cytokine signaling. ▶AP, ▶Jun, ▶transactivator, ▶SOCS-box, ▶CIS, ▶LFA; Harding TC et al 2001 J Biol Chem 276:4531.

$$\tilde{\theta} = n\hat{\theta} - (n-1) \frac{\sum_{i=1}^n \hat{\theta}_i}{n}$$

Jackknifing: A statistical device for the estimation of bias and variance of genetic parameters without

providing essential estimates on the distribution of the estimates. The jackknife estimator of a parameter is presented here where $\hat{\theta}$ is the usual estimator using the complete set of n observations. In the jackknife procedure each sample member in turn is omitted from the data, thus generating n separate samples each of $n-1$ size. This method may be used for the estimation of the size of misclassification in conjunction with discriminant analysis. ▶discriminant function, ▶bootstrap; LaPointe FJ et al 1994 Mol Phylogenet Evol 3(3) 256.

Jackpot Mutation: This occurs early during the growth of a population and is represented by more copies than mutations, which occur late. Jackpot mutations may bias the calculations of the mutation frequency if not identified. ▶mutant frequency

Jackpot Vessel: In a series of dilutions or in a fluctuation test one vessel has more than the expected number of cells caused either by a clump of cells or a pre-existing mutation. ▶fluctuation test

Jackson Laboratory Backcross DNA Panel Map Service: This makes available DNA from the reciprocal mouse crosses (C57BL/6J x *Mus spretus*), characterized by SSLP markers, proviral loci and several other sequences. Information: Lucy Rowe or Mary Barter, Jackson Laboratory, 600 Main Str., Bar Harbor, ME 04608, USA. Phone: 207-288-3371 ext. 1687. Fax: 207-288-5079, lbr@aretha.jax.org (L. R.) or meb@aretha.jax.org (M. B.)

Jackson-Lawler Syndrome: is a keratosis of the skin and may involve teeth already at birth. It is caused by mutations at two chromosomal loci 17q12-q21 and 12q13. ▶keratosis, ▶ichthyosis

Jackson-Weiss Syndrome: ▶Crouzon syndrome, ▶Pfeiffer syndrome, ▶Apert syndrome

Jacobsen Syndrome: This dominant fragile site involves human chromosome 11q23.3 and is located at a distance of 100 kb from the CBL2 oncogene and CCG repeats. This trinucleotide repeat is also called FRA11B. The CpG repeats are liable to methylation. It involves growth and psychomotor retardation, anomalies of the face, finger and toe development. ▶fragile sites, ▶FMR1, ▶trinucleotide repeats, ▶Huntington's chorea, ▶ataxia, ▶Machado-Joseph disease, ▶Kennedy disease, ▶dentatorubral-pallidolysian atrophy

Jak Kinases (Janus tyrosine kinases): Jak3 is required for the progression of the development of B lymphocytes. Jak kinases are involved in the transmission of interleukin signals. ▶signal transduction by interferon signaling, ▶interleukins,

►**immunosuppression**; O'Brien KB et al 2002 J Biol Chem 277:8673.

Jak-STAT Pathway: Several Jak kinases, signal transducers and activators of transcription (STATs) regulate the signal transduction of interleukins and interleukin-mediated transcription. The pathway may be activated by interferons, phospholipase C (PLC), growth hormones, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). The SOCS/JAB/SSI and CIS proteins exert negative control. The Jak-STAT pathway regulates heterochromatin in the cell. Over-expression of Jak can lead to tumorigenesis in *Drosophila* and disruption of the pathway can suppress tumorigenesis (Shi S et al 2006 Nature Genet 38:1071). This pathway is missing from *Caenorhabditis*. ►**PDGF**, ►**EGF**, ►**CSF**, ►**signal transduction**, ►**SOCS**, ►**JAB**, ►**SSI**; Schindler C, Darnell JE 1995 Annu Rev Biochem 64:621; Hilton DJ 1999 Cell Mol Life Sci 55:1568; O'Shea JJ et al 2002 Cell 109:S121; Schindler CW 2002 J Clin Invest 109:1133.

Jamaican Vomiting Sickness: This is caused by the consumption of unripe ackee fruit, a common food of the people of the island. The obnoxious component of the fruit hypoglycin A may reduce blood glucose content to 10 mg/100 mL and may even cause death. The compound is a specific inhibitor of isovaleryl-CoA dehydrogenase, and isovaleric acid accumulates in the blood leading to depression of the central nervous system. The poisoning has a similar effect as human isovalericacidemia. ►**sovalericacidemia**

Jamm Domain (Jab1/MPN domain-associated metallo-peptidase): It has a functional role in the proteasome lid. ►**Jab**, ►**MPN**, ►**protease**, ►**metalloprotease**; Ambroggio XI et al 2004 PloS Biol 2:E2.

Jansky-Bielschowsky Disease: ►**ceroid lipofuscinosis**

Janus Kinases: These include Jak kinases and Tyk2; they are non-receptor tyrosine phosphorylating enzymes. ►**Jak**

Jarcho-Levin Syndrome: ►**spondylocostal dysostosis**

Jarovization (yarowization): ►**vernalization**

Jasmonic Acid ([\pm]-1 α ,2 β -[Z]-3-oxo-2-[2-pentenyl]cyclopentanecarboxylic acid): is a fatty acid derivative protease inhibitor in plants and an activator of stress response genes in case of infection or wounding. Furthermore it controls a number of developmental processes (see Fig. J3). Jasmonate regulates catabolism of amino acids in the gut of herbivores and plays a role in protection against insects (Chen H et al 2005 Proc Natl Acad Sci USA 102:19237). Around 20 jasmonates and their conjugates perform complex and far-reaching regulatory roles. Several genes have

been identified in the pathways. Jasmonate signaling appears to mediate long distance information transmission; systemic transcriptional response shares an extraordinary overlap with the local herbivory and wounding responses, indicating that jasmonates may be pivotal to an evolutionarily conserved signaling network that decodes multiple abiotic and biotic stress signals (Truman W et al 2007 Proc Natl Acad Sci USA 104:1075). JAZ proteins (jasmonate ZIM domain proteins) function as repressors of jasmonate signaling and are degraded through the SCF^{COI1}-dependent 26S proteasome pathway. Protein-protein interaction studies indicate that jasmonoyl-isoleucine (JA-Ile) specifically promotes COI1-JAZ1 interaction in the absence of other plant proteins (Thines B et al 2007 Nature [Lond] 448:661; Chini A et al 2007 Nature [Lond] 448:666). ►**plant defense**, ►**wound response**, ►**insect resistance in plants**, ►**SCF**; Seo HS et al 2001 Proc Natl Acad Sci USA 98:4788; Turner JG et al 2002 Plant Cell 14:S153; Gfeller A, Farmer EE 2004 Science 306:1515.

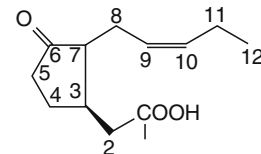


Figure J3. Jasmonic acid

Jaspar: This is the eukaryotic transcription factor binding profile database: <http://jaspar.cgb.ki.se>.

Jaundice (icterus): This may be caused by hyperbilirubinemia and is characteristic of several hereditary syndromes. ►**kernicterus**, ►**hyperbilirubinemia**

Java: This is a commercially available computer language for various applications.

Java Man: A representative of *Homo erectus* with a small cranium (brain \approx 815–1067 cm²) and robust jaws who lived about 100,000 years ago. ►**hominids**

JE: PDGF (platelet-derived growth factor) and serum-inducible cDNA. ►**PDGF**

Jefferson, Thomas: President's paternity. ►**Y chromosome**

Jellyfish: <http://www.ucis.uci.edu/biochem/steele/default.html>.

Jervell and Lange-Nielsen Syndrome: This is 21q22.1-q22.2 and 11p15.5 recessive heart and auditory (deafness) syndrome. In the electrocardiograms the interval Q - T is prolonged. In this method the excitation of the heart atrium is denoted by the P wave, followed by the QRS complex of deflections

and excitations (depolarization) of the ventricles, and the T waves indicate the repolarization of the ventricles. Fibrillations (uncoordinated arrhythmia) of the heart atrial muscles are also observed as a consequence of deficiency of potassium and/or sodium ion channels. Sudden death may occur. ▶heart disease, ▶deafness, ▶electrocardiography, ▶LQT, ▶HERG, ▶Ward-Romano syndrome, ▶Beckwith-Wiedemann syndrome, ▶ion channels; Neyroud N et al 1997 Nature Genet 15:186.

Jesuit Model: There are more potential replicational origins than actually selected in eukaryotes. ▶replication bubble

Jews and Genetic Diseases: Common diseases among Askenazi Jews are Riley-Day syndrome, Tay-Sachs disease, Gaucher's disease, Niemann-Pick syndrome, diabetes mellitus, pentosuria, dystonia and colorectal cancer. About 1% of women carries deletions at various positions in the BRCA1 and BRCA2 breast cancer genes, Cohen syndrome, Canavan disease, pentosuria and PTA deficiency disease. Diseases that are rare in this group include juvenile form of Gaucher's disease, Glucose-6-phosphate dehydrogenase deficiency and, Bloom's syndrome. A common disease among *Sephardic Jews* is Mediterranean fever, whereas Tay-Sachs disease is uncommon. Among *Oriental Jews* of Persian origin, hypoaldosteronisms and Dubin-Johnson syndromes are relatively common. In Libyan Jewish populations, Creutzfeldt-Jakob disease is disproportionally common. There is no valid explanation for these differences in the incidence of diseases (gene frequencies). It has been suggested that genetic drift in small isolated populations may be the cause. The fact that most of these diseases are based on mutations at different sites within the respective loci is at variance with this argument. The high incidence of Tay-Sachs, Gaucher, and Niemann-Pick diseases involves lysosomes but how this could be the cause is unclear. Selective advantage of the heterozygotes, specific for these particular populations has also been considered. See diseases at separate entries, ▶Ashkenazim, ▶Sephardic, ▶human intelligence, ▶Amish, ▶founder principle, ▶evolutionary distance, ▶aspartoacylase deficiency, ▶ethnicity; Adam A 1973 Isr J Med Sci 9:1383; Ostrer H 2001 Nature Rev Genet 2:891; Risch N et al 2003 Am J Hum Genet 72:812.

JIL-1: A chromosomal kinase which may upregulate gene expression in the single Y chromosome of *Drosophila* male. ▶dosage compensation

Jimpy Mice: This is a special strain of mice with a lower rate of cerebroside synthesis resulting in neurological defects. ▶cerebroside

Jimson Weed: ▶*Datura stramonium* (see diagram of seed capsule) (see Fig. J4).

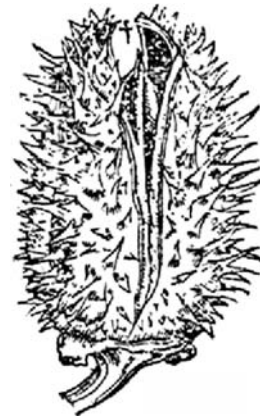


Figure J4. *Datura*

JIP: This is a JNK-interacting protein. ▶JNK

JNK (Jun amino terminal kinase): This kinase acts on the amino terminal of Jun oncogenes and other transcription factors. It is the same as SAPK. It belongs to the MAK family of protein kinases that are activated by stress (environmental stress, heat shock, tumor necrosis factor, etc.). SAPK appears to be inhibited by p21, a transforming protein. The activated JNK stimulates the transcriptional activity of AP1. The JNK interacting protein-1 (JIP-1) causes the retention of JNK in the cytoplasm and thus inhibits JNK-regulated gene expression. JNK signaling activates CD4 helper T cells (T_H), which during clonal proliferation release interleukins and become T_{H1} and T_{H2} effector cells and mediate inflammatory responses. JNK is also involved in the mitochondrial release of cytochrome c and the apoptotic path. Obesity increases JNK activity and JNK1 deficiency results in reduced adiposity and improves sensitivity to insulin (Tuncman G et al 2006 Proc Natl Acad Sci USA 103:10741). ▶aging, ▶SAPK, ▶MAPK, ▶p21, ▶p38, ▶T cell, ▶interleukins, ▶AP1, ▶Pyk, ▶JUN, ▶ATF2, ▶ELK, ▶NFAT, ▶MLK, ▶TRAF, ▶ASK1, ▶aspirin, ▶Ire, ▶apoptosis, ▶transdetermination, ▶insulin, ▶obesity; Davis RJ 2000 Cell 103:239; Bagowski CP, Ferrell JE Jr 2001 Curr Biol 11:1176; Weston CR, Davis RJ 2002 Curr Opin Genet Dev 12:14; Sabapathy K et al 2004 Mol Cell 15:713.

Jockey: ▶non-viral retrotransposable elements

Johanson-Blizzard Syndrome (JBS, 15q14-q21.1): This is a recessive pancreatic (UBR1) insufficiency disease characterized by nasal wing defect (aplasia), facultative scalp defects, imperforated (closed) anus,

deafness, hypothyroidism, dental defects, genitourinary malformation and generally mental retardation. In the absence of the UBR1 function intrauterine pancreatitis arises. The rate of prevalence is ~1/250,000. The UBR1 gene encodes at least four overlapping E3 ubiquitin ligases at the N-end rule pathway. ►ubiquitin, ►N-end rule, ►pancreatitis; Zenker M et al 2005 Nature Genet 37:1345.

Joining of DNA: ►ligase, ►blunt-end ligation, ►cohesive ends

Joint Probability: When two events are independent from each other, the probability of their joint occurrence can be obtained by multiplying the independent probabilities. The same rule also applies to more than two independent frequencies. Independence means that the occurrence of one has no bearing on the occurrence of the other(s). ►probability

Josephine Domain: This is a part of the ataxin-3 protein responsible for the neurodegenerative Machado-Joseph syndrome. Ataxin-3 functions as a polyubiquitin chain-editing enzyme as the Josephine domain is followed by an ubiquitin-interacting motif in spinocerebellar ataxia 3 (Mao Y et al 2005 Proc Natl Acad Sci USA 102:12700). ►Machado-Joseph syndrome; Nicastro G et al 2005 Proc Natl Acad Sci USA 103:10493.

Jost Factor: ►Müllerian inhibitory substance

Joubert Syndrome: Heterogeneous, autosomal recessive developmental defect of the human brain (cerebelloparenchymal disorder, cerebellar vermis agenesis) has been traced to human chromosome 9q34.3. The syndrome with oculo-renal defects was located to chromosome 11p12-q13.3 (Keeler LC et al 2003 Am J Hum Genet 73:656). Joubert and Meckel syndromes are associated with cilium dysfunction (Delous M et al 2007 Nature Genet 39:875). ►Meckel syndrome, ►cilia

Joule: 1 joule = 10^7 ergs, the energy expended per 1 second by an electric current of 1 ampere in a resistance of 1 ohm; approximately 0.24 calorie.

Juberg-Marsidi Syndrome: Xq12-q21 mental retardation, growth and developmental anomaly are based on mutation in a helicase. The same protein appears to be involved in X-linked α -thalassemia and mental retardation. ►thalassemia, ►mental retardation, ►ATRX

Judassohn-Lewandowsky Syndrome (pachyonychia congenita, PC1, 17q12-q21, 12q13): This is a hereditary recessive keratosis of the nails (onychogryposis), palm, sole and mouth. It is due to mutation in keratin 16. ►keratosis, ►ichthyosis

Judgment (iudicium): Denotes the power to arrive at a valid decision regarding facts that may not be fully understood. It is related to intuition, which means arriving at an understanding without conscious reasoning. Subjective expert judgment is the most important human quality in many areas of human activity. An important aspect of subjective judgment is its truth that can be assessed by Bayesian methods. ►Bayes' theorem; Prelec D 2004 Science 306:462.

Jukes-Cantor Estimate of Evolutionary Divergence: This is based on the number of nucleotide substitutions since the separation of two DNA sequences during evolution. $D = 2\alpha t$ where D = distance, α = the probability (p) that one nucleotide is replaced in time t . The separation in time $t = D/2\alpha$. ►evolutionary distance; Chen FC et al 2001 J Hered 92:481.

Jump Stations: A collection of links for genetic and biological information regarding databases, journals, news groups, etc. ►databases [general directories].

Jumonji: This is a catalytic domain of histone H3 demethylation. ►histone demethylation

Jumping Frenchman of Maine: This rare and obscure apparently autosomal recessive anomaly is characterized by very rapid emotional reactions.

Jumping Genes: These genes move in the genome because they are within transposons. ►transposable elements

Jumping Library: This is generated by circularizing large eukaryotic DNA fragments and cloning the junctions of the circle. The large fragments are obtained by using restriction enzymes that very rarely cut the DNA. ►chromosome jumping, ►linking library, ►slalom library, ►DNA library; Zabarovsky ER et al 1991 Genomics 11:1030.

Jumping Translocations: These involve one (donor) chromosome and multiple recipient chromosomes. Such unstable phenomena are common in cancers, mainly involving human chromosome 1. The break points are generally in regions of repetitions such as centromeric, telomeric and rRNA sequences. (See Levy B et al 2000 Cytogenet Cell Genet 88:25; Padilla-Nash HM et al 2001 Genes Chromosomes Cancer 30:349).

JUN (*jun*): The avian fibrosarcoma oncogene homolog JUN-A is in human chromosome 1p32-p31 and in mouse chromosome 4. Its homologs are present in other vertebrate species too and may be identical to a subunit of transcription factor AP-1. Along with the product of oncogene FOS, they activate several genes. The products of JUN and FOS are bound together with a leucine zipper and at their carboxyl

end they have a DNA-binding domain (5'-TGAGTCA-3'). They apparently form the C/EBP protein. JUN-B and JUN-D oncogenes are closely linked in mouse chromosome 8. JUN-B human homolog is in human chromosome 19p13.2. UV-irradiated mammalian cells may exit from the p-53 imposed block of the cell cycle by the induction of JUN. ▶AP1, ▶C/EBP, ▶oncogenes, ▶FOS oncogene, ▶JNK, ▶bZIP, ▶signal transduction, ▶de-etiolation, ▶UV, ▶psoriasis; Barr RK, Bogoyewitch MA 2001 Int J Biochem Cell Biol 33:1047.

Junction Complex: Refers to the assembly of various types of junctions (tight junctions, adhesion belt, desmosome) within cells. ▶gap junctions, ▶desmosome

Junction of Cellular Networks: These are integrators of molecular signals coming from different sources, and regulated by the interconnections. cAMP may represent such a *junction* because it is affected in a positive or negative manner by a variety of signals. Phosphokinase A as a *node* may then split the signals and directs them to multiple targets such as the cytoskeleton and cellular traffic, gene expression and cell growth, metabolism, ion channels, G protein-coupled receptors of signal transduction, and neuronal synapsis. Another example of a node is Cdc42, which receives signals through receptor tyrosine kinases (RTK) and G protein-linked receptors (GPCR) and then sorts them into serum response factor (SRF) and p21 activated kinase (PAK), S6 kinase affecting transcription, translation and cellular traffic. ▶signal transduction, ▶Cdc42, ▶RTK, ▶G proteins, ▶PAK, ▶S6 kinase, ▶coordinate regulation; Jordan JD et al 2000 Cell 103:193; McCarty DR, Chory J 2000 Cell 103:201; Vohradsky J 2001 FASEB J 15:864.

Junction Sequence: ▶introns

Junctional Diversification: When immunoglobulin genes are recombined to generate specific antibodies a few nucleotides may be lost or added to the recombining ends. ▶immunoglobulins, ▶antibody, ▶RAG, ▶combinatorial diversification; Wang C et al 1997 J Immunol 159:757.

Junctophilins: These are junctional membrane complex proteins. Junctophilin deficiency may lead to muscle and motor defects and Huntington's chorea type anomalies. ▶Huntington's chorea; Takeshima H et al 2000 Mol Cell 6:11; Holmes SE et al 2001 Nature Genet 29:377.

Jungles: These are chromosomal regions with a high frequency of recombination (genes). ▶deserts, ▶recombination by replication, ▶gene space

Juniper (*Juniperus communis*): This is an evergreen woody species, $2n = 22$.

Junk DNA: This term was coined in the 1970s to describe DNA that appeared without any obvious function such as some introns and spacers. It is now clear that several introns have maturase and other functions. Some of the non-coding DNA is interspecifically conserved, indicating some type of biological function. In animal chromosomes nearly 97% of the DNA is non-coding and this 'junk' DNA is predominantly intron material. Nowadays the term non-coding DNA is preferred. Contrary to earlier views, most of the bases in the DNA sequences are transcribed although all their functions are not yet known ▶ENCODE, ▶selfish DNA, ▶non-coding DNA, ▶trinucleotide repeats, ▶SINE, ▶LINE, ▶C value paradox, ▶TUF, ▶non-coding RNA, ▶antisense DNA, ▶antisense RNA; Wong GK-S et al 2000 Genome Res 10:1672.

Jurassic Period: Refers to a period nearly 190,000,000 to 137,000,000 years ago. During this period dinosaurs and reptiles were dominant although the ancestral forms of most vertebrates were also present and even primitive mammals had appeared.

Jurkat Cell Lines: These are derived from human T-cell leukemia and are used to study susceptibility to anti-cancer drugs and radiation.

Juvebione: ▶juvenile hormone

Juvenile Hormone: This is secreted in the larval state and prevents precocious metamorphosis into the pupal stage of the insect (see Fig. J5). The hormone has ethyl-polyprenyl components. Similar terpenes and terpene-related substances, e.g., juvebione (in balsam fir) and gossypol (in cotton) occur in plants and also affect the feeding insects. Synthetic hormones have been produced with similar physiological effects. ▶metamorphosis, ▶molting, ▶ecdysone, ▶pupa, ▶abscisic acid, ▶allostatin; Davey KG 2000 Insect Biochem Mol Biol 30(8-9):663; Gilbert LI et al 2000 Insect Biochem Mol Biol 30(8-9):614.

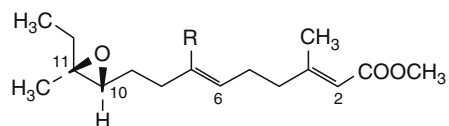


Figure J5. Insect juvenile hormone

Juvenile Mortality: Often this is a function of the consanguinity of the parents. One study, for example, noted that stillbirth and neonatal death was 0.044 if the parents were unrelated and 0.111 if the parents were first cousins (consanguinity 1/16), similarly

infant and juvenile death rates were 0.089 and 0.156, respectively. ► [coancestry](#), ► [inbreeding](#), ► [mortality](#)

Juvenile Onset: A hereditary condition appearing in childhood. ► [diabetes mellitus](#)

Juxtacrine Signaling: The membrane-anchored growth factors and cell adhesion molecules are signaled through juxtacrine mediators. ► [signal transduction](#)

JX₂ DNA: ► [PX DNA](#)

Historical vignettes

Peter Brian Medawar (cited by Colucci F et al 2002 Nature Immunol 3:807)

“The intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.”

Carl Wilhelm von Nägeli made an effort to convince Mendel about the insignificance of his experiments with peas because he felt it inconceivable that segregation in plants should obey statistical rules. Similarly, he was the founder and unbending adherent of the theory of pleomorphism of bacteria. According to this idea, bacteria did not have a stable heredity, but would change from one form to another by a change in the environment. Although Mendel's theory was not understood by his contemporaries, pleomorphism was subjected to serious criticism; yet von Nägeli's obvious influence definitely hampered bacteriology. Dr. W Migula, Professor at the College of Technology in Karlsruhe, gives a vivid account of the situation in his *System der Bakterien* (Fischer Vlg., Jena, 1897, p. 215):

“When Nägeli says, p. 20, that ‘Cohn [the founder of modern bacterial systematics in 1872] had established a system of genera and species, in which each function of the Schizomycetes [bacteria] is represented by a particular species; by this he expressed the rather widespread view exclusive to physicians. So far I have not come across any factual ground that could be supported by morphological variations or by pertinent definitive experiments.’ When Nägeli still says this in 1877, one must either assume that he was unaware of the work of the preceding 5 years, or that he chose to ignore it on purpose because it did not fit to his theory.”

K

K: ►kinase

K1: Non-nucleoidal methylation sites of *E. coli* transducer proteins, each spaced seven amino acid residues apart.

κ: ►symbionts, ►hereditary

κ Chain: ►immunoglobulins

K_a: ►dissociation constant

Ka: Thousand years before present time.

K_A/K_S: The ratio of non-synonymous and synonymous mutations. The former leads to amino acid replacement in the protein. The ratio indicates an adaptive change and it has been used to measure molecular evolution. It has been claimed that *Ka/Ks* is also strongly correlated with the mutation rate as measured by *Ks*, and that this correlation appears to have a similar magnitude as the correlation between *Ka/Ks* and selective strength. Thus the probability of correlation of fixation of non-synonymous codons and mutation rate may need reassessment of the use of *Ka/Ks* as a measure of molecular evolution (Wykoff GJ et al 2005 Trends Genet 21:381). Alternative splicing relaxes the *K_A/K_S* selection pressure in some cases by seven-fold and the same time increases the selection pressure against synonymous mutations, which in turn propagates into adjacent intron and strongly correlates with the level of alternative splicing of exons. Alternative splicing can generate evolutionary hot spots for proteins (Xing Y, Lee C 2005 Proc Natl Acad Sci USA 102:13526). *K_I* is the substitution rate within introns, *K₄* is the rate of synonymous substitution in fourfold degenerate sites. ►Grantham rule, ►molecular evolution, ►degenerate code, ►mutation beneficial, ►synonymous codon, ►alternative splicing, ►McDonald-Kreitman hypothesis; Navarro A, Barton NH 2003 Science 300:321, selection server: <http://selecton.bioinfo.tau.ac.il/>.

Kabat Database: ►immunoglobulins

Kabuki Syndrome (Niikawa-Kuroki syndrome): Mental retardation, eyelid defects, low stature, broad nasal tip, large earlobes, scoliosis, defective palates and other bone anomalies. Probably autosomal mutation is the major cause; deletions in chromosome 22q11.2, duplications in chromosome 1p13–1p22 and chromosome 8p23.1 have been reported. ►scoliosis; <http://www.orpha.net>.

KAI1: A prostate cancer antimetastasis gene at 11p11.2 (Dong J-T et al 1997 Genomics 41:25).

Kainate: Acyclic analog of glutamic acid that also forms a synaptic receptor. Kainate may be a neurotoxin and it is antihelminthic. (See Bailey A et al 2001 Eur J Pharmacol 431:305; Lauri SE et al 2001 Neuron 32:697).

Kairomones (allomones): Intraspecific and interspecific attractants similar to pheromones. ►pheromone, ►dodder

Kalanchoe: A bryophyllum of several species with chromosome numbers varying from 34 to nearly 300 among them. They have been used for studies of development and differentiation and had been a favorite subject for investigations of the effects of agrobacteria on plants. ►Agrobacterium

Kalilo: ►killer plasmids; Bok JW, Griffith AJ 2000 Plasmid 43(2):176.

K-Allele Model: Interprets mutation mechanisms. Accordingly there are *K* possible allelic states (at a gene or microsatellite) and each has a constant probability ($\mu/[K - 1]$) to undergo mutation to any of the other *K* – 1 allelic forms. In IAM *K* = infinite. ►IAM, ►SMM, ►TPM, ►microsatellite, ►minisatellite; Vitalis R, Couvet D 2001 Genetics 157:9111.

Kallikrein: Serine proteinases in the pancreas, saliva, urine, and blood plasma that cleave kallidin (a kind of kinin) from globulin and have a vasodilator and possibly some type of skin-irritating effect. (See Diamandis EP et al 2000 Trends Endocrinol Metab 11:54).

Kallmann Syndrome: Rare autosomal (8p11.2-p12, KAL2) recessive malfunction of the gonads resulting in infertility, lack of ability to smell (anosmia) and cleft palate and cleft lip. It is apparently caused by defects of the olfactory receptor neurons, in the steroid hormone receptor(s) and in the gonadotropin-releasing hormone neurons. There is also an X-linked (Xp22.3, KAL1) form of the disease. The autosomal form is about 5 times more common in males than in females. It has been suggested the X-linked 14 exons code for a cell adhesion (fibronectin) molecule. The KAL2 gene may control a fibroblast growth factor receptor, whereas KAL1 encodes a FGFR1 signaling molecule. ►FGF, ►infertility, ►hypogonadism, ►adrenal hypoplasia, ►gonadotropin-releasing hormone, ►olfactogenetics, ►N-CAM; Rugarli EI 1999 Am J Hum Genet 65:943; Dodé C et al 2003 Nature Genet 33:463.

Kam: ►K-allele model

Kammerer, Paul: Twentieth century Lamarckist who from 1905 reported hereditary changes in the coloration of salamanders and mid-wife toads by exposing the animals to yellow and dark backgrounds, respectively. The much-heralded experiments could not be confirmed under appropriate scrutiny and it turned out that the dark spots on the preserved specimens were marked by India ink rather than by genetic mechanisms. When the forgery came to light, Kammerer acknowledged the truth but denied personal fraud before committing suicide in 1926. The rumors were that an assistant or a janitor in Vienna, Austria played a practical joke on him. In the Soviet Union where he was invited as a professor, the withdrawal of his reports was never acknowledged because his claims were in line with the then current political dogmas. ▶[Lamarckism](#), Meinecke G 1973 Med Welt 24[38]:1462, in German.

Kanamycin (Km, kanamycin): An aminoglycoside antibiotic—synthesized by *Streptomyces kanamyceticus*—frequently used as a selectable marker in genetic transformation. Although some similar synthetic relatives of kanamycin are available, a specific mutant strain (12–6) of the bacterium has an amplified unit DNA (AUD), which may include more than 36 copies of the *Km* gene cluster of > 5.7 Mb and increased production (Yanai K et al 2006 Proc Natl Acad Sci USA 103:9661). ▶[antibiotics](#), ▶[antibiotic resistance](#), ▶[aminoglycoside phosphotransferase](#), ▶[transformation](#), ▶[genetic](#), ▶[vector](#), ▶[geneticin](#) (see Fig. K1).

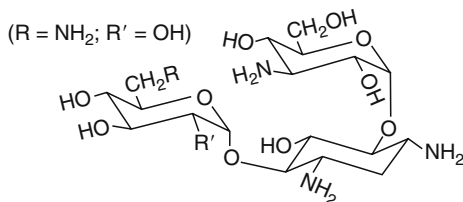


Figure K1. Kanamycin

Kangaroo: *Macropus rufus*, 2n = 20; Rat kangaroo (*Potorous tridactylus apicalis*), 2n = 13 in the male and 12 in the female.

Kanzaki Disease (Schindler Type II): An autosomal dominant lysosomal glycoaminoacid storage disease with angiokeratoma but no neurological defects. ▶[Schindler disease](#), ▶[angiokeratoma](#)

KAP: Human phosphatase with specificity for Thr¹⁶⁰ in Cdk2. ▶[Cdk2](#)

Kaplan-Meier Estimator of Survival (product limit estimator): Calculated in steps for the periods of time

of the survivor numbers of a treated experimental population. The formula at the time of the first death (t_1): $(Y_1 - d_1)/Y_1$ where Y (Y_1) stands for the residual number of animals at risk and d (or in general term d_i) = the number of death. After the second death time (t_2), the formula is $([Y_2 - d_2]/Y_2)$ and so on until t_n , when it is $([Y_i - d_i]/Y_i)$. At each step, a fraction is obtained and by multiplying these fractions we obtain the survival estimate at t_n . The cumulative hazard $H_t = -\ln \Sigma(t)$. ▶[MTD](#), ▶[LD50](#), ▶[MELD](#), ▶[genetic hazards](#); Dubin JA et al 2001 Stat Med 20:2951.

Kapok (*Ceiba*): A Southeast Asian bamboo fiber tree, 2n = 72–88 with unknown basic chromosome number.

Kaposi Sarcoma (hemangiosarcoma): Indicated by red-purple nodules and plaques that become tumorous. Occurs due to autosomal dominant genes but is also an opportunistic tumor because it is expressed mainly when some types of infections, such as *Pneumocystis* microorganisms are present as in the case in the AIDS and other immunodeficiencies.

Herpes virus KSHV/HHV8 is generally present in the tissues in a latent form as episomes. In primary effusion lymphoma (PEL) cells KSHV encodes LANA (latency associated nuclear antigen). The kaposin B protein of KSHV increases the expression of cytokines by blocking the degradation of their mRNA, which normally would be labile. Kaposin binds to mitogen-activated protein kinase (MK2), a target of the p38 mitogen-activated protein kinase signaling pathway and an inhibitor AU-rich element containing mRNAs. This is one way of activation of the latent KSHV virus (McCormick C, Ganem D 2005 Science 307:739). In PEL, the LANA and KSHV are co-localized in dots of interphase nuclei and they are in a diffuse form on mitotic chromosomes. The higher frequency and aggressiveness of Kaposi sarcoma in AIDS is explained by the synergism between the cellular basic fibroblast growth factor (FGF) and the Tat enhancer protein of the virus. A novel herpes virus (HHV8/KSHV [Kaposi sarcoma associated herpes virus]) has also been blamed for causing the disease. The HHV8 infection seems to be mediated by an interaction between the RGD peptides of the viral envelope protein and $\alpha\beta 1$ integrins. The virus transactivates the promoter of the reverse transcriptase of the telomerase. The Kaposi sarcoma virus binds to nucleosomal surface of acidic H2A-H2B folded region through the first 21 residues of the LANA antigen (Barbera AJ et al 2006 Science 311:857).

▶[acquired immunodeficiency](#), ▶[FGF](#), ▶[herpes virus](#), ▶[HHV8](#), ▶[telomerase](#), ▶[transactivator](#), ▶[MAP kinase](#), ▶[p38](#), ▶[microRNA](#); Lagunoff M et al

2001 J Virol 75:5891; Knight JS et al 2001 J Biol Chem 276:22971; Akula SM et al 2002 Cell 108:407.

Kappa Deleting Element: Assists in the rearrangement of the immunoglobulin κ chain. ►immunoglobulins; Seriu T et al 2000 Leukemia 14[4]:671.

Kappa Particles: Lysogenic bacterial symbionts that kill the sensitive hosts of *Paramecium aurelia*. ►symbionts, ►hereditary, ►*Paramecium*; Preer LB et al 1972 J Cell Sci 11[2]:581.

Kar1: Yeast protein regulating nuclear migration (congression) during karyogamy. ►cell cycle

Kar2: Cytoplasmic assembly protein regulating nuclear fusion. ►Hsp70, ►Sec63, ►karyogamy

Kar3: An 84-kDa motor protein of the kinesin family in yeast operating in nuclear fusion and microtubule sliding prior to anaphase. ►kinesin, ►cell cycle, ►mitosis

Karmellae: Nuclear-associated endoplasmic reticulum membrane components (Koning AJ et al 2002 Genetics 160:1335).

Kartagener Syndrome (dextrocardia, 9p21, 7p21, 5p15): A complex recessive syndrome of left-right inverted location of major visceral organs, also involving lack of ciliary movement and sperm motility, and nasal polyps. The basic defect seems to involve mutation in axonemal intermediate chain of dynein (DNAI1) or in the heavy chain (DNAH5). ►situs inversus viscerum, ►asymmetry of cell division, ►axis of asymmetry, ►left-right asymmetry, ►dynein, ►asthenozoospermia; Guichard C et al 2001 Am J Hum Genet 68:1030; Olbrich H et al 2002 Nature Genet 30:143.

Karyogamy: Nuclear fusion in fungi following fusion of the cytoplasms of two cells, plasmogamy. The word καρβον means kernel, γαμειν means to marry. ►fungal life cycles

Karyogram: Depiction of the karyotype (see Fig. K2). ►karyotype

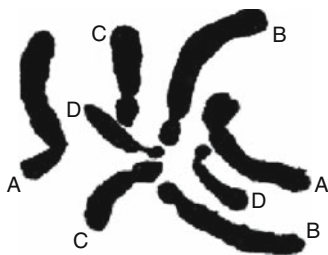


Figure K2. Karyogram of *Crepis parviflora*

Karyokinesis: Division of the cell nucleus. ►cell cycle, ►mitosis

Karyolymph: The fluid fraction of the cell nucleus in contrast to the particulate ones, for e.g., chromosomes. It is also called paralinin.

Karyopherin/importin (α and β): Cytosolic proteins that mediate nuclear traffic in cooperation with nucleoporin, with a GTPase and RAN. Importin- α (M_r 60 K) recognizes the nuclear localization sequences and importin- β (M_r 97 K) docks the nuclear pore complex. There are more than a dozen karyopherins in yeast and even more in higher eukaryotic cells. ►RNA export, ►nuclear pore, ►nuclear membrane, ►nuclear localization sequences, ►RAN, ►GTPase, ►importin, ►transportin, ►chromosome maintenance region 1, ►CAS, ►shRNA; Yoshida K, Blobel G 2001 J Cell Biol 152:729.

Karyoplast: Nucleus surrounded by only a thin layer of cytoplasm and membrane. ►cytoplast, ►transplantation of organelles

Karyosome: The mass of chromatin of the oocytes before metaphase of animal cells.

Karyotheca: Synonymous with nuclear envelope. ►nuclear membrane

Karyotype: Characteristics of a (mitotic) metaphase chromosome set by number, morphology, arm ratio, secondary constrictions, banding pattern among others. ►chromosome morphology, ►electrophoretic karyotyping, ►FISH, ►GISH

Karyotype Evolution: Chromosome number is an important characteristic of a species although identical number of chromosomes may not indicate any relationship (see Fig. K3).

The morphology of chromosomes and arm ratio are frequently used to assess similarities but substantial differences may exist within related groups and pericentric inversions may alter the relative position of the centromere. Centromere fusion and Robertsonian translocations may convert telocentric chromosomes into bi-armed ones. Misdivision may generate telocentrics from bi-armed chromosomes and change at the same time, the chromosome numbers. Paracentric inversions may serve the purpose of speciation and the sequence of change in the pattern of chromosome bands (in polytenic chromosomes or specially banded chromosomes) may be traced by the techniques of light microscopy. Translocations and other types of chromosomal aberrations may also be followed in related species. The similarities of the karyotypes can be assessed also on the basis of chiasma frequencies, if the species are closely related enough to permit meiotic analyses. FISH and GISH



Figure K3. Karyotype evolution in *Drosophila*. The haploid chromosome set in the subgenus *sophophora* of *Drosophila*. The lowest chromosomes are the X. Note the gradual fusion of the arms and chromosomes from left to right. The X chromosome of *D. anassae* probably evolved from that of *D. melanogaster* by a pericentric inversion. In *D. willistoni*, the small dot-like chromosome seems to be incorporated into the bi-armed X chromosome. (After Sturtevant AH 1940 Genetics 25:337)

are important tools of karyotyping. Chromosomal mapping of classical genetic markers or restriction fragments, sequence-tagged sites, RAPDs may also reveal the order of genes and nucleotide sequences and their evolutionary path. Karyotic changes (chromosome number and chromosome arm number) per evolutionary lineage per MY vary a great deal from 1.395 in horses to 0.025 in whales to 0.029 in other vertebrates (lizards, teleosts). ▶[chromosomal aberrations](#), ▶[inversion](#), ▶[misdivision](#), ▶[polytenic chromosomes](#), ▶[banding techniques](#), ▶[RFLP](#), ▶[RAPDs](#), ▶[sequence-tagged sites](#), ▶[polyploidy](#), ▶[evolution of the karyotype](#), ▶[fruit fly](#), ▶[FISH](#), ▶[GISH](#); Graphodatsky AS et al 2001 Cytogenet Cell Genet 92[3-4]:243, Yu K, Ji L 2002 Cytometry 48:202; Wang T-L et al 2002 Proc Natl Acad Sci USA 99:16156.

Karyrhexis: Fragmentation of the nucleus at cell death. ▶[apoptosis](#)

Kasabach-Merritt Syndrome: A condition whose inheritance pattern is unclear. Hemangioma and thrombocytopenia and other anomalies occur in infancy. ▶[hemangioma](#), ▶[thrombocytopenia](#)

Kasugamycin: Antibiotic that alters 16S rRNA and inhibits protein synthesis on the ribosome.

Katanin: An ATPase of the AAA protein family that cleaves and disassembles microtubules. ▶[ATPase](#), ▶[AAA proteins](#), ▶[microtubule](#); Hartman JJ, Vale RD 1999 Science 286:782.

Kazal (5q32): Serine protease inhibitor. Its defect may be responsible for chronic pancreatitis.

Kb: Kilobase, i.e., 1,000 bases.

Kbp: Kilobase pairs, thousand pairs of nucleotides in double-stranded nucleic acids.

KC: A cytokine protein, homologous to N51, MGSA and gro. ▶[cytokines](#), ▶[N51](#), ▶[MGSA](#), ▶[Gro](#)

KCNA: Potassium voltage-gated ion channel diseases encoded at several loci in the short arm of human

chromosomes 12 and 19, involving neurological disorders. ▶[ion channels](#), ▶[LQT](#); Charlier C et al 1998 Nature Genet 18:53.

KCNJ: A potassium/NaCl cotransporter.

K_d: ▶[dissociation constant](#)

kDa: Kilo Dalton (1,000 Da). ▶[dalton](#)

KDEL (Lys-Asp-Glu-Leu): Amino acid sequence serving as a conserved carboxy-terminal peptide in many endoplasmic reticulum (ER) luminal proteins involved in the traffic between ER and the Golgi apparatus. Proteins with KDEL are retained within the lumen. Several other motifs are also conserved in the transport systems. ▶[antibody intracellular](#), ▶[plantibody](#), ▶[ER](#); Gatti G et al 2001 J Cell Biol 154:525.

kDNA (kinetosome DNA): ▶[kinetosome](#)

KDR: A receptor for neuropilin. ▶[neuropilin](#)

Kearns-Sayre Syndrome: ▶[mitochondrial disease in humans](#), ▶[optic atrophy](#)

Keel: Two petals associated along the edge.

KEGG: ▶[Kyoto Encyclopedia of Genes and Genomes](#)

k_e Test: Detects electrophilicity of chemicals and indicating their potential to react with DNA and cause mutation or cancer. ▶[electrophile](#)

Keimbahn: ▶[germline](#) (see Fig. K4); A. Weissmann, 1885.

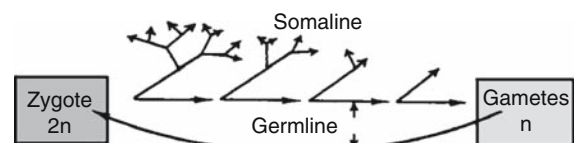


Figure K4. Keimbahn/germline

Keimplasma: ▶[germplasm](#)

Kelch Motif: First detected in *Drosophila*. Kelch repeats have propeller-like motor function and regulate motion through intercellular bridges (Xue F, Cooley L 1993 Cell 72:681)

Kell-Cellano Blood Group (KEL): The KEL antigen is a 93-kDa membrane glycoprotein, associated with the cytoskeleton and it is encoded in human chromosome 7q32 area. Its precursor substance (Kx) is coded in the X chromosome (McLeod syndrome). Its mutation may cause “horny” appearance of the erythrocytes (acanthocytosis) and granulous inflammations in response to infectious and other factors (see Fig. K5). The frequencies of the KEL and Kx alleles in England were found to be between 0.0457 and 0.9543, respectively. ▶blood groups, ▶erythrocyte, ▶McLeod syndrome; Lee S et al 2002 J Biol Chem 276:27281.

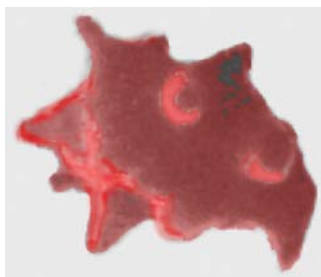


Figure K5. Horny erythrocyte

Kelp: Large brown algae.

Kelvin: Temperature scale is used primarily in thermodynamics; $0^{\circ}\text{C} = 273^{\circ}\text{K}$; the conversion between the $^{\circ}\text{C}$ and $^{\circ}\text{K}$ is: $^{\circ}\text{C} = ^{\circ}\text{K} - 273$, e.g., $100^{\circ}\text{C} = 373^{\circ}\text{K}$ or $0^{\circ}\text{K} = -273^{\circ}\text{C}$

Kenaf (*Hibiscus cannabinus*): Warm-climate fiber crop; $2n = 2x = 36$.

Ken-Box: An amino acid sequence (KENXXN/D) in degradative proteins in either the N or C terminus. ▶ubiquitin, ▶proteasome; Chen F et al 2002 Proc Natl Acad Sci USA 99:1990.

Kennedy Disease (SBMA): A non-lethal spinal bulbar muscular atrophy, sensory deficiency, frequently with gynecomastia and impotence expressed primarily in adults. The recessive gene was mapped to Xq12. The basic defect is a CAG repeat increase (11–33 CAG in normal → 38–66 in SBMA) within the first exon of the androgen receptor (AR) in the spinal cord, brains stem and sensory neurons. Glucocorticoid receptor (GR) localizes the repeat into the nucleus. Deletion or mutation in the C-terminal of GR suppressed aggregation and nuclear localization. Surprisingly mutation in the DNA-binding N-terminal domain increased aggregation and nuclear localization by

GR. Female heterozygotes for the repeats in AR are not affected and males with AR deletions do not show SBMA although usually are sterile and somewhat feminized. Increase in size is more common when the transmission is by an affected male than by a carrier female. Longer repeats increase the severity of the symptoms. [This syndrome is not named after President Kennedy's back ailment.]. ▶atrophy, ▶neuromuscular disease, ▶androgen receptor, ▶gynecomastia, ▶fragile sites, ▶trinucleotide repeats, ▶spinal muscular atrophy, ▶testicular feminization, ▶dihydrotestosterone, ▶glucocorticoid, ▶dynein

Kennewick Man: The ~9,200 year old skeletal remains of a person found in 1996 in Oregon, USA (see Fig. K6). It represents perhaps the first humans in North America. These old relics reveal important anthropological features among them the worn-down teeth due to eating wild grains loaded with dust. (See Chatters JC 2001 Ancient Encounters Simon & Schuster, New York).



Figure K6. Kennewick man

Keratin: A protein of the surface layer of skin, hair, nails, hoofs, wool, feather and porcupine quills among others. Keratins may be high-sulphur, acidic matrix proteins or low-sulphur, basic fibrous proteins (see Fig. K7). These two types usually appear in pairs and are controlled in humans by autosomal dominant genes. Point mutation in keratin genes in human chromosomes 12 and 17 may lead to various epithelial anomalies. ▶keratosis, ▶cathepsin, ▶hair, ▶melanocortin; Gene therapy: Lewin AF et al 2005 J Investig Dermatol Symp Proc 10:47.



Figure K7. Keratin fibril

Keratitis: Autosomal dominant inflammation of the cornea.

Keratoma (hyperkeratosis): Formation of keratoses on the palms and other parts of the body. Palmoplantar keratoderma (17q12-q21) is dominant epidermolytic condition due to mutation in the keratin 9 gene has potential carcinogenic consequences. Another

palmoplantar keratoma (12q11-q13) is frequently elicited by fungal infection and it is not causing epidermolysis. Striate palmoplantar keratoderma was located to 18q12.1-q12.2. Desmoplakin (6p24) mutation is responsible for striate II keratoderma. ▶keratosis, ▶Mal de Maleda

Keratosis: Either a wart-like flat or emerging (scaly) spot(s) that may become cancerous or soft friable (sometimes colored), non-invasive benign skin lesion. Both may have a number of different forms and are under the control of autosomal dominant genes. These skin lesions generally appear during adulthood but some start in very early childhood and develop progressively and may be the signals of more serious conditions (see Fig. K8). Sunburn may lead to keratosis and squamous cell carcinoma if mutation occurs in p53. ▶skin diseases, ▶psoriasis, ▶ichthyosis, ▶Darier-White disease, ▶Judasohn-Lewandowsky syndrome, ▶Jackson-Lawler syndrome, ▶pachyonychia, ▶intermediate filaments, ▶FGF, ▶dyskeratosis, ▶p53

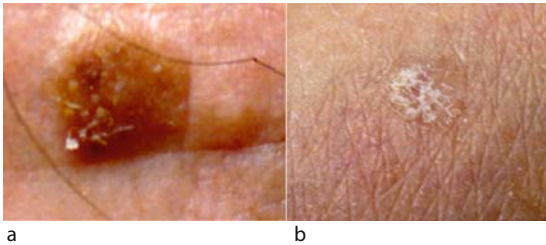


Figure K8. Keratosis on forehead (a), on leg (b). (M. Rédei, unpublished)

Kerma: Kinetic energy released to the medium upon irradiation.

Kermit: *Drosophila* transposable element (4.8 kb). ▶copia

Kernel: A “seed” (grain) covered by the pericarp (fruit) and not just with the seed-coat, such as a wheat or maize kernel; in barley it may also have glume (husks) attached (see Fig. K9).

Kernels: Regulatory subcircuits conserved in several developmental batteries of genes, representing the oldest networks of differentiation.

Kernicterus: A severe form of jaundice, afflicting the brain. ▶Icterus, ▶Crigler-Najjar syndrome

Ketoacidosis: Occurs in several human diseases when ketones accumulate due to a defect in succinyl-CoA, 3-ketoacid CoA-transferase, in diabetes mellitus, in Gierke’s disease (Type I glycogen storage disease), in



Figure K9. Wheat kernel

glycinemia, in methylmalonic aciduria and in lactic aciduria. ▶individual entries

Ketogenic Amino Acids: These include tryptophan, phenylalanine, tyrosine, isoleucine, leucine, lysine, which can serve as precursors of ketone bodies (acetoacetate, D-3-hydroxybutyrate, acetone) formed primarily from acetyl coenzyme A if fats are degraded. ▶Amino acid metabolism

Ketone: Closely resembles aldehyde; both have the same unsaturated carbonyl group (see Fig. K10).

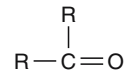


Figure K10. Keto group

Ketose: Monosaccharide with the carbonyl group being a ketone, such as fructose.

Ketosis: A condition with accumulation of ketone bodies, e.g., in diabetes mellitus.

The C = O group is generally joined to two other C atoms in the ketone bodies. ▶ketone

Ketotic: Showing ketosis. ▶ketosis

Ketothiolase: ▶methylacetoaceticaciduria

Keutel Syndrome: A human chromosome 12p12.3 area recessive defect involving lung, hearing, cartilage, and face. The gene encodes an 84-amino acid transmembrane protein MGP with a 19-amino acid signal peptide. It belongs to the family of extracellular matrix proteins. In all these proteins γ-carboxyglutamic acid is found. This residue potentiates high affinity for Ca, PO₄ and hydroxyapatite crystals and calcification of the extracellular matrix. ▶extracellular matrix, ▶Singleton-Merten syndrome

KeV (kilo electron volt): 1,000 electron volts. ▶electron volt

Keyhole Limpet Hemocyanin (KLH): A carrier protein (from *Megathura crenulata*) that can be linked to synthetic amino acid sequences with 12 to 15 hydrophobic residues through an NH₂ or COOH-terminal cysteine. The synthetic peptides can be used to raise antisera against them and these may be advantageous because their recognition is independent of the conformation of the whole protein.
 ▶antiserum, ▶monoclonal antibody, ▶hemocyanin

Key-Lock Theory: Enzymes are rigid molecules that can accommodate the substrate in the manner of jigsaw puzzles in contrast to the induced fit theory.
 ▶induced fit

KGK (keratocyte growth factor): Involved in epithelial cell development in wound repair.

KGMV (known genes with maximum variants): ▶duplication

KH Module: The K homology motif is present in the heterogeneous nuclear ribonuclear protein (RNP) K, protein, ribonuclease P, the Mer splicing modulator of yeast and the fragile X product. A common feature of these domains is the binding of single-stranded RNA.
 ▶FMR1, ▶hnRNA, ▶ribonuclease P, ▶splicing, ▶fragile X; Splicing Grishin NV 2001 Nucleic Acids Res 29:638.

KID: Kinase-inducible domain in transcription factors.
 ▶transcription factors, ▶CREB, ▶kinase

KID Syndrome: Ichthyosiformis erythroderma, deafness, and liver disease. ▶erythroderma

Kidd Blood Group (Jk): Apparently associated with human chromosome 18q11-q12. The frequency of the Jk^a allele in the world appeared to be 0.5142 and that of the Jk^b 0.4858. ▶blood groups

Kidney Diseases: Possibly caused by various environmental and genetic factors. ▶Urogenital dysplasia, ▶polycystic kidney disease, ▶renal dysplasia and retinal aplasia, ▶renal dysplasia and limb defects, ▶renal hepatic-pancreatic dysplasia, ▶renal tubular acidosis, ▶nephrosis, ▶nephrosialidosis, ▶nephritis, ▶kidney stones, ▶glomerulocystic kidney disease hypoplastic familial, ▶diabetes insipidus, ▶Bardet-Biedl syndrome, ▶Alport syndrome, ▶nephritis familial, ▶nephropathy juvenile hyperuricemic, ▶oncocytoma, ▶Addison disease, ▶glomerulonephritis, ▶renal cell carcinoma, ▶hypernephroma, ▶kidney stones, ▶glomerulonecrosis, ▶glomerulosclerosis focal and segmental familial, ▶Dent disease, ▶Fraser syndrome, ▶Goodpasture syndrome, ▶nephrolithiasis, ▶hypouricemia, ▶xanthinuria, ▶nephrotic syndrome, ▶steroid resistant, ▶Meckel syndrome

Kidney Stones (nephrolithiasis): Accumulation of primarily oxalate crystals in the kidneys caused by intestinal malabsorption of dietary salts. Polygenic and autosomal dominant control have been claimed to be responsible, although one form appears to be X-linked recessive (Xp11.22). In the X-linked form the defect is caused by various mutations in an outwardly rectifying chloride ion channel. The SLC26A6 (9p13) anion exchanger mediates Cl⁻-oxalate exchange and its defect leads to reduced intestinal oxalate secretion and increased net oxalate absorption causing bladder stones (urolithiasis). ▶kidney diseases, ▶ion channel, ▶Dent disease, ▶nephrolithiasis; Jiang Z et al 2006 Nature Genet 38:474.

KIF: A motor protein superfamily. KIF in cooperation with AP1 and other proteins facilitate vesicular transport between organelles ▶AP1, ▶kinesin, ▶midzone, ▶microtubules; Nagai M et al 2000 Int J Oncol 16:907.

Killer Cells (NK, natural killer cell): Parts of the immune system; Killer cells are large granular lymphocytes. They cooperate with other elements of the defense system to eliminate foreign organisms. The natural killer cells mount a cytotoxic reaction against invaders without prior sensitization. Similar to other lymphocytes, they kill some virus-infected cells and tumor cells. NK and CTL type T cells produce perforin, which organizes access channels on target cell membranes through which the destructive granzyme A complex is delivered. The killer cells are protected from self-destruction by means of cathepsins, which prevent perforin function on the self-membranes and thus the re-entry of granzymes (Kithiganahalli N et al 2002 J Exp Med 196:493). NK cells are controlled (inhibited) by MHC receptors, specific for Class I molecules of the major histocompatibility complex (Kim S et al 2005 Nature [Lond] 436:709). The NK cells do not express conventional receptors for antigens but their triggering is carried out by the surface molecules NKp46 (activating natural killer receptor p46, human chromosome 19), NKp30 (lymphocyte antigen 117, 6p21.3-p21.1) and NKp44 (lymphocyte antigen 95 [LY95], human chromosome 6) that are the natural cytotoxicity receptors (NCR). This system is coupled with signal transducers such as CD3ζ, FcεRIγ and KARAP/DAP12 (killer cell-activating receptor-associated protein). The MIC proteins select the targets for destruction. The MICA/B proteins in association with NKG2D protein are a part of the NK cell receptors and in association with other proteins (DAP10 [19q13.1], p85 [5q13], p110 [5q13]) activates killing by NK cells. 2B4 (1q22) and NKG2D (12p13.2-p12.3) appear to be co-receptors. NK cell may kill allogeneic cells because of the

absence of the autologous MHC molecules and cells that display different antigens because of viral infection. Human NK Class I receptors consist of an immunoglobulin domain containing lysine in the transmembrane section, whereas in mice the transmembrane portion of receptors resemble C type lectins. The lectin-like heterodimer CD94/NKG2 recognizes HLA-E molecules. The killer cell inhibitory receptors (KIR, human chromosome 19q13.4) recognize HLA-B (KIR3D) or HLA-C (KIR2D). The inhibitory receptors are characterized by ITIM (immunoreceptor tyrosine-based inhibitory motif) motifs. The ITIMs are phosphorylated but can attract and activate tyrosine phosphatases resulting in suppression of the cytotoxic function of the NK cells. Those cells, which have short receptors (without ITIM) remain phosphorylated and are killers. In case ITIMs are lacking or unavailable, proteins with ITAM (immunoreceptor tyrosine-based activation motif) can be phosphorylated by ZAP-70 and Syk kinases and thus become activated. One such ITAM protein is DAP12 ($M_r = 12$ K, 19q13.1). DAP12 also binds a killer cell activating receptor (KIR2DS2). The activity of the NK cells is increased by the secreted interferons, especially by γ interferon but IFN γ provides protection for normal cells against NKs. The NK cells secrete also chemokines MIP-1 α and RANTES. The NK cells usually cooperate with the cytotoxic T cells (CTL). They are often referred to as “non-MHC-restricted” cells because they can attack even cells that do not express MHC. The outermost layer of the human placenta lacks class I and class II MHC proteins and this is sufficient to protect the hemiallogeneic fetal cells against T cells but this would not, however, protect from NK killer cells. The trophoblast cells (extraembryonic ectodermal tissue) in contact with the placenta (the tissue connecting the maternal and fetal system) express the HLA-G class I molecules and this is sufficient to protect the pregnancy from some adverse immunological reaction. There are also mononuclear killer cells that have antibody-dependent cellular cytotoxic ability. Herpes viruses may produce MHC class I homologs that may interfere with NK-cell defense systems. ►antibody, ►immune system, ►CD1, ►lymphocytes, ►T cells, ►blood cells, ►allogeneic, ►autologous, ►lectin, ►cytotoxic T cells, ►HLA, ►MHC, ►anomalous killer cell, ►NKT cells, ►monocyte, ►ZAP-70, ►Syk, ►caspase, ►p85, ►p110, ►DAP, ►Mic-1 α , ►MICA/B proteins, ►RANTES, ►ITAM, ►ITIM, ►missing self hypothesis; Brown MG et al 1997 *Immunol Rev* 155:53; Biron CA et al 1999 *Annu Rev Immunol* 17:189; Guidotti LG, Chisari FV 2001 *Annu Rev Immunol* 19:65; Moretta A et al 2001 *Annu Rev Immunol* 19:197; Raulet DH et al 2001 *Annu Rev*

Immunol 19:291; Colucci F et al 2002 *Nature Immunol* 3:807; Vivier E et al 2004 *Science* 306:1517; KIR-like proteins: Bashirova AA et al 2006 *Annu Rev Genomics Hum Genet* 7:277.

Killer Genes: A well-known example of the antimorphic *killer of prune* mutations (*awd*^K, *abnormal wing disc*; at end the long arm of chromosome 3) in *Drosophila*, which are viable as homo- or hemizygotes but exert dominant killing effects on most of the hemizygous (male) third instar recessive *prune* mutations (*pn*; 1–0.8). The *awd* gene encodes a nucleoside diphosphate kinase and displays very high homology with the human gene(s) NM23 (17q22) which encode(s) metastasis inhibitor protein(s) and is detectable at reduced levels in several malignant cancers. The *prune* alleles encode a 45-kDa protein and control a lower level of pteridine (drospterin) pigments in the eye resulting in brownish rather than reddish color of the wild type. Some mutant *prune* alleles do not respond lethally to the *awd*^K mutations, others respond only in a temperature-sensitive manner and some are lethal. The biochemical mechanism of the lethal interaction between *pn* and *awd*^K is not clear. (See *Adv Genet* 35:207, Timmons L & Sheran S 1997, ►pollen-killer, ►killer plasmids, ►drospterin, ►temperature-sensitive mutation, ►medea factor, ►dosage compensation).

Killer Plasmids: The mitochondrial *kalilo* plasmid (8.6-kb) has 1,338-bp inverted terminal repeats in *Neurospora intermedia* from Hawaii. At the 5'-end it is covalently linked to a 120-kDa protein. The plasmid has two, non-overlapping, opposite orientation open reading frames. ORF1 codes for a RNA polymerase (homologous to that of phage T7) and ORF2 is a DNA polymerase gene. Integration of this kalDNA into the mtDNA causes senescence and death because it builds up at the expense of the normal mtDNA. It is transmitted in heterokaryons. The *maranhar* plasmid is prevalent in *Neurospora crassa* from South Asia. In function, *maranhar* is similar to *kalilo* although the proteins encoded are substantially different. In prokaryotes several killer systems are known. In plasmid of R1 group at least 13 *hok/sok* genes have been identified that kill cells which do not carry the plasmid. ►hok-sok-mok, ►killer strains, ►mitochondrial genetics, ►mitochondrial plasmids, ►senescence, ►mitochondrial disease in humans, ►pollen killer, ►plasmid maintenance; Schaffrath R, Meacock PA 2001 *Yeast* 18:1239.

Killer Strains: Killer strains of *Paramecium* harbor symbionts, which release toxins lethal to sensitive strains. Bacteria harboring colicinogenic plasmids may destroy colicin-sensitive strains. In yeast the double-stranded RNA viruses, L (4.6-kb) and M (two 1.8-kb dsRNA) result in the production of a killer

toxin, affecting sensitive strains. These two viruses occur together because only the L strain encodes the capsid protein whereas the actual toxin is encoded by the M genome. L and M do not exist outside the cells and are transmitted during mating. In some insects *Wolbachia pipientis* bacterial infection of the males kills all the offspring sired by these males. ▶ *Paramecia*, ▶ *symbionts*, ▶ *hereditary*, ▶ *colicins*

Killer Toxin: Secreted by many yeast cells. The producer cells themselves are immune to the toxin, but on the sensitive strains, a pore is bored and that kills the cells. The K1 killer strains contain two double-stranded RNA viral genomes: the M₁ dsRNA is 1.8-kb encodes the toxin (42-kDa) and the immunity substance precursors and the larger L-A dsRNA (4.6-kb) replicates and maintains M₁. These virus-like particles are transmitted during cell divisions and mating. Several genes are required for the maintenance of MAK (maintenance of killer), SKI (super-killer), KEX (killer expression, endopeptidase and subtilisin-like proteins), KRE (killer resistance) affects cell wall receptors and function of the killer state. The viral killer toxin, TOK1 activates plasma membrane potassium channels. ▶ *colicins*, ▶ *Paramecium*, ▶ *subtilisin*, ▶ *killer virus of yeast*

Killer Virus of Yeast: It has double-stranded satellite RNA as genetic material. Diploid cells of a/α mating type with the M dsRNA segment produce a protein toxin, which is lethal to non-infected cells but not to the infected cells and therefore are denoted as K⁺ (killer) and R⁺ (resistant) whereas the cells without this viral segment are K⁻ and R⁻. The killer and resistance substance are produced by different processing of the same gene (*KIL-d*) product. The killer can be M1 or M2 type and the two are mutually incompatible (exclusion) and usually M1 prevails. The yeast cells generally contain also a L-A dsRNA or a somewhat different helper viral genome. The a or the α cell display defective killer variegation. After mating *KIL-d* × *KIL-d* haploids the killer phenotype seems to “heal” in the diploids but in the haploid progeny of these diploids, the variegation reappears even as the defect remains mitotically stable. The “healing” seems to be the epigenetic result of the nuclear fusion and it is evoked apparently by the viral RNA. The *KIL-d* elements have prion-like properties. ▶ *killer toxin*, ▶ *mating type determination in yeast*, ▶ *prion*; Sesti F et al 2001 Cell 105:637.

Kilobase (kb): 1,000 bases in nucleic acids.

Kin Selection: In general, natural selection favors the survival of the fittest individuals. In some instances, this principle may not be so obvious because of altruism supports individuals for the benefit of the population that share their genes. Selfless females

may sacrifice themselves to predators in attempts to rescue their multiple offspring. In social insects (bees, ants, termites) only the queens and selected males reproduce yet the workers and soldiers of the colonies protect the reproductive individuals even at the cost of their life. The fitness of these non-reproducing castes is measured by the success of their mating sibs. Actually, the survival of their genes is assured indirectly through these reproducing individuals. It is nepotism, motivated by natural selection. Kin selection may be in conflict with competition under certain environmental factors (Griffin AS et al 2004 Nature [Lond] 430:1024). Olfactory stimuli frequently play a role in kin recognition. The birds (long-tailed tits, *Aegithalos caudatus*) recognize kins by vocalization learned from adults during nesting (Sharp SP et al 2005 Nature [Lond] 434:1127). ▶ *altruistic behavior*, ▶ *selection*, ▶ *fitness*, ▶ *inclusive fitness*, ▶ *male-stuffing*, ▶ *olfactogenetics*, ▶ *green beard*; Agrawal AF 2001 Proc R Soc Lond B Biol Sci 268:1099.

KIN17: A nuclear protein encoded at human chromosome 10p15-p14, and associated apparently with unrepaired DNA damage caused by ionizing radiation. ▶ *ionizing radiation*, ▶ *DNA repair*; Biard DSF et al 2002 J Biol Chem 277:19156.

KIN28: A cyclin-dependent kinase of *Saccharomyces cerevisiae*; it phosphorylates the C terminal domain of RNAP II to facilitate transcription. ▶ *CDK*, ▶ *RNAP*

KinA, KinB: *Bacillus subtilis* kinases affecting sporulation regulatory proteins SpoA and SpoF, respectively. ▶ *sporulation*

Kinase: Enzyme that joins phosphate to a molecule. Genes encoding kinases and phosphatases may represent up to 15% of the genome controlling certain developmental pathways. Phosphorylation/dephosphorylation may alter the structure/activity of proteins. Some cellular responses evoked only by multiplex inhibition of kinase function (Kung C et al 2005 Proc Natl Acad Sci USA 102:3587). In the human genome 551 genes encode protein kinases and 152 encode non-protein kinases. Of these genes, 270 were cloned and characterized (Park J et al 2005 Proc Natl Acad Sci USA 102:8114). In yeast, 122 protein kinases were assayed that phosphorylated 1,325 proteins. Some kinases acted on only one protein while others were credited by 256 phosphorylation events. Transcription factors were the largest classes of proteins subject to phosphorylation. Kinases play important role in signal transduction and may be associated with target genes (Pokholok DK et al 2006 Science 313:533). Protein chips monitored the phosphorylations and the results permitted the

construction of phosphorylation maps (Ptacek J et al 2005 Nature [Lond] 438:679). ►protein kinases; Bauman AL, Scott JD 2002 Nature Cell Biol. 4[8]: E203; Cheek S et al 2002 J Mol Biol 320:855; Kinase pathways: <http://kinasedb.ontology.ims.u-tokyo.ac.jp:8081/>; Kinases of the human genome: <http://www.itb.cnr.it/kinweb/>; Protein kinase-specific site predictor: <http://kinasephos2.mbc.nctu.edu.tw/>.

Kindler Syndrome (KIND1, 20p12.3): A rare, recessive neonatal blistering, sensitivity to sunshine, abnormal pigmentation, atrophy caused by loss of a membrane associated protein that apparently links the actin cytoskeleton to the extracellular matrix. ►cytoskeleton, ►extracellular matrix, ►skin diseases; Siegel DH et al 2003 Am J Hum Genet 73:174.

Kindred: A group of biological relatives with a determined pedigree. ►pedigree analysis

Kinectin: Membrane protein, binding intracellular vesicles to kinesin. ►kinesin

K

Kinesin: A cytoplasmic protein involved in moving vesicles and particles along the microtubule plus end; it assists segregation of chromosomes and transport of organelles (endosomes, Golgi complex, lysosomes, mitochondria, nerve axons) by using energy derived from ATP hydrolysis (see Fig. K11). The ca. 380-kDa NH₂ domain has the motor function whereas the COOH terminus probably binds to organelles or microtubules. The kinesins consist of two 120-kDa heavy chains and two 64-kDa light chains arranged in two (10-nm) globular ends, connected by linear molecule either N- or C-terminal or in the middle. Some kinesins may move in either plus or minus direction on the microtubules. The motor function may also be at different sites of the sequences with a total length of 80-nm. For each 8-nm step of movement kinesin hydrolyzes one molecule of ATP. The movement is either by the “hand-over-hand” or by the inchworm model. Movement by kinesin can also reverse direction (Carter NJ, Cross RA 2005 Nature [Lond] 435:308). Kinesins belong to the KIF family of motor associated proteins. Kinesin motors transport cargo vesicles toward the plus-end of the microtubules. The Ncd, minus-end-directed motor proteins facilitate the segregation of chromosomes. ►myosin, ►dynein, ►kinectin, ►cilia, ►centrosome, ►microtubules, ►axon, ►endocytosis [endosome], ►lysosome, ►golgi, ►dynein, ►bimC, ►monastrol, ►inchworm model, ►Hand-over-hand model; Kikkawa M et al 2000 Cell 100:241; Kikkawa M et al 2001 Nature [Lond] 411:439; crystal structure: Nitta R et al 2004 Science 305:678; Awsbury CL 2005 Current Opin Cell Biol 17:89.

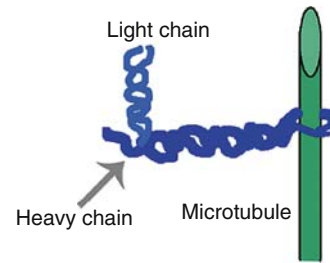


Figure K11. Kinesin

Kinetic Complexity: Measured by the reassociation kinetics of denatured DNA; the increase in complexity (large number of unique diverse sequences) requires longer time for re-association. ►c₀t curve, ►kinetics

Kinetics: Analysis of reaction rates. The reactions may run to completion or may remain incomplete. *0 order* of the reaction kinetics indicates that the velocity of the process is constant and independent from the initial concentration of the substrate (see Fig. K12). *First order* kinetics indicates that only one substrate is involved (monomolecular reaction). Mutation rates and terminal chromosomal deletions below a certain dose of mutagens or clastogens also follow first order kinetics. 2nd order kinetics indicates bimolecular reactions and ionizing radiation-caused chromosomal rearrangements (inversion, transposition, translocation) may also be in this category.



Figure K12. Reaction kinetics: Dose (concentration) plotted against time. The 0, 1st, 2nd, 3rd order kinetics are marked on the curves

Multiple order kinetics may be involved with more than two reacting factors. ►radiation effects, ►LET, ►clastogen, ►DNA repair

Kinetin (6-furfurylaminopurine): A cytokinin plant hormone (see Fig. K13). ►plant hormones

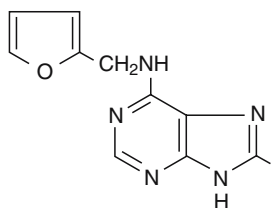


Figure K13. Kinetin

Kinetochore: The structural protein part of the centromere where spindle fibers are attached. Cdc42 regulates the process. The kinetochore is an assembly of more than 50 different proteins (Hauk S, Watanabe Y 2004 Cell 119:317). A synthetic lethal and synthetic dosage lethal screen in yeast identified 211 genes controlling kinetochore function (Measday V et al 2005 Proc Natl Acad Sci USA 102:13956). Ndc80 is an essential 4-unit heteromeric component of the budding yeast kinetochore forming ~570-Å long rod with globular ends (see Fig. K14). The Ndc80 kinetochore complex is shown in a cartoon below redrawn after Wei RR et al 2005 Proc Natl Acad Sci USA 102:5363.

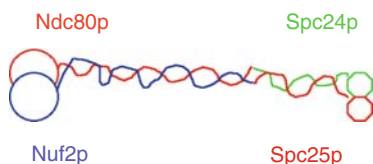


Figure K14. Four of the kinetochore proteins

The kinetochores associate with the microtubules that connect the chromosomes with the spindle pole. The interaction between the kinetochores and the spindle fiber microtubules requires the centromere binding factor CBF3 complex and is subject to regulation by Ipl1, the budding yeast Aurora B kinase, and the counteracting phosphatase PP1/Glc7. Besides CBF3 a complex of two chromosomal passenger proteins, Bir1/Survivin and Sli15/INCENP, connects CBF3-CEN DNA to microtubules in vitro. This connection is independent of Ipl1, and Bir1 and Sli15 control the activation and targeting of the process (Sandall S et al 2006 Cell 127:1179).

When yeast mutants *mec-1* or *rad53* (corresponding human genes are ATM/ATR and Chk-like kinase) are treated with replication inhibitors, replication integrity fails and the chromosomes are partitioned unreplicated because the checkpoint deficiency leads to deregulation of the microtubule-associated proteins Cin8 and Stu2 and cause premature separation of the chromosomes (Krishnan V et al 2004 Mol Cell 16:687). These microtubules pull then mitotic/meiotic chromatids/chromosomes to the

opposite poles. The plus end of the microtubules interact with the kinetochore and at that end with the protein Dam1 complex and forms a 16-fold symmetry ring around the microtubules. Depolymerization of the microtubules generates the force required to move the chromosome during anaphase toward the poles (see Fig. K15). Figure K15 was redrawn after the more precise electron micrographs of Westermann S et al 2006 Nature [Lond] 440:565. During meiotic anaphase the two sister chromatids are pulled to the same pole because the Mam1 subunit of the monopolin protein complex is tightly bound to the Hrr25 casein kinase and this complex is attached to one pole only. During mitosis the kinetochore attachment is bipolar and the sister chromatids are separated by the microtubules (Petronczki M et al 2006 Cell 126:1049). During interphase microtubule-kinetochore association does not exist. In *Schizosaccharomyces pombe* the formation of the spindle takes about 1.5 min at 36° C whereas its elongation takes about 6.2 min. ▶Roberts syndrome, ▶CENP, ▶SKP1, ▶MTOC, ▶SPB, ▶ATM, ▶ATR, ▶Chk1, ▶centromere, ▶neocentromere, ▶microtubules, ▶Cdc42, ▶cell cycle, ▶mitosis; Skibbogens RV, Hieter P 1998 Annu Rev Genet 32:307; Kitagawa K et al 1999 Mol Cell 4:21; He X et al 2001 Cell 106:195; Tanaka TU et al 2002 Cell 108:31; Shimoda SL, Soplomon F 2002 Cell 109:9; Kinetochore–spindle review: Kline-Smith SL et al 2005 Current Opin Cell Biol 17:35; yeast kinetochore: Westermann S et al 2007 Annu Rev Biochem 76:563.

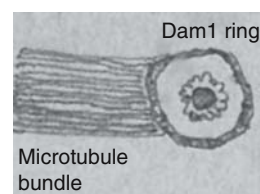


Figure K15. Dam1 complex interacts with the microtubule bundle

Kinetoplast: The mitochondrial DNA in some protozoa (*Trypanosoma*) is organized into kDNA (kinetoplast DNA), concatenated circular molecules. The ca. 20–50 copies of the *maxi-circular* genome (22-kbp) resemble the mtDNA of other species; the heterogeneous 5,000 to 10,000 copies of the *minicircles* are 0.5–2.8-kbp and represent about 95% of the kDNA. The sum of kDNA constitutes 7–30% of the total cellular DNA in the different *Trypanosoma* and *Leishmania* species. The maxicircle transcripts are subject to editing by adding or (rarely) by subtracting uridine from the primary transcript. Such editing, called also pan-editing, may cause some of the edited transcripts to have more than 50% uridine. The gene,

which encodes the transcript and subject to pan editing, is called a *cryptogene* because the sequences of the original transcripts are almost concealed by this process. In the minicircles short (50–100 base) sequences (guide RNA [gRNA]) remain complementary to the edited RNA. The kDNA may have major role in the life cycle of the protozoon while it is in the insect gut but not in the mammalian blood. The edited RNA of cytochrome bc₁ is translated. In Chagas disease, the kDNA can integrate at several sites of the host DNA and then be inherited. Particularly favorite targets for integration are the β -globin locus and the LINE-1 transposons (Nitz N et al 2004 Cell 118:175).
▶ *Trypanosoma*, ▶ *Leishmania*, ▶ mtDNA, ▶ gRNA, ▶ RNA editing, ▶ LINE, ▶ Chagas disease; Klingbeil MM et al 2002 Molecular Cell 10:175.

Kinetosome: ► kinetoplast

King George Madness (III, 1762–1830): Neurotic behavior caused likely by porphyria. ►[porphyria](#); Hindmarsh JT 1997 Lancet 349:364; Warren MJ et al 1996 Trends Biochem Sci 21(6):229.

Kingdoms of Taxonomy: The definition varies according to different authors: Prokaryotae, Archaea, Protista, Fungi, Plantae and Animalia or only Bacteria, Archaea and Eukarya

Kinin: A group of endogenous peptides acting on blood vessels, smooth muscles and (injury-sensing) nerve endings. ▶ [kininogen](#)

Kininogen: Kinin precursor α_2 -globulins of either 100,000–250,000 M_r or 50,000–75,000 M_r are split by kallikrein to bradykinin and l-lysyl-bradykinin (kallidin), respectively. The brady-kinins regulate blood vessel contraction, inflammation, pain and blood clotting. ► **Williams factor**, ► **kinin**, ► **eclampsia**

Kink: A distortion (twist) of the DNA double helix or in the secondary structure of RNA. The M_r 7K archaeon protein (Sac7d, Sso7d) binds to the minor groove of the DNA (GCGATCGC)₂ and (GTAATTAC)₂, and increases its melting temperature by kinking. (See Oussatcheva EA et al 1999 J Mol Biol 292:75; Klein DJ et al 2001 EMBO J 20:4214).

Kinome: The system of cellular protein kinases; the human kinome includes > 5000 kinases. ► [protein kinases](#); Manning G et al 2002 Science 298:1912.

Kinship: ► coefficient of coancestry

Kinship Theory: Genetic conflict theory.

KIP2 (p57KIP2): A cyclin-dependent kinase inhibitor protein, encoded in human chromosome 11p and in mouse chromosome 7. At some developmental stages it is expressed from the maternal chromosome. KIP1

(p27^{KIP1}) has also closely related function in the cell cycle. ►imprinting, ►CDK, ►cancer

KIR: Killer cell inhibitory receptor. ► [killer cell](#)

Kirsten-RAS (K-RAS): Oncogene of a rat sarcoma RNA virus at human chromosome 12p12.1. It encodes a 21-kDa membrane-associated protein involved in signal transduction. It is commonly responsible for pancreatic and other adenocarcinomas. ▶RAS, ▶p21, ▶oncogenes

KIS: Kirsten murine sarcoma virus oncogene.

Kiss (1q32): A 145/154 amino acid polypeptide (called metastatin) suppresses metastasis of melanoma and breast cancer but it does not affect tumorigenesis. It seems to be a ligand of a G protein-coupled receptor. ►metastasis, ►signal transduction; Ohtaki T et al 2001 Nature 411:613.

Kissing Interactions: Formed when unpaired nucleotides within two RNA hairpins (pseudoknots) pair with each other. These interactions stabilize the structures and may facilitate recognition by various ligands or metal ions. ▶[pseudoknot](#), ▶[retroviral recombination](#), ▶[kissing loop](#); Andersen AA, Collins RA 2001 Proc Natl Acad Sci USA 98:7730; Li PTX et al 2006 Proc Natl Acad Sci USA 103:15847.

Kissing Loop: A dimerization site of HIV at nucleotides 248–271 and it facilitates the incorporation of two genomic RNAs into the virion (see Fig. K16).
 ▶acquired immunodeficiency, ▶retroviral recombination



Figure K16. Kissing loop

KIT Oncogene: A homolog to the viral *v-kit* gene of a feline sarcoma. It is in human chromosome 4q12 and in chromosome 5 of the mouse. This proto-oncogene codes for transmembrane tyrosine kinase with homology to CSF1R and to PDGF. The KIT gene was assumed to be responsible also for piebaldism in humans and mouse. KIT also signals to spermatogenesis and oogenesis. Gastrointestinal stromal tumors may also be caused by gain-of-function mutations in the c-KIT gene. The receptor for the KIT appeared to be encoded by the *W* (*white*

fur) and the PDGF genes of mice, located to about the same or identical chromosomal site as the KIT homolog. The KIT/stem cell factor receptor is involved in hematopoiesis, melanogenesis and gametogenesis. Stem cell factor proliferation depends on phosphatidylinositol-3'-kinase (PIK). Mutation in the PIK binding site causes male sterility but no female sterility. Another mouse locus, *Sl* (*Steel*) encodes MGF (mast cell growth factor), a ligand for the growth factor receptor. The KIT oncogene product is required also for the phasic contraction of the mammalian gut and the control of hematopoietic cells. ▶piebaldism, ▶microphthalmos, ▶CSF1R, ▶PDGF, ▶oncogenes, ▶transmembrane proteins, ▶tyrosine kinase, ▶FLT, ▶hematopoiesis, ▶mast cells, ▶gain-of-function mutation, ▶stem cell factor, ▶PIK, ▶receptor tyrosine kinase, ▶CD117; Smith MA et al 2001 *Acta Haematol* 105:143; Kitamura Y et al 2001 *Mutation Res* 477:165; Heinrich MC et al 2003 *Science* 299:708.

KIX: The CREB-binding domain of CBP. ▶CBP, ▶CREB

Kjeldahl Method: Determines total nitrogen content in organic or inorganic material after hot sulfuric acid digestion in the presence of a catalyst (Se, Hg). After titration of the distilled ammonia in the presence of phenolphthalein, 1 mL 0.1N H₂SO₄ bound by the ammonia corresponds to 0.0014 g nitrogen, and the amount of nitrogen multiplied by 6.25 estimates protein content. ▶Lowry method, ▶Bradford method [for protein].

KL: A male fertility complex in the long arm of the Y chromosome of *Drosophila melanogaster*. ▶sex determination, ▶KS, ▶*Drosophila*

Klebsiella: A gram-negative, facultative anaerobic enterobacterial genus (closely related to *E. coli*) with several species, widely present in nature (including hospitals) and capable of causing urinary and pulmonary (lung) and wound infections but it has the desirable feature of fixing atmospheric nitrogen. ▶nitrogen fixation

Kleiber's Rule: ▶size

Kleinsins: Eukaryotic and prokaryotic proteins that interact with structural maintenance proteins of the chromosomes ▶SMC; Schleiffer A et al 2003 *Mol Cell* 11:571.

Klenow Fragment: The large fragment of bacterial DNA polymerase I lacking 5'-to-3' exonuclease activity (located in the small fragment of the enzyme) but retaining the 5'→3' polymerase and the 3'→5' exonuclease functions. It is generated by cleavage with subtilisin and other proteolytic enzymes. It has

been used for nick translation and the Sanger's dideoxy method of DNA sequencing. ▶nick translation, ▶DNA sequencing, ▶DNA replication in prokaryotes, ▶DNA polymerase I; Kuchta RD et al 1988 *Biochemistry* 27:6716.

KLH: ▶keyhole limpet hemocyanin

Klinefelter Syndrome: Caused most commonly by XXY chromosomal constitution, although XYY, XXXY, and XXXXY have similar consequences as well as some mosaicisms involving more one X and Y chromosomes. The XXY condition affects about one to two boys among 1,000 births. XYY is somewhat less frequent, and the more complex types are even rarer. The XYY males may be fertile although the other symptoms are common with those of XXY. Underdeveloped testes (hypogonadism) and seminiferous ducts characterize the Klinefelter syndrome (see Fig. K17).



Figure K17. Klinefelter syndrome

The afflicted individuals are generally sterile, although effeminate yet heterosexual in behavior. Their height is usually above average and the limbs appear longer than normal. About half of them show increased breast size and they are about as likely to develop breast cancer as women. They are more likely to develop insulin-dependent diabetes and heart failure (mitral valve prolapse) than normal males. Some develop speech problems. Their intelligence is generally low, particularly in those having a higher number of sex chromosomes. Klinefelter individuals are frequently slow in development and have learning disabilities. Although they tend to be shy and immature in behavior, they were considered

to be prone to violence but this latter classification turned out to be based on false statistics. It is also true that there is higher incidence of Klinefelter syndrome in prison populations but this is due to their mental deficiency. Klinefelter symptom occurs also in various other mammals. Among the sperm of human males in their 20s, the average frequency of XY sperm is 0.00075 and it gradually increases and by age 50s it may be 0.0176, i.e., 160% higher. ▶sex chromosomes, ▶sex determination, ▶sex mosaics, ▶sex chromosomal anomalies in humans, ▶XX males, ▶gynecomastia, ▶trisomy, ▶polysomic cells; Klinefelter HF Jr et al 1942 J Clin Endocrin 2:615; Smyth CM, Bremner WJ 1998 Arch Intern Med 158:1309; Lowe X et al 2001 Am J Hum Genet 69:1046; Photo: Courtesy of Dr. K.L. Becker, and by permission of the American Fertility Society.

Klippel-Feil Syndrome: In the autosomal dominant form, it is associated with fusion of cervical (neck) vertebrae and malformation of head bones conducive to conductive and/or sensorineural hearing loss. The autosomal recessive forms did not involve hearing deficit. ▶deafness

Klippel Trenaunay Syndrome: A defect of the blood-vessels. It involves venous and lymphatic capillaries and hypertrophy of bony or soft tissues. Generally it was assumed to be sporadic. Translocation (5; 11) (q13.3; p15.1) or mutation at the terminal segments of chromosome 5 have been suspected. Other studies implicated translocations 8q22.3 and 14q13 or mutations in either of these regions. VG5Q is a major susceptibility factor interacting with angiogenic factors E133K and TWEAK. The genetic determination appears somewhat complex. ▶VG5Q, ▶TWEAK, ▶angiogenesis; Tian X-L et al 2004 Nature [Lond] 427:640.

Klotho: ▶aging

Klotz Test: Estimates the statistical variance of two populations, which display identical median values. ▶variance, ▶median; Drinkwater NR, Lotz JH 1981 Cancer Res 41:113.

Kluyveromyces lacti: A yeast species in which the first time linear plasmids were found.

Kniest Dysplasia (metatropic dwarfism): An autosomal dominant disease concerned with the locus of collagen II α -1 polypeptide (human chromosome 12q13.11-q13.2). The defect involves a deficiency of the C propeptide that is required for normal fibril formation. The urine contains increased amounts of keratan sulfate. There are general problems with the cartilage. Specifically, the afflicted individuals cannot tightly close their fist, their palm is purplish, suffer from severe myopia (nearsightedness), the retina is

detached and various types of bone defects, including dwarfism, may be evident. ▶Stickler syndrome, ▶eye diseases, ▶collagen, ▶connective tissue disorders, ▶dwarfism, ▶keratin

Knirp (*kni*, map location 3–46): Zygotic gap mutation in *Drosophila*. The first seven abdominal segments are abnormal (fused/deleted) but the head, thorax, the eighth abdominal segments and tail are normal. The locus encodes a steroid/thyroid receptor protein, which responds to various ligands such as the product of gene *Krüppel*. ▶gap genes, ▶*Krüppel*

Knob: Heterochromatic cytological landmark of a chromosome. Knobs have been used to identify the fate of particular chromosomes during meiosis and evolution. Knobs were implicated in preferential segregation in maize and as affecting the frequency of recombination of syntenic markers (see Fig. K18).

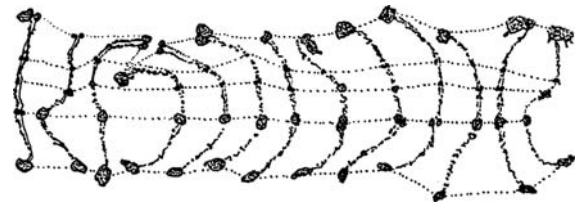


Figure K18. Chromosome knobs of the pachytene chromosomes of 13 different house crickets. The dotted lines connect homologies. (From Wenrich DH 1916 Bull Mus Comp Zool Harvard 60:58)

Knobs (altogether about 22) were observed on all chromosomes of maize. These are composed of tandem arrays of about 180-bp elements and may function as neocentromeres. Molecular evidence suggests that through inversion centromeric heterochromatin moved to the arm of the chromosome where it is composed largely of tandem repeats and retrotransposons. ▶preferential segregation, ▶neocentromere, ▶heterochromatin, ▶chromosome knob; Ananiev EV et al 1998 Genetics 149:2025; Hsu FC et al 2003 Genetics 164:1087.

Knob: The terminal part of the viral fiber on the capsid, an essential means of infection by recognizing host receptor (see Fig. K19). The knob may have targeting ligands attached (not shown on this Fig. K19). ▶retrovirus



Figure K19. Terminal part of viral fiber

Knobloch Syndrome (21q22.3): A retinal degeneration, meningocele (protrusion of the meninges [spinal cord and brain membrane], myopia (defect of focusing of the eye), etc. are caused by defects in collagen COL18A1 (Suzuki OT et al 2002 Am J Hum Genet 71:1320).

Knock-Down: Slowing down the expression of a particular gene either by transformation with mRNA digesting ribozymes or more practically by the introduction of synthetic 18–25 nucleotide antisense constructs. This procedure may be practical even when only an EST is known. Generally low levels of phosphorothioate are used to avoid toxicity and still protect against nucleases. ▶antisense technologies, ▶RNAi, ▶EST; Griffoni C et al 2000 Biochem Biophys Res Commun 276:756; Kohli M et al 2004 Nucleic Acids Res 32:e3.

Knock-In (Ki): Insertion of a functional copy or a domain into an inactive/active gene. Generally a vector cassette flanked by the *loxP* gene is employed. ▶knock-out, ▶gene replacement, ▶Cre/*loxP*; Golub R et al 2001 Eur J Immunol 31:2919.

Knock-Out (KO): Inactivation of a gene by any means (e.g., deletion, insertion, targeted gene transfer) to determine the phenotypic, metabolic, behavioral or other consequences, and to draw conclusions concerning its normal function. Removal of genes by site-specific recombination is expected to specifically knock out a discrete genic sequence. The consequence of the knockout may depend also on the neighboring genes. The general procedure involves first growing embryonic stem cell (ES) of mice. The cells are then electroporated with a gene construct carrying a selectable marker (e.g., neomycin resistance) within the coding sequence and thus it is inactivated. The disrupted gene is flanked by sequences homologous to the target to facilitate homologous double crossing over. The cells are grown out on selective media and recombinants are isolated. These recombinants will not be able to carry out the normal function of the target gene because of the insert in the coding sequence. Eventually the ES cells are injected into host blastocytes with a micromanipulator and transferred into the blastocoele. In case of success, the developing embryo becomes chimeric and some of the germline cells or the entire germline will carry the knock-out and transmit it to some of the progeny. In 17 days after the transfer knock-out, offspring may be obtained. The rate of success varies depending on the technical skills of the investigator and the mice concerned but it may be also quite high, over 50%. Huge knock-out libraries of mice are being generated now worldwide in order to understand all or as many as possible of the

vertebrate genes (Grimm D 2006 Science 312:1862). ▶site-specific mutagenesis, ▶targeting genes, ▶excision vector, ▶phenotypic knockin, RNA double-stranded Internet: <http://www.gdb.org/Dan/tbase/tbase.html>; mouse; Mak TW ed. 1998 The Gene Knockout FactsBook, Acad Press, Orlando, FL, USA; Thorneycroft D et al 2001 J Exp Bot 52:1593; Mansouri A 2001 Methods Mol Biol 175:397; KOMP Knockout Mouse Project: cryopreserved knockout mouse embryos: <http://www.knockoutmouse.org>; cryopreserved knockout mouse embryos: <http://www.informatics.jax.org/external/ko/>; Mutant Mouse Regional Research Center: <http://www.mmrrc.org>; Conditional Mouse Mutagenesis Center: <http://www.eucomm.org>, NorComm: <http://norcomm.phenogenomics.ca/index.htm>; Caenorhabditis Knockout Consortium: <http://celeganskoconsortium.omrf.org/>.

Knotted Circle of DNA: ▶concatenane (see Fig. K20).

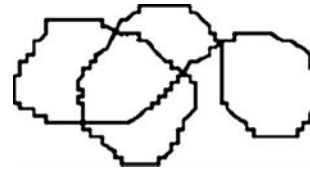


Figure K20. Knotted circle

Knowledge Discovery: Methods of extracting meaningful information from sets of sequence data of macromolecules. ▶data mining; Kurgan LA et al 2001 Artif Intell Med 23(2):149.

Knucklewalking: African apes do not use their palm but their knuckles (flexed fingers) to lean on in quadrupedal movement.

Knudson's Two-Mutation Theory: Postulates that in retinoblastoma, usually a germline mutation is followed by somatic mutation(s) in order to express the cancer. If a mutation is recessive, both alleles of a diploid must mutate to become detectable. The number of tumors in an individual indicates the rate of somatic mutation. Although in many different cancers one or more major genes have obvious role(s), an unknown number of additional genes control predisposition to cancer, i.e., the cancer risk is polygenically determined. A large-scale study of coding sequences (13,023 genes) of human breast and colorectal cancers revealed on average 90 mutant genes in these tumors but on average of about 11 of them affected the neoplastic process (Sjöblom T et al 2006 Science 314:268). Chronic myeloid leukemia (CML) is associated with the Philadelphia chromosome, which arises by a reciprocal translocation

between chromosomes 9 and 22 and harbors the BCR-ABL fusion oncogene. It is unknown whether any other mutations are needed for the chronic phase of the disease. The CML incidence increases as a function of age with an exponent of 3. A slope of 3 could indicate that there are two mutations, in addition to the Philadelphia translocation, that has not yet been discovered. An alternative hypothesis is that cancer initiation may require only a single mutation. A mutated cell has a net reproductive advantage over normal cells and, therefore, might give rise to clonal expansion. The cancer is detected with a probability that is proportional to the size of the mutated cell clone. This model has three waiting times: (i) the time until a mutated cell is produced, (ii) the time of clonal expansion, and (iii) the time until the clone is detected. Surprisingly, this simple process can give rise to cancer incidence curves with exponents up to 3. Therefore, the CML incidence data are consistent with the hypothesis that the Philadelphia translocation alone is sufficient to cause chronic phase CML (Michor F et al 2006 Proc Natl Acad Sci USA 103:14931). ▶cancer, ▶retinoblastoma, ▶genetic tumors, ▶Armitage-Doll model, ▶Moolgavkar-Venzon model, ▶Philadelphia chromosome, ▶leukemia; Hethcote HW, Knudson AG Jr 1978 Proc Natl Acad Sci USA 75:2493; Knudson AG 2000 Annu Rev Genet 34:1; Frank SA 2005 Proc Natl Acad Sci USA 102:1071.

KO: ▶knock-out

Koala: *Phascolarctos cinereus*, 2n = 16. A tree-dweller marsupial found in Australia. (see Fig. K21).



Figure K21. Koala bear

Kobberling-Dunnigan Syndrome: ▶Lipodystrophy

Kohara Map: In *E. coli* it is a restriction fragment map, based on partial digests of 3400 phage lambda clones with eight restriction endonucleases. ▶*E. coli*, ▶RFLP, ▶vectors, ▶cosmids; Rudd KE 1998 Microbiol Mol Biol Rev 62:985.

Kolmogorov-Smirnov Test: A non-parametric statistical procedure for the analysis of frequency distributions. It may be used in genetics for different problems, e.g., analysis of gene or physical marker frequency distributions in different populations. The method is usually applied to expected and observed cumulative

distributions. The differences are expressed as differences between relative cumulative frequencies and usually statistical tables are used to ascertain the maximum difference between observed and expected cumulative frequency at certain level of significance. The largest absolute vertical deviation (D) = maximum $|F_s(x) - T_T(x)|$ where $F_s(x)$ is the sample cumulative distribution frequency (CDF) and $T_T(x)$ = the theoretical CDF. The procedure is simple to carry out and computer programs are also available. Details can be found in Hays WL, Winkler RL 1971 Statistics: Probability, Inference and Decision, Holt, Rinehart and Winston, New York or in Sokal RR, Rohlf FJ 1969 Biometry, W.H. Freeman & Co, San Francisco, California. ▶Wald-Wolfowitz test

Kondrashov's Deterministic Model of Evolution of Sex:

Asexual females produce about twice as many daughters as sexual ones yet the number of asexual females is not increasing in the populations ("two-fold cost of sex"). In addition, sexual recombination breaks up co-adapted gene blocks. Despite these facts sexual reproduction is widespread among animals and even in plants. The cause of this is that sexual reproduction and selection has the potential of generating adaptation to the variable environment. ▶Red Queen hypothesis, ▶sex evolutionary significance; West SA et al 1999 J Evol Biol 12:1003.

KORF (known open reading frame): Its function is well understood. ▶ORF

Kosambi's Function: In the function, $x = 0.25 \ln[(1 + 2y)/(1 - 2y)]$, where x is the recombination frequency corrected by the mapping function and y is the observed recombination fraction. Kosambi's formula considers "average" interference, and it has been used in different species although interference may vary in different situations. ▶Haldane's mapping function, ▶coefficient of coincidence, ▶mapping genetic, ▶recombination frequency, ▶mapping function; Kosambi DD 1944 Ann Eugen 12:172.

Kosmotrope: ▶chaotrope

Kozak Rule: In eukaryotes, the most efficiently translated mRNAs start with AUGxG sequence. Commonly optimal translation occurs with AC-CAUGG. ▶ribosome binding, ▶ribosome scanning; Kozak M 1999 Gene 234(2):187.

k-RNA (kinetoplast RNA): Mitochondrial RNA in *Trypanosomas*. ▶*Trypanosoma*, ▶RNA editing

KRAB (Krüppel-associated box Zn-finger proteins, ZFB/ZNF/ZFP): Mostly transcriptional repressors. ▶Krüppel, ▶DNA binding protein domains; Looman C et al 2004 Mamm Genome 15:35.

Krabbe's Leukodystrophy (globoid cell leukodystrophy): A rare chromosome 14q31 recessive disease, called also galactosyl ceramide lipidosis. The enzymatic basis of the condition is the deficiency of galactocerebroside β -galactosidase/galactosylceramidase. The onset of the disease is expected within the first half year of life and it is generally fatal by around age 2. Exceptionally its onset may be delayed to late childhood. The early symptoms are irritability, hyperactivity that is followed by lethargy, degeneration of the nervous system resulting in blindness and deafness. Cerebrospinal fluid (CSF) proteins accumulate. In the white matter of the brain, myelin is reduced and infiltrated with globoid cells that are rich in galactosyl ceramides. When umbilical cord blood was transplanted into 12–44 days old asymptomatic and 142–352 days old symptomatic infants in the former group normal blood galactocerebroside level appeared, progressive myelination followed and apparently normal cognitive function was reached in the majority of the patients. Symptomatic babies however failed to show substantial improvement (Escolar ML et al 2005 New England J Med 352:2069). This procedure provides good evidence for the success of stem cell therapy. The *twitcher* mouse is an enzymatically appropriate animal model of this disease. [▶galactosidase](#), [▶sphingolipidoses](#), [▶sphingolipids](#), [▶saposin](#), [▶metachromatic leukodystrophy](#), [▶stem cells](#), [▶Addison disease](#), [▶metachromatic leukodystrophy](#); Matsuda J et al 2001 Hum Mol Genet 10:1191.

KRAS: [▶RAS oncogene](#)

Krebs-Szentgyörgyi Cycle: (1) Oxaloacetate \rightarrow (2) Citrate \rightleftharpoons cis-Aconitate (3) cis-Aconitate \rightleftharpoons Isocitrate (4) Isocitrate \rightleftharpoons α -Ketoglutarate (5) α -Ketoglutarate \rightleftharpoons Succinyl Co-enzyme A (6) Succinyl CoA \rightleftharpoons Succinate (7) Succinate \rightleftharpoons Fumarate (8) Fumarate \rightleftharpoons Malate (9) Malate \rightleftharpoons **Oxaloacetate**. This simplified outline does not show the energy donors and cofactors. This cycle is the most efficient path to generate energy. It is also called tricarboxylic acid cycle and citric acid cycle. A modified form is the glyoxylate cycle where isocitrate lyase converts isocitrate to glyoxylate and succinate. Glyoxylate then reacts with Co-A to form malate.

Krev-1: Probably the same as Rap1. [▶Rap](#)

Kringle: A disulphide-linked, triple-looped protein domain present in some plasma proteins, apolipoproteins, plasminogens, serine proteases, phosphoglycerate kinase, thrombin, hepatocyte growth factors. Some of the kringle proteins regulate angiogenesis,

cancer and metastasis. (See Ozhogina OA et al 2001 Protein Sci 10:2114)

KROX20: A serum inducible primary-response gene with Zn-finger, originally from *Drosophila*. It controls the myelination of the peripheral neurons. Krox20 promotes adipogenesis in a hormone-dependent manner (Chen Z et al 2005 Cell Metabolism 1:93). [▶serum response element](#), [▶zinc finger](#), [▶myelin](#), [▶neuron](#), [▶Egr](#), [▶C/EBP](#), [▶PPAR](#); Turman JE Jr et al 2001 Dev Neurosci 23[2]:113.

Krox-24: [▶NGKI-A](#), [▶Egr](#)

Krüppel (Kr, 2–107.6): The maternal effect gap gene of *Drosophila*, encoding a protein with regulatory Zn-finger domain interacting with Kni (knirps) and Hb (hunchback) proteins. Its monomers activate transcription in its vicinity by TFIIB and its dimer may repress transcription by interacting with the TFIIE β subunit. Kr-like factor controls also G₁-S progression. In the human genome there are an estimated 600–700 Krüppel-like (KLF) regulatory proteins. All of them bind a very similar GT-box (CACCC element). [▶transcription factors](#), [▶EKL](#), [▶kni](#), [▶gap genes](#), [▶morphogenesis in Drosophila](#), [▶Gli oncogenes](#), [▶cell cycle](#), [▶ \$\alpha\beta\$ T cell](#); Shields JM et al 1996 J Biol Chem 271:20009; Chen X et al 2001 J Biol Chem 276:30423; Bieker JJ 2001 J Biol Chem 276:34355.

Kruskal-Wallis Test: A non-parametric method of 'analysis of variance' by ranks. Each observation regarding groups of treatment, genotypes or phenotypes to be compared are ranked as shown in parenthesis (see Table K1).

Table K1. Kruskal-Wallis test

| Group 1 | Group 2 | Group 3 | |
|-----------------------|----------|-----------|--|
| 4 (1.5) | 11 (7) | 18 (11) | Total of N = 15 observations |
| 7 (4) | 12 (8.5) | 30 (15) | T _j = sum of ranks of group j |
| 10 (5.5) | 12 (8.5) | 24 (12.5) | T = total ranks of the groups |
| 4 (1.5) | 10 (5.5) | 24 (12.5) | |
| 6 (3) | 13 (10) | 25 (14) | |
| T _j (15.5) | (39.5) | (65) | |

T = 120, i.e.,

$$T = \frac{N(N+1)}{2} = \frac{(15)(16)}{2} = 120$$

if the ranking is correct.

$$\begin{aligned}
 H &= \frac{12}{(n(N+1))} \left(\sum_j \frac{T_j^2}{n_j} \right) - 3(N+1) \\
 &= \frac{12}{15(16)} \left(\frac{15.5^2 + 39.5^2 + 65^2}{5} \right) - 3(16) \\
 &= 12.25
 \end{aligned}$$

(in the example above [note 12 is a constant]).

$$1 - \left(\frac{\sum_i t_i^3 - t_i}{N^3 - N} \right)$$

If there are ties in the ranking the H value should be corrected by dividing H by the formula shown in the box. $1G$ = number of sets of tied observation, t_i = numbers of tied in any set of i . This correction may not make much difference if N is very small or the number of ties is very large. From the chi square table (see under chi square table) we can determine for $J-1 = 2$ degrees of freedom in the example shown above that the probability is less than 0.005 that these three sets would be identical. Generally much larger samples than shown are required to get meaningful results. It is considered to be a very powerful non-parametric test. ▶Mann-Whitney test, ▶non-parametric tests

KS A male fertility complex in the short arm of the Y chromosome of *Drosophila melanogaster*. ▶sex determination, ▶KL, ▶Drosophila

KSHV: (Kaposi sarcoma associated herpes virus): ▶Kaposi sarcoma, ▶HHV8

KSR (kinase suppressor of RAS): Structurally related to RAF and has similar role in cell proliferation and development of *Drosophila*. ▶RAF, ▶RAS, ▶CNK

KSS1: A protein kinase of the MAPK family. Along with Fus3, it causes arrest of yeast cells in G1 prior to mating. ▶signal transduction, ▶MAPK, ▶Ste, ▶Fus3

Ku: Heterodimeric (Ku70 [22q13] and Ku86 [2q35], kDa) serine/threonine protein kinases that bind to DNA in cooperation with transcription factors. Ku also interacts with the termini of DNA double strand breaks and is the binding domain of DNA protein kinase (DNA-PK), whereas the catalytic subunit of DNA-PK is encoded at 8q1. During telomere replication Ku is bound to a guanine-rich overhang in yeast. Ku has a role in DNA repair and recombination, including immunoglobulin V(D)J rearrangements. The deficiency of Ku70 leads to defect in B cell maturation and development of T cell lymphoma. The XRCC5 human gene is also encoded

at 2q35. Ku70 apparently mediates non-homologous chromosomal end-joining in somatic cells and though essential, appears to be absent during the meiotic prophase. Ku70 is involved in the internalization of *Rickettsia* bacteria (pathogen of the Mediterranean spotted fever) into mammalian cells (Martinez JJ et al 2005 Cell 123:1013). ▶transcription factors, ▶p350, ▶immunoglobulins, ▶RAG, ▶DNA-PK silencer, ▶XRCC, ▶lymphoma, ▶DNA-PK, ▶ligase DNA, ▶DNA repair, ▶PIK, ▶non-homologous end-joining, ▶chromosomal rearrangements, ▶NHEJ, ▶Mre11, ▶terminal deoxynucleotidyl transferase, ▶Bloom syndrome; Featherstone C, Jackson SP 1999 Mutation Res 434:3; Woodard RL et al 2001 J Biol Chem 276:15423; Walker JR et al 2001 Nature [Lond] 412:607; Li G et al 2002 Proc Natl Acad Sci USA 99:832.

Kufor-Rakeb Syndrome (KRS, 1p36): A rare recessive Parkinson disease involving defect in the ATPase of the pyramidal excitatory neurons. ▶Parkinson disease

Kugelberg-Welander Syndrome: A muscular atrophy expressed at infancy determined either by a dominant or recessive factor in human chromosome 5q11.2-q13.3. ▶neuromuscular disease, ▶atrophy

Kunkel Mutagenesis: Template DNA is generated in a bacterial strain of *dut ung* constitution. Such are defective in dUTPase (*dut*) and uracil-N-glycosylase (*ung*). Consequently several uracil residues are incorporated into the single-stranded M13mp19 phage DNA and these cannot be removed by DNA repair because of the defective glycosylase. To this DNA a mutagenic nucleotide primer is added and then in the presence of all four deoxyribonucleotides, a new strand is synthesized using the U-containing single-strand DNA template of M13. After the new M13 DNA synthesis is completed, the molecule is transfected into wild type *E. coli* which gets rid of the U-containing strand and synthesizes DNA containing the mutant nucleotide and the resulting phage plaques contain the localized, directed mutation. ▶homolog-scanning mutagenesis, ▶localized mutagenesis, ▶site-specific mutagenesis, ▶bacteriophages, ▶glycosylases; Kunkel TA 1985 Proc Natl Acad Sci USA 82:488.

Kupffer Cell: A large phagocytotic type cell with large nucleus and nucleolus in the liver similar to macrophages. Malaria infection apparently disables these cells to succeed (Frevert U et al 2005 PLoS Biol 3:e192). Kupffer cells can play a role also in atherogenesis by removal of low-density lipoproteins through the activity paraoxonase 1 (Bradshaw G et al 2005 Proc Natl Acad Sci USA 102:11029). ▶macro-phage, ▶IL-18, ▶LDL, ▶paraoxonase

Kurtosis: A departure from the symmetrical (normal curve) frequency distribution by displaying excess or deficiency at the shoulders compared to the tails and the highest point of the curve (peakedness) (see Fig. K22). At normal distribution $(x - \mu)^4 / \sigma^4 \cong 3$. A higher ratio indicates kurtosis. A *leptokurtic* distribution is characterized by higher number of observations or measurements at the mean and at the tails. *Platykurtic* distribution displays the opposite, i.e., less at the mean and tails than expected by normal distribution. ▶normal distribution, ▶skewness, ▶moments, diagrams redrawn after Hyperstat.

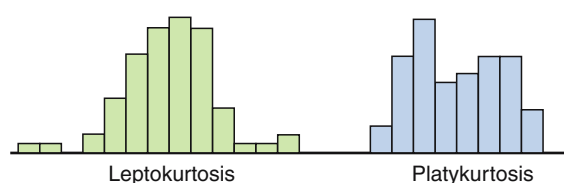


Figure K22. Kurtosis

Kuru: Infectious human chronic degenerative disease characterized by tremors, ataxia (lack of muscular coordination), strabismus (contorted visual axis in the two eyes), dysarthria (stemmering and stuttering), dysphagia (difficulties in swallowing), fasciculation (bundling of nerve and muscle tissues) among others. In general, death results within a year after onset. It affects about 1% of women of the Fore tribe of Papua New Guinea, and their daughters and sons. Kuru shows vertical transmission because in the Fore tribe populations, the females and their youngsters consume some flesh of dead relatives as a cannibalistic, religious ritual. It occurs sporadically also in neighboring tribes due to stenosis, LEOPARD syndrome, or it may be viral or it is due to prions. ▶prion, ▶Creutzfeldt-Jakob disease, ▶LEOPARD syndrome, ▶stenosis, ▶encephalopathies; Collins S et al 2001 J Clin Neurosci 8(5):384; Mead S et al 2003 Science 300: 640.

KUZ (Kuzbanian): ▶ADAM

kV: kilovolt, 1,000 V. ▶volt

KVLQT1: ▶Beckwith-Wiedemann syndrome

kW: kilowatt, 1,000 Watt. ▶watt

Kwashiorkor: A condition caused by malnutrition of humans on diets low in essential amino acids, particularly lysine, tryptophan and methionine. The

symptoms are emaciation with altered pigmentation in patches on the hair and skin. On dark spots of the limbs and back the epithelial layer may be shed showing raw flesh as pink blotches. If it is coupled also with a deficiency in caloric intake, the condition is further aggravated by losing both flesh and fats and generally coupled with dehydration as well (marasmic kwashiorkor). It is a widespread anathema particularly in the tropical and subtropical areas of the world with underdeveloped agriculture and political turmoil. The term's origin is an African Gold Coast (Ghanaian) language meaning pink boys, descriptive of the syndrome. This severe malnutrition primarily affects children. The condition is aggravated by infectious diseases (e.g., AIDS) and poisons in the food (e.g., aflatoxin). The therapy is a gradual return to balanced, nutritious diet. ▶essential amino acids, ▶high-lysine corn, ▶AIDS, ▶aflatoxin

Kwok: Polymorphism (SNIPs, duplications, deletions, rearrangements) in ESTs, named after P-Y. Kwok who first called to their usefulness for studying genomic variations. ▶SNIP, ▶EST; Kwok P-Y 2002 Hum Mut 19:315.

KYA: (kiloyears ago): 1 ky = 1,000 years. ▶MY

Kynurenine: An intermediate in tryptophan metabolism. In humans an autosomal recessive deficiency of the enzyme kynurinase results in excessive amounts in xanthurenic acid in the urine (see Fig. K23). Xanthurenic acid is a tryptophan metabolite that accumulates also in case of pyridoxal phosphate (vitamin B₆) shortage in the diet. The urine of the reproductively mature female masu salmon (*Oncorhynchus masou*) contains kynurenine as a male-attracting pheromone and it active at picomolar concentrations (Yambe H et al 2006 Proc Natl Acad USA 103:15370). ▶tryptophan, ▶Huntington chorea

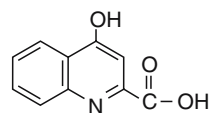


Figure K23. Kynurenic acid

Kyoto Encyclopedia of Genes and Genomes: <http://www.genome.ad.jp/kegg/>.

Kyphosis: ▶scoliosis, ▶lordosis

Historical vignette

W Haacke assumed in 1893 (*Biol. Zbl.* 13:525) that the waltzing - walking traits of mice are located in cytoplasmic elements (centrosome) whereas coat color (white-gray) segregation is assured by the reductional division of the chromosomes. ("I do not know whether the number of chromosomes present in mice had been recorded, but this number would enable us to establish the possible combinations".) The fact that he was able to obtain experimentally all 16 combinations of these 4 traits seemed to indicate to him the validity of this interpretation. Although C Correns and independently E Baur (*Zeitschr. Ind. Abst. Vererb.-Lehre* 1:291 and 330, respectively) reported genuine cytoplasmic inheritance in 1909, and their findings were abundantly confirmed, John R Preer, Jr., an eminent contributor to the field remarked: "Cytoplasmic inheritance is a little bit like politics and religion from several aspects. First of all, you have to have faith in it. Second, one is called upon occasionally to give his opinion of cytoplasmic inheritance and to tell how he feels about the subject". (P. 374 in *Methodology in Basic Genetics*, WJ Burdette, ed., Holden-Day, San Francisco, 1963.)

L

- λ:** Lambda bacteriophage. ► [lambda phage](#)
- λ:** The prevalence of a condition/gene in a population. ► [prevalence](#)
- L1:** LINE1 (long interspersed repeat). ► [LINE](#)
- L1:** ► [hybrid dysgenesis I–R](#)
- L1:** A cell adhesion molecule with important role in neurogenesis. It contains fibronectin domains. ► [fibronectin](#)
- L Box:** A tract in the leader RNA sequence of lysine biosynthetic genes that mediates either termination of transcription by excess lysine or regulates translation initiation. ► [lysine](#); Grundy FJ et al 2003 Proc Natl Acad Sci USA 100:12057.
- L Virus:** ► [killer strains](#)
- La:** An autoimmune antigen transiently associated with pre-tRNAs and 5S rRNAs. It mediates both transcription initiation and termination by Pol III. ► [Pol III](#), ► [ribosomal RNA](#)
- Labeling:** The attachment or incorporation of a radioactive or fluorescent compound into a molecule that permits the recognition of the molecule itself in the cell or in the extract of the cells or any molecule with which it is hybridized, attached or into which the label is inserted.
- Single-walled carbon nanotubes bound by single- and double-stranded DNA and carbon nanotube field effect transistors (NTNFET) selectively recognize DNA sequences with SNP. Single mismatch is thus detectable without the use of radioactive or fluorescent labeling at a low cost (Star A et al 2006 Proc Natl Acad Sci USA 103:921). ► [probe](#), ► [nick translation](#), ► [radioactive labeling](#), ► [immunoprobe](#), ► [fluorochromes](#), ► [radioactive tracer](#), ► [gene tagging](#), ► [nonradioactive labels](#), ► [biotinylation](#), ► [FISH](#), ► [immunofluorescence](#), ► [aequorin SNP](#), ► [nanotechnology](#)
- Labeling Index:** A labeling index shows the fraction of cells that incorporate labeled nucleotides, i.e., the percent of S phase cells in a tissue. The fraction of labeled cells in relation to DNA content permits a convenient estimate of the cells in the G1 phase (1 DNA unit), G2 + M (2 DNA units) phase, and in between 1 and 2 indicating the S phase. The fractions of cells can be analyzed with the aid of an automatic cell sorter. ► [labeling](#), ► [cell cycle](#), ► [cell sorter](#)
- Labor:** The process of child delivery.

Laboratory Management Software: <http://www.cato.com/biotech/bio-software.html> - LIMS.

Laboratory Safety: In laboratory safety, the most important prerequisite is to know the potential hazards of equipment and the biological and chemical materials to be employed. Develop plans how to cope with possible accidents and how to dispose of spillage, fumes, fire, and other laboratory waste etc. Most of the commercial suppliers provide safety information for chemicals ordered. Use nonporous (neoprene) gloves. Sometimes using bare hands may be justified because accidental contact can be immediately sensed and proper washing can decontaminate the body. Fume hoods (with proper air exchange) must be used with chemicals that evaporate or sublime. Appropriate sterilization and the use of certified laminar flow hoods could minimize biological hazards. Laboratory waste must be segregated for solids and liquids. Do not dump any chemical (mutagens and carcinogens) into drains as that may hurt plumbers and cause problems at the level of wastewater treatment. Monitoring with radiation counters and appropriate shielding may prevent radiation hazards. Keep workbenches clean. All laboratory personnel must be properly instructed about safety and checked regularly for compliance. Remember the admonition of Paracelsus, the fifteenth-century physician and scientist, that “Poison is everything and no thing is without poison. The dosage makes it either a poison or a remedy.” ► [environmental mutagens](#), ► [chemical mutagens](#), ► [ionizing radiation](#), ► [radiation hazard assessment](#), ► [gloves](#), ► [biohazards](#); Fleming DO, Hunt DL (Eds) 2000 Biological safety, ASM Press, Washington, DC; <http://www.cdc.gov/od/ohs>; <http://www.absa.org/>.

Laboratory Tests: ► [clinical laboratory tests](#)

Labrum: An anterior-most structure (mouth) of the head of arthropods. In general, morphology edges; lips are designated as such.

Labyrinth: A communication canal or cavity such as in the labyrinthine trophoblast connecting maternal and fetal tissues of the placenta, internal part of the ear, tubules in the kidney, etc.

Lac operon: *E. coli* can utilize the milk sugar lactose by splitting it into glucose and galactose with the aid of the β-galactosidase enzyme encoded by the *Lac z* gene. This enzyme is not made unless lactose or one of its analogs is present in the culture medium (inducible enzyme) and even then not until there is glucose available. This particular metabolic response is under a very precise and complex genetic regulation in prokaryotes. When transcription begins 3 genes are, in fact, transcribed into a 3-cistronic

RNA. The *Lac y* gene encodes a galactoside permease, a membrane protein that facilitates the uptake of the substrate for the galactosidase. The *Lac a* gene is a transacetylase that acylates the galactoside with the assistance of acetyl-coenzyme-A. The nucleotide sequence of this regulatory upstream region is shown.

For the sake of brevity the map (at 8 min) is shown. When galactosidase is not synthesized, a repressor protein blocks the repressor-binding sequences, a definite tract within a section of the promoter region, a part of the operator gene. The product of the *Lac I* (1040 bp) gene is 152-kDa, a 4-subunit repressor protein. The transcription of the *Lac I* gene is separately regulated from the genes that it controls by suppression (negative control). Since the repressor-binding site is within the operator gene where the transcriptase enzyme (RNA polymerase) is attached to carry out its function, it prevents the expression (transcription) of the down-stream genes (*z*, 3510 bp; *y*, 780 bp; *a*, 825 bp) of the operon. The Lac Z protein is 125-kDa, the *Lac y* and the *Lac a* are both about 30 kDa. Because of the coordinated operation of iuxta-positioned genes, the system was named *operon*. The *Lac i* gene is transacting because its product can flow to the operator irrespective of where the gene is located within the cell; it can be in the vicinity of the operon or it can be carried by a plasmid. Furthermore, if there is an inactive i^- gene next to the operon within the bacterial chromosome the *z*, *y* and *a* genes are transcribed. Introduction of a i^+ (wild type) suppressor gene in a plasmid, the transcription is blocked from this in trans position. Also it shows that the active form of *i* is dominant. The tetrameric repressor protein is normally a homotetramer, i.e., the four subunits are identical. If the cell has two different *i* genes that code differently-altered repressor monomers, the aggregate becomes a heterotetramer and may show *allelic complementation*. The i^d gene product in the presence of the wild type polypeptide imposes a conformational change on the repressor tetramer and renders it inactive by “dominant negative complementation”. This phenomenon also indicates that the monomers alone are not functional but their aggregate (quaternary structure) is the functional repressor. Base substitution mutations within the *Lac i* may abolish the ability of the protein to bind to the operator thus allowing protein synthesis to go on constitutively (without a need for induction). Mutations may also reduce its binding and thus without induction a reduced level of transcription can still continue. If the mutations affect the inducer-binding sites of the repressor, it may no longer bind the inducer and becomes a super-repressor mutation, i^S . The number of repressor molecules per cell is about 5 to 10.

Similarly, mutations within the operator region may alter the binding of the wild type suppressor. If the

repressor is bound to it rather than the RNA polymerase, the transcription of the three structural genes (*z*, *y*, *a*) cannot proceed. The repressor does not prevent the binding of the RNA polymerase to the promoter, it may even enhance the binding of the polymerase but it blocks the initiation of transcription. Since the RNA polymerase is at its site before induction, transcription is initiated almost immediately, as soon as the inducer makes contact with the repressor. The operator gene is unique because it does not have any product; it merely serves as the starter site for transcription if the RNA polymerase can attach to it. Therefore, the operator must always be in cis position, in front of the structural genes. The binding sequences within the operator shown in the Fig. L1 here have inverted repeats (RED) and the inactivating mutations are shown blue (see Fig. L1) (modified after Watson JD et al 1987 Molecular Biology of the Gene. Benjamin/Cummings, Menlo Park, California).

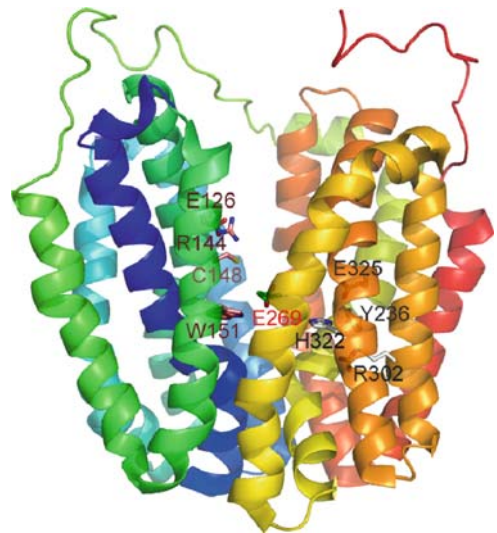


Figure L1. LacY is organized into two six-helix bundles with twofold pseudosymmetry separated by a large interior hydrophilic cavity open only to the cytoplasmic side and containing the side chains important for sugar and H⁺ binding. The residues involved in substrate binding [Glu-126 (helix IV), Arg-144, Cys-148, and Trp-151 (helix V)] are shown as pink sticks, and those involved in H⁺ translocation [Tyr-236 (helix VII), Arg-302 (helix IX), His-322, and Glu-325 (helix X)] are shown in yellow. The dualfunction residue Glu-269 (helix VIII) is shown in green. Cys-154 is shown as van der Waals spheres (yellow). Pro-28, Pro-31, Ile-32, and His-35 on helix I (yellow surface) and Gln-241, Gln-242, Ala-244, Asn-245, and Thr-248 on helix VII (cyan surface) form a periplasmic gateway. The black color represents the back-side of the surfaces (Courtesy of Dr. Lan Guan; see also Guan, L. *et al.* 2007 Proc. Natl. Acad. Sci. USA 104:15294)

The left side of the operator is more likely to render it unresponsive to repressor binding. If the repressor cannot bind to the operator, an operator-constitutive system emerges that is functional without induction (o^C). When the cells are grown without galactoside the number of galactosidase molecules may be less than 5 pe. After supplying galactose, within a couple of minutes, the number of galactosidase molecules increases by about a thousand-fold. If the inducer is used up, the system reverts to the uninduced state very rapidly because the half-life of the mRNA is only about three minutes, although the already synthesized proteins may linger on for a little longer. Induction can take place without β -galactoside if thiogalactosides, particularly the often-used isopropyl-thiogalactoside (IPTG), are provided. These thiogalactosides induce the synthesis of the galactosidase enzyme although the enzyme cannot use these analogs as substrates (see Fig. L2). These therefore

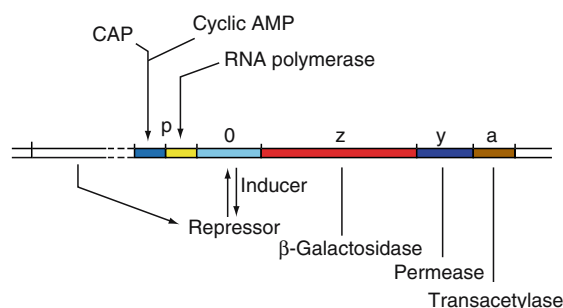


Figure. L2. General organization of the *Lac* operon

are *gratuitous inducers* (see Fig. L5). The presence of the slight amounts of the permease protein in the noninduced cells is required to initiate the uptake that eventually jump-starts the system. When the inducer is added to the system, it combines with the repressor and a change in the conformation prevents it from attaching to the repressor-binding sites in the operator region. The repressor protein has two essential sites; one that binds the inducer and the other that binds the operator. Although the binding of the repressor is not exclusively limited to the operator, it binds to this region by about 10 million-fold more effectively than to other sequences of the genome. When the cells take up the inducer, the unspecific binding to the whole of the genome does not change but the binding to the operator is almost completely relieved (see Fig. L6).

The mechanisms discussed here (negative control) are only parts of the total regulatory system and we will have to look at the role of the CAP-cAMP site upstream in the promoter. CAP stands for catabolite activator protein. It has also been called the cyclic AMP receptor protein (CRP, encoded by gene *crp* at

map position 73 min). CAP is a 22.5-kDa dimeric protein. Its subunits contain a DNA-binding and a transcription-activating site. Thus, CAP interacts both with DNA at the evolutionarily conserved upstream site and with α -subunits of the RNA polymerase. The CAP protein becomes active upon forming a complex with cyclic adenosine monophosphate (cAMP). cAMP is formed from ATP by the enzyme adenylate cyclase (the encoding *cya* gene is at map position 84 min) and its formation is reduced by glucose. We have discussed earlier that as long as glucose is available for the cells, β -galactosidase and companion enzymes are not formed in appreciable amounts. This phenomenon is called the glucose effect or, also, catabolite repression. The basis of this repression is that there is not enough cAMP to activate transcription by the CAP-cAMP complex. If the CAP-cAMP system is defective the *lac* operon cannot function even if the repressor is not formed and the operator is constitutive. Therefore, the CAP-cAMP complex constitutes a positive regulatory element of the *lac* operon in contrast to the negative regulatory *i-o* system, as seen in Figure L3. We can



Figure L3. The binding sequences within the *Lac* operator. (Modified after Watson JD et al. 1987 Molecular Biology of the Gene, Benjamin/Cummings, Menlo Park, CA)

also conclude that this system uses great wisdom in managing cellular energies: it calls to duty the enzymes only when they are needed and turns off the synthesis as soon as they are no longer needed. One of the products of the galactosidase, glucose reduces the synthesis of the enzyme that splits it off from lactose. The *lac* gene has also been used extensively as a reporter in eukaryotic systems (see Fig. L4) (Mills AA 2001 Genes Dev 15:1461).
 ▶suppression, ▶helix-turn-helix motif, ▶transcription, ▶translation, ▶allelic complementation, ▶galactose, ▶galactose utilization, ▶galactosidase, ▶ β -galactosidase [for assay], ▶cAMP receptor protein, ▶*Lac* repressor; Müller-Hill B 1996 The *lac* operon. De Gruyter, New York.

Lac Repressor: A protein that negatively regulates the *Lac* operon in the absence of lactose in the medium. When the repressor is combined with lactose (inducer) or isopropyl- β -D-thiogalactoside (gratuitous inducer), cAMP and CAP, the transcription of the structural genes may be started. The bound

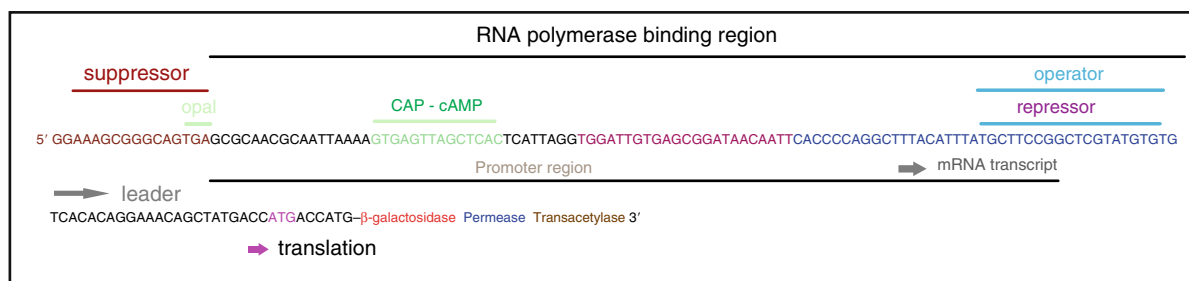


Figure L4. Base composition of some of the structural and functional elements of the *Lac* operon

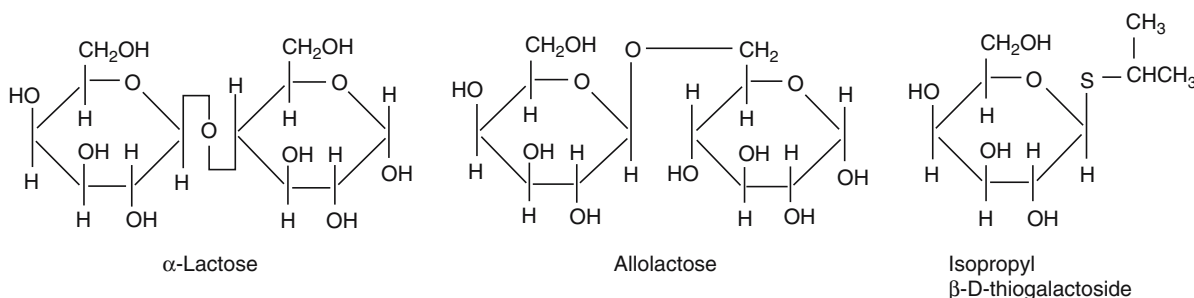


Figure L5. Inducers of the *Lac* operon

repressor either inhibits the binding of the RNA polymerase or prevents elongation of the transcript. The *Lac* repressor protein (LacR/LacI) has a small headpiece (the binding domain) and a large core (regulatory domain). The intact 38-kDa repressor forms a homotetramer of 152 kDa. Each of the two LacR core dimers arranges the headpieces in such a manner that they bind maximally to the operator. Headpiece monomers bind only weakly. In the presence of an inducer (IPTG) the binding is reduced by three orders of magnitude. The LacR also mediates DNA looping to make contact at multiple sites. There are about 20 members of the family of *Lac* repressor proteins. The lactose, fructose, and raffinose repressors are tetramers while the others are dimeric. The majority of the *Lac* repressor (*LacI*) family members are most effective if no other proteins bind to them. The PurR (purine repressor), however, requires the presence of a corepressor (hypoxanthine and guanine) ligand. [▶Lac operon](#), [▶purine repressor](#), [▶cAMP receptor protein](#), [▶hypoxanthine](#), [▶looping of DNA](#); Fried MG, Daugherty MA 2001 J Biol Chem 276:11226.

Laccase: Phenoloxidases (laccase and tyrosinase) are responsible for sclerotization (hardening) and pigmentation of insect cuticles (Arakane Y et al 2005 Proc Natl Acad Sci USA 102:11337).

LacI^f: A mutant *LacI* that synthesizes about 10 times more repressor than the wild type allele.

Lactacystin (C₁₅H₂₄N₂O₇S): A *Streptomyces*-produced inhibitor of proteasome by affecting the amino-terminal threonine. It inhibits several proteases and the cell cycle, and causes neurite outgrowth in neuroblastoma cells. It may inhibit the degradation of p53. [▶ubiquitin](#), [▶neurite](#), [▶neuroblastoma](#), [▶proteasome](#), [▶p53](#); Yamada Y et al 2000 Eur J Haematol 64(5):315.

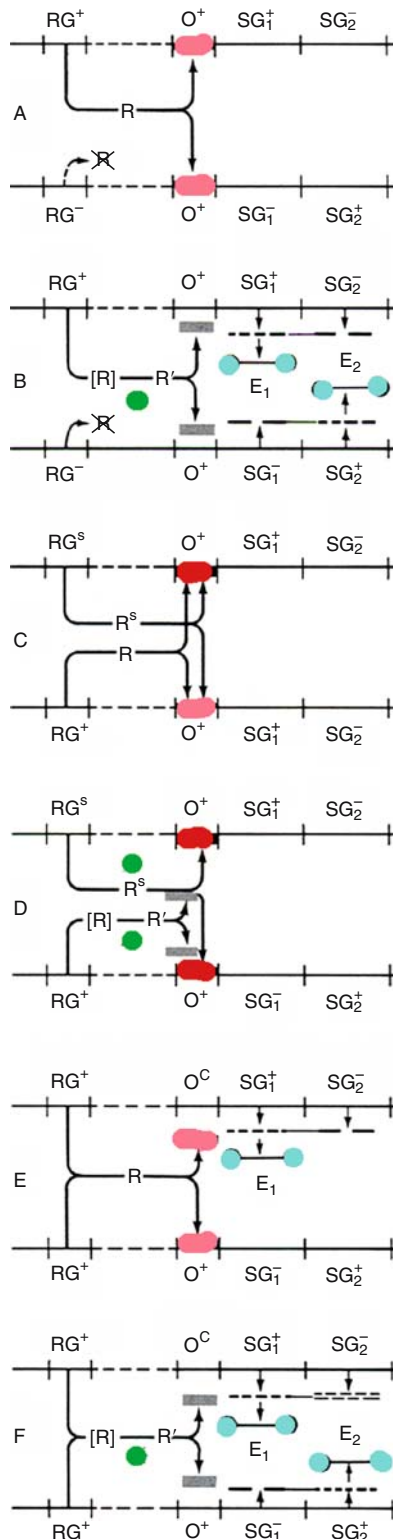
Lactam: A tautomeric form of uracil (see Fig. L7). [▶penicillin](#), [▶tautomeric shift](#), [▶pyrimidines](#)

Lactamase: [▶ \$\beta\$ -lactamase](#)

Lactase: Also known as β -galactosidase.

Lactase Deficiency: [▶disaccharide intolerance](#)

Lactate Dehydrogenase (LDH): Lactate dehydrogenase catalyzes the reaction: pyruvate + NADH + H⁺ \rightleftharpoons lactate + NAD⁺. Lactate is generally not utilized as such but it is converted back to pyruvate. The rationale of the reaction is to regenerate NADH for glycolysis in the skeletal muscles thus shifting the metabolic burden from muscle to liver. In yeast, the L-lactate dehydrogenase is also called cytochrome b₂. The mammalian enzyme is a tetramer consisting of four subunits, each with an approximate



A simplified model of the operation of negative control in an operon like lac. RG^+ : wild-type allele of regulator gene; RG^- : defective regulator gene; O^+ : wild-type operator gene; SG^+ : wild type; SG^- : mutant structural genes (responsible for enzyme proteins); (red oval) repressor.

The genetic conditions are identical to those at A, but an inducer (green dot) is provided. Now the repressor is neutralized (grey oval), and either functional (---) or defective (---) transcripts are made depending on the structural genes. The non-mutant mRNA of the SG^+ genes is translated into protein (blue circles).

A mutation from RG^+ to RG^s leads to the production of a superrepressor protein (red oval) which locks permanently into the operator. No mRNA and no protein are produced by the structural genes.

In the RG^+/RG^s heterozygotes the product of the RG^+ allele is receptive to the inducer (green dot) and is prevented from blocking the operator, but the superrepressor product (red oval) cannot be removed from the system. No mRNA and no protein are produced.

In the presence of two RG^+ genes (wild-type repressor), one of the operator alleles mutates to O^C (constitutive operator). In this case, the wild-type repressor protein is unable to bind to the O^C region even in the absence of an inducer. Consequently, transcription may proceed on one sequence of the operon.

The genetic constitution is identical to that diagrammed in E but inducer is provided for the system. Now transcription becomes possible on both sequences, and functional protein is made from the two wild-type structural alleles just as it is in the case illustrated in B.

Figure L6. *Lac* operon has been a paradigm of genetic regulation since its inception. The diagram illustrates some of the functional circuits involved by more general symbols. Of course not all genetic regulatory systems use exactly the same principles but several elements of it are valid for other regulations. (Modified after Jacob F and Monod J 1961 Cold Spring Harbor Symp. Quant. Biol. 26:193)

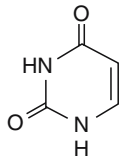


Figure L7. Lactam

M_r of 33,500. These subunits are encoded by two separate genes and can be combined into 5 different isozymic forms— A_4B_0 , A_3B_1 , A_2B_2 , A_1B_3 , A_0B_4 . In the skeletal muscles the A chains (synonymous with M) predominate whereas in the heart the B chains (synonymous with H) are dominant. The isozymic forms also vary during development. In cancer cells, the LDH isozymes are present in fetal rather than in the adult form. LDHA deficiency compromises the ability of cancer cells to proliferate under hypoxia, indicating the role of the enzyme in the maintenance of tumors. This fact may open an approach for controlling tumor growth (Fantin VR et al 2006 Cancer Cell 9:425).

L

In humans, the LDHA gene was assigned to chromosome 11p15.4, and LDHB to 12p12.1–12p12.2. The testes-specific LDHC protein is also encoded in the close vicinity of LDHA. The nucleotide and amino acid homology between human LDHA and LDHB varies between 68 and 75%. In mouse, LDHC displayed 72–73% homology with LDHA; in humans the similarity was just slightly higher between the two amino acid chains. In the Japanese population, LDHA and LDHB deficiencies occurred at frequencies of 0.19 and 0.16, respectively. These figures are supposed to be too high for other populations. LDHA deficiency in humans was associated with skin lesions, myoglobinuria, and fatigue. It was found that LDHA deficiency is caused by 20-bp deletions in exon 6 but nonsense mutation GAG → TAG at codon 328 was implicated at another human deficiency. LDHB deficiency was found to be due to a replacement of the highly conserved arginine 173 by a histidine. ▶isozymes, ▶code genetic, ▶dehydrogenase

Lactic Acid ($\text{CH}_3\text{CHOHCOOH}$, MW 90.08): Lactic acid is formed from pyruvate through glycolysis or by fermentation of lactose (yogurt). Lactic acid is the main end product of sugar metabolism of lactic acid bacteria. Lactic acid is formed in the skeletal muscles and oxidized in the heart for providing energy. It can also be converted again into glucose by gluconeogenesis. It is the most important preservative in silage fermented at moderate temperature. (See Gladden LB 2001 Proc Natl Acad Sci USA 98:395).

Lactic Acidosis: Lactic acidosis may be the result of deficiency of dihydrolipoamide dehydrogenase (7q31-32). It may also be due to pyruvate decarboxylase deficiency. ▶mitochondrial disease in humans, ▶Leigh encephalopathy

Lacticaciduria: Due to an autosomal recessive condition in which blood lactate and pyruvate level is increased. In the different forms of the disease, pyruvate carboxylase, pyruvate dehydrogenase, and phosphoenolpyruvate carboxykinase enzymes may be defective. Mental retardation, loss of hair, lack of muscle coordination and infant death may occur. ▶ketoacidosis

Lactobacillus acidophilus: A common, natural, non-pathogenic, useful, fermentative bacterium of the gut. The complete genome is 1,993,564 nucleotide pairs without any plasmid or prophages. Predicted open-reading frames are 1,864. (See Alterman E et al 2005 Proc Natl Acad Sci USA 102:3906).

Lactobacillus plantarum: A widely spread fermentative bacterium of 3,308,274 bp containing 3,052 predicted genes of which 70% have a putative function. The genome includes two prophages of 44 kb and 43 kb, respectively. For comparative genomics of *lactobacilli* see Makarova K et al 2006 Proc Natl Acad Sci USA 103:15611. (See Kleerebezem M et al 2003 Proc Natl Acad Sci USA 100:1990).

Lactobacillus salivarius UCC118: A sequenced, genetically studied, and prebiotic (beneficial) strain of human origin. It produces a bacteriocin in vivo that can significantly protect mice against infection with the invasive foodborne pathogen *Listeria monocytogenes*. *Lb. salivarius* UCC118 did not offer any protection when mice were infected with a strain of *L. monocytogenes* expressing the cognate immunity protein AbpIM. Thus the antimicrobial effect is a result of direct antagonism between *Lb. salivarius* and the pathogen, mediated by the bacteriocin Abp (Corr SC et al 2007 Proc Natl Acad Sci USA 104:7617). ▶bacteriocin, ▶Listeria

Lactococcus lactis: A Gram-positive bacterium of cheese making. The sequenced laboratory strain IL1403 contains 2,365,589 bp encoding 2,310 proteins. Among them 293 appear to be of prophage origin. It also contains 43 insertion elements. ▶prophage, ▶insertion element; Bolotin A et al 2001 Genome Res 11:731; <http://www.wzw.tum.de/proteomik/lactis/>.

Lactoferrin: An iron-binding glycoprotein in milk, in other secretions and in neutrophils. It defends the cells against infections and is a growth regulator. It modulates killer cells of the immune system. It is also a peptide messenger, binding to conserved DNA

sequences and activates transcription. ▶ **messenger polypeptide**, ▶ **killer cells**; Kanyshkova TG et al 2001 Biochemistry [Mosc] 66:1.

Lactose (milk sugar): A disaccharide of galactose + glucose. (See formula at ▶ **Lac operon**).

Lactose Intolerance: ▶ **disaccharide intolerance**

Lactose Permease: ▶ **Lac operon**

Lactosyl Ceramidosis: A deficiency of β -galactosyl hydrolase involving a hereditary sphingolipidosis type of disease. ▶ **galactosidase**, ▶ **sphingolipids**

Lacuna: A hole in the bacterial lawn caused by the production of bacteriocin.

LacZ: A gene for the β -galactosidase enzyme (map position 8 min). Another locus of *E. coli* (*ebgA*⁰, map position 67 min) may evolve into a β -galactosidase gene if the locus at position 8 is deleted. At least two different mutations are required to acquire this enzyme activity but it may evolve to this state through different paths. The new activity is based on an immunologically different protein from that of the *LacZ* product. ▶ **Lac operon**, ▶ **Xgal**, ▶ **galactosidase**

LacZ Δ M15: The amino terminal of the bacterial β -galactosidase gene is deleted. ▶ **Lac operon**

Ladd Syndrome (lacrimo-auriculo-dentato-digital syndrome, Levy-Hollister syndrome, 10q26): An autosomal dominant trait characterized by cup-shaped ears, insufficiency of lacrimal glands and ducts, small teeth, hearing loss, abnormal digits, etc. Fibroblast growth factor receptor (FGFR2) mutations affect the tyrosine kinase activity of the activation loop of the protein. Additional mutations involve FGFR3 and FGFR10 (Rohmann E et al 2006 Nature Genet 38:414). ▶ **FGF**

Ladder: A collection of oligonucleotides of precisely known length that can be used as standards for identifying the length of DNA fragments separated by electrophoresis. The synthetic ladders generally have a certain number of progressive base increments, e.g., 123, 246, 369. For the rainbow ladders of proteins the standards are labeled by fluorescent dyes and are detectable without staining (see Fig. L8).



Figure L8. Part of a molecular ladder

LaFora Disease (6q24): ▶ **myoclonic epilepsy**

Lag Phase: The lag phase of a culture is when growth is minimal and when, under favorable conditions, it may

be followed by exponential growth. ▶ **exponential growth**

Lagging Strand: The lagging strand of DNA facing the replication fork by its 5' end and the elongation can only be accomplished by adding 5'-P ends of the nucleotides to the 3'-OH ends by phosphodiester linkage. It therefore must be synthesized in pieces, in Okazaki fragments. ▶ **DNA replication**, ▶ **replication fork**, ▶ **leading strand**, ▶ **nucleic acid chain growth**, ▶ **gene distribution**

Laglidadg: A large family of homing endonucleases with the LAGLIDADG amino acid motif. ▶ **homing endonucleases**; Chevalier BS, Stoddard BL 2001 Nucleic Acids Res 29:3757.

Lagotrix (woolly monkey): ▶ **Cebidae**

Lair: Lairs are leukocyte receptors (encoded at human chromosome 19q13.4) containing two ITIMs. ▶ **ITIM**

LAK (lymphokine-activated killer cell): A special type of T lymphocyte of the immune system. ▶ **lymphokines**, ▶ **lymphocytes**, ▶ **immune system**

Laloo: A member of the Src family of protein tyrosine kinases that activates mesoderm formation in *Xenopus* using TGF- β and FGF signaling. ▶ **Src**, ▶ **TGF**, ▶ **FGF**, ▶ **Xenopus laevis**

Lamarckism: A largely discredited evolutionary theory embodying the ideas of the French biologist J.B. de Lamarck (1774–1829). He proposed a comprehensive theory claiming that evolution proceeds by the inheritance of gradually acquired characters. He supposed that the use or lack of use of a body structure eventually leads to reinforcement or lapse of that trait by strive and direct environmental influence. The giraffes stretched their neck to reach the treetops, thus the inner drive and the circumstances contributed to their familiar shape. Contrarily, the current concepts, the neodarwinian theory believes that the longer-necked animals could feed better and thus, through continuous selection of increased neck length, their progeny had a selective advantage and facilitated the propagation of cumulative mutations that assured the survival of the best adapted genotypes. Neo-Lamarckism is basically an identical dogma to Lamarckism, except it emphasizes the use or disuse idea rather than the inner drive or autogenesis aspects. ▶ **soviet genetics**, ▶ **lysenkoism**, ▶ **Kammerer**, ▶ **transformation**, ▶ **directed mutation**; Aboitiz F 1992 Med Hypotheses 38(3):194; Lamarck's contributions: <http://www.lamarck.cnrs.fr/>.

Lambda Chain (λ chain): An immunoglobulin light chain. ▶ **immunoglobulins**

Lambda Phage (λ): A temperate bacteriophage, an obligate parasite. It belongs to the family of *lambdoid* phages, that includes phages $\phi 21$, $\phi 80$, $\phi 81$, etc. Lambdoid phages are characterized by cohesive ends, the ability to recombine, and inducibility by UV. Each λ particle contains in its icosahedral head (0.05 μm in diameter) one double-stranded DNA molecule of ca. 49,502 bp that has been completely sequenced by 1982. In its *E. coli* host it can replicate either autonomously and produce hundred progeny particles in 50 min at 37°C. Alternatively, it may insert into the host chromosome as a prophage, generally near the map position of the galactose (*gal*) operon. Phage λ usually does not kill all bacterial cells and therefore its plaques are turbid.

Gene *cI* is the principal phage gene enforcing the lysogenic state (λ being a pro-virus in the host chromosome). In addition, *cI* assures immunity to infection by other λ phages. When *cI* is inactivated, the phage may enter productive growth, i.e., it is liberated from the host chromosome (induction) and begins autonomous replication resulting in lysis of the host. Spontaneous induction occurs at a frequency of 10^{-3} per generation. Exposure to UV light may cause induction in most cells. Mutations *recA⁻* and *cI ind⁻* prevent induction by radiation as well as by spontaneous means. The *N* gene of the phage regulates both *cI* (the repressor of autonomous replication) and the morphogenetic genes involved in operations during the lytic lifestyle (see Fig. L9).

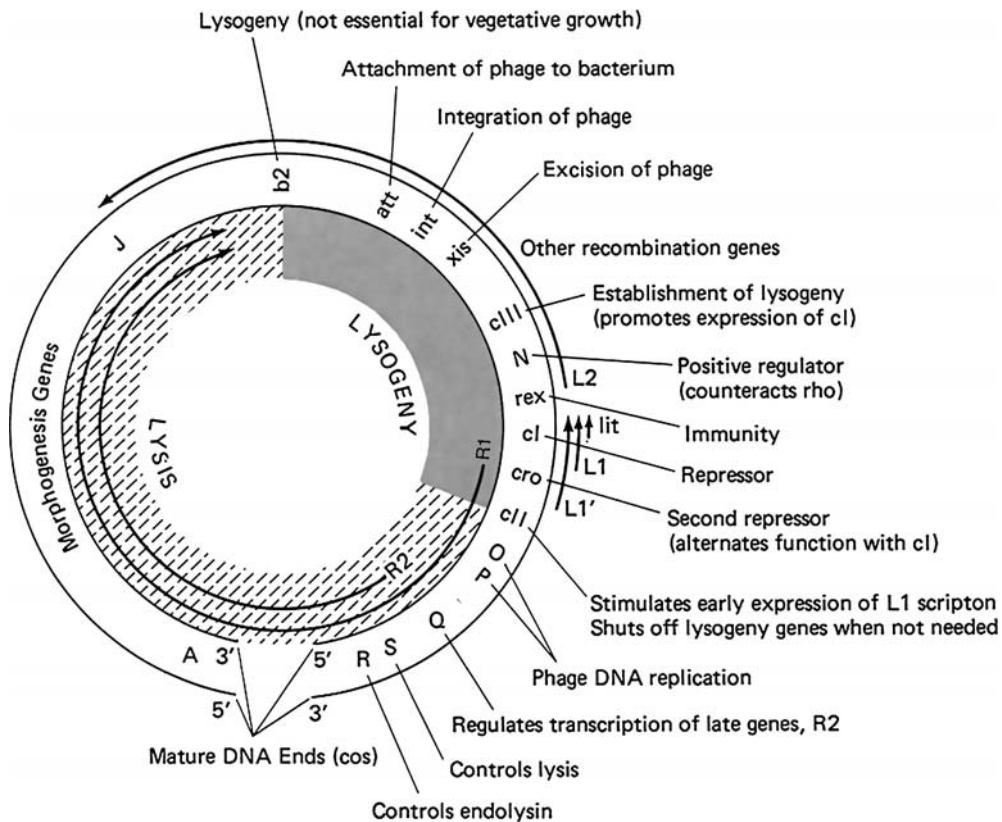


Figure L9. The major functional regions of phage lambda. The head and tail genes are essential for morphogenesis and for the packaging of foreign DNA into λ phage vectors. The region between J and N (the stuffer) can be removed and replaced by foreign genes in the replacement vectors. Just left of the DNA replication genes is the phage immunity region. Before gene *N* is the left *nin* and after gene *P* there is right *nin* region controlling transcription termination. The *ori* gene is the replicational origin and transcription may proceed left- or rightward from pL and pR, respectively. There are additional promoters for the delayed early genes (pI, internal), for the transcription of genes located in the replaceable region and pE and pM for the establishment and maintenance of *cI* repressor controlling the transition from lysogeny to morphogenesis in cooperation with other genes. The total length of the DNA in the wild type phage is about 49.5 kbp. In order to assure packaging, the total DNA in the vectors cannot be less than 78% and not more than 105% of the wild type genome. The region of the A to J genes (ca. 20 kb) and that from pR to the cos site (8 to 10 kb) must be retained for the viability of the particles

The λ genome may assume either a linear or circular form because at the ends (12 bp) of the DNA strands the complementary cohesive sites (*cos*) may open up to a linear form or circularize:

5'pGGGCGGCGACCT CCCGCCGCTGGAp 5'.

Between these ends the genes (encoding about 50 proteins) are in functional units corresponding to their temporal sequence of expression. This relatively small genome transcribes genes in both strands of the DNA double helix. Because of this, it has both left- and rightward transcriptions. The multiple promoters serve the purpose of most efficiently regulating the expression of the genes. The immunity region contains the major regulatory genes of the phage. After infection of the host cell or induction, transcription begins at either the leftward or at the rightward promoters. The leftward promoter, pL, mediates the transcription of genes involved in recombination (integration and excision) under the control of the (12.2 kDa) *N* gene product that may prevent transcription termination of genes using the pL or pR promoters. Some mutations (*ninL* and *ninR*) on both side of *N* may make the system insensitive to the *N* protein. A balance of the action of its own and some host genes determines the fate of the behavior of the phage. For lysogeny, genes *cII* and *cIII* (in opposite promoters, pR and pL, respectively) activate promoters pE (that includes the *cI*) and pL (that

includes gene *int*). The *cI*, the λ repressor, then produces a 236 amino acid protein that prevents the expression of genes involved in phage DNA synthesis and morphogenesis. It activates the synthesis of the *Int* and *Xis* proteins that in turn mediate recombination; thus the phage can integrate into the host chromosome as a prophage (see Fig. L10).

A and *cI* that exclude superinfection by other phages (immunity) and replication of phage DNA become synchronized with that of the host. Actually, the prophage appears as an integral part of the host chromosome. At this state the pM maintenance promoter regulates concentration of the *cI* repressor (see Fig. L11).

The recognition site of the lambda repressor is:

TATCACCGCCAGAGGTA
ATAGTGCGGTCTCCAT

The ability of λ to have a lysogenic state makes it a temperate phage. If, for any reason, *cI* is not functional the bacterial plate shows clear plaques, indicating that the phages are in the reproductive growth phase. The first gene turned on at the pR promoter is *cro* that is followed by *cII* that has gene *P*, the product of λ , a DNA pre-priming protein with host proteins. The expression of gene *Q* prevents transcription termination of the genes involved in lysis and morphogenesis. The products of the *S* and *R* genes mediate lysis of the host cell and this permits the liberation of the phage progeny. Under the

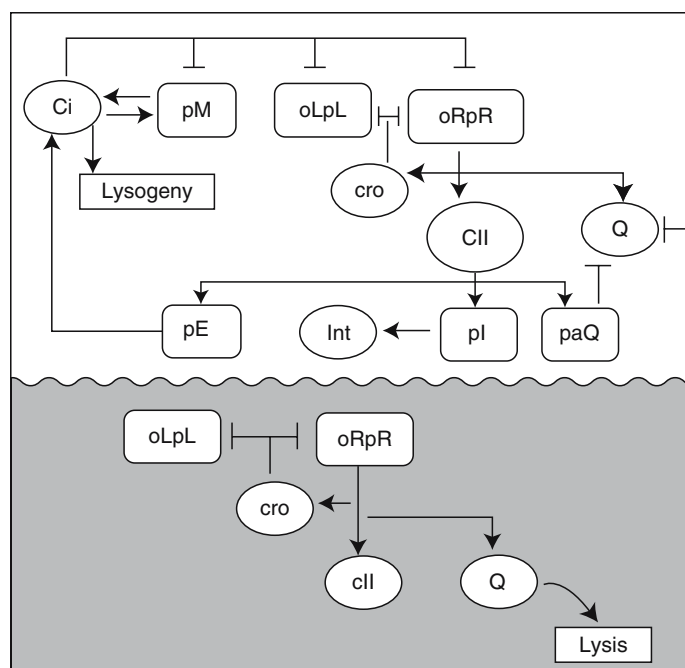


Figure L10. The network of lysogeny-lysis pathways. The ovals represent proteins and the squares stand for promoters. Arrows indicate positive actions while the bars, negative actions. (Redrawn after Kobiler O et al. 2005 Proc Natl Acad Sci USA 102:4470)

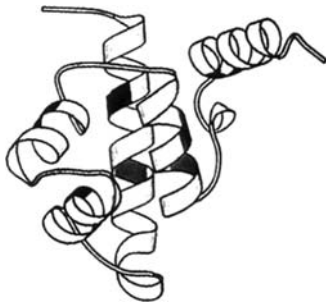


Figure L11. The structure of the lambda repressor. (From Alm E and Baker D 1999 Proc. Natl. Acad. Sci., USA 96:11305)

influence of protein Q the pR promoter assists in the transcription of all late genes and its role ends somewhere in the recombination-control region around the area of *b*. In the integrated state the prophage is replicated under the control of the host as if it would be an intrinsic part of the bacterial genome. Autonomous replication of phage DNA requires the function of the replicational origin (*ori*) where the O protein binds and replication originates. The replication is preceded by circularization of the phage DNA with the mechanical assistance of the cohesive (*cos*) ends which are then sealed by a DNA ligase. When the DNA injected into the host cell first replicates by the bidirectional theta (θ) replicational form, it generates monomeric DNA circles. When the function of the *gam* gene is turned on, replication is switched to the bacterial recBC protein-dependent rolling circle type (sigma replication, σ). This replication results in the formation of linear concatamers attached by the *cos* ends. These concatamers are then stuffed into the preformed phage heads (encapsidation) as shown by the Fig. L12.

The pR promoter mediates the transcription of the head and tail genes. The head and tail components are made and assembled separately before joining into the mature phage particle (see Fig. L12). In this process, the cooperation of host proteins (*groE*) is needed. The concatenated λ DNA molecules are then filled in into the pre-head. The DNA was synthesized in head-to-tail molecules, involving more than a single genome (concatamer). The protein products of the *NuI* and *A* genes bind to the DNA not far from the left *cos* sites and are brought to the pre-head. The *FI* gene product then reels it into the head until the terminal *cos* site is found where the NuI-A protein complex (terminase) cuts it off. The product of the *D* gene stabilizes the head shell and the FII protein completes the head that is now attached to the pre-fabricated tail assembly. The mature phage particle is equipped with injector mechanisms that facilitate the absorption of the particles to the host cell and introduction of its genome through the host cell membrane.

The phage genes under the control of the pL promoter are called early genes, those under pR are called delayed early and those regulated through pR are referred to as late genes. The two major promoters, pL and pR, may not necessarily stop at the termination signals represented by the arrowheads but may continue transcription and thus represent “read-through.” The regulation of the *N* gene product is accomplished by acting at the *nut* sites rather than at the terminator sequences (tL and tR). The *nutL* is located before the terminator, less than 60 bp from pL and the *nutR* is about 250 bp from pR. The *nut* regions have a dyad symmetry, including *boxA* and *boxB*. The region where the *Q* gene product binds is designated as *qut*. The activities of the N and Q proteins are frequently called antitermination function. The function of the λ N gene is also regulated by bacterial (N utilization) genes *nusA*, *nusB*, *nusE*, and *nusG*. *NusA* is a transcription factor while *nusG* encodes ribosomal protein 10. The nusB protein and S10 dimer bind to the *boxA* sequences in bacteria. The nusG assembles the other Nus proteins for binding to RNA polymerase. NusA can facilitate transcription termination by the N protein at intrinsic terminators but all Nus proteins are required for stopping transcription in rho-dependent termination. When the Nus complex and other proteins associate with RNA polymerase, it becomes modified at the *nut* site and can pass through the terminator sites without stopping transcription. The polymerase core can associate either with the σ subunit of the transcriptase or with the Nus N complex. When the N protein replaces the σ subunit of the RNA polymerase the termination signals are ignored. The *qut* sites permit a change in transcriptase to work faster and avoid stoppage at the terminator sites and proceed through the lytic phase into the vegetative growth stage.

Recombination of λ may be mediated by the closely linked genes *exo* (also called *redX*, *reda*, or *redA*) and the *bet* complex (also called β , *red β* , *redB*). These two *red* complexes are involved in general recombination and are not dependent on the function of the host *recA* function. The *exo* gene codes for a 5'-exonuclease (M_r 24,000) that can convert a branched DNA structure into an unbranched nicked duplex by the process called strand assimilation.

The *bet* gene product (subunit M_r 28,000) binds to the exonuclease and promotes reannealing with the complementary DNA strand. The *gam* gene product (M_r 16,500), in a dimeric form, binds to the bacterial host enzyme recBC and inhibits its activities. General recombination is affected by *Chi* (χ) sites near *A*, between *I* and *J*, *xis* and *exo*, within *cII*, between *Q* and *S* genes. *Chis* do not have any gene product; rather, they offer a suitable site for an enhancement of recombination (about five-fold, measured by burst size) through the RecBC pathway.

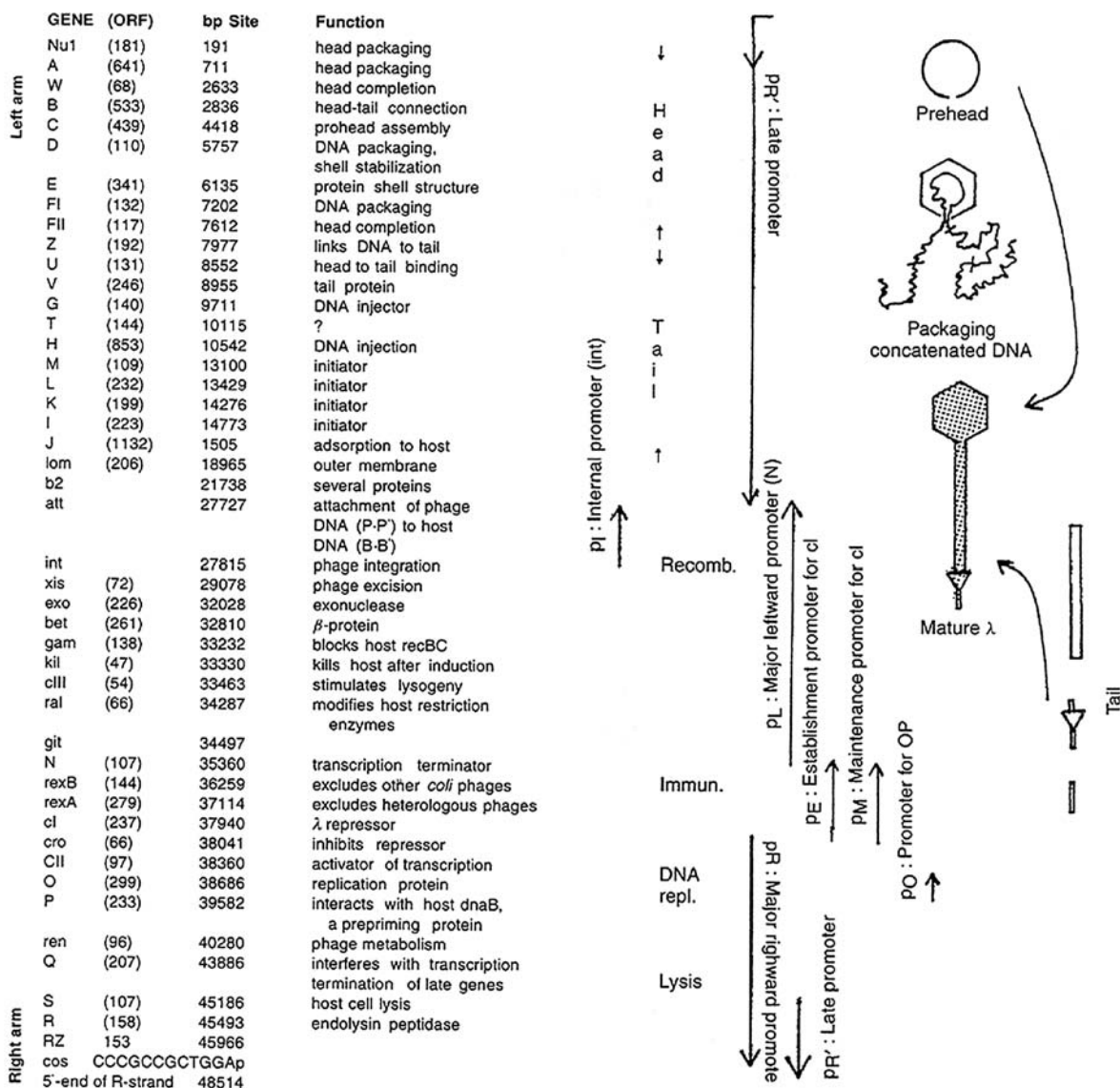
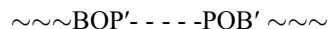


Figure L12. The map of bacteriophage lambda showing the order of the major genes. ORF indicates the size of the open-reading frames and bp site stands for the number of nucleotides starting at the left arm. The base sites may vary in different λ -phages. The morphogenetic pathway is also outlined. (Data from Hendrix RW et al. eds. 1983. *Lambda II*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.)

Near the *chi* sites an octamer consensus exists: 5'-GCTGGTGG-3'. The stimulation of recombination by *chi* is not limited to its location but it is effective over a considerable distance. *Chis* act "dominant" because it is enough to be present in one of the recombining partners. When *Chi* is present in only one of the partners, recombinants without active *chi* are much more frequent than the reciprocals (non-reciprocity). Enhancement of recombination to its left is greater than to its right side (directionality).

Recombination may also be site-specific, requiring a special nucleotide sequence, the primary *att* sites of high efficiency and the much lower efficiency

secondary *att* sites. The *att* sites have common 15-bp core sequences that are 70 to 80% AT. In the phage, the primary *attP* sites are represented as - - -POP' - - - and there is a corresponding site of homology in the bacterium *attB* (~~~BOB'~~~). After recombination (insertion) at the crossing over region (O), by the means of pairing as an inversion loop, in the bacterial cell there will be:



In excision, the process is reversed. The insertion is mediated by λ protein *Int* and the excision uses the products of λ genes *Int* and *xis*. Both processes

also require the bacterial integration protein factor (IHF, M_r 20,000) and other host gene products (see also Kazmierczak RA et al 2002 *Nucleic Acids Res* 30:5193). The coding region of *int* extends 84 to 1,151 bp right from the crossing over site. The M_r of the Int protein is about 40,000 and at the amino terminus it is rich in basic residues and it works as a topoisomerase. The Xis protein shares amino acid sequences with Int. The *xis* product contains 72 amino acids with 25% Lys and Arg. Because of the site-specific recombination, λ phage can mediate specialized transduction.

Phage λ has been used for the development of a number of genetic transformation vectors. Genes not exceeding 5% of the genome can be inserted at a single target site into the λ DNA and can be propagated (insertional vectors). The nucleotide sequences between genes J and N can be deleted (representing about 25% of the genome) and replaced. The DNA can still produce nearly normal size plaques as long as the total length of the DNA remains no less than 37 kb and not more than 52 kb (replacement vectors). In cosmid vectors it is essential to retain the *cos* sites plus 4–6 kb at both termini, including also the origin of replication. The vectors so constructed can propagate foreign DNA exceeding 30 kb.

Synthetic lambda circuits have been constructed. By replacing the CI repressor with another tunable module, Tet repressor and several cis-acting sites have been generated. Tet repressor lacks several important properties of CI, including positive auto-regulation and cooperative DNA binding. Using a combinatorial approach, phage variants were isolated with behavior similar to that of wild type. These variants grew lytically and formed stable lysogens. Lysogens underwent prophage induction upon addition of a ligand that weakens binding by the Tet repressor. Strikingly, however, the addition of a ligand that weakens binding by the *Lac* repressor also induced lysogens. This finding indicates that the *Lac* repressor was present in the lysogens and was necessary for stable lysogeny. Therefore, these isolates had an altered wiring diagram from that of lambda. It was assumed to be practical to customize gene regulatory circuits that would be regulated by small molecules or protein cofactors (Atsumi S, Little JW 2006 *Proc Natl Acad Sci USA* 103:19045). ▶Charon vectors, ▶cosmid vectors, ▶theta replication, ▶rolling circle, ▶rho terminator, ▶specialized transduction, ▶burst size, ▶chi elements, ▶recombination, ▶helix-turn-helix, ▶DNA-binding protein domains, ▶O-some; Hendrix RW et al 1983 *Lambda*, Cold Spring Harbor Lab. Press; Cue D, Feiss M 2001 *J Mol Biol* 311:233; Friedman DI, Court DL 2001 *Curr Opin Microbiol* 4(2):201; details of the λ regulatory networks: Oppenheim AB et al 2005 *Annu Rev Genet* 39:409.

Lambdoid Phages: Lambdoid phages are closely related to the λ phage such as P22 of *Salmonella*. ▶P22; Clark AJ et al 2001 *J Mol Biol* 311:657.

Lambert: A unit of luminous intensity: 1 lumen per cm^2 . The lumen is the unit of luminous flux emitted in a unit solid angle (steradian) by a uniform point source of one candela. ▶candela [candle]

Lamella: A thin plate or membrane sheet.

Lamellipodium: A sheet-like cellular extension involving actin and assisting cell movement. ▶filopodium

Lamina: The lamin structural network and associated proteins. The nuclear lamina surrounding the nucleus controls nuclear pores, regulates transcription and organization of the heterochromatin. ▶lamins

Laminin: A large glycoprotein (~1-MDa) localized in the synaptic cleft between the neuronal basal lamina of the muscle cell sheath and the acetylcholine receptors. ▶synapse, ▶acetylcholine, ▶agrin, ▶epidermolysis, ▶basement membrane; Koch M et al 1999 *J Cell Biol* 145:605.

Laminopathies: Laminopathies are human diseases involving laminins of the nuclear membrane such as the Emery-Dreifuss muscular dystrophy and Lamin B receptor mutations (Pelger-Huet anomaly, hydrops-ectopic calcification-moethaten skeletal dysplasia, osteopoikilosis, idiopathic torsion dystonia, lissencephaly). Laminopathies are involved in several other diseases affecting muscles, axon myelination, lipodystrophy, progeria, etc. (See diseases listed at separate entries, for review: Burke B, Stewart CL 2006 *Annu Rev Genomics Hum Genet* 7:369; Capell BC, Collins FS 2006 *Nature Rev Genet* 7:940).

Lamins: Lamins are intermediate filament proteins (encoded at 1q21). When they are polymerized, nuclear lamina are formed; during interphase, lamins support the nuclear membrane. The A-kinase anchoring protein 149 (AKAP149) seems to recruit lamins to the nuclear envelope and protein phosphatase 1 (PP1) modulates the membrane architecture during mitosis. Lamins also help to define embryonal polarity. In *Drosophila* ~500 transcriptionally silent and late-replicating genes interact with B-type lamin. These genes lack active histone marks and are widely spaced. Lamin target genes cluster in the genome and are coordinately regulated during development and are involved in the global organization of chromatin (Pickersgill H et al 2006 *Nature Genet* 38:1005). ▶intermediate filaments, ▶lipodystrophy, ▶muscular dystrophy [Emery-Dreifuss type], ▶cardiomyopathies [CMD1A], ▶Hutchinson-Gilford syndrome, ▶aging; Wilson KL et al 2001 *Cell* 104:647.

L-Amino Acids (levorotatory amino acids): The common natural amino acids. ► [D-amino acids](#)

Lamm Equation: The Lamm equation determines sedimentation or diffusion in analytical ultracentrifugation. ► [ultracentrifuge](#)

LAMP-1, -2 (lysosome-associated membrane proteins): LAMP-1 is a 120 kDa acidic glycoprotein (13q34) and its defect may account for some neurodegeneration in mice. LAMP-2 deficiency is associated with Danon disease (Xq24) characterized by impaired degradation (autophagy) of some liver proteins and various muscle anomalies (cardiomyopathy). ► [Danon disease](#); Winchester BG 2001 Eur J Paediatr Neurol 5(Suppl A):11.

Lampbrush Chromosome: A giant chromosome in oocytes (mainly in amphibia), with conspicuous loops extending about 40 μ m on a core resembling brushes used to clean the glass chimney of kerosene lamps (see [Fig. L13](#)). These loops are highly active in RNA synthesis, and although not polytenic, they are well visible under the light microscope. The photograph is a section of a long chromosome (Courtesy of Dr. Joseph G. Gall). A set of amphibian lampbrush chromosomes may display 10,000 loops alternating with condensed chromomeres. On the surface of the DNA loops the nascent RNA transcripts may be visible. This high activity may precede meiosis and continues during it in order to secure a good supply to later meet the needs of the rapidly developing zygote. ► [giant chromosomes](#), ► [newt](#); Gall JG, Murphy C 1998 Mol Biol Cell 9:733.

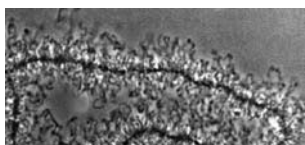


Figure L13. Lampbrush Chromosome

LANA (latency-associated nuclear antigen): ► [Kaposi sarcoma](#)

Lander-Green Algorithm: A multipoint linkage test using hidden Markov principle. ► [hidden Markov model](#), ► [Elston-Stewart algorithm](#); Lander ES, Green P 1987 Proc Natl Acad Sci USA 84:2363.

Landmark Genomic Scanning: Landmark genomic scanning visualizes restriction enzyme sites in genomic DNA by direct labeling and two-dimensional electrophoresis. ► [two-dimensional electrophoresis](#), ► [mDIP](#); Hirotsume IH et al 1994 DNA Res 1:239.

Landrace: Locally adapted variety of plants or breed of animals that may include a number of different genotypes and similar phenotypes. Landraces are the

products of intuitive selection of the growers or husbandrymen, respectively.

Lange-Nielssen Syndrome (cardio-auditory syndrome): The Lange-Nielssen syndrome involves heart arrhythmia and deafness, and sudden death. The gene responsible, KVLQT1, spans the region 11p15. This area also includes the Beckwith-Wiedemann syndrome. ► [Beckwith-Wiedemann syndrome](#), ► [LQT](#), ► [deafness](#)

Langer Mesomelic Dwarfism: ► [dyschondrosteosis](#)

Langer-Giedion Syndrome (LGS, 8q24.11-q24.13): The Langer-Giedion syndrome generally involves mental retardation, small brain (microcephaly), bulbous nose, sparse hair, emergences on the bones (exostosis), etc. The autosomal dominant phenotype is based on deletions in the 8p22-8q24.13 chromosomal regions. ► [deletion](#), ► [exostosis](#), ► [trichorhinophalangeal syndrome](#), ► [mental retardation](#), ► [head/face/brain defects](#)

Langerhans Cell: A dendritic antigen-presenting cell with an indented nucleus. They are present in the epidermis and some internal organs. ► [dendritic cell](#), ► [antigen-presenting cell](#)

Langerhans Islets: Cells with dentate nucleus in the pancreas, arranged in groups. They appear to have antigen-presenting abilities. From the β cell, the islets secrete insulin, from the α cells, glucagons, and from the δ cells, somatostatin. Mice that lack phosphatidylinositol kinase (PDK1) have a reduced number of β cells and suffer from hyperglycemia (diabetes). Haploinsufficiency for the Foxo1 transcription factor resulted in increased cell number but not in cell size and yet restored glucose homeostasis (Hashimoto N et al 2006 Nature Genet 38:589). ► [diabetes mellitus](#), ► [pancreas](#), ► [insulin](#), ► [insulin-like growth factor](#), ► [Fox](#), ► [PIK](#), ► [phosphatidylinositol kinases](#), ► [glucagons](#), ► [somatostatin](#)

Language: A unique feature of the human species that has apparently been determined by the FOXP2 gene (7q31), which has evolved at about a 60-fold higher rate than the same sequence in chimpanzees. Human toddlers may learn 10 words per day and humans may acquire a vocabulary of 60,000 words by the time of high school graduation. Dogs may also learn the meaning of ~200 words although by a process different from that of humans (Kaminski J et al 2004 Science 304:1682). The origin and evolution of languages is difficult to study using the currently available means because spoken words do not have paleontological records. Comparative genomics, hereditary speech defects, and anthropology may shed some light on the development of languages but there is no generally accepted theory for interpreting

scarce facts. Comparative linguistics can reveal the relationships among existing languages or extinct languages for which written records are available. The language of human populations has some relation to the genetic structure of the populations concerned (Cavalli-Sforza LL et al 1988 Proc Natl Acad Sci USA 85:6002). There are some problems, however, because language can spread horizontally whereas genes are transmitted only vertically. Also, population admixture is common during human migrations. In addition, there may be strong pressure to preserve or spread a language and culture beyond the boundaries of genetic groups (Hunley K, Long JC 2005 Proc Natl Acad Sci USA 102:1312). On the basis of language structure (sound system and grammar) the phylogeny of several Melanesian languages could be determined (Dunn M et al 2005 Science 309:2072). ▶[speech and grammar disorder](#), ▶[aphasia](#), ▶[MASA syndrome](#), ▶[chimpanzee](#), ▶[FOX](#); Zhang J et al 2002 Genetics 162:1825; Ferrer i Cancho R, Solé RV 2003 Proc Natl Acad Sci USA 100:788; Fisher SE, Marcus GF 2006 Nature Rev Genet 7:9; neural basis of language development: Friederici AD 2006 Neuron 52:941.

L

Language, Computer: A set of representations used by a computer program.

Language Impairment, Specific (SLI): About 4% of English-speaking children of normal intelligence and average environment suffer from low language skills for their age. It is a polygenic disorder and chromosomes 13q21, 16 and 19 sites are significantly involved. ▶[speech and grammar disorder](#); SLI Consortium 2002 Am J Hum Genet 70:384.

Langurs: ▶[Colobidae](#)

Lanosterol: A precursor of cholesterol (see [Fig. L14](#)). ▶[geranyl pyrophosphate](#), ▶[cholesterol](#)

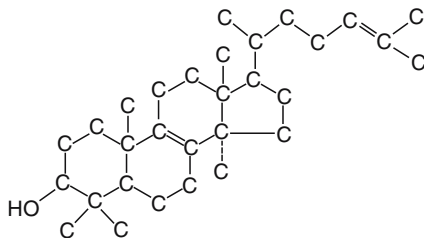


Figure L14. Lanosterol

Lantibiotics: Small peptide antibiotics produced primarily by *Lactococcus lactis*; other Gram-positive bacteria synthesize it too against competing bacteria. The best known among this group of antibiotics is nisin, which is used by the food industry and is useful because the body rarely develops resistance to it.

▶[nisin](#); van der Meer JR et al 1993 J Bacteriol 175:2578, nisin structure: Li B et al 2006 Science 311:1464.

Laparoscopy: The examination or treatment of the interior of the abdomen by a special device, the laparoscope, that may be equipped with a laser source.

Lapatinib: ▶[Trastuzumab](#)

Lard: An Apo-3 family TNF/NGF receptor. ▶[Apo-3](#), ▶[TNF](#), ▶[NGF](#)

Large Embryo/Offspring Syndrome: Bovine and ovine embryos, under unusual experimental conditions preceding the blastocyte stage, increase in size and involve problems of fetal loss, difficulties in parturition (birth), and developmental defects. In vitro embryo culture, nuclear transplantation, high urea diet of the mother, etc., may be responsible for the anomalies. Mice produced by nuclear transplantation tend to be large and obese but the condition is not transmitted to their offspring. ▶[nuclear transplantation](#), ▶[tetraploid complementation](#); Young LE 1998 Rev Reprod 3:155; Tamashiro KKK et al 2002 Nature Med 8:262.

Large T Antigen: ▶[SV40](#)

Lariat RNA: is formed during the splicing reaction of the primary transcript of eukaryotic genes. In the first step, the pre-mRNA is cut at the junction of exon 1 and intron resulting in a piece of RNA containing intron-exon 2. This “2/3 molecule” immediately forms a loop-like lariat (remining one of the tethering rope of cowboys). In the second step, the intron-exon 2 junction is cut and exons 1 and 2 are ligated (spliced). Afterward, the intron is released and the procedure follows for the other junctions. ▶[introns](#), ▶[splicing](#); Ooi SI et al 2001 Methods Enzymol 342:233.

Laron Type Dwarfism: ▶[pituitary dwarfism](#), ▶[dwarfism](#)

Larsen Syndrome (LRS1, 3p21.1-p14.1): Larsen syndrome is characterized by dominant knee dislocation, prominent forehead, cylindrical fingers, short digits, and a flat nasal bridge. ▶[bone diseases](#)

Larva: An insect at the developmental stage after hatching from the egg. It resembles more a worm than an adult insect (see [Fig. L15](#)). The imago emerges from it after pupation. During the larval stage the germline and the imaginal discs are laid down. ▶[Drosophila](#)



Figure L15. Larva

Lascaux Cave: The Lascaux cave is located in the caves of Dordogne, southwestern France. It reveals the remarkable art of the Cro-Magnon men, originated about 15,000 years ago. These colored paintings disclose a great deal about the types of animals present in the area in the paleolithic age and attest the intelligence and artistic abilities of the early European ancestors. More recently, even older (35,000–40,000 years) ancient artwork and artifacts have been discovered both in Europe (Grotte Chauvet) and Africa. The animal shown in [Figure L16](#) displays great similarity to a present-day longhorn bull. The success of animal breeding can be assessed by a comparison with the modern breeds of cattle. (See Guthrie RD 2006 *The Nature of Paleolithic Art* University of Chicago Press, Chicago, Illinois; Valladas H et al 2001 *Nature [Lond]* 413:479; <http://www.culture.fr/culture/arcnat/chauvet/en>).



Figure L16. Lascaux cave painting (Courtesy of the Caisse Nat. Mon. Hist. Sites, France)

Laser (light amplification by stimulated emission of radiation): Laser equipment produces electromagnetic radiation in the infrared and visible spectrum by stimulation of atoms. The laser beam does not diffuse like that of an electric light. The radiation travels in the same direction, at the same wavelength of a very narrow frequency band. Thus, it focuses all the energy to a fine point. Lasers can produce radiation at many wavelength and frequencies. Intense light source and electron currents can activate gases, semiconductors and ions in solid material to produce coherent laser light. The lasers can be pulsed or continuous. The former produces extremely high peaks of power, the latter is highly stable and gives pure emission. Laser radiation is applicable to different scientific instruments (e.g., laser scanners), photochemistry (e.g., laser photolysis), identification of fluorochrome-labeled molecules and also to surgery, etc. Laser beam exposure poses a risk for the eyes. (See entries ahead).

Laser-Capture Microdissection: This technique may be used to trace the event in cellular differentiation. Cell cultures or tissue sections are placed on a polymer

film activated by laser pulses. The shape of the cells and their DNA, RNA, and protein content is preserved. cDNA libraries can then be hybridized to thousands of genes and their expression in health and disease or patterns of DNA methylation studied and used for biological or diagnostic purposes. It may be used for isolation of pure cell types—without injury to macromolecules—from microscopic tissue sections and transferring them to laser-activated polymer films. The procedure permits molecular analysis (e.g., microarray hybridization) of tissue-, cell-specific alterations due to disease and/or therapy. ▶[microarray](#), ▶[laser](#); Emmert-Buck MR et al 1996 *Science* 274:998; Simone NL et al 1998 *Trends Genet* 14:272; Kerjean A et al 2001 *Nucleic Acids Res* 29(21):e106; Craven RA, Banks RE 2001 *Proteomics* 1:1200.

Laser Scanning Cytometry: Laser scanning cytometry analyzes DNA content of normal and cancer cells; it can be used to measure in situ hybridization by automation. ▶[multiphoton microscopy](#); Darzynkiewicz Z et al 1999 *Exp Cell Res* 249:1; LaSalle JM et al 2001 *Hum Mol Genet* 10:1729; Angenandt P et al 2004 *Anal Chem* 76:1844.

Last-Male Sperm Precedence: In many insects (e.g., *Drosophila*), the female stores the sperm in her spermatheca before fertilization. When multiple insemination takes place by different males, the sperm of the last male preferentially sires the majority of the offspring due to sperm displacement and inactivation (?). The sperm elimination is controlled by the seminal fluid produced by the accessory gland. ▶[certation](#), ▶[multipaternal litter](#), ▶[multiparental hybrid](#), ▶[sperm precedence](#); Hooper RE, Siva-Jothy MT 1996 *Mol Ecol* 5:449; Snook RR, Hosken DJ 2004 *Nature [Lond]* 428:939.

LAT: A class of herpes virus genes of mainly unclear function. They are transcribed when the virus is maintained in a quiescent state bound to the nucleosomes in the neurons. A LAT protein has an adapter function in TCR-mediated signal transduction. ▶[herpes](#), ▶[TCR](#), ▶[signal transduction](#); Aguado E et al 2002 *Science* 296:2036.

Late Genes: Late genes are transcribed only during the later life cycle of an organism. The viral genes involved in replication and in the synthesis of structural (coat) proteins (e.g., during the lytic phase of a bacteriophage). These genes use late promoters, different from the early ones. ▶[early genes](#), ▶[delayed-response genes](#)

Late Period: The late period of phage development starts with the beginning of DNA replication. ▶[development](#), ▶[lambda phage](#)

Latent Period: A latent period is when the infection has occurred but the symptoms are not yet manifested.

In phage biology, the latent period is the time between the injection of the phage DNA into the bacterium and the beginning of lysis. It is also the time from the initiation of a disease to the onset of symptoms.

►burst

Late-Replicating Chromosome: A late-replicating chromosome or chromosomal region is heterochromatic and genetically not active. ►Barr body, ►lyonization, ►heterochromatin

Lateral Plate Mesoderm: A lateral plate mesoderm is present in the neurula of vertebrates and gives rise to the nervous system, heart, blood vessels, blood, linings of the body cavities, and the mesodermal part of the limbs. ►left-right asymmetry, ►neurula

Lateral Transmission: Same as horizontal transmission. Lateral transmission is suggested generally when similar nucleotide sequences occur among species that may not be related by orthologous descent. Lateral transmission is common (1.5–14.5%) in bacteria by means of transformation by exogenous DNA, by phage-mediated transduction, and conjugational transfer of plasmids. According to a new estimate, using a different method among 57,670 prokaryotic gene families distributed across 190 sequenced genomes, at least two-thirds and probably all appeared to be affected by lateral transmission at some time in their evolutionary past (Dagan T, Martin W 2007 Proc Natl Acad Sci USA 104:870). A H-NS-like protein aids lateral transmission in bacteria (Doyle M et al 2007 Science 315:251).

Antibiotic resistance and virulence genes are commonly transmitted laterally and may become important factors of population adaptation and evolution. On the basis of the sequenced genomes of eukaryotes, the lateral transfer of genes might have occurred during evolution. The lateral acquisition of the number bacterial genes by the human genome has been estimated at 40 to over 200. A common objection to such claims is that the convergent evolution of these genes or sequences may not be ruled out with great certainty. Furthermore, many of the supposedly horizontally acquired sequences in vertebrates were already present in nonvertebrate lineages (Stanhope MJ et al 2001 Nature [Lond] 411:940). In addition, the endosymbiotic acquisition of chloroplasts and mitochondria and DNA traffic among these organelles poses additional problems in identifying the lateral transfers. ►transmission, ►transmission lateral, ►transposable elements, ►transformation, ►infectious heredity, ►orthologous genes, ►convergent evolution, ►operon selfish, ►H-NS; Garcia-Vallvé S et al 2000 Genome Res 10:1719; Andersson JO et al 2001 Science 292:1848; Brown JR 2003 Nature Rev Genet 4:121; Boucher Y et al 2003 Annu Rev Genet 37:283; Ochman H et al

2005 Proc Natl Acad Sci USA 102 (Suppl 1):6595; Maurelli AT 2007 FEMS Microbiol Lettr 267:1; method of detection and microbial results: <http://cbcsrv.watson.ibm.com/HGT/>; high-throughput genomic island discovery by using microarray-derived comparative genomic hybridization data and comparative analysis of the contents and contexts of tRNA sites (tRNA_{acc}) and/or other integration hot-spots in closely related bacteria: <http://mmml.sjtu.edu.cn/MobilomeFINDER/>.

Laterality Disorder: ►situs inversus viscerum, ►situs ambiguus, ►left-right asymmetry

Latexin: A mouse carboxypeptidase inhibitor with similarity to the putative human tumor suppressor TIG1; it has cysteine fold domains. ►carboxypeptidase, ►cystatine; Aagaard A et al 2005 Structure 13:309.

Lathyrism: Caused by the presence of β -cyanoalanine and its decarboxylation product, β -aminopropionitrile in the seeds of the food and forage legume, *Lathyrus sativus*. Some other contaminating weed legumes may also be major culprits in lathyrism. In some countries, the ground seed is used as a filler in bread making. As a feed its amount should be kept below 10% of the ration. Cooking reduces its adverse effect substantially. These compounds affect the cross-linking of collagen resulting in spasms, pain, paralysis of the lower extremities (paraplegia), abnormal sensitivity (hyperesthesia), burning sensation of the skin (paresthesia), curvature of the spine, rupture of the aorta, etc. ►collagen; Spencer PS et al 1993 Environ Res 62:106; Riepe M et al 1995 Nat Toxins 3:58.

Lathyrus odoratus (sweet pea): An ornamental legume ($2n = 14$), a favorite object of early studies on the gene-controlled anthocyanin synthetic pathways. The *L* dominant allele (long) and the recessive *l* allele (disc) determine the shape of the pollen (see Fig. L17). Although this is a gametophytic trait, the phenotype is determined by the genotype of the anther (sporophytic) tissue and thus is an example of delayed inheritance. ►delayed inheritance, ►sweet pea

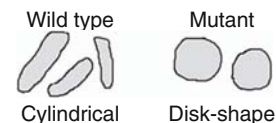


Figure L17. Pollen grains of *Lathyrus*

Latin Square: A square array of items in parallel columns and rows in such a manner that each must occur once but only once in each row and column (see Fig. L18). Such a design lends itself for the evaluation of experiments by analysis of variance. It can be

employed in agricultural field experiments and is useful for pharmacological, microbial and other research where the partition of the data into relevant variances is very important. ► [analysis of variance](#), ► [Graeco-Latin square](#)

| | | |
|---|---|---|
| B | A | C |
| A | C | B |
| C | B | A |

Figure L18. Latin square

Latrotoxin: A large peptide neurotoxin binding to neurexins. ► [neurexin](#)

LATS: (large tumor suppressor): A negative regulator of CDC2 and cyclin A. LATS1 deficiency in mice may produce soft-tissue sarcomas, ovarian tumors, and pituitary defects. ► [CDC2](#), ► [cyclin A](#), ► [sarcoma](#), ► [pituitary](#), Hori T et al 2000 *Oncogene* 19:3101.

Lattice: A three-dimensional pattern of atoms or points.

Lauryl Sulfate: ► [dodecyl sulfate sodium salt](#)

Law: Both civil and criminal law consider genetic principles and methods. Examples are: regulating marriage, social policy, demographic factors, using dermatoglyphics (fingerprinting), serological methods, DNA fingerprinting, patents, etc. The branch of genetics involved in legal matters is called forensic genetics. ► [forensic genetics](#), ► [paternity testing](#), ► [abortion](#), ► [stem cells](#), ► [genetic discrimination](#), ► [patents](#), ► [GMO](#), ► [animal genetics](#), ► [genetic privacy](#)

Law of Large Numbers: The increase in the size of a population assures a closer fit of the observed data to a valid null hypothesis or that the experimentally observed mean represents the true mean of the population dispersed according to the normal distribution. ► [normal distribution](#), ► [mean](#), ► [null hypothesis](#)

Lawn, Bacterial: A Petri plate containing nutrient agar and growing bacterial cell colonies (see [Fig. L19](#)).

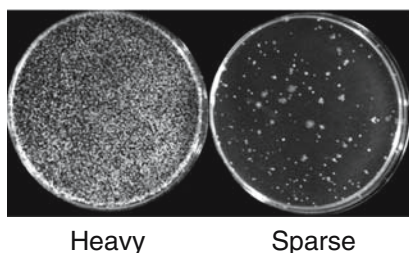


Figure L19. Bacterial lawn

Lawrence-Moon Syndrome: An autosomal recessive mental retardation involving retinal defects, underdeveloped genitalia, and partial paralysis.

Lawrence-Seip Syndrome: A lipodystrophy (loss of fat substance from under the skin); it is accompanied by enlargement of the liver, excessive bone growth, and insulin-resistant diabetes.

LB Agar: Add 1.5 to 2% agar to LB medium. ► [LB bacterial medium](#)

LB (Luria-Bertani) Bacterial Medium: H₂O, deionized, 950 mL; bactotryptone, 10 g; bacto yeast extract, 5 g; NaCl, 10 g; adjust pH to 7 with 5 N NaOH, fill up to 1 L.

LBD: Ligand binding domain. ► [ligand](#)

LC: Literature curated. ► [curated](#)

LC50: A lethal concentration 50 of a chemical is expected to cause death in 50% of the treated cells or individuals of a population. ► [LD₅₀](#), ► [LCLo](#), ► [LDLo](#)

LCA: LCA stands for last common ancestor of species compared.

LCA Oncogene: The LCA oncogene is isolated from human liver carcinomas; it was assigned to human chromosome 2q14-q21. ► [oncogenes](#)

LCK: A lymphocyte nonreceptor protein tyrosine kinase of the SRC family, located to human chromosome 1p35-p32. ► [oncogenes](#), ► [tyrosine kinase](#), ► [signal transduction](#), ► [T cell](#), ► [ITAM](#), ► [palmitoylation](#); Holdorf AD et al 2002 *Nature Immunol* 3:259.

LCLo: (lethal concentration low): The lowest concentration of a substance, in air, that causes death to mammals in acute (<24h) or subacute or chronic (>24 h) exposure. ► [LDLo](#)

LC-MS (liquid chromatography-mass spectrometry): A bioanalytical pharmaceutical tool used in conjunction with quadrupole mass spectrometers. ► [quadrupole](#), ► [proteomics](#); O'Connor D 2002 *Curr Opin Drug Discov Devel* 5:52.

LCR (locus control region): A nuclease-hypersensitive region far upstream or downstream or on other sites apart from the structural gene. Its presence is required for the expression of a particular gene locus and its role probably involves the opening of the chromatin for transcription. All the genes are in competition for the assistance of the LCR and those that are closer to it have an advantage. LCR may be at many kb distance from the locus it controls. The multiple genes appear to be transcribed alternately as the chromatin loops back and forth. In the LCR of the β -globin gene there are 5 DNase I hypersensitive sites, which synergistically activate the gene cluster (globin ϵ -G γ -A γ - δ - β) in a developmentally specific sequence. Hypersensitive site 4 is the most important for activation of transcription. Each of the hypersensitive sites bind transcriptional activators (E-box

factors, GATA-1, NF-E2, CACCC binding proteins [e.g., Sp1]) and yet they also have some specificities. For the globin cluster, the most important role of LCR is the steady maintenance of transcription. The globin gene LCR is very well conserved among the various species. The CACCC box of the β -globin genes has an important role in the transcriptional regulation of the γ - and β -gene promoters. The Sp1-related protein binds ubiquitously and the Krüppel-like proteins (EKLf) bind to this box only in the erythroid lineage. Although CACCC boxes are present in both the γ and β promoters, in the γ four repeating copies of a CCTTG sequence suppresses EKLf binding. Thus the functions appear to be controlled also by the structural/sequence context. The LCRs also include enhancer elements. At the LCR of the β -globin gene there is a (LARC) complex of a heterogeneous nuclear ribonucleoprotein (C1/C2), nucleosome remodeling complex (SWI/SNF), and nucleosome remodeling and deacetylating complex (NuRD)/MeCP1. LARC binds the hypersensitive 2 (HS2)-Maf (Maf is AP1/NF-E2, a basic leucine zipper protein) recognition element (MARE). The binding proteins assure β -globin transcription by chromatin remodeling (Mahajan MC et al 2005 Proc Natl Acad Sci USA 102:15012). ▶nuclease sensitive site, ▶regulation of gene activity, ▶heterochromatin, ▶chromatin, ▶position effect, ▶looping of DNA, ▶promoter, ▶chromatin remodeling, ▶E-box, ▶transcription factories, ▶GATA, ▶NF-E2, ▶Sp1, ▶EKLf, ▶Sp1; Fraser P, Grosveld F 1998 Curr Opin Cell Biol 10:361; Grosveld F 1999 Curr Opin Genet Dev 9:152; Johnson KD et al 2001 Mol Cell 8:465; Ho Y et al 2002 Mol Cell 9:291.

LD50: A calculated dose of a substance expected to kill 50% of the experimental population exposed to it. Rats have been used for the determination of LD₅₀. This type of test will be phased out to avoid cruelty to animals. ▶LDLo

λdash: A replacement vector for the stuffer DNA fragment which carries multiple cloning sites on both sides of *red* and *gam* genes and appropriate promoter (s) specific for T3 or Ty RNA polymerase and so the insertions can be transcribed without a need for recloning. ▶λFIX, ▶EMBL3, ▶stuffer DNA, ▶lambda phage, ▶cloning

LDB: LIMB domain binding factor. ▶Lim domain, ▶NLI

λdgal: A lambda phage deficient but carries the galactose gene. ▶specialized transduction

Ldj1, Ldj2: Ldj1 and Ldj2 are DnaJ-like farnesylated chaperones of higher plants. ▶DnaK, ▶chaperones, ▶prenylation

LDL: ▶low-density lipoproteins, ▶familial hypercholesterolemia, ▶sterol, ▶myocardial infarction

LDL Receptor: An LDL receptor mediates LDL endocytosis; it is encoded in human chromosome 19-p13.1-13.3. It is homologous with the EGF receptor. An LDL-related protein (LRP5) defect is the cause of a type of osteoporosis. ▶low-density lipoproteins, ▶EGFR, ▶lysosomes, ▶LDL, ▶osteoporosis; Gong Y et al 2001 Cell 107:513.

LDLo (lethal dose low): The lowest dose of a substance introduced by any route, except inhalation, over a period of time in one or more portions, and has caused death to mammals. ▶LClo, ▶LD50

L-DNase II: A post-translational product (from a serpin-like protease inhibitor or leukocyte elastase inhibitor) upon cytosolic acidification. It degrades DNA during apoptosis. ▶apoptosis, ▶serpins, ▶elastase

LDP (long-day plant): ▶photoperiodism

Lead Poisoning: Lead poisoning can cause kidney and growth problems as well as anemia, hearing loss, seizures, and coma. The most common source are house paint (before 1978) and old gasolines, and old plumbing.

Leader Peptide: Directs the translocation of proteins. In bacteria it consists of 16–26 amino acids involving a basic amino terminal, a polar central domain, and a non-helical carboxy domain. The latter is essential for recognition by leader peptidase to cut it off. For mitochondrial import, the leader has 10–70 residues and it is rich in positively charged and hydroxylated residues. Similar leader peptides mediate the import of proteins from the cytosol to the chloroplasts or to the nucleus. The leader sequences do not enter the target organelles. ▶signal peptide; Wang AH, Yang XJ 2001 Mol Cell Biol 21:5992.

Leader Sequence: A leader sequence is a nontranslated stretch of nucleotides at the 5'-end of the mRNA. Some mRNAs lack a leader, e.g., the lambda phage cI gene. The tobacco mosaic virus carrying the translational enhancer Ω works more efficiently in the absence of a Shine-Dalgarno sequence. ▶mRNA, ▶Shine-Dalgarno sequence; O'Donnell SM, Janssen GR 2001 J Bacteriol 183:1277.

Leading Strand: A leading strand of DNA faces the replication fork by the 3'-OH end and is extended by adding, directly, 5'-deoxynucleotidephosphates to that end after removal of the γ and β position phosphates from the nucleotide triphosphate precursors. In prokaryotes, the most essential genes (essential for viability) are transcribed from the leading strand and this bias is not a consequence of the level of expression of the genes. In *E. coli*, the DNA polymerase tends to slow down until the transcription is completed (co-oriented collision).

After the completion of transcription, replication may resume its normal rate. On the lagging strand replication stalls (head-on collision) when it encounters transcription and the RNA polymerase is displaced from the lagging strand. In eukaryotes, the principle of gene distribution is unclear because multiple DNA polymerases exist and each is somewhat different. ►lagging strand, ►replication fork, ►replication, ►DNA replication, ►gene distribution

Leadzyme: A ribozyme that can cleave itself at a specific phosphodiester site in the presence of lead ions (Pb^{2+}). The leadzyme has an asymmetric internal loop flanked by Watson-Crick hydrogen-paired nucleotides. The shaded section indicates the catalytic core (see Fig. L20). ►ribozyme, ►DNA-zyme; Doherty EA, Doudna JA 2000 Annu Rev Biochem 69:597.

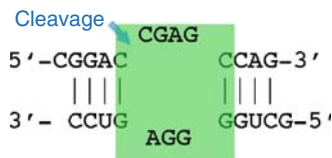


Figure L20. Diagram of leadzyme LZ4 after Wedekind JR and Mckey DB 1999 Nature Struct. Biol. 6:261

Leaf Skeleton Hybridization: A procedure carried out on plant leaves infected by the cauliflower mosaic virus vector with the same purpose as colony hybridization of bacteria, i.e., to detect foreign gene sequences in the CaMV vector. ►CaMV, ►colony hybridization; Melcher U et al 1992 Arch Virol 123(3-4):379.

Leaky Mutant: A leaky mutant has an incomplete genetic block in a synthetic step. ►genetic block, ►hypomorphic

Learning Behavior: Learning behavior is partly genetically controlled and it has been found that slow-learning mice have reduced amounts of protein kinase C in the hippocampus of the brain. It thus appears that the PKC gene is a part of the polygenic system affecting this complex trait. Learning is potentiated by the regeneration ability of the central nervous system. Increased histone acetylation and inhibition of histone deacetylase induced sprouting of dendrites, increased the number of synapses, reinstated learning behavior and access to long-term memory after some neuronal degeneration (Fischer A et al 2007 Nature [Lond] 447:178). ►brain human, ►Boolean algebra; Dubnau J, Tully T 1998 Annu Rev Neurosci 21:407; Chklovskii DB et al 2004 Nature [Lond] 431:782; Abbott LF, Regehr WG 2004 Nature [Lond] 431:796.

Learning Disability: ►Tourett's syndrome, ►dyslexia

Least Significant Difference (LSD): A measure of the significance among a set of means compared. The standard error of the difference between two means can be determined on the basis of the Student's t distribution using $\sqrt{2s^2/n}$ where s^2 is the standard error, n is the size of the population. The standard error of the difference is then multiplied by the minimal t value at a particular level of significance from the Student's t table and any value that exceeds this product constitutes the LSD. ► t value, ►Student's t distribution, ►F-distribution

Least Squares: The least squares formula is the basis for the theory of regression (b) where S means sum,

$$b = \frac{S(y[X - \bar{x}])}{S(X - \bar{x})}$$

where y = one of the variates, x = other variate, \bar{x} mean of x .

Least square methods are also used for the estimation of evolutionary distance. The smallest minimum sum of squared differences computed from paired data indicates the best topology for an evolutionary tree. ►minimum evolution method, ►four-cluster analysis, ►neighbor joining method, ►correlation, ►multiple regression

Least-Trimmed Square: A computational procedure used in regression analysis (LiLM 2005 Comp Stat Data Anal 48:717).

Leaving Group: The displaced molecular group in a chemical reaction.

Leber Congenital Amaurosis: ►amaurosis

Leber Optic Atrophy: About 95% of the cases involve mutations at mtDNA nucleotides 3460, 11778 and 14484. ►mitochondrial disease in humans, ►optic atrophy, ►amaurosis congenita, ►eye diseases; Howell N et al 2003 Am J Hum Genet 72:1460.

Lecithin: A glycerol phospholipid. It is also called phosphatidyl choline.

Lecithin-Cholesterol Acyltransferase Deficiency (Norum disease, Fish-eye disease): Lecithin-cholesterol acyltransferase deficiency is either a relatively rare recessive Norum disease coded in human chromosome 16q22.1 and in mouse chromosome 8 or is, by a dominant mutation at the same locus, the fish-eye disease. This defect in lipid metabolism causes proteinuria, anemia, renal and heart defects. In Norum disease, there is a general failure in esterification of cholesterol in high-density lipoprotein whereas in the fish-eye diseases the deficiency is more specific. The name comes from the opacity of the eye resembling that of boiled fish. ►lipoprotein, ►apolipoprotein, ►cardiovascular disease, ►West syndrome, ►vascular disease

Lectins: Lectins were first identified as plant proteins associated with glycans that agglutinate erythrocytes by virtue of binding to surface sugars (Dodd RB, Drickamer K 2001 *Glycobiology* 11:71R). Lectins also occur in invertebrate and vertebrate animals and may also serve as ligands in the natural killer cells. In addition, they play a role in general cell adhesion, managing of peptides in the endoplasmic reticulum, surface recognition and protection against bacteria and viruses. Natural killer cell receptors of lectin-like C-type—although heterogeneous—were preserved during the evolution of four orders of mammals (Hao L et al 2006 *Proc Natl Acad Sci USA* 103:3192). Lectins introduced into potato by genetic engineering may have adverse effects on experimental animals if consumed. ▶concanavalin, ▶selectin, ▶cell adhesion, ▶killer cells, ▶complement, ▶endoplasmic reticulum, ▶receptin, ▶DC-SIGN, ▶NOD2, ▶SIGN-R1; Weis WI, Drickamer K. 1996 *Annu Rev Biochem* 65:441; <http://plab.ku.dk/tcbh/lectin-links.htm>.

Leech: A hirundinaceous (blood-sucking) lower animal with only ≈350 nerve cells per ganglion (see Fig. L21). ▶ganglion; Stent GS et al 1992 *Int Rev Neurobiology* 33:109.



Figure L21. Leech

LEF (lymphoid-enhancer binding factor): A transcription factor regulating lymphocyte differentiation; it is a member of the high mobility group proteins. It interacts with β -catenin and regulates signal transmission to the nucleus. It binds to the TTCAAACC sequences in the TCR α enhancer region. LEF is similar to TCF and this family of proteins also regulates axis formation with the aid of β -catenin-associated proteins. Catenin-activation plays a role in human cancers. ▶high mobility group proteins, ▶lymphocytes, ▶Gardner syndrome, ▶melanoma, ▶catenins, ▶pilomatricoma, ▶R-spondin, ▶TCF; Liu T et al 2001 *Science* 292:1718.

Left-Handedness: ▶handedness

Left-Right Asymmetry: In vertebrates, the body plan appears almost entirely symmetrical by outward appearance; however, the arrangement of the internal organs (heart, pancreas, stomach, spleen, liver gall bladder) is not symmetrical. Left-right asymmetry is widely found in several syndromes of all higher organisms (prevalence $> 1 \times 10^{-4}$). In some humans the normal pattern of the location of organs is disturbed (Kartagener syndrome, situs inversus viscerum). The pattern of differentiation is under

the control of a cascade of events, which bears some similarities and differences in the various organisms.

The processes are under the control of genes and proteins with somewhat variable homology. *N*-cadherin appears to be an early regulator for establishing the asymmetry of the body. The initial signals emanate from the organizer where activins on the right side stimulate the fibroblast growth factor (FGF-8), which in turn blocks the Cerberus (Cer)/Dan/gremlin/Caronte (CAR) family of genes/proteins. The homologous macromolecules are so named in different organisms. On the left of the organizer/primitive streak, Sonic hedgehog (SHH) acts in a direction opposite to FGF-8; it activates CAR. CAR then interferes with the bone morphogenetic protein blocking-action and NODAL (Nod)/Lefty-2/Activin is/are turned on. Nod has a central morphogenetic function. On the left side, ACTIVIN RIIIB/SMAD-2 then blocks \emptyset SnR (Snail related). NODAL depends on Notch signals, which respond to extracellular calcium (Raya Á et al 2004 *Nature [Lond]* 426:121). ACTIVIN RIIIB also turns on PitX2/ NKX3.2/ bagpipe. On the right side of the lateral plate mesoderm the mirror image of the processes go on. What is activated on the left side is more or less attenuated on the right side.

In the midline, Lefty-1, stimulated by CAR, seems to stabilize the difference between the two sides of the mesoderm. Lefty-1 is highly homologous to Lefty-2. Although this simple model (see Fig. L22) provides a generalized picture, the processes actually involve additional genes and proteins in an interacting cascade of events. The EGF (epidermal growth factor)-Cryptic protein1 (224 amino residues in humans) complex interacts with Nodal and regulates laterality. The fibroblast growth factor induces the release of the sonic hedgehog signal and retinoic acid

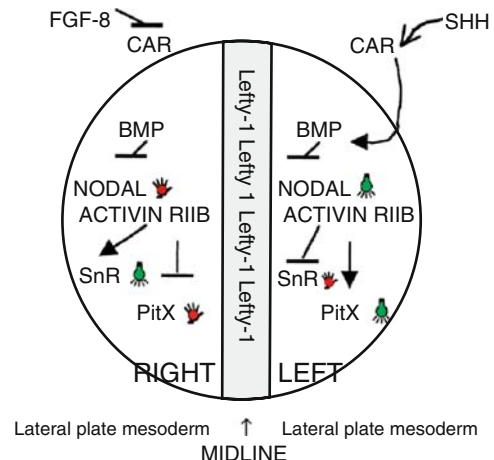


Figure L22. Some of the circuits in the determination of left-right asymmetries

and mediates the left–right determination (Tanaka Y et al 2005 Nature [Lond] 435:172). In the ventral node there is a leftward move of the nodal fluid propelled by cilia and the KIF3 motor complex (see Fig. L23). Conventional cilia in the trachea display

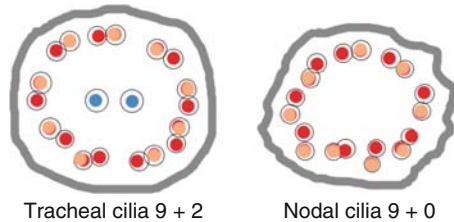


Figure L23. Abstract drawing of cilia base electron micrograph

9 + 2 microtubule arrangement whereas in a nodal form the arrangement is 9 + 0 due to a Hedgehog signaling pathway-mediated intracellular elevation of Ca^{2+} (Hirokawa N et al 2006 Cell 125:33). The normal asymmetry of the organ plan is called situs solitus whereas the reversed arrangement is situs inversus. Some other laterality differences are called isomerism. The overall normal pattern of left/right asymmetry is evolutionarily conserved in vertebrates. In *Caenorhabditis*, neuronal asymmetry is controlled by a microRNA (Johnston RJ, Hobert O 2003 Nature [Lond] 426:845). In *Drosophila*, myosin (Myo1A) and actin cytoskeleton regulate left–right asymmetry (Hozumi S et al 2006 Nature [Lond] 440:798; Spéder P et al 2006 Nature [Lond] 440:803). An intrinsically chiral structure, perhaps the centrosome, serves as a template for directing polarity in the absence of spatial cues. Such a template could help to determine left–right asymmetry and planar polarity in development (Xu J et al 2007 Proc Natl Acad Sci USA 104:9296). ▶situs inversus viscerum, ▶asymmetric cell division, ▶lateral plate mesoderm, ▶cilia, ▶chirality, ▶centrosome, ▶Kartagener syndrome, ▶organizer, ▶Rieger syndrome, ▶hedgehog, ▶FGF; diagram modified after Esteban CR et al 1999 Nature 401:243; Capdevila J et al 2000 Cell 101:9; Burdine RD, Schier AF 2000 Genes & Development 14:763; Garcia-Castro MI et al 2000 Science 288:1047; Mercola M, Levin M 2001 Annu Rev Cell Dev Biol 17:779; Hamada H et al 2002 Nature Rev Genet 3:103; Raya Á et al 2006 Nature Rev Genet 7:283; Tabin CJ 2006 Cell 127:27.

Leghemoglobin: A hemoglobin protein which is coded for by genes of leguminous plants. This protein accumulates in the root nodules formed by the presence of nitrogen fixing bacteria. The leghemoglobin transfers oxygen to the electron-transport system of the bacteria and prevents the accumulation

of toxic amounts of oxygen that would interfere with nitrogen fixation. ▶globin, ▶myoglobin, ▶hemoglobin; Kawashima K et al 2001 Plant Physiol 125:641.

Leghorn White: The poultry breeds White Plymouth Rock and White Wyandotte have plumage which is determined by recessive genes *ii cc*. The White Leghorn on the other hand has the *IICC* genotype where *I* is a dominant suppressor gene of color (*C*). Thus, when it is crossed to another white breed, e.g., White Wyandotte, in the F_2 of their hybrids the segregation is 13 white or speckled and three black. The blacks have the genotype either *iiCC* or *iiCc*. ▶chicken

Legionnaire's Disease: The airborne and potentially lethal, opportunistic infection is caused by the bacterium *Legionella pneumophila*, although over 40 different species exist. Some amoebae may be rarely responsible for similar disease. The bacterial chromosome contains 3,397,754 bp DNA, and has 45 kbp plasmid-like elements. (See Swanson MS, Hammer BK 2000 Annu Rev Microbiol 54:567; Chen J et al 2004 Science 303:1358; Chien M et al 2004 Science 305:1966).

Legit: A statistical concept worked out by R.A. Fisher (Biometrics 6:353) showing the change in allelic frequencies in a cline. If the allelic frequency is known, the legit can be read from the table published in the *Biometrics* article cited above. ▶cline, ▶diffusion genetic

Legumes: A taxonomic group of plants (e.g., pea, beans) with an ability to accumulate atmospheric nitrogen in symbiosis with some nitrogen-fixing bacteria. ▶Rhizobia, ▶nitrogen fixation, ▶Medicago, ▶Lotus, Glycine genome database: <http://www.comparative-legumes.org>.

Leigh's Encephalopathy (LS, 19q13, 11q13, 9q34): The autosomal recessive disorders occur in multiple forms and are characterized by high pyruvate and lactate concentrations in the serum and in the urine. The biochemical findings may be caused either by a defect of pyruvate carboxylase or a necessary cofactor of the enzyme, thiamin triphosphate (TTP). The latter deficiency may be brought about by the absence of thiamin pyrophosphate-adenosine triphosphate phosphoribosyl transferase. The pyruvate carboxylase gene appears to be in human chromosome 11. The nuclear-encoded (3q29 and 5p15) flavoprotein subunit of succinate dehydrogenase controls a mitochondrial enzyme complex II, including succinate dehydrogenase. Mutation in the SURF1 gene (9q34), encoding cytochrome c oxidase, is involved in some cases of the Leigh syndrome. At chromosome

2p16-p21, a mitochondrial cytochrome oxidase subunit deficiency is responsible for Leigh syndrome of the French-Canadian type (LSFC, Mootha VK 2003 Proc Natl Acad Sci USA 100:1605). A mutation in the mitochondrial NDUF complex may cause leukodystrophy and myoclonic epilepsy. Gluconeogenesis may become defective and necrotic brain lesions, heart and respiratory disorders may be present. Prenatal diagnosis is successful in some cases. A defect in the NADH-Ubiquinone Oxidoreductase Fe-S Protein (NDUFS8, 11q13) or a mutation in the 18-kDa NADH-Coenzyme Q Reductase (NDUFS4, 5q11.1), or the NADH-Coenzyme-Ubiquinone Oxidoreductase Fe-S protein 7 (NDUFS7, 19p13), or the NADH-Ubiquinone Oxidoreductase Flavoprotein 1 (DUFV1, 11q13) may also be the cause of Leigh syndrome. These proteins are all components of the mitochondrial respiratory chain that includes more than 40 subunits of which only seven are encoded in the mtDNA. ▶neuromuscular diseases, ▶gluconeogenesis, ▶mitochondrial diseases in humans, ▶encephalopathies, ▶NDUF, ▶lactic acidosis, ▶Saguenay-Lac-Saint-Jean syndrome

Leiner's Disease: Caused by deficiency of the C5 complement component resulting in low opsonization and various types of infections, primarily during childhood. ▶complement, ▶opsonin

Leiomyoma: Generally benign tumors of the smooth muscles occurring in the uterus, genitalia, kidney, gullet, etc., controlled by autosomal dominant genes and their translocations or deletions in several chromosomes (Sandberg AA 2005 Cancer Genet Cytogenet 158:1). Predisposition is coded in the long arm of human chromosome 1q42.3-q43. Up to 77% of women of reproductive age show this condition (Cramer SF, Patel A 1990 Am J Clin Path 94:435), but less than 0.1% of the cases develop into malignancy (see Fig. L24). The high-mobility group of proteins are frequently involved.

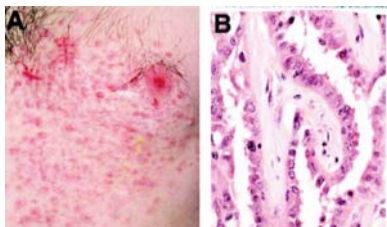


Figure L24. A. Firm skin-colored or light brown papules and nodules on the skin in leiomyoma. B. Histological image of papillary type II renal cell carcinoma. The cell cytoplasm stains by either alkalic or acidic dyes and the large nuclei display inclusion-like eosinophilic nucleoli. (From Toro JR et al 2003 Am J Hum Genet 73:95; courtesy of Dr. Jorge R. Toro)

Estrogen and progesterone receptor defects are common in leiomyomas. Renal cell cancer is frequently involved. Mutation in fumarate hydratase at 1q42.3-q43 acts as a suppressor of leiomyoma and is also responsible for neurological impairment and encephalopathy. Besides the main target, the uterus, other body parts may also be affected. ▶cancer, ▶fumarate hydratase, ▶high-mobility group of proteins; Walker CL, Stewart EA 2005 Science 308:1589.

Leishmania: The several species of a protozoon closely related to *Trypanosoma*. In mammals, including humans, it causes skin (T_H -1 response) and kalazar visceral ailments (T_H -2 response) that range from relatively mild to life-threatening depending on the species. The parasites invade neutrophils, monocytes, macrophages, dendritic cells, and fibroblasts. There are numerous minor genes that control human susceptibility; a major gene at 11q12 controls *L. donovani* susceptibility. Macrophages and monocytes spread the parasite all over the body. In mice, at least three genes control cutaneous leishmaniasis susceptibility; among them wound healing has a prominent role (Sakthianandeswaren A et al 2005 Proc Natl Acad Sci USA 102:15551). Susceptibility to the different forms and strains of the disease may be under the control of 1,000 genes. The activation of macrophages through IFN- γ may control the disease through the formation of antimicrobial substances, e.g., NO. The amastigote form occurs in mammalian blood and the promastigote form in the gut of the sandfly that spreads the infection. The virulence and transmission is controlled by lipophosphoglycan on the surface of the cells. The genome of this protozoon can now be effectively manipulated by molecular techniques. The *L. donovani* complex species are morphologically indistinguishable but have been identified by molecular methods, multifactorial genetic analysis that includes DNA sequences of protein-coding genes as well as noncoding segments, microsatellites, restriction-fragment length polymorphisms, and randomly amplified polymorphic DNAs, for a total of 18,000 characters for each of the 25 geographically representative strains. On this basis new taxonomic classification has been proposed (Lukes J et al 2007 Proc Natl Acad Sci USA 104:9375). ▶Trypanosomatids, ▶kinetoplast, ▶marker, ▶macrophage, ▶ T_H , ▶IFN- γ , ▶nitric oxide, ▶metacyclogenesis; Lipoldová M, Demanmt P 2006 Nature Rev Genet 7:294; Tamar S, Papadoupoulou B 2001 J Biol Chem 276:11662; Sacks, D, Kamhawi S 2001 Annu Rev Microbiol 55:453; genomes of three species causing different diseases: Peacock CS et al 2007 Nature Genet 39:839; http://www.sanger.ac.uk/Projects/L_major/.

Lek: A social mating group of animals.

Lemna: The upper cover bract of the grass flower, frequently bearing an awn at the tip (see Fig. L25).
▶palea



Figure L25. Lemna

Lemon (*Citrus limon*): $2n = 18$ or 36 . ▶orange, ▶grapefruit

Lemur: *Cheirogaleus major* and *C. minor*, $2n = 66$; *Hapalemur griseus griseus*, $2n = 54$; *Hapalemur griseus olivaceus*, $2n = 58$; *Lemur catta*, $2n = 56$; *Lemur coronatus*, $2n = 46$; *Lemur fulvus albifrons*, $2n = 60$; *Lemur fulvus fulvus*, $2n = 48$; *Lemur macaco*, $2n = 44$; *Lemur variegatus subcinctus*, $2n = 46$.
▶prosimii, ▶primates

Length Mutation: Length mutation is either the deletion, duplication, insertion or any other alteration of the chromosome or nucleic acid sequence affecting the size of a tract. ▶chromosomal aberrations

Lenticel: The structure on tree barks permitting passage of gaseous substances; lens-shaped glands at the base of the animal tongue.

Lentigines (singular lentigo): Lentigens are also known as freckles (see Fig. L26). ▶LEOPARD syndrome, ▶xeroderma pigmentosum

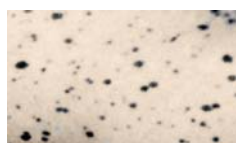


Figure L26. Lentigines

Lentil (*Lens culinaris*): A pulse, popular in the old world because of its high percentage of protein ($\approx 25\%$), $2n = 2x = 14$.

Lentiviruses (slow viruses): Cytopathic single-stranded RNA retroviruses with similar properties to HIV. They infect primates and domestic animals. The equine infectious anemia virus (EIAV) is contagious for horses. The Maedi visna virus (MVV) infects sheep; the caprine arthritis encephalitis virus (CAEV) is pathogenic for goats. The bovine immunodeficiency virus (BIV) attacks cattle. The feline immunodeficiency virus (FIV) is a threat to cats. The simian immunodeficiency virus (SIV) may be found in apes

and monkeys and may or may not affect them seriously but probably does lead to the evolution of the human immunodeficiency viruses, HIV1 and HIV2.

The HIV genome contains two identical repeats, coupled to a tRNA primer for reverse transcription. The two terminal repeats are essential for replication, transcription, polyadenylation, and integration. Besides three minimally needed genes (*gag*, *pol*, *env*) for the family, they may contain additional genes (▶acquired immunodeficiency syndrome). They are suitable for vector construction by pseudotyping and are promising in gene therapy. An advantage of these vectors is they are suitable for transformation of most nondividing cells because of their ability to pass through cell membranes and nuclear pores, using a system for nuclear localization factors. Some HIV-based vectors may, however, infect only activated cells (see Fig. L27). Some retroviral vectors can infect

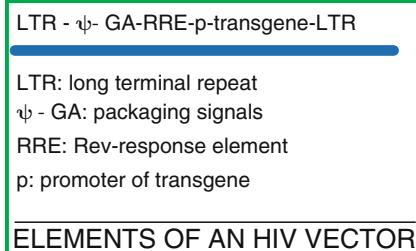


Figure L27. Elements of an HIV vector

cells only during mitosis when the nuclear membrane transiently disintegrates. Amphotropic, replication-deficient HIV vectors have been developed that retain the ψ signal as well as parts of the *gag* and the RRE domain of Rev and Tat, facilitating packaging as well transcription and cytoplasmic transfer of the vector transcripts. Their use may involve the potential danger of self-replication and activation of proto-oncogenes by insertion in their vicinity. For gene therapy the cells are transfected with three separate plasmids. One (the vector) contains the sequences required for infection and transfer of the gene selected. The packaging plasmid carries the elements (structural proteins but not the envelope protein) needed for vector production. The *env* gene must be avoided so the vector would not infect the $CD4^+$ T cells. The third plasmid carries a different envelope gene, encoding, e.g., the G glycoprotein of the vesicular stomatitis virus (see Fig. L28). This protein assures stability and can be employed at high titer. The three vectors lack overlapping sequences, as a result of which, reconstitution of a virion by recombination is prevented. Accessory proteins (Vpr, Vif, Tat) may be required for the efficient transfection of different cell types. The 5' LTR is needed as

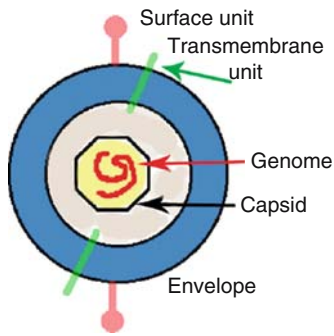


Figure L28. Lentivirus particle

a promoter. A deletion in the 3' LTR is incorporated into the 5' LTR during reverse transcription and prevents the production of vector RNA. Such constructs prevent the formation of replication competent lentivirions (RCL). A nonintegrative lentiviral vector derived from HIV1 with a class 1 integrase (IN) mutation (replacement of the 262RRK motif by AAH) displayed episomal expression—in vitro and in vivo—with 500–1,250 times less integration and thus substantially reduced the risk of insertional mutation (Philippe S et al 2006 Proc Natl Acad Sci USA 103:17684). ▶**HIV**, ▶**pseudo-typing**, ▶**ψ**, ▶**gene therapy**, ▶**retroviral vectors**, ▶**MoMuLV**, ▶**retroviruses**, ▶**cytomegalovirus**, ▶**adeno-associated virus**, ▶**vesicular stomatitis virus**; Lever, AML, p. 61 in Meager A (Ed) 1999 Gene therapy technologies, applications and regulations, Wiley, New York; Tang H et al 1999 Annu Rev Genet 33:133; Schnell T et al 2000 Hum Gene Ther 11:439; Kafri T 2004 Methods Mol Biol 246:367.

Lentz-Hogben Test: The Lentz-Hogben test is the same as the ascertainment test.

Leopard Cat (*Felis bengalensis*): $2n = 38$.

LEOPARD Syndrome: An acronym for Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of the genitalia, Retardation of growth, sensorineural Deafness, and autosomal dominant inheritance. The lentigines may turn neoplastic. The lesions in the PTPN11 gene are shared with the Noonan syndrome. ▶**lentigines**, ▶**hypertelorism**, ▶**stenosis**, ▶**sensorineural**, ▶**cancer**, ▶**Noonan syndrome**; Digilo MC et al 2002 Am J Hum Genet, 71:389.

Leopold of Albany: Hemophilic son of Queen Victoria, who died at age 31 of hemorrhage after a fall, and who transmitted this gene through his daughter, Alice and she transmitted it to his grandson (Rupert) Lord Trematon who also died from hemorrhage after an auto accident. ▶**hemophilia**

Leopold of Battenberg: The hemophilic grandson of Queen Victoria who died of hemorrhage after surgery at age 33. ▶**hemophilia**

Lepidotrichia: The bony structures of the fins of fishes.

Lepore: ▶**thalassemia**

Leprechaunism (Donahue syndrome): Dwarfism caused by a defect in the insulin receptor.

Leprosy (Hansen disease): A neurological disease caused by *Mycobacterium leprae* (3,268,203 bp) invading the Schwann cells and macrophages in the peripheral nervous system. It damages the host immune system and disfigures the extremities (arms and legs), head and other parts of the body. Only 49.5% of the genome codes for proteins, 27% are pseudogenes and 23.5% are noncoding but may have some regulatory functions. It appears that, during evolution, this bacterium (compared to other mycobacteria) lost significant functional parts. Gene expression profiles, e.g., that of the leukocyte immunoglobulin-like receptor family, helps in identifying the clinical stages of the disease (Blehariski JR et al 2003 Science 301:1527). Major human susceptibility loci are at 10p13 and at 6q25-q26 (Mira MT et al 2004 Nature [Lond] 427:636). A second linkage signal was detected in Vietnamese populations in the 6p21 chromosomal region (within HLA), and fine mapping placed the peak (lod score = 2.7) of the responsible lymphotoxin gene in that area (Alcaïs A et al 2007 Nature Genet 39:517). ▶**mycobacteria**, ▶**Bacillus Calmette-Guerin**, ▶**lymphotoxins**; Cole ST et al 2001 Nature [Lond] 409:1007; Young D, Robertson, B. 2001 Curr Biol 11:R381; Siddiqui MR et al 2001 Nature Genet 27:439; Cole ST et al 2001 Nature [Lond] 409:1007; Mira MT et al 2003 Nature Genet 33:412.

Leptin: Assumed to be a hormonal feedback signal (167 amino acids) produced by adipocytes. It acts on the ventromedial hypothalamus and regulates food intake and metabolic rate negatively (Dhillon H et al 2006 Neuron 49:191). Obesity may also be the result of resistance to leptin. A deficiency or resistance to leptin causes increased food intake in mice and humans whereas injection of leptin, the hormone, encoded by the *ob* gene of mice, reduces body weight by reduction of fat tissues and controls glucose and lipid metabolism.

Leptin has repressive effects on hepatic stearyl-CoA desaturase-1, an enzyme catalyzing the biosynthesis of monounsaturated fatty acids (Cohen P et al 2002 Science 297:240). Leptin also has angiogenic

activity. Glucosamine, hyperglycemia, and hyperlipidemia may stimulate leptin synthesis.

Recombinant human leptin corrects sterility caused by the *ob/ob* condition in female mice. The leptin receptor of mouse (*Ob-R*) gene encodes five alternatively spliced transcripts. Leptin-deficient humans are deficient in sexual development. Leptin signals through the STAT3 protein and modulates insulin activity (see Fig. L29). It activates ATP-sensitive K

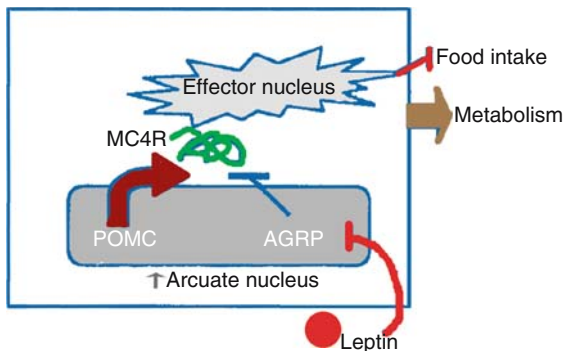


Figure L29. A simplified outline of the melanocortinergic pathway of leptin action. POMC = pre-pro-opiomelanocortin, AGRP = agouti-related protein, MC4R = melanocortin. (After Barsh GS et al 2000 Nature 404:644)

channels and inhibits hypothalamic neurons (nucleus arcuatus hypothalami and the nucleus paraventricularis hypothalami), but the arcuate nucleus may also stimulate the lateral hypothalamic neurons and the parasympathetic and preganglionic neurons may receive mixed signals. Neuropeptide Y interacts with leptin and may promote appetite. Leptin also affects the synthesis of the α -melanocyte-stimulating hormone (α -MSH) which down-regulates appetite. The melanin-concentrating hormone (MCH) is also high in the brain of *ob* homozygous rodents. Dopamine-deficient mice do not feed even when leptin is missing. The OBR-A receptor may also affect leptin transport. The suppressor of cytokine signaling (SOCS3) also appears to be a factor in mediating resistance to leptin. The synthesis of leptin may be suppressed by CART (cocaine- and amphetamine-regulated transcript). Leptin may inhibit bone formation by acting through the central nervous system. The leptin receptor (OB-R) occurs in several isoforms because of alternative splicing of its RNA transcript. The leptin and the insulin pathways may interact at several levels. Peroxisome proliferator-activated receptor γ (PPAR) co-activator (PGC-1) is an important regulator of energy output (thermogenesis). Administration of leptin to starving mice reversed the immunosuppressing effect of starvation.

Leptin-deficient mice, however, are protected from T cell mediated hepatotoxicity because of the reduction of TNF- α and IL-18. Malnutrition and starvation appears to be a serious factor in susceptibility to infectious diseases. It is not known whether treatment with leptin under conditions of hunger would be desirable because it increases energy storage and expenditure, and may further aggravate malnutrition. Leptin deficiency in rats leads to depression-like symptoms that can be remedied by intrahippocampal infusion of leptin but not by infusion of leptin into the hypothalamus (Lu X-Y et al 2006 Proc Natl Acad Sci USA 103:1593). ▶obesity, ▶STAT, ▶insulin, ▶brain human, ▶orexin, ▶ion channels, ▶angiogenesis, ▶melanocortin, ▶CART, ▶neuropeptide Y, ▶PYY₃₋₃₆, ▶AGRP, ▶melanocyte stimulating hormone, ▶opiocortin, ▶SOCS-box, ▶TNF, ▶IL-18, ▶ciliary neurotrophic factor, ▶ghrelin, ▶muscarinic acetylcholine receptors; Sierra-Honogmann MR et al 1998 Science 281:1683; Harris RBS 2000 Annu Rev Nutr 20:45; Forbes S et al 2001 Proc Natl Acad Sci USA 98:4233.

Leptokurtic: ▶kurtosis

Leptomycin: An antibiotic and nuclear export inhibitor in meiosis.

Leptonema: ▶leptotene stage

Leptotene Stage: The leptotene stage is distinguished in meiosis when the chromosomes appear under the light microscope as single strands although they have been doubled during the preceding S stage. The chromosomes are greatly relaxed and stretched out. The threads (leptonema) are usually quite tangled and their termini cannot be distinguished by light microscopy. Bead-like structures of localized condensations, the chromomeres, are usually visible. The photograph (courtesy of Dr. A. Sparrow) shows late leptotene (see Fig. L30). ▶meiosis, ▶chromomere

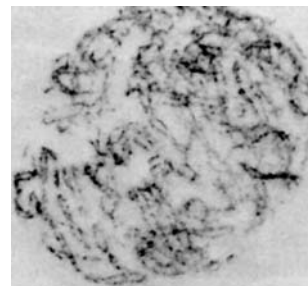


Figure L30. Leptotene stage

Leri-Weill Syndrome: ▶dyschondrosteosis, ▶pseudo-autosomal

Lesbian: A homosexual female. ► [homosexuality](#)

Lesch-Nyhan Syndrome: ► [HPRT](#)

***Lespedeza bicolor*:** A forage legume, $2n = 18, 20, 22$.

LESTR (leukocyte-expressed seven-transmembrane-domain receptor): LESTR is the same as fusin.

LET: LET or linear energy transfer is a measure of energy delivered by ionizing radiation in keV (kilo electron volts) per nanometer path within the target. Approximate LET values in biological material: gamma rays from ^{60}Co source (1.2 to 1.3 MeV): 0.3; hard x-rays (250 keV): 3.0; β -rays from ^3H (0.6 keV): 5.5; recoil proton from fast neutrons: 45; heavy nuclei from fission (α -particles): 5,000. ► [ionizing radiation](#), ► [kinetics](#), ► [DNA repair](#)

let-23: A gene of *Caenorhabditis* coding for a transmembrane receptor protein. ► [signal transduction](#)

Lethal Equivalent: The designation of genetic factors in an individual that, in combinations, are responsible for death. For example, if three genes each are expected to reduce life expectancy by a chance of 0.33, their combined lethal equivalent value is ≈ 1 , i.e., approximately the same as one that causes early death with 100% probability (see [Fig. L31](#)). The actual calculation must, however, be carried out by a different procedure because no information can be obtained on the number of the individual recessive sublethal genes. Thus, if it is observed that the infant mortality among the offspring of totally unrelated parents is ($F = 0$) 8%, and among the offspring of first cousins ($F = 1/16$) of the same population is 13% [F is the coefficient of inbreeding], the difference $0.08 - 0.13 = 0.05$, i.e., 5%; then, $5\% \times 16 = 0.8$, i.e., 80%. Since among diploids two recessive alleles at a locus are required for expression, the frequency of lethal equivalent recessive genes is $\sqrt{0.8} < 0.89$. Thus the number of lethal equivalent recessive genes per gamete in this particular population is ≈ 0.89 , close to 1 per gamete. The number of lethal equivalents in a population is $\sum q$ where q is the frequency of the recessives and s is the selection coefficient. ► [coefficient of inbreeding](#), ► [coefficient of coancestry](#), ► [genetic load](#), ► [incest](#), ► [selection coefficient](#); Makov E, Bittles AH 1986 *Heredity* 57 (3):377; Anderson NO et al 1992 *Plant Breed Revs* 10:93.



Figure L31. Lethal mouse embryo

Lethal Factors: Lethal factors have been extensively used for the genetic analyses of developmental pathways because they permit studies on the consequences of arrest of differentiation at particular stages. Conditional lethal mutations survive under certain temperature regimes or on supplemented nutritive media and offer particular advantages because they can be more easily analyzed by biochemical methods. The presence of lethal factors may modify segregation ratios. Dominant and recessive lethal factors may not permit the expression of syntenic genes or only at low frequency depending on the extent of recombination. Therefore, genes on the homologous strand may appear in excess. Semi-recessive lethal mutations may cause 2:1 segregation instead of 3:1 in F_2 ($1/1$ dead). ► [segregation distorter](#), ► [meiotic drive](#), ► [certation](#)

Lethal Mutation: A lethal mutation normally fails to survive. In *Caenorhabditis*, only 20–35% of the genes are mutable to an obvious visible, lethal or sterile phenotype and the majority of mutations appear like the wild type. This information resulted from the sequencing of the whole genome and has been interpreted by (partial) redundancy of the genetic material. In *Drosophila*, 24–30% of genes are estimated to be vital and apparently more than half of them are in the 2nd chromosome. ► [conditional lethal mutations](#)

Lethal Synthesis: Lethal synthesis occurs when a toxic analog of a metabolite is incorporated into a biological system and eventually exerts deleterious or lethal effects.

Lettuce (*Lactuca sativa*): A composite salad crop with chromosome numbers $n = 8, 9$ and 17.

Leucine Metabolism: Leucine $[(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{NH}_2)\text{COOH}]$ is a nonpolar amino acid; it may be formed from isoleucine $[\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}(\text{NH}_2)\text{COOH}]$. ► [isoleucine-valine biosynthetic pathway](#), ► [3-hydroxy-3-methylglutaryl CoA lyase deficiency](#), ► [methylcrotonylglycinemia](#), ► [methylglutaconic aciduria](#), ► [hydroxymethylglutaric aciduria](#)

Leucine-Rich Repeats: 15–29 leucines assist ligand recognition in processes such as signal transduction, cell development, DNA repair and RNA processing, and resistance to pathogens. ► [leucine zipper](#), ► [ligand](#), ► [DNA repair](#), ► [introns](#)

Leucine Zipper: Dimeric regulatory proteins of two subunits; at the COOH terminus, an amino leucine occurs at every seventh position; at the amino terminal domain, positively charged amino acids are found and this region is bound to DNA in a zipper-like manner (see [Fig. L32](#)). The leucine zippers may be homo- or heterodimeric and thus increase their

specificity by a combinatorial control mechanism. The basic leucine zipper (bZIP) contains 25 conserved amino acids of these nine substitutions and disrupts function. The binding domain is usually 100-amino-acid long. ▶DNA-binding protein domains, ▶binding proteins, ▶regulation of gene activity, ▶Max, ▶induced helical fork, ▶bZip; Rieker JD, Hu JC 2000 Methods Enzymol 328:282; Palena CM et al 2001 J Mol Biol 308:39.

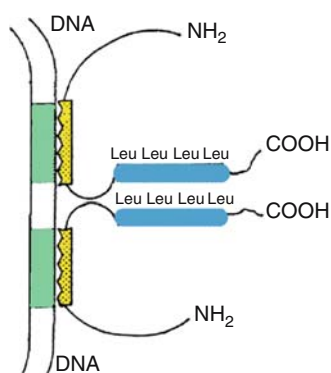


Figure L32. Leucine Zipper

Leucoplasts: Plastids without carotenoids and chlorophylls.

Leucyl tRNA Synthetase (LARS): Leucyl tRNA synthetase charges tRNA^{Leu} by leucine. Its gene is in human chromosome 5. ▶aminoacyl-tRNA synthetase

Leukalexins: These are released by effector cells and slowly degrade the DNA of the target cells. ▶immune system; Joag S et al 1989 J Cell Biochem 39(3):239.

Leukemia: A cancer of the blood forming organs characterized by an increase of the number of leukocytes and accompanied by an enlargement or proliferation of the lymphoid tissues. It involves anemia and increasing general weakness and tiredness. Two main types are generally distinguished: *acute myelogenous leukemia* (AML/FPD, 21q22.1-q22.2) that primarily affects adults. AML is frequently caused by the ectopic expression (through translocational gene fusion) of the *CDX2* homeobox gene. Fusion of the *ETV6* transcription factor gene has minimal or no effect for AML development (Rawat VPS et al 2004 Proc Natl Acad Sci USA 101:817). Reduction in the level of the PU.1 transcription factor decreases the levels of c-Jun and JunB oncogenes and blocks differentiation, increasing self-renewal of hematopoietic stem cells in AML (Steidl U et al 2006 Nature Rev Genet 38:1269). In chronic lymphocytic leukemia (CLL, 11q13.3) the circulating malignant cells are differentiated B

lymphocytes. Down-regulation of Death-associated protein kinase 1 (DAPK1, 9q34.1) by methylation of its promoter is common in CLL and in such a case hereditary predisposition occurs (Raval A et al 2007 Cell 129:879). MicroRNAs miR-15a and miR-16-1 downregulate the antiapoptotic effect of the Bcl2 and may play a role in the development of the cancer (Cimmino A et al 2005 Proc Natl Acad Sci USA 102:13944). A low-grade B-cell malignancy involves chromosomal aberrations at 13q14, a site concerned with about 25–50% of CLL, the position of a tumor suppressor. MicroRNA sequences are located in this region and their deletion occurs in about 68% of the CLLs (Calin GA et al 2002 Proc Natl Acad Sci USA 99:15524). The acute myelogenous leukemia (AML) may be preceded by haploinsufficiency of the core binding factor α subunit (CBFA2, 6p21). The acute myeloid leukemia involving inversion in human chromosome 16 is a fusion of the core binding factor- β (BGF/CBFB/PEBP2B) and the smooth muscle myosin heavy chain (MYH11). It results in transcriptional repression. About half of the AML cases involve cytological anomalies. A defect in JunB may lead to AML. The acute lymphoblastic leukemia (ALL) mainly affects children. It involves, primarily, chromosomal aberrations affecting several genes genomewide (Mullighan CG et al 2007 Nature [Lond] 446:758). Thiopurine methyltransferase assay (TPMT) is successful for determining the dosage of thiopurines appropriate for an individual (Weinshilboum R 2003 New England J Med 348:529). Blood asparagine level can be decreased along with chemotherapy. Such a treatment may result in drug resistance by upregulation of glutamine-dependent asparagine synthetase (Richards NGJ, Kilberg MS 2006 Annu Rev Biochem 75:629).

The acute myeloid form frequently involves a translocation between human chromosome 8 and 21 [t(8;21)(q22;q22)]. In chromosome 21 the breakpoints are generally within the same intron of the receptor for the granulocyte-macrophage colony-stimulating factor (CSF2R). At the same chromosome-21 location a basic helix-loop-helix protein, class B1 (BHLHB1), is encoded as shown by the t(14;21)(q11.2;q22) translocations. Patients in relapse usually have activated Jak-2 protein tyrosine kinase. Tyrphostins (AG-490) effectively block leukemic cell growth in these cases by inducing apoptosis in the cancer cells without affecting normal blood-forming cells. The *chronic myeloid leukemia* (CML) is generally associated with a translocation between chromosomes 22q11.21 and 9q34.1 (▶Philadelphia chromosome). The translocation is within the BCR (breakpoint cluster region) of chromosome 22 and in chromosome 9; the ABL gene (Abelson murine leukemia virus oncogene) is affected. The

translocation causes a fusion between the 5' proximal region of one of the BCR spanned loci and the ABL gene. The fused BCR-ABL region encodes a 210-kDa tyrosine kinase protein, which causes malignant transformation of leukocytes. Transplantation experiments in mice demonstrated hematological malignancies in the recipients of this protein. At the early stages of the disease the use of the drug STI-571 specifically and effectively blocks the kinase and counteracts the malignancy. Treatment at advanced stages involves resistance in about a year. Chronic lymphocytic leukemia Type2 (BCL2) is a follicular lymphoma involving translocations between chromosome 18q21 (immunoglobulin heavy chain gene J) and gene BCL in chromosome 18 and placing BCL under the influence of the IgJ_H enhancer. It leads to a low-grade malignancy. In another step, a translocation with chromosome 8 brought in the MYC c-oncogene (myelocytomatosis v-oncogene homolog in chromosome 8q24) and the double translocation caused a high-grade malignancy. Transfection with a BCL-2 construct resulted in oncogenic potential. The BCL-2 product is an integral mitochondrial membrane protein (M_r 25,000). A human chromosome 19q13 oncogene apparently causes B cell leukemia/lymphoma (BCL3 or BCL4). It usually involves translocations. Chronic B cell leukemia (BCL5) also involves a translocation between BCL-2 and a truncated MYC resulting in high-grade expression. Chronic lymphatic leukemia (CLL or BCL1) is clearly a familial disease involving translocations (11;14)(q13;q32). Again, the translocation involves the joining segments 3 and 4 of the heavy chain Ig in chromosome 14. As a consequence, the immune system is weakened and the leukemia is often associated with other disturbances of the immune system (hyperthyroidism, pernicious anemia, rheumatoid arthritis, autoimmune disease). Acute T cell leukemia (ATL/TAL/SCL) is due to the activation of the α -chain of the T cell receptor (TCRA, chromosome 11p13) by translocations t (11;14)(p13;q11). The 14q11 band contains the variable region of TCRA and the 11p15.5 is the location of the HRAS (Harvey rat sarcoma) oncogene. Lymphoid leukemia, LYL1, involves translocations between chromosome 7 at the T cell receptor β -chain gene (TCRB, 7q35) and the LYL1 gene, chromosome 19p13.

Myeloid/lymphoid mixed lineage leukemia (MLL/ALL/HRX) involves translocations of 11q23 to AF10 (at human chromosome 10p12 encoding a 1,27 amino acid protein) and displays lymphoid myeloid phenotypes. It is present in infancy. DOT1L (DOT1-like, homolog of yeast) encodes at human chromosome 19p13.3, a histone 3 methyltransferase that interacts with MLL; histone H3 is hypermethylated at lysine 79 and subsequently HOXA9 and other

leukemia-related genes are upregulated (Okada Y et al 2005 Cell 121:167). The sequences of 11q23 involve a postulated transcription factor and it is also frequently included in about 30 different translocations. Cleavage of the MLL gene (translocations) may be caused by inhibition of topoisomerase II by bioflavonoids (flavone, rutine, kaempferol, etc.). The MLL gene is an apparent regulator of a homeobox, shared by other animals. Taspase I (threonine aspartase) is an asparaginase enzyme processing MLL (Khan JA et al 2005 Structure 13:443). The very common B-cell precursor (BCP) leukemia responds favorably to the CD19-associated tyrosine kinase inhibitor, genistein. CD19 is a B cell-specific TK receptor and its destruction leads to apoptosis of 99.9 percent of leukemia cells. The stem cell leukemia (SCL) gene is normally involved in the differentiation of the hematopoietic cells but it may form a complex with the oncogene product LMO-2 and GATA proteins. The tetramer may act in the development of acute T cell leukemia. In the acute promyelocytic leukemia (APL) the translocation involves 15q21 (PML [promyelocytic leukemia inducer])-17q11.2 (RARA [retinoic acid receptor α]). A translocation between 11q23 (PLZF [promyelocytic leukemia Zn-fingers])-17q12 (RARA) is another cancerous gene fusion transactivating the p21 transforming protein. PLZF normally is a transcriptional repressor and it regulates limb and axial skeletal patterning. PML is also a tumor suppressor and it inhibits translation of hypoxia-inducible factor (HIF-1 α) by repressing TOR and neoangiogenesis supportive of tumor growth. Mutation in these proteins promotes cancer growth (Bernardi R et al 2006 Nature 442:779). PML bodies oppose nuclear AKT oncogene (Trotman LC et al 2006 Nature [Lond] 441:523). PML and PLZF heterodimerize and thus form nuclear bodies. The oncogenic domain of PML is involved in the degradation of ubiquitinated proteins. PML-RARA is retinoic acid responsive whereas PLZF-RARA is a retinoic acid resistant leukemia. The juvenile myelomonocytic leukemia is a complex disease encoded at 17q11.2, 12q24.1, and 5q31. It is frequently associated with neurofibromatosis and cases of the Noonan syndrome due to somatic or germline mutations of protein tyrosine phosphatase (PTPN11) (Tartaglia M et al 2003 Nature Genet 34:148).

In animal models, *N*-methylnitrosourea (MNU), 3-methylcolanthrene (MCA), ionizing radiation, Moloney mouse leukemia virus, etc., may induce leukemia. ►interferon, ►T cell, ►TCR, ►RAS, ►immunoglobulins, ►ABL, ►Abelson murine leukemia virus, ►FMS, ►ELL, ►Philadelphia chromosome, ►BCR, ►Myb oncogene, ►MYC, ►Mylotarg, ►colony stimulating factor, ►apoptosis,

▶ leukemia inhibitory factor, ▶ homeobox, ▶ Hodgkin's disease, ▶ non-Hodgkin lymphoma, ▶ CREB, ▶ C/EBP, ▶ neurofibromatosis, ▶ myelodysplasia, ▶ GATA, ▶ genistein, ▶ Gleevec, ▶ feverfew, ▶ RAR, ▶ p21, ▶ PLZF, ▶ PML, ▶ OL1p53, ▶ SMRT, ▶ N-CoR, ▶ MLV, ▶ RAR, ▶ LYT oncogene, ▶ topoisomerase, ▶ Hox, ▶ HTLV, ▶ Jun, ▶ microRNA, ▶ Bcl, ▶ apoptosis, ▶ AKT, ▶ HIF, ▶ TOR, ▶ angiogenesis, ▶ Knudson's two-mutation theory; Ross JA 2000 Proc Natl Acad USA 97:4411; Burmeister T, Thiel E 2001 J Cancer Res Clin Oncol 127:80; Armstrong SA et al 2002 Nature Genet 30:41; Staudt LM. 2002 Annu Rev Med 53:303; Kelly LM, Gilliland DG 2002 Annu Rev Genomics Hum Genet 3:179.

Leukemia Inhibitory Factor (LIF): The human cytokine (241 amino acids, encoded in chromosome 22q12.1-q12.2) is involved in negative and positive regulation of myeloid leukemia cell lines, in the development of motor neurons, and in a wide variety of other functions. LIF causes the dimerization of LIFR (LIF receptor) and glycoprotein gp130. LIF activates transcription factors STAT3 and BMP2 induces SMAD1. The STAT and Smad family of proteins bind p300 and are involved in the differentiation of astrocytes. BMP causes the tetramerization of the bone morphogenetic protein receptors (BMPR1 and BMPR2) and the heterodimer phosphorylates SMAD1. In all probability, p300 could be involved with the acetylation of histones and thereby the facilitation of transcription. Its receptor, encoded at 5p12-p13, is shared with other cytokines. An inactive LIF does not affect embryonic development in mice but it may be important for implantation of the egg. LIF^{-/-} males are normal but the females are sterile. ▶ neurons, ▶ cytokines, ▶ STAT, ▶ bone morphogenetic protein, ▶ Smad, ▶ p300, ▶ gp130, ▶ astrocyte, ▶ GFAP, ▶ TGF, ▶ histone acetyl transferase, ▶ APRF, ▶ Abelson murine leukemia virus, ▶ retroviral restriction factors; Stewart, CL et al 1992 Nature [Lond] 359:17; Cheng J-G et al 2001 Proc Natl Acad Sci USA 98:8680, structure of LIF-LIF Receptor binding: Huyton T et al 2007 Proc Natl Acad Sci USA 104:12737.

Leukocyte (leucocyte): A white blood cell. Their average numbers under normal conditions per mL of blood in humans is ~6,000. It is ~28,000 in chickens, ~15,000 in pigs, ~9,000 in dogs, and ~8,000 in horses and cattle. ▶ blood, ▶ erythrocyte

Leukocyte Adhesion Deficiency (LAD): LAD2 is a deficiency of CD15-fucose cell surface glycoprotein, ligand of selectins E and P. ▶ selectins, ▶ fucosyltransferase

Leukocyte Adhesion Deficiency (ITBG2, LAD): A human chromosome 21q22.3 dominant/recessive immunodefect that involves common infections, lack of pus formation, and impairment of granulocytes, monocytes and lymphocytes. ▶ selectins, ▶ fucosyltransferase

Leukocyte Antigen: ▶ HLA

Leukocyte Common Antigen: ▶ CD45

Leukocytosis: Activation of the leukocyte producing system. It is mediated by the leukocyte mobilization factor (LMF) formed from the α chain of the C3 complement component by enzymatic fragmentation. ▶ leukocytes, ▶ complement

Leukodystrophy: ▶ metachromatic leukodystrophy, ▶ Addison disease, ▶ Krabbe's leukodystrophy, ▶ Gaucher's disease, ▶ Pelizaeus-Merzbacher disease, ▶ Charcot-Marie-Tooth disease, ▶ cytotoxic T cell. Adult onset dominant leukodystrophy (chromosome 5q) is due to duplication of lamin B1; the homologous gene in *Drosophila* involves developmental eye anomaly (Padaiah QS et al 2006 Nature Genet 38:1114, see correction in Nature Genet. 39:276). The duplication causes progressive demyelination of the central nervous system with symptoms resembling multiple sclerosis. ▶ lamins, ▶ laminopathies, ▶ multiple sclerosis

Leukoencephalopathy: A group of neurological disorders. A dominant dementia, CADASIL, was located at 19p13.2-p13.1. Leukoencephalopathy with vanishing white matter and neurological deterioration is at the region 3q27 encoding the ϵ and β subunits of the translation initiation factor eIF2B. Swelling and cysts in the brain characterize a third type. The disease is caused by the human polyomavirus, JC, which infects in early childhood and is prevalent in immunocompromised adults. It enters the cells by a ligand-induced clathrin-dependent pathway (Elphic GF et al 2004 Science 306:1380). Recessive leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation is encoded in human chromosome 1. Sequencing of this region uncovered mutations in *DARS2*, which encodes mitochondrial aspartyl-tRNA synthetase (Scheper GC et al 2007 Nature Genet 39:534). ▶ CADASIL, ▶ eIF2B; Leegwater PAJ et al 2001 Nature Genet 29:383.

Leukopenia: A condition with reduced numbers of leukocytes and neutrophils in the blood.

Leukosis: The organic basis of leukemia. ▶ leukemia

Leukotomy: ▶ lobotomy

Leukotrienes: Leukotrienes are 20 carbon carboxylic acids with one or more conjugated double bonds and some oxygen substitutions. They are formed from arachidonic acid by lipoxygenase. They control inflammatory and allergic reactions such as asthma and, indirectly, obesity. Leukotrienes may activate the transcription factor peroxisome proliferator-activated receptor (PPAR) subunits that are involved in the regulation of enzymes of fatty acid oxidation, control of development, adipocyte differentiation, glucose metabolism, and, indirectly, in inflammatory reactions through macrophages. Leukotriene C4 synthase (LTC4S), a trimer, is encoded in human chromosome 5q35 (Schmidt-Krey I et al 2004 Structure 12:2009). The FLAP protein is required for the biosynthesis of leukotrienes. Its crystal structure shows that inhibitors bind in membrane-embedded pockets of FLAP, which suggests how these inhibitors prevent arachidonic acid from binding to FLAP and subsequently being transferred to 5-lipoxygenase, thereby preventing leukotriene biosynthesis. Leukotrienes play important roles in respiratory and cardiac functions (Ferguson AD et al 2007 Science 317:510). The cysteinyl leukotriene-1 receptor (CysLT₁) is encoded at Xq13-q21; its crystal structure is identified (Ago H et al 2007 Nature [Lond] 448:609) ▶[lipoxygenase](#), ▶[arachidonic acid](#), ▶[fatty acids](#), ▶[peroxisome](#), ▶[integrin](#), ▶[anemia](#), ▶[hemolytic anemia](#), ▶[PPAR](#), ▶[prostaglandins](#), ▶[myocardial infarction](#); Funk CD 2001 Science 294:1871.

Levorotatory: The plane of polarized light is rotated counterclockwise.

Levy-Hollister Syndrome: ▶[LADD syndrome](#)

Lewis Blood Group: The Lewis blood group is characterized by the expression of the *Le* gene coding for α -L-fucosyltransferase. Four different types can be characterized with the frequencies indicated: (1) *Lea*^{+/+}, 0.7 (genotype *Le/le Se/se*); (2) *Lea*^{+b-}, 0.20 (genotype *Le, se*); (3) 0.09 (genotype *le, Se/se*); (4) *Lea*^{b-}, 0.01 (genotype *le, se*). The ABH blood group may cause less severe reaction in incompatible application in blood transfusion than the ABO, yet it may cause serious hemolytic problems. The *Le*^y oligosaccharide non-protein antigen is overexpressed in the majority of human carcinomas. ▶[ABH antigen](#), ▶[ABO blood group](#), ▶[Bombay blood group](#), ▶[secretor](#)

Lewy Body: Lewy bodies are round (or other size and shape) structures in neural cytoplasm composed mainly of α -synuclein (see [Fig. L33](#)). They occur in Parkinson's disease and in other diseases with neuronal degeneration (Alzheimer's disease, Hallervorden-Spatz disease, Pick's disease, Gaucher's disease). Besides mutation in α -synuclein, Lewy bodies may

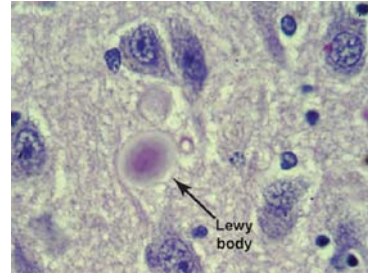


Figure L33. Lewy body in the brain. (Courtesy of National Institute of Genome Research and Dr. Wong, K. 2004 Armed Forces Institute of Pathology)

also occur by mutation in a leucine-rich repeat kinase 2. LB-like bodies have also been observed if the mitochondria were inhibited (Shults CW 2006 Proc Natl Acad Sci USA 103:1661).

Human α -synuclein transgenic mice vaccinated with α -synuclein antibodies promoted the degradation of the synuclein aggregates and lead to neuronal degeneration. Thus vaccination may be a potential therapeutic tool for Parkinson's disease (Mesliah E et al 2005 Neuron 46:857). ▶[synuclein](#), ▶[Parkinson's disease](#), ▶[ubiquilin](#); Gasser T 2001 Adv Neurol 86:23.

Lewy Neurites: Lewy neurites are neurons with α -synuclein deposits. ▶[synuclein](#), ▶[Parkinson's disease](#)

lexA: A gene of *E. coli* (map position 91) that controls resistance/sensitivity to X-rays and UV. It is a repressor of all SOS repair operons. Its protein product is autoregulated. The RecA protein cleaves the LexA repressor protein (22 kDa) and subsequently, the genes that it represses become activated. ▶[DNA repair](#); De Henestrosa F et al 2000 Mol Microbiol 35:1560; Luo Y et al 2001 Cell 106:585.

Lexicon Genetics: A public gene trap for mouse functional genomics (Skarnes WC et al 2004 Nature Genet 36:543).

Lexitropsins: Lexitropsins are organic molecules with the ability to recognize G-C in the minor groove of DNA. There are three major types of lexitropsins: pyrole, imidazole, and hydroxypyrole. They are of potential use for targeting genes and controlling their function. ▶[netropsin](#); Goodsell DS 2001 Curr Med Chem 8:509.

Leydig Cells: ▶[Wolffian ducts](#)

λ FIX: A replacement vector very similar to λ DASH. ▶ [\$\lambda\$ DASH](#)

LFA (lymphocyte-associated proteins): LFA belong to the integrin family present on T lymphocytes. They

promote cell adhesion and stimulate T cell activation in association with ICAM, CD28, and myosin motor proteins. ►CD28, ►ICAM, ►myosin, ►T cell receptor, ►antigen presenting cell, ►JAB

LFT: A low frequency transducing lysate generated when aberrant excision of a phage particle takes place from a single lysogen. ►HFT, ►lysogen

LGT (lateral gene transfer): A lateral gene transfer may occur during evolution. It is postulated on the basis that some genomes contain nucleotide sequences absent from close relatives but present in more distant ones. ►lateral transmission, ►transmission

LH (luteinizing hormone): ►luteinizing hormone, ►animal hormones

LHCP (light-harvesting chlorophyll protein complex): ►chlorophyll-binding protein complex

Lhermitte-Duclos Disease: ►multiple hamartoma syndromes, ►PTEN

LHX: LIM homeobox genes of mammals and similar genes in invertebrates. ►LIM, ►homeobox

Liability: The appearance of many human traits cannot be explained by simple genetic mechanisms because they show up more frequently in certain human families than in others or in the general population and yet the proportions of afflicted individuals vary a great deal. The manifestation of these traits is commonly explained by polygenic systems. Various environmental effects that make predictability of the manifestation quite difficult generally influence polygenic systems. The frequency of diabetes, schizophrenia, hypertension, dental caries, peptic ulcers, various forms of cancers, etc., belongs to these categories. Until a certain threshold is reached the person is considered healthy but beyond that point medical attention is necessary. The passing of the threshold requires special unidentified environmental conditions. Naturally, it is important to have some predictive ability regarding the liability of individuals to succumb to such diseases. A relatively simple statistical procedure exists to assess the heritability of the liability based on the normal distribution of these traits. In order to proceed with the empirical calculation, refer Table L1.

Q = the incidence of the trait, t = Student's t distribution with one-tail of the normal distribution, z = is the truncation point at the t value.

Assume that the incidence of the trait in the general population is $Q_p = 0.001$ and the incidence among the offspring of an afflicted individual is $Q_a = 0.1$. The truncation point in the general population thus is $t_p = 3.090$ (first column) and that in the afflicted family is $t_a = 1.282$ (6th column). The mean liability of the affected parent is $\mu^1 \cong z_a/Q_a = 0.0037/0.001 = 3.7$.

The mean liability of the offspring of the affected parent is $\mu^2 \cong t_p - t_a = 3.090 - 1.282 = 1.808$.

The heritability of the liability of the trait determined by offspring-parent regression is $h^2 = 2b_{OP}$ (where regression is on one parent rather than on the midparent value) and $b_{OP} = \mu^2/\mu^1 = 1.808/3.7 \cong 0.49$; hence heritability is $h^2 = 2 \times 0.49 = 0.98$. This hypothetical value is obviously very high for heritability. It must be kept in mind, however, that the trait has low penetrance for being controlled by a single gene and most likely it is under the control of multiple genes and is not expected to occur frequently because of the threshold event needed for its manifestation. Would have been the incidence of the trait in the general population $Q_p = 0.005$ and that of the afflicted family $Q_a = 0.500$, the heritability would have come out by this calculation as 0.65. The liability increases with consanguinity of the parents. ►normal distribution, ►Student's t distribution, ► z , ►correlation, ►heritability, ►polygenic inheritance, ►GTL, ►consanguinity, ►penetrance, ►recurrence risk, ►risk, ►threshold trait

Libido: Sexual drive. Libido is the motive for sexual contact although it may exist even in the absence of sexual potency such as in sterile mules.

Library, Genetic: A collection of cloned fragments, representing the entire genome (at least once). The construction of the library requires cutting up of the genome by one or more restriction enzymes or mechanical shearing. Subsequently, the DNA fragments are ligated into appropriate cloning vectors and transformation is carried out in a suitable host (most commonly into *E. coli*). The screening of the cloned colonies requires either nucleic acid hybridization, south-western analysis, immunochemical procedures, recombinational assays, or genetic analysis

Table L1. Liability calculation

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | ← Columns |
|------------|--------|--------|---------|---------|---------|---------|---------|-----------|
| Q → | 0.001 | 0.005 | 0.010 | 0.050 | 0.100 | 0.150 | 0.200 | |
| t → | 3.090 | 2.576 | 2.326 | 1.645 | 1.282 | 1.036 | 0.842 | |
| z → | 0.0037 | 0.1446 | 0.02665 | 0.10314 | 0.17550 | 0.23316 | 0.27996 | |

and identification through one or more of these final steps. ►gene bank, ►vectors, ►transformation, ►restriction endonucleases, ►south-western method

Licensing: The legal authorization for using or, in some cases, even patenting research inventions by another party (industry) for profit. ►patent; Thursby JG, Thursby MC 2003 Science 301:1052.

Licensing Factor (replicational licensing factor): Licensing is a quality control instrument in the immune system for the distinction of self from nonself molecules. Natural killer cells recognize and spare self by the attached self-ligands. ►MCM, ►geminin, ►killer cell; DePamphilis ML et al 2006 Current Opin Cell Biol 18:231.

Lid Domain: An oligopeptide that covers the top layer of the 26S proteasome. It is used for the recognition of ubiquitin, ubiquitin isopeptidase and some proteins with homology to signal transduction complexes. ►proteasome, ►ubiquitin

Liddle Syndrome (pseudoaldosteronism): An autosomal dominant moderate hypertension encoded in human chromosome 16p13-p12. It is involved in the control of a Na⁺ ion channel and renal sodium reabsorption. ►aldosteronism, ►mineral cortical syndrome, ►hypertension, ►degenerin, ►Bartter syndrome, ►Gitelman syndrome

LIF: Laser-induced fluorescence detector.

LIF: ►leukemia inhibitory factor, ►APRF

Life Beginning on Earth: Latest evidence indicates that life began on earth ~3,800 Myr before present. ►Myr

Life Cycle: The successive changes in generations of organisms, including the modes of reproductions. In higher organisms this includes the generation of gametes, fertilization and other modes of propagation and the development of the adult forms. ►gametophyte, ►sporophyte, ►germline, ►alternation of generations, and see also the name of individual organisms.

Life Expectancy: ►longevity

Life-Form Domains: Life-form domains include bacteria, archaea, and eukarya (see Fig. L34). ►archaea, ►prokaryotes, ►eukaryotes; Pace NR 2006 Nature [Lond] 441:289.

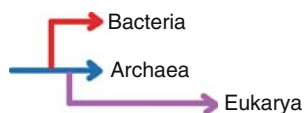


Figure L34. Life-form domains

Life Span: ►longevity

Li-Fraumeni Syndrome (LFS): In some families several types of cancers (breast, sarcomas, brain, lung, laryngeal, adrenal cancers, melanomas, prostate cancer, gonadal germ cell tumor, and leukemias) are found with about 50-fold increased incidence as compared to the general population. The assumption is that alleles of the dominant p53 tumor-suppressor gene segregate these families. LFS is encoded in human chromosome 17p13.1. In some LFS cases the p53 gene appears normal but various single nucleotide substitutions occur in the CHK2 gene. Some gain-of-functions mutations of p53 cause new types of symptoms and have increased effect compared to loss of p53 in mouse (Olive KP et al 2004 Cell 119:847; Lang GA et al 2004 Cell 119:861). (The human gene is homologous to the budding yeast G2 checkpoint kinase RAD53 that normally phosphorylates protein CDC25C.) ►tumor suppressor genes, ►P53, ►malignancy, ►cancer, ►Lynch cancer families, ►substitution mutation, ►RAD53, ►checkpoint, ►CDC25, ►small cell lung carcinoma

Lifting: ►phasmid

Ligand: A molecule that can bind (by noncovalent bonds) to a receptor by virtue of special affinity. Ligands include transcription factors, growth factors, activators, DNA-binding proteins, hormones, neurotransmitters, antigens, morphogens, and membrane receptors. Target-guided combinatorial assembly can screen ligands. In the first step, a set of potential binding elements, including common chemical linkage groups, are prepared. Then, their interaction with the selected target (enzymes, receptors, etc.) is determined. In a third step the combinatorial library of linked binding elements are connected by flexible linkers and in the fourth step this library is tested and classified for tightness of binding to the biological target. Understanding ligands that can selectively enhance or inhibit macromolecular function is important for drug development. Ligand-target relations can be studied by functional effects and nuclear magnetic resonance spectroscopy. ►NMR; Maly DJ 2000 Proc Natl Acad Sci USA 97:2419; Looger LL et al 2003 Nature [Lond] 423:185; Carlomagno T 2005 Annu Rev Biophys Biomol Struct 34:245; <http://www.genome.ad.jp/dbget/ligand.html>; <http://www.modelling.leeds.ac.uk/sb/>; protein ligand affinities: <http://www.agklebe.de/affinity>; ligand and protein structure: <http://www.idrtech.com/PDB-Ligand/>; functional residue templates and ligands: <http://firedb.bioinfo.cnio.es/Php/FireStar.php>.

Ligand Dependence Receptor: A ligand dependence receptor, when it is unoccupied by the proper ligand,

may be exposed to degrading enzymes (e.g., caspase) and initiate apoptosis.

Ligand-Activated Site-Specific Recombination: The Cre recombinase is fused to a ligand-binding domain of the estrogen receptor (ER) and thus the recombinase may be activated by tamoxifen (but not by estradiol). A DNA sequence flanked by loxP sites can then be excised. ▶[Cre/loxP](#), ▶[site-specific recombination](#), ▶[tamoxifen](#), ▶[estrogen](#), ▶[estradiol](#); Feil R et al 1996 Proc Natl Acad Sci USA 93:10887.

Ligase Chain Reaction: In a ligase chain reaction two pairs of complementary oligonucleotides are added at immediate vicinity of each other to both strands of denatured DNA and amplified. The ligation products are useful only for the signal amplification but not for amplifying other DNA copies. The method has wide applicability for diagnostics. (See Rodriguez H et al 2000 Methods 22:148).

Ligase, DNA: DNA ligase are enzymes that tie together the ends of single polynucleotide chains. The *E. coli* enzyme requires 5' phosphate and 3' OH termini and NAD, and the T4 enzymes require ATP for the reaction. The T4 enzyme can ligate both cohesive and blunt ends although the latter reaction is much slower; monovalent cations (NaCl) and polyethylene glycol (PEG) can increase its efficiency though. Human cells contain at least four ligase isozymes and all are ATP-dependent. The efficiency of these ligases depends on the total concentration of the substrates and also on the closeness of the ends to be ligated. Mammals have three known DNA ligases and they have an essentially natural role in replication and recombination. Ligase I joins Okazaki fragments and seals excision repair nicks. Ligase IV (3q22-q34) deficiency is lethal in mice and V(D)J joining is absent. Ligase IV is required for the repair of double-strand breaks and nonhomologous end joining. In the laboratory, DNA ligases are used for the sealing of DNA in vectors or for joining any DNA molecules. The proliferating cell nuclear antigen (PCNA), after being loaded onto the DNA by replication factor C, enhances ligase I activity up to five-fold. ▶[replication](#), ▶[recombination](#), ▶[vectors](#), ▶[V\(D\)J](#), ▶[Ku](#), ▶[DNA-PK](#), ▶[NHEJ](#), ▶[RF-C](#); Tom S et al 2001 J Biol Chem 276:24817.

Ligase, RNA: RNA ligase mediate the joining of RNA 5' and 3' ends in the presence of ATP; they have an important role in the final processing of RNA transcripts. There are a very large number of RNA ligase ribozymes that structurally belong to three classes and within those classes to several families. ▶[ligase DNA](#), ▶[ribozyme](#); Stage-Zimmermann TK, Ehlenbeck OC 2001 Nature Struct Biol 8:863.

Ligation: The covalent joining of nucleotide ends by DNA or RNA ligase, respectively.

Ligation of Embryos: Process of imposing a constriction on an embryo, e.g., *Drosophila* embryo. The development of the thoracic (central) structures requires the cooperation of both poles. Ligation at the blastoderm stage interferes with the development of only one segment. Ligation has various medical applications. ▶[morphogenesis](#), ▶[morphogenesis in Drosophila](#)

Light: ▶[electromagnetic radiations](#), ▶[HVEM](#)

Light Chain: ▶[DNA heavy chain](#), ▶[antibody](#)

Light Controlled Reactions in Plants: See Simoni RD, Grossman AR 2001 J Biol Chem 276:11447; Jiao Y et al 2007 Nature Rev Genet 8:217.

Light Directed Parallel Synthesis: Light directs simultaneous synthesis on solid support. The pattern of masking light activates different regions of the solid-state support and facilitates the chemical coupling reactions. The activation is the result of the removal of different photolabile protecting groups. After deprotection of the first set of building blocks (amino acids or nucleotides bearing the photolabile compound) the entire surface is exposed to light and the reaction takes place only in the areas which were exposed to light in the preceding step. Subsequently, the substrate is illuminated by using another mask and then a second block is activated. The masking and illumination pattern determines the location and the ultimate product. This way, complex molecules can be fabricated in a combinatorial manner and the product may be useful for industrial and molecular biology studies. ▶[array hybridization](#), ▶[microarray hybridization](#), ▶[DNA chips](#); Lipshutz RJ et al 1999 Nature Genet 21(Suppl 1):20; Barone AD et al 2001 Nucleosides, Nucleotides Nucleic Acids 20 [4-7]:525.

Light Harvesting Chlorophyll Protein Complex: ▶[LHCP](#), ▶[CAB](#)

Light Intensities: The light intensities of various emitters (in Lambert units [1 Lambert = 1 new candela/cm²/π]) are: sunshine at noon, 519,000; sun at the horizon, 1,885; moonlight, 0.8; Tungsten bulb of 750 watt, 7,500; mercury vapor light of 1,000 watt, 94,000. These are approximate average data. ▶[illumination](#), ▶[electromagnetic radiation](#)

Light Microscopy: Light microscopy is used for the study of small biological specimens, biological tissues, cells, and subcellular organs down to a resolution of 0.2 μm. The most essential elements of the light microscope are the objective lenses for viewing details of different sizes. The nosepieces

generally contain objectives with numerical aperture 0.1 (4X), 0.25 (10X), 0.65 (high dry, 40X), and 1.25 (oil-immersion, 100X) lenses. Eyepieces are usually 10X and permit the viewing of objects at about 1,000-fold larger, at maximum. The condensor focuses the light coming from a special low voltage illuminator. The microscope stand includes a stage for the slides on which the specimens are moved. It also has various adjustment knobs for focusing and adjusting light intensities. The light microscopes may be equipped with other devices too, e.g., the camera stand or built-in camera, and filters. The common light microscopes require special handling of the specimens before viewing, e.g., fixation, staining, and sectioning. On the slides, the specimen is generally covered by a very thin (about 0.13–0.25 mm) cover glass (slips). For viewing natural specimens in three dimensions, stereomicroscopes are used that may permit magnifications within the range of 2X to 160X, generally with zooming capabilities. ▶[resolution optical](#), ▶[fluorescence microscopy](#), ▶[phase-contrast microscopy](#), ▶[Nomarski](#), ▶[confocal microscopy](#), ▶[electron microscopy](#), ▶[fixatives](#), ▶[stains](#), ▶[sectioning](#)

L

Light Reactions: Light reactions can only be carried out in light. ▶[DNA repair](#)

Light Repair (of DNA): The splitting of pyrimidine (thymine) dimers by visible light-inducible enzymes. ▶[DNA repair](#)

Light Response Elements (LRE): Light response elements are nucleotide sequences binding transcriptional regulators of light receptor protein (e.g., phytochrome) genes. ▶[phytochrome](#), ▶[hormone response elements](#), ▶[photomorphogenesis](#)

Light-Sensitivity Diseases: ▶[albinism](#), ▶[xeroderma pigmentosum](#), ▶[Bloom syndrome](#), ▶[trichothiodystrophy](#), ▶[ataxia telangiectasia](#), ▶[Fanconi anemia](#), ▶[Cockayne syndrome](#), ▶[Hartnup disease](#), ▶[protoporphyrria](#), ▶[Rothmund-Thompson syndrome](#), ▶[RAD](#), ▶[DNA repair](#), ▶[excision repair](#)

Light-Sensitivity in Natural Populations: Light has many different functions in plant physiological processes, such as photosynthesis, photoperiodic response, diurnal rhythm of synthetic and catabolic reactions, etc. Relatively very large variations exist in *Arabidopsis* in light-sensitivity compared to some other plant species (See Maloof JN et al 2001 Nature Genet 29:441).

Lignin: A rigid woody polymer of coniferyl alcohol (derived from phenylalanine and tyrosine) and related compounds, occurring in plants along with cellulose. It is the industrial source of vanillin, dimethyl

sulphoxide. Lignin is used in manufacturing certain plastics, rubber, precipitation of proteins, etc.

Ligule: A “tongue-like,” frequently hairy outgrowth on the upper and inner sides of the leaf blade (at the leaf sheath) of grasses.

Likelihood: A statistical concept dealing with a hypothesis based on experimental data. It can be expressed as $L(H/R)$ where L is the likelihood, H is the hypothesis, and R the results obtained experimentally. In contrast, probability is fixed by the fit of the data to a preconceived null hypothesis (see [Fig. L35](#)). The likelihood ratio $LR = \text{likelihood of data model} / \text{likelihood data of null hypothesis}$ or the log likelihood ratio, i.e., $\log(LR)$. ▶[maximum likelihood](#), ▶[lod](#)

$$\lambda = -2 \ln(L_{H_0}/L_{H_1})$$

likelihood ratio λ , H_0 and H_1 are the 2 hypotheses

Figure L35. Likelihood ratio

Lilac: The plant *Syringa vulgaris* is an ornamental shrub ($2n = 46, 47, 48$); lilac is also a rodent fur color determined by the epistatic action of certain gene combinations.

Liliaceae: A family of monocotyledonous plants, many of which have been exploited for cytological studies because of their large chromosomes: *Lilium* subspecies ($2n = 24, \sim 1.8 \times 10^{11}$ bp), onion (*Allium cepa*, $2n = 16, 32$), hyacinth ($2n = 16$), *Trillium* subspecies, ($2n = 10$), *Bellevallia* $2n = 8, 16$). In 1928, John Belling counted 2,193 chromomeres in the pachytene chromosomes of *Lilium pardalinum*. He believed this number represented the number of genes in the species. In *Fritillaria davisii* ($2n = 24$), the DNA content in the somatic nuclei was estimated to be 295 pg (approximately 50 times the amount in human somatic cells or $\sim 1,000$ times that of *Arabidopsis* or *Drosophila*). ▶[DNA](#), ▶[genome](#), ▶[chromomeres](#), ▶[dalton](#), ▶[measurement units](#)

LIM Domain: A cysteine-rich zinc-binding unit facilitating protein-protein interactions in signaling molecules, transcription factors, cytoskeletal proteins, motor neuron pathways, axon guidance, etc. LIM has the properties of an organizer. The LIM proteins do not have functional relationships beyond the common feature of protein-protein binding and may convey both inhibitory and activation functions. The RLIM corepressor inhibits the LIM homeodomain transcription factors by recruitment of the histone deacetylase complex. ▶[adaptor proteins](#), ▶[Aurora](#), ▶[LHX](#), ▶[LMO](#), ▶[CRIP](#), ▶[CRP](#), ▶[PINCH](#), ▶[NLI](#),

►LDB, ►organizer, ►Williams syndrome, ►DNA-binding protein domains, ►histone deacetylase, ►cleft palate, ►TESTIN; Schmeichel KL, Beckerle MC 1994 Cell 79:211; Hobert O, Westphal H 2000 Trends Genet 16:75.

LIM Kinase: ►Williams syndrome

Lima: Lima are long interspersed nuclear genomic elements (LINEs) common across mammals.

Limb Bud: An embryonic cell group initiating limb development. The NF- κ B transcription factors and the regulatory REL proteins are required. NF- κ B seems to transmit fibroblast growth factor (FGF) signals between the ectoderm and the underlying mesenchyme cells during limb differentiation. ►AER, ►ZPA, ►NF- κ B, ►FGF, ►organizer; Capdevila J et al 2001 Annu Rev Cell Dev Biol 17:87.

Limb Defects in Humans: In humans, limb defects can be isolated but are most commonly associated with particular syndromes. In some cases entire limb(s) are absent (amelia) or there is a partial reduction (meromelia), i.e., frequently missing some parts between the extremities (hand or foot) and the trunk (phocomelia). Not uncommonly, extra fingers or toes are involved, or fusion or deformation(s) observed. The defects may be caused by teratogenic factors, chromosomal defects or mutations and may be accompanied by a variety of other symptoms of complex syndromes. ►adactyly, ►polydactyly, ►syndactyly, ►Holt-Oran syndrome, ►Moebius syndrome, ►Roberts syndrome, ►De Lange syndrome, ►Poland syndrome, ►ADAM complex, ►Chotzen syndrome, ►Pfeiffer syndrome, ►Greig's polysyndactyly, ►thrombocytopenia, ►orofacial-digital syndromes, ►Majewski syndrome, ►Patau's syndrome, ►exostosis, ►arthrogryposis, ►clubfoot, ►EEC, ►renal dysplasia and ►limb defects

Limb Girdle Muscular Dystrophy: ►muscular dystrophy

***Limnaea peregra*:** A freshwater snail displaying delayed inheritance of its shell shape (see Fig. L36). Left-right handed shell shape variations are common in various snail species (Ueshima R, Asami T 2003 Nature [Lond] 425:679). ►delayed inheritance, ►maternal effect genes



Figure L36. *Limnaea*

Limpet: ►keyhole limpet hemocyanin

LIMS (Laboratory Information Management System): LIMS is a guide to storage and to easy access of

experimental data. It has particularly great use in drug development laboratories or any type of large-scale genome and proteome research. (See Prilusky J et al 2005 Acta Crystallogr D Biol Crystallogr 61:671).

Lincoln, Abraham (1809–1865): President Abraham Lincoln is suspected to have had the relatively mild form of spinocerebellar ataxia although earlier it was also suggested that he might have had the Marfan or the Marfanoid syndrome. ►ataxia, ►Marfan syndrome, ►ataxia; Ranum LP et al 1994 Nature Genet 8:280.

Lincomycin: A 6-[1-methyl-4-propyl-2-pyrrolidinecarboxamidol]-1-thio-o-erythro-D-galacto-octopyramide antibiotic of Gram-positive bacteria and chloroplasts. It inhibits protein synthesis in the 23S and 16S 70S ribosomal RNA genes. (See Cséplő A et al 1993 Mol Gen Genet 236:163).

Line: A genetic stock with defined characteristics.

LINE (L1): L1 are long (≈ 5 –7 kbp) interspersed repetitive DNA sequences, including retroposons, genated by reverse transcription (see Fig. L37). They may occur in 10^4 to 10^5 copies in the eukaryotic genome. Sequencing of the human genome revealed 535 Ta and 415 pre-TA L1 elements. The LINE elements do not have long terminal repeats like the retrotransposons and yet they retain reverse transcriptase sequences which are frequently (>95%) non-functional. These are remnants of ancient retroviral insertions, but once they were inserted—because of the loss of the LTR [transposase] function—they generally remained at the position of insertion and can be used to trace phylogenetic descent of various species and wider taxonomic groups (Nishihara H et al 2006 Proc Natl Acad Sci USA 103:9929). The elements have internal promoters for RNA polymerase. The cDNA copies can then be inserted at new locations. The LINE endonuclease is a target-primed reverse transcription protein. DNA site recognition probably proceeds by accommodation of an extrahelical nucleotide within an enzyme pocket (Weichenrieder O et al 2004 Structure 12:975). At the mammalian telomeres endonuclease-independent LINE-1 transposition can take place (Morrish TA et al 2007 Nature [Lond] 446:208). The L1 elements are regulated by SOX type of proteins. In humans, L1s (mainly mariner type) are the most common retrotransposons. They, directly or indirectly, represent about 17% of the genome. The majority of these elements are truncated

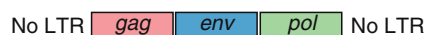


Figure L37. LINE element

and only 3,000 are of full length; ~40–100 are active retrotransposons. The retrotransposition-competent elements are about 6-kb long and contain 5'-UTR (untranslated sequences), two open-reading frames (ORF) and 3'-UTR in a poly-A tail. ORF1 encodes a DNA-binding protein and ORF2 encodes an endonuclease and reverse transcriptase (Badge RM et al 2003 Am J Hum Genet 72:823). The transposition of human L1 is subject to RNAi control (Soifer HS et al 2005 Nucleic Acids Res 33:846).

Several human pathological conditions involve LINE insertions. Blood coagulation protein VIII gene insertions were found to cause hemophilia. L1 endonuclease has limited specificity and thus the element can be inserted at many sites, including genes. L1 elements were indentified in Duchenne muscular dystrophy (DMD), adenomatous polyposis cancer (APC), and the β -globin genes. In mice, about 10% of the spontaneous mutations seem to be due to transposition. In humans, 1/600 to 1/1200 mutations may be due to retrotransposition and 1/8 to 1/50–100 individuals may carry an endogenous insertion. About 0.1% of the human mutation causing diseases are due to L1 movements.

The activity of the different L1 elements depends on their base sequences (Lutz SM et al 2003 Am J Hum Genet 73:1431). Regular L1 elements may be quite inefficient in movement but a synthetic one with 24% of the nucleotides altered, without changing the amino acids, displayed a 200-fold increase in transposition (Han JS & Boeke JD 2004 Nature [Lond] 429:314). The synthetic L1 element, *ORFeus*, containing two synonymously recoded open reading frames (ORFs) relative to mouse L1 was significantly more active for retrotransposition in cell culture than all native L1 elements tested. In a transgenic mouse model, in which a constitutive heterologous promoter controlled *ORFeus* expression, *ORFeus* retrotransposition activity was 20-fold higher, in both germ line and somatic tissues. Somatic transposition events occurred in 100% of the *ORFeus* donor-containing animals, and an average of 17 different insertions were easily recovered from each animal. The number of somatic insertions per animal exceeded this number by perhaps several orders of magnitude. Nearly 200 insertions were precisely mapped (An W et al 2006 Proc. Natl Acad Sci USA 103:18662). The human LINE retrotransposons can also mobilize the transcripts of other genes and thus create processed pseudogenes. Insertion of the L1 element into the Factor VIII gene can cause hemophilia A. Insertion into the Factor IX may be responsible for hemophilia B. Movement into the dystrophin gene can result in Duchene muscular dystrophy. Insertions may be responsible for X-linked dilated cardiomyopathy, β -thalassemia, chronic granulomatous disease, and retinitis pigmentosa. Somatic chromosome insertions

of L1 can account for colon cancer. L1 elements appear to regulate the inactivation of the mammalian X chromosome (Bailey JA et al 2000 Proc Natl Acad Sci USA 97:6634) as postulated by the Lyon hypothesis. Han JS et al (2004 Nature [Lond] 429:168) regard the L1 elements as general “rheostats” (fine-tuning regulators) of transcription. LINE 1 elements appear subject to RNAi degradation (Soifer HS et al 2005 Nucleic Acids Res 33:846). L1 can deliver siRNA and cause silencing (Yang N et al 2005 Nucleic Acids Res 33(6):e57). Variations in L1 contribute to genetic diversity in human populations (del Carmen M et al 2006 Proc Natl Acad Sci USA 103:6611). L1 transposition can also take place in nondividing human somatic cells (Kubo S et al 2006 Proc Natl Acad Sci USA 103:8036). All hA3 proteins of the APOBEC3 family are able to differentially suppress uncontrolled transposition of L1 retroelements (Kinomoto M et al 2007 Nucleic Acids Res 35:2975).

R2 is a non-LTR retrotransposable (LINE-like) element with rigid sequence specificity for a target site in the 28S rRNA genes of arthropods, platyhelminthes, tunicates, and vertebrates. As Christensen notes, R2 protein subunits bind both upstream and downstream of the 28S gene insertion site. The protein subunit bound upstream of the integration site cleaves the bottom DNA strand and uses the newly generated 3' end to prime reverse transcription of the R2 RNA starting at the 3' end of the R2 RNA transcript bound to this subunit. The protein subunit bound downstream of the integration site cleaves the top DNA strand. The strand cleavage sites are 2 bp apart. The N-terminal DNA domain has been shown to bind the downstream DNA sequences by means of highly conserved zinc-finger and myb motifs. The C-terminal domain encodes an endonuclease and apparently binds the upstream DNA sequences. The central domain of the ORF encodes the reverse transcriptase (Christensen SM et al 2006 Proc Natl Acad Sci USA 103:17602).

►SINE, ►Ta, ►T α , ►retroposon, ►retrotransposon, ►reverse transcriptase, ►mariner, ►HERV, ►alu, ►antihemophilic factors, ►muscular dystrophy, ►globins, ►p40, ►cis preference, ►SOX, ►processed pseudogene, ►APOBEC, ►lyon hypothesis, ►RNAi; Sheen F-M et al 2000 Genome Res 10:1496; Ostertag EM, Kazazian HH Jr 2001 Annu Rev Genet 35:501; Ostertag EM et al 2002 Nature Genet 32:655; Brouha B et al 2003 Proc Natl Acad Sci USA 100:5280; human, mouse, rat: <http://l1base.molgen.mpg.de>.

LINE1 (L1): The major mouse LINE that can be used for DNA fingerprinting of YAC sequences from the mouse genome. ►DNA fingerprinting, ►YAC

Lineage: The line of descent from an ancestral cell or ancestral individual(s). ► [cell lineage](#)

Lineage Addition: A feature of cancer cells whereby they maintain some of the properties of the original cell type from which they arose. On this basis antagonist therapies can be developed. ► [drug development](#)

Lineage Priming: A low level of transcription of genes involved in differentiation before actual differentiation is turned on at full extent.

Linear Energy Transfer: ► [LET](#)

Linear Function: A set of data (variables, parameters) without powers or multiplication of quantities, e.g., $3x_1 \pm 2x_2 \pm x_3$.

Linear Ion Trap Analyzer (L1): A linear ion trap analyzer is similar to quadrupole technology. LIT, optionally, can perform slow scanning and increased resolution. It has been effectively applied for the detection of post-translational phosphorylation of proteins (Olsen JV, Mann M 2004 Proc Natl Acad Sci USA 10:13417). ► [proteomics](#), ► [mass spectrum](#), ► [ion trap mass analyzer](#), ► [quadrupole](#)

Linear Programming: The analysis or solution of problems when linear functions are maximized or minimized.

Linear Quartet: Four megaspores in the embryo sac of plants; in the asci of some fungi, the four spores are arranged in the order they were formed during meiosis (See [Fig. L38](#)). ► [megaspore](#), ► [embryosac](#)



Figure L38. Spore quartet

Linear Regression: ► [correlation](#)

Linearization: The conversion of a covalently closed circular nucleic acid to an open linear form.

Lineweaver-Burk Equation: The Lineweaver-Burk equation is reciprocal of the Michaelis-Menten equation:

$$\frac{1}{v} = \frac{K_m + (S)}{V(S)} = \frac{K_m}{V} \left(\frac{1}{S} \right) + \frac{1}{V}.$$

Where v = velocity constant of the reaction,

$$K_m = \left(\frac{(E) - (ES)(S)}{(ES)} \right),$$

(S) = substrate concentration, V = maximal velocity of reaction.

The formula provides a simpler solution for representing enzyme kinetics; $1/v$ is plotted against $1/(S)$ or $(S)/V$ against (S) . ► [Michaelis-Menten equation](#) and the ► [Eadie-Hofstee](#)

Linkage: Linkage is the association of genes within the same chromosome but which can be separated by recombination. In a test cross, four phenotypic classes are expected in equal numbers if the segregation is independent (absence of linkage). These four classes can be designated AB (a), Ab (b), aB (c) and ab (d) for the n individuals. For the verification of linkage chi square tests (χ^2) can be used. First the segregation for A can be examined,

$$\chi^2_1 = \frac{[a + b - c - d]^2}{n}$$

Then, in a second step, the χ^2_2 (for B) = $\frac{[a - b + c - d]^2}{n}$ is determined. The linkage χ^2_L = $\frac{[a - b - c + d]^2}{n}$. Example: AB : 191, Ab : 37, aB : 36, ab : 203, and the Total is 467. Without linkage in each class 116.7 is expected in a test cross (see [Table L2](#)).

The segregation of each marker is very normal but the linkage chi square is extremely high indicating that the segregation is not independent. Another simpler formula that does not take into account the transmission of the markers (p = parental, r = recombinant) is shown below:

$$\chi^2 = \frac{(\text{observed}_p - \text{expected}_r)^2}{(\text{observed}_p - \text{expected}_r)}$$

Similarly, for F_2 , the chi squares for the A and the B locus and for linkage can be determined for the

Table L2. Linkage chi square determination in a hypothetical example

| | χ^2 | Degree of Freedom | Probability of Greater χ^2 |
|-----------------------|----------|-------------------|---------------------------------|
| Segregation for A — a | 0.259 | 1 | >0.5 |
| Segregation for B — b | 0.362 | 1 | >0.5 |
| Linkage | 220.645 | 1 | <10 ⁻¹⁰ |
| Total | 221.266 | 3 | |

$AB (\frac{9}{16}n)$, $Ab (\frac{3}{16}n)$, $aB (\frac{3}{16}n)$, $ab (\frac{1}{16}n)$ classes designated as a, b, c and d, respectively:

$$\chi^2_A = \frac{[a + b - 3c - 3d]^2}{3n},$$

$$\chi^2_B = \frac{[a - 3b + c - 3d]^2}{3n}$$

and

$$\chi^2_L = \frac{[a - 3b - 3c + 9d]^2}{9n}$$

Mather suggested the following χ^2 formula for the detection of linkage in F_2 in case the segregation is not normal:

$$\chi^2 = \frac{(a_1a_4 - a_2a_3)^2n}{(a_1 + a_2)(a_3 + a_4)(a_2 + a_4)(a_1 + a_3)}$$

Fisher proposed to detect linkage by using repulsion and coupling information combined in case of abnormal transmission as shown in Table L3.

Table L3. Abnormal transmission and linkage

| | ab | Ab | aB | AB | Sum |
|-----------|-----|-----|----|-----|-----|
| Repulsion | 30 | 70 | 2 | 24 | 126 |
| Coupling | 519 | 119 | 12 | 349 | 999 |

Then add separately for the repulsion and coupling data the $ab + AB$ and designate as α_1 and the $Ab + aB$ as α_2 . So, α_1 represents the recombinants in repulsion but the parentals in coupling and α_2 represent the parentals in repulsion and the recombinant in coupling (see Table L4). In the absence of linkage α_1 and α_2 are expected to be near equal. A 2×2 contingency chi square (►association test) can then be set up and the χ^2 is computed with the null hypothesis that there is no linkage:

$$\chi^2 = \frac{(868 \times 72 - 1341 \times 54)^2 1125}{126 \times 199 \times 203 \times 922} > 146$$

and for 1 degree of freedom it absolutely rules out independent segregation.

When we want to estimate the probability of finding a linkage all over the genome, the chance of

Table L4. Hypothetical alpha values for repulsion and coupling

| | α_1 | α_2 | Σ |
|-----------|------------|------------|----------|
| Repulsion | 72 | 54 → | 126 |
| Coupling | 131 | 868 → | 999 |
| Σ | 203 | 922 | 1125 |

finding one is relatively very small. The P value obtained by the χ^2 procedure can be converted to an actual estimate of linkage based on a Bayesian estimate: Probability of linkage = $1 - \left(\frac{P}{P + f_{\text{swept}}} \right)$ where P is the value obtained by χ^2 and f_{swept} is the fraction of the genome that appears to be linked around the marker within the so-called swept radius. The swept radius is the maximal distance on both sides of the marker between two loci with a certain probability. Usually a probability limit of 0.95 is chosen to be significant. Thus, the swept radius is (shown in parenthesis) for 10 cM (21%), 20 cM (35%) and 30 cM (44%), respectively, for this critical probability.

Estimating linkage in human populations is difficult because of small family sizes. Also, there are frequently other complications, such as paternity, penetrance, expressivity, etc. Classical human genetics devised a different formula (u statistics) for double backcrosses ($AaBb \times aabb$) as $u_{11} = (a-b-c+d)^2 - (a+b+c+d)$. For single back crosses: ($AaBb \times Aabb$): $u_{31} = (a-3b-c+3d)^2 - (a+9b+c+9d)$. For the progenies resembling: F_2 : $u_{33} = (a-3b-3c+9d)^2 - (a+9b+9c+81d)$; (a, b, c and d indicate the four genotypes as indicated above.) More recently, the lod scores are used for family data. In the case of no difference between female and male recombination the Z score = $\log \frac{P(F|\theta)}{P(F|0.5)}$ and where there is a sex difference the formula $\log \frac{P(F|\theta', \theta'')}{P(F/(0.5)(0.5))}$ is applicable. θ is the recombination fraction (θ' for males and θ'' for females). Linkage in humans is generally studied now by somatic cell hybridization, radiation hybrids, or by molecular techniques. For multipoint linkage analysis, the following computer programs are generally used: Vitesse (O'Connel R, Weeks DE 1995 Nature Genet 11:402) or MAPMAKER (Lander ES et al 1987 Genomics 1:174) or MENDEL (Lange KD et al 1988 Genet Epidemiol 5:471), or JOINMAP (Stam P 1993 Plant J 3:739) or several others listed by Terwilliger JD et al 1994 Handbook of Human Genetic Linkage, Johns Hopkins University Press, Baltimore, Maryland. This book includes sources of availability.

Microarray hybridization data indicate that, in yeast, 37% of the expression traits show two simultaneous linkages and 14% of the traits display epistatic interactions. Each gene expression level can be considered as a quantitative trait and computational methods have been developed for the simultaneous mapping of these loci (Storey JD et al 2005 PLoS Biol 3(8):e267). ►recombination frequency, ► F_2 linkage estimation, ►tetrad analysis, ►recombination mechanisms, ►mapping genetic, ►mapping function, ►interference, ►coincidence, ►linkage group, ►chi square, ►sex linkage, ►sex-linked lethal mutation, ►lod score, ►affected-sib-pair method,

►maximum likelihood method applied to recombination, ►Bayesian theorem, ►meta-analysis of linkage, ►somatic cell hybrids, ►radiation hybrid, ►GSMA, ►linkage disequilibrium, ►microarray hybridization, ►QTL; <http://linkage.rockefeller.edu/>.

Linkage, Complete: Linkage is practically complete in the heterogametic sex in insects, e.g., in the majority of the species of *Drosophila*, male (XY), and in the silkworm, female (WZ). Recombination in male flies has been observed, however, in the presence of transposable elements causing hybrid dysgenesis. Linkage is practically complete within inversions because the recombinant gametes or zygotes are lethal (balanced lethals). In cases of multiple translocations involving all or most of the chromosomes, even the genes situated in different chromosomes do not segregate independently and this is a characteristic of complex heterozygotes. ►inversions, ►translocations, ►hybrid dysgenesis, ►complex heterozygote; Morgan TH 1912 Science 36:719.

Linkage Detection, Non-Parametric: ►affected-sib-pair method; Abreu PC et al 1999 Am J Hum Genet 65:847.

Linkage Detection, Tetrads: The linear spore tetrads can be arranged as PD, TT, and NPD. At linkage the frequency of the double recombinant class (NPD) must be smaller than the single recombinant (TT) class. If the deviation between TT and NPD is very small a chi square test may be necessary by using the formula: $\chi^2 = \frac{(PD - NPD)^2}{PD + NPD}$. ►tetrad analysis, ►chi square, ►linkage

Linkage Disequilibrium (LD): Certain groups of genes are syntenic in higher frequency than expected on the basis of unhindered genetic recombination. In random mating populations linkage disequilibrium should disappear with time. In self-fertilizing plants—because of homozygosity—linkage disequilibrium is generally low but exceptions (*Hordeum*) of modest LD have been found (Morell PL et al 2005 Proc Natl Acad Sci USA 102:2442). The tighter the linkage between genes, the less the chance to reach linkage equilibrium. If two loci are independent, the frequency of their joint occurrence is the product of the two independent frequencies. A cause of persistent association may be based on their selective advantage as a group or recent introgression. With these possibilities in mind the linkage disequilibrium determined for several loci may provide information on the chromosomal location of a gene. Disequilibrium is expected to be the greatest for a group of markers that are closest to the gene which needs to be

assigned to a position. The quantitative measure of linkage disequilibrium is:

$$\delta = (p_D - p_N)/(1 - p_N)$$

where p_D and p_N represent the two different linkage phase chromosomes. The decline (Δ_n) of the linkage disequilibrium depends on the recombination frequency (unless a particular gene block has high selective advantage and linkage drag exists): $\Delta_n = \Delta_0(1-r)^n$ where r = recombination frequency, n = number of generations, and Δ_0 is the beginning of disequilibrium. Linkage disequilibrium may shed light on the origin or changes within and among populations. Hitchhiking may affect the linkage disequilibrium. In human populations, the extent of linkage disequilibrium varies in different chromosomes and chromosomal regions, depending also on the closeness of the physical location of the alleles studied. Recently, single nucleotide polymorphisms (SNP) have been successfully used to map genes on the basis of linkage disequilibrium. Gene flow between distinct populations generates admixture linkage disequilibrium. Errors in genotyping may seriously affect the outcome of the estimate. Studied at the molecular level, the exchange hot spots are not distributed at random and the intensity of exchange may vary considerably. In the human genome the variation may be two orders of magnitude (Clark AG et al 2003 Am J Hum Genet 73:285). In human chromosome 12q, a 987-kb block (including the gene ataxin 2 [ATXN2/SCA2]) is preserved in Americans of European descent (Scherer SE et al 2006 Nature [Lond] 440:346). These facts may affect the outcome of the calculations of linkage disequilibrium. Linkage disequilibrium may persist for a very large number of generations and different human populations can be characterized on the basis of linkage disequilibrium units (LDU) (Tapper W et al 2005 Proc Natl Acad Sci USA 102: 11835). ►Hardy-Weinberg equilibrium, ►genetic equilibrium, ►Haplotype blocks, ►Hap-Map, ►Recombination, ►genetic, ►coupling, ►repulsion, ►syntenic, ►mutation dating, ►transmission disequilibrium test, ►association mapping, ►sib TDT, ►SWT, ►hitchhiking, ►mitochondrial genetics, ►introgression, ►SNP, ►MALD, ►family-based association test; Huang J, Jiang Y 1999 Am J Hum Genet 65:1741; Reich DE et al 2001 Nature [Lond] 411:199; Jorde LB 2000 Genome Res 10:1435; Pritchard JK, Przeworski M 2001 Amer J Hum Genet 69:1; Rannala B, Reeve JP 2001 Am J Hum Genet 69:159; Jeffreys AJ et al 2001 Nature Genet 29:217; Morris AP et al 2002 Am J Hum Genet 70:686; linkage disequilibrium map: Dawson E et al 2002 Nature [Lond] 418:544; Wall JD, Pritchard JK 2003 Nature Rev Genet 4:587; <http://www.sph.umich.edu/csg/abecasis/GOLD/>.

Linkage Drag: Undesirable genes are preserved in a population on the basis of hitchhiking if no recombination occurs between the selected desirable genes and the undesirable genes. ▶hitchhiking, ▶Hill-Robertson effect, ▶genetic load; Hospital F 2001 Genetics 158:1363.

Linkage Equilibrium: ▶genetic equilibrium

Linkage Genome Screening: Linkage genome screening is used to approximately locate genes with low penetrance and/or expressivity to chromosomes on the basis of the λ_s value and maximum likelihood. ▶ λ_s , ▶maximum likelihood

Linkage Group: Syntenic genes (situated in one chromosome) belong to a linkage group. Therefore, the number of linkage groups equals the number of chromosomes in the basic set. When the linkage information about a chromosome is incomplete, it is possible to see two or more linkage groups for a particular chromosome because gene clusters may recombine freely when the distance between them is 50 map units or more. Linkage groups are generally designated by Roman numerals and chromosomes are identified by Arabic numerals. If trisomic analysis is used, all syntenic genes must appear as a linkage group, irrespective of their dispersal along the chromosome. In multiple translocations (complex heterozygotes) several interchanged chromosomes are transmitted together and form “super linkage groups” such as in the *Oenotheras* plants. Similar translocation complexes may also exist in animals. In the termite *Kaloterms approximatus*, meiotic chains of 11 to 19 chromosomes have been observed, forming a single male-determining linkage group.

▶mapping, ▶synteny, ▶trisomic analysis, ▶complex heterozygote

Linkage in Autotetraploids: ▶recombination in autotetraploids

Linkage in Breeding: In applied genetics, linkage may be very useful if advantageous traits are controlled by closely linked genes. The opposite is true if disadvantageous characters are syntenic. The breeder may benefit by knowing about linkages with neutral, visible, or easily detectable chromosome markers that permits the monitoring of the inheritance of sometimes hard-to-recognize quantitative traits. The male silkworm produces 25–30% more silk than the female. By having a dominant color (dark) gene in the Y chromosome, the less productive female-producing eggs (XY) can be separated by an electronic sorter before hatching, and eliminated. In baby chickens it is difficult to identify the males by genitalia, but the presence of the *B* (*Barring*) X-chromosome-linked gene reduces the color of head spots more effectively in two (XX) males than in single dose (XY) females. Thus, by autosexing, the males can be assigned to meat early on, and the females to egg production regimes.

The use of RFLP techniques facilitates the recognition of the linkage of quantitative trait loci with DNA markers. The knowledge of recombination frequency may facilitate the planning of the size of the populations for selecting a combination of desirable genes. The yellow seed coat color gene in flax is very tightly linked to the high quantity and high quality of oil. Unfortunately, low yields and susceptibility to disease are also linked in coupling. Therefore, it is practically difficult to produce a

Table L5. Expected recombination of desired genes depends on linkage intensities

| Recombination frequency | Genetic construction of the F ₁ | | |
|-------------------------|--|---------------|---------------|
| | (+++/- - -) | (+ + -/- - +) | (+ - +/- - -) |
| | (- - -/+++) | (- - +/+++) | (- + -/+ - +) |
| 0.000 | 62,500 | 0.000 | 0.000000 |
| 0.075 | 33,498 | 1.448 | 0.000063 |
| 0.225 | 8,134 | 57.787 | 0.410526 |
| 0.375 | 1,455 | 188.787 | 24.441630 |
| 0.450 | 523 | 234.520 | 105.094534 |
| 0.500 | 244 | 244.141 | 244.140625 |

The frequency of 6-fold double homozygous dominants for desirable genes located in two chromosomes. The numbers in the body of the table indicate the number of individuals carrying 12 advantageous alleles (+) in an F₂ population of 10⁶ size. (After Power, L. 1952. In *Heterosis*, Gowen, J. W., ed. Iowa State College Press, Ames, p. 315.)

commercially acceptable flax variety with yellow seed coat. The availability of appropriate linkage information may also facilitate the positional cloning of agronomically desirable genes. If the frequency of recombination is known the expected frequency of double homozygous dominant offspring can be predicted by the following formulas: for coupling, $0.25(1-p)^2$ and for repulsion, $0.25(p)^2$ where p = recombination frequency. Genetic transformation by cloned genes has an enormous advantage over classical breeding methods because it does not have to go through the tedious and long-lasting period of selection after crossing if the linkage is tight. ▶QTL, ▶autosexing, ▶gain, ▶chromosome substitution, ▶positional cloning, ▶transformation

Linkage Map: ▶genetic map, ▶mapping, ▶genetic, ▶physical map

Linked Genes: Linked genes are in the same chromosome and their frequency of recombination is less than 0.5. ▶linkage, ▶recombination

Linker: Very short DNA sequences (commercially available) that can be added by blunt-end ligation to DNA termini to generate particular cohesive ends for insertion of passenger DNA fragments in molecular cloning or transformation. ▶blunt-end ligation

Linker (in nucleosomes): The 40–60 nucleotides (generally associated with H1, and, sometimes, with H5 histone) that connect the cores of nucleosomes. ▶nucleosome, ▶histones

Linker Insertion: The insertion of a DNA sequence in place of deleted sequences to test for specific functional units in the region deleted. ▶linker scanning

Linker Scanning: A molecular method for the identification of upstream regulatory elements (see Fig. L39). The procedure is as follows: in defined lengths of upstream DNA fragments deletions are induced at different positions. The gaps are filled in such a way that the total original length of all fragments is neither reduced nor extended even by a single base pair. If the linker falls into the gaps that were normally the site of a regulatory element in front of the gene, expression is reduced or abolished, serving as evidence that the site of the deletion (now the linker) involved an essential upstream element. ▶linker, ▶promoter; Laumonnier Y et al 2000 J Biol Chem 275:40732.

Linking Library: The 5'-end of many genes is rich in NotI restriction enzyme recognition sites (GC↓GGCCGC). A NotI linking-clone containing, e.g., the transferrin receptor gene can be used as a point of jumping over NotI sequences and thus mapping genes. ▶jumping library, ▶Slalom library; Koshuba VI et al 1997 FEBS Lett 419:181.

Linking Number: A linking number indicates the number of times one strand of DNA double helix crosses over the other strand in space. The linking number may reflect the degree of supercoiling in a closed DNA molecule. The linking number has two components: the writhing number (W) and the twisting number (T); a change in linking number $\Delta L = \Delta W + \Delta T$. A change in the linking number requires the breakage of at least one strand. Molecules that are the same as their linking numbers are called topological isomers. After a break, one strand can be rotated about the other and such a reaction may change one isomer into the other by the action of

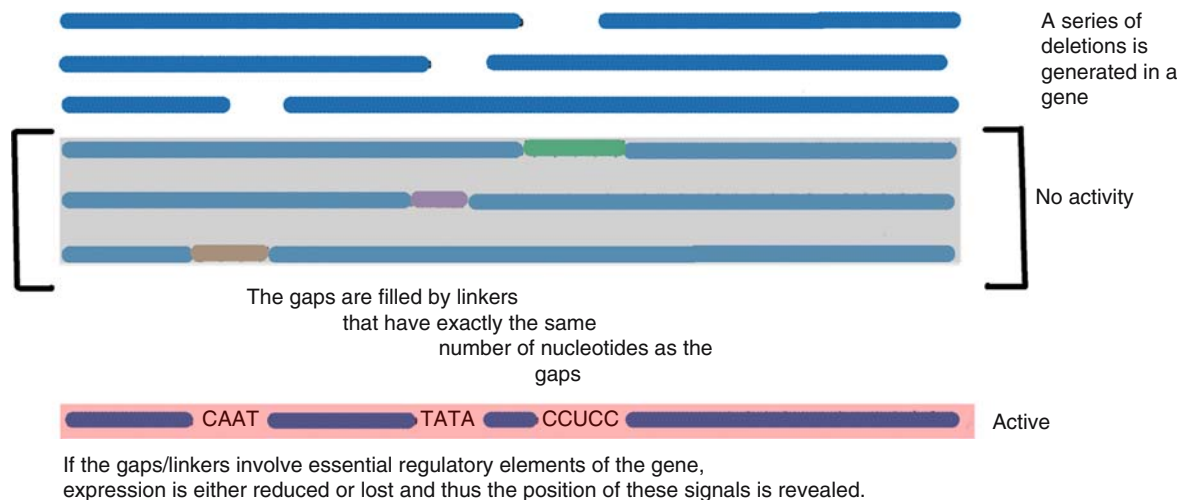


Figure L39. Linker scanning for the identification of the position of essential regulatory elements

DNA topoisomerases. These topological processes are the requisites for several functional activities of DNA such as replication, recombination, transcription and others. ▶ [Writhing number](#), ▶ [isomer](#), ▶ [topoisomerase](#), ▶ [supercoiled DNA](#); Quian H, White JH 1998 J Biomol Struct Dyn 16:663.

Linking Number Paradox: In a nucleosome the DNA is coiled by about 1 and 3/4 turns over the histone octamer and forms close to -2 superhelical turns. Yet, when the histones are removed from the DNA-histone fiber, only -1 negative supercoiled turn is found. The explanation of this paradox may be that the DNA released from the histones becomes more tightly coiled than in the nucleosome-restricted form, i.e., the bound DNA has different structural periodicity than the free form. ▶ [nucleosome](#), ▶ [supercoiled DNA](#), ▶ [histones](#); Prunell A 1998 Biophys J 74:2531.

linotte: A P element homing sequence gene where insertion may occur up to 20% frequency. ▶ [P element](#), ▶ [homing](#); Tailleburg E, Dura J-M 1999 Proc Natl Acad Sci USA 96:6856.

Linseed: ▶ [flax](#)

Linux: A free operating system similar to that of the UNIX. ▶ [UNIX](#)

Lion (*Panthera leo*): 2n = 38; lion x panther [leopard] (*Panthera pardus*) hybrids are sterile.

Lipase: Lipase are enzymes that digest triacylglycerols into fatty acids and mediate energy supply in the cell. ▶ [triacylglycerol](#), ▶ [lipids](#), ▶ [fatty acids](#)

Lipase Deficiency: Hepatic lipase (HL) dominant 15q21, the liposome lipase (8p22), results in triglyceride-rich high- and low-density lipoproteins. It also occurs in a recessive form at the same locus and its deficiency is then called chylomicronemia or hyperlipoproteinemia, respectively. There also is an autosomal dominant hormone-sensitive lipase (HSL). The pancreatic lipase deficiency and the lysosomal acid lipase are autosomal recessive. The lipoprotein lipase gene (LPL, 10 exons) was mapped to human chromosome 8p22. Endothelial lipase normally reduces the level of HDL in the liver, lungs, kidneys, and placenta but not in the skeletal muscles. Lysosomal acid lipase (LAL, 10q24-q25) is Wolman's disease. Lipase deficiency loci are also found at 15q21-q23 (hepatic triglyceride lipase, LIPC), at 9q34.3 (carboxylester bile-salt-dependent lipase, CEL) and at 10q26.1 (pancreatic lipase, PNLIP). ▶ [lipids](#), ▶ [HDL](#), ▶ [Wolman's disease](#); Henderson HE et al 1996 Biochem Biophys Res Commun 227:189; Du H et al 2001 Hum Mol Genet 10:1639.

Lipid Antigen: Lipid antigens are recognized by CD1a proteins, which present foreign antigens to the T cells.

The alkyl chains of amphipathic lipids are fitted into a deep hydrophobic groove of the CD1 heavy chain. This places carbohydrates or other hydrophilic elements of the antigen on the outer surface of CD1 and can directly contact T cell receptors. This way they play an antibacterial effect. ▶ [antigen](#), ▶ [T cell](#), ▶ [CD1](#); Moody DB et al 2004 Science 303:527.

Lipid Bilayer: The main structural element of membranes with two layers of hydrophobic lipid tails facing each other and the hydrophilic heads exposed at the outer parts (see [Fig. L40](#)). Proteins occur within the lipids and some transmembrane proteins pass through the lipid bilayer. ▶ [cell membrane](#), ▶ [seven-membrane proteins](#)

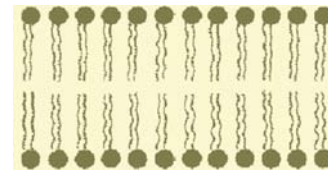


Figure L40. Lipid bilayer

Lipid, Neutral: A neutral lipid is soluble only in very low polarity solvents. ▶ [lipids](#), ▶ [lipids cationic](#)

Lipid Peroxidation: Lipid peroxidation may be a substantial source of mutagenic/carcinogenic alterations in DNA. ▶ [malondialdehyde](#)

Lipid Storage Disease: ▶ [lysosomal storage disease](#)

Lipidogenesis: The biosynthesis of lipids proceeds through fatty acids and it is essential for the formation of many cellular functions of membranes, steroids, hormones, cholesterol, isoprenoids, etc.

Lipidome: All the lipids of an organism.

Lipidoses: ▶ [lysosomal storage diseases](#), ▶ [sphingolipidoses](#), ▶ [lipid storage disease](#)

Lipids: Lipids are usually large molecules polymerized from fatty acids and associated frequently with sugar, protein, and inorganic components. Lipids are the principal material of membranes; they are insoluble in water but readily soluble in nonpolar organic solvents and detergents. The genetic analysis of lipids in higher organisms is quite difficult because of their indispensable function in maintaining cell viability. In *E. coli*, several mutations have been identified in the phospholipid biosynthetic pathways. Lipids I and II are involved in the synthesis of bacterial cell wall peptidoglycans (Mahapatra S et al 2005 J Bacteriol 187:2747). Antibiotic peptides (polycyclic peptides or unusual amino acids) can remove lipid II from the bacterial cell division site (septum) and thereby block

cell wall synthesis. They thus represent a novel type of antibiotic action (Hasper HE et al 2006 Science 313:1636). ►fatty acids, ►sphingolipids, ►sphingosine, ►steroids, ►cell membranes, ►low-density lipoproteins, ►high-density lipoproteins, ►liposome, ►phosphoinositides; Dowhan W 1997 Annu Rev Biochem 66:199; Kersten S 2001 EMBO Reports 2:282; <http://www.lipidat.chemistry.ohio-state.edu>; pathways: <http://www.lipidmaps.org/>; <http://www.lipidmaps.org/data/structure/>; <http://www.lipidmaps.org/tools/>.

Lipids, Cationic: Cationic lipids are synthetic molecules which form a bilayer. They are suitable for the construction of nucleic acid delivery vehicles and enhance the internalization of nucleic acid fragments 5–20-fold and that of antisense oligonucleotides up to 3 orders of magnitude. The cargo may pass through the nuclear pores into the nucleus but its degradation is more likely than in liposomes. They are made of 12–18 carbon atom chains and single or multiple cations of amines. The vehicles frequently use DOTMA (*N*-[2,3-dioleoyl-oxy]propyl]-*N,N,N*-trimethyl ammonium chloride), DOGS and DOPE (dioleoyl phosphatidylethanolamine). Cationic lipids are not allergenic and are nontoxic and can be administered through the vascular system. In case the vector is equipped with cell or tissue-specific promoters, its expression may be successfully targeted. Monoclonal antibodies or other ligands to (tumor) cell surface antigens may facilitate targeting. In addition, the cationic lipids may be immunostimulatory, a feature meaningful for cancer gene therapy. In some instances DOPE and other lipids have reduced the expression of the gene that they carried. Various versions of liposome-mediated gene transfer are under clinical trials (<http://clinicaltrials.gov/ct/gui/c/r>). ►liposomes, ►DOGS, ►cancer gene therapy, ►gene therapy, Audouy S, Hoekstra D 2001 Mol Membr Biol 18(2):129.

Lipinski's Rule: The criteria to be met for orally administered drugs. 1). Molecular mass <500 daltons; 2). hydrogen bond donor <5; 3). hydrogen bond donors <10; 4). coefficient of passing biological membranes <5 (Lipinski CA et al 1997 Drug Delivery Rev 23:3). ►drug development

Lipoate: A carrier of H atoms and acyl groups in α -keto acids.

Lipocalin: A family of secreted proteins that recognizes and transports small molecules, retinol, and pheromones and has diverse functions (Akerstrom B et al 2000 Biochim Biophys Acta 1482:1).

Lipo-Chitooligosaccharide: ►nodule

Lipodystrophy, Familial: A complex of autosomal dominant, recessive and X-linked anomalies of partial or predominant loss of lipid tissues especially in some areas of a body and an increase at others. Familial lipodystrophy may be associated with cystic angiomatosis (neoplasia of the blood vessels or lymphatic ducts), microphthalmia or anophthalmia (reduced eyes), mental retardation, and insulin resistant diabetes. It is surprising that both obesity and lipodystrophy can cause diabetic symptoms. The Seip-Berardinelli congenital lipodystrophy is at 9q34.1. Another locus at 11q13 is also responsible for the recessive Berardinelli-Seip syndrome involving much-reduced adipose tissue and severe insulin resistance at birth. In addition, acanthosis nigricans, hyperandrogenism, hepatomegaly, and hypertriglyceridemia are typical. The Kobblerling-Dunnigan syndrome, a partial lipodystrophy (human chromosome 1q21-q22), involves defects in lamins and is encoded at the same location as the LMNA gene. ►lamin, ►angioma, ►eye diseases, ►obesity, ►diabetes mellitus, ►SREBP, ►acanthosis nigricans, ►hepatomegaly, ►triacylglycerols, ►androgen, ►Dunnigan syndrome, ►Berardinelli-Seip congenital lipodystrophy; Magré J et al 2001 Nature Genet 28:365; Phan J, Reue K 2005 Cell Metabolism 1:73; Agarwal AK, Garg A 2006 Annu Rev Genomics Hum Genet 7:175.

Lipofection: Lipofection is genetic transformation by liposome-mediated transfer. ►liposomes, ►lipids cationic

Lipofuscin: A yellow/brown pigment product (aging pigment) of blood cell breakdown. It accumulates in aging heart muscles, macula, liver, and in earwax. ►lipofuscinosis, ►Macular degeneration, ►Stargardt disease

Lipofuscinosis: ►ceroid lipofuscinosis

Lipoic Acids: ►lipoate

Lipomatosis: Lipomatosis is the development of usually benign tumors in fat tissues. They may be under autosomal dominant control and are frequently associated with breakpoints in human chromosome 12q13-q14. An autosomal recessive lipomatosis of the pancreas (Schwachman-Bodian syndrome) involves frequent chromosomal breakage. ►cancer, ►high-mobility group proteins

Lipophilic: A lipophilic is soluble in nonpolar solvents such as fat, chloroform, benzene, etc., and poorly soluble in a polar solvent like water.

Lipopolysaccharide: ►LPS

Lipoprotein: A lipid-protein (apolipoprotein) complex that transports hydrophobic lipids. ►LDL, ►HDL, ►cholesterol, ►coronary heart disease

Lipoprotein Lipase Deficiency: ►hyperlipoproteinemia

Liposarcoma, Mixoid: A mixoid liposarcoma usually involves balanced translocations (t(12;16)(q13;p11), but additional chromosomal aberrations also occur. The C/EBP transcription factor (also called CHOP, 12q13.1-q13.2) forms a fusion protein with the product of chromosome 16.

Liposomes: Liposomes are delivery vehicles from macromolecules to cells. Within a protective coat of unilamellar vesicles consisting of phosphatidyl serine and cholesterol (1:1), they can carry DNA first to the cell membrane, and then, after fusion, to the nuclear membrane, and eventually into the nucleus. The loading of the liposomes requires DNA in a buffer and thoroughly mixed with the ether-lipid mixture. The ether is then removed. The delivery may be facilitated by polyethylene glycol, polyethyleneimine, and dimethyl sulfoxide. With appropriate coating (e.g., monoclonal antibody, DNA, viral vectors, drugs, etc.), they can be targeted to specific sites within the cell. Guanidinium-cholesterol cationic lipids (BGSC, BGTC) can be used for construction of eukaryotic vectors. Good results are obtained by the use of the cationic lipid DOTAP (dioleoyl trimethylammonium propane) and the so-called neutral helper lipid DOPE (dioleoyl phosphatidyl ethanolamine) mixtures and also with the mix of DOPC (dioleoyl phosphatidylcholine) and DOTAP. DMR1E (1,2-dimyristoyloxypropyl-3-dimethylhydroxyethyl ammonium bromide) promotes the transfer of reporter and therapeutic genes. The delivery of the DNA is quite efficient when the linear cationic lipid monolayer is transformed into hexagonal lattices. Apparently, endocytosis mediates the uptake of liposomes. The entry of the liposomal content into the nucleus is not efficient but it can be increased by four orders of magnitude if human papilloma-virus enhancer elements are incorporated into the upstream regulatory region in the plasmid replicon. Liposome vehicles can deliver very large amounts of DNA (1 Mbp) and, in contrast to viral vectors, they do not evoke an immune response. Liposomes are also used for the delivery of vaccines and drugs. ►lipids, ►lipids cationic, ►DOGS, ►fusogenic liposome, ►cytofectin, ►lipofection, ►raft, ►vaccines, ►deoxyribonucleotide-gated channels, ►immunoliposome, ►vectors, ►polyplex; Chesnoy S, Huang L 2000 Annu Rev Biophys Biomol Struct 29:27; Torchilin VP et al 2003 Proc Natl Acad Sci USA 100:1972.

Lipotropin: Adenocortical peptides controlling lipolysis. ►opiocortin

Lipoxygenase (LOX): Oxygenates arachidonic acid into leukotrienes. 15-lipoxygenase integrates into membranes of cellular organelles and mediates the access of proteases to the integral and luminal membrane proteins. As a consequence, in some special cells (e.g., erythrocytes, eye lens) mitochondria are degraded. 12-lipoxygenase controls the angiotensin pathway and 5-lipoxygenase mediates leukotriene metabolism. Lipoxygenase-3 and lipoxygenase-12 mutations may be involved in non-bullous congenital ichthyosiform erythroderma (17p13.1). The lipoxygenase activating protein (ALOX5AP, 13q12-13) almost doubles the risk of myocardial infarction and stroke by an increase in leukotriene and inflammation of the arterial wall (Helgadottir A et al 2004 Nature Genet 36:233). 5-Lipoxygenase is part of a complex trait and has pleiotropic effects on body fat, lipid levels, and bone density (Mehrabian M et al 2005 Nature Genet 37:1224). ►leukotriene, ►arachidonic acid, ►angiotensin, ►cyclooxygenase, ►integrin, ►erythroderma, ►myocardial infarction, ►stroke; van Leyen K et al 1998 Nature [Lond] 395:392; Feussner I, Wasternack C 2002 Annu Rev Plant Biol 53:275.

Lip-Print: The pattern on the human lip is rather characteristic for each individual and it had been considered as a substitute for the dermal ridges of the fingers and palms (see Fig. L41). ►fingerprints, ►forensic genetics



Figure L41. Lips

Liprin: ►synaps

Liquid Crystal: ►mesogen

Liquid-Holding Recovery: A type of genetic repair, which takes place in irradiated cells if kept in liquid medium (and allowed to utilize energy) for two days before plating.

Liquid Scintillating Counter: ►scintillation counters

LIR (long inverted repeat): A DNA sequence of about 100 or more base pairs that is either palindromic, or may have an insertion between the inverted repeats.

Such motifs are conducive to recombination or to deletion. ►repeat inverted, ►palindrome

LIR: ►ILT

LISA (localized in situ amplification): ►PRINS, ►amplification, ►PCR

Lisch Nodule: Lisch nodules are bloody spots (hamartomas) on the iris, a characteristic sign of neurofibromatosis. ►neurofibromatosis, ►hamartoma

Lissencephaly, Norman-Roberts Type (Xq22.3-q23): The Norman-Roberts type of lissencephaly involves “smooth” brain, cerebellar hypoplasia, abnormal migration of cortical neurons, and abnormal connectivity of axons. The incidence of the dominant disease is about $2-3 \times 10^{-5}$ or less. The “double cortex” anomaly is at the same location. The 388-kDa RELN (reelin) protein is encoded at the same chromosomal site at 7q22. There are other diseases with lissencephaly. ►PAF-AH, ►Miller-Dieker syndrome, ►tubulins

Listeria monocytogenes: A 2.95-Mb bacterium, which causes abortion, heart/lung infections, diarrhea, and inflammation of the brain. It also causes similar ailments in sheep and cattle. Its surface protein internalin binds to the intestinal transmembrane protein E-cadherin for infection. The bacteria move along the cytoskeleton within the cells by taking advantage of the ezrin protein, which links the plasma membrane and the cytoskeleton. They move from cell to cell in a protected state with the aid of cell protrusion (Pust S et al 2005 EMBO J 24:1287). The host specificity of the different virulent forms depends on the amino acid sequence of the cadherin molecule. Mouse chromosomes 5 and 13 modify susceptibility to this bacterium. ►cadherins, ►ezrin, ►inflammasome, ►vaccines, ►herpes, ►Lactobacillus salivarius, ►host-resistance genes; Boyartchuk VL et al 2001 Nature Genet 27:259; database: <http://leger2.gbf.de/cgi-bin/expLeger.pl>.

Literature Mining: Literature mining involves information retrieval (IR) including entity recognition (ER), e.g., of a certain gene. In case specific facts and functions are also retrieved during the search it is called information extraction (IE). ►text mining; Jensen LJ et al 2006 Nature Rev Genet 7:119.

Literature Search Assistance: ►MeSH, ►databases, ►literature mining

Lithium: A drug used for the treatment of manic depression. It causes various developmental anomalies in diverse organisms. It appears that lithium antagonizes the enzyme glycogen synthase kinase-3 β , which affects bipolar human disorders as well as

the circadian clock (Yin L et al 2006 Science 311:1002). ►manic depression, ►circadian rhythm

Lithography, Photo: ►DNA chips

Litter: A litter refers to youngsters given birth to at the same time by a multiparous animal.

Liver: ►hepatocyte

Liver Cancer (liver cell carcinoma, LCC): Liver cancer is generally initiated upon the integration of the hepatitis B virus in one or more chromosomal location. Antitrypsin deficiency, hemochromatosis, and tyrosinemia may also constitute conditioning factors. When the viral infection takes place in an individual genetically susceptible to the liver carcinoma he/she may have an eventual incidence of 0.84 (males) and 0.46 (females) of the cancer. Without the viral integration the chances for the cancer are 0.09 and 0.01, respectively, even when the genetic constitution is permissible for its development. One of the viral integration sites (17p12-p11.2) is near the p53 tumor suppressor gene. The flanking sequences are homologous to the autonomously replicating sequence (ARS1) required for the replication of the *Saccharomyces cerevisiae* integrative plasmids. Other integration sites identified are 11p13 and 18q11.1-q11.2. ►cancer, ►antitrypsin, ►hemochromatosis, ►tyrosinemia, ►ARS, ►yeast vectors, ►hepatitis B virus, ►tumor suppressor gene, ►chi elements

Liverwort: ►bryophytes

L19 IVS (intervening sequence lacking 19 nucleotides): The 395-nucleotide linear RNA left after 19 nucleotides were consumed by the *Tetrahymena* ribozyme intron which was originally 414 nucleotides long. This RNA molecule is capable of nucleotidyl transferase activity and can elongate various nucleotide sequences in a protein enzyme type manner. Preferred substrates are the nucleotide sequences that can pair with guanylate rich sequences in L19IVS, i.e., have C residues. ►ribozyme, ►intron, ►Tetrahymena

LKB: ►polyposis hamartomatous; Alessi DR et al 2006 Annu Rev Biochem 75:137.

LMO: A class of proteins with only LIM domain. ►LIM, ►CRIP, ►CRP, ►PINCH

LMO (living modified organism): LMO is the same as GMO. ►GMO

LMP-2, LMP-7: Proteasomal subunits. ►proteasome

LM-PCR (ligation-mediated PCR): Ligation-mediated PCR is used for the study of DNA double-strand breaks. ►PCR

LMYC: ►MYC

LNA: ►locked nucleic acids

LNFR: A low molecular weight nerve growth factor receptor. ►HNGFR, ►nerve growth factor [NGF]

Load: ►genetic load

Loading Test: Heterozygotes for many metabolic defects appear usually very close to the normal because the normal allele is dominant under ordinary conditions. In case large amounts of the metabolite are given to them, which the homozygotes would be unable to process, the heterozygotes are also slower than the normals to clear them from the system. For example, normal persons and phenylketonuria heterozygotes, at fasting, displayed the following concentrations of phenylalanine ($\mu\text{moles/mL}$) in the plasma: 0.067 ± 0.032 and 0.103 ± 0.029 (1.54), respectively. An hour after an oral dose of 0.1g phenylalanine/kg body weight, the observations were 0.55 ± 0.186 and 1.14 ± 0.18 (2.07), respectively. Histidine loading in case of heterozygosity for B₁₂ or folate deficiency increases excessively the amounts of formiminoglutamic acid in the urine. ►heterozygote proportions, ►phenylketonuria, ►vitamin B₁₂ defects, ►His operon, ►folic acid

Lobotomy: Surgery of the skull for (nowadays questionable) psychotherapeutic ends during the first half of the twentieth century before psychotherapeutic drugs were discovered.

Localized Determinants: In some species, different parts of the egg determine the formation of different

blastomeres depending on what cellular portions they received during cleavage. ►blastomere, ►cleavage

Localized Mutagenesis: Localized mutagenesis involves in vitro and in vivo manipulations. An amber mutation in a phage can be corrected by synthesizing a short DNA sequence complementary to a section of ΦX174 DNA single strand having a single mismatch at one base (A) corresponding to the amber codon (see Fig. L42).

The synthetic sequence will have, correctly, C (cytosine) there. The short synthetic DNA is then extended to a double-stranded form. After a cycle of replication the corrected strand makes a correct complementary copy of itself, and its progeny is thus permanently corrected by localized mutagenesis (see Fig. L43). The other old single strand of the DNA will produce another amber mutant phage.

Similar methods can be applied to any DNA that can be transferred to cells by transformation. Site-directed transposon mutagenesis is feasible by identifying genes, which contain a P element within or near a particular gene. P elements are preferentially inserted at the 5'-ends of genes and thus gene-specific promoters can be placed there. ►insertional mutagenesis, ►site-specific mutagenesis, ►hybrid dysgenesis, ►gene replacement, ►PCR-based mutagenesis, ►TAB mutagenesis, ►Kunkel mutagenesis, ►cysteine-scanning mutagenesis, ►homologue-scanning mutagenesis, ►targeting genes

Location Score: The natural logarithm of the likelihood of the odds ratio for linkage. It is determined by multiplying the lod score by 4.6. ►lod score

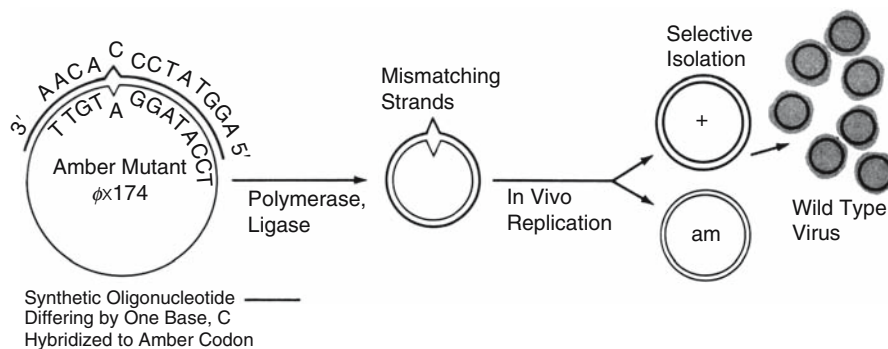


Figure L42. An amber mutation is corrected by a short DNA sequence containing a cytosine rather than an adenine in the codon. Adding the appropriate nucleotides and through the use of a DNA polymerase the synthetic nucleotide strand is completed and the strands are tied together by DNA ligase. The new single-stranded DNA has a single mismatch. After transfection of the phage to *E. coli* bacteria, each strand replicates and both amber and wild type Φx174 genomes are made. By selective screening the wild-type phages can be isolated as the result of this directed, local mutation. (Modified after Itakura K, Riggs AD. 1980 Science 209:1401)

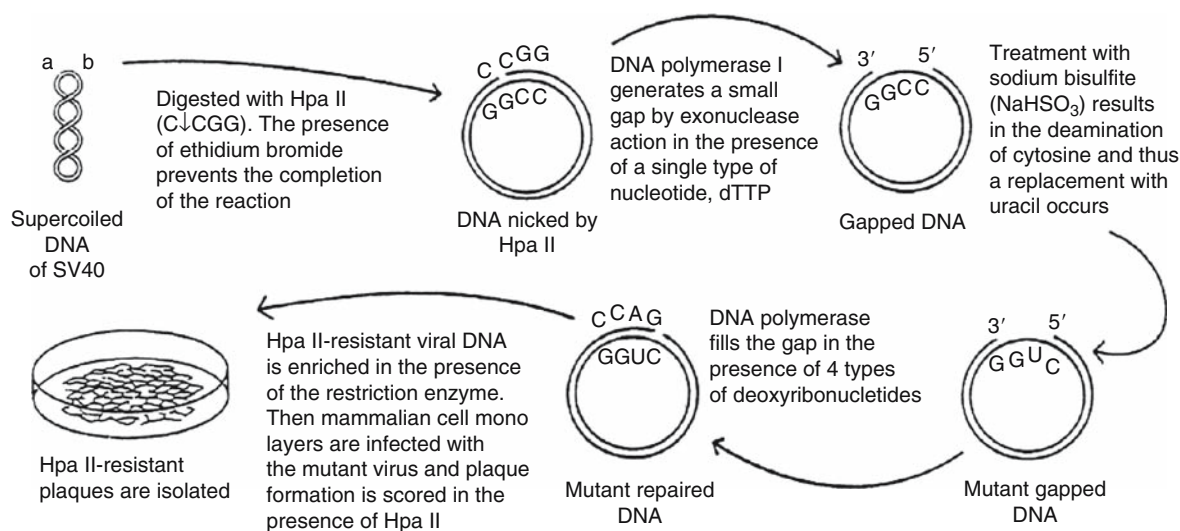


Figure L43. Local mutagenesis using restriction endonuclease gapping and in vivo mutagenesis followed by DNA polymerase correction of the gap. (After Shortle D and Nathans D 1978 Proc. Natl. Acad. Sci. USA 75:2170)

Locational Candidate Region: ►genomic screening

Locked Nucleic Acids (LNA): 2'-O,4'-C methylene-bridged (MOE) nucleic acids display enhanced binding to double-stranded DNA (see Fig. L44). Double-stranded DNA has very high hybridization to nucleic acids and is extremely resistant to nucleases. It is potentially applicable to gene therapy by stabilizing siRNA (Elmén J et al 2005 Nucleic Acids Res 33:439). In animal experiments hepatotoxicity was observed as early as four days after a single administration of LNA. In contrast, the corresponding MOE showed no evidence of toxicity while maintaining the ability to reduce target mRNA (Swayze EE et al 2007 Nucleic Acids Res). ►triple-helix-forming oligonucleotide, ►antisense technologies, ►RNAi, ENA; Uneda OS 2001 Bioorg Med Chem 9:1001; Di Giusto DA, King GC 2004 Nucleic Acids Res 32(3):e32.

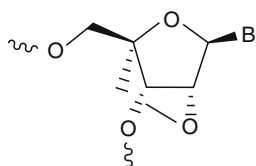


Figure L44. LNA

Locule: A fruiting body of fungi; the cavity of the ovary of plants occupied by the ovule; or the place of the uterus of some mammals where the embryo is attached (see Fig. L45).

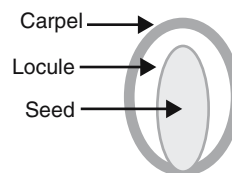


Figure L45. Locule

Locus: The site of a gene in the DNA (or RNA) or the site of a gene in the chromosome.

Locus Content Map: A locus content map displays the observations on the presence or absence of genes in chromosome fragments produced by ionizing radiation. This information may not be suitable for genetic mapping if contrasting alleles are not available. The data obtained can be confirmed by physical mapping. ►radiation hybrids; Teague JW et al 1996 Proc Natl Acad Sci USA 93:11814.

Locus Control Region: ►LCR

Locus Exclusion: Locus exclusion occurs when both alleles at a locus are prevented from expression in deference to allele(s) at another locus. ►allelic exclusion, ►idiotype exclusion

Locus Heterogeneity: When the same phenotype is produced by more than one combination of the genetic constitution it is termed locus heterogeneity.

LocusLink: Provides information about genes as a central hub. On 1 March 2005 it was replaced by ENTREZ GENE (<http://www.ncbi.nlm.nih.gov/entrez/>)

query.fcgi?db=gene). ►RefSeq, ►gene prediction, ►entrez gene

Locus Specific Database (LSDB): A human mutation database: <http://www.hgvs.org/entry.html>.

Locust: *Locusta migratoria*, 2n = 23; B chromosomes occur (see Fig. L46).

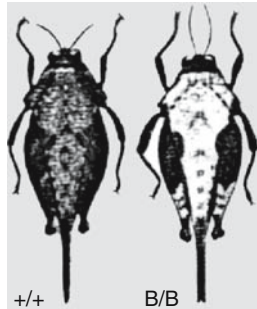


Figure L46. Locust (*Paratettix texanus*)

Lod Score: A lod score expresses the relative probability of linkage compared to the odds against linkage (log odds) because the score is obtained by dividing the sum of logarithms indicating linkage by the sum of logarithms suggesting independent segregation. The principle briefly is:

Probability of linkage (P) = $\frac{\text{Recombination Frequency } \theta}{\text{Recombination Frequency } 1/2}$

Here θ stands for any value of recombination, and 1/2 recombination indicates independent segregation. In case several linkage probabilities exist, the formula above can be rewritten as (see Table L6):

Relative linkage (P) = $\frac{p_1(\theta_1)p_2(\theta_2) \dots p_n(\theta_n)}{p_1(1/2)p_2(1/2) \dots p_n(1/2)}$

hence the relative odds of linkage is expressed as:

$$\begin{aligned} &\text{Log}_{10}(\text{odds of linkage}) \\ &= \frac{\log p_1(\theta_1) + \log p_2(\theta_2) + \log p_n(\theta_n)}{\log p_1(1/2) + \log p_2(1/2) + \log p_n(1/2)} \\ &= \text{lod score} \end{aligned}$$

Table L6. Z(θ) values of lod scores

| θ | θ^2 | $(1 - \theta)^2$ | $2[\theta^2 + (1 - \theta)^2]$ | Z(θ) |
|----------|------------|------------------|--------------------------------|---------------|
| 0 | 0 | 1 | 2.00 | 0.30303 |
| 0.05 | 0.0025 | 0.9025 | 1.81 | 0.25768 |
| 0.10 | 0.0100 | 0.8100 | 1.64 | 0.21484 |
| ↓ | ↓ | ↓ | ↓ | ↓ |
| 0.50 | 0.2500 | 0.2500 | 1.00 | 0 |

The lod scores for all θ (recombination frequency) values summed up is expressed as Z(θ) (see Table L6). This value may be empirically defined at various values of θ : Thus a lod score, if $\theta = 1/2$, is 0 because $\log 1 = 0$. A lod score >3 indicates approximately 95% probability of linkage but a lod score of >4 gives a probability of about 99.5%. A lod score of -2 indicates independent segregation. Lod scores between -2 to 3 are considered inconclusive. It is most useful for sequential data as available from (human) pedigrees. It is widely used also for mapping restriction fragments (RFLP). The homogeneity of the lod scores among different families can be tested by chi square analysis. The probability of two genes being independent may also be obtained by the formula based on Bayes' Theorem, e.g., for the 22 human autosomes:

$$P(\theta) = 1/2 = \frac{21}{\lambda + 21}$$

where λ is the average value of $\lambda(\theta)$ and it is equal to antilog Z(θ).

The chance that any particular unknown gene would be in a human autosome is 21/22 and the chance for another gene being in the same chromosome is 1/22. The computation, based on maximum likelihood, is somewhat complicated when multi-point crosses are evaluated but computer programs (e.g., Mapmaker, Joinmap, LINKAGE, MENDEL, VITESSE, FAST-LINK, LODLINK) are available for linkage estimation. The lod score can be used for other biological comparisons too, e.g., evolutionary relationships of nucleotide or protein sequences. ►mapping genetic, ►linkage, ►antilog, ►genomic screening, ►word score, ►Mod score; O'Connel JR, Weeks DE 1995 Nature Genet 11:402; Lander E, Kruglyak L 1995 Nature Genet 11:241; Nyholt DR 2000 Am J Hum Genet 67:282; Ott J 2001 Advances Genet 42:125.

Lodicule: The scale-like structures at the base of the ovary of grasses; they mediate the opening of the flower when the pollen is shed in allogamous species (see Fig. L47).

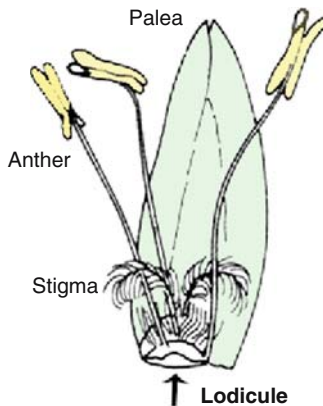


Figure L47. Lodicule

Loeys-Dietz Syndrome (LDS, aortic aneurism, 9q33-q34, 3p22): The Loeys-Dietz syndrome is caused by dominant mutations in the transforming growth factor receptor (TGFBR) with variable expression. Its symptoms include hypertelorism, cleft palate, arterial twisting (tortuosity), aneurysm heart disease, and mental retardation. Patients suffering these diseases may also benefit by the use of artan, an antagonist of angiotensinogen II receptor and TGF- β . ▶[TGF](#), ▶[hypertelorism](#), ▶[cleft palate](#), ▶[aneurysm](#), ▶[glucose transporters](#), ▶[Marfan syndrome](#)

Löfgren (Loefgren) Syndrome: ▶[sarcoidosis](#)

Lognormal Distribution: Logarithms of the data may approximate the normal distribution. Mutation rates may show this type of distribution and the variance $(\sigma^2) \sim \mu$ (mean).

Log Phase: ▶[exponential growth](#)

Loganberry (*Rubus loganobaccus*): A fruit shrub, $2n = 42$.

Logarithm: A logarithm can be defined as $x = b^y$ and from this $y = \log_b x$ or, in words, y is the logarithm of x to the b base. The common (Briggs) logarithm uses base 10, the base of the natural logarithm is called e and it is 2.71828 (to five digits). Logarithms can be determined to any base and can be converted to each other, e.g., the natural logarithm, \log_e (commonly designated also as \ln), can be converted to common logarithms as $\log_{10} x = \log_e x (1/\log_e 10)$. ▶[antilogarithm](#)

Logarithmic Growth: ▶[exponential growth](#)

Logarithmic Stability Factor: The logarithmic stability factor (LSF) measures the developmental homeostatic values of individuals of certain genotypes under

different environmental conditions. LSF is calculated as the absolute difference between two logarithmic means. If $LSF = 0$ the developmental homeostasis is maximal. ▶[homeostasis](#); Li SL, Rédei GP 1969 Theor Appl Genet 39:68.

Logic: The study of the methods of reasoning; it deals with propositions, their implications, possible contradictions, conversions, etc. Symbolic logic employs mathematical symbols for the propositions, quantifiers, mutual relations among propositions, etc. Logic is one of the most important tools of science for interpreting the experimental data. ▶[syllogisms](#)

Logic Gate: A concept of Boolean algebra where complex statements are connected by “and”, “not”, and “or” relations. Such a system may be used in synthetic biology for the generation of novel interacting networks. ▶[Boolean algebra](#), ▶[synthetic biology](#)

Logistic Regression: Regression analysis for binary variables using logit transformation such as $\text{logit}(p) = \ln \frac{p}{1-p}$ where p tends to be 0 and $\text{logit}(p)$ tends to be $-\infty$, and as p tends to be 1, $\text{logit}(p)$ tends to become $+\infty$. ▶[binary variables](#), ▶[Logit](#); Agresti A 1990 Categorical Data Analysis. Wiley, New York.

Logit: Logit is very similar to the cumulative normal distribution. The transformation is: $l = \log (P/1-P)$. ▶[probit](#)

Logo: ▶[sequence logo](#)

LOH: Loss of heterozygosity or LOH is mediated by mutation (deletion) or somatic recombination or gene conversion. It is a common cause of cancer when a cancer suppressor gene is lost. Nontoxic levels of several mutagenic agents increased LOH by an order or two orders of magnitude in mouse stem cells (Donahue SL et al 2006 Proc Natl Acad Sci USA 103:11642). ▶[pseudodominance](#), ▶[tumor suppressor gene](#), ▶[LOS](#), ▶[mitotic recombination](#), ▶[gene conversion](#)

Lollipop Structure: When single strands of DNA carrying palindromic terminal repeats are allowed to fold back, the complementary ends pair while the noncomplementary sequences in-between remain single-stranded and thus form a stem and loop configuration as shown in [Figure L48](#). Denatured insertion elements may also display lollipop structures if the complementary sequences are allowed to pair within the single strand. ▶[palindrome](#), ▶[insertion element](#)

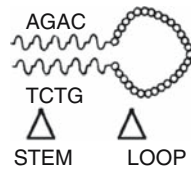


Figure L48. Lollipop structure of nucleic acids

Lon: A monomeric eukaryotic polypeptide with one of the domains associated with ATPase and functions as a chaperone; the other domain functions as a protease.

►C/p

Long Branch Attraction: The placement, in evolutionary trees, of sequences that are not truly relevant to their phylogenetic relationship. ►evolutionary tree; Qiu YL et al 2001 Mol Biol Evol 18:1745.

Long-Day Plants: These plants usually require more than 12 hr daily illumination to be able to develop flower primordia. ►photoperiodism, ►short-day plants, ►primordium

Long Interspersed Nucleotide Element: ►LINE

Long-Patch Repair: The repair of longer mismatches. In humans, DNA polymerase β may have the major role although pol δ and pol ϵ are also repair polymerases. Base excision and nucleotide excision repairs are short-patch repairs. ►DNA repair, ►excision repair, ►mismatch repair, ►DNA polymerases, ►PARP; Podlasky AJ et al 2001 EMBO J 20:1477.

Long-Term Selection: ►artificial selection

Long Terminal Repeat (LTR): Retroviruses at the two flanks may have 2–8 kb repeated nucleotide sequences; similarly a few hundred repeats are found at the ends of retrotransposons. ►retroviruses, ►transposable elements, ►retrotransposons, ►solitary LTR

Longevity: Longevity represents the length of life. It can be measured as replicative aging or as chronological aging. Life span is the biologically determined potential of an organism to live. Life expectancy is the actual, expected duration of life under certain conditions. The average human life expectancy in years in the USA in 1850 was 38.3 for males and 40.5 for females; by 1950 it became 66.5 and 73.0, respectively. It has increased since by approximately 7–8 years. In 2003, the life expectancy in the USA for white males was 75.4 years, for black males 69.2, for white females 80.5, and for black females 76.1. It is quite likely that the current trend of widespread obesity will reduce life expectancy in the twenty-first century. Raymond Pearl, an American pioneer of

human population genetics, found (during the early years of the twentieth century) that the life expectancy at birth of sons of fathers who died before ages 50, 50–79 and over 80 to be 47, 50.5 and 57.2 years, respectively. Despite regression, approximately similar life expectancy differences continued after the age of 40. Currently, the average life expectancy is in the mid-70s in the USA and if the present trends continue it may increase by about 10 years in about 50 years. Presently, the estimated maximal human life span is about 120 years. Compared to the US 1900 cohort, male siblings of centenarians were about 17 times as likely to attain age 100 themselves, while female siblings were at least eight times as likely (Perls TT et al 2002 Proc Natl Acad Sci USA 99:8442). Some theories predict that aging does not affect the evolution of longevity because at older ages the reproductive rate diminishes. On the other hand, longevity has selective fitness value for descendants because the support provided for the offspring assures greater survival of the youngsters. Thus, parental or grandparental care is of selective value for longevity (Lee RD 2003 Proc Natl Acad Sci USA 100:9637). A Danish study found 0.26 heritability of longevity for males and 0.23 for females (Herskind AM et al 1996 Hum Genet 97:319). In humans, few genes are known that affect longevity although apolipoproteins seem to have an effect (Corder EH et al 1996 Arch Neurol 53:418; Atzmon G et al 2006 PLoS Biol 4(4):e113). Lower levels of apolipoprotein APOC3 involved lower hypertension, less cardiac disease and diabetes. Christensen K et al (2006 Nature Rev Genet 7:436) tabulated the candidate genes affecting human life span. Many genes with small individual effects and environmental factors—diseases in particular—determine longevity.

In *Drosophila*, increased egg-production, receipt of male accessory fluid and courtship shorten the life span. Mating and courtship also shorten the life span of flies. Caloric restriction in the diet or mutation in a sodium dicarboxylate co-transporter or overexpression of a protein repair methyltransferase extends the life span of flies. The gene *Indy* (for I am not dead yet) encodes a membrane protein that transports Krebs cycle intermediates. The hermaphrodite *Caenorhabditis* has a shorter life if mated, but this is independent from egg production or receipt of sperm. The males of this species are not affected by mating. Some single genes of *Caenorhabditis* (*daf*, *age-1*) may extend the life span two to three times. Two 14-3-3 proteins interact with Sir2 and Sir1 proteins in *Caenorhabditis* and activate the DAF-16 transcription factor and extend the life span (Berdichevsky A et al 2006 Cell 125:1165). In this nematode the life span is also regulated by sensory perception and defects in the sensory neurons. Some suggestions were made

regarding correlation between longevity and MHC alleles, apolipoproteins E and B, angiotensin-converting enzyme, upregulation of superoxide dismutase activity, etc. When the insulin-like growth factor (IGF-1) receptor DAF-2 reduces the level of the DAF-16 (a forkhead/winged helix type transcriptional regulator [FKH]) protein the worm's life span is doubled. Besides DAF-16, DAF-12 (a nuclear hormone) plays a beneficial role. This pathway (DAF-2) is under germline-controlled negative regulation. The somatic gonad also affects aging. In *Caenorhabditis*, about 50 genes have major effect on longevity. Reduction of the activity of microRNA *lin-4* reduces the life span of nematodes and accelerates aging. Overexpression of *lin-4* reduces the expression of microRNA *lin-14* and prolongs the life span. The *lin-4*-*lin-14* pair affects longevity through the insulin/insulin-like growth factor 1 pathway (Boehm M, Slack F 2005 Science 310:1954). In *Drosophila*, the loss of an insulin-receptor substrate protein significantly extends the life span. *Drosophila* longevity is increased by 4-phenylbutyrate without apparent side effects (Kang H-L et al 2002 Proc Natl Acad Sci USA 99:838). Abolishing the expression of the Rpd3 histone deacetylase extends the longevity of *Drosophila*. The p66^{Shc} protein (encoded by SHC gene) protects mammalian cells from oxidative stress (ROS) and may increase the life span of mice by 30% and homozygosity for the Prop^{df} and Pit1^{dw} mutation (affecting growth factor production) may expand the life span by 50 to 40%. Mutation in lipid metabolism in the mitochondria extends the life span in *Drosophila* (Mourikis P et al 2006 Proc Natl Acad Sci USA 103:1307). In the fungus *Podospora anserina*, the inactivation of subunit V of the mitochondrial COX5 gene channels respiration to an alternative pathway decreases the production of reactive oxygen species and strikingly increases longevity. In *Saccharomyces*, the activation of the gene silencing protein Sir2 by NAD contributes to longevity (Anderson RM et al 2003 Nature [Lond] 423:181). Longevity among taxonomic groups may be positively correlated with the size of the genome. ▶mortality, ▶aging, ▶replicative aging, ▶chronological aging, ▶age and mutation, ▶age-specific birth and death rates, ▶copulation, ▶apolipoproteins, ▶MHC, ▶angiotensin, ▶menopause, ▶superoxide dismutase, ▶Dauer larva, ▶eIF-4E, ▶FKH, ▶SHC, ▶ROS, ▶COX, ▶silencer, ▶NAD, ▶insulin, ▶sirtuin, ▶ecdysone, ▶microrna, ▶protein 14-3-3 Tuljapourkar S et al 2000 Nature [Lond] 405:789; Clancy DJ et al 2001 Science 292:104; Chavous DA et al 2001 Proc Natl Acad Sci USA 98:14814; Larsen PL, Clarke CF 2002 Science 295:120; Perls T et al 2002 Current Op Genet Dev 12:362; Muñoz MJ, Riddle DL 2003 Genetics 163:171; <http://www.mortality.org/>.

Longhorn Cattle: A primitive form, used extensively as draft farm animal before the era of mechanization. Longhorn cattle resemble the cattle depicted (15,000 years ago) by neolithic humans in European caves. ▶Lascaux cave

Long-Period Interspersion: Long sequences of repetitive DNA alternating with long unique sequences.

Long QT Syndrome (KCNQ1/LQT1, 11p15.5; LQT2, 7q35-q36): The long QT syndrome involves voltage-gated potassium channel defects. Congenital long QT syndrome involves ventricular heart arrhythmias and sudden death. Among the 1,534 descendants, the proportion of genetically affected offspring was significantly greater than that expected: 870 were carriers of a mutation (57%) and 664 were noncarriers (43%, $P < 0.001$). Among the carriers, the allele for the long QT syndrome was transmitted significantly more often to female (55%) offspring than to male (45%) offspring (Imboden M et al 2006 New England J Med 355:2744). ▶ankyrin, ▶LQT, ▶Ward-Romano syndrome, ▶ion channels, ▶arrhythmogenic right ventricular cardiomyopathy; Marx SO et al 2002 Science 295:496; zebrafish model: Arnaout R et al 2007 Proc Natl Acad Sci USA 104:11316.

Longitudinal Study: A longitudinal study is carried out for a longer time through age and developmental stages. ▶cross-sectional study

Long-Term Depression: ▶memory

Long-Term Potentiation (LTP): The activation of synaptic junctions in the brain relating to memory. The non-associative LTP is induced by high-frequency stimulation of the presynaptic termini. The associative type LTP increases the probability that neighboring synapses on the same neuron will be strengthened if activated within milliseconds. This provides an opportunity to encode associations between different events if they occur concurrently. Ca²⁺/calmodulin-dependent protein kinase (CaMKII) and cAMP both regulate LTP. A single phosphorylation site on eIF2 α is a key regulator of LTP and long-term memory in mice (Costa-Mattioli M et al 2007 Cell 129:195). Inhibition of protein phosphatase-1 (PP1) can substitute for the cAMP function, which uses PP1 to gate CaMKII signaling. ▶memory, ▶Hebbian mechanism, ▶cAMP, ▶calmodulin, ▶eIF2, ▶ATF; Malenka RC, Nicoll RA 1999 Science 285:1870; Matynia A et al 2002 Annu Rev Genet 36:687; review: Malenka RC, Bear MF 2004 Neuron 44:5.

Look-Through Mutagenesis: A method to generate mutation in the complementarity-determining regions (CDR) of the variable heavy and variable light

domains of antibodies by synthetic procedures. Nine amino acids, representative of chemical functionalities (small, nucleophilic, hydrophobic, aromatic, acidic, amide, basic), were used in a combinatorial fashion. The best replacement combinations improved affinities by 500–870-fold and neutralized TNF- α by 15–30-fold. Such non-stochastic mutagenesis greatly and systematically increases antibody effectiveness and appears superior to other procedures of site-specific mutagenesis. It can find therapeutic application in a variety of conditions, from organ rejection and cancer to autoimmune diseases. ▶CDR, ▶site-specific mutation, ▶TNF; Rajpal A et al 2005 Proc Natl Acad Sci USA 102:8466.

Loop: Single-stranded (unpaired) nucleic acids sequences (loops) alternating with double-stranded, paired regions in isolated molecules (see Fig. L49). Paired regions of the meiotic chromosomes of inversion heterozygotes, unpaired regions of normal chromosomes “paired” with deletions. The nondeleted strand pops out opposite the deletion. ▶lollipop, ▶inversion, ▶tRNA, ▶deletion, ▶looping of DNA, ▶lampbrush chromosome

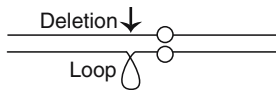


Figure L49. Loop

Loop Domains Model: The DNA fibers form 5- to 100-kb loops that are attached to the nuclear matrix (protein) at the matrix attachment region (MAR). These domains of the chromatin are supposed to be transcriptional and replicational units. The matrix is also called nuclear scaffold. The MAR regions are expected to regulate the expression/silencing of genes ▶chromatin, ▶A box, ▶T box

Looping of DNA: DNA looping is brought about by protein binding to DNA at two different positions ranging from ten to thousands of nucleotides apart (see Fig. L50). The association of proteins with specific DNA sequences permits the DNA to fold back from a longer distance to the location of the promoter of the gene and thus regulate the expression, recombination and replication of the genetic material. Looping may involve short (~100 bp) sequences that show the twistability and flexibility of the DNA. One of the several proteins that mediate the changes in the structure of DNA in the bacterial nucleoid is the heat unstable nucleoid protein, which, in association with the galactose repressor, regulates the expression of

the gene by looping the DNA and controlling both promoters of the gene (Lia G et al 2003 Proc Natl Acad Sci USA 100:11373). (See Fig. L50 modified after Lia, G. et al., ▶hormone response elements, ▶transcription factors inducible, ▶regulation of gene activity, ▶LCR, ▶RNA TRAP; Irani MH et al 1983 Cell 32:783; Schleif R 1992 Annu Rev Biochem 61:199; Geanocopoulos M et al 2001 Nature Struct Biol 8(5):432; Cloutier TE, Widom J. 2005 Proc Natl Acad Sci USA 102:3645.

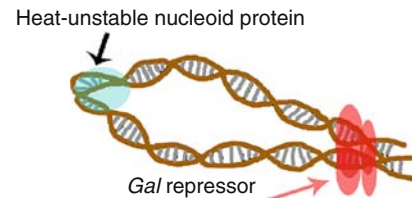


Figure L50. Looping of DNA

Loop-out–Loop-in Mutagenesis: Generation of deletions and the replacing of deleted segments with other sequences.

LOR: Human low-copy repetitive sequences in about five copies per genome. ▶redundancy

Lordosis (curvature of the spine): The term is generally applied to the condition where the curvature is expressed above the normal level such as, e.g., in some types of muscular dystrophy. Rodent females receptive to mating display an arched back and raised tail and hind body parts. ▶muscular dystrophy, ▶scoliosis, ▶kyphosis

Lorisidae: A family of prosimii. *Arctocebus calabrensis* 2n = 52; *Galago crassicaudatus* 2n = 62; *Galago demidovii* 2n = 58; *Galago senegaliensis braccatus* 2n = 36, 37, 38; *Perodicticus potto* 2n = 62. ▶prosimii

LOS: The loss of heterozygosity mutation. In a heterozygote, one of the alleles (infrequently both) is lost. If the remaining allele is nonfunctional or suffers a secondary (somatic) mutation, the normal function of the gene is discontinued. ▶LOH

Loss-of-Function Mutation: Generally results in a recessive phenotype but only 1/3 or 1/4 of the *Drosophila* genes can be classified by phenotype as loss-of-function mutation because of redundancy. ▶gain-of-function mutation, ▶LOH

Lotka-Volterra Formula: Lotka-Volterra formula quantifies the competitive interactions between populations:

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{(N_1 + \alpha_{12} N_2)}{K_1} \right) \text{ and } \frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{(N_2 + \alpha_{21} N_1)}{K_2} \right)$$

Subscripts 1 and 2 stand for the two populations (N); dN_1/dt and dN_2/dt are the calculus symbols for the rate of change; $1/K$ is the effect of an individual of species 1 on the growth of species 1; and, α_{21}/K_1 is the effect of an individual of species 2 on species 1. Similarly, $1/K_2$ and α_{12}/K_2 stand for the influence of one individual of species 1 on species 2, and r is the constant of intrinsic rate of growth. (See Drossel B, Mckane A 2000 J Theor Biol 204(3):467).

Lotoaustralin: A glucoside linked with cyanide and making some white clover varieties toxic or lethal (if 1 to 2 kg is consumed) to animals (50 kg). This toxic effect has been circumvented by breeding white clovers deficient in the synthesis of the glucoside and in linamarase. Several other plant species (Sudan grass, flax, some beans, almond, apricot) produce potentially toxic cyanides. ▶cyanogenic glucosides

Lou Gehrig's Disease: ▶amyotrophic lateral sclerosis

Louis-Bar Syndrome: Ataxia telangiectasia. ▶ataxia

Lovastatin (mevinolin/monacolin K): An inhibitor of the (3S)-hydroxy-methylglutaryl-coenzyme (see Fig. L51). A reductase, which normally reduces its substrate (HMG-CoA) to mevalonate, a precursor of cholesterol. It is a natural product of the fungus *Aspergillus terreus*. ▶cholesterol

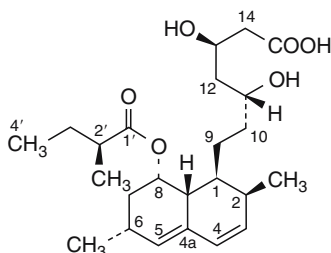


Figure L51. Lovastatin (acid)

Low Frequency Transducing Lysate: ▶LFT

Low-Complexity Sequences: Low-complexity sequences contain repetitions of the building blocks or tracts of repetitions.

Low-Copy Repeats: Low-copy repeats may constitute 5% of the genome of 10 to 40 kb size and ~95–97% similarity. These repeats may be responsible for

genomic instabilities and disease because of recombination among these similar sequences (Stankiewicz P, Lukski JR 2002 Current Op Genet Dev 12:312).

Low-Density Lipoproteins (LDL): Low-density lipoproteins form 22-nm diameter particles containing bilayered vesicles of about 1,500 cholesterol molecules, esterified to long-chain fatty acids and form a vehicle of delivery of lysosomes from where the cholesterol is made available for membrane synthesis. If there is a defect in the synthesis of the receptor proteins (19p13.2, 12q13.1-q13.3, 1p34, 2q24-q31, 4p16.3, 11p12-p11.2) the cell may not draw cholesterol from the blood resulting in atherosclerosis and eventually artery disease. LDL receptors are involved in high affinity and broad specificity endocytosis such as the macrophage scavenger receptors that are supposed to mediate cell adhesion, host defense, and atherosclerosis. Mutations in the PCSK9 692-amino acid glycoprotein also cause hypercholesterolemia. In a sample analyzed, African-Americans have much higher frequency (2%) of nonsense mutations in the PCSK9 gene than Whites or Hispanics, <0.1% (Cohen J et al 2005 Nature Genet 37:161). ▶atherosclerosis, ▶cholesterol, ▶lysosome, ▶hypertension, ▶HDL, ▶Alzheimer disease, ▶VLDL, ▶hypercholesterolemia, ▶apolipoproteins, ▶ethnicity

Low-Energy Phosphate: A compound that can release relatively low energy upon hydrolysis, e.g., glucose-6-phosphate.

Lowe's Oculocerebrorenal Syndrome (OCRL): An X-chromosome-linked (Xq26.1) eye defect, mental retardation, aminoaciduria, kidney anomaly, rickets, etc. The defect is in an inositol-5-phosphatase, synaptojanin. ▶mental retardation, ▶synaptojanin

Lowry Test: The test (J. Biol. Chem.193:265 [1951]) quantitatively estimates total protein in tissue extracts using 1% CuSO₄ (0.5 mL), 2.7% Na-K-tartrate (0.5 mL), 2% Na₂CO₃ in 0.1 M NaOH (50 mL). Add 5 mL to 1 mL sample protein (25–500 µmL), mix and allow to stand for 10 min. Then add 0.5 mL Folin & Ciocalteu reagent and mix; after 30 min determine O.D. at 750 nm and compare to bovine serum albumin standard solution series (detergents interfere with the test). ▶Bradford method, ▶Kjeldhal method

Lox (*loxP*): ▶Cre/Lox

L-Phase: Due to various shocks (temperature, osmotic, antibiotics, etc.) the bacteria may lose their walls in a possibly reversible manner and yet they can multiply.

LPS (endotoxin): Lipopolysaccharide, lipid-carbohydrate complexes existing on the walls of some bacteria. The infection of mammalian cells by Gram-negative bacteria leads to the release of

toxic LPS, which in turn activates TNF and other toxic cytokines. ▶TNF, ▶cytokines, ▶endotoxins, ▶capsule

LQT: A cardiac (heart) disease involving left ventricular arrhythmia. Several genetic defects result in the same symptoms (SCN5A, LQT3 [chromosome 3p21], HERG [LQT2, chromosome 7], KVLQT1/KCNQ1 [LQT1, chr. 11p15.5], and another in chr. 4). All of these loci are involved in the control or regulation of muscle cell K^+ or Na^+ ion channels. ▶cardiovascular diseases, ▶ankyrin, ▶ion channels, ▶Jervell and Lange-Nielson syndrome, ▶Ward-Romano syndrome, ▶electrocardiogram for LQT, ▶KCNA, ▶Beckwith-Wiedemann syndrome, ▶Timothy syndrome; Bennett PB et al 1995 Nature [Lond] 376:640; Schwartz PJ et al 2001 Circulation 103:89; Keating MT, Sanguinetti MC 2001 Cell 104:569.

LRE: ▶light response elements

LRF (luteinizing hormone releasing factor): ▶luteinization, ▶corticotropin

LRR (leucine-rich repeats): ▶host-pathogen relations

λ_S : Risk of relatives/population risk may be used to determine the genetic part of a disease. A recessive disease is expected among the relatives of a proband at a frequency of 0.25. If the prevalence of this disease in the general population is say 0.0005, then $\lambda_S = 0.25/0.0005 = 500$. In case a dominant gene controls the disease then λ_S will be larger. The higher is λ_S the greater the risk of recurrence. λ_S larger than 2 indicates a significant genetic component in the disease. In case the disease is under the control of multiple loci, the risk may diminish in successive generations. ▶sibling, ▶risk, ▶prevalence

LSD1 (histone lysine demethylase): LSD1 is involved in epigenetic modifications.

LSDB: See Locus specific database <http://www.hgvs.org/entry.html>.

LSIRF (IRF4): A transcription factor, specific for mature B and T cells.

LT, LTβ: Both are proteins of the TNF/NGF family encoded at the HLA gene cluster. ▶TNF, ▶NGF, ▶HLA

LTD: ▶memory

LTR: Also known as long terminal repeats in movable genetic elements and oncogenic viruses. ▶retroviruses, ▶transposable elements

LUC: The firefly luciferase gene. ▶luciferase

Luciferase: Luciferase can be effectively used as a tissue- or developmental stage-specific reporter of gene expression (see Fig. L52).

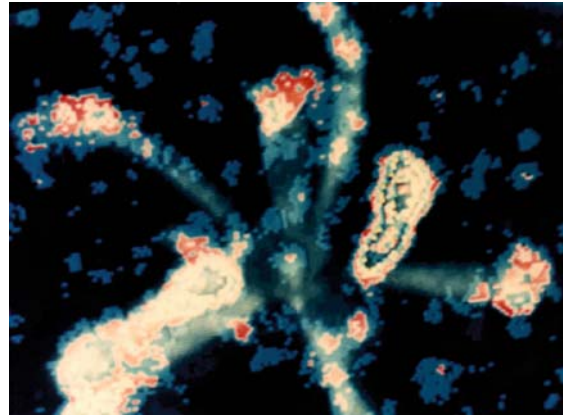


Figure L52. *Arabidopsis* plant transgenic for the bacterial luciferase *Luxaβ* genes. The most intense expression is indicated by red color. (From Rédei GP, Koncz C, Langridge, WHR, unpublished)

The luciferase of the firefly (*Photinus pyralis*) is a single polypeptide of 550 amino acids. In the presence of oxygen (O_2), and Mg-ATP (or coenzyme A) it oxidizes luciferin to oxyluciferin, resulting in the visible emission of yellow-green light flashes, which can be monitored also by luminometers, scintillation counters or by extended exposure to highly sensitive photographic film. Other insects also produce luciferases, which produce somewhat different light emission. The light emission spectrum depends on the conformation/amino acid composition of the luciferase enzyme (Nakatsu T et al 2006 Nature 440:372). The generation of the light flashes is part of the courtship process and reproduction in insects. The bacterial luciferases such as the one produced by *Vibrio harveyi* or other similar strains consist of two subunits A and B. The substrate of the bacterial luciferase enzymes is n-decyl aldehyde (decanal) and for the emission of light reduced flavin mononucleotide (FMNH₂) is required. While the aldehyde (RCHO) is converted to acid (RCOOH) in the presence of oxygen (O_2), water (H_2O), FMN and light is generated. The luminescent bacterium *V. fischeri* uses a quorum-sensing signal, which, combined with the enzyme LuxI, activates LuxR, and which in turn binds to specific activating domains in the bacterial DNAs to turn on the genes required for light emission. About 20 additional genes cooperate with, and modulate, the expression of the bacterial luciferase. The light can be monitored in the tissues without destruction by the use of a microchannel plate enhanced photon counting image analyzer that uses a video camera, an image processor, a TV processor, and computerized controls. Such equipments may detect even a single photon. A much less expensive luminometer can also be used with ground tissues. ▶image analyzer, ▶GUS, ▶Quorum-sensing;

Baldwin TO et al 1995 Curr Opin Struct Biol 5:798; Pazzagli M et al 1992 Anal Biochem 204:315; Olsson O et al 1988 Mol Gen Genet 215:1.

Luciferin: Upon activation, cleaves a pyrophosphate off ATP to form luciferyl adenylate. Upon the action of firefly luciferase—in the presence of O_2 —light is emitted. Oxyluciferin is then generated in the presence of CO_2 and AMP. Subsequently, through some steps, luciferin is reformed. These reactions are suitable for monitoring gene expression and for the quantitation of ATP. ▶[luciferase](#), ▶[ATP](#); Wilson T, Hastings JW 1998 Annu Rev Cell Dev Biol 14:197.

Lucy: 3-million-year old *Australopithecus afarensis* skeleton of about 1 m height (discovered in 1974 in Ethiopia), believed to be a representative of the origin of the human family tree. Although—as the name implies—the skeleton was assumed to be that of a female (because of the small size), some paleoanthropologists argue that she was rather a male because the pelvis would not have been sufficient for child bearing. ▶[hominids](#)

Ludwig Effect: Biological habitats are generally divided into numerous microniches and the species respond to these by selection.

Luft Disease: A rare human hypermetabolism due to a defect in the coupling of oxidative and phosphorylation processes in the mitochondria. The genetic determination is not entirely clear; autosomal recessivity is suspected. ▶[mitochondrial disease in humans](#)

Lujan Syndrome: An X-linked mental retardation with marfanoid features. ▶[mental retardation](#), ▶[Marfanoid syndromes](#)

Lumen: The interior compartment of a membrane-enveloped structure in the cell; also a unit of luminous intensity. ▶[lambert](#)

Luminescence: Light emission from cool sources such as excited gases (neon light), fluorescent tubes, television and computer screens, and bioluminescence of fireflies, glowworms and certain fishes and bacterial luciferase. ▶[luciferase](#)

Lung Cancer: ▶[small cell lung carcinoma](#), ▶[non-small-cell lung carcinoma](#), ▶[pulmonary adenoma](#)

Lupines (leguminous plants): Yellow lupine (*Lupinus luteus*, $2n = 46, 48, 52$); blue lupine (*L. angustifolius*, $2n = 40$); and white lupine (*L. albus*, $2n = 30, 40, 50$) are crop plants used for “green manure” or in alkaloid-free forms as forage crops in acid soils. The perennial lupine (*L. polyphyllus* ($2n = 48$)) is an attractive ornamental plant. The alkaloid-free lupines are one of the best examples of scientific plant breeding. ▶[alkaloids](#)

Lupus Erythematosus: A variety of skin and subcutaneous inflammations, each with a specific medical name (see [Fig. L53](#)). The genetic basis is not clear as certain



Figure L53. Lupus erythematosus

drugs (e.g., procaine anesthetics) apparently cause some of the common symptoms. In other cases, viral infection has been suspected because of similar symptoms observed in family dogs. Some indications point to the involvement of steroid hormone problems because of its incidence with the Klinefelter syndrome. In some cases, along with the normal DNA, a low molecular weight DNA was associated with the disease. In other individuals, anti-RNA or antinuclear antibodies were identified. The Ro autoantigen (60 kDa) is a major target in the disease. Ro binds misfolded small RNAs and seems to play a role in RNA quality control. Ro contains a von Willebrand factor A domain and a doughnut-shape domain of HEAT repeats. In this complex the small, so-called Y RNAs bind to the outer surface of the HEAT ring and the single-stranded RNA binds to the toroid hole (Stein AJ et al 2005 Cell 121:529). Lymphocyte defects were also shown in some afflicted individuals. The serum complement deficiencies involve major risk of onset. C1q deficient individuals carry a risk of ~90%. C1q is assembled from 18 polypeptide chains including the C1r and C1s serine protease homodimers. After C1q binds to the antibody the proteases are activated and the C3 convertase is formed from the C2 and C4 complement parts. Females are about eight-fold more likely to be afflicted by it than males in the age group 15–50, but later or earlier the relative risks differences are much less. Protein p21 appears to be responsible for preventing lupus-like diseases in females. The lifetime risk for a US Caucasian female is about 0.15% and much less for Blacks or Hispanics. A mouse model indicates that the secretion of the BAFF protein by T cells or dendritic cells initiates the abnormal stimulation of B-cell proliferation. Furin protease cleaves off BAFF from the surface of the cells that secreted it. When BAFF goes into the blood

stream it recognizes the B cell receptors BCMA and TACI and in cooperation with CD40 activates the B cells. Decoy receptors for BAFF may alleviate the inflammation. Antinuclear antibodies, presumably due to deficiency of DNase1, which normally removes them, characterize the systemic lupus erythematosus (SLE, 4p16-p15.2). As a consequence, immune reactions afflict blood vessel walls, and joints and arthritis symptoms develop as well as cognitive impairment when NMDA reaches BBB, the blood-brain barrier (Kowal C et al 2004 Immunity 21:179). In lupus erythematosus, a molecular mimic of Asp/Glu-Trp-Asp/Glu-Tryr-Ser/Gly pentapeptide is antigenic to double-stranded DNA and it is also present in murine and human NMDA receptor NR2 subunits. As a result, neurons are subject to apoptosis and to this autoimmune disease. B cells may acquire autoreactivity during normal development by a process of somatic hypermutation and the mutation may entail selection of high affinity anti-DNA B cells (Wellmann U et al 2005 Proc Natl Acad Sci USA 102:9258).

A lupus-like disease in mouse develops as a consequence of increase in IL18, which in turn activates INF- γ . Interference with this path (vaccination) may have therapeutic value in humans (Bossù P et al 2003 Proc Natl Acad Sci USA 100:14181).

A major susceptibility gene was localized to 1q31. Earlier, a number of chromosome-1 sites were assumed to be involved but these, as well as the role of CD45, could not be rigorously confirmed (Johannesson B et al 2002 Am J Hum Genet 71:1060). In the human locus 1q41-q42 susceptibility alleles reside in various ethnic groups. An association between the Toll-like receptor regulating inflammatory responses and lupus appears well founded and nonsense mutation at TLR^{392STOP} protects against autoimmunity (Hawn TR et al 2005 Proc Natl Acad Sci USA 1032:10593). Another susceptibility locus was assigned to 12q24 (Nath SK et al 2004 Am J Hum Genet 74:73). The Fc γ RIIB antibody receptor may restore tolerance to lupus in susceptible animals (McGaha TL et al 2005 Science 307:590). Mutations in the interferon pathway (INF5) can increase the risk of lupus erythematosus (Graham RR et al 2006 Nature Genet 38:550). ▶autoimmune disease, ▶gene copy number, ▶von Willebrand disease, ▶toroid, ▶complement, ▶convertase, ▶HLA, ▶procaine anesthetics, ▶RoRNP, ▶p21, ▶B cell, ▶T cell, ▶dendritic cell, ▶TACI, ▶CD40, ▶CD45, ▶NMDA, ▶BBB, ▶decoy receptors, ▶antibody; Gray-McGuire C et al 2000 Am J Hum Genet 67:1460; Yasutomo K et al 2001 Nature Genet 28:313; DeGiorgio LA et al 2001 Nature Med 7:1189.

Luria-Bertani Medium: ▶LB

Luteinization: After ovulation the ovarian follicle is converted into a corpus luteum (yellow body). ▶corpus luteum, ▶Graafian follicle, ▶luteinizing hormone-releasing factor, ▶ovarian cancer

Luteinizing Hormone: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly:NH₂. ▶animal hormones

Luteinizing Hormone-Releasing Factor (LH-RF or LRF, gonadotropin-releasing factor): A hypothalamic neurohormone stimulating the secretion of pituitary hormones. It is involved in the control of mammalian fertility. When administered to mammals—including humans—it induces ovulation. ▶GnRHA, ▶in vitro fertilization, ▶ART, ▶corticotropin, ▶puberty precocious, ▶uterus; Latronico AC, Segaloff DL 1999 Am J Hum Genet 65:949.

Lutheran Blood Group: This blood group is so named after the first patient identified in 1945. The Lu(a⁻b⁻) phenotype is determined by either dominant or recessive alleles of the gene in human chromosome 19cen-q13, distinguishable by hereditary pattern and by serotype. The frequency of Lu(a) allele is about 0.04 and that of Lu(b) is about 0.96. The Lu phenotype may be caused by dominant inhibitors identified as mice antigens A3D8 and A1G3 under the control of a locus in human chromosome 11p. This 80-kDa antigen apparently has different epitopes on the same protein molecule. The Lu system appears to be identical to the Auberger blood group. ▶blood groups, ▶epitope

Lux: ▶luciferase genes of bacteria, ▶LUC

LUX: A unit of illumination; 1 Lux = one lumen/m². ▶lambert

Luxuriance: The hybrid vigor displayed by the somatic tissues of hybrids between different species or genera that are sterile or have reduced fertility. ▶hybrid vigor

Luxury Genes: These genes are not involved in functions indispensable for the viability of a cell and common basic function, but rather only in differentiated, special cells.

Luzula purpurea (Juncaceae, n = 3): *Luzula purpurea* and other related plant species have holocentric chromosomes and polyploid as well as aneuploid series. ▶holocentric, ▶polyploid, ▶aneuploid

LW Blood Group: Produces the rodent anti-Rhesus antibody. ▶Rh blood group

LXR: A group of liver hormone receptors regulating cholesterol metabolism. ▶cholesterol

Lyase: An enzyme that catalyzes additions or the removal of double bonds.

Lychnis: A dioecious plant species. *Melandrium* and *Silene* are synonyms. Male karyotype is shown in Figure L54 (After Warmke HE 1946 Am J Bot 33:648).

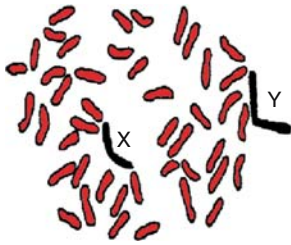


Figure L54. *Lychnis*

Lycopene ($C_{40}H_{56}$): A carotenoid pigment. ▶carotenoids

Lyell Syndrome (toxic epidermal necrolysis, TEN): An adverse reaction to drugs due to lytically active FAS ligand causing apoptosis. ▶FAS

LYL: A lymphoid leukemia oncogene, encoded in human chromosome 19p13.

Lymantria: *Lymantria dispar*, $2n = 62$. It has been used for studies on sex determination. The heterogametic female (see Fig. L55) and the homogametic male (see Fig. L52) have different colors. The intersex forms may resemble more the male than the female and frequently display light-color sectors. Its English name is gypsy moth. *Lymantria* is an obnoxious invader in the US and causes serious damage and extermination of deciduous trees (Johnson DM et al 2006 Nature [Lond] 444:361). ▶intersex

Lyme Disease (borreliosis): ▶*Borrelia*, ▶*Ixodoidea*

Lymph A transparent fluid filtered through the capillary blood vessels from blood.

Lymph Glands: (yellowish or sometimes pinkish): Lymph glands are hematopoietic (blood-forming) organs of insects (*Drosophila*). (See Mandal L et al 2007 Nature [Lond] 446:320; Krzemien J et al 2007 Nature [Lond] 446:325).

Lymph Nodes: Lymph nodes are small (1 to 25 mm) nodules in the body where lymphatic vessels, lymphocytes, and antigen-presenting cells accumulate.

They play defensive roles by removing toxic and infectious agents. ▶lymph, ▶lymphocytes, ▶lymphoma, ▶Hodgkin's disease, ▶thymus, ▶T cell, ▶T cell receptor, ▶antigen-presenting cell

Lymphedema Distichiasis (FOXC2, Meige disease, 16q24.3): The failure of the lymphnodes to drain properly. Symptoms include double eyelashes that turn against the eyeball. Translocations involving site 16q24 also cause the disease. Another lymphedema (Milroy disease) involving the VEGFR-3 gene was mapped to chromosome 5q35.3. Hypotrichosis-lymphedema-telangiectasia is caused by a defect in the SOX18 transcription factor, encoded at 20q13 (Irrthum A et al 2003 Am J Hum Genet 72:1470). ▶eyelashes, ▶long, ▶distichiasis, ▶VEGF, ▶hypotrichosis, ▶telangiectasia, ▶SOX, ▶forkhead; Finegold DN et al 2001 Hum Mol Genet 10:1185.

Lymphedema, Hereditary (Milroy disease, 5q35.3): Hereditary lymphedema is dominant with incomplete penetrance; In general, it displays edema below the waist. The basic defect is in the epidermal growth factor receptor/receptor tyrosine kinase or VEGFR-3. ▶EGFR, ▶receptor tyrosine kinase, ▶VEGF

Lymphoblast: A lymphocyte progenitor, which, after enlargement, divides about four times daily eventually forming a clone of about 1,000 lymphocytes. ▶lymphocytes

Lymphoblastoid Cell: A B cell infected with the Epstein-Barr virus. ▶Epstein-Barr virus

Lymphochips: Microarrays facilitating the recognition of genes that are turned on/off in the process of the development of the immune reaction. ▶microarray hybridization

Lymphocyte Homing: The immune processes are systematically distributed through movement of lymphocytes from their origin (bone marrow for B cells and thymus and bone marrow for T cells) to lymph nodes, glands, tonsils, and spleen. In these organs, microbial antigens are deposited and the naïve B and T cells are exposed to them. That propels their differentiation into memory cells and effector cells, respectively. These differentiated cells then home in on the bone marrow (B cells) or to extralymphoid effector sites (T cells). These are



Figure L55. *Lymantria* larva and imagos; the male is at right

complicated processes and may go through multiple and reversible substeps. The passage from the blood vessel requires an interaction of the lymphocyte receptors with vascular ligands, activation by G-protein-linked receptors and finally passage through the vessel wall (diapedesis). After stepping out and entering special tissues they home in on, e.g., B cell follicles or T zones during memory cell formation in germinal centers. They also seek sites of inflammation. In each of these niches lymphocytes are subject to various regulatory forces by attaching, e.g., to TGF β -regulated integrin that directs them to intraepithelial sites by attachment to cadherin. They exchange signals with antigen presenting cells, surface receptors, chemoattractant receptors, immunoglobulins, antigen receptors, chemokines, etc. Probably the RHO homolog of the RAS oncogene plays a central role in the signaling paths and the antigens also affect trafficking. There is also some sort of competition and orderly assignment of the various lymphocytes to specific sites. ▶memory immunological, ▶germinal center, ▶TGF β , ▶integrin, ▶cadherin, ▶RHO, ▶antigen presenting cell, ▶chemokines, ▶immunoglobulins, ▶antigen, ▶signal transduction, ▶receptors, ▶ligand; Wiedle G et al 2001 Crit Rev Clin Lab Sci 38:1.

Lymphocytes: Lymphocytes are cells produced in fetal hepatocytes and in adults by bone marrow (see Fig. L56). They may differentiate into T lymphocytes

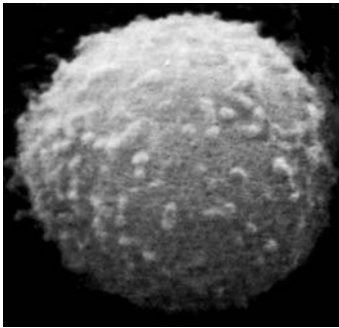


Figure L56. T Lymphocyte

and B lymphocytes. In the thymus, the T cell receptor immunoglobulins undergo rearrangement and the terminal nucleotidyl transferase generates additional diversity. The T lymphocytes are involved in cell-mediated immunity; the B cells are responsible for the humoral antibodies. During the development of B cells the secreted and the membrane-bound immunoglobulin (Ig) undergoes a series of events. The B cell antigen receptor (BCR) is formed by complexing a membrane Ig with the heterodimer of Ig- α and Ig- β (pro-B stage). The complex now contains an extracellular Ig-like domain, a transmembrane

domain and a short cytoplasmic domain. The signal transducing part of the receptor contains a two-tyrosine motif in the α and β cytoplasmic domains. When the hematopoietic stem cell of the bone marrow becomes committed to B cell development the Ig gene undergoes a series of rearrangements. In the first step a D_H (diversity heavy chain; ▶immunoglobulins) joins a J_H (junction heavy chain) gene. The one of the V_H (variable heavy) is attached to the D_H J_H segment in order to form a functional heavy chain. Under normal conditions a functional μ heavy chain is expressed (pre-BI stage). This transition from pro-B to pre-BI constitutes an important checkpoint, contingent of the formation of Ig- β . The next step (pre-BII) is reached when a temporary light chain immunoglobulin attaches to the VpreBI globulin. After this, the Ig- κ chain undergoes a rearrangement and it joins a V-J _{κ} (variable kappa light chain gene) and the development thus arrives to the Immature B Stage. The λ 5-VpreB chain is replaced by a κ - μ -BCR (B Cell Receptor) complex and the so formed Mature B Cell emerges from the bone marrow in the presence of a functional Ig- α cytoplasmic domain. This B cell is then activated when it comes into contact with an antigen and secretes Ig. This requires the Ig- α cytoplasmic domain and the expression of a cytoplasmic (Btk) tyrosine kinase. For T cell-dependent antigen response Ig- α and Btk are not needed. The tumor infiltrating lymphocytes have potential use in cancer therapy. The differentiation and maintenance of the lymphocytes requires interleukine-7 (IL-7) and its receptor (IL-7R). The transcription factor Ikaros (a Zn-finger protein) is specific for lymphoid cell differentiation. This protein has binding sites in several other genes involved in lymphocyte development such as CD3-T cell receptor, CD4, CD2, terminal nucleotidyl transferase, interleukine-2R α , and NF- κ B. In young adult mice, $2-4 \times 10^7$ new T cells are produced daily by 100 to 200 million thymocytes but only a couple percent enter the T cell pool. The rest are disposed of by apoptosis. The survivors differentiate into CD4⁺CD8⁺ T cells and subsequently to single-positive CD4⁺ MHC Class-II restricted and CD8⁺ MHC Class-I-restricted T cells in the peripheral T cell pool. Selective elimination of the inadequately activated T cell continues. The retained T cells undergo IL-2 stimulated clonal expansion after antigenic challenge. After the challenge some T cells die and others become memory T cells. ▶T cells, ▶T_H, ▶B cell, ▶TCR, ▶ $\alpha\beta$ T cells, ▶immune system, ▶immunoglobulins, ▶antibody, ▶TIL, ▶memory immunological, ▶lymphocyte homing, ▶monocyte, ▶germinal centers, ▶Cd3, ▶CD4, ▶CD8, ▶NF- κ B, ▶dendritic cell, ▶macrophage, ▶monocyte, ▶neutrophil, ▶basophil, ▶eosinophils, ▶immunoglobulins; Israels LG, Israels ED 1999 Stem Cells 17:180.

Lymphoedema: A dominant human chromosome 5q mutation in VEGFR-3 disabling normal lymphatic functions. ►vascular endothelial growth factor

Lymphohistiocytosis, Hemophagocytotic, Familial (HPLH2, 10q22; HPLH1, 9q; HPLH3, 17q25.1; HJCD, 11q25; FHL 6q24): A highly heterogeneous disease involving various anomalies of the immune system. (See zur Stadt U et al 2005 Human Mol Genet 14:827).

Lymphoid Organs: The primary ones are the thymus and bone marrow; the secondary ones are the lymph nodes, spleen, tonsils, mucosal lymphoid tissues, and Peyer's patches. Antigens entering the body are ferried to these secondary lymphoid organs. After prospecting, B and T lymphocytes detect the presence of antigens at these sites wherein antigen-specific B and T cells move in on the cues represented by chemokines. ►chemokines

Lymphoid Protein Tyrosine Phosphatase, Non-Receptor (1p13, 1q32.1): Non-receptor lymphoid protein tyrosine phosphatase is a negative regulator of T lymphocyte activation. Some mutant alleles play roles in autoimmune diseases such as diabetes, Graves disease, and Crohn's disease, and are regarded as general susceptibility factors in autoimmunity. ►autoimmune disease

Lymphoid Protein Tyrosine Phosphatase, Receptor-Type: (CD45, 1q31-q32): The receptor-type lymphoid protein tyrosine phosphatase is essential for the activation of T and B cells. Its deficiency may affect the expression of several diseases involving the immune system. ►CD45

Lymphokines: Proteins secreted by lymphocytes in response to specific antigens. They are involved in multiple ways in serological defense mechanisms of the body and in differentiation. Interferons (IF), interleukins (IL), granulocyte colony stimulating factors (G-CSF), granulocyte-macrophage colony stimulating factors (GM-CSF), macrophage activity factor (MAF or IFN gamma), T cell replicating factor (TRF), migration inhibition factor (MIF), and tumor necrosis factor (TNF) belong to this large group. ►immune system, ►cytokines, ►chemokines, ►interleukins, ►interferons, ►tumor necrosis factor, ►cytotoxic T cells, ►rel; Webb DR et al 1988 Molecular Basis of Lymphokine Action, Humana, Totowa, New Jersey.

Lymphoma: Cancer of the lymphocytes (leukemia); a neoplasia of lymphoid tissues. In follicular B-cell lymphoma, because of a chromosome 18 translocation, the BCL-2 gene expression is aberrant and as a consequence apoptosis is reduced. DNA ligase deficiency may cause it. ►Chédiak-Higashi

syndrome, ►lymphoblastic lymphoma, ►leukemia, ►anaplastic lymphoma, ►Mantle cell lymphoma, ►non-Hodgkin lymphoma, ►diffuse large B-cell lymphoma, ►MALT, ►translin, ►Burkitt's lymphoma, ►Duncan syndrome, ►Hodgkin's disease; Staudt LM 2002 Annu Rev Med 53:303.

Lymphopenia: A recessive deficiency of lymphocytes (cytokines); an autoimmune anemia. ►lymphocyte, ►autoimmune disease, ►cytokines, ►immunodeficiency, ►sphingosine SIR/SIRT

Lymphopoiesis (development of lymphocytes): A continuous process beginning at hematopoietic stem cells. (See Gounari F et al 2002 Nature Immunol 3:489).

Lymphoproliferative Diseases, X-linked (immunoproliferative disease, Xp25, XLP): A protein domain SH2D1A defect may be involved in X-linked lymphoproliferative diseases. This protein was also called SAP (for association with SLAM [signaling lymphocyte activation molecule, 1q23]) and inhibits SLAM signaling. Deficiency of X-linked inhibitor of apoptosis (XIAP, Xq25) is a major cause of the disease (Rigaud S et al 2006 Nature [Lond] 444:110). ►Epstein-Barr virus, ►FAS, ►SH2, ►SAP, ►SLAM, ►Canale-Smith syndrome, ►Duncan syndrome; Morra M et al 2001 Annu Rev Immunol 19:657; CzarMJ et al 2001 Proc Natl Acad Sci USA 98:7449.

Lymphotactin: C type cytokine, i.e., lacking two of the four cystin residues characteristic of chemokines. Lymphotactin is expressed in CD4⁺ T cells and CD4⁺ and CD8⁺ T cell receptor $\alpha\beta^+$ thymocytes. It has no chemotactic activity for monocytes and neutrophils. ►blood, ►lymphocytes, ►monocytes, ►cytokines, ►chemokines, ►T cells; Ju DW et al 2000 Gene Ther 7(4):329; Cerdan C et al 2001 Blood 97:2205.

Lymphotoxins: Lymphotoxins are forms of lymphokines of the tumor necrosis factor family that cause the lysis of some cells, e.g., cultured fibroblasts. They are required for growth, differentiation, and regulation of the immune system. They are encoded within the human HLA gene cluster. Lymphotoxin- α secretion, regulated by galectin-2 (galactose-binding lectin), and may affect myocardial infarction. ►lymphokines, ►HLA, ►TNF, ►immune system, ►ectodermal dysplasia; Yin L et al 2001 Science 291:2162

LYN: Tyrosine protein kinase of the SRC family involved in the differentiation of B lymphocytes. In the nervous system, LYN is associated with the AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor. AMPA is a ligand-gated cation channel, which mediates the fast component of the

excitatory post-synaptic currents. It is also a cell-surface signal transducer. LYN is activated by Ca^{2+} and Na^{+} influx and it activates the MAPK signal pathway. ▶SRC, ▶Csk, ▶B lymphocyte receptor, ▶signal transduction, ▶ion channels, ▶BTK; Luciano F et al 2001 *Oncogene* 20:4935.

Lynch Cancer Families: Groups of dominant genes responsible for the development of certain cancer syndromes such as endometrial cancer, adenocarcinoma of the colon and others. The instability may be caused by defects of the genetic repair system. ▶colorectal cancer, ▶Li-Fraumeni syndrome

Lyon Hypothesis: Postulates that in mammalian cells with more than one X chromosome, usually all but one are heteropycnotic (highly condensed and thus dark-stained at all stages) and form $n-1$ Barr bodies. The heteropycnosis may not affect the entire length of the chromosome equally. Mary Lyon, a British geneticist, suggested that the frequently observed mosaicism in these animals is the phenotypic consequence of chromosomal behavior. The heteropycnotic chromosomes carry their genes in an inactivated state (possibly key nucleotides are methylated) and depending on which allele of a heterozygote is expressed, sectorial mosaicism is displayed. In order to carry out the inactivating switch the X chromosome must have an intact inactivation center. During development the X chromosomes may switch between their inactive-active states. These decisions are not made entirely by the X chromosome (s) because in human triploids with XXY constitution both X chromosomes remain active. A typical example is the tortoiseshell cat color that is observed almost exclusively in females heterozygous of yellow-black fur color. The exceptional (less than 1/500) tortoiseshell male cats are of XXY constitution (Klinefelter syndrome). A similar genetic heterogeneity has also been observed in humans when in heterozygous females two classes of lymphocytes were observed, one with normal and the other without testosterone binding capacity. The LINE (L1) elements appear to regulate the inactivation of the mammalian X chromosome (Bailey JA et al 2000 *Proc Natl Acad Sci USA* 97:6634) and may spread the lyonization along the X chromosome or even to translocated autosomal segments fused to the X chromosome. ▶Barr body, ▶heteropycnosis, ▶methylation of DNA, ▶regulation of gene activity, ▶lyonization, ▶dosage effect, ▶LINE; McBurney MW 1988 *Bioassays* 9:85.

Lyonization: Variegation in mammalian females as predicted by the Lyon hypothesis. In an XX mammalian female one of the X chromosomes remains in a condensed state (see Fig. L57). It



Figure L57. Lyonization in rodent

replicates its DNA asynchronously and its genes are not transcribed after the blastocyst stage, 3.5–4.5 dpc in the trophectoderm and 5.5–6.5 dpc in the embryo cell initials of the female mouse. In the germline, the inactive X is reactivated at the time of beginning of meiosis (12.5–13.5 dpc; the average time of gestation in the mouse is 19 days). In the male, X-chromosomal inactivation is limited to the duration of meiosis, presumably to restrict deleterious recombination with the Y chromosome. After fertilization, and before implantation, inactivation recurs in the female. The inactive X chromosome moves to the perinuclear position during S phase where it is silenced (Zhang L-F et al 2007 *Cell* 129:693). The other X chromosome displays a more open structure and its gene content is expressed. The majority of the genes in the inactive X replicate late but those which escape inactivation (>20) replicate synchronously with the active X chromosome. One of the X chromosomes is selected for inactivation by a chromosomal locus, Xic (X-chromosome inactivating center, Xq13). This Xic locus (450 kb) is responsible for counting (encoded within the 6th exon) the number of X chromosomes to be inactivated. In case of more than 2 X chromosomes only one remains active normally. In addition, the Xic must be in cis position to the genes to come under its influence (spreading effect). Thus Xic also selects the chromosome to be inactivated (choice function). If the XIC locus is lost after inactivation has been initiated, the inactive state is maintained. There is another functional site within the XIC locus, Xce (X control element). Xce/Xce homozygotes undergo normal, random inactivation. In Xce heterozygotes there is a higher chance that the chromosome remains active if it carries a strong Xce allele. The Xce locus seems to control non-random (skewed) inactivation. In monozygotic human twins skewed distribution (non-concordance) of inactivation was observed. Skewing may also be due by selection against mutant alleles or chromosomal abnormalities. The product of XIC is XIST (X inactive specific transcript) that is transcribed from the 15-kb site within XIC in only the inactive X chromosome after inactivation has taken

place. In XIST/Xist heterozygotes there is a large RNA transcript (ca. 15 kb) in the nucleus, apparently associated with the inactive X, and it cannot be translated. Thus, it appears that RNA mediates the regulation. During early embryogenesis Xist expression precedes the inactivation of the X chromosome and in XY males it is expressed in the male germ tissues alone and only before meiosis. A protein (not translated from the XIST transcript) is preferentially associated with the inactive X chromosome. This protein called mH2A (macroH2A) bears resemblance in its N-terminal third to H2A histone but the rest of the molecule is different from any of the histones.

The mH2A protein in females accumulates in dense macrochromatin bodies in proportion to the number of inactive X chromosomes. In marsupials, the inactive X chromosome is the paternally transmitted one. Similar observations were also made in the extraembryonic endoderm cells of some rodents and to some extent in humans. About 20 human X-chromosomal short arm genes (especially in the vicinity of the pseudoautosomal region) escape inactivation in a discontinuous manner, e.g., Xg blood group, the closely linked steroid sulfatase locus (ichthyosis) and the tissue inhibitor of metalloproteinases (TIMP1). This region of the human X chromosome appears to be a more recent evolutionary addition (XAR) to the ancestral X conserved region (XCR) and the coordination between the two has not been completed yet. (The marsupials do not have the XAR.) At the tip of the long arm of the human X there is a very short pseudoautosomal stretch that carries one escapee and one inactivated gene. In the inactivation, differential methylation between the active X and the inactive X chromosome is implicated although overall methylation appears to be the same. In the inactive X chromosome, CpG islands in 5' region are mostly methylated whereas in the active ones they are not. The inactive X-chromosomal regions are hypoacetylated at lysine residues of the core histones whereas genes escaping inactivation are hyperacetylated. Aging may reactivate some genes. Microarray hybridization applied to cloned X-chromosomal fragments representing 1,317 genes indicated that rather than silenced, 53 genes displayed elevated activity in the presence of multiple X chromosomes and many just escaped inactivation (Sudbrak R et al 2001 Hum Mol Genet 10:77). The expression is variable for about 10% of genes and 15% escape inactivation (Carrel L, Willard HF 2005 Nature [Lond] 434:400). Although differential inactivation is a common property of X-chromosomal genes, asynchronous replication has been observed between homologous autosomes too, in mice (Singh N et al 2003 Nature Genet 33:339). X chromosomal inactivation is somehow related to imprinting. A

deleted Xist allele in the maternal X chromosome does not affect the viability even of the adults but the Xist allele deleted from the paternal X chromosome prevents survival of the embryo after implantation.

In mouse the presence of two maternal X chromosomes (maternal disomy) is very detrimental to the development of the embryo. In contrast, in humans, maternal X disomy is not detrimental or even trisomy (XXX) or the Klinefelter syndrome (XXY), irrespective of the origin of the Xs, are of the same viability. Although X-chromosomal inactivation occurs in all mammals, the pattern of inactivation varies. The X chromosome of the mouse is acrocentric and it is not covered with Xist RNA while the human X is submetacentric and has Xist. Nevertheless, the mouse and human genes display great homology. The microarray technologies may provide further insight into the factors subjected or involved in inactivation/reactivation. ▶Lyon hypothesis, ▶dosage effect, ▶dosage compensation, ▶ectodermal dysplasia anhidrotic, ▶Wiskott-Aldrich syndrome, ▶Xg, ▶ichthyosis, ▶pseudoautosomal, ▶Barr body, ▶Xic, ▶Xist, ▶Tsix, ▶dpc, ▶imprinting, ▶methylation of DNA, ▶histones, ▶metalloproteinases, ▶tortoise shell, ▶calico; Heard E et al 1997 Annu Rev Genet 31:571; Avner P, Heard E 2001 Nature Rev Genet 2:59; Maxfield Boumil R, Lee JT 2001 Hum Mol Genet 10:2225; Mak W et al 2004 Science 303:666, illustration by courtesy Lyon MF 1963 Genet Res 4:93.

Lyophilization: ▶freeze drying

Lysate: When a cell is lysed (dissolved) its contents are released; the lysis of bacterial cells may produce bacteriophage particles as lysate. ▶lysogeny

Lysenkoism: T.D. Lysenko (1898–1976) infamously presided over one of the greatest scandals in cultural history. Beginning in the 1930s, and culminating with his almost complete victory in 1948, he destroyed genetics and most of biology in the erstwhile Soviet Union. His group of followers from non-scientific and often dubious backgrounds had an unfortunate influence on biology in the Soviet Union and other countries in her political interest sphere, almost totally destroying scientific study. The Lysenkoists rejected the Mendelian inheritance, cytogenetics, biochemical genetics and statistics as “capitalist fraud”. The movement traced its origin to Mitchurin, an uneducated railwayman, who successfully practiced empirical plant breeding and attempted to interpret his observations without being familiar with scientific principles and facts. The Lysenkoists denied the existence of genes, the role of “hard heredity”; rather, they claimed the inheritance of the phenotype and continuous change of heredity under

the influence of nutrition, temperature, day-length and other environmental conditions. This was a revival of the ancient myths of pangenesis, Lamarckism, inheritance of acquired characters, directed genetic change by agrotechnical methods (fertilizers, irrigation), grafting, vernalization (yarowisation), and blood transfusion. Although by themselves these ideas were appalling, the major problem was that Lysenkoism became a political doctrine of the state, imposed on and substituted for all scientific activities in biology, totally subjugating agriculture and making inroads even into medicine. Marx and Engels were supporters of Lamarckism in the hope that the future of the human race may be improved by these doctrines. The Soviet dictator Stalin embraced Lysenkoist ideas as they promised instant increases in agricultural productivity by the application of vernalization, summer culture of potatoes, species transformation, graft hybridization, supplementary pollination, etc., during a period of famines, caused by the senseless social experimentation of the Soviet bureaucracy. The promised results failed to materialize and agricultural productivity further declined, partly because of the application of Lysenkoism. The Lysenkoists then attributed these failures to sabotage. Therefore, after 1948, Stalin granted virtually unlimited power to Lysenko to purge the universities and research institutes from his and the "people's enemies." Thousands of scientists actually lost their lives either by execution or imprisonment. Genetics had enjoyed reasonably good support before 1948, but thereafter even world-renowned scientists of the Soviet Union were persecuted, forced underground or physically eliminated. Resurrection of genetics in Russia would come only after Stalin's death. ► **Lamarckism**, ► **Soviet genetics**, ► **Acquired characters**, ► **pangenesis**, ► **vernalization**, ► **directed mutation**, ► **hard heredity**; Medvedev ZA 1969 *Rise and Fall of TD Lysenko*, Columbia University Press, New York.

Lysergic Acid: A psychomimetic alkaloid-derivative. ► **ergot**, ► **psychomimetic**

Lysidine: A cytidine with a lysine residue qualifying it for recognition of the AUA codon by the tRNA (Ikeuchi Y et al 2005 *Mol Cell* 19235). ► **tRNA**, ► **aminoacylation**, ► **cytidine**, ► **genetic code**

Lysin: A complement-dependent lytic protein such as hemolysin, bacteriolysin and the sperm lysin, which creates a hole in the egg envelope for penetration. Mutation in lysin may lead to reproductive incompatibility and speciation. ► **complement**, ► **antibody**, ► **speciation**

Lysine Biosynthesis ($\text{NH}_2[\text{CH}_2]_4\text{CH}[\text{NH}_2]\text{COOH}$): Some fungi and algae synthesize the positively charged amino acid, lysine, from α -amino adipic

acid ($\text{HO}_2\text{CCH}[\text{NH}_2]\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$). Bacteria, some fungi and higher plants make lysine from ($\text{HOOCCH}(\text{NH}_2)(\text{CH}_2)_3\text{CH}(\text{NH}_2)\text{COOH}$), diamino-pimelic acid. Aspartate semialdehyde is also a precursor of lysine. For mammals it is an essential amino acid and they rely on the diet to meet their needs. Some food or feed may have very low levels of this amino acid to be able to meet the requirements and it results in human malnutrition or low weight. Some mutant plants, e.g., high lysine maize may be used to avoid nutritional problems. The degradation of lysine may take place in a number of different ways. A common intermediate is α -ketoglutarate. Mono-, di-, and trimethylation of histones are important for epigenetic regulation of gene expression and protein function (Simon MD et al 2007 *Cell* 128:1003). ► **high-lysine corn**, ► **Kwashiorkor**, ► **lysine intolerance**, ► **lysine malabsorption**, ► **hyperlysinemia**, ► **histones**; Galili G 2002 *Annu Rev Plant Biol* 53:27.

Lysine Intolerance (lysinuric protein intolerance, LPI): A recessive human disorder (14q11.2) resulting in periodic vomiting, growth retardation, muscle hypotonia, hepatosplenomegaly (liver and spleen enlargement) and possibly coma based on a defect in the membrane transporter (γ^+ LAT-1, also named SLC [solute carrier]) of basic (cationic) amino acids. ► **lysine biosynthesis**, ► **dibasic aminoaciduria**

Lysine Malabsorption: Lysine malabsorption causes excessive amounts of lysine in the urine and low levels in the serum due to a recessive autosomal mutation. ► **lysine biosynthesis**

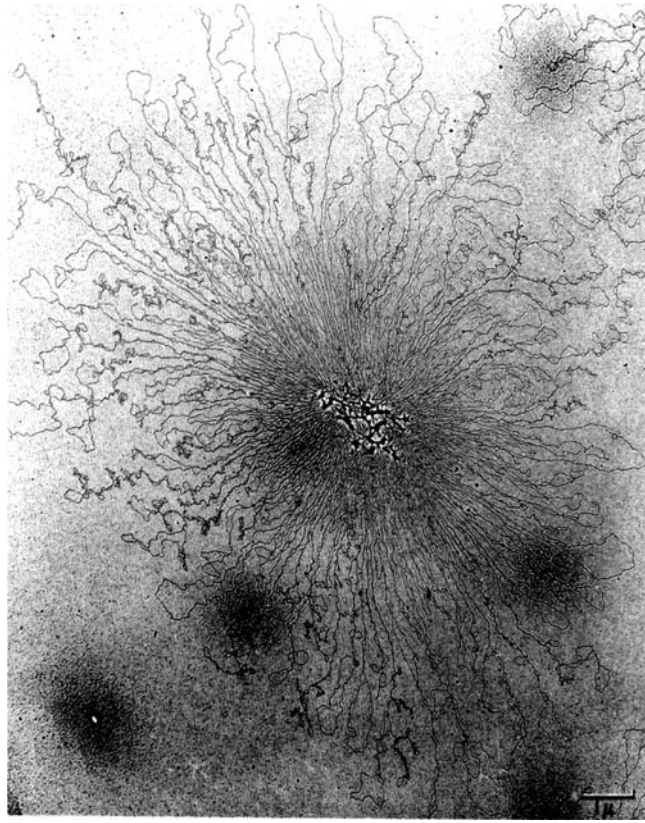
Lysinuria (lysinuric protein): ► **lysine intolerance**

Lysis: The disruption of the (bacterial) cell (before the release of a virus or plasmid from a cell) by spontaneous or any other means such as exposure to a lysozyme, by boiling or alkaline treatment, or the dissolution of eukaryotic cells or cellular organelles by a lysozyme or detergents (see Fig. L58). ► **lysis inhibition**, ► **rapid lysis**, in the Fig. L58: spread of the folded *E. coli* chromosome by courtesy of Dr. Ruth Kavenoff, Brian C Bowen 1977 *Stadler Symp.* 9:159.

Lysis From Without: When too many phages (>20) attack a single bacterial cell, the bacterium may disintegrate because of the perforations suffered.

Lysis Inhibition (LIN): In case of shortage of bacterial cells (that the phage senses by some means) it postpones lysis for several hours and produces the maximal possible number of virions from that cell (e.g., 400 copies of T4). Lysis is controlled by the *r* genes of the phage. ► **rapid lysis**

Lysogen: A bacterium with phage integrated into its genome. In such a state the replication of the phage DNA is under the control of the host and the phage's own replication system is repressed (stable lysogen).



L

Figure L58. Lysis

Rarely does the suppression of the replication of the phage fail after insertion (abortive lysogeny) and the prophage not replicated and lost by dilution during subsequent divisions of the host. ▶[lambda phage](#); McAdams HH, Shapiro L 1995 Science 269:649; Kihara A et al 2001 J Biol Chem 276:13695.

Lysogenic Bacterium: Lysogenic bacterium can harbor temperate phage in an integrated state in the chromosome; after induction, phage particles can be formed and released. ▶[prophage](#), ▶[lysis](#)

Lysogenic Immunity: ▶[immunity in phage](#)

Lysogenic Repressor: Prevents the lysis of a lysogen. ▶[Lambda phage](#)

Lysogeny: The phage coexists with the bacterium as a prophage. ▶[symbionts hereditary](#); Bertani G 1958 Advances Virus Res 5:151.

Lysophosphatidic Acid (acyl/oleoyl-sn-glycero-3-phosphate): Derived from L- α -phosphatidic acid dioleoyl by the action of phospholipase A. It stimulates smooth muscle contraction and may affect blood pressure, cell adhesion, mitogenesis, etc. ▶[Pyk-2](#), ▶[endophilin](#); Metastasis, Hla T et al 2001 Science 294:1875.

Lysopin: An octopine type opine. ▶[opines](#)

Lysosomal Storage Diseases: These involve defects in lysosomal hydrolase enzymes (~ 50) and accumulation of the products of these hydrolases which affect, in a variable manner, various organs. The cumulative prevalence may be 5×10^{-4} . Glycosphingolipid storage diseases are the Tay-Sachs disease and Gaucher's disease, and according to a mouse model *N*-butyldeoxynojirimycin may hinder the accumulation of the substrate for β -hexosaminidase A and may alleviate the symptoms of the Tay-Sachs disease. Enzyme replacement or modified autologous bone marrow transplantation have been attempted in some types of these diseases. Gene transfer into hematopoietic cells or into the central nervous system using herpes or adenovirus vectors is also being studied. Some mucopolysaccharidoses may be treated by implantation of neo-organs, tissues of skin fibroblasts, secreting β -glucuronidase or α -L-iduronidase. ▶[mucopolipidoses](#), ▶[mucopolysaccharidoses](#), ▶[lipidoses](#), ▶[neuroaminidase deficiency](#), ▶[glycoprotein storage disease](#), ▶[glutamyl ribose-5-phosphate glycoproteinosis](#), ▶[lipase deficiency](#), ▶[Tay-Sachs disease](#), ▶[Gaucher's disease](#), ▶[Farber's disease](#), ▶[Fabry's disease](#), ▶[Hurler's syndrome](#), ▶[Hunter syndrome](#), ▶[Sanfilippo syndrome](#), ▶[Maroteaux-Lamy syndrome](#), ▶[Hermansky-Pudlak syndrome](#),

►Coffin-Lowry syndrome, ►Schindler disease, ►Kanzaki disease, ►Krabbe's leukodystrophy, ►Niemann-Pick disease, ►Metachromatic leukodystrophy, ►gangliosidoses, ►neuromuscular disease, ►mannosidosis, ►sialidosis, ►lysosomes, ►viral vectors, ►iduronic acid, ►glucuronic acid, ►miniorgan therapy, ►miniorgan, ►glutamyl ribose-5-phosphate glycoproteinosis; Desnick RJ, Schuchman EH 2002 *Nature Rev Genet* 3:954.

Lysosomes: Lysosomes are cytoplasmic organelles (in eukaryotes) containing hydrolytic enzymes. The digestion is either by phagocytosis-type mechanism or by selective ingestion and lysis of molecules. The latter type process requires Mg-ATP or molecular chaperones (heat shock proteins 73 and 70). The receptor for the uptake may be a 96-kDa (Lamp2) lysosomal membrane protein. Clathrin also plays a role in targeting proteins to the lysosomes by its KFERQ amino acid sequence motif. Within the lysosomes, in an acidic environment, inter- and intrachain disulfide bonds of the proteins are destroyed by the enzyme thioredoxin. ►lysosomal storage diseases, ►lysozymes, ►LDL receptor, ►clathrin, ►thioredoxin, ►endocytosis, ►phagocytosis, ►proteasomes, ►Wolman disease, ►Griscelli syndrome, ►Chédiak-Higashi syndrome, ►Hermanski-Pudlak syndrome; de Duve C, Wattiaux R 1996 *Annu Rev Physiol* 28:435; Dell'Angelica EC, Payne GS 2001 *Cell* 106:395.

Lysozymes: Enzymes capable of digesting bacterial cell walls; they have an important role in phage infection and liberation. The protein has served as a model for the study of protein folding, enzyme catalysis and mechanism, x-ray crystallography, enzyme evolution, and protein engineering. Certain

mutations in the enzyme render the protein amyloidogenic. The protein has been synthesized by chemical procedures (Durek T et al 2007 *Proc Natl Acad Sci USA* 104:4846). ►lysosomes

Lyst: ►Chédiak-Higashi syndrome

LYT Oncogene: Associated with lymphoblastic leukemias and non-Hodgkin type lymphomas when the gene (in human chromosome 10q24) is translocated to chromosome 14q11 or 14q32. Genes neighboring the 14q32 area (TNG1, TNG2) activate the T cell leukemia genes TCL1 and TCL2 located at 14q23.1. The normal product of LYT is similar to that of NFκB (NF-κB) products that are transcription factors. ►NFκB, ►REL oncogene, ►Hodgkin's disease, ►leukemias

Lytic: Capable of initiating and performing lysis.

Lytic Cycle: The life cycle of the phage involving infection, growth (one-step-growth) and lysis of the host to liberate the infectious phage particles. ►Lambda phage, ►one-step growth

Lytic Infection: ►lysis of bacteria

λZap: Carries the *lacIq* and tetracycline resistance in an F' plasmid. This vector is very effective for cDNA cloning. Its cloning capacity is about 10 kb at multiple cloning sites. In the presence of helper M13 or f1 helper phages, the cloned DNA is excised and placed into a small plasmid to facilitate the restriction mapping or sequencing of the insert. It is also suitable for making RNA transcripts of either strand using T3 or T7 transcriptases. L►lambda phage, ►F' plasmid, ►filamentous phages, ►cloning site, ►helper phage, ►restriction enzyme, ►sequencing of DNA

Historical vignette

Erwin Chargaff, the discoverer of the Chargaff Rule in 1949, six years before the "breaking of the DNA code" made the following statement (Istituto Lombardo [Rend. Sc.] 89:101, 1955). It must be remembered that his Rule was one of the cornerstones for the construction of the Watson & Crick model of the Double Helix.

"I believe, however, that while the nucleic acids, owing to the enormous number of possible sequential isomers, could contain enough code- scripts to provide a universe with information, attempts to break the communications code of the cell are doomed to failure at the present very incomplete stage of our knowledge. Unless we are able to separate and to discriminate, we may find ourselves in the position of a man who taps all the wires of a telephone system simultaneously. It is moreover, my impression that the present search for templates, in its extreme mechanomorphism, may well look childish in the future and that it may be wrong to consider the mechanisms through which inheritable characteristics are transmitted or those through which the cell repeats itself as proceeding in one direction only."

M

M: Abbreviation for mitosis or in statistics for the mean.

►mitosis, ►mean

M9 Bacterial Minimal Medium: 5 concentrated salt solution g/L H₂O, Na₂HPO₄ 7 H₂O 64, KH₂PO₄ 15, NaCl 2.5, NH₄Cl 5 → 200 µL, 1M MgSO₄ 2 mL, glucose 4 g, fill up to 1 L after any supplement (e.g., amino acids) added.

M Component: Same as paraprotein.

M Cytotype: ►hybrid dysgenesis

M13 Phage: ►bacteriophages, ►DNA sequencing

M Phase: Part of the cell cycle when the structure, movement and separation of chromosomes or chromatids are visible and the nuclear divisions are completed. ►mitosis and ►meiosis

M Phase Histone-1 Kinase: ►growth-associated kinase

M Phase Promoting Factor (MPF): Same as maturation promoting factor.

M RNA: ►Cowpea mosaic virus (CPMV)

M Virus: ►killer strains

Ma (*mille mille annus*): A million years. ►My

MAb: Monoclonal antibody.

Mab: Mouse antibody.

MAC: Mammalian artificial chromosome. ►HAC, ►HAEC, ►YAC, ►BAC, ►PAC, ►SATAC; Grimes B, Cooke H 1998 Hum Mol Genet 7:1635.

MAC-1: The oligonucleotide-binding heparin-like integrin on the surface of neutrophils, macrophages and killer cells (NK). ►integrin, ►heparin, ►killer cell, ►blood

Macaca: Rhesus Old World monkeys. ►cynomolgus, ►Rhesus, ►Cercopithecidae

Macadamia Nut (*Macadamia* spp): A delicious nut, $2n = 2x = 28$.

Macaloid: A clay colloid capable of adsorbing ribonuclease during disruption of cells and can be centrifugally removed from the RNA preparation after extraction by phenol. ►RNA extraction

Macaroni Wheat (hard wheat): *Triticum durum* ($2n = 4x = 28$) varieties containing the AB genome and taxonomically classified as a subgroup of *T. turgidum* (see Fig. M1). The endosperm of the commercially used varieties has more β -carotenes and therefore, the

milled products show yellowish color, desirable for pastas. It is milled to a grainier product (semolina) that favors cooking quality. The durum wheats have higher protein and mineral content than the soft wheats. The turgidum wheats, except the durums, are not used for food. ►Triticum

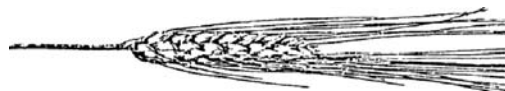


Figure M1. Macaroni wheat (*Triticum durum*)

Macrozyme: A pectinase enzyme of fungal origin; it is used for the preparation of plant protoplasts in connection with a cellulase. ►cellulase, ►protoplast

MACH (caspase 8): ►caspases

Machado-Joseph Syndrome (Azorean neurologic disease, spinocerebellar ataxia Type 3, MJD): It is a 14q32.1 chromosome dominant defect of the central nervous system involving ataxia, and other anomalies of motor control. In the gene locus, abnormally increased number of CAG repeats (from 13–36 in normal→61–84 in disease) occurs. If the long CAG repeats are translated into polyglutamine, cell death may result. The neurodegeneration may be suppressed by the chaperone HSP70. ►ataxia, ►muscular atrophy, ►fragile sites, ►trinucleotide repeats, ►spinocerebellar ataxia, ►RNAi, ►Josephin domain

Machine, Biological: A set of interacting components performing functional specialized role. ►network

Machine Learning: The study of computer algorithms in the interest of improving the study of scientific data. A machine can learn from experience or extract knowledge from a database. ►support vector machine; Mjolsness E, DeCoste D 2001 Science 293:2051.

Machine Reading: A new form of computer, searching the scientific literature is under development. Its eventual use, if all publishers consent and either the user or the owner(s) of the publications consent it may revolutionize data mining. It may link various concepts across the field of interest, e.g., disease and molecule(s) in an extremely efficient way. See for example: http://arrowsmith.psych.uic.edu/arrowsmith_uiuc/index.html.

Macroarray Analysis: Mutations of unknown function are grown in the presence of compounds that make them sensitive if they are defective, e.g., cell wall-binding calcofluor dyes (fluorescent brightener 28/Tinopal) detects a group of yeast mutations defective in cell wall biogenesis. Mutations in several different gene loci involved in microtubule functions

are sensitive to benomyl/benlate ($C_{14}H_{18}N_4O_3$, a fungicide and ascaricide). Genetic defects in sugar utilization may not grow on the non-fermentable glycerol if the mutation affected a certain domain of the protein product. Thus, this type of analysis can find NORFs involved in certain pathways. ▶genomics, ▶NORF, ▶microarray hybridization, ▶synexpression; <http://strc.herts.ac.uk/bio/BioArray/doc/BioArray.htm>.

Macrocephaly: A common feature of several mental retardations; it is classified as such when the circumference of the head of an individual exceeds by more than 2 standard deviations the mean of the population. ▶microcephaly

Macroconidium: A large multinucleate conidium (see Fig. M2). ▶conidia, ▶microconidia, ▶fungal life cycle

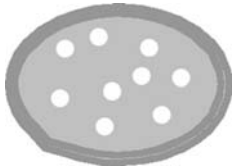


Figure M2. Macroconidium

M

Macrochromatin: ▶lyonization

Macrocycles: These are cyclic macromolecules or a portion of macromolecules or low-molecular weight synthetic compounds. A DNA library can be translated into small macrocycles. These can be targeted to proteins and subjected to selection and used for probing biological functions (Gartner ZJ et al 2004 Science 305:1601).

Macroencapsulation: ▶microencapsulation

Macroevolution: A major genomic alteration, which produced the taxonomic categories above the species level. ▶evolution, ▶microevolution

Macrogametophyte: A megaspore. ▶gametogenesis in plants

Macroglobulinemia (Waldenström syndrome): HLA-linked immunodeficiency resulting in increase in IgM in the blood, thrombosis, skin, nose and gastrointestinal bleeding. ▶immunodeficiency, ▶immunoglobulins, ▶multiple myeloma

Macroglossia: An abnormally large tongue; occurs in Down syndrome, Beckwith-Wiedemann syndrome and other hereditary disorders.

Macrolesion: Visible alterations in the chromosomes in genetic toxicology. ▶Gene-Tox

Macrolide: Type of antibiotic (including more than one keto and hydroxyl groups such as erythromycin, troleandomycin) associated with glycoses. *Streptomyces* bacteria produce these compounds that inhibit the 70S ribosomes by binding to the large (50S) subunit and interfering with peptidyl transferase. ▶antibiotics, ▶maytansinoids, ▶glycoses, ▶*Streptomyces*, ▶protein synthesis, ▶ribosome, ▶hysteresis; Retsema J, Fu W 2001 Int J Antimicrob Agents 18 Suppl 1:3; Berisio R et al 2003 Nature Struct Biol 10:366.

Macromere: A large blastomere. ▶blastomeres

Macromelic Dwarfism (Desbuquois syndrome): A skeletal and digital anomaly.

Macromolecule: Molecules with molecular weight of several thousands to several millions such as DNA, RNA, protein and other polymers; macromolecular structure database: <http://www.ebi.ac.uk/msd>.

Macromutation: A genetic alteration involving large, discrete phenotypic change.

Macronucleus: A larger type of polyploid nucleus in Protozoa. While inheritance is mediated through the small micronucleus, the macronucleus is directing metabolic functions by being transcriptionally active and the latter is responsible for the phenotype of the cells. After the internally eliminated sequences (IES) are removed from the micronuclear DNA, the leftover tracts are joined into macronuclear-destined sequences (MDS) to form the macronucleus. The macronuclear genome is derived at sexual reorganization during conjugation. This involves various chromosomal rearrangements. Also during conjugation, the germline sequences are transcribed to produce double-stranded RNA, which can guide specific DNA deletions in the macronuclei. This mechanism—resembling RNAi—provides a means for elimination of transposons and other invaders (Yao M-C et al 2003 Science 300:1581; Yao M-C, Chao J-L 2005 Annu Rev Genet 39:537). Macronuclear differentiation includes site-specific fragmentation of the micronuclear chromosomes. A 15-bp site that is required for fragmentation marks each fragmentation site. The two ends of the fragments form telomeres and thus become *autonomously replicating pieces* (ARP). Although normally inheritance is mediated by the micronucleus or the mitochondria, in some instance, macronuclear inheritance is detected. In this case, apparently the old macronucleus determines some rearrangements (deletions) in the new macronucleus. The participation of a short scanning RNA (sRNA) has been suggested. The macronucleus contains about 45 copies of the ~300 subchromosomal fragments except the rDNA, which is amplified by ca. 10,000 times. The

macronucleus divides by fission rather than by mitosis yet recombination between and within genes occurs. In the absence of recombination, groups of genes may stay together and this phenomenon is called *coassortment*. The genes of these polyploid macronuclei may sort out to pure form of the initial heterozygous state by a process of *phenotypic assortment*. On the basis of the assortments the genes may be mapped genetically. The macronuclei are formed by the fusion of two diploid micronuclei of the zygotes (see Fig. M3). ▶ *Paramecium*, ▶ *Tetrahymena*, ▶ chromosome diminution, ▶ protozoa, ▶ IES, ▶ RNAi; Katz LA 2001 Int J Syst Evol Microbiol 51(pt4): 1587.

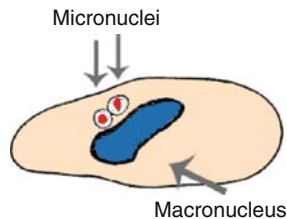


Figure M3. Paramecium

Macronutrient: Required in relatively large quantities by cells.

Macroorchidism: A condition of larger than normal testes. ▶ *fragile X*

Macropexophagy: The reduction of the number of peroxisomes in yeast grown on methanol after exposure to excessive amounts of glucose or ethanol. ▶ *micropexophagy*, ▶ *pexophagy*

Macrophage (Mφ): Phagocytic cell of mammals with accessory role in immunity. Macrophage cells are produced by the bone marrow stem cells as monocytes, which enter the blood stream, and within two days of circulation they enter the various tissues of the body and develop into macrophages. The macrophages may differ in shape but generally, they have single large round or indented nuclei, extended Golgi apparatus, lysosomes and vacuoles for the ample storage of digestive enzymes. The cell membrane is forming microvilli of various sizes, suited for phagocytosis (engulfing particles) and pinocytosis (uptake of fluid droplets) and thus are important as part of the cellular defense mechanism against foreign antigens, including even tumor antigens. The macrophages have a wide array of receptors, including the Fc, complement, carbohydrate, chemotactic peptide and extracellular matrix receptors. Some macrophages phagocytize apoptotic cells (see Fig. M4). Tumor necrosis factor (TNFα) moved from endosomes to the surface of the cells by VAMP facilitates its function in immunity

(Murray RZ et al 2005 Science 310:1492). Macrophages can mediate angiogenesis, cell migration and metastasis of cancer. Because they are genetically quite stable, they may be good targets of therapeutic intervention in some cancers (Condeelis J, Pollards JW 2006 Cell 124:263). ▶ *granulocytes*, ▶ *immune system*, ▶ *antibody*, ▶ *apoptosis*, ▶ *phagocytosis*, ▶ *TNF*, ▶ *VAMP*, ▶ *angiogenesis*, ▶ *metastasis*



Figure M4. Macrophage cell ingesting bacteria.

Macrophage Activity Factor: MAF is a lymphokine, identical to IFN-gamma. ▶ *lymphokine*, ▶ *interferon*

Macrophage Colony Stimulating Factor (M-CSF, 5q33.2-q333): M-CSF's receptor is the KIT oncogene. The receptor MCSFR is a protein tyrosine kinase. It promotes B cell proliferation with the assistance of IL-7. ▶ *FMS*, ▶ *KIT oncogene*, ▶ *colony stimulating factor*, ▶ *RAS*, ▶ *signal transduction*, ▶ *GM-CSF*, ▶ *G-CSF*, ▶ *IL-7*, ▶ *B cell*, ▶ *osteoclast*; ▶ *cherubism*, Csar XF et al 2001 J Biol Chem 276:26211.

Macrophage-Stimulating Protein (MSP): MSP is the 80-kDa serum protein stimulating responsiveness to chemoattractants in mice, that induces ingestion of complement-coated erythrocytes and inhibits nitric oxide synthase in endotoxin- or cytokine-stimulated macrophages. MSP is structurally homologous to hepatocyte growth factor, scatter factor (HGF-SF) but their targets are different. MSP has been located to human chromosome 3p21, a site frequently deleted in lung and renal carcinomas. ▶ *HGF-SF*, ▶ *Met*, ▶ *Ron*, ▶ *macrophage*, ▶ *scatter factor*; Stella MC et al 2001 Mol Biol Cell 12:1341.

Macrothrombocytopathy: ▶ *thrombocytopenia*, ▶ *giant platelet syndrome*

Macrospore: ▶ *megaspore*

Macula: A spot or thicker area, particularly on the retina, often colored. The macula of the eye contains photoreceptor cone cells, critical for color and other aspects of vision. ▶ *retina*, ▶ *choroidoretinal degeneration*, ▶ *macular degeneration*, ▶ *macular dystrophy*, ▶ *foveal dystrophy*

Macular Corneal Dystrophy (MCD, 16q22): MCD involves progressive recessive opacity of the cornea. Two types may be distinguished on the bases of absence (MCDI) and presence (MCDII) of keratan sulphate in the serum. A third type (CHST6) has

a defect involving corneal N-acetylglucosamine-6-sulphotransferase, which has overlapping mutations within the two other types. ► **Stargardt disease**, ► **hypotrichosis**

Macular Degeneration: Dominant-acting 6q25 deletion causing degeneration of the vitelline layer of the eye. The dominant 2p16 located disease Malattia Leventinese and Doyme honeycomb retinal dystrophy are similar, to some extent, to macular degeneration (see Fig. M5) and show drusen (bright speckles on the retina) due to mutation in the epidermal growth factor (EGF)—containing fibrillin-like extracellular matrix protein 1 (EFEMP1).

The Stargardt like STGD3 locus is in human chromosome 6q14. This gene is responsible for ELOVAL4 (elongation of very long chain fatty acid) and autosomal dominant macular dystrophy (see Fig. M6). These diseases manifest with some variations in expression and onset. Age-related macular degeneration (ARMD) causing yellow deposits (drusen) in the outer layer of the retinal epithelium is a very common cause of blindness in the West and it is controlled by several independent as well as by cooperative loci (Majewski J et al 2003 Am J Hum Genet 73:540). One major ARMD locus is at 15q21 (Iyengar SK et al 2004 Am J Hum Genet 74:20). Single amino acid substitution at site 402 (tyrosine→histidine) of the complement H gene accounts for the increased risk factor of ARMD from 4.6 (heterozygotes) to 7.4 (homozygotes) in the families (Klein RJ et al 2005 Science 308:385; Edwards AO et al 2005 Science 308:421). Age-related macular degeneration risk loci were confirmed in complement factor H (*CFH*, 1q32), and functionally related genes in chromosome 10q26.13 (Loc387715) and in genes C2 and BF in chromosome 6q21.3 (Maller J et al 2006 Nature Genet 38:1055; Li M et al Nature Genet 38:1049). Deletion of *CFHR1* and *CFHR3* is associated with lower risk of age-related macular degeneration (Hughes AE et al 2006 Nature Genet 38:1173; see corrigendum in Nature

Genet. 39:567). Polymorphism of the HTRA1 promoter (10q26) greatly increases the risk of developing ARMD (DeWan A et al 2006 Science 314:989).

Nornicotine, a metabolic product of cigarette smoke catalyzes retinal isomerization and is a promoting factor of ARMD (Brognan AP et al 2005 Proc Natl Acad Sci USA 102:10433). Oxidative stress appears to play a role in age-related macular degeneration and *Sod1*^{-/-} mouse appears to be workable model for studies (Imamura Y et al 2006 Proc Natl Acad Sci USA 103:11282). The ApoE E4 (apolipoprotein) allele increases susceptibility to ARMD as well as to Alzheimer disease (Malek G et al 2005 Proc Natl Acad Sci USA 102:11900).

Although several approaches are being suggested to control ARMD, only laser irradiation has limited success to curtail the choroidal neovascularization, the underlying cause of the visual impairment of wet macular degeneration. The newly formed blood vessels leak fluid and blood under the retina, form scar tissues and gradually destroy vision. One potential cure involves injecting antibodies against vascular endothelial growth factor A (VEGF-A) into the eye, a procedure under clinical trial. The ciliary margin of the retina contains active stem cells capable of self-renewal and provides possibilities for the cure of retinal disease (Coles B L K et al 2004 Proc Natl Acad Sci USA 101:15772). Currently RNAi technology is under clinical evaluation. The light-induced blindness, affecting the early microscopists such as August Weismann (1834–1914), has a molecular cause different from macular degeneration, and it is caused by degradation of rhodopsin (Lee S-J, Montell C 2004 Current Biol 14:2076). In June 2006, the US Federal Drug Administration approved the use of two new drugs for treatment. The (48 kDa) is a recombinant humanized monoclonal IgG1 kappa isotype antibody fragment produced in an *E. coli* expression system. It is not glycosylated and is used for intraocular injection. Bevacizumab (149 kDa) is also a recombinant humanized monoclonal IgG1 antibody



Figure M5. Macular degeneration. Left to right: Normal eye, age-related dry macular degeneration, macular degeneration with hemorrhage and fluid leakage. (The photographs are the courtesy of Dr. Timothy Holecamp and Ms. Jackie Bowman)



Figure M6. Peripheral vision in wet macular degeneration

produced in a Chinese-hamster-ovary mammalian-cell expression system, is glycosylated and used for intravenous infusion. Both the antibody fragment and the full-length antibody bind to, and inhibit all the biologically active forms of vascular endothelial growth factor (VEGF) A and are derived from the same mouse monoclonal antibody. Both drugs are promising, require repeated administration and are expensive (Steinbrook R 2006 *New England J Med* 355:1409). ▶*macula*, ▶*eye diseases*, ▶*RNAi*, ▶*stem cells*, ▶*vascular endothelial growth factor*, ▶*angiogenesis*, ▶*Stargardt disease*, ▶*complement*, ▶*monoclonal antibody*, ▶*immunoglobulins*, see Fig. 166; Marx J 2006 *Science* 311:1704; ARMD: de Jong PTVM 2006 *N Engl J Med* 355:1474; review: Rattner A, Nathans J 2006 *Nature Rev Neurosci* 7:860; Stone EM 2007 *Annu Rev Med* 58:477.

Macular Dystrophy: Autosomal recessive (8q24) and X-linked forms with symptoms similar to macular degeneration. The 1.4 Mb vitelline macular dystrophy (VMD2) gene (human chromosome 11q11-q13.1) encodes a 585 amino acid protein (bestrophin), named after the other name of the condition, Best's disease (autosomal dominant at 11q13). Its prevalence in the USA is about 3×10^{-5} . ▶*macula*, ▶*eye diseases*, ▶*Stargardt disease*, ▶*retinal dystrophy*

MAD: Multiwavelength anomalous dispersion analysis is a physical method for the determination of crystal structure of molecules.

Mad (*Mothers against decapentaplegic*): *Drosophila* gene controlling several developmental events in the fly. Its human homolog is called SMAD1 (Sma in *Caenorhabditis*). SMAD is a TGF (transforming growth factor)/BPM (bone-morphogenetic protein) cytokine family-regulated transcription factor involving

serine/threonine kinase receptors. The Mad family of proteins can be found in a wide range of organisms and upon dimerization with MAX they function as transcriptional repressors. The repressor function is correlated with the recruitment of the Sin3 protein binding to the Sin3-Mad interaction domain (Mad-Sid). SMAD is also called hMAD; MADR is its receptor. Mad is a component of the N-CoR/Sin3/RPD complex mediates the repression of certain classes of genes. ▶*tumor growth factor*, ▶*cytokines*, ▶*dpp*, ▶*serine/threonine kinase*, ▶*MYC*, ▶*RPD*, ▶*SMAD*, ▶*Dpp*, ▶*histone deacetylase*, ▶*decapentaplegic*

mad (*many abnormal discs*; 3–78.6): A homozygous disc and cell autonomous lethal, affecting several morphogenetic functions in *Drosophila*.

MAD2, MAD1 (mitotic arrest deficient, MAD2L1, 4q27; MAD2L2, 1p36): These are anaphase-regulating proteins, interacting with estrogen receptor- β . These are essential for normal mitosis checkpoints and their defect may lead to chromosome instability, cancer and embryonic lethality. Mad1 and Mad2 regulate the bipolar orientation of the chromosomes of yeast (Lee MS, Spencer FA 2004 *Proc Natl Acad Sci USA* 101:10655). The kinetochore localization of MADs requires the expression of Hec1/Ndc80p. The human Hec is highly expressed in cancer. Mad2 interacts with the kinetochores (Vink M et al 2006 *Current Biol* 16:755). ▶*anaphase*, ▶*cell cycle*, ▶*spindle*, ▶*BUB*; Skoufias DA et al 2001 *Proc Natl Acad Sci USA* 98:4492; Martin-Lluesma S et al 2002 *Science* 297:2267.

MADM: ▶*Mosaic Analysis with Double Marker*

Mad/Max: Sequence-specific heterodimeric transcriptional repressors.

Mad Cow Disease: ▶*encephalopathy*

MADS Box: A conserved motif of 56 residues in a DNA-binding protein of transcription factors involved in the regulation of *MCM1* (yeast mating type), *AG* (agamous homeotic gene and a root morphogenesis gene of *Arabidopsis*) *ARG80* (arginine regulator in yeast), *DEF A* (deficient-flower) mutation of *Antirrhinum* and SRF (serum response factor in mammals) regulating the expression of the c-fos protooncogene. The MADS box has amino terminal sequence specificity and carboxyl dimerization domains. In addition, the SRF recruits accessory proteins such as ELK1, SAP-1 and MCM1 and relies on MAT α 1 and MAT α 2, STE12 and SFF. MADS box genes control vernalization responses in cereals. (See separate entries, ▶*mating type determination in yeast*, ▶*vernalization*, ▶*MEF*; Jack T 2001 *Plant Mol Biol* 46:515).

Madumnal Allele: Derived from the female. ► [Padumnal allele](#)

MAF (macrophage activity factor): A lymphokine, an oncogene and a regulator of NF-E2 transcription factor. Heterodimers of Maf protooncogene family members promote the association with and the expression of NF-E2, whereas the homodimers are inhibitors of it. ► [macrophage](#), ► [lymphokine](#) 4, ► [oncogenes](#), ► [NF-E2](#), ► [homodimer](#), transcription factors; Swamy N et al 2001 J Cell Biochem 81:535.

MAF: Minor allele frequency.

MAFA (12p12–13): Inhibitory immune receptors on myeloid, mast and natural killer cells.

MAFFT-5: ► [CLUSTAL W](#), ► [interalign](#)

Magainin: ► [antimicrobial peptides](#)

MAGE: The melanoma antigens encoded by several genes and expressed in different tumors. In normal tissue, MAGE is limited to the testes and wound healing. In normal tissues, the MART-1/Melan-A differentiation antigen represents the melanoma lineage. The immunogenic epitopes for MAGE-1 are EADPTGHSY and SAYGEPRKL and for MAGE-3: EVDPIGHLV, FLYGPRALV, MEVDPIGHLV. Each has different HLA specificity. The MART-1 peptide epitopes are: AAGIGILTV, ILTVILGVL, and GIGILTVL. ► [antigen](#), ► [melanoma](#), ► [tumor antigen](#), ► [amino acid symbols in protein sequences](#), ► [Cancer-testis antigen](#); Otte M et al 2001 Cancer Res 61:6682.

MAGE (microarray and gene expression): ► [microarray hybridization](#); <http://www.mged.org/Workgroups/MAGE/mage.html>.

MAGI-2 (membrane-associated guanylate kinase inverted-2): A scaffold protein enhancer of PTEN. ► [PTEN](#); Vazquez F et al 2001 J Biol Chem 276:48627; Wu X et al 2000 Proc Natl Acad Sci USA 97:4233.

Magic Bullet: A specific monoclonal antibody is supposed to recognize only one type of cell surface antigen (e.g., one on a cancer cell) or growth factor receptors or differentiation antigens, and carries either the *Pseudomonas* exotoxin, or the diphtheria toxin, or ricin or maytansinoids (an extract of tropical shrubs or trees) or a radioactive element (such as ^{90}Y) capable of selectively unloading these harmful agents at the target cell and thus killing the cancer cell without much harm to any other cell. One such approach is to develop a special organ-homing peptide motif and combined with pro-apoptotic peptide domain. The homing peptide allows internalization only into the tumor cells where it unloads and disrupts the mitochondrial membranes and causes apoptosis (Ellerby HM et al 1999 Nature

Med 5:1032). Some of these new drugs (Rituximab) carry an anti-CD20 monoclonal antibody and radio-nuclides are effective against B-cell non-Hodgkin lymphoma (Milenic DE et al 2004 Nature Rev Drug Discov 3:488). CD22 and CD33 proteins can be effectively targeted by monoclonal antibodies in lymphomas with the associated CalichDMH (*N*-acetyl- γ -chaliceamicin dimethyl hydrazid), which is a potent DNA-binding antibiotic (DiJoseph JF et al 2004 Blood 103:1807). There may be some problems with monoclonal antibodies because the same tumor tissue may express different antigens (Scanlan MJ et al 2002 Immunol Revs 188:22). ► [ADEPT](#), ► [vascular targeting](#), ► [hybridoma](#), ► [monoclonal antibody](#), ► [receptor](#), ► [antigen](#), ► [diphtheria toxin](#), ► [ricin](#), ► [immunotoxin](#), ► [maytansinoid](#), ► [isotopes](#), ► [CD20](#), ► [CD22](#), ► [CD33](#); Frankel AE et al 2000 Clinical Cancer Rev 6:326.

Magic Number: The 64 triplet (4^3) combinations of the four nucleotides specify the 20 natural amino acids in all organisms. (See Gamov G, Yčas M 1955 Proc Natl Acad Sci USA 41:1011).

Magic Spots: These are pppGpp and ppGpp nucleotides that serve as effectors of the stringent control. RelA has apparently two catalytic sites, one for the synthesis of (p)ppGpp and another for hydrolysis. (p)ppGpp controls the elongation of DNA replication in response to the nutritional status of the cell (Wang JD et al 2007 Cell 128:865). ► [stringent control](#), ► [Rel oncogene](#); Schattenkerk C et al 1985 Nucleic Acids Res 13:3635.

Magnaporthe grisea: Rice blast pathogenic fungus with sequenced genome of 37,878,070 bp and with predicted 8,868 protein coding sequences in 7 chromosomes (See Rice, Dean RA et al 2005 Nature [Lond] 434:980). For efficient initiation of infection of rice, the formation of an appressorium, the conidial cells must die (Veneault-Fourray C et al 2006 Science 312:580). Insertion mutagenesis using *Agrobacterium* vector revealed 202 new pathogenicity loci in the fungus (Jeon J et al 2007 Nature Genet 39:561). ► [rice](#), ► [appressorium](#)

Magnesium Transport: The level of Mg^{2+} is important for many cellular processes such as ATP-dependent reactions and stabilization of membranes and ribosomes. A two-component system acting at the 5'-untranslated sequences regulates magnesium transporter (MgtA) protein synthesis. In *Salmonella* in low- Mg^{2+} environment, the PhoQ senses magnesium and promotes phosphorylation of the DNA-binding PhoP of the two-component regulatory system. Phosphorylated PhoP binds to the single stem-loop structure in the promoter of *MgtA* and

stimulates Mg^{2+} increase into the cytoplasm. When the level of Mg^{2+} reaches a higher level a two-loop structure forms in the 5'UTR and shuts off the transcription of the transporter (Cromie MJ et al 2006 Cell 125:71). ►two-component system

Magnetic Relaxation Switches: The nanometer-size colloidal metal particles may be coupled to affinity ligands and used as chemical sensors. Highly uniform magnetic nanoparticles can be covalently and stoichiometrically attached to oligonucleotides, nucleic acids, peptides, proteins, receptor ligands and antibodies. These nanomagnetic probes can be assembled also into larger units. These superparamagnetic scale particles can efficiently dephase the spins of the surrounding water protons and enhance spin-spin relaxation times. This technology can thus detect at miniaturized scale DNA–DNA, Protein–Protein, Protein–Small Ligand and enzyme reactions. Thus, e.g., non-sense DNA sequences, green fluorescent mRNA can be identified even in cell lysates. (See Perez JM et al 2002 Nature Biotechnol. 20:816).

Magnetic Resonance: ►nuclear magnetic resonance spectroscopy

Magnetic Targeting: Magnetic particles (ferrofluids) bound to mitoxanthrone (a cytostatic anthraquinone derivative) when injected into arteries can be concentrated in an external magnetic field aimed at a tumor (e.g., squamous cell carcinoma) can effectively cause remission without toxicity (Alexious C et al 2000 Cancer Res 60:6641). Similar procedure using superparamagnetic nanoparticles permit the tracking of progenitor cells (Lewin M et al 2000 Nature Biotechnol 18:410) or interaction of biomolecules within cells (Won J et al 2005 Science 309:121). ►magnetic relaxation switches

Magnetoreception: The response of organisms to the magnetic field of the Earth for behavior and orientation.

Magnetosome: Intracellular organelles in microbes that contain mineral crystals within a lipid membrane (see Fig. M7). The aquatic magnetotactic bacteria can follow the magnetic field lines of the earth. The magnetosomes may appear in rows. (See Bazylinski DA, Frankel RB 2004 Nature Rev Microbiol 2:217; Komelli A 2007 Annu Rev Biochem 76:351).

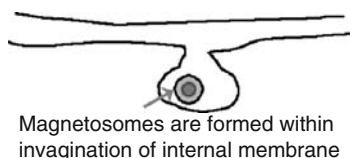


Figure M7. Magnetosome

Magnification: Increase in the units of ribosomal genes, hypothesized to occur by extra rounds of limited replication or unequal sister-chromatid exchange. At the *bobbed* (*bb*, 1–66.0) locus present in both sex-chromosomes of *Drosophila* in about 225 copies organized as large tandem arrays, separated by non-transcribed spacers. The copy numbers of *bb* in wild population Y-chromosomes may vary 6-fold. ►ribosomes, ►microscopy

MAGUKs (membrane-associated guanylate kinases): Mediate nuclear translocation and transcription. Membrane-associated guanylate kinases (PSD post-synaptic density-MAGUKs) mediate synaptic targeting, with remarkable functional redundancy within this protein family. PSD-95 and PSD-93 independently mediate AMPA-Receptor targeting at mature synapses. The loss of either PSD-95 or PSD-93, silences largely nonoverlapping populations of excitatory synapses. In adult PSD-95 and PSD-93 double knockout animals, SAP-102 (synaptic protein) is upregulated and compensates for the loss of synaptic AMPA-Rs (Elias GM et al 2006 Neuron 52:307). ►zona occludens, ►ELL, ►AMPA; McMahon L et al 2001 J Cell Sci 114 (pt 12):2265.

Maintenance Methylase: Keeps up methylation through cell divisions. ►methylation of DNA

Maize (*Zea mays*): It belongs to the family of *Gramineae* (grasses) and the tribe *Maydeae* along with teosinte (*Euchlena mexicana*) and the genus *Tripsacum* (with a large number of species). The male inflorescence of maize is more similar to that of teosinte than the female inflorescence. The ear or maize carries generally 8 to 24 rows of kernels whereas teosinte has only two rows. The teosinte ear is fragile the maize ear is not. The seed as is commonly named is really a karyopse (caryopse), a single-seed fruit (kernel). The basic chromosome number $x = 10$. *Tripsacum* resembles more some members of the *Andropogonaceae* family than to these two closer relatives and its basic chromosome number $x = 18$. Teosinte can be crossed readily with maize and the offspring is fertile whereas *Tripsacum* is more or less strongly isolated sexually and their hybrids are not fully fertile. Teosinte genes display the same chromosomal and gene arrangements as maize in contrast to *Tripsacum* that is more dissimilar. The evolution of modern maize has been traced to teosinte (Jaenicke-Després V et al 2003 Science 302:1206). The seed of teosinte is covered by a tough glume, which does not make it suitable for human consumption. Mutation in a single gene (*teosinte glume architecture*, *tg1*, maize chromosome 4) rendered maize grains naked during evolution and valuable for domestication (Wang H et al 2005 Nature [Lond] 436:714). All three genera have evolved in the

Western Hemisphere. Maize is one of the most thoroughly studied plants in genetics. It is a monoecious species; under natural conditions, it is allogamous. Approximately 500 kernels may be fixed on the cob for easy Mendelian analysis for a good number of endosperm, pericarp and embryo and seedling characters. Mendelian genes have been identified at about 1000 loci and more than 500 have been mapped. RFLP maps are also available. The gene number in maize is estimated to be ~33,000 to 54,000 (Fu Y et al 2005 Proc Natl Acad Sci USA 102:12282). The characteristic pachytene chromosomes facilitate cytogenetic analyses. Several genes controlling meiosis have been identified. Cytogenetic studies with maize contributed significantly to the understanding of chromosomal rearrangements. Transposable genetic elements were first recognized in maize (see Fig. M8).



Figure M8. Segregation in a maize ear

Transformation is possible but requires either electroporation or the biolistic technique. The discovery and the commercial production of hybrid corn (heterosis) made an unprecedented increase in the food and feed supply. ►biological control, ►domestication, ►non-coding DNA, for detailed chromosomal map of 1736 loci see Davis GL et al 1999 Genetics 152: 1137; Doebley J 2001 Genetics 158:487; Liu K et al 2003 Genetics 165:2117; evolution of maize: Doebley J 2004 Annu Rev Genet 38:37; genetics and genomics: <http://www.maizegdb.org>; <http://maize.tigr.org>; molecular and functional diversity: <http://www.panzea.org>; maize database: <http://www.maizegdb.org>.

Majewski Syndrome: The autosomal recessive phenotype has many similarities with oral-facial-digital syndromes, particularly with the Mohr syndrome. It is distinguished from the latter on the basis of laryngeal (throat) anomalies and polysyndactyly of the feet. ►Oro-facial-digital syndromes, ►polydactily

Major Facilitator Superfamily (MFS): These are ubiquitous transporters (more than 1000 members) in all biological groups. They transport ions, sugars, amino acids, peptides, nucleosides, drugs, neurotransmitters, etc. Their mutations may result in various diseases (seizures, diabetes, etc), may be responsible for antibiotic resistance, cancer chemotherapy (controlling drug efflux). ►membrane transport; Huang Y et al 2003 Science 301:616.

Major Gene: Determines clear, qualitative phenotypic trait(s). ►minor gene

Major Groove: The DNA helix as it turns displays two grooves in a 3.46 nm pitch; the wider one (almost 2/3 of the pitch) is the major groove ↗ (see Fig. M9). ►DNA, ►hydrogen pairing, ►Watson and Crick model



Figure M9. Major Groove

Major Histocompatibility Complex (MHC in humans, H-2 in mice): Triggers the defense reactions of the cells against foreign proteins (invaders). Their existence was first recognized by incompatibilities of tissue grafts. The MHC molecules are transmembrane glycoproteins encoded by the HLA complex in humans and by H-2 in mouse. The class I molecules have three extracellular domains at the NH₂ end and the COOH terminus reaches into the cytosol. The extracellular domains are associated with β₂ microglobulin. The class II MHC molecules are formed from α and β chains without the microglobulin. The class I heavy chain and the β₂ microglobulin are translocated to the endoplasmic reticulum before their translation is completed and their assembly takes place there with the assistance of the chaperones, BiP (a heatshock protein) and calnexin (glycoprotein). The MHC I molecules then associate with TAP and is ready for picking up a foreign antigenic peptides. After a peptide is bound, the system is released and after passing through the Golgi where their attached carbohydrates may be modified, exocytosis moves them to the surface of the cell membrane and this provides a chance for the CD8⁺ T cells (CTL) to react to them. At this stage, the cells that recognize self-antigens are eliminated by apoptosis. The MHC molecules resemble immunoglobulins, and the class II molecules, especially the β chains are highly polymorphic (The HLA-DRB 1 locus has more than 100 alleles.). The MHC molecules bind foreign antigens and present them to the lymphocytes. The murine CD1 proteins bear similarities to the MHC molecules but they present to the T cells lipids and glycolipid

antigens. MHC Class I proteins accumulate the cut pieces of peptides from inside the cells whereas Class II MHC proteins are attached to the pieces of antigens from outside the cell. Before a Class II protein is loaded with an invader peptide, it carries a neutral (dummy) peptide called CLIP which is then replaced by foreign pieces regulated by acidic conditions in the presence of DA. The Class I molecules are expressed on practically all cells that T cells recognize. Class II molecules are found on CD4⁺ B cells and other antigen presenting cells. MHC class I peptides (CTL epitopes) stimulate the CD8⁺ cytotoxic T cells and the MHC class II peptides are recognized by the CD4⁺ T cells. The T_H cells destroy any cell that present the antigen with MHC II molecules. The helper T cells do not directly attack the invaders but stimulate the action of macrophages. The MHC genes rely on transactivation by CIITA (non-DNA-binding) and RFX5, NF-X, NF-Y and other DNA-binding transcription factor proteins. There is a great diversity among MHC molecules. Gene conversion may create variations in 10⁻⁴ range in sperms. The histocompatibility system of rabbits is called RLA, in rats RT1, in guinea pigs GPLA. MHC I homologs of herpesviruses may disarm natural killer T cells. ▶HLA, ▶Ii, ▶immune system, ▶blood cells, ▶T cells, ▶αβ T cells, ▶CTL, ▶microglobulin, ▶DA, ▶proteasome, ▶TAP, ▶antigen presenting cell, ▶antigen processing and presentation, ▶Bare lymphocyte syndrome, ▶apoptosis, ▶self-antigen, ▶RFX; Beck S, Trowsdale J 2000 Annu Rev Genomics Hum Genet 1:117; Horton R et al 2004 Nature Rev Genet 5:889; <http://www.meddb.info/index.php.en?cat=6&subcat=104>; DNA and clinical resources: <http://www.ncbi.nlm.nih.gov/mhc/MHC.cgi?cmd=init>.

Majority Class Spores: ▶polarized recombination

Mal de Maleda (MDM, 8q24.3): A rare, recessive keratoderma, redness on the face, brachydactyly and nail abnormalities. The basic defect is in a secreted Ly-6/uPAR domain related protein (defined by disulfide bonding pattern between 8 or 10 cysteine residues). ▶keratoma, ▶brachydactyly; Fischer J et al 2001 Hum Mol Genet 10:875.

Malaria: An infectious disease affecting 300–500 million people annually (Snow RW et al 2005 Nature [Lond] 434:214), and causing 1.5–2.7 million deaths among them. It is caused by one or another species of the *Plasmodium* protozoa (see Fig. M10). Transmission is mediated by *Anopheles* mosquito bites but transplacental infection or transfusion with contaminated blood may transmit it. The infection relies on a Duffy-like cysteine-rich module of the parasites that recognize host cell surface receptors. The crystal structure of this domain has been revealed



Figure M10. *Plasmodium* merozoites

(Kumar Singh S et al 2006 Nature [Lond] 439:741). This disease is prevalent in the subtropical and tropical areas of the world. The symptoms are chills, fever, sweating, anemia, etc. The attacks are recurring according to the major reproductive cycles of the parasite. Heterozygotes of sickle cell anemia are somewhat resistant to the disease and that explains the higher than expected frequency of this otherwise deleterious gene. *Plasmodium* degrades hemoglobin by two plasmalepsin proteases. Hemoglobin C may provide some protection by abnormal display of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) on the erythrocytes and by reducing their sequestration in the microvasculature (Fairhurst RM et al 2005 Nature [Lond] 435:1117). Two minor and one major quantitative trait loci have been identified in *Anopheles gambiae* that inhibit the development of *Plasmodium cynomolgi* B in the midgut of the mosquito. The human body defends itself by the cytotoxic T cells. The human immune response cannot prevent the infection because the malaria-infected erythrocytes attach and slow down the maturation of the antigen-presenting dendritic cells and thus fail to activate properly the T lymphocytes. In some populations HLA and other ligands may cooperatively down-regulate this immune response. During the development of the parasite, the surface antigens are altered providing immune evasion and chances of reinfection after a period of apparent curing. Some success was obtained by vaccination before the parasite reaches the blood infection stage. Viral vector-delivered multigenic DNA vaccines encoding different epitopes and applied before the parasite would reach the blood stage may overcome the problems caused by the antigenic variations. The PEMP1 protein is responsible for most of the antigenic variation in the parasite. More than 50 var genes encode this multimodular (DBL, CIDR) adhesion protein. Various vaccines are under development either to prevent the multiplication of the parasite (sterilizing immunity) or by anti-disease approach that would prevent the development of malaria-associated pathology of the brain or the placenta in the infected individuals. Antibodies can be generated against many different, known antigens of the parasite but because of mutation in single proteins

may eliminate lasting protection against single antigen. Transcriptome analysis indicates that about 197 proteins can potentially be targeted for vaccine development. The thrombospondin-related adhesive protein (TRAP) and the apical membrane antigen 1 (AMA-1) are expressed in the *Plasmodium falciparum* sporozoite surface microneme vehicles and later proteolytic cleavage generates soluble fragments. These microneme proteins are critical for the invasion of blood and hepatocytes. A subset of serine protease inhibitors can prevent proteolytic cleavage, essential for infection and are good targets for vaccine development (Silvie O et al 2004 J Biol Chem 279:9490; Waters A 2006 Cell 124:689). Application of attenuated sporozoite vaccines have been considered but were plagued by practical, technical difficulties.

One possible means of protection appears to immunize (rodents) by *uis3* deficient sporozoites. The *UIS3* gene (upregulated in infective sporozoites 3) is essential for the early liver-stage development and in its absence, the *Plasmodium berghei* will not establish the blood-stage infection (Mueller A-K et al 2005 Nature [Lond] 433:164). Transgenic mosquitos may fail to transmit the parasites (Ito J et al 2002 Nature [Lond] 417:452). First time gravid humans are more susceptible to malaria because the parasite attaches to the chondroitin sulfate A on the placenta. By subsequent pregnancies a partially protective anti-adhesion response develops. The size of the *Plasmodium falciparum* genome is ~30 Mb (~82% A = T) located in 14 chromosomes. It has two organelle genomes: the mitochondrial is 5.9-kb (tandemly repeated) and ~35-kb in the apicoplast, a plastid-like organelle. The technology of molecular biology greatly facilitates the identification of the biology of the protozoa and the development of more effective control measures. (Le Roch KG et al 2003 Science 301:1503). *P. falciparum*, the most fatal species is rapidly developing resistance to the drug chloroquine and to several newer drugs. More recently high hopes were placed in the protective effect by the old Chinese herbal plant extract artemisinin of *Artemisia* (see Fig. M11). Now even that treatment may result in the development of resistance in *Plasmodium falciparum* (Duffy PE, Sibley CH 2005 Lancet 366:1908). *Plasmodium* has 400 putative genes involved in targeting erythrocytes of which 225 encode virulence proteins and 160 apparently remodel host erythrocytes. Switching to positions conducive to transcription and heterochromatin remodeling regulate virulence genes (*var*), which control antigenic variation (Freitas-Junior LH et al 2005 Cell 121:25). These genes are potential targets of antimalarial drugs (Mart M et al 2004 Science 306:1930). New drugs (fosmidomycin) blocking the non-mevalonate pathway of isoprenoid biosynthesis in the apicoplast

appear promising alternatives. Oil-based suspension sprays containing *Beauveria bassiana* and *Metarhizium anisopliae* directed against both *Plasmodium* and *Anopheles* mosquitos was up to ~90% effective control of malaria transmission (Blanford S et al 2005 Science 308 1638; Sholte E-J et al 2005 Science 308:1641).



Figure M11. *Artemisia*

The cerebral form of malaria attacks the brain and causes mental disorders, hyperthermia and about half of the infections is lethal. Malaria may mitigate Hepatitis B viral infections.

P. falciparum is the major cause of lethal malaria in humans but in chimpanzees, only moderate parasitization and no severe infection occurs. *P. reichenowi* is very similar to *P. falciparum* but affects only chimpanzees and other apes but not humans. This remarkable difference is based on the lack of N-glycolylneuraminic acid on human erythrocytes in contrast to other primates. *P. reichenowi* erythrocyte-binding antigene-175 requires this sialic acid (Martin MJ et al 2005 Proc Natl Acad Sci USA 102:12819; note figures scale bars are correctly 100 μ m). ►hemoglobin, ►thrombospondin, ►microneme, ►sickle cell anemia, ►*Plasmodium*, ►merosome, ►CD36, ►QTL, ►glucose-6-phosphate dehydrogenase, ►cytotoxic T cell, ►HLA, ►immunization genetic, ►apicoplast, ►Oct-1, ►chloroquine, ►refractory genes, ►neuraminic acid, ►serpine, ►Duffy blood group; de Koning-Ward TF et al 2000 Annu Rev Microbiol 54:157; Kappe SHI et al 2001 Proc Natl Acad Sci USA 98:9895; Nature [Lond] 2002 Insight 415: 670–710; *Anopheles* genome: Science 298, 4 Oct. 2002; malaria issue: Nature [Lond] 430:925–944, 2004; <http://www.malaria.org>.

Malate Dehydrogenase: The product of the MDH1 (human chromosome 2p23) is cytosolic whereas the MDH2 enzyme (encoded in 7p13) is located in the mitochondria. ►Krebs-Szentgyörgyi cycle, ►mitochondria

Malattia Leventinese: ►macular degeneration

MALD (mapping by admixture linkage disequilibrium): The mapping on the basis of linkage disequilibrium in a population. Complex diseases, based on more than a single gene are difficult or impossible to map on the basis of conventional linkage. Association mapping is more effective but requires too much genotyping. The efforts can be reduced if neighboring markers of the haplotypes are considered. Unfortunately, even this approach requires 300,000 to 1,000,000 single nucleotide polymorphic markers (SNP) to be successful, and its cost is too high for single disease. When populations are mixed by gene flow (e.g., European, Asian and African ethnic groups), temporarily large haplotypes blocks form linkage disequilibrium. The association of these blocks (disequilibrium) can be statistically analyzed though the centuries and the association of disease with haplotypes markers can be inferred. Such a study requires 200–500 fewer markers than whole genome haplotype mapping. MALD is carried out in five steps. 1. A group of people (cohort) is selected from the admixed population that have high incidence of the disease. 2. Cases and controls are genotyped using markers of high frequency and informative for ancestry. 3. The patchwork of the ancestry is determined for individuals. 4. Chromosomal regions with elevated frequency of the ancestry markers and disease are identified. 5. The candidate genes are located then by the use of SNP-association. This procedure is best suited for diseases, which differ substantially in frequency between the ancestral groups. Environmental differences may confound and frustrate the analysis. It is necessary that the admixture would be higher than 10%. The range of admixture generally varies a great deal geographically. Continued introgression also influences the outcome. The required population size depends on the allele frequencies and extent of the

admixture. Genes displaying similar frequencies in the ancestral populations are not informative. It is also important that the target genes could be safely identified (few false positives). The analysis requires ethical considerations because of racial sensitivities. ▶ [linkage disequilibrium](#); Smith MW, O'Brian SJ 2005 Nature Rev Genet 6:623; Collins-Schramm HE et al 2002 Am J Hum Genet 70:737.

MALDI/TOF/MS: Matrix-assisted laser desorption ionization/time of flight/mass spectrometry can detect minute differences in masses of large DNA molecules ($\sim 2,000$ nucleotide) in \sim femtomole (10^{-15}) size samples. This technology is used for characterization and identification of proteins and protein fragments. It detects post-translational modifications and any alteration in protein mass during development and modulation of function.

For proteomics, generally tryptic peptide mixture is used. Trypsin cuts proteins at arginine and lysine residues and on that basis, unknown proteins may be identified on the basis of matches with known proteins in the databases. For post-translational modification of proteins, the tryptic peptides can be analyzed in two steps. First, the mass spectrum (MS) of the intact peptide fragments can be determined. Second, (MS/MS) peptide ions are fragmented in a gas phase to identify protein sequence and modifications. For these analyses MALDi or electrospray ionization (ESI) are used. By this “bottom-up” approach, the full spectrum of the fragmentation ladder generally cannot be obtained. Alternatively, the “top-down” approach can be used where intact protein ions are introduced into the gas phase of ESI and obtaining molecular mass of the proteins and protein ion fragmentation ladders (see Fig. M12). This latter process permits now fragmentation of

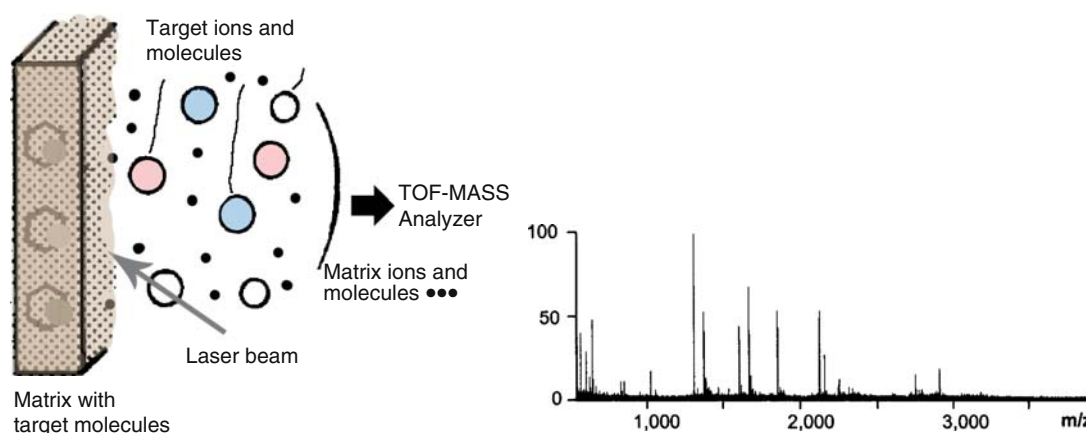


Figure M12. Diagram of the principle of MALDI/TOF/MS at left; MALDI/TOF/MS protein profile (for m/z see Mass Spectrum) Maldi/tof/ms protein profile (for m/z see Mass spectrum)

molecular masses up to 200 kDa (Chait BT 2006 Science 314:65; Han X et al 2006 Science 314:109).

The analytical procedure requires that the target molecules be co-precipitated with an excess matrix consisting of either α -cyano-4-hydroxycinnamic acid or dihydrobenzoic acid (DBH). The material is then dried on a metal surface and irradiated by a flanking nanosecond nitrogen laser at a wavelength of 337 nm to generate ionization. MALDI is used for relatively simple mixtures whereas ESI is integrated with liquids chromatography and is suitable for more complex mixtures. The sample is analyzed by a mass spectrometer (see Fig. M12). Some recent developments make these types of analyses very useful for biomedical applications (proteomics, pathology, tissue imaging, diagnostics, cancer monitoring, metabolomics, identification of biological agents, drug analysis, pharmaceutical process monitoring, in forensics and national security). ►DNA chips, ►proteomics, ►protein chips, ►electrophoresis, ►mass spectrometer, ►mass spectrum, ►fragmentation ladder, ►DESI, ►SIMS genomics, ►CID, ►SNIPS, ►quadrupole, ►electrospray MS, ►ESI, ►mole, ►PMF; Li L et al 2000 Trends Biotechnol 28:151; Mann M et al 2001 Annu Rev Biochem 70:437; Bennett KL et al 2002 J Mass Spectrom 37:179; Cooks RG et al 2006 Science 311:1566, <http://prowl.rockefeller.edu/>, OMSSA.

M

Male Contraceptive: The oldest form is a mechanical barrier to the sperm (condom) to prevent its penetration of the reproductive tract of the female. Primarily females practice physiological fertility control in animals and humans. Adjudin (1-[2,4-dichlorobenzyl]-1H-indazole-3-carbohydrazide) is capable of inducing germ cell loss from the Sertoli cell epithelium. Oral dose of Adjudin (50 mg per kg body weight for 29 d) resulted, however, in liver inflammation and muscle atrophy. If Adjudin is specifically targeted to the testis by conjugating it to a recombinant follicle-stimulating hormone mutant as its vector infertility was induced in adult rats when 0.5 μ g Adjudin per kg body weight was injected intraperitoneally with the same effectiveness as at the high oral dose (Mruk DD et al 2006 Nature Med 12:1323). There may eventually be a chance for human applications. ►contraceptive

Male-Driven Evolution (α): It is indicated by the higher rate of mutation in males than females. The extent of the ratio is not universally agreed upon. (See Makova KD, Li WH 2002 Nature [Lond] 416:624).

Male Gametocide: A chemical that destroys male gametes and thus may facilitate cross-pollination in plants or may serve as a human birth-control agent. ►crossing, ►birth control

Male Gametophyte: ►gametophyte

Male Recombination: It is normally absent in *Drosophila* (except when transposable elements are present; up to 1%) and in the heterogametic sex (females) of the silk worm. In case of the presence of a P element, most of the recombination is site-specific within a 4-kb tract near the element. Recombination then involves either adjacent duplication and deletion of a few to > 100-bp. Genetic markers can be mapped relative to known P element sites. Mitotic recombination may occur, however, even in the absence of the meiotic one. In maize and *Arabidopsis*, certain cases indicate reduced frequency of recombination in the megasporocytes compared to the microsporocytes. In rainbow trout the average female: male recombination ratio is 3.25:1 but shows significant variation according to chromosomal regions and families. Generally, in most species the recombination frequency in the heterogametic sex is slightly lower. ►recombination frequency, ►MR, ►hybrid dysgenesis, ►HEI, ►achiasmate; Meneely PM et al 2002 Genetics 162:1169; Hellig R et al 2003 Nature [Lond] 421:601.

Male-Specific Phage: It infects only those bacterial cells that carry a conjugative plasmid.

Male Sterility: Caused by various chromosomal aberrations, such as inversions, translocations, deficiencies, duplications, aneuploidy, polyploidy, etc., and by cytoplasmic factors. Generally in plants, male sterility is more common than female sterility because the pollen, the male gametophyte, has a more independent life phase than the megaspore and cannot rely well on support by sporophytic tissues. In plants, the male sterility may be caused by a mutation in the male gametophyte or it may be the result of the abnormal development of the anthers or other parts of the flower, e.g., failure to release the normally developed pollen. Common cause of male sterility is an alteration of the mitochondrial DNA, cytoplasmic male sterility (*cms*). Incompatibility between nuclear genes and certain cytoplasm as well as viral infection may also cause male sterility. Certain chemicals (mutagens), chromosome-breaking agents (maleic hydrazide) may have gametocidal effects. Male sterility may result in transgenic plants when a tapetum-specific promoter drives a ribonuclease gene within the anthers and thus destroy the pollen (see Fig. M13). The fertility can be restored if the sterile plants are employed as female in crossing with a male carrying the transgene *barstar* inhibiting the ribonuclease. Other self-destroying–restoring combinations have also been considered. A healthy human male ejaculates 25–40 million sperms each time, and if for any reason this number is reduced to 20,000 or below, male

infertility/sterility may result although only a single sperm functions in fertilization. Polymorphy for hybrid male sterility is a factor in speciation (Reed LK, Markow TA 2004 Proc Natl Acad Sci 101:9009).
 ▶cytoplasmic male sterility, ▶chromosomal defects, ▶gametocides, ▶KIT oncogene, ▶azoospermia, ▶oligospermia, ▶asthenospermia, ▶speciation, ▶hybrid sterility, ▶*msl*; Hackstein JHP et al 2000 Trends Genet 16:565.



Figure M13. The male sterile pollen does not stain and is shrunken

Malécot Equation: Employed for estimation of marker frequency probability in linkage disequilibrium in populations: $(1 - L)Me^{-\epsilon d} + L$, where L is an asymptote of the association for long distance and the intercept M represents association in the population founders, ϵ is a constant. ▶linkage disequilibrium; Lonjou C et al 2003 Proc Natl Acad Sci USA 100:6069.

Male-Stuffing: In some social insects the workers may force (and kill) males into empty cells in order to keep them from using the scarce food and thus making it available to the larvae. The relatedness among workers in single-mated queen colonies is 75% whereas to males it is only 25%. Thus, this behavior is a form of kin selection. ▶kin selection

Malformation: The abnormal formation of body parts.
 ▶dysplasia

Malignant Growth: A defect in the regulation of cell division that may lead to cancer and may cause the spreading of the abnormal cells. ▶metastasis, ▶cancer, ▶oncogenes, ▶cell cycle

Malondialdehyde (MDA): A mutagenic carbonyl compound, generated by lipid peroxidation. ▶adduct, ▶pyrimidopurinone, ▶lipid peroxidation

Malonic Aciduria (16q24): A recessive deficiency in malonyl-CoA decarboxylase and causes abnormally large amounts of malonic acid in the urine. It involves developmental retardation, constipation, abdominal pain and infantile death.

Malpighian Tubules: Excretory channels of arthropods emptying into the hindgut performing kidney-like function.

Malpractice: Improper practice due to negligence or misconduct or inadequate training or lack of adequate experience and causing physical, mental or financial harm in medicine or any other business activity.

Malsegregation: When the two homologous chromosomes are not recovered in 2:2 proportion at the end of meiosis. ▶segregation distorter, ▶meiotic drive, ▶nondisjunction

MALT (mucosa-associated lymphoid tissue lymphoma): It is most common in the gastrointestinal tract and in non-Hodgkin lymphoma. MALT is frequently associated with translocations t(1;14)p22;p32 and to the apoptotic signaling gene BCL10. MALT1 gene is involved in the activation of NF- κ (Talwalkar SS et al 2006 Mod Pathol 19:1402). ▶lymphomas, ▶Hodgkin disease, ▶BCL, ▶apoptosis, ▶fungal diseases

Malt: The specific activator of the bacterial maltose operon. ▶maltose

Malthusian Parameter: It assumes that the age distribution in a population remains constant from one generation to the next. In case the age-specific birth and death rates would continue without any hindrance, the population growth would ultimately reach that level, frequently denoted by r . ▶age-specific birth and death rate, ▶population growth; Fisher RA 1958 The Genetical Theory of Natural Selection. Dover, New York; Demetrius L 1975 Genetics 79:535.

Malthusian Theorem: Postulates that population growth exceeds the rate of food production and thus jeopardizes the survival of humans. This nineteenth century idea was contradicted by the fact that between 1961 and 1983 the available food calories per capita has increased from 2320 to 2660 (over 7% in two decades). Unfortunately, this growth is slowing down again, and from 1984 to 1990, the increase was only about 1%. For about 2,000 years, the global human population grew by an annual rate of about 0.04%. From 1965 to 1970, the rate increased to 2.1% and in 1995 it was about 1.6% per year. ▶human population growth; Black JA 1997 BMJ 315:1686; Lee RD 1987 Demography 24:443.

Maltose (glucopyranosyl glucose): A disaccharide. The Snf1 protein kinase controls the Mig1 transcriptional repressor of *SUC2* (sucrose), *GAL* (galactose) and *MAL* (maltose) genes. Induction of *MAL* requires transcriptional activator. Maltose utilization is controlled by several operons. A common activator of these is a 103-kDa activator MalT. Glucose and the global

repressor *Mlc* repress *MalT*. The maltose transporter system is an integral part of maltose utilization. A maltose transporter is essential for starch degradation and carbohydrate export from the site of photosynthesis (Niittylä T et al 2004 Science 303:87). ► [glucose effect](#), ► [catabolite repression](#), ► [Snf](#); Boos W, Böhm A 2000 Trend Genet 16:404.

MAMA (monoallelic mutation analysis): The mutations are screened in somatic cell hybrids of lymphocytes and hamster cells with aid of DNA techniques. ► [mutation detection](#); Jinneman KC, Hill WE 2001 Curr Microbiol 43(2):129.

Mammalian Comparative Mapping Database: A part of the Mouse Genome Database URL: <http://www.informatics.jax.org>; questions, problems, etc. can be addressed to Mouse Genome Informatics Project: mgi-help@informatics.jax.org; tel: (207) 288–3371 ext. 1900, fax (207) 288–2516.

Mammalian Genome: A monthly publication of the Mammalian Genome Society. Contact V.M. Chapman, Dept. Molecular and Cellular Biology, Roswell Park Cancer Institute, Elm & Carlton, Buffalo, NY 1463, USA. ► [databases](#) for additional addresses.

Mammalian Species: See <http://www.science.smith.edu/departments/Biology/VHAYSEN/msi/>.

Mammaprint: A government approved, high-cost 70-marker microarray test for the prediction of status and prospect of breast cancer at high accuracy (Glas AM et al 2006 BMC Genomics 7:278). (See information for physicians and patients: <http://www.agendia.com/us/>).

Mammary Tumor Virus of the Mouse (MTV): It causes an estrogen-stimulated adeno-carcinoma. The virus is transmitted through the milk. ► [glucocorticoid response element](#); Kang CJ, Peterson DO 2001 Biochem Biophys Res Commun 287:402.

Mammoth (*Mammothus primigenius*): The best known of these now extinct Elephantine species of the Pleistocene era in Siberia. These animals were somewhat comparable to the Asian elephants (*Elephas maximus*) in size but they were well adapted to the harsh climate by having long wool and thick layers of fat under skin all over the body. The nuclear DNA is not well preserved even in the arid caves or permafrost region. The nuclear DNA fragments (average length 84 bp) analyzed matched (to 95% identity) the available sequences of the African elephant (*Loxodonta Africana*) in 30% but only in 0.4% to human DNA. The estimated divergence between the two animals is 5–6 million years. Better specimens of DNA (~89 bp in average length) could be prepared from bone mitochondria and could be

amplified by PCR and the sequences matched in 95.93% to that of the African elephant (Poinar HN et al 2006 Science 311:392). By multiplex amplification, the entire mitochondrial DNA has been reconstructed and mapped (Krause J et al 2006 Nature [Lond] 439:724). The mastodon (*Mammut americanum*) is a North American relative (diverged 24–28 million years ago [mya] from the Elephantine lineage); its mitochondrial DNA has been sequenced from fossil Alaskan tooth. The ancestors of African elephants diverged from the lineage leading to mammoths and Asian elephants approximately 7.6 mya, and mammoths (see Fig. M14) and Asian elephants diverged approximately 6.7 mya. (Rohland N et al 2007 PLoS Biol 5(8):e207). ► [ancient DNA](#), ► [elephants](#), ► [ancient organisms](#); Rogaev EI et al 2006 PLoS Biol 4(3):e73.



Figure M14. Mammoth in cave art of Rouffignac, France

Manatee (*Trichechus manatus latirostris*): Large herbivorous aquatic mammal, $2n = 48$.

MANET: The evolution of protein structure in metabolic networks: Kim HS et al 2006 BMC Bioinformatics 7:351, <http://www.manet.uiuc.edu/>.

Mango (*Mangifera*): A tropical fruit tree, $2n = 2x = 40$.

Mania: A pathological neuronal disorder of mental and/or physical hyperactivity.

Mannans: The yeast cell wall polymers of mannose. ► [mannose](#)

Manic Depression (MAFD1): A psychological condition characterized by recurrent periods of excessive anguish (unipolar) or by manic depression (bipolar). The latter form is accompanied, in addition, by hyperactivity, obsessive preoccupation with certain things or events. Depression and other affective disorders may involve 2 to 6% of the human populations although the incidence of unipolar

depression may be as high 21% among females and 13% among males during the entire lifetime. The concordance among monozygotic twins may be as high as 80% whereas among dizygotic twins, it is about 8%. It appears that the recurrence in the families is higher with the early onset types. Also, the bipolar types appear to have higher hereditary components. The genetic control of depression is unclear, X-linked recessive, autosomal dominant (chromosome 11p) genes have been implicated but the majority of assignments were not well reproducible. These may be major genes but other genes are also involved. Susceptibility loci were assigned to 0 12q23-q24, 18p and 18q, 5q, 8p, 21p22, and others. MFAD2 (major affective disorder 2 or bipolar affective disorder; BPAD) was assigned to Xq28. The physiological bases may also vary from defects in neurotransmitters to electrolyte abnormalities, etc. Commonly recommended therapy involves monoamine oxidase inhibitors, tranquilizers (prozac), lithium, etc. ▶affective, ▶disorders, ▶schizophrenia, ▶bipolar mood disorder, ▶tyrosine hydroxylase, ▶lithium; Molecular genetics of bipolar disorder and depression: Kato T 2007 Psychiatry Clin Neurosci 61:3.

Mannopine: N2-(1'-deoxy-D-mannitol-1'-yl)- L-glutamine. ▶opines, ▶Ti plasmid

Mannose: An aldohexose (see Fig. M15).

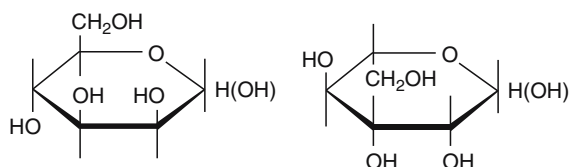


Figure M15. D Mannose and L Mannose

Mannosephosphate Isomerase (MPI): A Zn^{2+} monomeric enzyme converts mannose-6-phosphate into fructose-6-phosphate. It is coded in human chromosome 15q22.

Mannose-6-Phosphate Receptor (MPR): Same as insulin-like growth factor; it plays a role in signal transduction, growth and lysosomal targeting. LOH mutation of this receptor (human chromosome 6q26-q27) causes liver carcinoma. MPR is also a death receptor for granzyme B during CTL-induced apoptosis. ▶insulin-like growth factor, ▶LOH, ▶death receptor, ▶granzyme, ▶CTL, ▶apoptosis, ▶RAB, ▶TIP47, ▶GGA

Mannosidosis: The recessive (α -mannosidase B) deficiency has been located to human chromosome

19cen-q12 (MAN2B1) and involves large increase of mannose in the liver causing susceptibility to infection, vomiting, facial malformations, etc. Another mannosidase defect at another autosome (4q22-q25, MANBA) caused excessive mannosyl-1-4-N-acetylglucosamine and heparan in the urine, apparently involving glycoprotein abnormalities and a variety of physical and mental defects.

Mannosyltransferases: Defects in several genes involve mental retardation, psychomotor defects, hypomyelination, coloboma, etc.

Mann-Whitney Test: A powerful non-parametric method for determining the significance of difference between two normal-distributed populations. This method is useful for evaluating scores of samples even if their size is not identical. The procedure is illustrated by small samples, however samples of $n > 20$ are preferred. The scores are ranked (T) in Table M1 (in case of ties the average ranks are assigned to the two):

Table M1. A hypothetical example for the use of the Mann-Whitney test

| | | | | | | | | |
|-------------|---|----|---|---|----|----|-----------------------|---------------------------|
| Populations | I | II | I | I | II | II | Sum of I = $T_I = 10$ | |
| Scores | 1 | 4 | 5 | 7 | 8 | 9 | 10 | Sum of II = $T_{II} = 18$ |
| Rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | $n_I = 3, n_{II} = 4$ |

The null hypothesis to be tested is that the distribution of the two populations (I and II) is identical. Then the U is determined for sample I: $U_I = n_I n_{II} + \{[n_I(n_I + 1)]/2\} - T_I = 3 \times 4 + (12/2) - 10 = (12 + 6) - 10 = 8$. In case the resulting U value is larger than $(n_I n_{II})/2$ then calculate $U' = n_I n_{II} - U_I$. For large populations, the sampling distribution for U is approximately normal and $E(U) = (n_I n_{II})/2$ and the variance is determined $\sigma^2 = [n_I n_{II} (n_I + n_{II} + 1)]/12$; hence the z value (the standard normal variate) = $[U - E(U)]/\sigma_U$ and the probabilities corresponding to z can be read from statistical tables of the cumulative normal probabilities and a few commonly used corresponding values are as follows for $z = 1.65, 1.96, 2.58$ and 3.29 , the P values are 0.90, 0.95, 0.99 and 0.999, respectively. (See Wilcoxon's signed rank test, Standard deviation, Probability, Null hypothesis).

Mantel Test: Estimates the common odds ratio in two-by-two contingency tables that result from different populations. The formula for the estimation is: $\sum_{i=1}^k a_i d_i / \sum_{i=1}^k c_i b_i$, where k is the number of the two-by-two tables and a_i, b_i, c_i and d_i are the counts in the tables. ▶association test

Mantle Cell Lymphoma (MCL, human translocation [11;14][q13;q32] or mutation at 11q22-q23): A non-Hodgkin type lymphoma. Derived from naïve CD5⁺ B cells of the primary follicles or of the mantle zones of the secondary follicles. The segment deleted from chromosome 11q22-q23 includes the ataxia telangiectasia locus. The translocation juxtaposes cyclin D1 (CCND1) and the transcriptional control element of the immunoglobulin G gene although other factors (c-Myc) are also required for the development of the lymphoma. ▶anaplastic lymphoma, ▶ataxia telangiectasia

Manx Cat: Tailless, because of fusion, asymmetry and reduction in size of one or more caudal vertebrae (see Fig. M16). A dominant gene that is lethal in homozygotes causes this phenotype. The Manx protein is essential also for the development of the notochord of lower animals. ▶brachyury, ▶notochord



Figure M16. Caudal end of Manx cat

MAO (monoamine oxidase): This enzyme is involved in the biosynthetic path of neurotransmitters from amino acids. Mutation in the 8th exon (amino acid position 936) converted the glutamine codon CAG to TAG (chain termination codon) and resulted in mild mental retardation, continued and impulsive aggression, arson, attempted rape, and exhibitionism in human males with this X-chromosomal recessive defect. The block of MAOA resulted in accumulation of normetanephrine (a derivative of the adrenal hormone epinephrine), and tyramine (an adrenergic decarboxylation product of tyrosine) and a decrease in 5-hydroxyindole-3-acetone. The heterozygous women were not affected behaviorally or metabolically; monoamine oxidase B level remained normal. Both enzymes are in human chromosome Xp11.2-p11.4 and the enzymes are located in the mitochondrial membrane. The enzymes may affect various psychiatric disorders such as the Gilles de la Tourette syndrome, panic disorder, alcoholism, etc. ▶mitochondria, ▶Norrie disease, ▶Tourette syndrome

MAP: see Microtubule associated proteins. ▶ASE1, ▶microtubule, ▶centrosome, ▶map genetic

MAP (multi-use affinity probe): A biarsenic tag of amino acids in proteins facilitating easy monitoring

interactions (Cao H et al 2007 J Amer Chem Soc 129: 12123).

MAP-1 (modulator of apoptosis): A mitochondria-associated protein and activates BAX when it is translocated into the mitochondria from the cytosol upon apoptotic signals. RNAi regulates MAP-1. ▶apoptosis, ▶BAX, ▶RNAi; Tan KO et al 2005 Proc Natl Acad Sci USA 102:14623.

MAP-Based Cloning (positional cloning): Isolation of gene(s) on the basis of chromosome walking and propagation usually by YAC and/or cosmid clones. After a genome sequence has been completed, positional cloning will no longer be needed as long as the function of the gene is also known. Positional cloning may be complicated by the fact that some phenotypes are affected by more than a single locus. ▶chromosome walking, ▶chromosome landing, ▶position effect; Lukowitz W et al 2000 Plant Physiol 123:795; Tanksley SD 1995 Trends Genet 11:63.

MAP Distance: Indicates how far syntenic genes are located from each other in the chromosome as estimated by their frequency of recombination; 1 map unit = 1% recombination = 1 centi Morgan. The greater the distance between two genes, the higher is the chance that they are separated by recombination. A single recombination between two genes in a meiocyte produces maximally 50% recombination that is 50 map units. The distance between syntenic genes may exceed 50 map units several times; these longer distances are determined then in a staggered manner, proceeding step-wise from left to right and right to left. In prokaryotes, using conjugational transfer and recombination, map distances are measured in minutes of transfer. ▶conjugational mapping, ▶recombination frequency, ▶radiation hybrids, ▶mapping function

MAP Expansion: The distance between two distant markers exceeds the sum of the distances of markers in between; it is commonly observed in gene conversion. ▶gene conversion; Holliday R 1968 p 157. In: Replication and Recombination of Genetic Material. Peacock WJ, Brock RD (Eds.) Australian Acad Sci, Canberra.

Map, Genetic: The order of genes (markers) in chromosomes determined on the basis of recombination frequencies. ▶mapping, ▶recombination frequencies, ▶physical map, ▶radiation hybrids, ▶RFLP, ▶RAPD, ▶mapping function; Human genes: OMIM; <http://linkage.rockefeller.edu/>; genetic & physical of various organisms: <http://www.ncbi.nlm.nih.gov/Genomes/index.html>.

Map Genetic Versus Physical Map: ►coefficient of crossing-over, ►gene number; Ashburner M et al 1999 Genetics 153:179.

Map Kinase (MPK): A family of serine/threonine protein kinases associated with mitogen activation (growth) and stress responses. Three groups exist: ERK, cJun N-terminal kinase (JNK) and p38. These paths of responses interact at various levels. They have a key role in signal transduction pathways. The p42 and p44 MPKs are also called ERK2 and ERK1, respectively. The MAP kinase family is activated by STE20, RAS, Raf protein serine/threonine kinases. In normal T cells, T cell receptor and CD28 synergistically activate p38. An alternative activation pathway involves Tyr323 by antigen-stimulated T cells but not B cells (Salvador JM et al Nature Immunol 6:390). MAPK81P1 (11p11.2-p12) may be a transactivator of SLC2A2 gene encoding GLUT2 glucose transporter and one of the factors responsible for MODY diabetes. The MAP kinases follow the signaling path: MAPKKK → MAPKK → MAPK. ►cell cycle, ►signal transduction, ►MAPK, ►JNK/SAPK, ►ERK, ►p38, ►STE diabetes, ►MODY, ►GLUT; Cobb MH 1999 Progr Biophys Mol Biol 71:479; English J et al 1999 Exp Cell Res 253:255; Chang L, Karin M 2001 Nature [Lond] 410:37; Dong C et al 2002 Annu Rev Immunol 20:55; Park S-H et al 2003 Science 299:1061; Schwartz MA, Madhani HD 2004 Annu Rev Genet 38:725.

MAP Kinase Kinase (MAPKK): ►Ste 7

MAP Kinase Kinase Kinase (MAPKKK): ►Ste 11

MAP Kinase Kinase Kinase Kinase (MAPKKKK): ►Ste 20

MAP KINASE PHOSPHATASE (MPK): MPK-3 dephosphorylates phosphotyrosine and phosphothreonine and inactivates the MAP kinase family proteins. Binding activates it by its non-catalytic C-end to ERK2 without a need for phosphorylation. The homologous MPK-4 is also activated by ERK2 but also by JNK/SAPK and p38. ►signal transduction and other proteins under separate entries; Zhang T et al 2001 Gene 273:71.

Map Manager v 2.5: The software for storing, organizing genetic recombination data and data base for RI strains of mouse. Information: K.F. Manly, Roswell Park Cancer Institute, Elm & Carlton, Buffalo, NY 14263, USA. Phone: 716-845-3372. Fax: 716-845-8169. kmanly@mcbio.med.buffalo.edu.

Map, Metric: An on-scale ordered FISH map where cosmid clones can orderly be positioned. ►FISH, ►cosmid

Map, Physical: ►physical map

Map, Self-Organizing: Constructed on the basis of mathematical cluster analysis; recognizes and classifies complex multidimensional data such as information of an array of genes involved in differentiation or other complex pathways. ►cluster analysis

Map Unit: 1% recombination = 1 map unit (m.u. or 1 centiMorgan, c.m. or cM). In approximate kilobase pairs equivalent to one centiMorgans in a few species: *Arabidopsis* ≈140; tomato ≈ 510; human ≈ 1,108 (in human chromosome 10 the recombination frequency is 1.32 cM/Mb⁻¹); maize ≈ 2,140. The *Salamanders* have the largest known genetic map 7291 cM. ►recombination frequency

Map Viewer: Provides genomic information by chromosomal location of a variety of eukaryotic organisms from animals to plants, fungi and protozoa. It can be queried by gene name, sequence alignment (BLAST), etc. ►genome, ►BLAST; <http://www.ncbi.nlm.nih.gov/mapview/>.

MAPCS (multipotent adult progenitor cells): These are “universal stem cells” present in small numbers in some adult tissues and have the capacity to produce other types of cells in a manner similar to embryonic stem cells. ►stem cells; Jiang Y et al 2002 Nature [Lond] 418:41; Schwartz RE et al 2002 J Clin Invest 109:1291.

MAPK (mitogen-activated protein kinase): Distinct kinases responding to different environmental cues and sets into motion different development/physiological pathways. The family includes KSS1 (filamentous growth), HOG-1 (hypertonic stress), FUS3 (mating), Mpk1 (cell wall remodeling), SLT-2, sapk-1 (stress activated protein kinase), FRS (FOS regulating kinase), erk-1 (extracellular signal regulated kinase), Smk1 (sporulation), etc. In yeast association with the Ste12 transcriptional activator regulates the specificity. Ste12 in combination with other proteins may bind to the pheromone response element (PRE). Ste12 protein associates with the filamentation and invasion response element (FRES), including A Ste12 protein binding site (TGAAACA) and a neighboring CATTCTY sequences specific for the Tec1 (non-receptor tyrosine kinase) transcription factor. The mating and filamentous growth pathways are initiated in a similar way but for mating the FUS kinase is activated rather than the KSS. In the absence of phosphorylation KSS inhibits the Ste12-Tec1 complex and filamentous growth. The Dig proteins appear to be cofactors of the inhibitory path. In the inhibitory MAPKs (KSS), there is the MKI (MAP kinase insertion) site, which is remodeled upon phosphorylation and thus conversion into an activator. The specificity of the MAPKs is secured also by the complexes of recruited proteins, and each of these

selects the appropriate MAPK. ►signal transduction, ►MAPKK, ►MEK, ►arrestin, ►Ask, ►JNJ FOS, ►Ste, ►anthrax; Ito M et al 1999 Mol Cell Biol 190:7539; Roberts CJ et al 2000 Science 287:873; Pouyssegur J 2000 Science 290:1515; Barsyte-Lovejoy D et al 2002 J Biol Chem 277:9896.

MAPKK (mitogen-activated [MAP] protein kinase kinase): This protein mediates signal transduction pathways by phosphorylating RAS, Src, Raf and MOS oncogenes. When such an active kinase was introduced into mammalian cells, the AP-1 transcription factor was activated and the cells formed cancerous foci and became highly tumorigenic in nude mice, indicating that MAPKK is sufficient for tumorigenesis. ►signal transduction, ►tumor, ►anthrax, ►NPK

MAPKKK: Mitogen activated protein kinase kinase. ►TAK1

Maple (*Acer* spp.): Hardwood trees; sugar maple is used for collecting syrup, $2n = 26$.

Maple Syrup Urine Disease: ►isoleucine-valine biosynthetic pathway

Mapmaker 3.0: A software for constructing linkage maps using multipoint analysis in testcross and F_2 . MAPMAKER/QTL is for quantitative trait loci. Available for Sun (Unix), PC (DOS) and Macintosh. Contact: Eric Lander, Whitehead Institute, 9 Cambridge Center, Cambridge, MA 02142, USA. Fax: 617-258-6505. INTERNET: mapmaker@genome.wi.mit.edu.

Mapping: Establishes the sequential location of genes, restriction fragments or PCR products. Molecular mapping of individual genomic DNA molecules labeled with fluorescent dyes at specific sequence motifs by the action of nicking endonuclease followed by the incorporation of dye terminators with DNA polymerase can be used. The labeled DNA molecules are then stretched into linear form on a modified glass surface and imaged using total internal reflection fluorescence (TIRF) microscopy. By determining the positions of the fluorescent labels with respect to the DNA backbone, the distribution of the sequence motif recognized by the nicking endonuclease can be established with good accuracy in a manner similar to reading a barcode (Xiao M et al 2007 Nucleic Acids Res 35(3):e16). ►genome

projects, ►physical maps, ►recombination, ►restriction endonuclease, ►PCR, ►SNIPs, ►radiation hybrids, ►databases; <http://linkage.rockefeller.edu/>.

Mapping by Admixture Linkage Disequilibrium: ►MALD

Mapping by Dosage Effect: If the activity of enzymes is proportional to their dosage and disomics can be distinguished from critical trisomics, genes (for the enzymes) located in a specific trisome can be identified and assigned to that specific chromosome or in the case of telotrisomic to a particular chromosome arm. Theoretically, the enzyme activity is expected as follows if the locus is situated in the long arm of a particular chromosome (see Fig. M17).

In human trisomy 21 several genes show increased expression ranging from 1.21 to 1.61 relative to the normal disomic condition. Thus, in practice, the dosage effect may not be perfectly additive, yet it may be clear enough for classification. ►trisomics; Carlson PS 1972 Mol Gen Genet 114:273.

Mapping, Genetic: The mapping of chromosomes can be carried out on the basis of recombination frequencies of chromosomal markers, either genes or DNA markers such as RFLPs, RAPDs, etc., or molecular methods used in physical mapping (chromosome walking). As a hypothetical example assuming that genes *a*, *b*, *c*, *d* and *e* are syntenic, the recombination frequencies between them was found to be:

a 0.06 *b* 0.04 *c* 0.06 *d* 0.16 *e* 0.18 *g*

The sum of the recombination frequencies is $0.06 + 0.04 + 0.06 + 0.16 + 0.18 = 0.50$ indicating that the segregation between *a* and *g* is independent. The results shown could be obtained between two genes at a time but such a two-point cross would not have permitted the determination of the order of the genes relative to each other. For the determination of genes at “left” and genes at “right” a three-point cross is required as a minimum, and multipoint crosses are even more helpful ►recombination frequencies. For the results of a hypothetical three-point testcross see Table M2.

According to the data, the number of recombinants in interval I was $10 + 2$ and in interval II $20 + 2$ (the double recombinants had recombination in both interval I and II and their number must be added to the numbers observed). Thus the frequency of

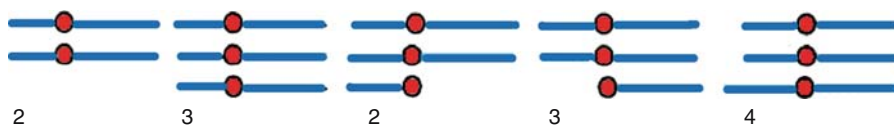


Figure M17. Mapping by dosage effects

Table M2. A hypothetical three-point testcross

| Phenotypic classes → | ABD | abd | Abd | aBD | ABd | abD | AbD | aBd |
|-----------------------|----------|-----|-------------------------|-----|--------------------------|-----|-------------------------------|-----|
| Number of individuals | 34 | 34 | 5 | 5 | 10 | 10 | 1 | 1 |
| | Parental | | Recombinants interval I | | Recombinants interval II | | Recombinants intervals I + II | |
| Total of 100 | 68 | | 10 | | 20 | | 2 | |

recombination between *A* and *B* is $12/100 = 0.12$ and between *B* and *D* $22/100 = 0.22$. The number of recombinations between *A* and *D* is $10 + 20 + 4 = 34$ (the 4 is the double of the number of recombinants in intervals I and II because these represented double recombination events).

Thus the relative map positions are *A* – *B* – *D*. Had it been found that the combined parental numbers were 68 but the recombinants *Abd* plus *aBD* 10 and *ABd* plus *abD* 2, and *AbD* plus *aBd* 20, it had to be concluded that the gene order was *A* – *D* – *B*, because the lowest frequency class ($0.10 \times 0.20 = 0.02$) must have been the double recombinants, and thus the gene order would have been *A* – *D* – *B*. The observed recombination frequencies may have to be corrected by mapping functions because not all double-crossovers might have been detected (see Mapping functions). The recombination frequencies may be biased also by interference when the frequency of double-crossovers are either higher or lower than expected on the basis of the product of the two single-crossovers (see ►Coincidence, Interference). The (corrected) recombination frequencies can be converted to map units by multiplication with 100 and 1 map unit (m.u. or centiMorgan [cM]) is 0.01 frequency of recombination. Recombination frequencies can be estimated also in F_2 by using the product ratio method (see ►Product ratio method). In the latter case recombination frequencies can be calculated only between pairs of loci yet from the data of two pairs involving 3 loci, the gene order can be determined. On the basis of SNIPs human linkage maps of 3.9 cM resolution have been generated (Matisse TC et al 2003 Am J Hum Genet 73:271). Availability of complete nucleotide sequences of the genomes does not obviate the calculations of recombination frequencies because the physical maps and the genetic map lengths are not necessarily identical. ►Recombination frequencies, ►crossing over, ►QTL, ►deletion mapping, ►chromosome walking, ►physical maps, ►mapmaker, ►joinmap, ►maximum likelihood method applied to recombination, ►mapping functions, ►radiation hybrids, ► F_2 linkage estimation, ►genomic screening, ►skeletal map, ►comparative map, ►unified genetic map, ►integrated map, ►consensus, ►SNIPs, ►linkage,

►coefficient of crossing over, ►exclusion mapping; Multilocus mapping algorithm for humans: Lander ES, Green P 1987 Proc Natl Acad Sci USA 84:2363; Ott J, Hoh J 2000 Am J Hum Genet 67:289; Grupe A et al 2001 Science 292:1915; survey of newer multipoint algorithms: Gudbjartsson DF et al 2005 Nature Genet 37:1015.

Mapping Functions: Correct map-distance estimates from recombination frequencies when the recombination frequency in an interval exceeds 15–20% and double crossing overs are undetectable because of the lack of more densely positioned markers. ►Haldane's mapping function, ►Kosambi's mapping function, ►Carter-Falconer mapping function, ►mapping, ►recombination frequency, ►coefficient of coincidence, ►stationary renewal process, ►count-location models; Zhao H, Speed TP 1996 Genetics 142:1369.

Mapping in Silico: Feeding phenotypic information to a computer program facilitates fast information gathering on the regulation and chromosomal locations of the multiple factors involved in a polygenic disease. ►polygenic; Grupe A et al 2001 Science 292:1814.

Mapping Panels: These are DNA sequences with known chromosomal location and can be used to locate unknown sequences to chromosomes. ►radiation hybrid panels

Mapping Sets: ►genomic screening

MapSearch: Locates regions of a genomic restriction map that resemble best a local restriction the so-called probe.

MapShow: A computer program displaying MapSearch alignments and draws Probe-to-Map alignments in Sun Workstations. ►mapping

MAR (matrix attachment region): Attaches chromatin loops to the nuclear matrix. The attachment region has a consensus of so-called A box (AATAAATCAA) or a T box (TTA/TAA/TTTA/TTT). The MARs are about 100 to 1,000 bp long and frequently include replication origins and transcription factor binding sites. ►chromatin, ►loop domains mode, ►scaffold; Stratling WH, Yu F 1999 Crit Rev Eukaryot Gene Expr

9(3–4):311; Pemov A et al 1998 Proc Natl Acad Sci USA 95:14757; <http://www.futuresoft.org/MAR-Wiz>.

Maranhar: ►killer plasmids, ►*Neurospora*

Marburg Virus: A negative-sense single-stranded RNA virus containing seven genes within a lipid envelope (see Fig. M18). Besides transcribing its full genome, it produces subgenomic RNAs without encapsidation and these can also be translated into viral protein. The name comes from the German city Marburg where it was discovered in 1967 in monkeys shipped from Uganda. The virus causes hemorrhagic fever and very high mortality. Current efforts are directed to the development of efficient vaccine and RNAi based defense systems. ►Ebola virus, ►RNAi, ►vaccines; Fowler T et al 2005 J Gen Virol 86:1181.



Figure M18. Marburg virus

MARCKS (myristoylated alanine-rich C kinase substrate): Protein substrates of the protein kinase C (PKC), involved in differentiation; they bind actin filaments. (See Spizz G, Blackshear PJ 2001 J Biol Chem 276:32264).

mardel10: A supernumerary human chromosome 10 with a large deletion at the regular centromere. The deletion, however, activates, a functional neocentromere at 10q25, which lacks α -satellite and CENP-B centromeric protein although it shows some other centromere proteins. ►centromere, ►neocentromere, ►human artificial chromosome; Voullaire LE et al 1993 Am J Hum Genet 52:1153; Choo KH A 1997 Am J Hum Genet 61:1225.

Marek's Disease: A lymphoproliferative viral chicken disease. The growth hormone, GH1 conveys resistance. ►herpes, ►Epstein-Barr virus; Liu H-C et al 2001 Proc Natl Acad Sci USA 98:9203; Levy AM et al 2005 Proc Natl Acad Sci USA 102:14831.

Marfan Syndrome (MFS, FBN1): Common symptoms include tall thin stature, long limbs and fingers, chest deformations. The three most consistent defects are skeletal, heart-vein (cardiovascular) and eye (ectopia lentis) abnormalities. The disease may affect the development of the fetus and may be recognized in early development and the life expectancy in serious cases may not much exceed 30. The cause of death is generally heart failure but the defect may be surgically corrected in some cases. The penetrance appears very good but the expressivity is highly variable. The symptoms frequently overlap with other anomalies, particularly with those of the Ehlers-Dunlop syndrome.

The latter involves a defect in collagen. The primary defect in MFS involves the elastic fiber system glycoprotein, fibrillin. This protein of the connective tissue contains repeats resembling sequences in the epidermal growth factor (EGF) where the lesion observed leads to the identification of the basic molecular cause. Formerly a collagen defect was suspected.

Several investigators confirmed a transversion mutation at codon 293 leading to CGC (Arg) → CCC (Pro) replacement. Similar molecular defects have been identified in *Drosophila*, *Caenorhabditis* and cattle. This dominant gene has been assigned to human chromosome 15q21.1. Interestingly, mosaicism for trisomy 8 causes similar symptoms. The prevalence of MFS/FBN1 is about 1×10^{-4} but this figure may not be entirely reliable because of the wide range of manifestation of the symptoms (see Fig. M19). The recurrence risk is about 50%; 15–30% of the cases may be due to new mutation that is the cause of the most severe cases, whereas the familial incidence generally entails milder symptoms. The estimated mutation rate is $4 - 5 \times 10^{-6}$. FBN1 may be dominant negative. The mutation in fibrillin-1 affects the regulation of transforming growth factor (TGF- β) resulting in apoptosis of the alveolar cells of the lung. Excessive signaling of TGF- β family cytokines can cause aortic aneurysm in mice and can be blocked by angiotensin II type1 receptor blocker drug, Losartan (Habashi JP et al 2006 Science 312:117).

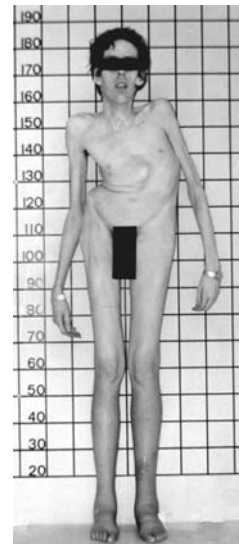


Figure M19. Marfan syndrome. (Courtesy of Dr. D.L. Rimoin, Los Angeles)

A higher probability of ectopia lentis was found for patients with a missense mutation substituting or producing a cysteine, when compared with other

missense mutations. Patients with an FBN1 premature termination codon had a more severe skeletal and skin phenotype than did patients with an inframe mutation. Mutations in exons 24–32 were associated with a more severe and complete phenotype, including younger age at diagnosis of type I fibrillinopathy and higher probability of developing ectopia lentis, ascending aortic dilatation, aortic surgery, mitral valve abnormalities, scoliosis, and shorter survival (Faivre L et al 2007 Am J Hum Genet 81:454).

It has been suggested that President Abraham Lincoln, the famous musician Niccolò Paganini, renowned composer Sergey Rachmaninof and Pharaoh Akhenaten were afflicted with this type of anomaly. ►Marfanoid syndromes, ►coronary heart disease, ►cardiovascular disease, ►connective tissue disorders, ►penetrance, ►expressivity, ►transversion mutation, ►Ehlers-Dunlop syndrome, ►fibrillin, ►angiotensin, ►aneurysm, ►dominant negative, ►TGF, ►apoptosis, ►arachnodactyly, ►inbreeding depression, ►frameshift mutation; Dietz HC, Pyeritz RE 1995 Hum Mol Genet 4:1799; Neptune ER et al 2003 Nature Genet 33:407.

Marfanoid Syndromes: It may resemble the Marfan syndrome but one of the forms has no ectopia lentis (displacement of the crystalline lens of the eye). Another form does not involve cardiovascular defects. The marfanoid-craniosynostosis is called Shprintzen-Goldberg syndrome and the anomaly is caused by mutation in the fibrillin-1 gene. ►Marfan syndrome, ►eye diseases, ►Craniosynostosis syndromes, ►fibrillin, ►Lujan syndrome

Marijuana: ►cannabinoids, ►Cannabis

Mariner: Probably the smallest transposable element in eukaryotes (1,286 bp). It has not been observed in *Drosophila melanogaster* but has been detected in African species of the *D. melanogaster* subgroup, *D. sechellia* (1–2 copies), *D. simulans* (usually 2 copies), *D. yakuba* (about 4 copies), *D. teissieri* (10 copies), and *D. mauritiana* (20 to 30 copies). Mariner-like element has been detected also in soybeans.

Mariner contains 28-bp inverted terminal repeats and a single open reading frame (1,038-bp) beginning with an ATG codon at position 172 and termination

with an ochre (TAA). Overlapping AATAA bases may serve as polyadenylation signal (see Fig. M20).

The target in the untranslated leader of the w^{pch} is 5'-TGGCGTA↓TAAACCG-3'. The arrow marks the insertion and the TATA indicate probably the target site duplication. *Mariner* is different from other transposable elements inasmuch as inducing a high frequency of somatic sectors (4×10^{-3}) at the w^{pch} (white *peach*) locus. Germline mutation is about 2 to 4×10^{-3} , with about twice as high in the males than females (no sex difference in somatic mutation).

Before the transposable element was recognized, the somatic instability was attributed to the factor named *Mos* in chromosome 3. This element also causes dysgenesis but it does not display the reciprocal difference observed in the *P-M* and *I-R* systems, however, *mariner* transmitted through the egg shows higher rates of somatic excisions. *Mariner* homologs occur in other species too, including humans but the (*human*) sequences are pseudogenic although increase unequal crossing over in human chromosome 17p11.2-p12. The mariner type DNA-based transposons are most common in the human genome, representing ~1.6% of it. The *mariner* sequences are also expressed in *Leishmania* and *Caenorhabditis*. ►hybrid dysgenesis, ►transposable elements, ►Charcot-Marie-Tooth syndrome, ►neuropathy, ►HNPP, ►unequal crossover, ►MLE, ►MITE, ►Leishmania, ►sleeping beauty; Hartl DL et al 1997 Annu Rev Genet 31:337; Zhang L et al 2001 Nucleic Acids Res 29:3566; Feschotte C, Wessler SR 2002 Proc Natl Acad Sci USA 99:280.

Marinesco-Sjögren Syndrome (MSS, 5q31): The major symptoms of the recessive hereditary disease are cerebellar ataxia, cataracts, retarded developmental/mental maturation. Hypergonadotropic hypogonadism is also a common feature of the condition. Chylomicron retention deficiency is coded in the same chromosomal region but physiologically not linked to this disease. The SIL1 nucleotide exchange factor for the Hsp70 chaperone BiP mutations are the primary cause of MSS. Affecting the endoplasmic reticulum may explain the multiple consequences of the mutations. ►hypergonadotropic hypogonadism, ►chylomicron, ►nucleotide exchange factor, ►endoplasmic reticulum, ►Hsp70; Senderek J et al 2005 Nature Genet 37:1312.

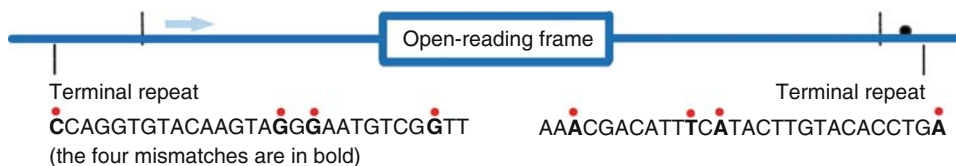


Figure M20. *Mariner* transposable element

Marker: Any gene or detectable physical alteration in a chromosome (e.g., knobs, microsatellites) or cytoplasmic organelle, used as a special label for that chromosome or chromosomal area. Molecular marker is a macromolecule (nucleic acid or protein) of known size and electrophoretic mobility to be used as a reference point in estimating the size of unknown fragments and molecules. In genomics Type I markers are the protein-coding genes, Type II markers are the highly polymorphic microsatellites and Type IIIs are SNPs. ▶RFLP, ▶RAPD, ▶AFLP, ▶ladder, ▶microsatellite, ▶minisatellite, ▶SNIPs, ▶linkage, ▶association test; Schlötterer C 2004 *Nature Rev Genet* 5:63; plant markers: <http://markers.btk.fi/>.

Marker-Assisted Selection: Used for animal and plant breeding once linkage has been established between physical markers (RFLP, microsatellite loci) and others, economically desirable traits (e.g., disease resistance, productivity) that have low expressivity and/or poor penetrance because of the substantial environmental influences can be better identified. The physical markers should not have ambiguity of expression and thus may facilitate much faster progress in breeding. ▶RFLP, ▶microsatellite, ▶expressivity, ▶penetrance, ▶QTL; Hospital EF 2001 *Genetics* 158:1363; Davierwala AP et al 2001 *Biochem Genet* 39(7–8):261; Hayes B, Goddard ME 2001 *Genet Sel Evol* 33(3):209.

Marker Effect: Theoretically, by generalized transduction, any bacterial gene should be transferred by the transducing phage. In fact some genes are transduced 1,000 fold better than others. The differences have been attributed to the distribution of *pac* sites in the bacterial chromosome. Also recombination by transduction may vary along the length of the bacterial chromosome. Marker effects have been observed also in eukaryotic recombination. ▶generalized transduction, ▶*pac* site

Marker Exchange Mutagenesis: ▶targeting genes

Marker Exclusion: Occurs upon joint infection of bacteria by phages T4 and T2. In the progeny, T2 genes are recovered in about 30% rather than 50% as expected. The apparent basis of the bias is that T4 harbors 13 sequence-specific endonucleases that selectively eliminate particular tracts from the other phage. ▶homing endonucleases; Edgell DR 2002 *Current Biol* 12:R276.

Marker Panels: DNA probes or genes that cover reasonably well portions of the genome regarding linkage. ▶probe, ▶linkage

Marker Rescue: The integration of markers into normal DNA phage from mutagen-treated (irradiated) phage during mixed infection of the host; it is similar to cross

reactivation where from defective phages by recombination normal phages can be obtained. Alternatively, a wild type DNA fragment can be inserted by recombination into a mutant one and the mutation can thus be mapped. Marker rescue is the most commonly used method of mapping in phages. ▶reactivation, ▶multiplicity reactivation, ▶Weigle reactivation; Barricelli NA, Doermann AH 1961 *Virology* 13:460; Thompson CL, Condit RC 1986 *Virology* 150:10.

Marker Transfer: Gene replacement by recombination.

Markov Chain Monte Carlo Algorithm: It applies Bayesian inference for evaluation of the posterior distribution. It is used also in classical likelihood calculation. (See Gilks WR et al (Eds.) 1996 *Markov Chain Monte Carlo in Practice*. Chapman and Hall, London, UK; Larget B, Simon DL 1999 *Mol Biol Evol* 16:750; ▶Monte Carlo method, ▶Bayes' theorem).

Markov Chain Statistics: A sequence $x_1, x_2 \dots$ of mutually dependent random variables constitutes a Markov chain if there is any prediction about x_{n+1} . Knowing $x_1 \dots x_n$ may without loss be based on x_n alone. Among others, it is used in physical mapping of genomes, for ascertaining frequency distributions in populations. The *hidden Markov model* (HMM) type analysis—seeks the probabilities of an event occurring also prior to and after another event—permits the identification of protein domains in peptide chains or in nucleotide sequences and frequency distribution through time. ▶TB-parse, ▶alignment; Stephens DA, Fisch RD 198 *Biometrics* 54:1334.

Marmosets: New World Monkeys. In marmoset (*Callithrix kuhlii*) twins all somatic tissue types sampled were found to be chimeric by the use of microsatellite DNA (see Fig. M21). Chimerism was present in hematopoietic tissues and also in germ-line tissues, an event never before documented as naturally occurring in a primate. Chimeric marmosets often transmit sibling alleles acquired in utero to their own offspring. Thus, an individual that contributes gametes to an offspring is not necessarily the genetic parent of that offspring. Chorions of the twins'



Figure M21. Marmoset

placentas begin to fuse on day 19 and the process is complete by day 29, forming a single chorion with anastomoses connecting the pre-somite stage embryos. The fusion of the chorions and a delay in embryonic development at this stage allows the exchange of embryonic stem cells via blood flow between the twins. As a result, the infants are genetic chimeras with tissues derived from self and sibling embryonic cells (Ross CN et al 2007 Proc Natl Acad Sci USA 104:6278). ▶ *Callithrichidae*, ▶ *Chimera*

Marmota (groundhog, woodchuck): Squirrel-like rodents; *Marmota marmota* 2n = 38; *Marmota monax* 2n = 38 (see Fig. M22).



Figure M22. Marmota

Maroteaux-Lamy Syndrome: ▶ *mucopolysaccharidosis*

Marquo Syndrome: ▶ *mucopolysaccharidosis*

Marriage: In every state of the United States and many other countries marriages between parent and child, grandparent-grandchild, aunt-nephew, uncle-niece and brother-sister are illegal. In about half of the states first cousin and half sibling unions are also prohibited. In some societies, consanguineous marriages are legal. ▶ *consanguinity*, ▶ *miscegenation*

Marry-in: A member of a pedigree without his parents being members of the pedigree. ▶ *pedigree*

Mars Model: Developed to interpret the fate of mitochondria during the development of an organism. The acronym is derived from (i) accumulation of defective mitochondria, (ii) accumulation of aberrant proteins, (iii) effect of oxygen-free radicals and antioxidant enzymes, (iv) turnover of proteolytic scavengers. ▶ *mitochondria*, ▶ *aging*

Mars Shield: A symbol of male; in pedigrees usually squares are used (see Fig. M23). ▶ *venus mirror*



Figure M23. Mars shield

Marshall Syndrome: ▶ *Stickler syndrome*

Marsupial: A mammalian group of animals that carry their undeveloped offspring in a pouch, e.g., the kangaroos and other Australian species, also the North-American opossum. The organization of the genetic material of marsupials differs in several ways from other placental mammals. Ohno's law is not entirely complied with inasmuch as genes in the short arm of the eutherian X chromosomes are dispersed in three autosomes. Marsupial Y chromosomes are extremely small yet they contain testis-determining and other sequences homologous to other mammals although the Y chromosome is not critical for sex determination. Their sex chromosomes also carry a pseudoautosomal region at their tip but do not form synaptonemal complex and do not recombine. ▶ *Eutheria*, ▶ *Monotreme*, ▶ *Ohno's law*, ▶ *SRY*, ▶ *pseudoautosomal*, ▶ *vomeronasal organ*; Marshall Graves JA 1996 Annu Rev Genet 30:233; Zenger KR et al 2002 Genetics 162:321.

MART-1 (Melan-A): ▶ *MAG*

Marten (*Martes americana*): 2n = 38.

Martin-Bell Syndrome: ▶ *Fragile Xq27.3*

Martsof Syndrome: An apparently autosomal recessive cataract-mental retardation-hypogonadism. ▶ *cataracts*, ▶ *hypogonadism*, ▶ *mental retardation*, ▶ *Cerebro-oculo-facio-skeletal syndrome*; Hennekam RC et al 1988 Eur J Pediatr 147:539.

MaRX: A method of isolation of mammalian cells of a certain type. A DNA library is introduced into a packaging cell line (linX cells) with the aid of retroviral vectors. The virus-infected cells are subjected then to selection for the desired phenotype. Provirus are recovered and used for the production of virus and further screening. ▶ *DNA library*, ▶ *retroviral vectors*, ▶ *provirus*, ▶ *packaging cell line*; Hannon GJ et al 1999 Science 283:1129.

MAS: ▶ *Marker-assisted selection*

MAS Oncogene: MAS1 was assigned to human chromosome 6q27-q27; it encodes a trans-membrane protein. ▶ *transmembrane protein*, ▶ *oncogenes*

MASA Syndrome (Xq28): Involves mental retardation, aphasia, shuffling gate, adducted and/or clasped thumb, etc. The basic defect is in L1 CAM cell adhesion molecule of 143 molecular mass of 1,256 amino acids. MASA is allelic to X-linked hydrocephalus (prevalence: $\sim 3 \times 10^{-4}$). ▶ *aphasia*, ▶ *hydrocephalus*, ▶ *CAM*

Masculinization: ▶ *sex reversal*

MASDA (multiplex allele-specific diagnostic assay): A mutation detection test capable of simultaneous detection of up to 100 nucleotide changes in multiple genes concerned with disease. ▶ *single strand*

conformation polymorphism, ►peptide nucleic acids; Shuber AP et al 1997 Hum Mol Genet 6:337.

MASH2: A mammalian helix-loop-helix transcription factor controlling extraembryonic trophoblast development but not that of the mouse embryo. ►MYF-3, ►DNA-binding protein domains

Mask: A computer program that produces ambiguous files in order to protect confidential DNA sequences in EcoSeq programs. ►EcoSeq

Masked mRNA: It is present in eukaryotic cells in such a form and cannot be translated until a special condition is met. ►mRNA; Spirin AS 1996 p 319. In: Hershey JWB et al (Eds.) Translational Control, Cold Spring Harbor Lab. Press, Cold Spring Harbor, NY.

Masked Sequences: Masked sequences of nucleic acids are associated with either proteins or other molecules to protect them from degradation.

Masking DNA Sequences: It is replacing nucleotide regions with certain properties with 'N' characters, or by converting the nucleotides within the region to lower-case letters. The program called RepeatMasker most frequently used to mask repeats: <http://www.repeatmasker.org/>. Repeats around SNPs may cause failure of assay or give mixed signals from different genomic regions. Variations may cause biased signal due to allele-specific binding of primers. Automatic masking tool: <http://bioinfo.ebc.ee/snpmasker/>.

Maspin: A protease inhibitor of the serpin family; maspin sequences are frequently lost from advanced cancer cells. Maspin is an inhibitor of angiogenesis. ►serpin, ►angiogenesis; Maass N et al 2000 Acta Oncol 39:931; Futscher BW et al 2002 Nature Genet 31:175.

Mas6p: ►mitochondrial import

Mass-Coded Abundance Tagging (MCAT): A method of protein characterization for proteomic studies. It is based on differential guanidination of the C-terminal lysine residues in tryptic peptides and followed by capillary liquid chromatography–electrospray tandem mass spectrometry. ►capillary electrophoresis, ►electrospray MS, ►proteomics, ►trypsin; Cagney G, Emili A 2002 Nature Biotechnol 20:163.

Mass Spectrum: When in the mass spectrometer molecules are exposed to energetic electrons they are ionized and fragmented. Each ion has a characteristic mass to charge ratio, m/e or m/z . The m/e values are characteristic for particular compounds and provide the mass spectrum for chemical analysis. Quantitative mass spectrometry uses the incorporation of a stable isotope (N^{15}) derivative that shifts the mass of the peptides in a known extent. The ratio

between the derivatized and underivatized target can be measured. Shotgun mass spectrometry identifies components of a protein mixture by first identifying the mass of peptide fragments. ►laser desorption mass spectrum, ►electrospray mass spectrum, ►affinity-directed mass spectrometry, ►genomics, ►proteomics, ►MALDI, ►MS/MS, ►quadrupole, ►electrospray; Oda Y et al 1999 Proc Natl Acad Sci USA 96:6591; Mann M et al 2001 Annu Rev Biochem 70:437; Figeys D et al 2001 Methods 24:230; Cohen SL 2001 Annu Rev Biophys Biomol Struct 30:67; Aebersold R, Mann M 2003 Nature [Lond] 422:198; OMSSA, for protein structure: Sharon M, Robinson CV 2007 Annu Rev Biochem 76:167; virtual lab exercises: <http://mass-spec.chem.cmu.edu/VMSL>; Ms/Ms peptide spectra search: <http://pubchem.ncbi.nlm.nih.gov/omssa>.

Massively Parallel Signature Sequencing (MPSS): The method permits large-scale analysis of transcription templates of an entire genome without physical separation of the DNA fragments. The 16–20 base fragments were generated by repeated digestion with restriction endonucleases and ligated by appropriate adaptors. Complex DNA mixtures are cloned in vitro onto glycidyl methacrylate microbeds in quantities sufficient for biochemical and enzymatic analyses using fluorescent probes. The template-containing microbeads are assembled in a flow cell in a close planar, fixed array while the sequencing reagents are pumped through. The sequencing is monitored with the aid of the fluorescent signals. The procedures facilitate the early recognition of gene products involved in the development of disease and may permit intervention. The improved system is capable of sequencing 25 million bases within four hours in picoliter size wells 1.6 million on a 6.4-cm² slide, using a modified pyrophosphate-based method (pyrosequencing). It is about two-order magnitude faster than the standard Sanger method and has an accuracy of >99%. It does not require subcloning of the DNA in bacteria. Although it seems very convenient for relatively small (microbial) genomes, it is not yet practical with large (mammalian) systems (Margulies M et al 2005 Nature [Lond] 437:376). ►gene expression, ►microfluidics, ►small RNA, ►DNA sequencing, ►pyrosequencing; Brenner S et al 2000 Nature Biotechnol 18:630; Reinartz J et al 2002 Brief Funct Genomic Proteomic 1:95; Hood L et al 2004 Science 206:640; <http://www.massivelyparallel.com/>.

Mass-to-Charge (m/e , m/z): ►mass spectrum

Mast Cells: They reside in the connective or hemopoietic tissues and play an important role in natural and acquired immunity. They release TNF- α (tumor

necrosis factor), histamines and attract eosinophils (special white blood cells) and destroy invading microbes especially if they have IgE or IgG (immunoglobulins) on their surface. They are responsible for the inflammation reactions in allergies and susceptibility to bee and snake venoms by facilitating vascular permeability. On the other hand, they release carboxypeptidase A and probably other proteases, which can degrade the venoms (Metz M et al 2006 Science 313:526). Mast cells are essential for regulatory T-cell controlled immune tolerance. ▶IL-10, ▶IL-9, ▶immune system, ▶TNF, ▶immunoglobulins, ▶carboxypeptidase, ▶venome, ▶T cell regulatory, ▶immune tolerance

Mast Syndrome: A recessive (15q22.31) brain developmental disorder (paraplegia, dementia) caused by premature termination of transcription of the maspardin protein gene due to single nucleotide pair insertion. The protein is situated in the endosomal/trans-Golgi transport vesicles. ▶paraplegia, ▶endosome, ▶Golgi; Simpson MA et al 2003 Am J Hum Genet 73:1147.

Master Chromosome: The large circular genome within the mitochondria. ▶mtDNA

Master Genes: They have major role in a range of functions. (See Prior HM, Walert MA 1996 Mol Med 2:405; Silver LM 1994 Mamm Genome 5:S291).

Master molecule: Regulates series of reactions in differentiation, involving several genes. ▶morphogenesis in *Drosophila*, ▶neuron-restrictive silencer factor

Master-Slave Hypothesis: The hypothesis interpreted redundancy in the genomes by multiple copying 'the slaves' from the original 'master' sequences based on the structure of the loops of the lampbrush chromosomes of the newt *Triturus*. ▶redundancy, ▶Lampbrush chromosomes; Callan HG 1967 J Cell Sci 2:1.

MAT1: A RING finger protein subunit stabilizing cyclin H-CDK7 complex or CAK. ▶RING finger, ▶cyclin, ▶CDK, ▶CAK, ▶four-hybrid system; Devault A et al 1995 EMBO J 14:5027.

MAT Cassette: ▶mating type determination in yeast

MAT Locus: In yeast, it is involved in the determination of mating type in yeast. ▶mating type determination in yeast

Matched Pairs t-Test: Checks the equality of the means of paired observations. The difference between the matched pairs is tested by the formula: $t = \frac{\bar{d}}{s_d/\sqrt{n}}$
 \bar{d} = the mean of the differences, s_d = standard

deviation and t is determined at $n - 1$ degrees of freedom from a t table. The null hypothesis is that the means of the paired observations are true. ▶mean, ▶standard deviation, ▶Student's t table, ▶Null hypothesis

Mate Killer: mu particle. ▶symbionts hereditary

Mate Pairs: Randomly sequenced DNA fragments are fit together by their matching mate pair ends into a continuous sequence. DNA sequences read from opposite ends of fragments are the mate pairs. ▶WGS, ▶Human genome

Maternal Behavior: A very complex trait, it is regulated by hormones such as estradiol, progesterone, prolactin, oxytocin and β -endorphin. The Mest/Peg1 (mouse chromosome 6, human chromosome 7q32) is expressed only from the paternally transmitted allele and its defect leads to altered maternal behavior. ▶hormones under separate entries, ▶imprinting

Maternal Contamination: During amniocentesis, maternal cells may contaminate the sample withdrawn and may become a cause of genetic diagnostic error. ▶amniocentesis

Maternal Coordinate Genes: Expressed during oogenesis and determine positional information in the egg.

Maternal Effect Genes: Display delayed inheritance because only the offspring of the homozygous or heterozygous dominant females is affected; these females themselves may appear normal. Also, genes with products (RNA, protein) in the follicle and nurse cells that may diffuse into the oocytes and the embryo, and thus not just the zygotic genes, affect early development. After the initial phases, the maternal transcripts and proteins are destabilized. (See Fig. M24 of ▶morphogenesis, ▶delayed inheritance, ▶cadherin, ▶indirect epistasis, ▶trans-generational effect, ▶imprinting; Evans MMS, Kermicle JL 2001 Genetics 159:303; Tadros W et al 2003 Genetics 164:989.

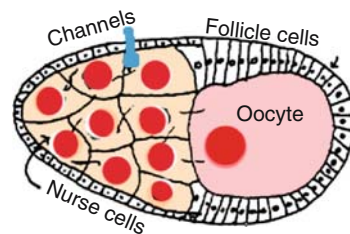


Figure M24. The *Drosophila* egg chamber cysts are surrounded by follicle cells and inside the diploid primary oocyte is shown with the often polyploid nurse cells. These are connected by cytoplasmic bridges. The maternal genes affect oogenesis and the early development of the embryo

Maternal Embryo: Develops from an unfertilized egg.
 ▶apomixis, ▶parthenogenesis

Maternal Genes: ▶maternal effect genes, ▶*Limnaea*

Maternal Inheritance: Genetic elements (generally extranuclear) are transmitted only through the female.
 ▶mtDNA, ▶mitochondrial genetics, ▶doubly uniparental inheritance, ▶chloroplast genetics

Maternal Performance: A complex of physiological and behavioral traits of the mother that affects the wellbeing and survival of the offspring. It includes such maternal attributes as nursing, grooming, nest building, etc. The heritability of such traits is variable and generally low yet it contributes measurably to fitness. ▶maternal behavior; Peripato AC et al 2002 Genetics 162:1341.

Maternal Tolerance: The embryo expresses antigens that is supposed to be foreign to the maternal tissues yet usually the embryo does not suffer immunological rejection. The cause of the tolerance appears to be due to the secretion of corticotropin-releasing hormone (CRH) and the activation of the pro-apoptotic Fas ligand (FasL) resulting in killing of activated T lymphocytes. Some of the female infertility may be caused by lack of adequate level of CRH in the endometrium. ▶incompatibility, ▶corticotropin releasing factor, ▶FAS, ▶apoptosis, ▶T cell; Makrigiannakis A et al 2001 Nature Immunol 2:1018.

Maternity Verification: Rarely needed as the Romans held “mater certa” (mother is certain); in case of legal disputes, the methods of forensic genetics are available. ▶forensic genetics, ▶paternity testing

MATH (meprin and TRAF homology): The protein domain shared by metalloendopeptidases and TRAF proteins regulating the folding to activable forms of the molecules. ▶meprin, ▶TRAF

Mating Assortative: ▶assortative mating

Mating Bacterial: ▶conjugation (see Fig. M25).

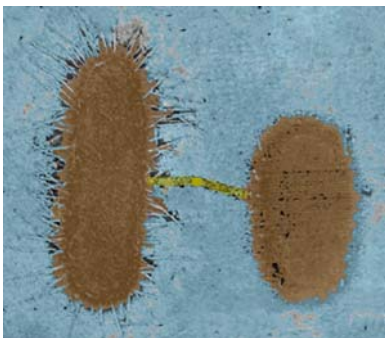


Figure M25. Mating bacteria

Mating Controlled: ▶controlled mating

Mating Interrupted: ▶interrupted mating, ▶conjugation mapping

Mating Nonrandom: ▶inbreeding, ▶assortative mating, ▶autogamy (self-fertilization), ▶controlled mating

Mating, Physiological Consequences: In some species the male seminal fluid may contain substances toxic to the female. In contrast, the seminal fluid of the male cricket (*Gryllus lineaticeps*) increases the life expectancy of the female by about a third and multiple matings (common in this species) almost doubles the fertility of the female (Wagner WE Jr et al 2001 Evolution 55:994).

Mating Plug: A gelatinous material deposited at vulva after mating of hermaphroditic *Caenorhabditis*. During mating between some hermaphroditic males, plugs may be visible at the head. ▶vaginal plug

Mating Random: ▶random mating, ▶mating systems

Mating Success (K): Expressed as

$$\frac{\text{No. of females mated by mutants/No. of mutant male}}{\text{No. of females mated by wild types/No. of wild type males}}$$

Increasing success in mating in insect species may reduce the level of phenoloxidasases in both sexes. Thus, a major humoral immune component is weakened and the individuals become more susceptible to infection. Therefore, copulation may adversely influence fitness. (See Rolff J, Siva-Jothy MT 2002 Proc Natl Acad Sci USA 99:9916).

Mating Systems: It can be random mating, self fertilization, inbreeding, assortative mating or a combinations of these. ▶Hardy-Weinberg theorem

Mating Type: The designation of individuals with plus or *a* (“male”) and minus or *α* (“female”) labels when sex like in higher eukaryotes cannot be recognized yet genetically two types exist that do not “mate” within group but in between groups, and the diploid zygote subsequently undergoes meiosis and reproduces the mating types in 2:2 proportion. (See Ferris PJ et al 2002 Genetics 160:181).

Mating Type Determination in Yeast: *Saccharomyces cerevisiae* yeast can exist in homothallic and heterothallic forms. The heterothallic yeast cells are haploids and are either of *a* or *α* mating type. The homothallic yeast cells are diploid and heterozygous for the mating type genes (*a/α*). The diploid cells arise by fusion of haploid cells. Recognition of the

opposite mating type cells is mediated by pheromones, the α factor (13 amino acids) and the a factor (12 amino acids) peptide hormones, respectively. The two types of cells are equipped also by surface receptors for the opposite mating type pheromones. The diploid cells lack these factors and receptors and do not fuse but may undergo meiosis and sporulate by releasing both α and a haploid cells.

The two mating types are coded by genes in chromosome 3 on the left and right sides of the centromere, respectively. These genes are clustered within the so-called mating type cassettes and are silent at their positions named *HML α* and *HMR a* locations. They are expressed when transposed to the mating-type site, *MAT*. At *MAT*, either the left *HML α* or the right *HMR a* cassette can be expressed within a particular homologous chromosome. The *MAT* site is approximately 2-kb and it is about 187 kb from *HML α* and at about 93 kb from *HMR a* .

(See Fig. M26 for the overall structure of the regions). In the outline the *MAT* site is shown empty but in reality either the *HML α* or by the *HMR a* cassette occupies it. When one or the other silent complex is unidirectionally transposed to the *MAT* site, the expressed *MAT α* and *MAT a* , respectively, are generated. At the original (left and right) locations the *Y α* (747 nucleotides) and the *Y a* (642 nucleotides) are kept in place and silent by the product of the *SIR1–4* gene (Silent Information Regulator). Actually four Sir proteins exist, 1, 2, 3 and 4. Repression is mediated also by the autonomous replication sequences (ARS) and the pertinent enhancer (E) elements. The transposition activity of a *MAT* cassette requires also the presence of nuclease hypersensitive sites in the flanking regions. The transposition at the *MAT* sites is initiated when the HO endonuclease makes a staggered cut at the *YZI* junction-generating strands with four base overhangs:

The *HO* gene is expressed only in the haploid cells but not in the diploids, and only at the end of the G1 phase of the cell cycle and both new cells have the same mating type and can transpose their mating type gene only after the completion of the next cell cycle. The product of gene *SIN1–5* represses the function of *HO* and the expression of gene *SWI–5* is required for the expression of *HO*. Mother cells selectively transcribe *HO*. In daughter cells, Ash1p suppressor

of *HO* may accumulate as a result of asymmetric mRNA distribution. For the actual mating the function of other (sterility, *STE*) genes are also needed. *STE2* and *STE3* are cell type-specific receptors of G proteins. *GPA1* encodes the $G\alpha$ subunit, *STE4* the $G\beta$ subunit and *STE18* the $G\gamma$ subunit. The $G\beta G\gamma$ subunits, after activation, regulate further downstream units of the pheromone-signaling pathway, including the kinases *STE20*, a series of MAP kinases (encoded by *STE11*, *STE7* and *FUS/KSS* genes). The Ste5p protein (encoded by *STE5*) is presumed to be a scaffold for organizing all the kinases.

Transposition involves pairing with the homologous *Z* sequences, followed by an invasion of a double-stranded receiving *Y* site and degradation of these *Y* sequences. Subsequently the *X* site is invaded. New DNA synthesis then takes place using as template the sequences of the invader molecule that is replacing the old DNA tract. Integration is mediated in the pattern of a gene conversion mechanism as suggested by the Holliday model of recombination.

The α mating type gene has two elements $\alpha 1$ (transcribed from right to left) that induces the α mating functions and $\alpha 2$ (transcribed in left to right similarly to *a*) that keeps in check the expression of the *a* mating type expression. The simultaneous expression of $\alpha 1$ and $\alpha 2$ represses also *SIR* and other haploid-specific genes. These processes recruit also proteins PRTF (Pheromone Receptor Transcription Factor) and GRM (General Regulator of Mating type) that recognize specific nucleotide sequences within the haploids and diploids. The $\alpha 2$ protein also interacts the MCM1 DNA binding and the MADS box proteins. The binding of *MAT $\alpha 2$* with MCM1 represses α -specific genes in haploids but in diploid cells *MAT $\alpha 2$* heterodimerizes with *MAT $\alpha 1$* and thus haploid-specific genes are repressed (see Nature [Lond] 391:660 for the structural interactions of these proteins). In *Candida albicans* (and some other fungi) an apparently evolutionarily more ancient regulation operates the basically identical mating type determination system (Tsong AE et al 2006 Nature [Lond] 443:415).

Whether *HML* or *HMR* switching occurs depends on the surrounding sequences and it is not intrinsic to the elements. *Mat a* cells recombine with *HML* almost an order of magnitude more frequently than

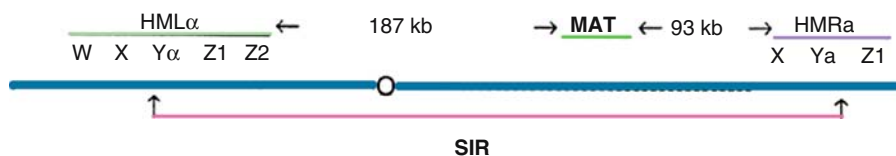


Figure M26. Mating type region in yeast

5'-GCTTT↓CGGCAACAGTATA-3' *MATa*
 3'-CGAAAGGCG↑TTGTCATAT-5'

5'-ACTTCGCGC AACA↓GTATA-3' *MATr*
 3'-TGAAGCGCG↑TTGTCATAT-5'

Figure M27. Nucleotide sequences in the *MAT* loci

with *HMR* (see Fig. M27). *MATa* cells recombine in 80–90% of the cases with *HMR*. The switching is controlled by 700-kb element 17-kb proximal to *HML* by a recombinational enhancer.

The expression of the mating type genes involves a complex cascade of events. The mating type protein factors interact with G protein-like receptors situated in the cell membrane. These G proteins then transduce the mating signals through a series of phosphorylation reactions to transcription factors that control the turning on/off genes mediating the cell cycle, cell fusion and conjugation. The industrial strains of yeast are frequently diploid or polyploid and may be heterozygous for mating type. In such a case, they fail to mate. If they are plated on solid medium, they may sporulate and the chromosome number will be reduced. ▶*Holliday model*, ▶*signal transduction*, ▶*cell cycle*, ▶*silencer*, ▶*HML* and *HMR* sex determination, ▶*Candida albicans*, ▶*pheromones*, ▶*MCM1*, ▶*MADS box*, ▶*homothallic*, ▶*heterothallic*, ▶*rare-mating*, ▶*regulation of gene activity*, ▶*Ty*, ▶*Schizosaccharomyces pombe*, ▶*ORC*, ▶*RAP1*, ▶*Abf*; Haber JE 1998 Annu Rev Genet 32:561; Dohlgan HG, Thorner JW 2001 Annu Rev Biochem 70:703; Rusche LN et al 2003 Annu Rev Biochem 72:481; Tsong AE et al 2003 Cell 115:389.

Matrilineal: Descended from the same maternal ancestor, e.g., the mtDNA. ▶*mtDNA*

Matrix: Solutes in cells, organelles or chromosomes, etc.; the *extracellular matrix* fills the space among the animal cells and it is composed of a meshwork of proteins and polysaccharides, secreted by the cells. The viral matrix connects the genomic core with the envelope. ▶*nuclear matrix*

Matrix Algebra: It deals with elements that are arranged as shown in the figure. A matrix with r rows and c columns is of order $r \times c$ or an $r \times c$ matrix. If $r = c$, it is a *square matrix* (see Fig. M28). A matrix with 1 row is *row vector* and a matrix with only 1 column is a *column vector*. A *weight matrix* can be generated for a particular motif by the use of Bayes' theorem. Each column in the matrix represents one position of the motif. Each row of the matrix corresponds to the probability that a corresponding, e.g., nucleotide, occurs at a position in the motif. Matrix algebra can be used for correlations, in numerical taxonomy, evolution, comparative genomics, etc. ▶*motif*,

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 4 | 7 | [| 2 | 1 |] |
| 2 | 5 | 8 | | 4 | 6 | |
| 3 | 6 | 9 | | | | |

Figure M28. Matrix arrangements

▶*Bayes's theorem*; Hays WL, Winkler RL 1970 Statistics: Probability, inference and decision. Holt, Rinehart and Winston, New York.

Matrix Attachment Region: ▶*MAR*

Matrix-Assisted Laser Desorption Ionization/Time of Flight/Mass Spectrometry (MALDI-TOF): A procedure for separation of DNA fragments mixed with a carrier that is painted subsequently on the surface of a solid face target. Laser desorbs and ionizes the fragments and acceleration in a mass spectrometer is used to determine fragment length. The MALDI-TOF procedure may detect as small as a nucleotide change in the length of a DNA sequence (ca. 100 perhaps 1,000 bp) or changes in the microsatellite numbers. This technique can be utilized in DNA sequencing, discrimination among mutations of a gene, for identification of STS. It may eventually be used also for clinical and diagnostic procedures. ▶*laser*, ▶*mass spectrum*, ▶*laser desorption mass spectrum*, ▶*microsatellite*, ▶*SNIPs*, ▶*proteomics*, ▶*STS*, ▶*TOFMS*, ▶*MALDI-TOF*; Shahgholi M et al 2001 Nucleic Acids Res 29:E91; Chu J et al 2001 Clin Chim Acta 311:95; Nordhoff E et al 2001 Electrophoresis 22:2844.

Matrix Diseases: These diseases periodically/seasonally reoccur, frequently in a somewhat different form such as the annual influenza epidemics or the occasional pandemics.

Matroclinous: The offspring resembles the mother because it developed either from an unfertilized egg or from an egg that underwent nondisjunction and carries two X chromosomes or from a female with attached X-chromosomes or by imprinting or dauermodification or due to sets of dominant genes or the failure of transmission of a particular chromosome through the sperm or caused by non-nuclear (mitochondrial, plastid) genes. ▶*Rosa canina*, ▶*chloroplast genes*, ▶*mtDNA*, ▶*mitochondrial genetics*

Matthiola (garden stock, wallflower): A cruciferous ornamental ($2n = 14$). Lethal factor (*l*), is tightly

linked to the simple flower character (*S*), has been of special interest (see Fig. M29). This causes the appearance of the “ever-segregating “full-flower” trait (*s*) in 1:1 proportions rather than in 3:1. By sophisticated breeding techniques and seed selection in trisomic offspring, the commercially available seed germinates and develops into nearly 100% full-flower/double flower plants that are, however, completely sterile due to the recessive lethal factor. Thus, the seed supply is entirely dependent on commercial sources. (See Kappert H 1937 Ztschr Ind Abst- Vererb-lehre 73:233; Roeder AHK, Yanofsky MF 2001 Dev Cell 1:4).



Figure M29. Matthiola

Maturases: Proteins that mediate a conformational change in the pre-mRNA transcript and cooperate in the splicing reactions. ▶introns, ▶mitochondrial genetics

Maturation Divisions: Same as meiosis.

Maturation of DNA: Phage proteins cut the linear, continuous DNA into pieces that can be accommodated by the phage capsids.

Maturation Promoting Factor: ▶MPF

Maurice of Battenberg: A hemophiliac grandson of Queen Victoria of England; son of carrier daughter Beatrice. ▶hemophilias

Mauriceville Plasmid: ▶*Neurospora* mitochondrial plasmids

MAVS: ▶RIG oncogene

MAX: A b/HLH/LZ (basic helix-loop-helix/leucine zipper) protein hetero-oligomerizes with the MYC oncoproteins, and this state is required for malignant transformation by c-MYC. MAX alone lacks the transactivator domain of MYC. Its DNA recognition site is CACGTG. MAX may be orchestrating the biological activities of b/HLH/LZ transcription factors. The basic α helices follow the major groove of the DNA in a *scissors grip*. ▶MYC, ▶helix-loop-helix, ▶RFX, ▶leucine zipper, ▶Mxi/Max, ▶major groove

Maxam-Gilbert Method: ▶DNA sequencing

Maxicells: Bacterial cells that lost most or their entire chromosomal DNA because of heavy irradiation by UV light. Therefore, they do not replicate their DNA. The plasmid they contain may have escaped the irradiation, and represents an appropriate replicon, and can carry on replication of that plasmid and direct the synthesis of plasmid-coded proteins. This makes such cells ideal for the expression of the plasmid-born protein without a background of cellular proteins. Especially useful are those maxi cells containing lambda vectors, which have sufficient expression of the phage repressor and thus do not permit λ protein expression. ▶mindless, ▶lambda phage, ▶replicon, ▶plasmids; Jemiole DK et al 1988 Methods Enzymol 164:691.

Maxicircle: The large mitochondrial genome. ▶mtDNA; Carpenter LR, England PT 1995 Mol Cell Biol 15 (12):6794.

Maximal Equational Segregation: It takes place when a gene is segregating independently from the syntenic centromere. It has particular significance in polyploids because it facilitates an increase of double (or multiple) recessive gametes and thus affects segregation ratios as a function of the map distance between gene and centromere. ▶autopolyploids, ▶trisomic analysis, ▶syteny, ▶polyploidy; Mather K 1935 J Genet 30:53; Rédei GP 1982 Genetics. Macmillan, New York.

Maximal Parsimony: ▶evolutionary tree

Maximal Permissive Dose: ▶radiation hazard assessment

Maximization of Gene Expression: It can be achieved by the selection or modification of optimal promoters or in prokaryotes by varying the bases immediately after the Shine-Dalgarno sequence or manipulation of the triplet preceding the first methionine codon. ▶regulation of gene expression, ▶regulation of protein synthesis, ▶Shine-Dalgarno

Maximum Likelihood Method Applied to Recombination Frequencies: The justification for the use of the maximum likelihood principle in estimating recombination frequencies is that the value obtained has the smallest variance among all procedures. The estimation is based on the maximization of:

$$\frac{n!}{a_1!a_2!\dots a_t!} (m_1)^{a_1} (m_2)^{a_2} \dots (m_t)^{a_t}$$

where n is the population size, $a_1\dots a_t$ stand for the number of individuals in the different phenotypic or genotypic classes, $m_1\dots m_t$ represent the expected proportions of individuals in classes $1\dots t$. After maximizing the logarithm of the likelihood (L)

expression with respect to the recombination fraction (p), we have:

$$L = C + a_1 \log m_1 + a_2 \log m_2 + \dots a_t \log m_t,$$

where C is a constant of the maximum likelihood that is eliminated upon differentiation:

$$\frac{dL}{dp} = a_1 \frac{d \log m_1}{dp} + a_2 \frac{d \log m_2}{dp} + a_t \frac{d \log m_t}{dp} = 0$$

For the coupling experiment (Table M3) below:

$$L = 4032 \log\left(\frac{1}{2} - \frac{1}{2}p\right) + 149 \log\left(\frac{1}{2}p\right) + 152 \log\left(\frac{1}{2}p\right) + 4035 \log\left(\frac{1}{2} - \frac{1}{2}p\right)$$

After maximization and differentiation:

$$\frac{dL}{dp} = \frac{4032}{1-p} + \frac{149}{p} + \frac{152}{p} - \frac{4035}{1-p} = 0 \text{ and } p = \frac{149 + 152}{8368} \cong 0.03597$$

The standard error s_p is calculated:

$$-\frac{1}{V_p} = S\left(mn \frac{d^2 \log m}{dp^2}\right)$$

Since

$$a \frac{d \log m}{dp}$$

was defined earlier, after a second differentiation and substitution (mn) for (a), we obtain:

$$-\frac{1}{V_p} = -\frac{n}{2} \times \frac{1}{1-p} + \frac{1}{p} + \frac{1}{p} + \frac{1}{1-p} = \frac{n}{p(1-p)} \cong \frac{8368}{0.034676} \cong 241,319$$

and hence

$$V_p = 0.000004143$$

and

$$s_p = \sqrt{V_p} \cong 0.00204$$

or by the general formula

$$s_p = \sqrt{\frac{p[1-p]}{n}}$$

Recombination in F_2 can also be estimated with the aid of the maximum likelihood principle and a coupling phase progeny will exemplify it (see Table M4):

Table M3. Hypothetical test cross examples

| | Parental | Recombinant | Recombinant | Parental | |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|--------|
| Gametic genotypes → | AB | Ab | aB | ab | Σ |
| Observed in coupling | 4032 | 149 | 152 | 4035 | 8368 |
| Expected coupling | $\frac{1}{2}n(1-p)$ | $\frac{1}{2}n(p)$ | $\frac{1}{2}n(p)$ | $\frac{1}{2}n(1-p)$ | n |
| | Recombinant | Parental | Parental | Recombinant | |
| Gametic genotypes → | AB | Ab | aB | ab | Σ |
| Observed repulsion | 638 | 21,379 | 21,096 | 672 | 43,785 |
| Expected repulsion | $\frac{1}{2}n(p)$ | $\frac{1}{2}n(1-p)$ | $\frac{1}{2}n(1-p)$ | $\frac{1}{2}n(p)$ | n |

Table M4. Recombination in F_2 coupling

| | Parental | Recombinant | Recombinant | Parental | |
|--------------------|--------------------|--------------------|--------------------|----------------|---------|
| Phenotypic classes | AB | aB | Ab | ab | Σ |
| Expectation | $\frac{n}{4}(2+P)$ | $\frac{n}{4}(1+P)$ | $\frac{n}{4}(1-P)$ | $\frac{n}{4}P$ | n (1) |
| Observed | 663 | 36 | 40 | 196 | 935 |

$$L = 663 \log\left(\frac{1}{2} + \frac{1}{4}P\right) + 36 \log\left(\frac{1}{4} - \frac{1}{4}P\right) + 40 \log\left(\frac{1}{4} - \frac{1}{4}P\right) + 196 \log\left(\frac{1}{4}P\right) \quad (2)$$

Upon maximization:

$$\frac{dL}{dP} = \frac{663}{2+P} - \frac{36}{1-P} - \frac{40}{1-P} + \frac{196}{P} = 0 \quad (3)$$

This can be reduced:

$$\frac{663(1-P(P))}{2P-P^2-P^3} - \frac{76(2+P)(P)}{2P-P^2-P^3} + \frac{196(2+P-2P-P^2)}{2P-P^2-P^3} \quad (4)$$

Common denominator omitted and multiply

$$663(P-P^2) - 76(2P+P^2) + 196(2+P-2P-P^2) \quad (5)$$

Multiplication completed:

$$663P - 663P^2 - 152P - 76P^2 + 392 + 196P - 392P - 196P^2 \quad (6)$$

Terms summed up: $392 + 315P - 935P^2 = 0.0001585$
(close to zero)

$$\begin{array}{ccc} \uparrow & \uparrow & \uparrow \\ \text{(Designate terms)} & c & b & a \end{array} \quad (7)$$

The right side of eq. (7) can be determined only after solving the quadratic equation below:

$$\begin{aligned} P &= -b \pm \frac{\sqrt{b^2 - 4ac}}{2a} = 315 \pm \frac{\sqrt{99225 + 1466080}}{1870} \\ &= -315 \pm \frac{\sqrt{1565305}}{1870} = -315 \pm \frac{1251.1215}{1870} = \frac{-1566.1215}{1870} \\ &= -0.837498; \text{ after changing sign, } P = 0.837498 \end{aligned}$$

Thus $P = 0.837498$, and $\sqrt{P} = 0.9151492 = 1 - p$, and hence the recombination fraction $p = 1 - 0.9151492 = 0.0848508$.

The variance of P ,

$$V_P = \frac{2P[1-P][2+P]}{n[1+2P]} = 0.0004495,$$

where $n (= \Sigma) = 935$ and the variance of p ,

$$V_p = \frac{VP}{4P} = 0.0001342$$

and the standard error

$$s_p = \sqrt{V_p} = \sqrt{0.0001342} = 0.01158$$

Thus, the frequency of recombination between the two genes is $\sim 0.085 \pm 0.012$. Data may be entered at

step (6) to expedite routine calculations. ▶ [maximum likelihood principle](#), ▶ [recombination frequency](#), ▶ [F₂ linkage estimation](#), ▶ [information](#); Mather K 1957 The Measurement of Linkage in Heredity. Methuen, London, UK; Wu R, Ma C-X 2002 Theor Population Biol 61:349.

Maximum Likelihood Principle: It provides a statistical method for estimating the optimal parameters from experimental data. The best statistics for the computations is that it provides the smallest variance., E.g., the variance of the median of a sample is $\frac{\pi a^2}{2n}$ which is $\frac{\pi}{2} = 1.57$ times the size of the variance of the mean (\bar{x}). Therefore the mean is a much better characteristic of the population than the median. The binomial probability is expressed as: $\binom{n}{r} p^r (1-p)^{n-r}$ giving the probability (p) that (r) events occur in a sample of (n).

The relative probability of r/n events for different values of (p) is called the *likelihood*. The procedure that facilitates finding a population parameter (θ) that maximizes the likelihood of a particular observation is a *maximum likelihood procedure*. If the dispersion of a population follows the normal distribution, the variance $V = \sigma^2$, is a maximum likelihood estimator of the distribution of that population. All other methods need to be compared with and tested against this method before their results can be accepted and used.

Naturally, all statistics provide only predictions and not direct proof regarding the biological mechanism concerned. Therefore, careful collection of data, replications, sufficient sample sizes, etc., are indispensable for accuracy and predictability. The maximum likelihood mandates that the choice of the parameter (θ) makes the likelihood, $L(X_1, X_2, \dots, X_n | \theta)$ the largest value. Example: a random sample of 20 is obtained and among them, say 12 belongs to a particular class. We can hypothesize that the true frequency of this class is either (I): $p = 0.6$ or (II): 0.5 or (III): 0.7 . According to the normal distribution then:

$$\begin{aligned} \text{(I)} \binom{20}{12} (0.6)^{12} (0.4)^8 &= \frac{20!}{12!8!} (0.6)^{12} (0.4)^8 \\ &= 125.970 \times 0.002176782 \\ &\quad \times 0.00065536 \\ &\cong 0.17971 \end{aligned}$$

$$\begin{aligned} \text{(II)} \binom{20}{12} (0.5)^{12} (0.5)^8 &= \frac{20!}{12!8!} (0.5)^{12} (0.5)^8 \\ &= 125.970 \times 0.000244140 \\ &\quad \times 0.00390625 \\ &\cong 0.12013 \end{aligned}$$

$$\begin{aligned}
 \text{(III)} \binom{20}{12} (0.7)^{12} (0.3)^8 &= \frac{20!}{12!8!} (0.7)^{12} (0.3)^8 \\
 &= 125.970 \times 0.013841287 \\
 &\quad \times 0.00006561 \\
 &\cong 0.11440
 \end{aligned}$$

Obviously, hypothesis (I) has the maximum likelihood to be applicable to this case. After this simple demonstration, we can generalize the likelihood function as:

$$L(X_1, X_2, \dots, X_N | p) = \binom{N}{r} p^r (1-p)^{N-r}$$

where X are the samples, N = population size, p = probability, and $r = 0, 1, \dots, N$. The maximized likelihood is conveniently expressed by the logarithm of the likelihood function:

$$\log L = \log \binom{N}{r} + (r) \log(p) + (N-r) \log(1-p)$$

After differentiation to (p) and equating it to zero:

$$\frac{d}{dp} \log L = \frac{r}{p} - \frac{N-r}{1-p} = 0.$$

After bringing it to the common denominator:

$$\frac{r(1-p) - (N-r)p}{p(1-p)} = 0$$

The denominator omitted:

$r(1-p) - (N-r)p = 0 = r - rp - Np + rp$, and hence $p = r/N$ and this is the *maximum likelihood estimator* of p . Similarly, it can be shown that for a population in normal distribution the arithmetic mean of the sample $\left(\frac{\sum x_i}{N}\right)$ is the maximum likelihood estimator of the μ . The probability P for a multinomial distribution is: $\frac{N!}{x_1!x_2! \dots x_r!} p^x q^y r^z$ where p, q, r, \dots are the probabilities of X, Y, Z, \dots classes. Although we may not know these probabilities but we may have experimentally observed the classes (genotypes, alleles, etc.), and we can derive the likelihood function which permits the estimation of the parameters of p, q , etc. If in a random mating population the proportion of A is p^2 , that of B is $2pq$ and that of C is q^2 , we can write the likelihood function as:

$$L = \frac{N!}{A!B!C!} (p^2)^A (2pq)^B (q^2)^C$$

from which after logarithmic conversion and differentiation we can obtain the value of $p = \frac{2A+B}{2N}$ and $q = \frac{2C+B}{2N}$ and the variance $V_p = \frac{pq}{2N}$.

For an in-depth treatment of maximum likelihood, mathematical statistics monographs should be consulted. The maximum likelihood method is widely used in decision-making theory. In genetics, it is most commonly used for the estimation of recombination and allelic frequencies. (See maximum likelihood method applied to recombination frequencies, probability, information)

Maximum Parsimony: same as maximal parsimony.
▶evolutionary tree

Maximum Tolerated Dose (MTD): It does not cause more than 10% weight loss, does not cause clinical toxicity, death or disease that would shorten life span.

Maxizyme: A dimeric ribozyme

May-Hegglin Anomaly (Dohle leukocyte inclusions with giant platelets): An asymptomatic dominant granulocyte and platelet disorder resulting often in thrombocytopenia located to chromosome 22q12.3-q13.1. The locus is about 0.7 megabase DNA. In the granulocytes, spindle-shaped cytoplasmic inclusions have been observed that appear to be the depolarization relics of ribosomes. The Fechtner syndrome and the Sebastian syndrome share the major characteristics and the chromosomal location (22q13.3-q13.2). The non-muscle myosin heavy chain IIA (MYH9) mutations appear to account for the three diseases. The Alport syndrome shares some of the symptoms also although that is a different disease.
▶hemostasis, ▶platelet anomalies, ▶giant platelet; Martignetti JA et al 2000 Amer J Hum Genet 66:1449; Kelley MJ et al 2000 Nature Genet 26:106.

Maytansinoids: The extract of tropical trees or shrubs with an LDLo of 190 $\mu\text{g/kg}$ as intravenous dose for humans (see Fig. M30). Related compounds are rifamycin, streptovaricin, macrolides, etc.
▶magic bullet, ▶LDLo

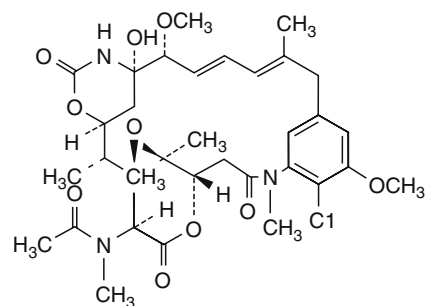


Figure M30. Maytansin

MBD (methyl-binding domain): MBD proteins are members of the histone deacetylase complex and bind to DNA and remodel the chromatin resulting in

gene silencing. *Mbd2*⁻ homo or heterozygous mice displayed fewer intestinal tumors than the wild type for the gene. ▶[histone deacetylase](#), ▶[5-azacytidine](#); Sansom OJ et al 2003 Nature Genet 34:145.

MBF: ▶[Mbp1](#), ▶[Swi](#)

MBP: Maltose binding protein, encoded by gene *malE* (91 min) of *E. coli*.

Mbp: Megabase pair, 1 million base pair.

Mbp1 (mitotic binding protein): The components of the MBF (microtubule-binding factor) with Swi6, mediate S phase expression of the cell cycle. ▶[cell cycle](#), ▶[SBF](#), ▶[Swi](#); Iyer VR et al 2001 Nature [Lond] 409:533.

μC (microcurie): 3.7×10^4 dps [disintegration/second]. ▶[Curie](#), ▶[isotopes](#)

MCA (metabolic control analysis): The study of complex enzyme systems in response to any changes in substrate(s). It may facilitate the detection of thresholds potentially leading to disease. It may permit the classification of genes and protein regarding their role in metabolic networks and thus may help drug discovery. ▶[proteomics](#); Cascasnte M et al 2002 Nature Biotechnol 20:243.

McArdle's Disease: ▶[glycogen storage disease type V](#)

McCune-Albright Syndrome (MAS, GNAS1, 20q13.2): A pituitary neoplasia resulting from excessive secretion of growth hormone, caused by mutation and constitutive expression of the GTP-binding subunit (*G_s*) of a G-protein. It is characteristically a polyostotic fibrous dysplasia, café-au-lait skin lesion, and gonadotropin-independent gonadal precocious activation. MAS is generally not inherited, probably because germline *G_s*-activating mutations are lethal. It is believed that the somatic mutation in MAS patients occurs early in development, and therefore the clinical spectrum in each individual is determined by the tissue distribution of mutant-bearing cells (Rey RA et al 2006 Hum Mol Genet 15:3538). ▶[pituitary gland](#), ▶[pituitary tumor](#), ▶[G-proteins](#), ▶[securin](#), ▶[Albright hereditary osteodystrophy](#), ▶[pseudohypoparathyroidism](#), ▶[gonadotropin](#), ▶[café-aut-lait](#)

McDonald-Kreitman Hypothesis: The excess of replacement substitutions in the amino acids in proteins indicates that they are the consequences of selectively advantageous mutations. Reduction in non-synonymous mutations indicates that they are selected against. ▶[mutation neutral](#), ▶[amino acid replacement](#), ▶[Ka/Ks](#), ▶[selection inferred from DNA sequences](#); McDonald JH, Kreitman M 1991 Nature [Lond] 354:114.

MCF Oncogene (synonymous with DBL, ROS): The human mammary carcinoma proto-oncogene was assigned to human chromosome Xq27. It encodes a serine-phosphoprotein (p66). ▶[oncogenes](#), ▶[ROS](#)

MCH (melanin-concentrating hormone): MCH reduces appetite and increases metabolic rate. It encodes a neuropeptide precursor at 12q23 and PMCHL1 at 5p14 and PMCHL2 at 5q13 are truncated versions of MCH. ▶[obesity](#), ▶[leptin](#), ▶[melanin](#)

Mch: ICE-related proteases. ▶[ICE](#), ▶[apoptosis](#)

MCK: A muscle-specific kinase. ▶[MyoD](#)

MKusick-Kaufman Syndrome (MKKS, 20p12): A recessive developmental anomaly including accumulation of fluids in the uterus and vaginal area (hydrometrocolpos), extra finger at the area of the little finger (postaxial polydactyly), heart disease, etc. Several other genes map apparently to the same chromosomal location, e.g., that of the Bardet-Biedl (BBS) syndrome. The distinction between MKKS and BBS is by the three criteria named above. Some of the symptoms are shared also the Ellis-van Creveld syndrome that is at another chromosomal location. The critical protein appears to be a chaperonin. ▶[Bardet-Biedl syndrome](#), ▶[Ellis-van Creveld syndrome](#); David A et al 1999 J Med Genet 36:599; Slavotinek AM et al 2000 Nature Genet 26:15.

McLeod Syndrome (XK): A recessive human Xp21 region deficiency of the Kx blood antigen precursor. The symptoms vary because of overlapping defect with closely linked genes, particularly CGD (chronic granulomatous disease). It may be associated with acanthocytosis, characteristic for abetalipoproteinemia. ▶[abetalipoproteinemia](#), ▶[granulomatous disease chronic](#), ▶[Kell-Cellano blood group](#), ▶[contiguous gene syndrome](#)

MCM1 (licensing complex): A yeast DNA-binding protein, product of the minichromosome maintenance gene also involved in the regulation of mating type; it controls the entry into mitosis. All eukaryotes have apparently at least six different MCMs assisting in DNA replication. MCM 2–7—a putative helicase—appears to become activated in telophase before the exit cell cycle (Dimitrova DS et al 2002 J Cell Sci 115:51). Some have helicase and DNA-dependent ATPase function. Mcm10 is a component of the replication fork and apparently is required for the function of DNA polymerase-α (Ricke RM, Bielinsky A-K 2004 Mol Cell 16:173). The licensing actually means that the chromatin must be subject to quality control to qualify for replication after mitosis. MCM also prevents the re-entry into S phase. ▶[mating type determination in yeast](#), ▶[MCM3](#), ▶[ARS](#), ▶[Cdc45/Cdc46/Mcm5](#), ▶[cell cycle](#), ▶[CDC19](#), ▶[CDC21](#),

►Cdc6, ►Cdc18, ►Cdt1, ►geminin, ►reinitiation of replication, ►DNA polymerases, ►sex hormones; Tye BK 1999 Annu Rev Biochem 68:649; Lee J-K, Hurwitz J 2000 Proc Natl Acad Sci USA 98:54; Nishitani H et al 2001 J Biol Chem 276:44905.

MCM3: It is apparently the same as the replicational licensing factor (RLF), that appears in tight binding to DNA during interphase but released during S phase. This factor assures that within a cell just one cycle of DNA replication occurs. This protein belongs to the family of MCM1 to MCM5 factors detected in yeast. ►MCM1, ►replication licensing factor, ►cell cycle

MCP (membrane cofactor protein, CD46): MCP regulates (along with other proteins such as DAF, factor H and C-4 binding protein) complement functions and protects the cells from attacks by their own defense system. MCP and DAF control also reproductive functions (spermatozoa, extrafetal tissues) besides infectious diseases and xenografts. These functions are encoded in human chromosome 1q3.2 region. MCP (14 exons) has four isoforms generated by alternative splicing of a single transcript. MCP shares a 34 amino acid signal peptide with DAF (11 exons). The signal sequence is followed by *complement control protein repeats* (CCPR) where C3b and C4b complement components bind. Glycosylated and serines, threonines, prolines (STP) residues follow the CCPR sequences. The other regions of MCP and DAF are different. ►complement, ►decay accelerating factor, ►xenotransplantation, ►signal sequence, ►atherosclerosis; Kemper C et al 2001 Clin Exp Immunol 124(2):180.

MCP-1 (monocyte chemoattractant protein): It controls (along with IL-8) adhesion of monocytes to the vascular epithelium. It is inducible by the platelet-derived growth factor (PDGF). Mice lacking these receptors are more prone to atherosclerosis. ►atherosclerosis, ►chemokines, ►monocytes; Yamamoto T et al 2001 Eur J Immunol 31:2936.

MCR (mutation cluster region): A segment of a gene where mutations occur at high frequency.

mcr: ►methylation of DNA

MCS: Multiple cloning sites. ►polylinker

M-CSF: ►macrophage colony stimulating factor, ►macrophage

MDA (multiple displacement amplification): MDA can be carried out from crude whole blood or tissue culture cell. As small as 1–10 copies of human genomic DNA can be amplified to 20–30 microgram. It has been used for analysis of the entire genome of single microbial cells. The product is suitable for various genetic analyses such as SNP, Southern blots,

and various diagnostic purposes. ►amplification, ►SNP, ►Southern blot; Dean FB et al 2002 Proc Natl Acad Sci USA 99:5261.

Mda-7 (IL24): Encodes a cytokine, which selectively inhibits human melanoma cancer cells without conspicuous side effects. ►IL24; Fisher PB et al 2003 Cancer Biol Ther 2 Suppl 1:S23.

MDC1: A mediator of DNA checkpoint control. ►checkpoint, ►histone variants; Lou Z et al 2003 Nature [Lond] 421:957.

mdg: ►copia

mDIP (methylated DNA immunoprecipitation): It uses antibodies specific for 5-methylcytosine residues and the procedure can distinguish between some cancerous and normal tissues (Keshet I et al 2006 Nature Genet 38:149). ►landmark genomic scanning

Mdl1: A mitochondrial export protein of the AAA transporter family. ►AAA proteins

MDM2 (murine double-minute homolog, MDM2 is at 12q14.3-q15): A cellular oncoprotein that can bind and downregulate p53 tumor suppressor, attach to the retinoblastoma suppressor, and can stimulate transcription factors E2F1 and DP1, and thus may promote tumorigenesis. MDM2 is an E3 ubiquitin ligase that assists in the degradation of p53. The cis-imidazole analogs (nutlins) are antagonists of MDM2 and can activate the p53 pathway, leading to cell cycle arrest, apoptosis (see Fig. M31) and inhibition of tumor growth (Vassilev LT et al 2004 Science 303:844). Nutlin prevents the interaction of MDM2 with p53, and the growth of half of the cancers by the normal tumor suppressor function of p53 is restored (Harris C 2006 Proc Natl Acad Sci USA 103:1659; Tovar C et al 2006 Proc Natl Acad Sci USA 103:1888).

MDM2 can suppress TGF- β effect also without the inactivation of p53. MDM2 is regulated by RASA through the Raf/Mek/Map kinase pathway. Raf also activates p19^{ARF}, an inhibitor of MDM2. MDM2 involves TGF resistance in various tumor cell lines. MDM2 prevents transcriptional activation by Sp1 but the retinoblastoma protein displaces Sp1 from MDM2 and restores Sp1 transcriptional activity. The RING

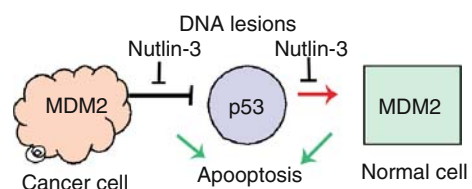


Figure M31. MDM2 functions

domain of MDM2 may stimulate ubiquitins (Minsky N, Oren M 2004 Mol Cell 16:631). Loss of MDM2 or MDM4 leads to lethality in p53-dependent manner in the mouse. Mice lacking MDM2 in the central nervous system develops hydranencephaly after 14.5 days of pregnancy whereas lacking MDM4 results in porencephaly (cerebrospinal fluid-filled cavities of the brain) after 17.5 days of embryonic development. Both mutations can be rescued by inhibition of p53 (Xiong S et al 2006 Proc Natl Acad Sci USA 103:3226). Similar diseases are known also in humans that are encoded in different chromosomes. ►[oncogenes](#), ►[transcription factors](#), ►[retinoblastoma](#), ►[E2F](#), ►[DP1](#), ►[p53](#), ►[TGF](#), ►[cyclin G](#), ►[ubiquitins](#), ►[ARF](#), ►[apoptosis](#), ►[anencephaly](#), ►[endocytosis](#), ►[Zinc finger](#); Johnson-Pais T et al 2001 Proc Natl Acad Sci USA 98:2211.

MDR: ►[multidrug resistance](#)

MDS (macronuclear destined sequences): From the germline DNA during vegetative development of ciliates internal sequences are eliminated by the process of chromosome diminution and only the MDS is retained in the macronucleus. ►[chromosome diminution](#), ►[Paramecium](#), ►[macronucleus](#); Prescott DM 1997 Curr Opin Genet Dev 7:807.

Meal Worm (*Tenebrio molitor*): A larger X and a smaller Y chromosome in this insect determine sex. ►[anti-freeze protein](#)

Mealybug: A member of the coccidian taxonomic group of animals with the name reflecting the “mealy” appearance of the wax coat of the body of the insects and the mealy appearance of their colonies on the surface of plants (see Fig. M32). They received attention by the peculiarity of their chromosome behavior. During the cleavage divisions immediately after fertilization, all the chromosomes are euchromatic. After blastula one-half of the chromosomes ($2n = 10$) becomes heterochromatic in the embryos which develop into males. At interphase these heterochromatic chromosomes clump into a chromocenter. By metaphase, the heterochromatic and euchromatic sets are no longer distinguishable. In the males, the first meiotic division is equational and during the second division the two types of chromosomes go to opposite poles. Two of the four nuclei are heterochromatic and two euchromatic. The heterochromatic nuclei then disintegrate and the euchromatic cells proceed to



Figure M32. Mealybug

spermiogenesis. The euchromatic set of the fathers becomes later the heterochromatic chromosomes of the sons. This was verified by X-raying the females and males. Only 3% of daughters of males irradiated by 16,000 R survived but the sons were unaffected even after 30,000 R. Some sons survived even after 90,000 R exposure of the fathers. Thus, sex appears to be determined developmentally in these insects. ►[chromosomal sex determination](#); Nur U 1967 Genetics 56:375; Palotta D 1972 Can J Genet Cytol 15:809.

Mean: The *arithmetic mean* \bar{x} is equal to the sum (Σ) of all measurements (x) divided by the number (n) of all measurements, or $\bar{x} = \frac{\sum x}{n}$. The *geometric mean* (G) is the n th root of the product of all measurements: $G = \sqrt[n]{x_1 \cdot x_2 \cdot \dots \cdot x_n}$. The *harmonic mean* (H) is the inverse average of the reciprocals of the measurements $H = \frac{n}{\sum 1/x}$.

Examples:

$$\bar{x} = \frac{2 + 8}{2} = 5, G = \sqrt[3]{2 \times 8 \times 4} = \sqrt[3]{64} = 4,$$

$$H = \frac{2}{[1/2] + (1/8)} = 3.2.$$

The *weighted mean* is the calculated mean multiplied by the pertinent frequency of the groups in a population. (See variance)

Mean Lethal Dose: Mutagens or toxic agents are denoted by LD_{50} . ►[LD₅₀](#), ►[LDLo](#), ►[LC50](#)

Mean Squares: The average of the squared deviations from the mean; it is obtained by dividing the sum of the squared deviations by the pertinent degrees of freedom. Basically, this is the estimated variance. ►[variance](#), ►[variance analysis](#), ►[intraclass correlation](#)

Meander: When two consecutive β -sheets of a protein are adjacent and antiparallel. ►[protein structure](#)

Measles: An infectious viral disease, practically eliminated in the USA since compulsory vaccination was introduced in the 1960s. Sporadically—after importation from a foreign country—local measles outbreaks have however occurred (Parker AA et al 2006 N Engl J Med 355:447).

Measurement Units: Length: 10 ångström (Å) = 1 nanometer (nm), 1000 nm = 1 micrometer (µm), 1000 µm = 1 millimeter (mm), 10 mm = 1 centimeter (cm), 100 cm = 1 m.

Volume: 1000 microliter (µL or λ = 1 milliliter (mL), 1000 mL = 1 liter (L);

Weight: 1000 picogram (pg) = 1 nanogram (ng), 1000 ng = 1 microgram (µg), 1000 µg = 1 milligram (mg), 1000 mg = 1 gram (g), 10 g = 1 dekagram (dg), 100 dg = 1 kilogram (kg).

Generally: milli = 10^{-3} , micro = 10^{-6} , nano = 10^{-9} , pico (p) = 10^{-12} , fempto (f) = 10^{-15} , atto (a) = 10^{-18} and kilo (k) = 10^3 , mega (M) = 10^6 , giga (G) = 10^9 and tera (T) = 10^{12} . ▶*M_i*, ▶dalton, ▶agricultural measures; Unit Converter: [http:// mypage.bluewin.ch/berthod/vuc/](http://mypage.bluewin.ch/berthod/vuc/).

MEC: ▶degenerin, ▶ion channels

MEC1: A kinase locus of yeast (member of the PIK family); its phosphorylates RAD53 and RAD9, signal transducers of DNA damage. Mec3 protein seems to regulate telomere length. Mec1 and Rad53 are also involved in the G1, S and G2 checkpoint control. Tel1 can carry out the Mec1 function also. The homologs are *SAD3*, *ESR1*, and the human gene is homologous to AT, responsible for ataxia telangiectasia. ▶ataxia, ▶RAD, ▶signal transduction, ▶DNA replication, ▶cell cycle, ▶checkpoint, ▶double-strand break, ▶PIK, ▶telomeric silencing; Tercero JA, Diffley JFX 2001 Nature [Lond] 412:553; Lopes M et al 2001 Nature [Lond] 412:557.

Mechanism-based Inhibition: ▶regulation of enzyme activity

Mechanosensory Genes: These are involved in the neurobiological control of proprioceptive sensations. The proprioceptive nerve terminals are located in the muscles, joints, tendons and the ears and perceive the information about movements, touch, balance and hearing. The process converts mechanical forces into electrical signals through special ion channels. ▶zona pellucida

Mecillinam: A β -lactam type antibiotic, which targets the penicillin-binding protein 2 (PBP2) required for the elongation of the bacterial cell wall. ▶ β -lactamase

Meckel Syndrome (MKS): A rare complex recessive syndrome (MKS1, 17q22-q23) with most specific characteristics are the brain defects, cystic kidneys and polydactyly. MKS1 is also called the Meckel-Gruber syndrome. In Finnish populations, it may occur however in the near 10^{-4} range. The mouse homolog is at chromosome 11; similar genes occur in the majority of organisms and appear to have ciliary functions (Kyttälä M et al 2006 Nature Genet 38:155). MKS genes were located also at 11q13, and at 8q21.13-q22.1. The latter encodes a 995-amino acid seven-transmembrane receptor protein (meckelin) of unknown function (Smith UM et al 2006 Nature Genet 38:191). ▶neural tube defects, ▶polydactyly, ▶kidney diseases, ▶cilia, ▶Joubert syndrome

MeCP1 (methyl-CpG binding protein, MBD1): It binds methylated CpG sequences in the DNA and is part of a transcriptional repression complex along with histone deacetylase. It is encoded at human chromosome 18q21. ▶CpG, ▶islands, ▶histone deacetylase, ▶methylation of DNA

MeCP2: methyl-CpG binding protein encoded at Xq28 and it is involved with the Rett syndrome autism. It seems to be involved in brahma-containing SWI/SNF chromatin remodeling system (Harikrishnan KN et al Nature Genet. 38:964). ▶autism, ▶brahma, ▶Rett syndrome; Chen WG et al 2003 Science 302:885.

MED-1: ▶null promoter

Medaka (*Oryzias latipes*): A small, fertile fish (see Fig. M33) well suited for developmental studies because it is genetically pigment-free (due to four recessive genes). Transparent stock is available that permits the direct visualization through a stereoscopic microscope, the major internal organs (heart, spleen, blood vessels, liver, gut, gonads, kidney, brain, spinal cord, eye lens, air bladder, etc.) in live animals. Medaka draft genome (700 megabases), is less than half of the zebrafish genome and 20,141 genes are predicted (Kasahara M et al 2007 Nature [Lond] 447:714). ▶zebrafish; Wakamatsu Y et al 2001 Proc Natl Acad Sci USA 98:10046; ▶pufferfish; [http:// medaka.utgenome.org](http://medaka.utgenome.org).



Figure M33. Medaka female (courtesy of Dr. Yuko Wakamatsu)

Medea Factor (maternal effect dominant embryonic arrest): A lethality factor transmitted through the egg cytoplasm, which kills the offspring, in, e.g., *Tribolium*, unless it inherits from either parent a rescuing M factor. ▶killer genes, ▶*Tribolium*; Beman RW, Fries KS 1999 Heredity 82:529; Grossniklaus U et al 1998 Science 280:446.

Median: A statistical concept that indicates that equal numbers of (variate) observations are on its sides at both minus and plus directions. ▶mean, ▶mode

Median-Joining Networks: A statistical procedure for reconstructing phylogenies from intra-specific data. The difficulties are in the large required sample sizes and small genetic differences and a network of potential evolutionary paths overcomes these obstacles to construct simple evolutionary trees. It proved useful for the analysis of mitochondrial DNA phylogenies (Bandelt HJ et al 1999 Mol Biol Evol 16:37).

Mediator: Assembly factors of RecA and like recombinases and single-strand DNA binding proteins. The mediator of the GAL gene of yeast is associated with

the upstream activator sequences and not with the core promoter or with TBP or TFIID (Kuras L et al 2003 Proc Natl Acad Sci USA 100:13887). ►[RecA](#), ►[core promoter](#), ►[UAS](#), ►[TBP](#), ►[transcription factors](#); Gasior SL et al 2001 Proc Natl Acad Sci USA 98:8411.

Mediator Complex (Meds): A group of ~20 or more proteins involved in the facilitation of transcription by RNA polymerase II in yeast and other eukaryotes (see Bjorklund S et al 1999 Cell 96:759). The mediator complex is a co-activator, co-repressor and a general transcription factor. These proteins share subunits and participate in a large variety of different complexes, which have different functions in gene expression and developmental control. They may mediate chromatin remodeling, interact with various proteins (activators), general transcription factors and directly or indirectly with RNA polymerase II. One form of RNA polymerase II includes an additional polypeptide, Gdown1 and it is called Pol II(G). The latter type of polymerase definitely requires the Mediator for efficient transcription (Hu X et al 2006 Proc Natl Acad Sci USA 103:9506). The yeast Mediator proteins interacting with Med17(Srb4) as a 223 kDa complex is called a *mediator head module*. It interacts with an RNA polymerase II-TFIIF complex, but not with the polymerase or TFIIF alone. This interaction is lost in the presence of a DNA template and associated RNA transcript, recapitulating the release of Mediator that occurs upon the initiation of transcription (Takagi Y et al 2006 Mol Cell 23:355). MSA specifically restricts PIC (preinitiation complex) function in the absence of the Mediator. This function is fully restored in the presence of the Mediator, indicating that Mediator dependency in the metazoan cell is imparted, at least in part, through factors that negatively modulate unregulated PIC function. That one such activity resides in a complex containing hSpt5 and hSpt4, which were previously identified as components of the transcription elongation factor DRB sensitivity-inducing factor DSIF (Malik S et al 2007 Proc Natl Acad Sci USA 104:6182). ►[Srb](#), ►[DRIP](#), ►[NAT](#), ►[chromatin remodeling](#), ►[activator proteins](#), ►[transcription factors](#), ►[TBP](#), ►[TAF](#), ►[co-activator](#), ►[re-initiation](#), ►[elongator](#), ►[preinitiation complex](#), ►[DRB](#), ►[DSIF](#), ►[PIC](#); Svejstrup JQ et al 1997 Proc Natl Acad Sci USA 94:6075; Gustafsson CM et al 1998 J Biol Chem 273:30851; Myers LC, Kornberg RD 2000 Annu Rev Genet 69:729; Gustafson CM et al 2001 Mol Microbiol 41:1; Boube M et al 2002 Cell 110:143; Conaway RC et al 2005 Trends Biochem Sci 30:250.

Medicago: ►[alfalfa](#)

Medical Error: It kills 44,000 to 98,000 people in US hospitals annually (Hayward RA, Hofer TP 2001 J Am Med Assoc 286:415).

Medical Genetics: Genetics applied to medical problems. ►[clinical genetics](#), ►[human genetics](#), ►[genomic medicine](#); <http://research.marshfieldclinic.org/genetics/>.

Medical Terminology (UMLS): <http://umlsks.nlm.nih.gov>, acronyms: <http://invention.swmed.edu/argh/>; <http://medstract.med.tufts.edu/acro1.1/index.htm>; abbreviations: <http://www.hpl.hp.com/research/idl/projects/abbrev.html>.

Medicine: ►[diseases in humans](#), ►[preventive medicine](#); history and encyclopedia of medicine: <http://www.mic.ki.se/History.html>.

Medicinal Chemistry: It is involved with drug design and development.

Mediterranean Fever, Familial (FMF): A human chromosome-16p13 recessive disease with recurrent spells of fever, pain in the abdomen, chest and joints and red skin spots (erythema). It is a type of amyloidosis. The basic defect involves a 781-amino acid protein, pyrin. In some populations the prevalence, gene frequency and carrier frequency may be 0.00034, 0.019, and 0.038, respectively. ►[amyloidosis](#); Schaner P et al 2001 Nature Genet 27:318.

Medline: A medical bibliographic system of the National Library of Medicine USA. It can be reached on-line as part of the MEDLARS database, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed>. ►[BITOLA](#)

MedMiner: It extracts and organizes relevant sentences in the scientific literature based on a gene, gene-gene or gene drug query. (See <http://discover.nci.nih.gov/textmining/main.jsp>).

medRNA: mini-exon-dependent RNA. ►[Trypanosoma brucei](#)

Medulla: The inner part of organs, the basal part of the brain connecting with the spinal chord. ►[brain human](#)

Medullary Bone: An ephemeral tissue inside the long bones of female birds. It is formed during ovulation by the increased level of estrogen. Its role is to accumulate calcium that is mobilized for the building of eggshells.

Medulloblastoma (17p13.1-p12, 10q25.3-q26.1, 1p32): A brain cancer of childhood. Its frequency in adenomatous polyposis increases by about two orders of magnitude. Dysregulation of the sonic hedgehog signaling may lead to the disease. ►[Gardner](#)

syndrome, ►nevoid basal cell carcinoma, ►squamous, ►sonic hedgehog

Meekrin-Ehlers-Danlos Syndrome: A connective tissue disorder.

MEF: A series of myocyte enhancer binding factors that specifically potentiate the transcription of muscle genes and thus differentiation of various types of muscles and myoblasts. The MEF group belongs to the family of MADS domain protein. MEF2 is a Ca^{2+} -regulated transcription factor and it is actively transcribed during development of the central nervous system. MEF2 is activated when it dissociates from histone deacetylase in response MAPK signals. Nur77 and Nor1 steroid receptors mediate apoptosis of T cell receptors controlled by MEF2. Mutation in MEF-2 may lead to coronary heart disease and myocardial infarction (Wang L et al 2003 Science 302:1578). The MEF2C is involved in inflammation responses and it is stimulated by lipopolysaccharides of Gram-negative bacteria. MEF2C transactivation is regulated through phosphorylation by p38. ►MADS box, ►MAPK, ►MyoD, ►MYF5, ►MRF4, ►myocyte, ►p38, ►Gram-negative, ►Nur77, ►Nor1, ►apoptosis, ►coronary heart disease, ►myocardial infarction, ►T cell; Mora S et al 2001 Endocrinology 142:1999; Han A et al 2003 Nature [Lond] 422:730; regulation of excitatory synapses: Flavell SW et al 2006 Science 311:1008.

Megabase (Mb): 1,000,000 nucleic acid bases.

Megablast: ►BLAST; <http://genopole.toulouse.inra.fr/blast/megablast.html>.

Megabyte (MB): 1 megabyte is 1024 K (1 K= 1024 bytes [2^{10}]; 1 byte = 8 bits [binary digits]). Conversion of pages into MB may be affected substantially by font size, formatting, size of the window, illustrations included, etc.

Megadalton (Mda): Mda is 10^6 dalton; 1 da (or Da) = 1.661×10^{-24} g.

Megalencephalic Leukoencephalopathy (MLC, 22qtel): The recessive enlargement of the brain, defective motor functions (ataxia, spasms) and mental deterioration caused by defects in a transmembrane protein. Onset is within a year of birth and a slow progressive realization of the symptoms follows.

Megaevolution: The process and facts of descent of higher taxonomic categories. ►evolution, ►macroevolution

Megagametophyte: One of the four, the functional, haploid products of female meiosis (megaspores) in

plants, it develops into embryo sac. Its origin and most prevalent developmental paths are outlined in a figure at gametophyte. ►gametophyte [female]

Megakaryocytes: Large cells in the bone marrow with large lobed, polyploid nuclei; their cytoplasm produces the platelets. Megakaryocyte formation from stem cells is regulated by surviving, the cytokine receptor cMpl and its ligand the megakaryocyte lineage-specific growth factor (meg-CSF), which is homologous to erythropoietin and has both meg-CSF and thrombopoietin-like activities. ►erythropoietin, ►thrombopoietin, ►platelet, ►survivin

Megalin: A cell surface apolipoprotein-B receptor. Its deficiency may lead to holoprosencephaly. There is some disagreement concerning megalin-mediated pathway of sex steroid movement (Rosner W 2006 Cell 124:455; Willnow TE, Nykjaer A 2006 Cell 124:456). ►holoprosencephaly, ►cholesterol, ►apolipoprotein; Barth JL, Argraves WS 2001 Trends Cardiovasc Med 1:26.

Megaloblast: Large, nucleated, immature cells giving rise to abnormal red blood cells.

Megaloblastic Anemia: The autosomal dominant (human chromosome 5q11.2-q13.2) deficiency of dehydrofolate reductase (involved in the biosynthetic path of purines and pyrimidines) resulting in hematological and neurological anomalies. Megaloblastic anemia 1 (MGA1, 14q32) is a vitamin B12 absorption defect. The symptoms may be alleviated by 5-formyltetrahydrofolic acid. A rare recessive type (10p12.1) is caused by intestinal malabsorption of vitamin B₁₂, due to defects in cubilin, the intrinsic factor (IF)-B₁₂ receptor. In the Imerslund-Grasbeck syndrome (11q12) the vitamin 12 deficiency is not corrected by cubilin alone but with co-administration of B12 it is effective (Tanner SM et al 2005 Proc Natl Acad Sci USA 102:4130).

Another form (TRMA, Rogers syndrome, 1q23.2-q23.3) responds favorably to thiamin. In chromosome 5p15.3-p15.2 methyl-cobalamine and methionine synthase reductase have been located. Megaloblastic anemia may be found in several other syndromes too. ►phosphatase [ACPI], ►megaloblast, ►folic acid, ►thiamin, ►anemia, ►transcobalamine deficiency; Tanner SM et al 2003 Nature Genet 33:426.

Megalocytosis: Induction of gradually increasing cell size.

Megaspore: ►megagametophyte, ►gametogenesis, ►megasporocyte

Megaspore Competition: It determines which of the four products of meiosis (megaspore) in the female (plant)

becomes functional (see Fig. M34). It occurs only in a few species such as *Oenotheras*. ►certation, ►pollen, ►gametogenesis

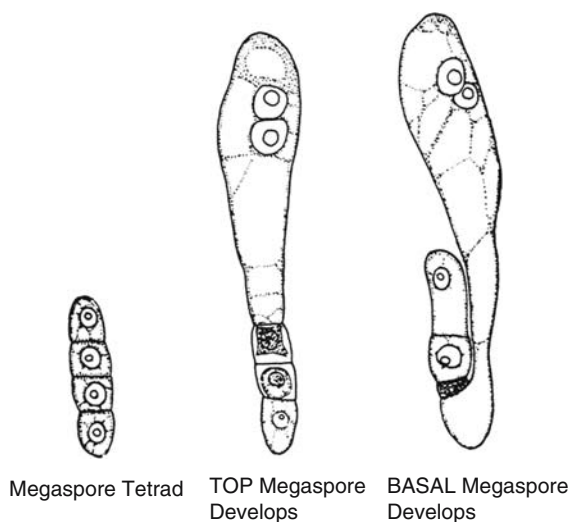


Figure M34. Megaspore competition in the *Oenotheras* where normally the top spore of the tetrad is functional but in case there is a deleterious gene in the top spore, the basal spore may compete with it successfully. (After Renner O. from Goldschmidt R 1928 Einführung in die Vererbungswissenschaft. Springer-Vlg. Berlin, Germany)

Megaspore Mother Cell: A diploid cell that produces the haploid megaspores through meiosis in the female plant (see Fig. M35). ►gametophyte [female]

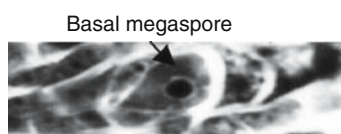


Figure M35. Megaspore mother cell

Megasporocyte: The same as megaspore mothercell. ►gametogenesis, ►gametophyte

MEI41: A 270-kDa *Drosophila* phosphatidylinositol kinase. When inactivated meiotic recombination is reduced. ►PIK

Meiocyte: The cell that undergoes meiosis. ►meiosis

Meiosis: The two step-nuclear divisions, which reduce somatic chromosome number ($2n$) to half (n) and is usually followed by gamete formation. (See Fig. M36). Meiosis is genetically the most important step in the life cycle of eukaryotes. Meiosis proceeds

from the 4C sporocyte (in diploids) and includes one numerically reductional and one numerically equational chromosome divisions.

Synapsis takes place at prophase I to metaphase I. Chiasmata may be visible by the light microscope during prophase I. Centromeres do not split at anaphase I and the sister-chromatids are held together at the centromeres during the separation of the bivalents at anaphase I. At the completion of meiosis I the chromosome number is reduced to half ($2C$) and by the end of meiosis II, the C-value of each of the 4 haploid daughter cells is 1. The major stages of meiosis are shown in the diagram. These stages are rather transitional than absolutely distinct. The nucleolus is not shown. The nuclear membrane is generally not discernible by the light microscope from metaphase to anaphase but reappears at telophase. Dashed and solid thin lines represent the spindle fibers. The genetic consequences of the meiotic behavior of the chromosomes are best detected in ascomycete fungi with linear tetrads.

The duration of meiosis generally much exceeds that of mitosis and the longest is the prophase stage. In the majority of plants, the completion of mitosis requires 1–3 hours whereas meiosis may need from 1–8 days. In yeast, meiosis takes place in about 7 hours. The stages most revealing for the cytogeneticist, pachytene (2–8), diplotene (0.5–1), metaphase I (1.5–2), and anaphase I (0.5–1) require generally the number of hours indicated in parenthesis (see Fig. M37). In human females meiosis begins at the early embryonic stage (in mice ovaries it is microscopically detectable by day 12.5) and it stalls at the late prophase stage, at dictyotene, and the subsequent divisions take place only before the onset of ovulations (and following fertilization), a period repeated approximately 13 times annually during about 40 years. In males, meiosis is initiated in the testes only after birth. In both ovaries and testes, the onset of meiosis is under the control of gene *Stra8* (*stimulated by retinoic acid gene 8*). Retinoic acid is key regulator of the initiation of meiosis in both sexes (Koubova J et al 2006 Proc Natl Acad Sci USA 103:2474).

The activation of meiosis requires C_{29} sterols in both male and female. In *Schizosaccharomyces pombe* starvation initiates the switch from mitosis to meiosis. Starvation stimulates the expression of the *ste11* gene through cAMP-dependent protein kinase. Ste11 protein activates many genes, including *mei2*, which produces an RNA-binding protein. The meiRNA is transcribed from gene *sme2*. Mutant *ste11* cannot support meiosis. The Mmi1 RNA-binding protein is required for the elimination of RNA conducive to meiosis. Actually, a larger number of mRNAs must be blocked for meiosis to proceed

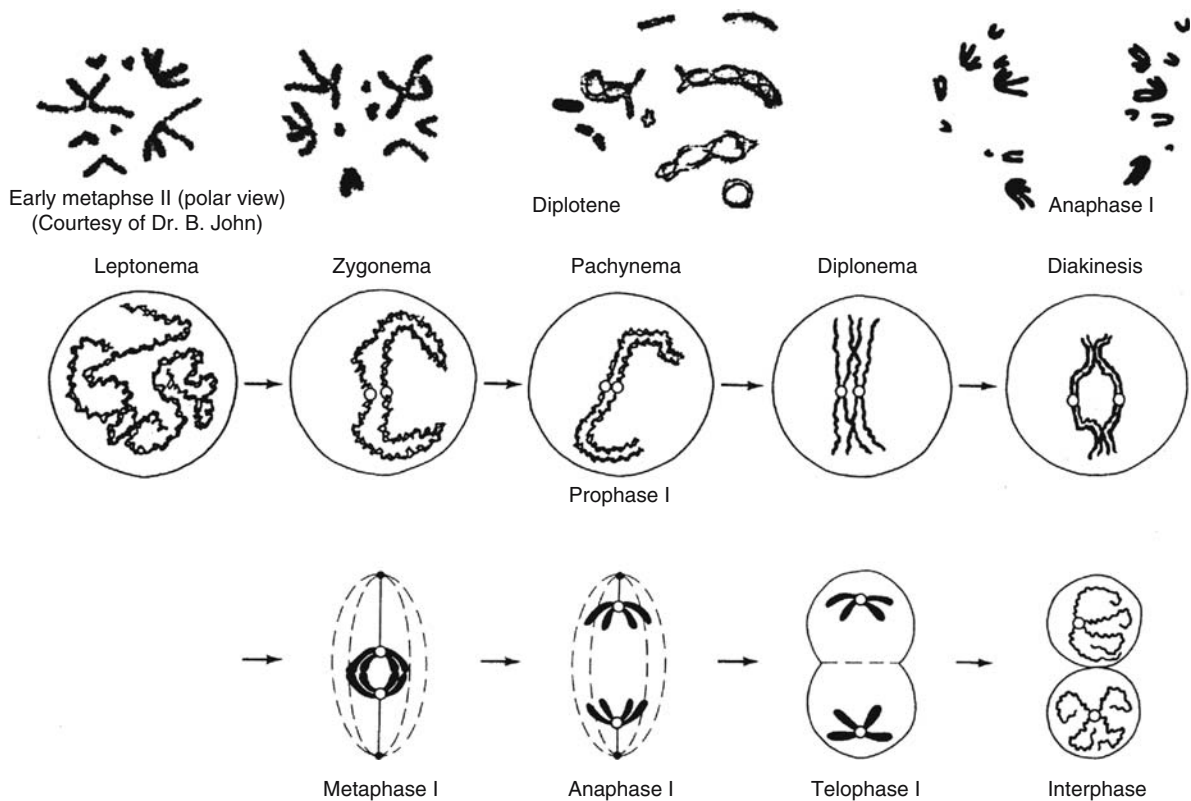


Figure M36. A generalized course of meiosis represented by only one pair of chromosomes with characteristic photomicrographs of the male grasshopper *Chortippus paralellus*

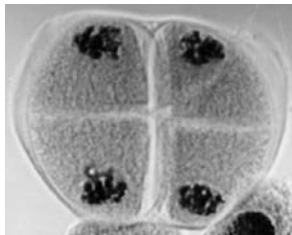


Figure M37. The four male meiotic products in plants

(Harigaya Y et al 2006 Nature [Lond] 442:45). Under such conditions protein kinase Pat1/Ran1 is inactivated by the expression of the *mei3⁺* gene. The substrate of this kinase is the RNA-binding protein Mei2. Dephosphorylation of Mei2 protein also causes a change from mitosis into meiosis. Mei2 is required for premeiotic DNA synthesis and the polyadenylated meiRNA promotes the first nuclear division. Mei2 is localized in the cytoplasm in mitotic cells but during meiotic prophase, it has been visualized in the microtubule-organizing center. Meiosis in budding yeast is controlled by about 150 genes but meiosis affects the expression of over ten times more loci.

Maternal mRNA is transmitted and stored in the egg and it is selectively translated after fertilization during the early stages of embryogenesis. Testicular mRNA is present in the sperm and it is translated postmeiotically. The translation is developmentally regulated, depending on the nature of the genes concerned (Iguchi N et al 2006 Proc Natl Acad Sci USA 103:7712). ▶leptotene, ▶zygotene, ▶pachytene, ▶diplotene, ▶diakinesis, ▶metaphase, ▶anaphase, ▶cohesin, ▶separin, ▶shugoshin, ▶interphase, ▶tetrad analysis, ▶mitosis, ▶dictyotene, ▶nucleolus, ▶cell cycle, ▶gametophyte, ▶C amount of DNA, ▶Ran1, ▶Pat1, ▶Cdc28, ▶sister chromatid cohesion, ▶monopolin, ▶recombination; Zickler D, Kleckner N 1998 Annu Rev Genet 32:619; Zickler D, Kleckner N 1999 Annu Rev Genet 33:603; Rabitsch KP et al 2001 Curr Biol 11:1001; Davis L, Smith GR 2001 Proc Natl Acad Sci USA 98:8395; Forsburg S 2002 Mol Cell 9:703; Nakagawa T, Kolodner RD 2002 J Biol Chem 277:28019; Nakagawa T, Kolodner RD 2002 J Biol Chem 277:28019; Lemke J et al 2002 Am J Hum Genet 71:1051, general and species-specific features of meiosis: Gerton JL, Hawley RS 2005 Nature Rev Genet 6:477.

Meiosis I: It is the first stage of meiosis when through reduction of the chromosome number the 4C amount of DNA in the meiocyte takes place and each of the two daughter nuclei has 2C amounts of DNA. During meiosis I, the sisterchromatids are held together at the centromere by the protective action of the shugoshin proteins until meiosis II. Shugoshins are localized to the centromere by the kinase Bub1 (Vaur S et al 2005 Curr Biol 15:2263). The cohesin protein complex mediates the cohesion of the sisterchromatids. This complex includes protein Scc1. During meiosis, Rec8 replaces Scc1 and Rec8 persists until metaphase II. Anaphase promoting complex (APC) mediates the degradation of securin, which releases Esp1 endopeptidase and that in turn cleaves Scc1 and leads to the termination of the cohesion (Kitajima TS et al 2004 Nature [Lond] 427:510). ▶meiosis, ▶C amount of DNA, ▶cohesin, ▶securin, ▶cohesin, ▶separin, ▶shugoshin, ▶Esp1, ▶Bub1, ▶Scc, Fig. M36.

Meiosis II: It follows meiosis I, and is basically an equational division of the chromosomes resulting in four daughter nuclei of the meiocyte that each have only 1C amount of DNA. Mes1 protein is essential for the completion of meiosis II but it is non-essential for mitosis. ▶meiosis, ▶cohesin, ▶separin, ▶shugoshin, ▶C amount of DNA, ▶CDC13

Meiotic Drive: It results in unequal proportions of two alleles of a heterozygote among the gametes in a population because certain meiotic products are not or less functional and consequently the proportion of other gametes increases. In spite of the preferential transmission of the segregation distorters, the various populations display fewer carriers of the distorter than expected. Meiotic drive usually requires the *drive locus* (with driving and non-driving alleles) and the *target locus* (with sensitive and resistant alleles). These two loci are usually tightly linked in repulsion. Coupling the drive and sensitive alleles is expected to eliminate the system. These loci are usually within inversions and they involve the sex chromosomes more commonly than the autosomes probably because the two sex chromosomes (X and Y) in *Drosophila* do not recombine, except in pseudoautosomal region. Meiotic drive may become a microevolutionary factor because it may alter gene frequencies. Meiotic drive may favor selectively disadvantageous gene combinations and thus may contribute to the genetic load of a population. Meiotic drive may be subject to genetically determined modification. Meiotic drive operates in the males or in the females but not in both. In the mouse, cytoplasmic factors may affect meiotic drive and it has been attributed also to the effect of the paternal allele of the *Om (ovum)* locus by inducing the maternal allele to go preferentially to the polar body after fertilization. Meiotic drive may be caused by

deletions from the pericentromeric heterochromatin of the X chromosome and Y chromosome—autosome translocations. X-linked insertions containing the 240-bp rRNA intergenic spacer or the rRNA genes may restore the normal conditions. The failure of pairing in the pseudoautosomal region causes meiotic drive and XY nondisjunction. Meiotic drive may be detected by sperm typing. ▶segregation distorter, ▶preferential segregation, ▶spacer DNA, ▶rRNA, ▶pseudoautosomal, ▶polarized segregation, ▶certation, ▶megaspore competition, ▶genetic load, ▶transmission, ▶polycystic ovarian disease, ▶symbionts hereditary, ▶killer strains, ▶brachyury, ▶sexual dimorphism, ▶sexual selection, ▶sex-ratio, ▶sperm typing, ▶mitotic drive; Hurst GD, Werren JH 2001 Nature Rev Genet 2:597; Jaenike J 2001 Annu Rev Ecol Syst 32:25.

meiRNA: The polyadenylated meiotic RNA cooperates with meiotic non-phosphorylated protein Mei2 to promote premeiotic DNA synthesis and nuclear division. ▶meiosis, ▶Pat1, ▶Ran; Ohno M, Mattaj IW 1999 Curr Biol 9:R66.

Meisetz: A meiosis-induced factor containing a PR/SET and a zinc-finger domain is a histone methyltransferase required for the progression of early meiotic prophase. The PR/SET domain is the catalytic domain of histone methyltransferases. It only trimethylates lysine 4 of histone H3. It is important for the formation of sex body, fertility, homologous chromosome pairing and double-strand DNA repair. ▶histone methlyltransferases, ▶sex body; Hayashi K et al 2005 Nature [Lond] 438:374.

MEIV (multilocus exchange with interference and viability): A statistical model of recombination and achiasmate segregation in tetrads. (See Zwick ME et al 1999 Genetics 152:1615).

MEK: A member of the extracellular signal-regulated kinase (ERK) family. About 30% of human cancers have activated MEK1 and MEK2 tyrosine/threonine protein kinase activity. The similar structures have a pocket that binds inhibitors, causes conformational changes in the unphosphorylated proteins and inhibition (Ohren JF et al 2004 Nature Struct Mol Biol 11:1192). ▶signal transduction, ▶BRAF, ▶MAPK, ▶MP1, ▶Cranio-facio-cutaneous syndrome; Widmann C et al 1999 Physiol Rev 79:143.

MEKK (196-kDa protein serine/threonine kinase): MEK kinase (i.e., a kinase kinase). ▶MEK, ▶signal transduction; Yujiri T et al 1998 Science 282:1911.

MEL Oncogene: Isolated from human melanoma although its role in melanoma is unclear; it was assigned to the broad area of human chromosome 19p13.2-q13.2). ▶melanoma, ▶oncogenes, ▶p16^{INK4}

Melancholy: Severe depression (seeing the world bitter dark; melano: dark, chole: bile). Increased level of norepinephrin appears in the cerebrospinal fluid and increases the chances for heart failure (Gold PW et al 2005 Proc Natl Acad Sci USA 102:8303). ▶depression, ▶animal hormones

Melandrium (synonymous with *Lychnis*, *Silene*): A dioecious plant (see Fig. M38) ($2n = 22 + XX$ or $22 + XY$). *Caryophyllaceae*. ▶intersex, ▶*Lychnis*; Lardon A et al 1999 Genetics 151:1173; Lebel-Hardenack S et al 2002 Genetics 160:717.



Figure M38. *Melandrium*

Melanin: ▶albinism, ▶pigmentation of animals, ▶piebaldism, ▶agouti, ▶hair color, ▶melanosome

Melanie: A computer software package that can match two-dimensional protein gel data to information in database. ▶databases, ▶annotation; <http://www.expasy.org/melanie/>.

Melanism: Increased production of the dark melanin pigment. ▶melanin, ▶industrial melanism, ▶*Biston betularia*

Melanocortin: Synthesized as a complex pre-pro-opiomelanocortin, which by processing contributes to the formation of the adrenocorticotropin hormone (ACTH), melanocyte-stimulating hormone (MSH) and β -endorphin. UV-induction of POMC/MSH under the control of p53 regulates the response of the cells to ultraviolet light by tanning (Cui R et al 2007 Cell 128:853). MSH regulates the brain melanocortin-4-receptor (MC4R) and thereby leptin. Haplo-insufficient, morbid autosomal (18q29) mutation in MC4R leads to obesity in the carriers. The agouti and related gene products are natural antagonists of the MC4R ligand MSH. In many fair-skinned individuals melanocortin 1 receptor (MC1R) is not functional and therefore lack protection against UV light that would be secured by tanning. In this case melanocyte-stimulating hormone fails to stimulate pigmentation in the keratinocytes (see Fig. M39). In red/blonde mice forskolin application can restore pigmentation even in the absence of UV and functional MC1R. This information indicates the

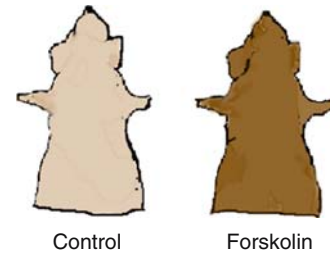


Figure M39. Mice pigmentation

topical application of this chemical can protect against skin damage and cancer (D'Orazio JA et al 2006 Nature [Lond] 2006 443:340). ▶opiocortin, ▶ACTH, ▶melanocyte stimulating hormone, ▶POMC, ▶p53, ▶leptin, ▶endorphin, ▶agouti, ▶pigmentation of animals, ▶nociceptor, ▶haplo-insufficient, ▶hyperphagia, ▶melanoma, ▶forskolin, ▶keratin, ▶tanning, ▶ultraviolet light; Huszar D et al 1997 Cell 88:131; Kistler-Heer V et al 1998 J Neuroendocrinol 10:133; Chen AS et al 2000 Nature Genet 26:97.

Melanocyte: Produces melanin. ▶melanin

Melanocyte Stimulating Hormone (MSH): MSH exists in forms α -MSH, β -MSH and γ -MSH. These adenocortical hormones regulate melanization and also energy utilization. ▶opiocortin, ▶agouti, ▶pigmentation of animals, ▶leptin, ▶syndecan; Haskell-Luevano C et al 2001 J Med Chem 44:2247.

Melanoma (CMM1, 1p36; CMM2, 9p21): Forms of cancer arising in the melanocytes or other tissues. The most prevalent form appears as a mole of radial growth of reddish, brown and pink color with irregular edges that penetrate, as they progress, into deeper layers. It may originate in dark freckles on the head or other parts of the body. Excessive exposure to sunlight may condition its development although autosomal dominant genes determine susceptibility to melanoma. Three alleles of the melanocortin receptor (MC1R, 16q24.3) double the cutaneous malignant melanoma in MC1R variants (CMM1) risk for red-haired individuals. Mutations in BRAF strongly increase the incidence of melanoma among Caucasians who are not exposed chronically to sun-induced skin damage (Landi MT et al 2006 Science 313:521). Melanoma may be one of the most aggressively metastatic cancers. The development of melanoma is regulated by the melanoma mitogenic polypeptide, encoded by GRO human gene in chromosome 4q21. The melanoma-associated antigen, ME49 appears in the early stages of this cancer, and it is coded by an autosomal dominant locus (MLA1) in human chromosome 12q12-q14. Melanoma-associated

antigen, MZ2-E, is coded for by another autosomal dominant locus. The melanoma-associated antigen p97, a member of the iron-binding transferrin protein family, is coded by an autosomal dominant gene, MAP97 (MF12) at human chromosome 3q28-q29. An autosomal dominant gene in human chromosome 15 encodes the melanoma-specific chondroitin sulfate proteoglycan, expressed in melanoma cells. In cultured melanoma and metastatic tissues a mutant CDK4/CDKN2A (p21 protein) was found that was unable to bind the p16^{INK4a} protein and thereby interferes with normal regulation of the cell cycle inhibitor. The ERK growth factor is hyperactivated in up to 90% of melanomas. RAS-ERK and phosphoinositide-3-OH kinase signal to its development. The microphthalmia-associated transcription factor (MITF, 3p14.1-p12.3) is a regulator of melanomas. Therapies may involve several drugs targeted to various kinases in the melanoma development pathways (Gray-Schopfer V et al 2007 Nature [Lond] 445:851).

In human chromosome 11 several presumptive melanoma suppressors have been found. Many of the hereditary melanomas are attributed to G→34T mutation at this locus. Because of this mutation an AUG initiation codon is created at site -35 and the resulting 4-kDa translation-product shows no homology to CDKN2A/p16. Deletions of p16 may frequently be responsible for malignant melanoma. Catenin seems to be a transcriptional coactivator of Tcf and Lef and seems to affect melanoma progression. Approximately 5 to 10% of the melanoma patients have at least one afflicted family member. Non-melanoma skin cancer in fair skinned redheads may be associated with the melanocortin-1 receptor (MCR1). The *fat-1* mutation in mice can convert n-6 fatty acids into n-3 and it reduced melanoma development in melanoma transgenic animals and establish a favorable balance between the two groups of fatty acids. In *fat-1* mice prostaglandin E3 and PTEN were upregulated (Xia S et al 2006 Proc Natl Acad Sci USA 103: 12499). Genetic hybrids between the species of the platyfishes (*Xiphophorus*) are prone to develop melanoma. Melanoma is frequently an aggressive cancer and is refractory to anticancer drugs. Cisplatin is sequestered into subcellular organelles of melanosomes and thus hindered from accessing the nucleus (Chen KG et al 2006 Proc Natl Acad Sci USA 103:9903). ▶**MEL oncogene**, ▶**p16**, ▶**melanocyte**, ▶**cancer**, ▶**catenins**, ▶**Tcf**, ▶**Lef**, ▶**MAGE**, ▶**metastasis**, ▶**freckles**, ▶**cisplatin**, ▶**Apaf**, ▶**survivin**, ▶**CDKN2A**, ▶**skin cancer**, ▶**mole**, ▶**BRAF**, ▶**fatty acids**, ▶**obesity**, ▶**prostaglandin**, ▶**PTEN**; Mellado M et al 2001 Curr Biol 11:691; van der Velden P et al 2001 Am J Hum Genet 69:774; melanoma statistics database: <http://www.pcab.cupmc.edu/main.cfm?dis=statmel>.

Melanoma Growth-Stimulatory Factor (GROα): An interleukin-related protein like SDF. ▶**IL-8**, ▶**SDF**, ▶**CXCR**, ▶**chemokines**; Wang et al 2000 Oncogene 19:4647.

Melanopsin: A sensory retinal photopigment in mammals and other species (Bellingham J et al 2006 PLoS Biol 4(8):e254).

Melanosomes: Specialized pigment-containing organelles of animals produced by the melanocytes. They include tyrosinase, and related proteins, GP100, etc. and bear resemblance in function to lysosomes. ▶**melanocyte**, ▶**albinism**, ▶**pigmentation of animals**, ▶**lysosomes**, ▶**skin color**, ▶**amyloids**; Kishimoto T et al 2001 Proc Natl Acad Sci USA 98:10698; Marks MS et al 2001 Nature Rev Mol Cell Biol 2:738.

Melas Syndrome: ▶**mitochondrial disease in humans**

Melatonin: Hormone synthesized in the pineal gland and is controlling reactions to light, diurnal changes, seasonal adjustment in fur color, aging, sleep, and reproduction. It is a scavenger of oxidative radicals and it protects from ionizing radiation without substantial side effects. It is synthesized from serotonin by serotonin N-acetyltransferase and regulated by cAMP. ▶**serotonin**, ▶**sulfhydryl**, ▶**radio-protectors**, ▶**circadian rhythm**; Reiter RJ et al 2007 World Rev Nutr Diet 97:211.

MELD: Overlapping, Merged DNA fragments.

MELD₁₀ (mouse equivalent lethal dose): ▶**LD50**

Melibiose (galactopyranosyl-glucose): A fermentable disaccharide (see Fig. M40).

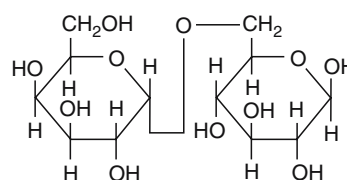


Figure M40. Melibiose

MELK (multi-epitope-ligand-‘Kartographie’): Technology capable of analyzing the pattern, topological arrangement and interaction of proteins within single cells rather than cell homogenates. It thus detects single combinatorial protein patterns (s-CCP) and combinatorial protein pattern motifs. The pattern may provide specific signatures of cell types, cell states in health and disease and response to drugs. It provides information in parallel also on carbohydrates nucleic acids and lipids and reveals their interaction networks the topome. ▶**genetic networks**; Schubert W 2003 Adv Biochem Engin/Biotechnol 83:189.

Melnick-Needles Syndrome (xq28): A hereditary bone defect due to mutation in filamin A. ► [filamin](#)

Melt-and-Slide Model: The dual functions of DNA polymerase I are carried out by pol I occupying the duplex primer-template site for the polymerase action, and for the editing reaction the DNA melts (strands separate), unwinds and the single-strand DNA is transferred to the exonuclease site of the polymerase enzyme. ► [DNA repair](#), ► [DNA replication](#)

Meltdown, Mutational: Can occur when the mutation rate is high, the genetically effective population size is small and genetic drift is high. It may lead to extinction. ► [effective population size](#), ► [genetic drift](#), ► [extinction](#); Zeyl C et al 2001 *Evolution* 55:909.

Melting: The breakdown of the hydrogen bonds between paired nucleic acid strands (► [Denatur-A-tion](#), ► [breathing of DNA](#), ► [Watson and Crick model](#)).

Melting Curve of DNA: Higher temperatures cause progressively higher disruption of the hydrogen bonds between DNA strands; it is affected also by the base composition of the DNA because there are three hydrogen bonds between G≡C and two between A=T. ► [re-naturation](#), ► [C₀t curve](#), ► [hydrogen pairing](#), ► [melting temperature](#)

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Melting Temperature: The temperature where 50% of the molecules is denatured (T_m); the DNA strands may be separated (depending on the origin of the DNA, G≡C content, solvent, and homology of the strands) generally above 80° C and melting may be completed below 100°. ► [C₀t curve](#), ► [hyperchromicity](#), ► [melting curve of DNA](#)

Meltrins: Metalloproteinase proteins mediating the fusion of myoblasts into myotubes. ► [myotubes](#), ► [metalloproteinase](#), ► [ADAM](#); Inoue D et al 1998 *J Biol Chem* 273:4180.

Memapsins: Cloned and sequenced aspartic proteases with β secretase activity. ► [secretase](#)

Membrane: Lipid protein complexes surrounding cells and cellular organelles and forming intracellular vesicles. Synthetic membranes can now be engineered on polymer surfaces and their functions studied along with associated proteins using semiconductor technology. The function of membranes is important for many physiological mechanisms, including screening for pathogens and drugs. ► [cell membranes](#), ► [semiconductor](#); Tanaka M, Sackmann E 2005 *Nature [Lond]* 437:656.

Membrane Attack Complex (MAC): C5b can be converted to C5b6 and then to C5b67 by binding to C6 and C7 complement components and then with C8 and C9 resulting in the formation of MAC.

This complex can protect the cells against certain foreign, intruder cells but it must be regulated to protect the cells own membrane system. The so-called homologous restriction factor (HRF) is a 65-kDa glycoprotein bound to cell membranes through glycosylphosphatidylinositol (GPI) can perform this task. A smaller (20-kDa) immunoglobulin G (IgG1) called also HRF20 (CD59), and MIRL (membrane inhibitor of reactive lysis) function in a similar manner. In paroxysmal nocturnal hemoglobinuria is a mutational defect in GPI anchoring of HRF20 to the hematopoietic membrane. ► [complexment](#), ► [paroxysmal nocturnal hemoglobinuria](#), ► [phosphoinositides](#), ► [immunoglobulins](#), Linton S 2001 *Mol Biotechnol* 18:135.

Membrane Channels: These permit passive passing of ions and small molecules through membranes. ► [cell membrane](#), ► [ion channel](#)

Membrane Filters: Used for clarification of biological or other liquids, trapping macromolecules, for exclusion of contaminating microbes, for Southern and Northern blotting, etc. The filters may be cellulose, fiberglass, nylon and might have been specially treated to best fit for the purpose.

Membrane Fusion: Maintains sub cellular compartments. The process requires ATPases (NSF), accessory proteins (SNAP), integral membrane receptors of SNAP (SNARE) and GTPases (RAB) and additional proteins. The SNARE function may be transient. Vacuoles Ca^{2+} /calmodulin regulates membrane bilayer mixing in the final steps (see Fig. [M41](#)). Protein phosphatase 1 (PP1) has essential role in membrane mixing. Infection by viral pathogens—penetration of the egg by the sperm, vesicular transport, etc.—involves fusion of membranes.

► [ATPase](#), ► [RAB](#), ► [SNAP](#), ► [SNARE](#), ► [protein phosphatases](#); Eckert DM, Kim PS 2001 *Annu Rev Biochem* 70:777; Jahn R, Grubmüller H 2002 *Current Opin Cell Biol* 14:488; Ostrowski SG et al 2004 *Science* 305:71.

Membrane Potential: Eelectromotive force difference across cell membranes. In an average animal cell inside it is 60 mV relative to the outside milieu. It is caused by the positive and negative ion differences between the two compartments.

Membrane Proteins: These may be *integral* parts of the membrane structure and cannot be released. The *transmembrane* proteins are single amino acid chains folded into (seven) helices spanning across the membrane containing lipid layers. The latter have a hydrophobic tract that passes through the lipid double layer of the membrane and their two tails, one pointing outward from the membrane and the other

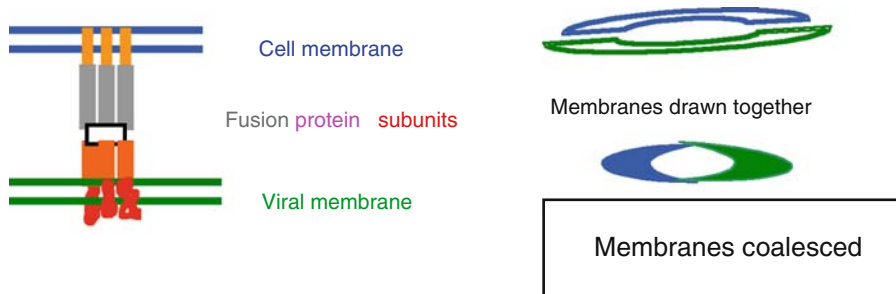


Figure M41. Fusion of viral membranes with the cell membrane during infection. The several subunits of the fusion protein complex draws the membranes together. This is an oversimplified representation. (See Modis Y et al 2004 Nature [Lond] 427:313; Gibbons DL et al 2004 Nature [Lond] 327:320)

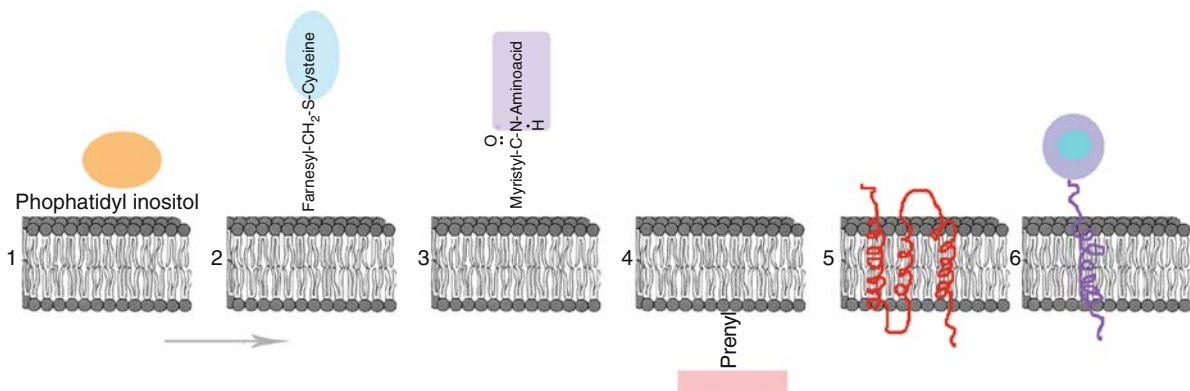


Figure M42. 1. Globular protein is attached to the outer surface by a glycosyl-phosphatidyl inositol anchor. 2. The protein is attached to the outer layer of the lipid bilayer by a thioether linkage between the sulfur of cysteine and a farnesyl molecule. 3. Amino acid and myristil anchor join a protein to the outer surface of the membrane. 4. Prenyl residue anchors the protein to the inner part of the membrane. 5. Transmembrane protein chain passes through the membrane three or seven times. 6. Transmembrane protein anchors another protein without covalent linkage

reaching into the cytosol, are hydrophilic. Some of the membrane proteins are attached only the outer or to the inner layer of the membrane lipids and they are called *peripheral membrane proteins*. The topology of >50,000 prokaryotic and ~15,000 eukaryotic membrane proteins have been determined and there is a remarkable similarity between these two groups (Kim H et al 2006 Proc Natl Acad Sci USA 103:11142). The membrane proteins regulate not just the cell membranes but cell morphology by anchoring to cytoskeleton, pH, ion channels and general physiology of the cell. The structure of membranes can now be analyzed with the aid of membrane mutants, available in several organisms. Method has been developed for the computational design of peptides that target (TM) transmembrane helices in a sequence-specific manner. The designed peptides specifically recognized the TM helices of two closely related integrins in micelles, bacterial membranes, and mammalian cells (Yin H et al 2007 Science

315:1817). (See Fig. M42, ►prenylation, ►farnesyl pyrophosphate, ►myristic acid, ►cell membranes, ►cytoskeleton, ►integrins; Dalbey RE, Kuhn A 2000 Annu Rev Cell Dev Biol 16:51; Sachs JN, Engelman DM 2006 Annu Rev Biochem 75:707; membrane protein structure: Elofsson A, von Heijne G 2007 Annu Rev Biochem 76:125.

Membrane Segment: Antigen receptor immunoglobulins possess a membrane-bound segment at the C-end of their heavy chains. The transmembrane part is composed of 25–26 highly conserved amino residues and the intracellular portion is of 25-amino acids in IgG and 14 in IgE and IgA in mouse. Membrane bound IgG, IgE and IgA are involved in the stimulated B cell receptors whereas IgM and IgD are parts of the naive (immature) B cell receptors. ►immunoglobulins

Membrane-Spanning Helices: ►membrane proteins, ►seven membrane proteins

Membrane Transport: The movement of polar solutes with the aid of a transporter protein through cell membranes. ► [cell membrane](#), ► [ABC transporters](#), ► [major facilitator superfamily](#); Kaback HR et al 2001 *Nature Rev Mol Cell Biol* 2:610, membrane traffic: Pfeiffer SR 2007 *Annu Rev Biochem* 76:629; membrane transport proteins: <http://www.membrane-transport.org/>.

MEME: A unit of cultural transmission (imitation), which bears some similarities to the gene that it is “transmitted” horizontally and not vertically from generation to generation as cultural inheritance and not as a biological entity. (See Boyd R, Richerson PJ 2000 *Sci Amer* 283(4):70).

MEME: Replicator functions of organisms that also control co-evolution of genes and organisms. (See Bull L et al 2000 *Artif Life* 6(3):227; motif alignment tool: <http://meme.nbcr.net/meme/intro.html>).

Memory: Information storage in the brain or in a computer. The mammalian brain deals with synaptic strength as memory. If synapses are used repeatedly, the strength is improved and long-term potentiation (LTP) takes place. Arc/Arg3.1 regulates endophilin 3 and dynamin 2, two components of the endocytosis machinery. Genetic ablation of *Arc/Arg3.1* in mice or overexpression in culture suggests that Arc/Arg3.1 regulates AMPA receptor trafficking and synaptic plasticity (See *Neuron* 52(3):445–474 2006). The opposite of LTP is LTD (long-term depression). The latter may erase the effect of LTP. Acetylcholine, dopamine and norepinephrine mediate different memory signals acting in the prefrontal cortex of the brain. Both of these mechanism are triggered by the inflow of Ca^{2+} , regulated by an ion channel (NMDAR), glutamate-activated N-methyl-D-aspartate receptor channel. Multiple protein kinases (adenylate cyclase, CREB) appear to be involved in extremely complex manners. It is not entirely clear how discrimination between LTP and LTD is accomplished. Nerve growth factor (NGF) gene transfer to basal forebrain of rats resulted in recovery from age-related memory loss. There are some indications that memory is controlled by positive and negative signals. LTP seems to require protein synthesis but long-term memory (LTM) may not. Long-term memory seems to require synthesis of new proteins in the dendrites (Sutton MA, Schuman EM 2006 *Cell* 127:49). Modern neurobiology uses a variety of techniques for exploring the mechanisms of memory and learning, including mutations, knock-outs, transgenes, tomography, magnetic resonance imaging, etc. Unwanted memories are eliminated by increased dorsolateral prefrontal activation

and reduced hippocampal activation in the brain (Anderson MC et al 2004 *Science* 303:232). *Explicit* (declarative) *memory*: the remembrance of facts, resides in the hippocampal region of the brain. *Implicit* (non-declarative) *memory* involves perceptual and motor skills (based on basal ganglia) that may be more widely distributed; memory of conditional fear appears to be in the corpus amygdaloideum (an almond-shaped part in the temporal lobe of the brain with connections to the hippocampus, thalamus and hypothalamus). The *working memory* functions during the period when a mental task is performed. *Social memory* (parental care, etc.) in mice is based on olfactory functions controlled by oxytocin in the brain. *Drosophila* mutants *dunce* (encoding cAMP phosphodiesterase) and *rutabaga* (encoding adenylate cyclase) appear to have an ability to learn yet display short memory. The mutant *amnesiac* is defective in a pituitary peptide required for activation of adenylate cyclase, and mutation *linotte* is affected in a helicase-like function. In *Aplysia* and mice CREB affects long-term memory but not the short-term memory. All these pieces of information point to the role of cAMP in memory. Ca^{2+} /calmodulin dependent protein kinase (CaMKII) is an important signaling molecule for memory. Dynamin, a microtubule-associated GTPase is important for synaptic vesicle recycling. Protein phosphatase 1 seems to be a suppressor of learning and memory (Genoux D et al 2002 *Nature [Lond]* 418:970). Single amino acid substitutions in brain derived neurotrophic factor (BDNF) in rats seem to effect long-term potentiation of memory (Egan MF et al 2003 *Cell* 112:257). Recalling olfactory memory in *Drosophila* requires the function of the mushroom bodies although this organelle is not necessary for learning or storage of information. In *Drosophila*, the most central part of the brain—in the so-called fan-shaped body (FB)—stores short-term memory of visual pattern recognition. Memories of different shape patterns are localized in groups of neurons in different, parallel, horizontal branches of FB. In the flies the rutabaga protein (an adenylate cyclase regulated by Ca^{2+} /calmodulin and G_α protein) is required for conditioned and unconditioned memory. For the experiment *rut⁻* mutants were employed. Then the investigators looked for neurons where transgenic *rut⁺* restored learning. Using sophisticated genetic regulatory system and well-controlled environment providing behavioral (and memory) control permitted mapping the visual memory pattern in the brain (Liu G et al 2006 *Nature [Lond]* 439:551).

Diacylphosphatidyl ethanol (present in fish oil) in the diet may significantly increase learning capacity of young rats but not the old ones (Barceló-Coblijn G et al 2003 *Proc Natl Acad Sci USA* 100:11321). Age

in humans generally reduces memory and may result in Alzheimer disease. In mice, which express human amyloid- β protein precursor (APP), a variant of 56-kDa amyloid- β plaques accumulate in the neurons by aging and cause memory loss (Lesné S et al 2006 *Nature [Lond]* 440:352). ►brain, ►human, ►mushroom body, ►ARC, ►AMPA, ►dynammin, ►endophilin, ►synaps, ►ion channels, ►long-term potentiation, ►NMDAR, ►flyn, ►hebbian mechanism, ►synapse, ►adenylate cyclase, ►oxytocin, ►dopamine, ►acetylcholine, ►norepinephrine, ►C/EBP, ►CREB, ►long-term potentiation, ►knock-out, ►transgene, ►tomography, ►nuclear magnetic resonance spectroscopy, ►Alzheimer disease; Silva AZ et al 1997 *Annu Rev Genet* 31:527; Zars T et al 2000 *Science* 288:672; Sweatt JD 2001 *Curr Biol* 11: R391; Waddell S, Quinn WG 2001 *Science* 293:1271; Wadell S, Quinn WG 2001 *Annu Rev Neurosci* 24:1283; maintenance of long-term memory: Bailey CH et al 2004 *Neuron* 44:49.

Memory, Epigenetic: ►epigenetic memory

Memory, Immunological: Immunological memory rests with the lymphocytes and this is the basis of vaccination. There are three phases in its development: (i) activation and expansion of the CD4 and CD8 T cells, (ii) apoptosis, and (iii) stability (memory). During phase (i), lasting for about a week the antigen selects the appropriate cells and an up to 5,000-fold expansion of the specific cells takes place. They also differentiate into effector cells. Between a week and a month's time, as the antigen level subsides, the T cells die and effector function declines. This is called activation-induced cell death (AICD). THE AICD is a defense against possible autoreactive function. The memory stage may then last for many years and they respond to low exposure of the reintroduced antigen and respond very rapidly. A certain level of antigen maintenance seems to be required to keep memory cell at high level but it appears that memory cells can be saved even in the absence of the antigen (Maruyama M et al 2000 *Nature [Lond]* 407:636). The conditions for CD4 and CD8 cell maintenance appear different. Memory B and T cells do not provide immediate protection against infection but after infection they start rapid formation of effectors. The duration of the memory depends on the strength of immunization. The protection against peripheral re-infection is antigen-dependent. The long-term success of immunization depends on the presence of memory cells. Therefore there is much significance in selecting T cells that may become memory cells. The division of CD8⁺ memory T cells is slow and it can be increased by IL-15 but IL-2 has the opposite effect. T-bet and

omesodermin transcription factors facilitate cytokine-dependent memory T cell and natural killer cell formation. These two transcription factors enhance the expression of CD122, which mediates interleukin-15 (IL-15) responsiveness (Intlekofer AM et al 2005 *Nature Immunol* 6:1236). Eomesodermin (Eomes) is a T-box transcription factor homologous to T-bet. Thus these memory T cells are under the control of interleukin balance. The 'central memory cells' have CCR7⁺ receptors whereas the 'effector memory T cells' are CCR7⁻. ►immune system, ►apoptosis, ►CD4, ►CD8, ►lymphocytes, ►germinal center, ►T cell, ►B cell, ►T-bet, ►omesodermin, ►killer cell, ►immunization, ►vaccines, ►immunotherapy active specific, ►and affinity maturation, ►IL-15, ►IL-12, ►CCR, ►effector, ►CD8; Mackay CR, von Andrian UH 2001 *Science* 291:2323; Sprent J, Tough DF 2001 *Science* 293:245; Fearon DT et al 2001 *Science* 293:248; Sprent J, Surh CD 2002 *Annu Rev Immunol* 20:551.

Memory, Molecular: Heritable specific pattern of gene expression.

Memory, Transcriptional: Maintains transcriptional state and transmits it epigenetically to cell progeny. In yeast the ATP-dependent SWI/SNF chromatin-remodeling system is essential for the GAL1 gene and it antagonizes the ISWI system (Kundu S et al 2007 *Genes & Dev* 21:997). ►ISWI, ►SWI/SNF, ►Gal

MEN (multiple endocrine neoplasia): MEN1 (dominant) was located to human chromosome 11q13, responsible for the production of a 610 amino acid protein, Menin, encoded by 10 exons predisposing to pancreatic islet cell tumors. Menin is both a tumor suppressor and a cofactor of mixed lineage leukemia (MLL) oncoprotein (Yokoyama A et al 2005 *Cell* 123:207). MEN1 homozygosity is lethal. MEN2 is encoded at 10q11.2 and puts individuals at risk of thyroid cancer. The RET tyrosine kinase is defective. ►endocrine neoplasia, ►p27, ►ganglioneuromatosis, ►RET oncogene; Crabtree JS et al 2001 *Proc Natl Acad Sci USA* 98:1118; Krapp A et al 2004 *Current Biol* 14:R722.

MEN (mitotic exit network): Includes cyclin-dependent kinase (CDK) inactivators, CDC15, CDC14, CDC5, DBF, TEM1, etc. (See factors named, ►mitotic exit, ►FEAR; Asakawa K et al 2001 *Genetics* 157:1437).

Menaquinone (vitamin K₂): Synthesized by bacteria and is an electron carrier. ►vitamin K

Menarche: The first menstruation event, followed by a period of about three years of no ovulations before the regular menstruation begins and continues until menopause. ►menstruation, ►menopause

Mendelian Laws: The term was first used by Carl Correns (1900), one of the rediscoverers of these principles, which he named (1) Uniformitäts- und Reziprozitätsgesetz, (2) Spaltungsgesetz, (3) unabhängige Kombination). *First law:* uniformity of the F_1 (if the parents are homozygous) and the reciprocal hybrids are identical (in the absence of cytoplasmic differences). *Second Law:* independent segregation of the genes in F_2 (in absence of linkage). *Third law:* independent assortment of alleles in the gametes of diploids. Thomas Hunt Morgan (1919) also recognized three laws of heredity: (1) free assortment of the alleles in the formation of gametes, (2) independent segregation of the determinants for different characters, (3) linkage-recombination. In some modern textbooks only two Mendelian laws are recognized but this is against the tradition of genetics that the first used nomenclature is upheld. Mendel himself never claimed any rules as such to his credit. He did not observe any linkage among the 7 factors he studied in peas although he had less than 1% chance for all factors segregating independently. This was called “Mendel’s luck”. If he had found the linkage it would have in all probability been recorded in his notes. Unfortunately after his death, his successor at the abbey, Anselm Rambousek, disposed most of the records. After he experimented with *Hieracium*, an apomict (unknown that time), he developed some doubt about the general validity of his discoveries. Yet, before ending his career he stated: “My scientific work has brought me a great deal of satisfaction, and I am convinced that I will be appreciated before long by the whole world”. That appreciation began in 1900, 16 years after his death and continues since. In 1936, the famous statistician and geneticist Ronald Fisher (Annals of Sci. 1:115) questioned the authenticity of Mendel’s observations on the basis

that the data were ‘too good to be true’. Fisher’s criticism has been widely touted by many without thoroughly studying the original paper of Mendel or that of Fisher. The statistician F. Weiling (1966 Züchter 36:359) pointed out that Fisher misunderstood some of the experiments and erred in his analysis too. More recently Hartl & Fairbanks (2007 Genetics 175:975) concluded, “Fisher’s allegation of deliberate falsification can finally be put to rest, because on closer analysis it has proved to be unsupported by convincing evidence.” The experimental data accumulated during the one and a half century since the publication of Mendel’s paper convincingly prove that Mendel was right and honest (Rédei GP 2002 p 1. In: Quantitative Genetics, Genomics and Plant Breeding. Kang MS (Eds.) CABI Publishing, New York). ►Mendelian segregation, ►epistasis, ►modified Mendelian ratios

Mendelian Population: A collection of individuals, which can share alleles through interbreeding. ►population, ►genetics

Mendelian Segregation: Mendelian segregation for independent loci can be predicted on the basis of the Table M5. Mendelian segregation ratios may show only apparent deviations in case of epistasis (see Fig. M43). Reduced penetrance or expressivity may also confuse the segregation patterns and in such cases it may be necessary to determine the difference between male and female transmission. The wrinkled/shrunken seeds shown in Fig. M43 accumulate water-soluble sugars at the expense of complex starch and when the seed dries it shows the wrinkled phenotype. ►epistasis, ►penetrance, ►expressivity, ►segregation distorter, ►certation, ►modified Mendelian ratios

Table M5. Mendelian expectations

| | | | | | |
|--|---|----|----|-----|-------|
| Number of different allelic pairs | 1 | 2 | 3 | 4 | n |
| Kinds of gametes and number of phenotypes in case of dominance | 2 | 4 | 8 | 16 | 2^n |
| Number of phenotypes (in case of no dominance) and number of genotypes | 3 | 9 | 27 | 81 | 3^n |
| Number of gametic combinations | 4 | 16 | 64 | 256 | 4^n |



Figure M43. Segregation for smooth and wrinkled within a pea pod

Mendelizing: Segregation corresponds to the expectations by Mendelian laws. ▶ [Mendelian laws](#), ▶ [Mendelian segregation](#)

Ménière Disease (COCH, 14q12-q13): A late-onset, dominant non-syndromic deafness although in some cases vertigo (dizziness-like sensation of whirling of the body or the surroundings) and tinnitus (ringing inside the ears) may occur periodically. In the majority of cases mutation at nucleotide position C-T²⁰⁸ results in proline⁵¹→serine substitution in the COCH protein. ▶ [deafness](#)

Menin1: A tumor suppressor protein (binding JunD) encoded at 11q13 by the gene responsible for multiple endocrine neoplasia. ▶ [endocrine neoplasia](#), ▶ [Jun](#); Guru SC et al 2001 Gene 263:31.

Meninges: The three membranes (pia, arachnoid, dura maters) surrounding the brain and the spinal cord.

Meningioma: A slow proliferating brain neoplasias classified into different groups on the basis of anatomical features. Generally meningiomas involve the loss of human chromosome 22 (hemizygosity) or part of its long arm or some lesions at 22q12.3-q13 where the SIS oncogene, responsible for a deficit of the platelet derived growth factor (PDGF) is located. Chromosomes 1p, 14q, and 17 have also been implicated. ▶ [SIS](#), ▶ [cancer](#), ▶ [neurofibromatosis](#), ▶ [meninges](#), ▶ [ERM](#)

Meningocele: ▶ [spina bifida](#)

Menkes Syndrome (MNK, kinky hair disease): The gene is situated in the centromeric area of the human X-chromosome (Xq12-q13). The phenotype involves hair abnormalities, mental retardation, low pigmentation, hypothermia and short life span. Apparently, the defect is in the malabsorption of copper through the intestines resulting in copper deficiency of the serum. The prevalence is in the 10⁻⁵ range or less. It is detectable prenatally and the heterozygotes can be identified although its inheritance is apparently recessive. Lysyl oxidase and other copper-dependent enzyme levels (tyrosinase, monoamine oxidase, cytochrome c oxidase, ascorbate oxidase) are reduced in the afflicted individuals. In the mouse homolog, Mottled-Bridled, the non-exported copper is tied up by metallothionein and the afflicted individual dies within a few weeks after birth. The Occipital Horn Syndrome may be an allelic variation of MNK and of cutis laxa. ▶ [mental retardation](#), ▶ [Wilson disease](#), ▶ [acrodermatitis](#), ▶ [hemochromatosis](#), ▶ [Ehlers-Danlos syndrome](#), ▶ [Cutis laxa](#), ▶ [collagen](#), ▶ [metallothionein](#)

Menopause: The end of the periodic ovulation (menstruation) and fertility around age 50 in human females. Animals in the wild usually stay fertile in old age. The evolutionary cause of menopause is not

known but it has been hypothesized it is a protection against the increase of chromosomal aberrations in old egg cells. An alternative hypothesis assumes that life beyond menopause may aid the rearing of the last offspring or grandchildren and this conveys fitness by kin selection. ▶ [menstruation](#), ▶ [menarche](#), ▶ [andropause](#), ▶ [age-specific birth and death rates](#), ▶ [kin selection](#), ▶ [dictyotene stage](#), ▶ [porin](#)

Menses: Same as menstruation

Menstruation: The monthly discharge of blood from the human (primate) uterus in the absence of pregnancy. If the egg is not fertilized, it dies and the endometrial tissue of the uterus is removed amidst the bleeding. Fertilization takes place within the oviduct. About three days are required for the egg to reach the uterus through the oviduct where it is implanted within a day or two, and about a week after being fertilized. Fertilization may occur if the coitus takes place in period about two weeks after the beginning of the last monthly menstruation. The calendar rhythm method of birth control relies on knowledge of this receptive period. Unfortunately, its effectiveness is not very high. ▶ [hormone receptors](#), ▶ [sex hormones](#), ▶ [ovulation](#), ▶ [menarche](#)

Mental Retardation: A collection of human disabilities caused by direct or indirect genetic defects and acquired factors such as diverse types of infections (syphilis, toxoplasma coccidian protozoa), viruses (rubella, human immunodeficiency virus, cytomegalovirus, herpes simplex, coxsackie viruses), bacteria (*Haemophilus influenzae*, meningococci, pneumococci, mechanical injuries to the brain pre-, peri- and postnatally, exposure to lead, mercury, addictive drugs, alcoholism or deprivation of oxygen during birth, severe malnutrition, deficiency of thyroid activity, social and psychological stress, etc. An estimated 2 to 3% of the population is suffering from mild (IQ 50–70%) or more or less severe (IQ below 50%) forms of it. Special education programs can help an estimated 90% of the cases. Approximately 10% of the human hereditary disorders have some mental-psychological debilitating effects.

Autosomal dominant type hemoglobin H disease associated mental retardation due to a lesion in the α -globin gene cluster with chromosomal deletion and without it have been observed. Other cases of mental retardation were also observed involving autosomal dominant inheritance caused by breakage in several chromosomes. Autosomal recessive inheritance was involved in mental retardation associated with head, face, eye, and lip abnormalities, hypogonadism, diabetes, epilepsy, heart and kidney malformations, phenylketonuria. X-chromosome linked mental retardation was observed as part of the syndromes involving the development of large heads, intestinal

defects, including anal obstructions, seizures, short statures, weakness of muscles, obesity, marfanoid appearance, etc. In some cases the “kinky hair” syndrome (Menkes syndrome), caused apparently by abnormal metabolism of copper and zinc, also involved mental retardation. A fragile site in the X chromosome (Xq27-q28) apparently based on a deficiency of thymidine monophosphate caused by insufficient folate supply is associated with testicular enlargement (macroorchidism), big head, large ears, etc. A defect in the IL-1 receptor accessory protein, encoded at Xp22.1–21.3, affects learning ability and memory. The transmission of the fragile X sites (FRAX) is generally through normal males. The carrier daughters are not mentally retarded and generally do not show fragile sites. In the following generation, about a third of the heterozygous females display fragile sites and become mentally retarded. This unusual genetic pattern was called the Sherman paradox and it is interpreted by some type of a pre-mutational lesion. The pre-mutation ends up in a genuine mutation only after being transmitted by a female, which already had a microscopically undetectable rearrangement.

The risk of the sons was estimated to be 50% from mentally retarded heterozygous females, 38% from normal heterozygous mothers, and 0% from normal transmitting fathers. The probability of these sons being a mentally sound carrier was estimated as 12, 0 and 0%, respectively. The risk of the daughters of the same mothers to become a mentally affected carrier was calculated to be 28, 16 and 0%, and being a mentally normal carrier was estimated 22, 34 and 1%, respectively. The chance of mental retardation for the brother of a proband whose mother has no detectable fragile X site, may vary from 9–27% and among first cousins this is reduced to 1–5%. It was proposed (Laird 1987 Genetics 117:587) that the expression of the fragile X syndrome is mediated by chromosomal imprinting. The imprinting can, however, be erased by transmission through the parent of the other sex. The fragile X syndrome is apparently caused by localized breakage and methylation of CpG islands at the site (Bardoni B, Mandel J-L 2002 Current Op Genet Dev 12:284). Currently, the most reliable diagnosis of this condition is based on DNA probing. Submicroscopic deletions (1.5–2.9 Mb) associated with mental retardation can be detected by microarray hybridization (Vissers LELM et al 2003 Am J Hum Genet 73:1261). In addition, the fragile X syndrome autosomal and sex-chromosomal trisomy and chromosome breakage associated with translocations may be contributing factors of mental retardation. Human chromosome 17q21.31 microdeletions accompanied mental retardation and face morphology as detected by fluorescence in situ hybridization (Koolen DA et al 2006 Nature Genet

38:999). Further, mutations causing metabolic disorders (phenylketonuria, homocystinuria), defects in the branched-chain amino acid pathway (maple syrup urine disease) anomalies in amino acid uptake (Hartnup disease), defects involving mucopolysaccharids (Hunter, Hurler and Sanfilippo syndromes), gangliosidoses and sphingolipidoses (most notably the Tay-Sachs disease, Farber’s disease, Gaucher’s disease, Niemann-Pick disease, etc.), galactosemias, failure of removal of fucose residues from carbohydrates (fucosidosis), defects in acetyl-glucosamine phosphotransferase (I-cell disease), defects in HGPRT (Lesch-Nyhan syndrome), hypothyroidism, a variety of defects of the central nervous system, and other genetically determined conditions may be responsible for mental retardation. The incidence, establishment of genetic risks and possible therapies are as variable as the underlying causes.

Mental retardation is defined as borderline: IQ \approx 70–85, mild in case of IQ \approx 50–70, moderate: IQ \approx 35–50, severe: IQ \approx 25–35 and profound: IQ \leq 20.

In utero radiation exposure may cause mental retardation; 140 rad during the first 8–15 weeks may result in such damage in 75% of the fetuses and in 46% of the irradiated at any stage. (For more specific details see ►Huntington’s disease, ►biotinidase deficiency, ►myotonic dystrophy, ►muscular dystrophy, ►hydrocephalus, ►craniofacial dysostosis, ►spina bifida, ►tuberous sclerosis, ►neurofibromatosis, ►Menke’s syndrome, ►Smith-Lemli-Opitz syndrome, ►Smith-Magenis syndrome, ►Seckel’s dwarfism, ►Laurence-Moon syndrome, ►Noonan syndrome, ►Lowe’s syndrome, ►mental retardation X linked, ►Apert syndrome or Apert-Crouzon disease, ►Prader-Willi syndrome, ►Rubinstein syndrome, ►cerebral gigantism, ►Langer-Giedion syndrome, ►Miller-Dieker syndrome, ►Walker-Wagner syndrome, ►Wilms tumor, ►Roberts syndrome, ►Russel-Silver syndrome, ►Opitz-Kaveggia syndrome, ►De Lange syndrome, ►Bardet-Biedl syndrome, ►focal dermal hypoplasia, ►ceroid lipofuscinosis, ►autism, ►dyslexia, ►human intelligence [IQ], ►psychoses, ►aspartoacylase deficiency, ►glutamate formiminotransferase deficiency, ►CADASIL, ►Cohen syndrome, ►Coffin-Lowry syndrome, ►Juberg-Marsidi syndrome, ►fragile sites, ►FMR1 mutation, ►trinucleotide repeats, ►human intelligence, ►human behavior, ►head/face/brain defects, ►craniosynostosis, ►double cortex, ►periventricular heterotopia, ►oligophrenin, ►heritability, ►QTL, ►PAK, ►neurodegenerative diseases, ►neurotrypsin, ►IL-1, ►serpines, ►tetraspanin, ►microdeletion; Shea SE 2006 Semin Pediatr Neurol 13(4):262).

Mental Retardation X-Linked (MRX): These hereditary defects occur in a variety of forms: (i) MRXS with

diplegia (bilateral paralysis), (ii) associated with psoriasis (skin lesions), (iii) with lip deformities, obesity and hypogonadism, (iv) Renpenning type with short stature and microcephaly, (v) with seizures (EFMR), (vi) with Marfan syndrome-like habitus, (vii) with fragile X-chromosome sites among others. Altogether more than a dozen different types have been characterized. Translocation involving chromosome 7 results in nonsyndromic cognition deficit due to a defect in a zinc-finger protein (ZNF41). Several of the MRX disorders map in the human Xq28 region and in this general area apparently 12 genes are located. At Xp22.1–21.3 there is the IL1RAPL (IL-1 receptor accessory protein) gene, expressed in the hippocampus. Translocations involving Xq26 and 21p11 (ARHGEF6) involve defects in a guanine exchange factor for Rho GTPases. Some of the sequences observed at Xp22 are found also at Yq11.2 where infertility and azoospermia factors are situated. ▶ [Marfan syndrome](#), ▶ [fragile X-chromosome](#), ▶ [Juberg-Marsidi syndrome](#), ▶ [Lowe's syndrome](#), ▶ [Coffin-Lowry syndrome](#), ▶ [Rett syndrome](#), ▶ [West syndrome](#), ▶ [Partington syndrome](#), ▶ [mental retardation](#), ▶ [oligophrenin](#), ▶ [tetraspanin](#), ▶ [non-syndromic](#); Fukami M et al 2000 Am J Hum Genet 67:563; Chelly J, Mandel J-L 2001 Nature Rev Genet 2:669; Shoichet SA et al 2003 Am J Hum Genet 73:1341; review: Skuse DH 2005 Human Mol Genet 14 (1):R27.

Mentalizing: The ability to read the mental states of others and self in the process. It engages many neural processes (Frith CD, Frith U 2006 Neuron 50:531).

Menthos: A group of dicotyledonous species of plants of various (frequently aneuploid) chromosome numbers. *M. arvensis*: 2n = 12, 54, 60, 64, 72, 92; *M. sylvestris*: 2n = 24, 48; *M. piperita*: 2n = 34, 64. They were the source of menthol (peppermint camphor) and other oils used in cough drops, nasal medication, anti-itching ointments, candy, liquors, etc. Menthol appeared non-carcinogenic although doses above 1 g/kg may cause 50% death in laboratory rodents when administered subcutaneously or orally.

Mentor Pollen Effect: The simultaneous application of dead or radiation damaged compatible (mentor) pollen with incompatible pollen may in some instances help to overcome the incompatibility of the latter and fertilization may result. ▶ [incompatibility alleles](#); Stettler RF 1968 Nature [Lond] 219:746.

Menu: In a computer, menu lists the various functions to choose. The menu bar on top of the screen of the monitor displays the titles of the menus available.

Meprin: A metalloendoprotease with α and β subunits. The β subunit is a kinase-splitting membrane protease. The α subunit stays in the endoplasmic

reticulum until its transmembrane and cytoplasmic domains are cleaved off and then it moves out. (See Ishmael FT et al 2001 J Biol Chem 276:23207).

MEPS (minimal efficient processing segment): The identical nucleotide tract length required for efficient initiation of recombination. ▶ [recombination mechanisms in eukaryotes](#)

MER (from the Greek μέρος, part): It is used as, e.g., octamer, indicating it is built of 8 units (octomer would be a Latin-Greek hybrid to be avoided even by geneticists).

MER: Medium reiteration frequency sequence; ~35 copies/human genome. ▶ [redundancy](#)

Mer: Human T cell protooncogene encoded receptor tyrosine kinase. It mediates phagocytosis and apoptosis of thymocytes. ▶ [TCR](#), ▶ [thymocytes](#), ▶ [phagocytosis](#), ▶ [apoptosis](#), ▶ [receptor tyrosine kinases](#)

Mer⁻ Phenotype: Mammalian cell defective in methyl-guanine-O⁶-methyltransferase.

Mercaptoethanol: Keeps SH groups in reduced state and disrupts disulphide bonds while proteins are manipulated in vitro. ▶ [DTT](#), ▶ [thiol](#)

Mercaptopurine: A purine analog inhibiting DNA synthesis and is therefore cytotoxic. The drug 6-mercaptopurine (6-MP) is effective against acute lymphoblastic leukemia (see Fig. M44). The enzyme thiopurine-S-methyltransferase (TPMT, 245 amino acids, encoded at human chromosome 6p22.3) catalyzes S-methylation of 6-MP and inactivation. The dominant allele (frequency ~0.94) determines high activity whereas the recessive (frequency ~0.06) conveys no detectable activity in the homozygotes and in the heterozygotes a low intermediate level occurs. At low or no TPMT activity 6-MP treatment may be fatal to the patients (about 1% of the population). The testing for TPMT may help to adjust the dosage yet some physicians do not favor it because delaying the treatment may also be risky. ▶ [leukemia](#), ▶ [TPMT](#)

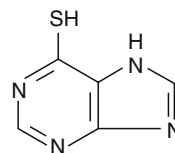


Figure M44. Mercaptopurine

Merge: Merged images.

Merged Sequence Contig: The overlapping initial sequence contigs are merged. ▶ [initial sequence contig](#), ▶ [contig](#)

Mericlinal Chimera: The surface cell layers are different from the ones underneath just like in the periclinal chimeras but the difference is that the different surface layer does not cover the entire structure but only a segment of it (see Fig. M45). ▶[chimera](#), ▶[periclinal chimera](#); Jørgensen CA, Crane MB 1927 J Genet 18:247.

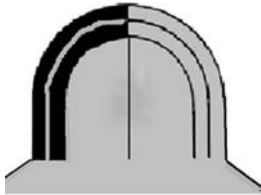


Figure M45. Mericlinal chimera

Meristem: Undifferentiated plant cells capable of production of various differentiated cells and tissues, functionally similar to the *stem cells* of animals. (See Fig. M46, ▶[stem](#), ▶[cells](#), ▶[flower differentiation](#), ▶[Seed germination](#), ▶[Arabidopsis mutagen assay](#); Weigel D, Jürgens G 2002 Nature 415:751; Nakajima K, Benfey PN 2002 Plant Cell 14:S265; axial patterning of shoot meristem: Grigg SP et al 2005 Nature [Lond] 437:1022.

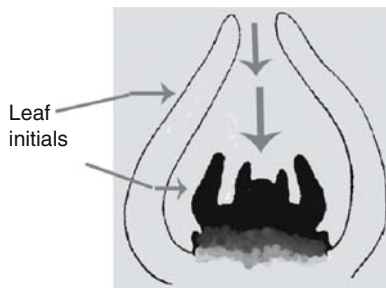


Figure M46. Apical meristem

Meristemoid: For example, stomatal precursor cell. ▶[stoma](#)

Meristic Traits: Quantitative traits that can be represented only by integers, e.g., the number of kernels in a wheat ear or the number of bristles on a *Drosophila* body. ▶[quantitative traits](#)

7mer-9mer: Seven or nine base long conserved sequences in the vicinity of the V-D-J (variable, diversity, junction) segments of immunoglobulin genes in the germline DNA. ▶[immunoglobulins](#)

Merit, Additive Genetic: The same as the breeding value of an individual.

MERLIN (moesin, ezrin, radixin-like protein): The same as schwannomin. ▶[neurofibromatosis](#), ▶[ERM](#);

Bretscher A et al 2000 Annu Rev Cell Dev Biol 16:113.

MeRNA: Metal-binding RNA is required for proper folding of the molecule: <http://merna.lbl.gov/>.

Merodiploid: ▶[merozygous](#)

Merogenote: ▶[merozygous](#)

Merogone: A fragment of an egg.

Meromelia: ▶[limb defects in humans](#)

Merosin: ▶[muscular dystrophy](#)

Merosome: Parasite-filled transport vehicles of malaria that mediate migration in the bloodstream of the host and thus evade immunity. ▶[malaria](#); Sturm A et al 2006 Science 313:1287.

Merotelic Attachment: The capture of single kinetochores by microtubules from both centrosomes, i.e., the kinetochore is attached to both spindle poles. It may cause aneuploidy. ▶[kinetochore](#), ▶[centrosome](#), ▶[aneuploidy](#), ▶[spindle pole](#); Stear JH, Roth MB 2002 Genes & Development 16:1498.

Merozoite: ▶[Plasmodium](#)

Merozygous: A prokaryote, diploid for part of its genome (merogenote). Prokaryotes are functionally haploid but transduction or plasmid may add another gene copy into the cell. ▶[transduction](#), ▶[conjugation](#); Wollman E L et al 1956 Cold Spring Harbor Symp Quant Biol 21:141.

MERRF: ▶[mitochondrial diseases in humans](#)

MERRY: ▶[M genes causing developmental defects of the germ cells in the offspring](#)

MES (maternal effect sterility): MES occurs due to recessive genes causing developmental defects of the germ cells in the offspring.

Meselson-Radding Model Of Recombination (1975 Proc Natl Acad Sci USA 72:358): Explains gene conversion (occurring by asymmetric heteroduplex, symmetric heteroduplex DNA) and crossing over occurring from one initiation event as indicated by the data of *Ascobolus* spore octads. In yeast the aberrant conversion tetrads arise mainly from asymmetric heteroduplexes as suggested by the Holliday model ▶[Holliday model](#)). Symmetric heteroduplex covers the same region of two chromatids whereas asymmetric heteroduplex means that the heteroduplex DNA is present in only one chromatid. The heteroduplexes can be genetically detected very easily in asci containing spore octads. In the absence of heteroduplexes, the adjacent (haploid) spores are identical genetically. If the heteroduplex area carries different alleles the two neighboring spores may

become different after post-meiotic mitosis. Actually heteroduplexes may be detectable also in yeast (that forms only 4 ascospores) by sectorial colonies arising from single spores. Branch migration indicates that the exchange points between two DNA molecules can move and eventually they can reassociate in an exchanged manner in both DNA double helices involved in the recombination event. Rotary diffusion indicates that the joining between single strands can take place by movement of the juncture in either direction, thus making the heteroduplex shorter or longer. See Fig. M47, ►recombination models, ►recombination molecular mechanisms

Meselson-Stahl Model: Proved that in bacteria DNA replication is semi-conservative. See Fig. M48 ►semi-conservative replication; Meselson M, Stahl FW 1958 Proc Natl Acad Sci USA 44:671; Hanawalt PC 2004 Proc Natl Acad Sci USA 101:17894.

Mesenchyma: Unspecialized early connective tissue of animals that may give rise also to blood and lymphatic vessels. The epithelial–mesenchymal transition is mediated by transcription factors that repress E-cadherin expression. As a consequence embryonic morphogenesis can proceed. The transition also plays a part in the initiation of metastasis.

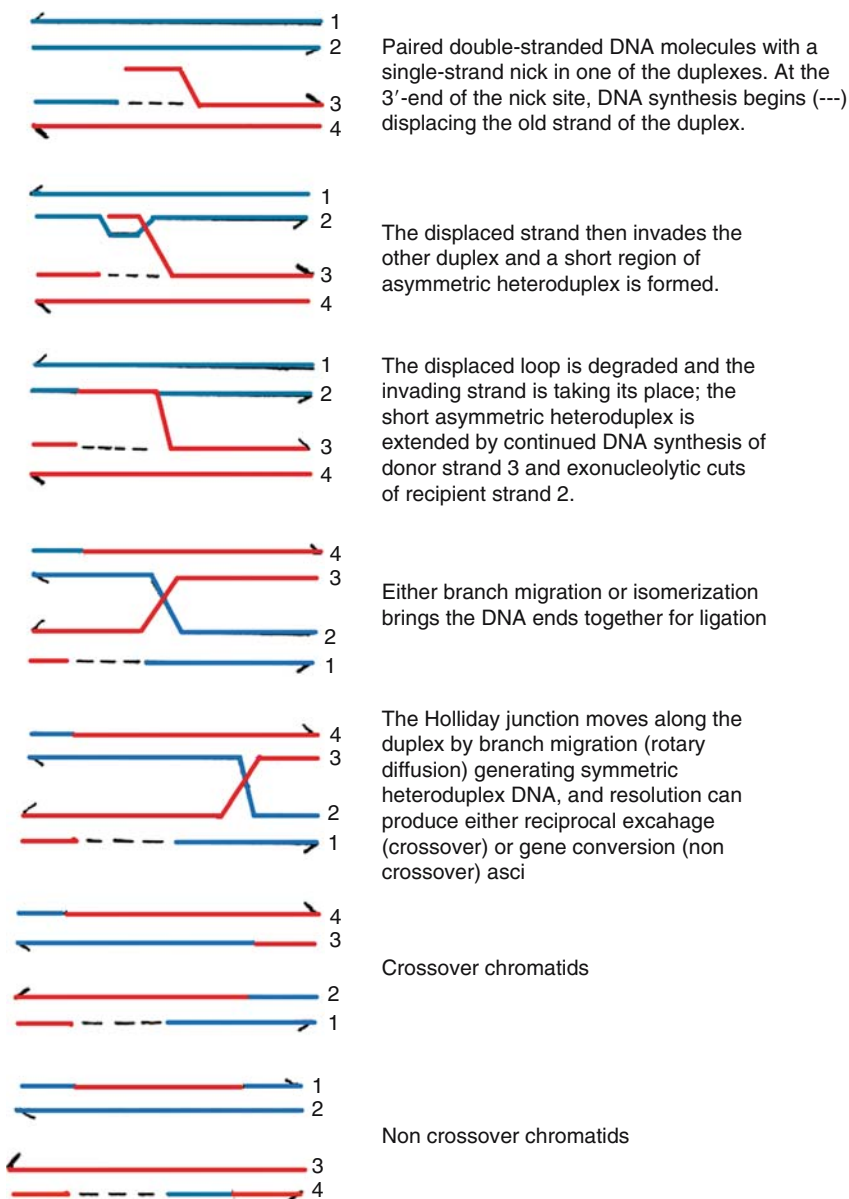


Figure M47. Meselson and Radding model of recombination

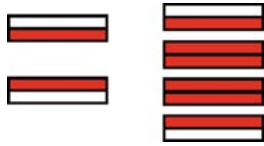


Figure M48. Density labeling was used (open box light DNA single strands), colored box (heavy strands). At left: the original double-stranded DNA molecule, in the middle: the first generation after one replication, at right: the second generation daughter molecules. This experiment thus indicated semi-conservative replication rather than conservative one in the absence of recombination

Mesenchymal stem cells are pluripotent and a balance between Runx2 and PPAR γ determine whether osteoblasts or adipocytes develop from the stem cells. The transcriptional activator with PDZ-binding domain (TAZ), a 14–3–3-binding protein coactivates Runx-dependent gene transcription and represses PPAR and functions like a rheostat (Hong J-H et al 2005 Science 309:1074). ▶osteoblast, ▶adipocyte, ▶RUNX, ▶PPAR, ▶PDZ, ▶mesoderm, ▶metastasis, ▶cadherins, Kang Y, Massagué J 2004 Cell 118:277.

MeSH: Database for information retrieval using certain MEDLINE terminologies. (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh&cmd=search&term=>).

Mesocarp: The middle part of the fruit wall. ▶exocarp, ▶endocarp

Mesoderm: The middle cell layer of the embryo developing into connective tissue, muscles, cartilage, bone, lymphoid tissues, blood vessels, blood, notochord, lung, heart, abdominal tissues, kidney and gonads. Members of the transforming growth factor (TGF β) family of proteins regulate mesoderm development. ▶morphogenesis, ▶TGF, ▶eomesoderm, ▶endomesoderm, Furlong EEM et al 2001 Science 293:1629; Kimelman D 2006 Nature Rev Genet 7:360.

Mesogen (liquid crystal): Some compounds may exhibit transitions between crystalline and liquid forms and can be manipulated by rotation or external electric fields causing rotation. They have various applications (in cellular phones, pocket computers, etc) and because of these properties they may also be used for detection of binding of ligands to specific molecules. Heat responding mesogens may generate optical anisotropy and thus may transduce optical signals and thus facilitate molecular diagnostics without invasive procedures.

Mesokaryote: Organism(s) that occupy some kind of a middle position between prokaryotes and eukaryotes.

They are endowed with cytoplasmic organelles like plant cells but their nuclear structure reminds of prokaryotes. The amount of chromosomal basic proteins in the nucleus is low, the chromosomes are attached to the membrane yet they develop a nuclear spindle apparatus. Several microtubules pass through the nuclear membranes and in the majority of the species then pull the chromosomes to the poles with the membrane and without being attached to the chromosomes. In the dinoflagellate *Cryptocodinium cohnii* 37% of the thymidylate is replaced by 5-hydroxymethyluracil. More than half of the DNA is repetitious. The vegetative cells appear to be haploid and thus mutations can be readily detected. Both homo- and heterothallic species are known. ▶prokaryote, ▶eukaryote, Hamkalo BA, Rattner JB 1977 Chromosoma 60:39.

Mesolithic Age: Period about 12,000 years ago when domestication of animals and agriculture started. ▶paleolithic, ▶neolithic

Mesomere: A blastomere of about medium size. ▶blastomeres

Mesonephros: Secretory tissue of the embryo along the spinal axis supporting the development of the gonads.

Mesophyll: The parenchyma layers of the leaf blade (see Fig. M49) (below cuticle and epidermis).

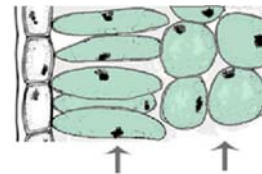


Figure M49. Mesophyll

Mesophyte: Plants avoiding extreme environments such as wet, dry, cold or warm.

Mesosome: An invaginated membrane within a bacterial cell.

Mesothelin (MSLN/MPF, human chromosome 16): A 33kDa protein expressed in the lung and other organs. Various monoclonal antibodies have been developed that react with ovarian cancer (Chang F, Pastan I 1996 Proc Natl Acad Sci USA 93:136). ▶ovarian cancer, ▶monoclonal antibody, ▶humanized antibody

Mesothorax: The middle thoracic segment of insects, bearing legs and possibly wings (see Fig. M50). ▶Drosophila

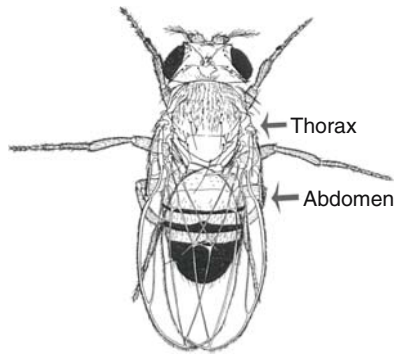


Figure M50. Mesothorax

Mesozoic: Geological period in the range of 225 to 65 million years ago; age of the life and extinction of dinosaurs and several other reptiles. ► [geological time periods](#)

Messenger Polypeptides: Extracellular signaling molecules that can pass the cell membrane, enter the cell nucleus, recognize in the DNA a special sequence motif and activate then transcription. These messengers are different from hormones or other signaling molecules because they do not need membrane receptors or special ligands or series of adaptors or phosphorylation to be activated and becoming nuclear co-activators of gene expression. ► [lactoferrin](#)

Messenger RNA: ► [mRNA](#)

Mestizo: Offspring of Hispanic and American Indian parentage. ► [miscegenation](#), ► [mulatto](#)

MET Oncogene: Hepatocytic growth factor receptor gene in human chromosome 7q31. Its α subunit is extracellular and its β subunit is an extra- and transmembrane protein. It is a tyrosine kinase as well as a subject for tyrosine phosphorylation. The receptor of HGF-SF (hepatocyte growth factor/scatter factor) is the product of Met. Expression of the MET oncogene in the liver leads to hepatocarcinogenesis after blood coagulation and internal hemorrhages. The pathogenesis involves the upregulation of plasminogen activator inhibitor type 1 (PAI-1) and cyclooxygenase (COX-2) genes (Boccaccio C et al 2005 Nature [Lond] 434:396). An engineered decoy for MET inhibits its binding to the hepatocyte growth factor receptor; interferes with tumor proliferation, angiogenesis, suppresses or prevents metastasis synergizes with radiotherapy without affecting the physiological functions in mice (Michielli P et al 2004 Cancer Cell 6:61). ► [tyrosine kinase](#), ► [oncogenes](#), ► [hepatocyte growth factor](#), ► [papillary renal cancer](#), ► [cyclooxygenase](#), ► [plasminogen activator](#);

Birchmeier C et al 2003 Nature Rev Mol Cell Biol 4915.

$$\chi^2_{2m} = -2 \sum_{i=1}^m \ln(P_i)$$

Meta-Analysis of Linkage: Used when the information in an experiment is inadequate for drawing definite conclusions. In such cases, data from other comparable experiments are pooled the best possible way. Usually the formula of R.A. Fisher (Statistical Analysis for Research Workers) is used where the P = the probability of obtaining as or more extreme information under the assumption that there is no linkage, m = the data sets. The χ^2 is calculated by 2 degrees of freedom. Meta-analysis may be used for other synthetic purposes when the information available is inconclusive. Its conclusions, therefore, may have to be regarded with some reservations. Meta-analysis may reveal substantial variation/heterogeneity in the genetic association of disease symptoms. ► [linkage](#), ► [chi square](#), ► [association test](#), ► [GSMA](#); Allison DB, Heo M 1998 Genetics 148:859; Wise LH et al 1999 Ann Hum Genet 63 (Pt 3):263; Ioannidis JPA et al 2001 Nature Genet 29:306.

Metabolic Block: A non-functional enzyme (due to mutation in a gene, or to an inhibitor) prevents the normal flow of metabolites through a biochemical pathway.

Metabolic Footprinting: Monitors extracellular metabolites in the culture medium during different physiological states of wild type and mutant cells with the aid electrospray ionization-mass spectrometry. (See Electrospray MS, Allen J et al 2003 Nature Biotechnol 21:692).

Metabolic Pathway: A series of sequential biochemical reactions mediated by enzymes under the control of genes. Genetic studies greatly contributed to their understanding along with the use of radioactive tracers. ► [radioactive tracer](#), ► [auxotrophy](#), ► [MCA](#); <http://expasy.ch>; <http://ecocyc.PangeaSystems.com/ecocyc>; <http://path-a.cs.ualberta.ca>; metabolic pathway annotation tool: <http://kobas.cbi.pku.edu.cn/>; pathway reconstruction tool: <http://bioinformatics.leeds.ac.uk/shark/>; pathway networking tools for downloading: <http://biocyc.org/download.shtml>.

Metabolic Syndrome (MetS): The syndrome develops through the interplay of obesity and metabolic susceptibility. It provides information and guidance on insulin signaling, intensity of drug therapy for elevated cholesterol, aspirin prophylaxis, blood pressure and glucose control in cardiovascular disease (Grundy SM 2007 J Clin Endocrinol Metab 92:399; Petersen KK et al 2007 Proc Natl Acad Sci USA 104:12587). ► [diabetes](#), ► [heart disease](#), ► [cholesterol](#)

Metabolism: Enzyme-mediated anabolic and catabolic reactions in cells. ►BRENDA, ►MetaCyc, ►EX-Prot, ►MCA; compound/enzymes/reactions: <http://www.genome.ad.jp/ligand/>.

Metabolite: The product of metabolism. ►metabolism; <http://metacyc.org/>.

Metabolite Connectivity: The number of reactions of a metabolite. ►pathway tools

Metabolite Engineering: The transformation of certain genes into a new host may lead to production of substances that the organisms never produced before. It can also synthesize larger quantities or different qualities of certain proteins. Examples include: production of indigo or human insulin in *E. coli* or novel antibiotics or expressing antigens of mammalian pathogens in plants or changing the pathway of diacetyl formation in yeast to acetoin production and thus shortening the lagering process in brewing beers, etc. ►genetic engineering, ►protein engineering; Kholodenko BN et al 2000 Metabol Eng 2(1):1.

Metabolome: A complete set of (low-molecular weight) intermediates in a cell or tissue metabolism. Plants produce about 200,000 metabolites. ►gene function; Tweeddale H et al 1998 J Bacteriol 180:5109; Fiehn O 2002 Plant Mol Biol 48:155; human metabolome: <http://www.hmdb.ca>.

Metabolon: A supramolecular-associated complex of sequential metabolic enzymes. (See Reithmeier RA 2001 Blood Cells Mol Dis 27:85).

Metabonomics: The study of the metabolic status in the biofluids of animals (urine, serum, tissues) by high-resolution nuclear magnetic resonance spectroscopy and appropriate statistics to reveal possible toxic effects of chemicals used for drug development. Metabonomic studies may make possible personalized drug treatment if predose phenotyping variations are considered before administration of drugs to which individual differences in response can be predicted. Besides the metabonomic state a number of other factor nutritional state, gut microbiota, age, disease and co- or pre-administration of other drugs may have great influence (Clayton TA et al 2006 Nature [Lond] 440:1073). ►nuclear magnetic resonance spectroscopy; Robosky LC et al 2002 Comb Chem High Throughput Screen 5:651.

Metabotropic Receptor: The binding of a ligand initiates intracellular metabolic events. Many have transmembrane regions and may respond to second messengers such as cAMP, cGMP or inositol triphosphate. ►ionotropic receptor; Ramaekers A et al 2001 J Comp Neurol 438(2):213.

Metacarpus: The area of the hand between the wrist and fingers (see Fig. M51). ►metatarsus



Figure M51. Metacarpus

Metacentric Chromosome: Chromosome whose two arms are nearly equal in length (see Fig. M52). ►chromosome morphology



Figure M52. Metacentric chromosome

Metachondromatosis: Autosomal dominant multiple exostoses particularly on hands, feet, knees and limb bones, without deforming the bones or joints and which disappears with time. ►exostosis, ►fibrodysplasia

Metachromasia: When the same stain colors different tissues in different hues.

Metachromatic Leukodystrophy (MLD): A sulfatide lipidosis. Two distinct forms have been identified that are due to two recessive alleles of a gene, mutations in *A* and *I*, in human chromosome 22q13.31-qter. Due to the deficiency arylsulfatase A, cerebroside sulfate accumulates in the lysosomes. The accumulation of galactoside-sulfate-cerebrosides in the plasma membrane and particularly in the neural tissues (myelin) causes a progressive and fatal degeneration in the peripheral nerves, liver and kidneys. As a consequence failure of muscular coordination (ataxia), involuntary partial paralysis, hearing and visual defects as well as lack of normal brain function arise after 18 to 24 months of age and usually causes death in early childhood. In the juvenile form of the disease the symptoms appear between age 4 and 10 years. There is also an adult type of the disease with an onset after age 16 and involves schizophrenic symptoms. The mutations involve either a substitution of tryptophan at amino acid residue 193, or at threonine 391 by serine or a defect at the splice donor site at the border of exon 2. MLD has been observed also in animals. The reduced activity of the enzyme can be identified also in cultured skin fibroblasts of heterozygotes and prenatally in cultured amniotic fluid cells of fetuses. ►arylsulfates, ►sphingolipidoses, ►sphingolipids, ►Krabbe's leukodystrophy, ►prenatal diagnosis, ►lysosomal storage diseases, ►saposin

Metacline Hybrids: In *Oenotheras*, called the exceptional progeny that occurred only in reciprocal crosses due to the difference in transmission through egg and sperm of the different complex translocations. ▶ **complex heterozygotes**, ▶ **certation**, ▶ **mega-spore competition**

MetaCyc: A database of more than 445 metabolic pathways involving more than 1,115 enzymes in >300 organisms. ▶ **pathway tools**; <http://metacyc.org/>; <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=99148>; <http://bioinformatics.ai.sri.com/ptools/>.

Metacyclic Trypanosoma: Parasitic eukaryote that lives in the salivary gland of insects, which spread sleeping sickness. ▶ *Trypanosoma*

Metacyclogenesis: The differentiation of the promastigote of *Leishmania* into a highly infective form in the sandfly. ▶ *Leishmania*

Metadata: Data about the data, i.e., closer information regarding the methods of collection, analysis, etc., of data available in databases or in reviews or in other publications.

Metafemale: Having more than the usual dose of female determiners; it may be XXX (see Fig. M53). ▶ *Drosophila*, ▶ **triplo-X**, ▶ **euploid**

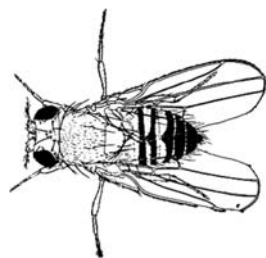


Figure M53. Euploid metafemale *Drosophila*

Metagene: Metagene has several meanings.

1. A gene-predicting commercial software.
2. Network of genes mediating certain physiological functions as revealed by joint expression in microarrays and which display similarities across evolutionary boundaries (Stuart JM et al 2003 Science 302:249).
3. A mystical, hypothetical RNA formed under exceptional conditions imparting superhuman qualities to individuals, which form it.

Metagenesis: Sexual and asexual generations alternate.

Metagenomics: The analysis of the genomes of groups of organisms in samples from the environment, including special environmental locations, such as deep sea, hospital waste, acid mine water, and

archeological remains. Generally nucleotide sequences and functions are used. Such studies yield valuable information on evolution, new genes, new functions and new antibiotics. The human intestinal microbiota is composed of 10^{13} to 10^{14} microorganisms and their collective genome contains at least 100 times as many genes as the human genome (Gill SG et al 2006 Science 312:1355). ▶ **genomics**, ▶ **microbiome**; Riesenfeld CS et al 2004 Annu Rev Genet 38:525; Green Tringe S, Rubin EM 2005 Nature Rev Genet 6:805.

Metal Metabolism And Disease: ▶ **Wilson syndrome**, ▶ **Menkes syndrome**, ▶ **Occipital horn syndrome**, ▶ **hemachromatosis**, ▶ **acrodermatitis enteropathica**, ▶ **hyperzincemia**, ▶ **selenium-binding protein**, ▶ **glutathione peroxidase**, ▶ **aceruloplasminemia**, ▶ **metalloproteinases**, ▶ **metallothionein**, ▶ **protoporphyrin erythropoietic**, ▶ **porphyria**, ▶ **coproporphyrin**; Thompson KH, Orvig C 2003 Science 300:936.

Metallo-Base Pairing: The nucleobases (e.g., hydroxy-pyridone) are modified and paired not by hydrogen bonds but by an interstrand metal such as copper. The metal-containing bases are incorporated into the DNA by phosphoramidite chemistry or by automated DNA synthesis. Such a duplex may have advantage for some applications because of higher thermal stability or for the construction of molecular magnets. ▶ **hydrogen pairing**, ▶ **phosphoramidates**, ▶ **DNA chemical synthesis**; Tanaka K et al 2003 Science 299:1212.

Metalloprotein: The prosthetic group of the protein is a metal, e.g., hemoglobin. ▶ **hemoglobin**, ▶ **zinc-finger**; Annotations and Structure: Shi W et al 2005 Structure 13:1473; <http://metallo.scripps.edu>.

Metalloproteinases (metalloproteases): Cell surface endopeptidase enzymes mediating the degradation of the extracellular matrix, cartilage formation, the release of tumor necrosis factor α , a cytokine involved in inflammatory reactions, in embryogenesis, and cell migration. Membrane-bound metalloproteinase (matrix metalloproteinase, MMP3, stromelysin 1, 11q13) deficiencies cause cranio-facial anomalies, arthritis, dwarfism and other defects due to collagen and connective tissue problems. MMP11 (stromelysin III, 22q11.2) is overexpressed in metastatic breast cancers. Cancer tissues are associated with increased protease activities and it is supposed that these activities facilitate the bursting out of the tumor from the normal cell milieu and increase angiogenesis. MMP-9 (gelatinase, 20q11.2-q13.1) is a contributor to skin carcinogenesis. MMP8 I is collagenase I (11q21-q22), MMP2 is collagenase type IV (16q13) mediating endometrial breakdown during menstruation and may facilitate carcinogenesis by promoting angiogenesis. MMP1 is also a collagenase (11q22-q23). MMP26 (matrilysin 2,

11p15) is involved in tissue healing and remodeling. MMP7 (11q21-q22) is a relatively short uterine matrilysin protein. MMP15 (16q13-q21) and MMP16 (8q21) are membrane enzymes with roles in normal physiological as well as pathogenic processes at special organs. Metalloproteinase inhibitors are explored for cancer therapy. ▶*tace*, ▶*meltrin*, ▶*stromelysin*, ▶*collagenase*, ▶*bone morphogenetic protein*, ▶*night blindness* [Sorsby syndrome], ▶*ADAM*, ▶*arthritis*, ▶*disintegrin*, ▶*extracellular matrix*; Nagase H et al 1992 Matrix Suppl 1:421; Bode W et al 1999 Cell Mol Biol Life Sci 55:639; Sternlicht MD, Werb Z 2001 Annu Rev Cell Dev Biol 17:463; Coussens LM et al 2002 Science 295:2387; Egeblad M, Werb Z 2002 Nature Rev Cancer 2:163; Saghatelian A et al Proc Natl Acad Sci USA 101:10000.

Metallothionein: It is an SH-rich metal-binding protein in mammals. Its main function is detoxification of heavy metals. The promoter is activated by the same heavy metal the protein product binds. This promoter is very useful for experimental purposes because structural genes attached to it can be turned on and off by regulating the amount of heavy metal in the drinking water of the transgenic animals. It is encoded in human chromosome 16q13. ▶*transgenic*, ▶*Menke's disease*, ▶*metals*; Vasák M, Hasler DW 2000 Curr Opin Chem Biol 4:177.

Metals: They may contribute oxidative damage to the DNA and may hinder repair and enhance radiation damage. Beryllium, chromium and lead salts may enhance radiation damage. ▶*metallothionein*

Metamale: ▶*supermale*, ▶*Drosophila*

Metamerism: Anterior–posterior segmentation of the body of annelids and arthropods (see Fig. M54). In chemistry it is rarely used for a type of structural isomerism when different radicals of the same type are attached to the same polyvalent element and give rise to compounds possessing identical formulas.

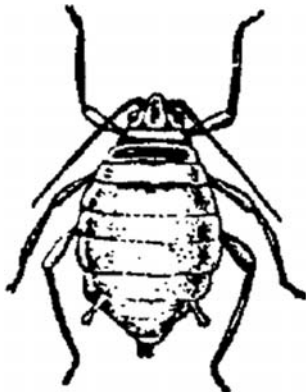


Figure M54. Metameric insect

Metamorphosis: The distinct change from one developmental stage to another, such as from larva to adult or from tadpole to toad. ▶*Drosophila*

Metanomics: The use of gas chromatography and mass spectrometry to trace metabolic changes upon mutation or environmental changes. ▶*gas-liquid chromatography*, ▶*mass spectrum*

Metaphase: A stage in mitosis and meiosis when the eukaryotic chromosomes have reached maximal condensation and spread out on the equator of the cell (metaphase plane) and their arm ratios and some other morphological features can be well recognized. In meiosis I the bivalent chromosomes may be associated at their ends if chiasmata had taken place during pro-phase. The ring bivalents indicate crossing over between both arms whereas rod bivalents are visible when crossing over was limited to only one of the two arms. Figure M55 shows a HeLa cell at metaphase stained with DAPI, anti-tubulin (green) and human anti-centromere autoantibody (red), chromatin (blue). Courtesy of Kevin F. Sullivan, Department of Cell Biology, The Scripps Research Institute, San Diego, California and Don W. Cleveland, Ludwig Institute for Cancer Research, University of California, San Diego, California. ▶*meiosis*, ▶*mitosis*, ▶*chromosome rosette*, ▶*ring bivalent*

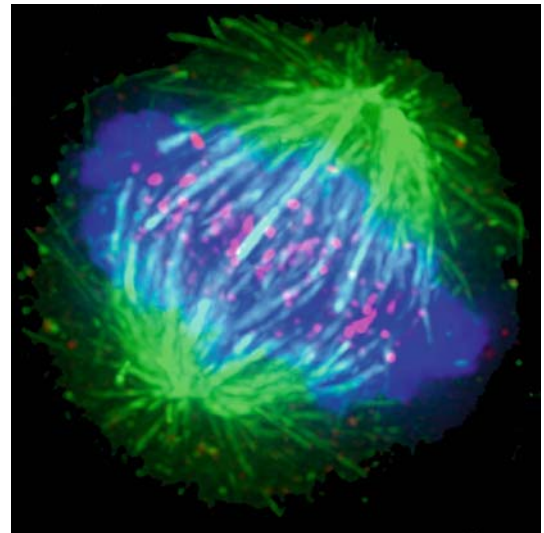


Figure M55. A fluoro-chrome-stained metaphase of HeLa human cells

Metaphase Arrest: Can occur if toxic agents or two separate kinetochores joined by translocation block the nuclear division. Homologous recombination does not lead to metaphase arrest indicating kinetochore tension may be responsible for the event. ▶*meiosis*

Metaphase Plane: The central region of the cell where the chromosomes are located during metaphase. Often incorrectly called metaphase plate (but no plate is involved). ▶mitosis, ▶meiosis

Metamphetamine (ecstasy): A psychoactive, addictive drug. In the presence of white light and riboflavin it is photodegradable to the non-psychoactive enantiomer via a type I photooxidation process by monoclonal antibody derived from mouse (Xu Y et al 2007 Proc Natl Acad Sci USA 104:3681).

Metaplasia: One cell type gives rise to another and in the tissue the two may be adjacent. Normally these two cell types are not expected to occur together. The phenomenon is attributed to different activation of a particular cell(s). ▶stem cells; Tosh D, Slack JMW 2002 Nature Rev Mol Cell Biol 3:187.

Metapopulation: A large population composed of smaller, local populations. (See Coalescent F, Hanski I et al (Eds.) 1997 Metapopulation Biology: Ecology, Genetics, and Evolution. Academic Press, San Diego).

Metastable: A potentially transitory state; it can change to more or less stable form.

Metastasis: The spread of cancer cells through the blood stream and thus establishing new foci of malignancy in any part of the body although, e.g., breast cancer cells frequently metastase to the lung or to the liver. Metastasis has been attributed to epigenetic changes and/or mutation during cancer progression. Several genes have been identified that predispose lung cancer to metastase specifically or mainly to lung (Minn AJ et al 2005 Nature [Lond] 436:518). Three membrane-anchored proteases, type-1, type-2, and type-3 metalloproteinases, independently confer cancer cells with the ability to proteolytically open the basement membrane scaffolding, initiate the assembly of invasive pseudopodia, and propagate transmigration (Hotary K et al 2006 Genes Dev 20:2673). VEGFR1-positive hematopoietic bone marrow progenitor cells scout out

suitable niches where metastatic cells can attach and support the incoming lung tumor cells. The VEGFR1 (vascular endothelial growth factor receptor) cells also express integrin $\alpha 4 \beta 1$, which upregulate fibronectin, an integrin ligand and have essential role in establishment of cancerous growth of metastized cells (Kaplan RN et al 2005 Nature [Lond] 438:820).

The invasiveness of cancer cells requires an active state of the integrin system, cell surface gelatinases (collagenases, proteases) so they could penetrate the extracellular matrix of the target cells. On the cell surface actually precursors of the gelatinases are found that are proteolytically activated by metalloproteinases. Heatshock protein 90 α seems to an activator of the surface metalloproteinase 2 (Eustace BK et al 2004 Nature Cell Biol 6:507). The plasminogen activator proteases include urokinase and tissue type activators. Plasminogen activator inhibitor (PAI1) is also required. IL-18 and TNF- α may promote cell adhesion and metastases by upregulating vascular cell adhesion molecule (VCAM-1, 1p32-p31) synthesis. Also ICE may facilitate metastasis after processing the precursors of IL-1 β and IL-18 proinflammatory cytokines. The CCR gene product appears to suppress metastasis by apoptosis of small cell lung carcinoma and melanoma cells. CXCR4 and CCR7 are highly expressed in breast cancer cells and metastasis.

Migrastatin, a macrolide antibiotic produced by *Streptomyces* and their synthetic analogs inhibit 91–99% of migration of some tumor cells of mouse and human tumor cells but did not inhibit cell proliferation at relatively low toxicity. These compounds were highly selective in their effect on tumor cells compared to normal cells (see Fig. M56). (Shan D et al 2005 Proc Natl Acad Sci USA 102:3772).

It seems that these chemokine receptors and chemokines play important role in metastasis. The direction of invasiveness may depend on the organs/tissues where these receptors are expressed. TIP30 kinase, which appears to be the same as CC3, up-regulates some apoptotic genes by phosphorylating the C-terminal domain of the largest subunit of DNA-dependent RNA polymerase II. Some interfering RNAs

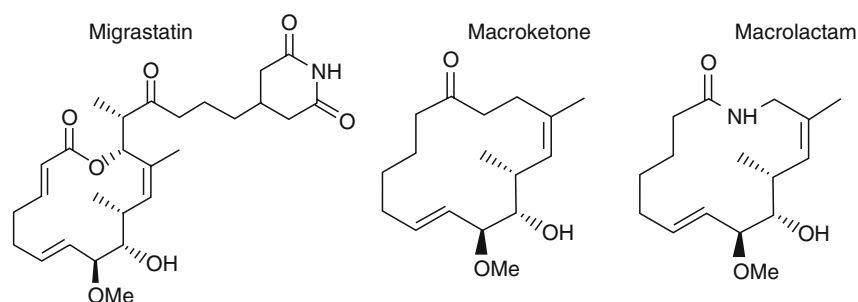


Figure M56. Migrastatin, Macroketone, Macrolactam

(RNAi) suppressed metastasis of ovarian cancer cell line (SKOV3) by affecting a cyclin-dependent kinase (CDK7), a dual-specificity tyrosine phosphorylation-regulated kinase (DYRK1B), mitogen-activated protein kinase (MAP4K4) and serpin (SCCA-1). Such a procedure may have therapeutic potential for cancer (Collins CS et al 2006 Proc Natl Acad Sci USA 103:3775).

Mucin-type glycoprotein precursor of the core 3 structure (GlcNAc β 1–3GalNAc α 1-Ser/Thr) is synthesized by the enzyme β 1,3-*N*-acetylglucosaminyltransferase 6. Core 3 structure is markedly reduced in gastric and colorectal carcinomas in comparison to the Core 1 structure (Gal β 1,3GalNAc α 1-Ser/Thr) and core 2 structure and metastasis occurs. When the Core 3 synthase activity is restored by transfection of the active gene, metastasis is suppressed (Iwai T et al 2005 Proc Natl Acad Sci USA 102:4572). Platelet-derived lysophosphatidic acid promotes the progression of breast and ovarian cancer metastasis to bone. Silencing its receptor by siRNA provided effective protection (Boucharaba A et al 2006 Proc Natl Acad Sci USA 103:9643).

Lysyl oxidase (LOX) expression is regulated by hypoxia-inducible factor (HIF) and the high level of LOX presents poor prognosis for breast cancer and other tumors in mice (Erler JT et al 2006 Nature [Lond] 440:1222).

In *Drosophila* cooperation between Ras^{V12} and one of the cell polarity genes results in metastasis of tumor cells (Pagliarini RA, Xu T 2003 Science 302:1227). Techniques have been designed for the identification of genes, which control/suppress metastasis. In a forward mutation test of mice, disulfide isomerases (thiol isomerases), which catalyze disulfide bond formation, reduction and isomerization, were found to mediate metastasis. Overexpression of ERp5 promotes both in vitro migration and invasion and in vivo metastasis of breast cancer cells. These effects were shown to involve activation of ErbB2 and phosphoinositide 3-kinase (PI3K) pathways through dimerization of ErbB2. Activation of ErbB2 and PI3K subsequently stimulates RhoA and β -catenin, which mediate the migration and invasion of tumor cells (Gumireddy K et al 2005 Proc Natl Acad Sci USA 104:6696).

Hammerhead ribozyme proteins are hooked to RNA helicases. Such a system may destroy the transcripts of metastasis suppressor genes and thus enhance cell migration and can be assayed by an in vitro system (Suyama E et al 2003 Proc Natl Acad Sci USA 100:5616). Metastasis of melanoma cells may be initiated by an increase in the expression of fibronectin, RhoC and thymosin β 4 as visualized by microarray hybridization. Microarray hybridization of primary tumor tissue transcripts may permit the prognostication of tumor progression and patient

survival. ▶CD44, ▶cancer, ▶oncogenes, ▶malignant growth, ▶organizer, ▶contact inhibition, ▶saturation density, ▶collagen, ▶extracellular matrix, ▶VEGF, ▶fibronectin, ▶Rho, ▶thymosin, ▶metallopotein, ▶DAP kinase, ▶intravasation, ▶KISS, ▶urokinase, ▶plasminogen activator, ▶TNF, ▶ICE, ▶IL-1, ▶IL-18, ▶apoptosis, ▶PRL-3, ▶anoikis, ▶RAGE, ▶CCR, ▶CXCR, ▶ACIS, ▶ADM, ▶FAST, ▶macrolide, ▶wound-healing assay, ▶lysophosphatidic acid, ▶ERBB1, ▶PIK, ▶catenins, Al-Mehdi AB et al 2000 Nature Genet 6:100; Müller A et al 2001 Nature [Lond] 410:50; Liotta LA, Kohn EC 2001 Nature [Lond] 411:375; Trusolino L, Comoglio PM 2002 Nature Rev Cancer 2:289; Chambers AF et al 2002 Nature Rev Cancer 2:563; Dudley ME et al 2002 Science 298:850; Ramaswamy S et al 2003 Nature Genet 33:49; Steeg PS 2003 Nature Rev Cancer 3:55; Christofori G 2006 Nature [Lond] 441:444; Nguyen DG, Massagué J 2007 Nature Rev Genet 8:341.

Metatarsus: The middle bones beyond the ankle but preceding the toes in a human foot. In insects the basal part of the foreleg distal to the tibia but proximal to the tarsal segments and the claw (see Fig. M57). It carries the sexcombs in the male *Drosophila*. ▶*Drosophila*, ▶sex comb, ▶metacarpus

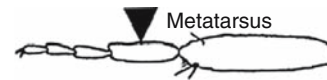


Figure M57. Metatarsus


Metaxenia: A physiological modification of maternal tissues of the fruit in plants by the genetically different embryo, e.g., in green hybrid apples the exocarp (skin) may become reddish if the pollen carries a dominant gene for red color. ▶xenia, ▶fruit

Metazoa: All animals with differentiated tissues; thus protozoa are excluded.

Methacrylateaciduria: β -hydroxyl-isobutyryl CoA deacylase deficiency—involving the catabolism of valine—leads to urinary excretion of cysteine and cysteinamine conjugates of methacrylic acid, and to teratogenic effects. Methacrylic acid [$\text{CH}_2=\text{C}(\text{CH}_3)\text{COOH}$] is a de-gradation product of isobutyric acid [$(\text{CH}_3)_2\text{CHCOOH}$] and the amino acid valine [$(\text{CH}_3)_2\text{CH}(\text{NH}_2)\text{CHCOOH}$]. ▶isoleucine-valine biosynthetic pathway

Methanococcus jannaschii: Bacterium with a genome of 1.67×10^6 bp DNA and 1,738 ORF. *Methanococcus thermoautotrophicum*'s genome is 1.75×10^6 and has 1,855 ORF. ▶ORF, ▶missing genes; Bult CJ et al 1996 Science 273:1058.

Methylacetoaceticaciduria (11q22.3–23.1): A 3-oxothiolase deficiency in the degradation of isoleucine resulting in 2-methyl-hydroxybutyric acid, 2-methylacetoacetic acid, tiglylglycine and butanone in the urine. Tiglic acid [$\text{CH}_3\text{CH}:\text{C}(\text{CH}_3)\text{CHO}$] is trans-2-methyl-2-butenic acid. ►isoleucine-valine biosynthetic pathway

Methylase: Enzymes in bacteria protect the cell's own DNA from type II restriction endonucleases by transferring methyl groups from *S*-adenosyl methionine to specific cytosine or adenine sites within the endonuclease recognition sequence (cognate methylases). When eukaryotic DNAs are transferred to *E. coli* cells by transformation for cloning, their methylation pattern may be lost because the methylation system of the prokaryotic cell is different from that of the eukaryote. *E. coli* does not methylate the C in a 5'-CG-3' but the *dam* methyltransferase methylates A in the 5'-GATC-3' sequence and the *dcm* methyl transferase methylates the boxed C in the 5'-c[]A GG-3' group. Such methylations may change the restriction pattern of cloned DNAs depending whether the particular restriction enzyme can or cannot digest methylated DNA. ►methylation of DNA, ►methylation-specific PCR; Cheng X, Roberts RJ 2001 Nucleic Acids Res 29:3784.

M

Methylation Filtration: The procedures that separate methylated and unmethylated DNA sequenced. Since in, e.g., maize ~95% of the exons are unmethylated, active, functional genes and active transposons can be separated from the bulk DNA. In higher plants, generally 60–80% of the DNA is repetitive and methylated; only ~7% of the repetitive DNA is unmethylated. In *E. coli* strain JM107MA2 the *McrA* and *McrC* modification-restriction systems are defective and do not permit cloning of methylated DNA. Thus cloning enriches the unmethylated genic and retroposon sequences and this “filtration” can reduce the difficulties of sequencing of genes of large eukaryotic genomes (Palmer LE et al 2003 Science 302:2115; Whitelaw CA et al 2003 Science 302:2118; Rabinowicz PD et al 1999 Nature Genet 23:305). ►methylation of DNA, ►cot filtration

Methylation Interference Assay: Detects whether a binding protein can attach to the specific DNA sites and thus provides information on the binding site and on the protein. The analysis is carried out by combining DNA and binding proteins and followed by treatment with methylating enzyme. If the protein binds to a specific guanine site(s), that base will not be methylated. Piperidine breaks DNA at bases modified by methylation, and sites protected from methylation by bound protein are not cleaved by piperidine.

►methylation of DNA; Shaw PE, Stewart AF 2001 Methods Mol Biol 148:221.

Methylation of DNA (DNMT): In many eukaryotes 1–6% or more of the bases in DNA is methylcytosine. In T2, T4 and T6 bacteriophage DNA 5-hydroxymethylcytosine occurs in place of cytosine. Methylation of other bases thymine (= 5-methyluracil), adenine and guanine may also occur in prokaryotes. Adenoviral DNA is not methylated but adenoviral as well as other foreign DNA integration into the mammalian genome may be followed by methylation of cytosine (Orend G et al 1995 J Virol 69:1226). The extent of methylation of the same 5'-CG-3' nucleotides varies in different tissues. Some of the alkylations of DNA bases lead to mutations by base substitutions. Methylation protects DNA from most of the restriction endonucleases (►restriction endonuclease types). In the majority of *E. coli* strains two enzymes are responsible for DNA methylation, *dam* and *dcm* methylase; *dam* methylates adenine at the N⁶ position within the sequence 5'-GATC- 3'. This sequence occurs at the recognition sites of a number of frequently employed restriction enzymes (Pvu I, Bam HI, Bcl I, Bgl II, Xho II, Mbo I, Sau 3AI, etc). Mbo I (↓GATC) and HpaII (C↓CGG) are sensitive to methylation but Sau 3AI and MspI, respectively, are not, and their recognition sites are identical (isochizomers), therefore when the DNA is methylated, the latter ones still can be used. For several restriction enzymes to work, the DNA must be cloned in bacterial strains that do not have the *dam* methylase. Mammalian DNA is not methylated at the N⁶ position of adenine, therefore Mbo I is always supposed to work, as well as Sau 3AI. The DNAs of eukaryotes are most commonly methylated on C nucleotides, in CG sequences. The *dcm* methylase methylates the internal C positions in the sequences 5'-CCAGG-3' and 5'-CCTGG-3'; this methylation interferes with cutting by EcoRII [↓CC(A/T)GG] but not by BstNI, although at another position [CC↓(A/T)GG] of the same sequence. *E. coli* strain K also has methylation-dependent restriction systems that recognize only methylated DNA: *mrr* (6-methyladenine), *mcrA* [5-methyl-C(G)], *mcrB* [(A/G)5-methyl C]. Mammalian DNA with extensive methylation at 5-methyl C(G) is, for, e.g., restricted by *mcrA*. Once the DNA is methylated, this feature may be transmitted to the following cell generation(s) by an enzyme, *maintenance methylase* although methylation is usually lost through the meiotic cycle. In bacteria, the expression of methylated genes may be reduced by a factor of 1000 but in mammals, the reduction may be of six orders of magnitude. Methylation in the promoter region usually prevents transcription initiation but not RNA chain elongation of that gene in mammals.

In the mouse, *Dnmt3a* and *Dnmt3b* are necessary for embryonic survival (*b*) or development after birth (*a*). The double mutants (*a, b*) cannot develop beyond gastrulation (Li E et al 1992 Cell 69:915). *Dnmt1* is incapable for de novo methylation; its role is maintenance methylation of the unmethylated strand generated by replication across the methylated strand in the double helix. Dnmt 1 and PCNA (proliferating cell nuclear antigen) are attracted to damaged DNA sites and this assures the maintenance of the methylated state after replication and repair (Mortusewicz O et al 2005 Proc Natl Acad Sci USA 102:8905). Inactivation of DNMT1 does not affect the status of methylation of CpG doublets in human cancer cells that is involved in the silencing of tumor susceptibility genes in several types of cancers (see Fig. M59). In melanoma and several solid tumors about 40% of the promoter of the p16^{INK4a} gene is hypermethylated. In endometrial, colon and gastric cancer cells the microsatellite instability is accompanied by up to 70–90% methylation. By base specific cleavage of DNA and the use MALDI/TOF/MS using high-throughput technology methylation pattern can be identified (Ehrich M et al 2005 Proc Natl Acad Sci USA 102:15785). The DAP kinase gene in Burkitt's lymphoma may be completely methylated. Mutation in the human DNMT3B gene is responsible for the rare immunodeficiency, ICF. ICF (20q11.2) involves immunodeficiency, pericentromeric hypomethylation and instability in lymphocytes and facial malformations. In some fungi (*Ascobolus*, *Neurospora*) peptide chain elongation may also be inhibited. The inhibition of initiation is attributed to the reduced binding of transcription factors to methylated DNA. Also, methylation-dependent DNA-binding proteins (MDBP) may suppress transcription. Methylation by Dnmt1 may affect also histone deacetylation and chromatin remodeling.

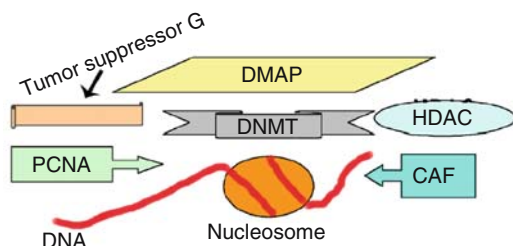


Figure M59. Some of the major factors controlling gene silencing. Proliferating Cell Nuclear Antigen (PCNA) and Chromatin Assembly Factor (CAF) cooperate in building the nucleosomal structure. DNA Methyltransferase (DNMT) is assisted by DNA Methyltransferase Associated Protein (DMAP) and the Tumor Suppressor Gene 101 methylates primarily cytosine residues and silences gene. Histone Deacetylase (HDAC) joins the system

Proteins MeCP1 and MeCP2 mediate silencing of gene expression due to methylation of CpG. MeCP1 effect on silencing depends on the density of methylation near the promoter. MeCP2 binds only single methylated CpG pairs and can act at a distance from the transcription factor binding sites. The effect of MeCP2 is apparently not gene-specific, it is rather global. Genomic imprinting is caused by differential methylation. In mice demethylation or lack of MeCP2 may prevent the normal completion of the embryonic development. In *Arabidopsis* plants demethylation to about 1/3 of the normal level caused either by a DNA (*ddm1*) demethylation mutation or by introducing by transformation an antisense RNA of the cytosine methyltransferase (MET1) caused alterations in the morphogenesis and developmental time of the plants. Demethylation of the *XIST* leads to its expression but that inactivates both X-chromosomes in the female and the single X in the male, an obviously lethal condition. The gene silencing by methylation in *Arabidopsis* is controlled by the *MOM* gene. This protein contains a sequence with similarity to the ATPase region of SWI2/SNF2 protein family, which is involved in chromatin remodeling. Inactivating *MOM* by antisense technology releases heavily methylated genes from the silenced state. In *Arabidopsis* the *mom1* mutation releases silencing independently from DNA demethylation (Mittelsten Scheid O et al 2002 Proc Natl Acad Sci USA 99:13659). Genome-wide methylation of *Arabidopsis* DNA has been mapped at 35-bp resolution. Pericentromeric heterochromatin, repetitive sequences and small interfering RNA regions are heavily methylated. About one-third of the expressed genes contain methylated bases within transcribed areas contrary to expectations. These genes are constitutively and highly expressed. Only 5% of the promoters display methylation and frequently show tissue-specific expression. Methylation epigenetically controls hundreds of genes and intergenic noncoding RNAs (Zhang X et al 2006 Cell 126:1189). Moderately transcribed genes of *Arabidopsis* are most likely to be methylated, whereas genes at either extreme are least likely. In turn, transcription is influenced by methylation: short methylated genes are poorly expressed, and loss of methylation in the body of a gene leads to enhanced transcription (Zilberman D et al 2007 Nature Genet 39:61).

Demethylation of tumor suppressor genes (by antisense technology) restores their suppressor function whereas methylation of the same genes silences them (Robert M-F et al 2003 Nature Genet 33:61). In some organisms with small genomes (*Caenorhabditis*) methylation of the DNA is very low, thus methylation may not have a general developmental regulatory role. In *Drosophila* DNA 5-methylcytosine is detectable only at very low frequency and mainly in

the embryo but interestingly the genome encodes two proteins that resemble cytosine DNA methyltransferase and methyl-CpG-binding-domain proteins. RNAi and microRNA in several organisms are also epigenetic silencing factors.

If 5-methylcytosine is deaminated, thymine results and a C≡G pair may suffer a transition mutation to T = A. It seems that the genome of higher eukaryotes, including humans, includes 35% or more active or silent transposable elements. It had been suggested that methylation of infective (inserted) DNA is part of the eukaryotic defense system. Actually most of the methylated cytosines in mammals are in the parasitic transposable elements. This methylation suppresses their transcription and the C→T mutation leads to the formation of pseudogenes. In the small invertebrate chordate *Ciona intestinalis* non-methylated transposons and normally methylated genomic sequences were detected (Simmen et al 1999 Science 283:1164). Not uncommonly the DNA of cancer cells is undermethylated at C residues indicating the demethylation of their parasitic sequences (SINE, LINE, Alu, etc.) and leading to the destabilization of the genome. The DNA methylase (methyltransferase) enzymes therefore have been supposed to be the means to defend the genome against the deleterious effects of the infective transposable/viral elements. In repetitive DNA CpG methylation is 37% higher than in non-repetitive sequences (Meunier J et al 2005 Proc Natl Acad Sci USA 1023:5471). Although this hypothesis is in agreement with many observations, it does not seem to be of general validity, particularly for the methylation of plant transposable elements. The epigenetic state of methylation can be transferred in the ascomycete, *Ascobolus* by a mechanism resembling or related to recombination. After fertilization, the methyl moieties are generally removed from the CpGs and an unmethylated state is maintained through blastula stage. Some of the genes involved in tumorigenesis display an increased methylation on aging. Housekeeping genes stay unmethylated whereas the methylation of tissue-specific genes varies by tissues. Reduced methylation causes developmental anomalies in plants and animals. The maternal genomes in haploid and diploid gynogenetic one-cell mammalian embryos are always methylated. The polar bodies are always methylated. The paternal genomes in haploid or diploid androgenetic embryos are de-methylated. Triploid digynic embryos show two methylated maternal and one de-methylated paternal chromosome set. In the diandric triploid embryos the methylation pattern is the opposite (Barton SC et al 2001 Hum Mol Genet 10:2983). In the mammals, the active X chromosome displays more than two times as much allele-specific methylation as the inactive X. This methylation is concentrated at gene bodies, affecting

multiple neighboring CpGs. Before X inactivation, all of these active X gene body-methylated sites are biallelically methylated. A methylation-demethylation program results in active X-specific hypomethylation at gene promoters and hypermethylation at gene bodies (Hellman A, Chess A 2007 Science 315:1141). Methyltransferase enzymes comprising enhanced zinc-finger arrays coupled to methyltransferase mutants are functionally dominated by their zinc-finger component. Both in vitro plasmid methylation studies and a novel bacterial assay reveal a high degree of target-specific methylation by these enzymes (Smith AE, Ford KG 2007 Nucleic Acids Res 35:740).

Changes in methylation are apparently not required for the regulation of development of zebrafish. Methylation of the normally barely methylated *Drosophila* DNA reduces viability. In the embryonic tissues of mice CpA and CpT are also methylated to some extent not just CpG. The methylation pattern of cancer cell DNA is usually altered (the promoter of tumor suppressor genes is heavily methylated) but the overall extent of methylation is lower. Methylation of the promoter may interfere with the attachment of the transcription factors. The silencing effect of methylation may be associated with the simultaneous deacetylation of the nucleosomes. Selective methylation of specific DNA sequences may be an important goal of regulating gene expression. The DNA adduct of an oligonucleotide-quinon methide may mediate the transfer of the methide to a complementary base and thus may assure selective targeting (Zhu Q, Rokita SE 2003 Proc Natl Acad Sci USA 100:15452). Methylation may strongly suppress recombination between repeated elements and thus preventing deleterious rearrangements of the genome (Maloisel L, Rossignol JL 1998 Genes Dev 12:1381). Genomic methylation is important factor in epigenetic modification of DNA and development. The program HDFINDER can detect CpG methylation in the human genome with ~86% accuracy (Das R et al 2006 Proc Natl Acad Sci USA 103:10713). ▶transposition, ▶transposable elements, ▶LINE, ▶SINE, ▶Alu, ▶silencing, ▶cross linking, ▶chemical mutagens, ▶alkylation, ▶mDIP, ▶paramutation, ▶imprinting, ▶regulation of gene activity, ▶lyonization, ▶cancer, ▶Sp1, ▶methylation resistance, ▶demethylation, ▶hypermethylation, ▶hypomethylation of DNA, ▶ascomycete, ▶5-azacytidine, ▶HMBA, ▶methylation-specific PCR, ▶methyltransferase, ▶PCNA, ▶CpG islands, ▶MeCP, ▶histone deacetylase, ▶base flipping, ▶RIP, ▶MIP, ▶miRNA, ▶RISC, ▶integration, ▶chromatin remodeling, ▶histone deacetylase, ▶histone methyltransferases, ▶methylation of RNA, ▶housekeeping genes, ▶carcinogenesis, ▶RLSG, ▶immunodeficiency, ▶methylome, ▶PAD4, ▶epigenesis, ▶DAM, ▶digyny, ▶diandry, ▶RNAi,

►microRNA, ►RNAs-directed DNA methylation, ►methylation filtration, ►bisulfite reaction, ►MALDI/TOF/MS, ►MS-RDA, ►AP-PCR, ►DMH, ►Rett syndrome, ►ATR-X, ►fragile X chromosome, ►choline, ►chromomethylase; Bird AP, Wolffe AP 1999 Cell 99:451; Robertson KD, Wolffe AP 2000 Nature Revs Genet 1:11; Baylin SB et al 2001 Hum Mol Genet 10:687; Reik W et al 2001 Science 293:1089; Aoki A et al 2001 Nucleic Acids Res 29:3506; Bender J 2001 Cell 106:129; Cervoni N et al 2002 J Biol Chem 277:25026; DNA methylation and cancer: Laird PW 2003 Nature Rev Cancer 3:253; DNA methylation in *Arabidopsis*: Chan S W-L et al 2005 Nature Rev Genet 6:351; Goll MG, Bestor TH 2005 Annu Rev Biochem 74:481, <http://www.methdb.net>.

Methylation of DNA in Human Disease: ►imprinting, ►Albright hereditary osteodystrophy, ►Angelman syndrome, ►Beckwith-Wiedemann syndrome, ►cancer, ►diabetes mellitus, ►muscular dystrophy, ►fragile X syndrome, ►Prader-Willi syndrome, ►Rett syndrome; Robertson KD 2005 Nature Rev Genet 6:597.

Methylation of Proteins: Reversible post-translational alteration involved in regulation most frequently at arginine and lysine sites. ►histone methyltransferases; Server for methylation prediction: <http://www.bioinfo.tsinghua.edu.cn/~tigerchen/memo.html>.

Methylation of RNA: 2'-O-methyladenosine, 2'-O-methylcytidine, 2'-O-methylguanosine, 2'-O-methyluridine, 2'-O-methylpseudouridine are minor nucleosides in RNA. The cap of mRNA is a 7-methyl guanine, and a N⁶-methyladenosine occurs near the polyadenylated tract. DNA methyltransferase homolog Dnmt2 does not methylate DNA rather it methylates tRNA^{Asp} at cytosine 38 in mouse, *Drosophila* and *Arabidopsis* (Goll MG et al 2006 Science 311:395). ►capping enzyme; Santoro R, Grummt I 2001 Mol Cell 8:719.

Methylation Resistance: ►MNNG

Methylation-Specific PCR (MSP): Methylation of DNA is usually detected by the inability of the majority of restriction endonucleases to cleave methylated sites. MSP detects methylated CpG sites in minute amounts of DNA. The DNA is treated with sodium bisulfite to convert all non-methylated cytosines to uracil. Two different primers designed to represent original CpG rich sequences then amplify the methylated and unmethylated DNAs. The amplified DNA can then be sequenced to compare the differences between the two samples. Alternatively, the DNA is digested by restriction enzyme HpaII, which does not cut at sites

of methylated DNA (CC^mGG) but its isoschizomer MspI does. The DNA is exposed also RsaI (GT^mAC) to generate smaller fragments. The fragments are amplified by PCR in the presence of α³²P-dCTP and separated by gel electrophoresis. If a fragment is present in both the RsaI and (RsaI + HpaII) digest but not in the (RsaI + MspI) samples, it is considered to be methylated. Other isoschizomer pairs with one methylation-sensitive restriction enzyme can be used similarly. ►methylation of DNA, ►polymerase chain reaction, ►bisulfite reaction; Velinov M et al 2001 Genet Test 5(2):153; Oshimo Y et al 2004 Int J Cancer 110:212.

Methylated DNA-Binding Proteins: They bind methylated DNA and recruit additional proteins and the methylome silences transcription of DNA. ►methylation of DNA; Nan X et al 1998 Nature 393:311; Ng HH et al 1999 Nature Genet 23:58.

Methylator: It simultaneously methylates several sites in different cancer suppressor genes. ►CIMP, ►tumor suppressor, ►methylation of DNA

3-Methylcrotonyl Glycinemia: It is caused by the deficiency of a mitochondrial enzyme involved in the degradation of leucine, β-methylcrotonyl-CoA-carboxylase (MCCA, 19 exons, 3q25-q27). The β subunit is encoded at 5q12-q13 (MCCB, 17 exons). As a consequence of this autosomal recessive condition, muscle defects, and in some cases urinary overexcretion of 3-methylcrotonyl glycine and 3-hydroxyisovaleric acids occurs. Some patients respond favorably to biotin because this vitamin is a cofactor of the enzyme. ►isoleucine-valine metabolic pathway, ►isovaleric acidemia, ►3-methylglutaconaciduria, ►3-hydroxy-3-methyl-glutaricaciduria, ►amino acid metabolism; Gallardo ME et al 2001 Am J Hum Genet 68:334.

5-Methylcytosine (5mC): Common in tRNA and DNA of eukaryotes. Methylcytidylic acid is frequently called the fifth nucleotide. Deamination of 5-methylcytosine at CpG sites into thymidine is one of the most common causes of disease and accounts for 20% of all human point mutations (see Fig. M60). The methyl-CpG-binding domain protein MBD4 enzymatically removes T or U from the mismatched sites and protects against tumorigenesis (Millar CB et al 2002 Science 297:403). Thymine DNA glycosylase (TDG) has similar repair function. Sodium bisulfite converts cytosine but not 5mC into uracil. On this basis the location of 5mC in the nucleotide sequence can be determined. ►5-hydroxymethyl cytosine, ►5-azacytidine, ►bisulfite reaction, ►methylation of DNA; Clark SJ et al 1994 Nucleic Acids Res 22:2990.

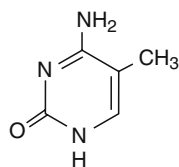


Figure M60. 5-Methylcytosine

Methyl-Directed Repair: ►mismatch repair

Methylene Blue: Aniline dye, for microscopic specimens, an indicator of oxidation-reduction, an antiseptic, an antidote for cyanide and nitrate poisoning.

5,10-Methylenetetrahydrofolate Dehydrogenase (MTHFD1): An enzyme in folate and purine biosynthesis is encoded in human chromosome 14q24. ►folic acid

Methylenetetrahydrofolate Reductase (MTHFR, 1p36.3): MTHFR deficiency is responsible for homocystinuria and may affect human chromosomal nondisjunction. ►homocystinuria, ►nondisjunction

Methylglutaconicaciduria: The autosomal recessive condition is caused by a deficiency of 3-methylglutaconyl-CoA hydratase, an enzyme mediating one of the steps in the degradation of leucine. The patients may develop nerve disorders such as partial paralysis, involuntary movements, eye defects, etc. In some cases there is a marked increase of methylglutaric and methylglutaconic acid (an unsaturated dicarboxylic acid) in the body fluids. Leucine administration may exaggerate the symptoms. 3-methylglutaconic aciduria (MGA) type III is encoded at 19q13.2–q13.3. ►isoleucine-valine metabolic pathway, ►isovalericacidemia, ►3-hydroxy-3-methylglutaricaciduria, ►amino acid metabolism, ►endocardial fibroelastosis; Anikster Y et al 2001 Am J Hum Genet 69:1218; Ijlst L et al 2002 Am J Hum Genet 71:1463.

Methylgreen-Pyronin: A histological stain; coloring DNA blue-green and RNA red. ►stains; Brachet J 1953 Quart J Microscop Sci 94:1.

Methylguanine-O⁶-Methyltransferase: An enzyme that reverses the alkylation of this base, and it is thus antimutagenic and anticarcinogenic. Cells defective in the enzyme (Mer⁻, Mex⁻) are extremely sensitive to DNA-alkylating agents. Mutant enzymes with increased methylguanine-O⁶-methyltransferase activity

may decrease the cells's sensitivity to alkylating mutagens. ►methylation of DNA, ►antimutator; Lips J, Kaina B 2001 Mutation Res 487:59; Zhou Z-Q et al 2001 Proc Natl Acad Sci USA 98:12566.

2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase

Deficiency (HADH2, Xp11.2): This deficiency results in motor function disorder, blindness and epilepsy due to inborn error of isoleucine metabolism. ►isoleucine-valine biosynthetic pathway; Ofman R et al 2003 Am J Med Genet 72:1300.

Methylimidazole: ►pyrrole

Methyljasmonate: The fragrance of jasmine and rosemary plants; it is a proteinase inhibitor.

Methylmalonicaciduria: There are several forms of the metabolic disorder, methylmalonic-CoA mutase deficiency (MUT), in human chromosome 6p21, and another is caused by a defect in the synthesis of adenosyl-cobalamin (cblA, vitamin B₁₂) a necessary co-factor in the biosynthesis of succinyl-CoA from L-methylmalonyl-CoA by MUT. A third type of methylmalonic aciduria is due to a defect in the enzyme epimerase (racemase) that converts D-methylmalonyl-CoA to the L form. This pathway is represented in Fig. M61. In these disorders methylmalonic acid and glycine may accumulate in the body fluids, and the affected individuals may show serious (growth and mental retardation, acidosis [keto acids in the blood]) or almost no adverse effects. High protein diet (valine, isoleucine) may aggravate the condition. Administration of vitamin B₁₂ may alleviate the problem in some cases. ►methylcrotonylglycemia, ►amino acid metabolism, ►vitamin B₁₂ defects, ►ketoaciduria

Methylmercuric Hydroxide (MMH): MMH may be added to the electrophoretic agarose running gel of RNA, and when it is stained with ethidium bromide in 0.1 M ammonium acetate the color of the RNA is enhanced. It is also used to treat mRNA for preventing the formation of secondary structure during the synthesis of the first strand of cDNA. Note that MMH is an extremely toxic volatile compound. ►cDNA, ►electrophoresis

Methylmethanesulfonate: A powerful alkylating agent and mutagen/carcinogen. ►ethylmethane sulfonate

Methylome: The methylated part of the genome, the factors involved in methylation of DNA. ►methylation of DNA, ►methylated DNA binding proteins;

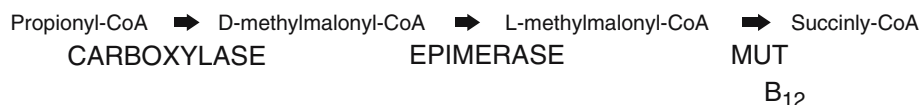


Figure M61. Methylmalonyl pathway

methylome of the *Arabidopsis* genome: Silberman D et al 2007 Nature Genet 39:61.

Methylphosphonates: Oligonucleotide analogs used for antisense operations. They are readily soluble in water and resistant to nucleases. The oligonucleoside methylphosphonates form stable complexes with both RNA and single- and double-stranded DNA. They have both antiviral and anticarcinogenic effects (see Fig. M62). ▶[antisense technologies](#), ▶[mixed backbone oligonucleotide](#); Schweitzer M, Engels JW 1999 J Biomol Struct Dyn 16(6):1177.

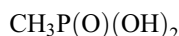


Figure M62. Methylphosphonic acid

Methyltetrahydrofolate Cyclohydrolase Deficiency: Affects folate and purine metabolism. ▶[phosphoribosylglycinamide formyltransferase](#), ▶[folic acid](#)

Methylthioadenosine Phosphorylase (MTAP): MTAP is encoded in human chromosome 9p21 area, and its defect or deletion is characteristic for many malignant tumors, and it may be associated (linked) to a tumor suppressor activity of CDK-4. Methylthioadenosine is abundant in some human tissues and it is an important donor for methylation. ▶[CDK](#), ▶[methylation of DNA](#); Hori Y et al 1998 Int J Cancer 75:51.

Methyltransferase, DNA (dnmt1, dnmt1-b, 19p13.3-p13.2): Responsible for the methylation of CpG sites. These are encoded in humans by the same gene locus but the transcript is spliced alternatively. The activity of these enzymes is increased during the initiation and progression of carcinogenesis but the methylation of DNA in tumors is altered and usually reduced. The 1,620-amino acid mammalian dnmt is essential for embryonic development of the mouse. Methyltransferases have important role in regulation of gene activity, restriction-modification in bacteria, mutagenesis, DNA repair, cancer, imprinting, chromatin organization and lyonization. DNA methylating enzymes are scarce in some insects (*Drosophila*), which do not have methylation in the genetic material. ▶[cancer](#), ▶[methylation of DNA](#), ▶[methylguanine-O⁶-methyltransferase](#), ▶[immunodeficiency](#), ▶[restriction-modification](#), ▶[set motif](#), ▶[histone tail](#), ▶[histone methyltransferases](#); Adams RLP 1995 Bioassays 17:139; Bestor TH 2000 Hum Molec Gen 9:2395; Kiss A 2001 et al 2001 Nucleic Acids Res 29:3188; Verdine GL, Norman DPG 2003 Annu Rev Biochem 72:337; Goll MG, Bestor TH 2005 Annu Rev Biochem 74:481.

Methylviolet: An aniline dye for bacterial microscopic examination.

Metree: A computer program package for inferring and testing minimum evolutionary trees; designed by the Institute of Molecular Evolution, Pennsylvania State University, Philadelphia, PA, USA. ▶[evolutionary tree](#)

METRO (message transport organizer): A mechanism and center for sorting out molecules within the developing oocyte. ▶[morphogenesis](#), ▶[RNA localization](#)

Metronidazole (2-methyl-5-nitro-1-imidazole ethanol): A radiosensitizing agent and mutagen for chloroplast DNA, and a suspected carcinogen (see Fig. M63). ▶[chloroplast genetics](#), ▶[formula](#)

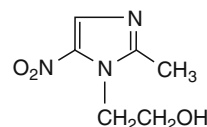


Figure M63. Metronidazole

MeV (mega electron volt): A million electron volt. ▶[electron volt](#)

Mevalonicaciduria (MVK, 12q24): A recessive (human chromosome 12q24) defect with huge increase of mevalonic acid in the urine, caused by a defect in mevalonic acid kinase. ▶[hyperimmunoglobulinemia](#); Houten SM et al 2002 Hum Mol Genet 11:3115.

Mex⁻ (methylation excision minus): Deficient in methyltransferase DNA repair.

Mex67: Protein carrying leucine-rich nuclear localization signal and which serves as an export adaptor. ▶[export adaptor](#), ▶[nuclear localization sequence](#)

MF1: A 5' to 3' exonuclease. ▶[DNA replication eukaryotes](#)

Mfd: Prokaryotic protein, which repairs preferentially the template strand of a transcriptional unit. ▶[backtracking](#); Stanley LK, Savery NJ 2003 Arch Microbiol 179:381.

MFG: A Moloney murine leukemia retrovirus-based vector.

MFISH (multicolor in situ hybridization): Detects probes in 27 fluorescent colors. ▶[FISH](#), ▶[in situ hybridization](#)

MGD: ▶[Mouse genome database](#)

Mge1: A 26-kDa GrpE homolog in *Saccharomyces* mitochondria. ▶[Grp](#).)

MGMT: ▶[Methylguanine-O⁶-methyltransferase](#)

MGSA (melanoma growth stimulating activity): ▶[KC](#), ▶[N51](#), ▶[gro](#)

MGT: The MGMT group of enzymes; they are encoded in human chromosome 10q and protect the cells against the genotoxic, recombinogenic and apoptotic effects of O⁶-methylguanine with the aid of mismatch repair. When MGMT is expressed at high level the formation of O⁶-methylguanine is substantially reduced. ▶MGMT, ▶Mer; Kaina B et al 2001 *Progr Nucleic Acid Res Mol Biol* 68:41.

MHC: Major histocompatibility complex is involved in immunological reactions; it is controlled by linked multigene families (HLA) determining cell surface antigens and thus cellular recognition. The acronym is used also to the myosin heavy chain. ▶HLA, ▶Immune system, ▶major histocompatibility complex; MHC binding peptides: <http://www-bs.informatik.uni-tuebingen.de/SVMHC/>.

MHC Restriction: ▶immune system

MIAME (minimum information about a microarray experiment): A required standard for acceptance of microarray data by the major journals since 2002. (See *Nature Genet* 32:333; *Science* 298:539; *Gene Expression Omnibus*; <http://www.mged.org>).

MIC: Minimal inhibitory concentration. ▶micRNA

M

MICA/B Proteins: Intracellular proteins, which mark (cancer) cells for destruction by natural killer cells. Association of MICA with endoplasmic reticulum protein 5 (similar to disulphide isomerase) potentiates shedding of tumor-associated killer cell ligand NKG2D and promotes the immune evasion of tumor cells (Kaiser BK et al 2007 *Nature [Lond]* 447:482). ▶killer cells, ▶disulphide bridge, ▶immune evasion

Micelle: A round body of (protein) substances surrounded by lipids.

MICER (mutagenic insertion and chromosome engineering resource): A collection of 93,960 insertional targeting vectors; 5,925 of them inactivate genes with 28% efficiency (Adams DJ et al 2004 *Nature Genet* 36:867). ▶targeting genes, ▶insertional mutation, ▶chromosome engineering

Michaelis–Menten Equation: It measures enzyme kinetics in a process:

$$(E) + (S) \xrightleftharpoons[k_2]{k_1} (E) \xrightarrow{k_3} \text{Product(s)} + (E), \text{ where } k_1, k_2, k_3 \text{ are constants of the reactions, } (E) = \text{enzyme, } (S) = \text{substrate concentration and } v = \frac{V(S)}{K_m + (S)} \text{ or } K_m = (S) \left[\frac{V}{v} - 1 \right] \text{ where } v \text{ is the velocity of the reaction when half of the substrate molecules is combined with the enzyme, } V = \text{the maximum velocity, and } K_m = \frac{[(E)-(ES)](S)}{(S)}$$
 is the Michaelis–Menten constant. also ▶Lineweaver–Burk plot).

Michel Syndrome (oculopalatoskeletal syndrome): An autosomal recessive multiple defect involving the eyelid, opacity of the cornea, cleft lip and palate, defects of the inner ear and spine column, etc. It causes complete deafness. ▶deafness, ▶eye diseases

micRNA (messenger RNA-interfering RNA): This RNA is transcribed on short sections of the complementary strand DNA; prevents gene expression. ▶antisense RNA, ▶RNAi, ▶microRNA; Mizuno T et al 1984 *Proc Natl Acad Sci USA* 81:1966.

Microarray: ▶Microarray hybridization, ▶DNA chips, ▶small molecule microarray, ▶protein array, ▶protein chips; microarray data repository: <http://www.ebi.ac.uk/arrayexpress-old/>.

Microarray Hybridization: A microtiter tray with wells containing DNA to which fluorochrome-labeled-RNA can be hybridized. After incubation and scanning the amounts of the mRNAs derived from the same tissue can then be quantitated (by fluorescence intensity). A microarray tray looks similar to the pattern shown in the Fig. M64. Its size may be as small as 18 × 18 mm. The thousands of genes expressed on a single tray may

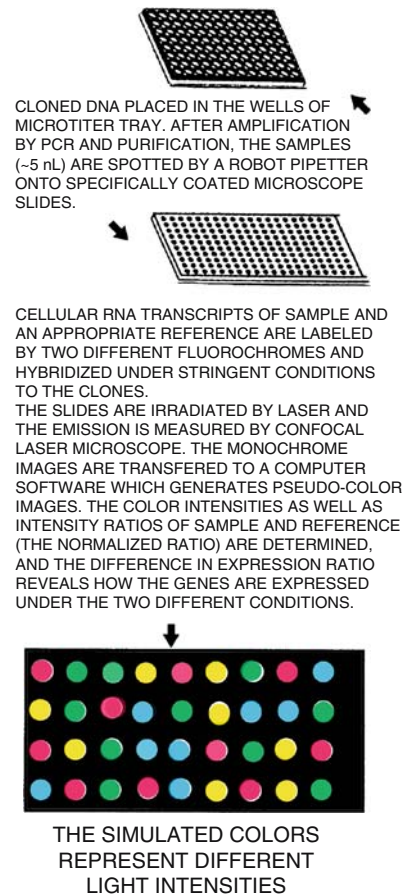


Figure M64. Microarray Hybridization

display different fluorescent colors according to the fluorochrome labeling of the probe in a spot test. Such an analysis may identify the simultaneous expression of large sets of genes at a particular developmental or disease/health stage and thus, permits a functional study at the entire genome level. Most commonly, the colors shown in the publications represent the intensity of hybridization (red the highest).

If the tissues are, for, e.g., from healthy and diseased sources, the genetic cause of the disease can be inferred on the basis of the level of expression. Depending on the type of fluorescent label used, the RNA sample may vary from 10 µg to 50 ng and the number of cells needed to extract this much material may vary from >1 to 10^9 . The analysis may begin with cDNA clones or PCR-amplified samples transferred to glass plates or nylon filters where appropriate probes are hybridized to the arrays. For the glass slides, usually fluorochrome labeling is used whereas with the nylon support phosphor imager (P^{33} , half-life ~ 25 days) is employed. The data is first evaluated by image processing after the information is fixed in JPEG or GIF formats. Then statistical and biological methods are applied (JPEG, TIFF and GIF are Adobe PhotoShop computer formats). The information reveals the function of many genes in a context in different tissues, developmental or pathological states, and may be used for simultaneous characterization of many tumor biopsies. By sophisticated computer-based analysis of the biological meaning of the information, *data mining* permits the identification of genes, which are either expressed simultaneously or in certain tissues; in a specific state of a disease or diseases; which appear epistatic or respond to a particular condition.

Microarray interrogated with short synthetic RNA oligomers permit the analysis of polymorphism at $\sim 2\%$ accuracy in up to 40,000 genes per microarray, which is more than enough for a genome the size of yeast. By the use of hierarchical clustering algorithms, parameterization or profiling methods, gene expression can be “mapped” not unlike the methods of genetic or physical mapping. However, clustered functions are independent from the physical location of the genes but may indicate the co-transcribed compartments and interaction of gene products. The pattern of expression reflects the dynamic network of timing, the physiological and developmental processes. The microarrays may be used to study the co-regulation of genes and the exploration of the global or particular effects of mutation or repression of single genes. Furthermore, the co-expression patterns of pathogens and host cells can also be revealed.

The *spotting method* outlined above uses a single clone for the analysis of each mRNA. The GeneChip Expression (Affymetrix, 3380 Central Expressway, Santa Clara, CA 95051) employs about 16 pairs

of specific oligonucleotide probes to interrogate each transcript. (The description given is based on information and images provided by Affymetrix and Gene Microarray Shared Resource, Ohio State University.) The latter procedure is better suited for reducing and identifying non-specific hybridization and background effects and therefore it is more sensitive and more accurate. Basic principles can be outlined as follows. A *target sequence* of ~ 600 nucleotides of gene is selected from a public database. About 16 to 20 *probes* are generated to match the sequences of the database. A pair of 25-base probe is of two types.

The *perfect match* (PM) is entirely identical to a tract of the DNA. The *mismatch probe* (MM) is the same as the PM except for a single mismatch in the middle. The rationale for using a MM probe is to have a control for non-specific hybridization. These probes are synthesized on a GeneChip, a small glass plate. The synthesis is a light-directed process (photolithographic fabrication) yielding large quantity of accurate probes at an economical manner (see Fig. M65).

From the biological sample, biotinylated mRNA is prepared, fragmented by heat and applied to a *probe array*, which is 1.28×1.28 cm glass surface held on a small tray. Hybridization is allowed for about 16 hours. The extent of hybridization is ascertained by the fluorescence intensity as detected by a laser scanner.

From a small segment of image, the intensity of the hybridization (i.e., the identity of the target and the probe pair) may have the alternative matches shown below. White corresponds to high hybridization intensity, black no measurable hybridization signal. Intermediate shades or colors correspond to intermediate signals. When the Perfect Match and the Mismatch signals are inconsistent, the hybridization is not detectable (see Fig. M66).

The Microarray Suite (MAS) software manages the Affymetrix GeneChip experiments. The relative expression of a transcript is determined by the difference between each probe pair (PM minus MM) and averaging the difference over the whole probe set (*Avg Diff*). The term *Abs Call* for a probe set is a qualitative measure based on three different determinations collected by MAS 4.0. The Absolute Call for a probe set can be “A” for non-detectable, “M” for marginal and “P” for present. *Diff Call*, difference call is the qualitative call for a probe set representing the outcome of one array set compared to another. There are five possibilities:

“I” increased, “MI” moderately increased, “NC” no change, “MD” moderately decreased and “D” decreased call.

Microarray hybridization is an essential tool in proteomics, for the study of genetic networks that

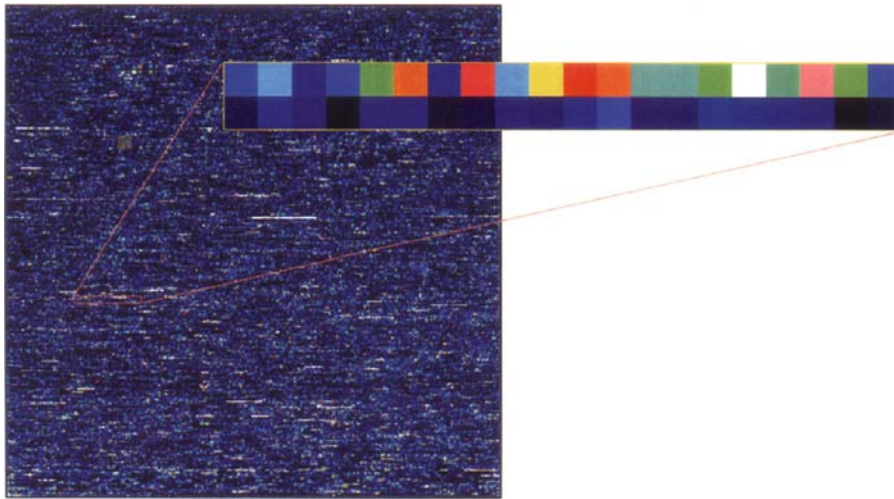


Figure M65. DNA chips. Different 25-mer oligonucleotide probes in an area of 1.28×1.28 cm. The array contains probe sets for more than 6,800 human genes, and the image was obtained after overnight hybridization of an amplified and labeled human mRNA sample. Image by courtesy of Affymetrix Inc. and from Fields S et al 1999 Proc Natl Acad Sci USA 96:8825; [Copyright by the National Academy of Sciences, U.S.A. 1999]

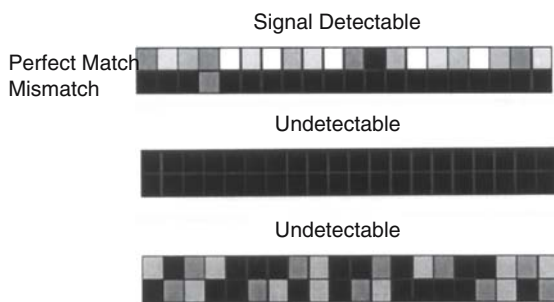


Figure M66. Hybridization signal evaluation

play an important role in development and in studies of the reaction to drugs. The impact of stress or cancer on gene expression may become amenable to interventions. The simultaneous effect of various drugs on a family of genes can be assessed. The availability of these methods is completely revolutionizing information gathering on the expression of genes, and may be exploited for the study of the simultaneous expression of many genes involved in a pathway or related pathways. A number of factors may affect the efficiency of hybridization, such as temperature, base composition (A=T versus G=C) and even at the same composition, the actual sequences of the bases, secondary structures, sequence length, distribution of mismatches, etc. Unexplained variations have also been seen with the present-day—steadily improving—technologies. An alternative approach for monitoring gene expression pattern optically measures light emission of transcriptional gene fusions of luciferase structural genes to

promoters of operons or regulons. Gene expression (mRNA), and protein levels can be analyzed under a variety of conditions and an integrated picture can be derived of metabolic networks. The same basic principle has also been applied to an array of animal cells, which are transfected with a variety of cDNAs and the expression of the transgenes that affect cellular physiology is monitored. ▶SAGE, ▶laser desorption MS, ▶electrospray MS, ▶two-hybrid method, ▶DNA chips, ▶epistasis, ▶synexpression, ▶operon, ▶regulon, ▶luciferase, ▶transcriptional gene fusion, ▶base-calling, ▶IMAGE clones, ▶genetic network, ▶global single cell reverse transcription-polymerase chain reaction, ▶macroarray analysis, ▶genomics, ▶interrogation genetic, ▶cluster analysis, ▶support vector machine, ▶activity-based protein profiling, ▶TOGA, ▶protein arrays, ▶lymphochips, ▶SOM, ▶tissue microarray, ▶light directed parallel synthesis, ▶MAGE, ▶MELANIE, ▶MIAME, ▶Atlas™ human cDNA, ▶linkage; Ermolaeva O et al 1998 Nature Genet 20:19; Nature Genet 21(1) Supplement Nature Biotechnol 17:974; Scherf U et al 2000 Nature Genet 24:236; Van Dyk TK et al 2001 Proc Natl Acad Sci USA 98:2555; Ideker T et al 2001 Science 292:929; Ziauddin J, Sabatini DM 2001 Nature [Lond] 411:107; Stoughton RB 2005 Annu Rev Biochem 74:53; computations: Quackenbush J 2001 Nature Rev Genet 2:418; Zhao LP et al 2001 Proc Natl Acad Sci USA 98:56321; Schulze A, Downward J 2001 Nature Cell Biol 3:E190; Yang YH, Speed T 2002 Nature Rev Genet 3:579; Nature Genet Suppl 2002 32:461–552; transcript concentration analysis: Held GA et al 2003 Proc Natl Acad Sci

USA 100:7575; statistical analysis of gene expression during development in microarrays: Storey JD et al 2005 Proc Natl Acad Sci USA 102:12837; data analysis: Allison DB, Page GP 2006 Nature Rev Genet 7:55; [note Fig. 1 y-axis should have been $-\log_{10} \times \left(\frac{|p\text{-value}|}{1-|p\text{-value}|}\right)$]; extensions of the classical microarrays: Hohenheisel JD 2006 Nature Rev Genet 7:200; GE OMNIBUS: <http://www.ncbi.nlm.nih.gov/geo/>; <http://www.ebi.ac.uk/microarray/>; <http://www.ebi.ac.uk/arrayexpress/>; <http://www.biocchipnet.de/>; <http://www.genomethods.org/caged/>; microarray standards: <http://www.mged.org/>; comparison of published microarray data to experimenter's results and can help in interpreting the biological and medical meaning of the results: <http://depts.washington.edu/l2l/>; gene expression pattern analysis tool: <http://gepas.bioinfo.cipf.es/>; gene expression pattern comparison software: http://ihome.cuhk.edu.hk/~b400559/arraysoft_image.html; Affymetrix and Applied Biosystem microarray analysis tool: <https://carmaweb.genome.tugraz.at/>; prokaryotic microarray–gene ontology tool: <http://www.jprogo.de/>; tools and software: <http://smd.stanford.edu/>; copy number variations: aCGH; microarray expression pathway: <http://bioinfoserver.rsbs.anu.edu.au/utis/PathExpress/>.

Microarray Image Analysis: It performs gridding (location of spots on the slide), segmentation (differentiates the pixels between spots and background), information extraction (calculation of fluorescence intensity from the segmentation information). ► [microarray hybridization](http://ihome.cuhk.edu.hk/~b400559/arraysoft_image.html); http://ihome.cuhk.edu.hk/~b400559/arraysoft_image.html.

Microbe: Small organisms like the eukaryotic fungi, algae and protozoa and the prokaryotic blue-green algae, bacteria and viruses. The 2–3 billion microbial species exhibit enormous genetic diversity and are largely unknown. They are frequently associated with disease. The identification of particular microbes may be quite difficult by morphology or culture methods. Recently, broad-range polymerase chain reaction, representational difference analysis and expression library screening for specific sequences became feasible and greatly improved identification by molecular means. ► [RDA](#), ► [PCR broad-base](#), ► [microarray hybridization](#), ► [microbiome](#); <http://pbil.univ-lyon1.fr/emglib/emglib.html>; microbial genomes: <http://microbialgenome.org/>; <http://www.biocrawler.com/encyclopedic/Microorganism>; microbial orthologous groups: <http://mbgd.genome.ad.jp/>.

Microbial Safety Index: The logarithm of the reciprocal number of microbes that have survived after a procedure of sterilization. Sterilization, in principle, is the destruction of all infective agents but, in

practice, a small fraction of $\sim 10^{-6}$ may survive the treatment.

Microbiome: The collective genomes of the very large number of microbes that inhabit the human or animal body or a particular space. Their populations of 500–1000 species were estimated to exceed that of the number of somatic cells of the body. The human gut may include 10^{11} foreign cells per mL of proximal colonic content. There are 2 to 4 million genes encode metabolic capacities absent from the human proteome and thus play important roles in human nutrition (Xu J et al 2003 Science 299:2074). One study found 128 phylotypes (belonging to a taxonomic phylum) of microbes in the human stomach and the microbial community was different than that in the mouth or in the esophagus (Bik EM et al 2006 Proc Natl Acad Sci USA 103:732). The human oral cavity may harbor ~ 500 different microbial species (Paster BJ et al 2001 J Bacteriol 183:3770). The human intestinal flora of bacteria is transmitted during the birth process (vaginal delivery) from the mother and maintained in the offspring. It may be different, however, between marital partners although some changes may occur depending on toilet use, antibiotic treatment, shift in diet or infection with different parasites. Some lateral gene transfer among the various bacteria within the gut does occur yet it does not entirely homogenize the populations. The microbiome inhabiting different mammalian species is different although some similarities may be established by environmental factors and selection. The host immune system may be somewhat responsive to these microbes yet does not eliminate them. When gut microbiome was reciprocally transplanted between germ-free mouse and zebrafish the transplanted community resembled its origin but in the lineage, it resembled the abundance of the recipient host indicating a selective pressure of the host gut habitat (Rawls GF et al 2006 Cell 127:423).

According to a new estimate there appears to be 10^{16} prokaryotes in a ton of soil, much more than the estimated number of stars in the galaxy (10^{11}). These estimates may not be entirely accurate because they are based on some data and hypothesis and mathematics (Curtis TP, Sloan WT 2005 Science 309:1331). The secretion through/by the roots—that varies according to species—determines the microbe communities in the rhizosphere (Mark GL et al 2005 Proc Natl Acad Sci USA 102:17454). ► [gut](#), ► [metagenomics](#), ► [oral bacterial film](#), ► [vagina](#), ► [inclusive fitness](#), ► [Paneth cell](#); gastrointestinal microbial flora in metabolism and health: Nicholson JK et al 2005 Nature Rev Microbiol 3:431; plant pathogenic RNA viruses in human feces: Zhang T et al 2006 PLoS Biol 4(1):e3; review of human

intestinal microflora: Ley RE et al 2006 Cell 124:837; human microbiome: <http://bioinformatics.forsyth.org:7070//homd/>; human oral microbiome: http://bioinformatics.forsyth.org/old_homd/.

Microbodies: ► **peroxisomes** (see Fig. M67)

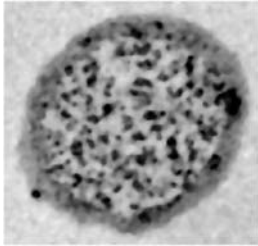


Figure M67. Microbody

Microcalorimetry: Detects the minute change in heat energy resulting from molecular interactions, associations, and dissociations. Two procedures are used: *differential scanning calorimetry* (DSC) to record the changes in temperature while proteins are unfolding and *isothermal titration calorimetry* (ITC) to record the changes in temperature while the solutions are mixed. ► **immunoprecipitation**, ► **surface plasmon resonance**

Microcell: A micronucleus, a piece of chromatin, a chromosome or a few chromosomes surrounded by a membrane. Microcells are suitable vehicles for the transfer of blocks of genetic material or entire chromosomes between organisms. ► **transchromosomal**, ► **micronucleus**

Microcell Hybrid: Contains a single (e.g., human) chromosome in a complete other (e.g., mouse) genome. The hybrid, using deletions, may permit the identification of specific functions associated with segments of the critical chromosome. ► **somatic cell genetics**, ► **transchromosomal**; Cao Q et al 2001 Cancer Genet Cytogenet 129(2):131.

Microcephaly (19.13.1, 15q15, 9q33, 1q31, 13q12.2): Abnormal smallness of the head (brain volume $\sim 400 \text{ cm}^3$); generally involves mental retardation. It is a condition due to various genetic and environmental causes (e.g., X-ray, exposure of the fetus to heat [febrile]). The incidence of the autosomal recessive form is about 2.5×10^{-5} . A deletion of chromosomal segment 1q25-q32 or mutation in 1q31-32 may be the cause of severe cases. The 8p23 locus encodes the microcephalin protein regulating brain size and it continuously undergoes adaptive positive selection for larger brain (Evans PD et al 2005 Science 309:1717). It has been suggested that the microcephalin gene was acquired by introgression into

modern human genomes 37,000 years ago and was an important factor of evolution of brain size (Evans PD et al 2006 Proc Natl Acad Sci USA 103:18178). Some of the suggestions concerning correlations among genes for microcephalin and ASPM (abnormal spindle-like, microcephaly-associated gene; human locus 1q31) and evolution of intelligence are controversial (Curat M et al 2006 Science 313:172).

Recurrence risk among sibs was estimated to be 0.19 but the risks might vary depending on the cause of the defect. It is generally accompanied by other abnormalities. Microcephaly with normal intelligence characterizes the autosomal recessive Nijmegen breakage syndrome. The latter is associated with chromosomal instability, immunodeficiency and radiation sensitivity. Microcephaly with immunodeficiency is caused by mutation in (Cernunnos) NHEJ protein factor (Buck D et al 2006 Cell 124:287). ► **mental retardation**, ► **hydrocephalus**, ► **brain**, ► **craniofacial dysostosis** (Crouzon syndrome), ► **cerebral gigantism**, ► **NHEJ**, ► **macrocephaly**; Pattison L et al 2000 Am J Hum Genet 67:1578; Bond J et al 2005 Nature Genet 37:353.

Microchaetae (pl.): Hairs of insects. ► **chaetae** for illustration

Microchannel Plate Detector: Analytical equipment for the detection of radioactive labels in proteins separated by 2-dimensional gel electrophoresis. ► **two-dimensional gel electrophoresis**; Richards P, Lees J 2002 Proteomics 2:256).

Microchimerism: The survival of donor cells in the recipient after transplantation of foreign tissues or organs. Preliminary evidence indicates the rate of survival of pig cells in humans appears to be as low as 10^{-5} . ► **xenograft**, ► **xenotransplantation**, ► **PERV**; Johnson KL et al 2001 Arthritis Rheum 44:2107.

Microchip: Integrated computer circuitry. ► **DNA chip**

Microchromosomes: Very small chromosomes of the avian genome uniform in size and rich in GC content. They replicate ahead of the larger (macro) chromosomes. Their density of genes appears very high probably because their introns are short. ► **intron**, ► **human artificial chromosome**; McQueen HA et al 1996 Nature Genet 12:321.

Microcin: An enterobacterial heptapeptide (Acetyl-Met-Arg-Thr-Gly-Asn-Ala-Asp-X) inhibiting protein synthesis where the first amino acid is acetylated and X is an acid labile group. Microcin J25 obstructs the nucleotide uptake channel of the RNA polymerase (Mukhopadhyay J et al 2004 Mol Cell 14:739; Adelman K et al 2004 Mol Cell 14:753). It is encoded by 21 bps and thus appears to be one of the smallest translated genes. ► **gene size**

Microcinematography: A time-lapse motion photorecording of living material. Successive frames delayed in real time, are projected at normal speed giving the sensation as if the events, movements of cells or chromosomes, etc., would have taken place at an accelerated time sequence. Thus, for instance the progress of mitosis that requires 1–2 hours can be seen in motion, in minutes. ▶ [phase contrast microscopy](#); Nomarski, Matter A 1979 Immunology 36(2):179.

Micrococcal Nuclease: Prepared from *Staphylococcus aureus* degrades DNA (with preference for heat-denatured molecules) and RNA and generates mono- and oligonucleotides with 3'-phosphate termini.

Microconidia: Small uninucleate conidia. ▶ [macroconidium](#), ▶ [conidia](#), ▶ [fungal life cycles](#)

Microcytotoxicity Assay: Detects allelic variants of MHC proteins. Cells are usually labeled by the green fluorescein diacetate and exposed to two different antibodies. The immunologically reacting cells are lysed and their nuclei are stained red by propidium iodide. Thus, the two alleles are distinguished in vitro. (See Wahlberg BJ et al 2001 J Immunol Methods 253:6).

Microdeletion: The loss of a segment too short to be visualized by light microscopy. Comparative genomic hybridization can detect submicroscopic alteration of 100 kb in the chromosome. Conventional karyotyping can detect changes only of 5–10 million bases. In 10% of mentally retarded individuals, 540 kb to 12 Mb de novo alterations were identified (Bert B et al 2005 Am J Hum Genet 77:606). ▶ [karyotype](#), ▶ [comparative genomic hybridization](#)

Microdose: Generally 1% of a therapeutic dose of a drug, labeled by a radioactive tracer to facilitate imaging (by positron emission tomography or accelerator mass spectrometry) without toxicity to the treated individual. The microdose permits detection of absorption, distribution, metabolism and excretion of the drug (Lappin G, Garner RC 2003 Nature Rev Drug Discovery 2:233). ▶ [tomography](#), ▶ [mass spectrum](#)

Microdot DNA: A molecular version of steganography (concealing text) used to communicate secret spy messages. The messages are represented in nucleotide sequences generated by PCR using 20-base forward and reverse primers. The encrypt code may be represented by base triplets, e.g., CGA for the letter A, CCA for B, etc. The sequences within the PCR products can be hidden within the total human DNA or a mixture of DNAs of different organisms from where it can be fished out despite the enormous complexity of the mix. This total mixture, including the secret PCR message in ~10 ng would not occupy a much larger microdot than about a full stop (.) on a

filter paper. Primers may permit amplification of the message, and it can be sub-cloned and sequenced. If the cipher is known, the message is readable in English (or any other language) by those who are familiar with the primers but for those who are not it is virtually impossible to decipher it. (See C. Taylor C et al 1999 Nature [Lond] 399:533, ▶ [PCR](#)).

Microelectrodes: Chemical sensors with micrometer or smaller dimension. The potentiometric units can detect changes across chemically selective membranes. The voltametric units are microscopic in size and detect substances on the basis of their oxidation or reduction and can detect charge changes involved in neurotransmission and in other biological systems (Wightman RM 2006 Science 311:1570). ▶ [electrode](#)

Microencapsulation: To envelop cells with a thin, generally spherical, semipermeable polymer film. The capsule protects cell viability, permits diffusion, and may release its content. Chemically and mechanically fragile structure may be used for cell therapy. Microencapsulation involves the use of a hollow cylinder of selectively permeable, thicker membrane filled with cells suspended in a matrix and sealed. Its utility is similar to microcapsules. It may damage the tissues during manipulations.

Microencephaly: Abnormal smallness of the brain caused by developmental genetic blocks or degenerative diseases. ▶ [microcephaly](#)

Microevolution: A minor variation within species that may lead to speciation. ▶ [evolution](#), ▶ [macroevolution](#); Hendry AP, Kinnison MT 2001 Genetica 112:1.

Microfilaments: Actin and myosin containing fibers in the cells serving as part of the cytoskeleton and mediate cell contraction, amoeboid movements, etc. ▶ [cytoskeleton](#)

Microfluidic Digital PCR: It can analyze single cells by multiplex PCR. ▶ [PCR multiplex](#); Ottesen EA et al 2006 Science 314:1464.

Microfluidics: These systems reduced to micrometer scale behave differently from what we usually see in the physical world. Diffusion, surface tension and viscosity affect the movement of fluids (10^{-9} to 10^{-18} liters) in a different way such as in cells and other microscopic systems. Devices that integrate diverse cellular parameters within sub-nanoliter volumes for the characterization of systems biology and such a medicine is now opening up for experimental approaches. The major merits of microfluidics are the small volumes used, small quantities of reagents are needed, high resolution and high sensitivity in analysis is possible by taking advantage of new developments in microelectronics. Microfluidics has potential for many

different applications such as separations coupled to mass spectrometry, high throughput screening and synthesis of drugs, examination of single cells or single molecules and synthesis of labeled compounds for positron emission tomography, development of new medical diagnostic tools, etc. A microfluidic genetic analysis system performs nucleic acid purification through solid-phase extraction, followed by target sequence amplification by PCR and microchip electrophoretic amplicon separation and detection is completed in <30 min. The presence of *Bacillus anthracis* (anthrax) in 750 nl of whole blood from living asymptomatic infected mice and of *Bordetella pertussis* in 1 μ l of nasal aspirate from a patient suspected of having whooping cough could be confirmed by the resultant genetic profile (Easley CJ et al 2006 Proc Natl Acad Sci USA 103:19277). ▶systems biology, ▶massive parallel signature sequencing, ▶dielectrophoresis, ▶tissue engineering, ▶protein synthesis, ▶anthrax, ▶whooping cough; Werdich AA et al 2004 Lab Chip 4:357; Shaikh KA et al 2005 Proc Natl Acad Sci USA 102:9745; Atencia J, Beebe DJ 2005 Nature [Lond] 437:648; Whitesides GM 2006 Nature [Lond] 442:368.

Microfusion: The fusion of protoplast fragments with intact protoplasts to generate cybrids (generally by electroporation). ▶cell fusion, ▶somatic hybridization, ▶cybrid

Microglia: The mesodermal cells supporting the central nervous system and constitute about 10% of the central nervous system. Microglia are a class of monocytes capable of phagocytosis. They can bind, through scavenger receptors, β -amyloid fibrils (present in Alzheimer plaques) resulting in the production of reactive oxygen species and leading to cell immobilization, and cytotoxicity toward neurons. ▶monocyte, ▶Alzheimer disease; Giulian D 1999 Am J Hum Genet 65:13; Nakajima K, Kohsaka S 2001 J Biochem 130:169; Fetler L, Amigorena S 2005 Science 309:392.

Microglobulin β_2 : The class I MHC α chain is non-covalently associated with this polypeptide, which is not encoded by the HLA complex. The α_3 domain and the microglobulin are similar to immunoglobulins and they are rather well conserved, in contrast to the α_1 and α_2 domains, which are highly variable. Its defect results in renal amyloidosis. ▶TAP, ▶HLA, ▶amyloidosis; Hamilton-Williams EE et al 2001 Proc Natl Acad Sci USA 98:11533.

Micrognathia: Abnormally small jaws.

Microgonotropens (MGT): These are inhibitors of transcription factor—DNA interactions. Transcription factors usually bind to the major groove of the

DNA, whereas MGTs associate primarily with the minor groove but to some extent also to the major groove. Efficient MGTs may regulate gene expression and may be of therapeutic value. ▶transcription factors, ▶DNA grooves; Wemmer DE, Dervan PB 1997 Curr Opin Struct Biol 7:355; White CM et al 2001 Proc Natl Acad Sci USA 98:10590.

Micrograph (photomicrograph, electronmicrograph): The photograph taken through a microscope (light- or electronmicroscope). ▶microscopy

Microinjection: A method of delivery of transforming DNA or other molecules into animal or other cells by a microsyringe. This procedure is not considered as a highly efficient method of transformation in plants. An advantage is, however, that the delivery can be targeted to cells but not into chromosomal location unless gene targeting is used. ▶transformation animals, ▶caged compounds, ▶targeting genes, ▶gene transfer by microinjection

Microinversions: Short inverted DNA sequenced in the genomes microinversions that occur across all species at a frequency of about once per megabase per 66 million years of evolution. Microinversions have low homoplasy and thus provide ample characters for phylogenetic studies. Algorithms are available for their analysis (Chaisson MJ et al 2006 Proc Natl Acad Sci USA 103:19824). ▶inversion, ▶evolution of the karyotype, ▶homoplasy

Microlesion: In genetic toxicology it denotes microscopically undetectable change in the genetic material.

Micromanipulation of the Oocyte: The penetration of some types of disadvantaged sperms can be facilitated by mechanically opening an entry point through the zona pellucida (a non-cellular envelope of the oocyte) and thus facilitating the penetration of the sperm (PZD). Alternatively, with the aid of a microneedle the sperm can directly be deposited under the zona pellucida (SZI) into the space before the vitellus (egg yolk). ▶ART, ▶preimplantation genetics, ▶in vitro fertilization, ▶oocyte donation

Micromanipulator: A mechanical device usually employing glass needles or microsyringes to carry out dissections or injections of cells, while viewed under the microscope.

Micromere (small micromeres): Small cells in the vegetal pole arising from the 8-cell blastomere and giving rise to the coelom. ▶vegetal pole, ▶blastomere, ▶coelom

Micromirror: A spatial light modulator (SLM) that provides excellent resolution, high contrast, brightness, true colors and fast response. Due to these qualities, it is used in imaging nucleic acid microarrays and for many other purposes. It is a type of

a liquid crystal display that has been used in computer monitors, high-definition TV, watches and various types of optical devices.

Microneme: The tubular organelle of apicomplexan protozoa that develop into rhoptry at the apex of the organism. ▶apicoplast, ▶*Plasmodium*, ▶malaria, ▶rhoptry

Micronucleus: The reproductive nucleus of *Infusoria*, as distinguished from their vegetative macronucleus; also a small additional nucleus containing only one or a few chromosomes in other taxonomic groups. In some organisms, broken chromosomes may be visible as micro-nuclei. ▶macronucleus, ▶*Paramecium*, ▶*Tetrahymena*, ▶microcell, ▶micronucleus formation as a bioassay, ▶protozoa

Micronucleus Formation as a Bioassay: Micronuclei are formed when broken chromosomes, chromosomal fragments fail to be incorporated into the daughter nuclei during cell division. Also, the damage to the spindle apparatus may result in the appearance of micro-nuclei. These phenomena have been exploited for testing mutagenic agents specifically causing these types of genetic damage to animal and plant cells. Such assays can be done in cultured cells but in vivo assay of meiotic plant cells or mammalian bone marrow polychromatic erythrocytes have also been used. ▶bioassays in genetic toxicology, ▶*Tradescantia*, ▶protozoa; Riccio ES et al 2001 Environ Mol Mutagen 38:69, (see Fig. M68).

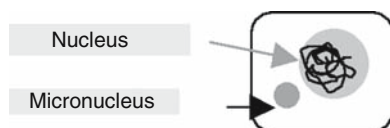


Figure M68. Micronucleus

Micronutrients: They are required for nutrition in small or trace amounts. This class of approximately 40 different compounds includes vitamins, minerals, etc. The deficiency of folate, Vitamins B12, B6, niacin, C and E, etc., have been suggested to be responsible for chromosomal damage and certain types of tumors (See Ames BN 2001 Mutation Res 475:7, and ff. articles in the same issue). Some of the micronutrient deficiencies also cause mitochondrial decay with oxidant leakage and cellular aging and are associated with late onset diseases such as cancer (Ames BN 2006 Proc Natl Acad Sci USA 103:17589).

Microorganisms: *prokaryotic* → bacteria, *eukaryotic* → protozoa, fungi, algae.

Micropenis: It is much reduced in length but the testes are normal in size (see Fig. M69). This condition

occurs in several developmental anomalies as part of the syndrome.



Figure M69. Micropenis

Micropexophagy: The destruction of excess peroxisomes when the need for them is reduced. ▶peroxisome, ▶pexophagy

Microphthalmia: ▶microphthalmos

Microphthalmos (nanophthalmos): Genetically determined (dominant and recessive) forms involve (extreme) reduction of the eye(s) (see Fig. M70). In some instances, it does not involve additional defects. Its frequency in the general population is low, about 0.004%, and the incidence among Caucasian sibs is about 12–14% in the recessive form. Transformation of mice with diphtheria toxin genes attached to eye-specific (γ -crystalline, a globulin of the lens) or the pancreas-specific Elastase I, a collagen-digesting enzyme, promoted this developmental condition (ablation). The microphthalmia-associated transcription factor (MITF) mutations transform fibroblasts into melanocytes. Some of the *Mitf* mutations in mice involve partial or entire-body albinism.



Figure M70. Reduction of eye in microphthalmos

Stimulation of melanoma cells by Steel Factor (SF) activates a MAP kinase that phosphorylates the MITF resulting in the transactivation of a tyrosinase pigmentation promoter (see Fig. M71). In humans, ~5 loci control the condition. Single amino acid replacement mutations at 14q24.3 of the retinal homeobox gene CHX10 have been identified (Heilig R et al 2003 Nature [Lond] 421:601). Dominant colobomatous microphthalmia was assigned to 15q12-q15. ▶eye

diseases, ▶anophthalmos, ▶Waardenburg syndrome, ▶ablation, ▶Kit oncogene, ▶Steel factor, ▶coloboma; Planque N et al 2001 J Biol Chem 276:29330; Mitf function, regulation and signaling: Steingrímsson E et al 2004 Annu Rev Genet 38:365.



Figure M71. Dominant eyeless *Drosophila*

Micropia: ▶*copia*

Micropasmid (miniplasmid): π VX, ▶recombinational probe

Microprocessor: A multiprotein complex, also containing Drosha ribonuclease and it generates microRNAs. ▶microRNA, ▶Drosha; Gregory RI et al 2004 Nature [Lond] 432:235.

Microprojectile: ▶biolistic transformation

Micropropagation: Regeneration plants from somatic, usually apical meristem cells, by in vitro techniques. It may be useful for rapid propagation of rare plants or non-segregating hybrids or secure virus free stocks. ▶synthetic seed, ▶embryo culture; Evans DA et al (eds) 1983 Handbook of Plant Cell Culture. Macmillan, New York.

Micropyle: A pore of the plant ovule, between the ends of the integuments, through which the pollen tube (sperms) reaches the embryo sac. The diagram shows the plant micropyle at the eight-nucleate stage of the embryo sac (see Fig. M72). The pores on the ovules of arthropods (and some other invertebrates) serve for the penetration of the sperm. ▶embryosac

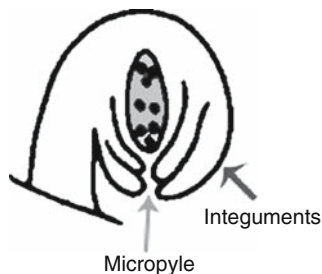


Figure M72. Plant ovule with micropyle

microRNA (micRNA/miRNA): About 18–25 nucleotide long regulatory molecules of diverse sequence.

miRNAs have an imperfect match to the 3' region of the mRNA. Experimental data suggest that association with any position on a target mRNA is mechanistically sufficient for a microribonucleoprotein to exert repression of translation at some step downstream of initiation (Lytle JR et al 2007 Proc Natl Acad Sci USA 104:9667). In the human genome there are > 500 miRNA genes, which target thousands of genes. Apparently, the loss of a single miRNA is not much consequence because there seems to be enough redundancy among miRNAs and in *Caenorhabditis*, three miRNAs (mir-46, mir-84 and mir-241) jointly affect a developmental stage (Abbott AL et al 2005 Dev Cell 9:403). Perfect pairing with 6- to 8-base is not a generally reliable predictor for an interaction of a miRNA. Rather, it can interact functionally with its target site only in specific 3' UTR contexts (Didiano D, Hobert O 2006 Nature Struct Mol Biol 13:849).

Exportin, a RAN-GTP dependent cargo transporter protein that carries pre-miRNAs (ca. 70 nucleotides) is transported to the cytoplasm. The first Drosha, then Dicer RNase III cut them from one arm of endogenous hairpins and they regulate translation/transcription. For the proper function of Dicer-1 there is a requirement for a double-strand RNA-binding domain protein (DGCR), Loquacious in *Drosophila* or TRBP in humans (Förstemann K et al 2005 PLoS Biol 3(7):e236). Some of the miRNAs apparently do not cause the degradation of their target(s). The let-7 microribonucleoproteins or the Argonaute protein may interfere with recognition of the cap of human mRNAs and inhibit initiation of translation (Pillai RS et al 2005 Science 309:1573). MicroRNA interference can provide viral immunity in *Drosophila* (Wang X-H et al 2006 Science 312:452). Human RISC (RNA-induced silencing complex) associates with a multiprotein complex that contains MOV10 – a translational repressor – and proteins of the 60S ribosomal subunit. This complex contains the anti-association factor eIF6 (also called ITGB4BP or p27BBP), a ribosome inhibitory protein known to prevent productive assembly of the 80S ribosome. Depletion of eIF6 in human cells specifically abrogates miRNA-mediated regulation of target protein and mRNA levels (Chendrimada TP et al 2007 Nature [Lond] 447:823).

Several methods are available for the detection of microRNAs (Jiang J et al 2005 Nucleic Acids Res 33:5394). In plants, it may not be a Drosha but one of the multiple Dicers that assumes this role after moving to the nucleus. Uridine (less frequently adenosine) is added to the 3' or 5' ends of the miRNA that enhance the decay of the RNA (Shen B, Goodman BM 2004 Science 306:997). The so-called *seed*

sequence (2–7 nucleotides) at the 3' end of the miRNA initiates the binding to the 5' end of the mRNA (Bartel DP 2004 Cell 116:181; Brennecke J et al 2005 PLoS 3: e85) although other elements may affect their effectiveness. Presence of Argonaute protein(s) is required for initiating the cleavage in the target; the Piwi domain of this protein binds the 5' end and the PAZ domain attaches to the 3' end of miRNA. The Piwi domain is a slicer structural homolog of ribonuclease H (Liu J et al 2004 Science 305:1437). miRNA affects translation by attaching to the cap-binding protein eIF-4E or it may accelerate decay of mRNA through the polyA tail (Humphries DT et al 2005 Proc Natl Acad Sci USA 102:16961). After the cut, the RNA is released to the cytoplasm where exosome and Xrn1 exonuclease destroy the fragments (Orban TL, Izaurralde E 2005 RNA 11:459). miRNA and siRNA bound to Argonaute2 may move to the cytoplasm to the site of P bodies, which can destroy them.

A mouse chromosome 12 (human chromosome 14q32) encodes two micRNAs (*mir-136*, *mir-127*) expressed in the maternally inherited chromosome and act as antisense to retroposon-like gene (*Rtl1*) expressed only from the paternal allele (imprinting, Seitz H et al 2003 Nature Genet 34:261). The Kaposi sarcoma-associated herpes virus encodes 11 distinct micRNAs; some of them are expressed in up to 2,200 copies per cell and facilitate the maintenance of the infected state by suppressing mammalian gene expression (Cai X et al 2005 Proc Natl Acad Sci USA 102:5570). Cellular miRNA provides defense against the primate retrovirus (PFV-1), a foamy virus in humans (Lecellier C-H et al 2005 Science 308:557). In *Caenorhabditis* there are about 130 miRNAs and ~800 (regulating 5,300 genes) are expected in humans; among them 53 are unique to primates (Bentwich I et al 2005 Nature Genet 37:766). The Epstein-Barr virus also encodes miRNAs to control both host and viral gene expression (Pfeffer S et al 2004 Science 304:734). Human cytomegalovirus produces miRNAs, which target the major histocompatibility complex class I-related chain B (MICB) gene. MICB is a stress-induced ligand of the natural killer (NK) cell activating receptor NKG2D and is critical for the NK cell killing of virus-infected cells and tumor cells and thus constitutes an immune evasion means (Stern-Ginossar N et al 2007 Science 317:376).

The small RNAs play an important role in the development of animals and plants by inhibiting or degrading specific mRNAs, for, e.g., the mRNAs coding for the TCP transcription factors. miRNAs can affect differentiation by acting on chromatin structure through methylation of the DNAs (Bao N et al 2004 Dev Cell 7:653). Brain morphogenesis in

zebrafish requires miRNAs (Giraldez AJ 2005 Science 308:833). Methylation is important for the biogenesis of plant micRNA through the action of the HEN1 protein, which can bind glutathione-S-transferase (Yu B et al 2005 Science 307:932). All small RNAs of plants are apparently modified by a proteinase at the 2' hydroxyl of the terminal ribose (Ebhardt HA et al 2005 Proc Natl Acad Sci USA 102:13398). Application of the advantages of mRNAs may be enhanced by the use of vectors that can provide regulatable expression of miRNAs. A lentiviral system (pSLIK) permits tetracycline-regulated expression of mRNA-like short hairpin RNAs in any organism, including mouse (Shin K-J et al 2006 Proc Natl Acad Sci USA 103:13759).

miRNAs regulate leaf polarity in dicots and monocot of plants (Juarez MT et al 2004 Nature [Lond] 428:84). Both endogenous and synthetic miRNAs can be effectively targeted to genes controlling morphogenesis of the stem of *Arabidopsis* as well as in tomato and tobacco (Alvarez JR et al 2006 Plant Cell 18:1134; Schwab R et al 2006 Plant Cell 18:1121). About 30% of the human genes appear to be conserved targets for miRNA (Lewis BP et al 2005 Cell 120:15). The various small non-coding RNAs such as the miRNA, RNAi, siRNA are basically identical. In plants, generation of siRNAs most often (but not always) requires two cleavage events (Axtell MJ et al 2006 Cell 127:565). Some miRNAs down regulate a large number of mRNAs and proteins (Lim LP et al 2005 Nature [Lond] 433:769) and coordinately regulate cell-specific target genes. The *mir-17–92* cistron (13q31) modulates the expression of several cancer genes (He L et al 2005 Nature [Lond] 435: 828). The core promoter region contains two functional E2F transcription factor-binding sites. *miR-17–92* promotes cell proliferation by shifting the E2F transcriptional balance away from the pro-apoptotic E2F1 and toward the proliferative E2F3 transcriptional network (Woods K et al 2007 J Biol Chem 282:2130). Two miRNAs negatively regulate the E2F1 transcription, and the c-Myc proto-oncogene activates the expression of six clustered miRNAs in human chromosome 13 (O'Donnell KA et al 2005 Nature [Lond] 435:839). MicroRNA arrays are generally quite different in a variety of cancer cells compared to normal cells. The level of most of the miRNAs increases in solid tumors but others display reduction and they present a signature for cancer. In ovarian cancer 37.1%, in breast cancer 72.8% and in melanoma 85.9% of the miRNA genes displayed copy number changes and presumably functional differences (Zhang L et al 2006 Proc Natl Acad Sci USA 103:9136). Several miRNAs are shared by different tumors (Volinia S et al 2006 Proc Natl Acad Sci USA 103:2257). *miRNA-372* and *miRNA-373*

down-regulate RAS and p53 tumor suppressors and contribute to the formation of germ cell tumors (Voorhoeve PM et al 2006 Cell 124:1169). Statistically significant association was found between the chromosomal location of miRNAs and those of mouse cancer susceptibility loci that influence the development of solid tumors (Cevignani C et al 2007 Proc Natl Acad Sci USA 104: 8017).

Hepatitis C virus replication is apparently aided by human miRNA-122 but it did not affect mRNA translation or stability (Jopling CL et al 2005 Science 309:1577). Several good computational methods exist for the identification and prediction of miRNA targets in different organisms (Krek A et al 2005 Nature Genet 37:495; Rajewsky N 2006 Nature Genet 38 Suppl 1: S8; Miranda KC et al 2006 Cell 126:1203). Several human miRNAs are most abundant in the cells where their mRNA targets are expressed yet several highly abundant mRNAs in the same cells do not have miRNA recognition sites (Sood P et al 2006 Proc Natl Acad Sci USA 103:2746). In human hepatocarcinoma cells, the cationic amino acid transporter 1 (CAT-1) mRNA and reporters bearing its 3'-UTR can be relieved from the miRNA miR-122-induced inhibition under stress conditions (Bhattacharyya SN et al 2006 Cell 125:1111). ▶RNAi, ▶shRNA, ▶stem cells, ▶antagomir, ▶tncRNA, ▶small RNA, ▶imprinting, ▶RNA non-coding, ▶TCP, ▶PAZ domain, ▶P body, ▶eIF-2, ▶eIF-4E, ▶imprinting, ▶Dicer, ▶Drosha, ▶exosome, ▶Xrn1, ▶Kaposi sarcoma, ▶DiGeorge syndrome, ▶microprocessor, ▶Simian Virus 40, ▶Invader, ▶longevity, ▶polyadenylation signal; Ambros V 2001 Cell 107:823; Hutvagner G, Zamore PD 2002 Science 297:2056; Carrington JC, Ambros V 2003 Science 301:336; Palatnik JF et al 2003 Nature [Lond] 425:257; Lee Y et al 2003 Nature [Lond] 425:415; MicroRNA Registry: Griffith-Jones S 2004 Nucleic Acids Res 32; Database issue D109, He L, Hannon GJ 2004 Nature Rev Genet 5:522; review: Zamore PD, Haley B 2005 Science 309:1519; genomics: Kim NV, Nam JW 2006 Trends Genet 22:165; review of applications to neurology: Kosik KS, Krichevsky AM 2005 Neuron 47:779; microRNA and disease: Chang T-C, Mendell TC 2007 Annu Rev Genomics Hum Genet 8 (Sept) doi: 101146; review of miRNA and development: Plasterk RHA 2006 Cell 124:877; MicroRNA base: <http://www.sanger.ac.uk/Software/Rfam/mirna>; MicroRNA Database: <http://microrna.sanger.ac.uk/sequences/>; <http://mimamap.mbc.nctu.edu.tw/>; miRNA target server: <http://www-ab.informatik.uni-tuebingen.de/software/welcome.html>; miRNA target prediction: <http://bibiserv.techfak.uni-bielefeld.de/mahybrid/>; miRNA target sites in QTLs: <http://compbio.utmem.edu/miR SNP/>; miRNA targets in viruses: <http://vita.mbc.nctu.edu.tw/>;

human miRNA analysis and prediction: <http://cbit.snu.ac.kr/~ProMiR2/>; animal miRNA organization; co-transcription and targeting: <http://www.diana.pcbi.upenn.edu/miRGen>; true pre-miRNA identification: <http://www.bioinf.seu.edu.cn/miRNA/>.

Microsatellite: The mono-, tetra- or hexanucleotide repeats distributed at random (10 – 50 copies) in the eukaryotic nuclear and mitochondrial chromosome, and can be used for constructing high-density physical maps, for the rapid screening for genetic instability, evolutionary relationships, detection of cancer in bladder cells found in the urine, etc. It was initially assumed that the alterations at the microsatellites follow a step-wise pattern and are therefore, very useful for following changes within populations or between populations. However, these expectations were not entirely realized because the variability depends on the length of the arrays such as possible size constraints to the expansion, possible increase in the flanking regions due to mutations, etc. The microsatellite region may expand (most commonly) or contract and thus, result in genetic instabilities. Microsatellite loci may mutate at a frequency of ~0.8% per gamete, more frequently than in somatic cells. Some estimates for eukaryotes are in the 10^{-4} to 10^{-5} range and make them useful for linkage analysis using PIC. The rate of mutation varies according to organisms, the microsatellite length and site, etc. In bacteria, the mutation rate in repeats appears two orders of magnitude higher. In general, longer repeats display higher mutation rates. The length of the microsatellite repeats appears longer in vertebrates than in *Drosophila*. In the majority of the cases, the expansion of the loci does not change the linkage phase of the flanking markers and therefore gene conversion is implicated. In humans they estimated one (≥ 4 bp) microsatellite per 6 kbp genomic DNA. Three quarters of the repeats are A, AC, AAAN or AG. The CA and TG repeats are distributed at random in the genome and used most commonly for linkage studies. In the human X chromosome, 3 and 4 base repeats occur in every 300–500 bp. The most common poly(A)/ poly(T) repeats are not well suited for genetic studies because of instability at PCR. Large-scale survey indicates that most of the microsatellites were generated as a 3' extension of retrotranscripts and may serve as pilots to direct integration of retrotransposons. Defective mismatch repair may be caused by mutations in the human gene MBD4/MED1 at 3q21-q22 leading to carcinomas with microsatellite instability. The *perfect microsatellite* represents one repeated motif without any insertion of a different base. The *imperfect microsatellite* has repeats with one base different from the

main type. *Interrupted microsatellite* contains several bases repeated that are different from the pattern of the rest of the repeat structure. *Compound microsatellite* includes two or more different types of repeats in adjacent microsatellites. In *Saccharomyces* the poly(AT) sequences are common. Prokaryotes display relatively few repeats and they are mainly poly(A)/poly(T). About 30% of the human microsatellites are conserved in murines. The microsatellites appear to have regulatory roles but some may be transcribed and translated as coding trinucleotides (e.g., the CAG polyglutamine tracts). Some of the untranslated upstream repeat elements are conserved among related species and may serve as enhancers by binding transcription factors. The enhancer activity may be only moderate but may increase or decrease by high copy number. Discrete repeat lengths may carry specific adaptive value in some populations. Diversity in microsatellite repeats may be generated by replicational slippage, unequal crossing over (although the reciprocal products are not always present), by gene conversion, additions and deletions. The microsatellites show a tendency of association with the non-repetitive portion of the genome. Microsatellite repeat length in the vicinity of the vasopressin 1a receptor gene of voles (*Microtus*) is correlated with behavioral traits, such as grooming the females and offspring care by males. Since vasopressin is supposed to affect social behavior, microsatellite length appears regulatory to gene expression (Hammock EAD, Young LJ 2005 Science 308:1630). ▶hereditary non-polyposis colorectal cancer, ▶mismatch repair, ▶trinucleotide repeats, ▶minisatellite, ▶VNTR, ▶PIC, ▶DNA fingerprinting, ▶PCR, ▶cryptically simple sequences, ▶unequal crossing over, ▶slippage, ▶enhancer, ▶stutter bands, ▶slip-strand mispairing, ▶IAM, ▶SMM, ▶TPM, ▶KAM, ▶behavior genetics, ▶oxytocin; Graham J et al 2000 Genetics 155:1973; Tóth G et al 2000 Genome Res 10:967; Morgante M et al 2002 Nature Genet 30:194; free software for small repeats:

<http://www.bio.net/hypermail/methods/2000-November/086109.html>; microsatellite markers in Taiwanese human populations: <http://tpmd.nhri.org.tw>; http://tpmd.nhri.org.tw/php-bin/index_en.php; insect microsatellite database: http://210.212.212.8/PHP/IN_SATDB/home.php.

Microsatellite Mutator (MMP): MMP increases frame-shift and other mutations in G-rich microsatellites. ▶microsatellite, ▶minisatellite

Microsatellite Typing: In case of linkage disequilibrium the inheritance of microsatellite markers can be followed on PCR amplified DNA. Example the CAAT repeat in the human tyrosine hydroxylase genes (chromosome 11p15.5) using the Z alleles displayed the pat-tern of segregation (see Table M6) in the ethidium bromide stained non-denaturing gel. (After Hearne CM, Ghosh S et al 1992 Trends Genet 8:288). ▶DNA fingerprinting, ▶paternity testing, ▶microsatellite, ▶PIC; Calbrese PP et al 2001 Genetics 159:839.

Microscopic Polyangiitis: An autoimmune blood vessel inflammation: <http://vasculitis.med.jhu.edu/typesof/polyangiitis.html>.

Microscopy: The use of a special optical device for viewing objects that are not discernible clearly by the naked eye. ▶light microscopy, ▶stereomicroscopy, ▶resolution, ▶fluorescence microscopy, ▶multiphoton microscopy, ▶second-harmonic imaging microscopy, ▶dark-field microscopy, ▶phase-contrast microscopy, ▶Nomarski, ▶confocal microscopy, ▶electronmicroscopy, ▶atomic force microscopy, ▶atom microscopy, ▶scanning electronmicroscopy, ▶scanning tunneling, ▶photoactivated localization microscopy, ▶two-photon microscopy, ▶ADM, ▶FAST, ▶Cryo-EM; Sharpe J et al 2000 Science 296:541; Jain RK et al 2002 Nature Rev Cancer 2:266; Stephens DJ, Allan VJ 2003 Science 300:82;

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Table M6. Microsatellite typing

| Father | Mother | Sib-1 | Sib-2 | Sib-3 | Paternal grandfather | Paternal grandmother | Alleles |
|--------|--------|-------|-------|-------|----------------------|----------------------|---------|
| ■■■ | ■■■ | | □□ | ■■■ | ■■■ | | Z |
| | | | | | ■■■ | | 4 |
| | ■■■ | ■■■ | | | | ■■■ | 12 |
| ■■■ | | ■■■ | | ■■■ | | ■■■ | 16 |

The ■ symbolize gel bands and the □ stand for homozygosity of the Z allele

Hadjantonakis A-K et al 2003 Nature Rev Genet 4:613; <http://micro.magnet.fsu.edu/>.

Microsomes: The membrane fragments with ribosomes and enzymes obtained after grinding eukaryotic cells and separating the cellular fractions by centrifugation. After about 9,000 x g force (10 min) the microsomes (S9) float, while other cellular particulates sediment. For the Ames genotoxicity bioassay, generally Sprague-Dawley rat livers are used. The rats are previously fed the drinking water with polychlorinated biphenyl (PCB), Araoclor 1254, a highly carcinogenic substance (requires special caution of disposal!) in order to induce the formation of the P-450 monooxygenase activating enzyme system associated with the endoplasmic reticulum.

► Ames test, ► activation of mutagens, ► carcinogen, ► centrifuge

Microspectrophotometer: A spectrophotometer, which can measure monochromatic light absorption of microscopical objects. ► spectrophotometer

Microsporangium: The sac that contains the microspore tetrad of plants and the microspores of fungi and some protozoa. ► microspore

Microspore (small spore): The immature male spore of plants that develops into a pollen grain. ► microspore mother cell, ► microspores, ► microsporocyte, ► meiosis, ► gametogenesis

Microspore Culture: The in vitro method for the production of haploid plants by direct or indirect androgenesis. (See Fig. M73).

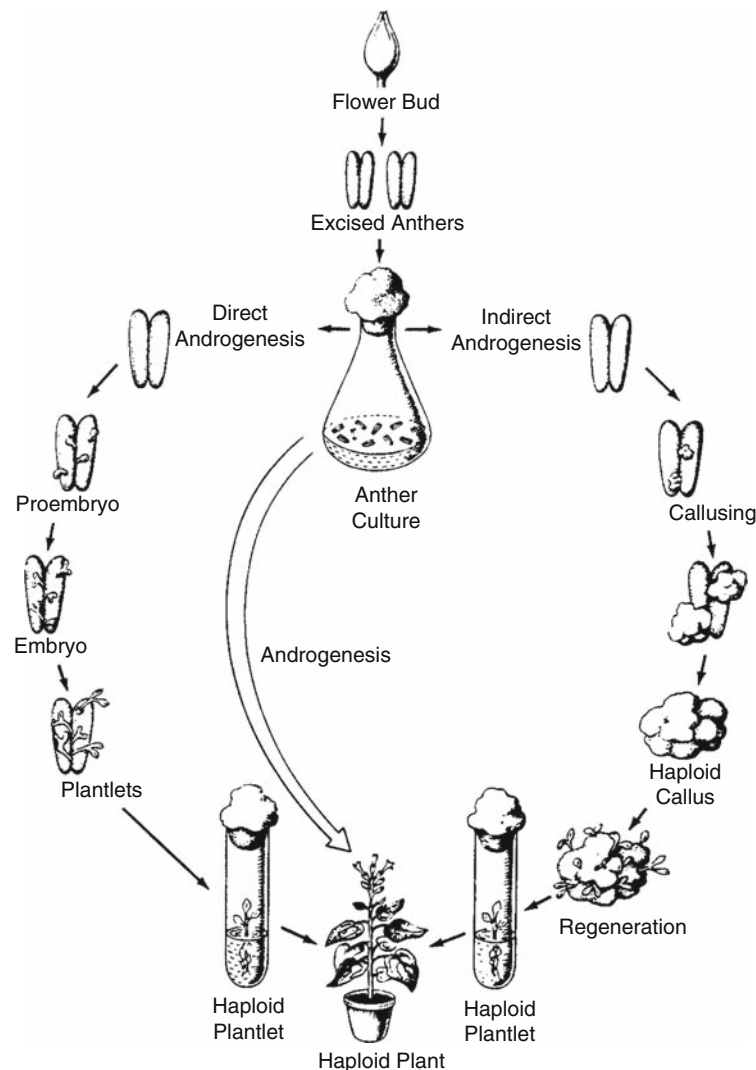


Figure M73. Microspore culture (After Reinert J and Bajaj YPS 1977 Plant Cell, Tissue and Organ Culture. Springer, New York)

Microspore Dyad: The microspore mother cell after the end of the first meiotic division is divided into two haploid cells (the microspore dyad). ► [meiosis](#)

Microspore Mother Cell: ► [microsporocyte](#)

Microspores: Haploid products of male meiosis in plants that develop into pollen grains, and the smaller generative cells of lower organisms. ► [microsporocyte](#), ► [megaspore](#)

Microsporidia: (Archezoa): It represents an evolutionary branch of anaerobic protists, which diverged from the main line of Eukarya before the acquisition of mitochondria. ► [evolution](#)

Microsporocyte: The cell within which meiosis takes place and the microspores develop. ► [microspore](#), ► [gametogenesis](#)

Microsporogenesis: see ► [Meiosis in plants](#), Ma H 2005 Annu Rev Plant Biol 56:393.

Microsporophyll: A leaf on which microsporangia develops in lower plants.

Microsurgery: Dissection or other surgical operations carried out under the microscope, generally with the aid of a micromanipulator. ► [micromanipulator](#)

Microtechnique: The procedures used for the preparation of biological specimens for microscopic examination (involving fixation, staining, sectioning, squashing, etc.).

Microtiter Plates: It most commonly contains 96 wells but 384 or even 9600-well (etched glass or silicon wafers) are also used for storage of samples. ► [microarray hybridization](#)

Microtome: An instrument that, by means of various (sliding or rotating or rocking) motions, cuts serial thin (usually within the range of 1–20 μm) sections of the embedded or frozen specimens to be examined by light or electronmicroscopy. The cutting edge may be steel or glass. Electronmicroscopy also requires sectioning of the specimens, usually employing a diamond knife. ► [embedding](#), ► [sectioning](#), ► [stains](#), ► [smear](#)

Microtubule: Various types of long cylindrical filaments of about 25 nm in diameter within cells built by polymerization of α and β tubulin and actin proteins. Microtubules are hollow tubulin filaments of the spindle apparatus of the dividing nuclei, elements of the cytoskeleton, cilia, flagella, etc. The energy for polymerization is provided by hydrolysis of GTP to GDP. The beginning of the polymerization of the microtubules is called nucleation and in animal cells that begins at the centrosomes. Microtubule elongation is a polarized process. Microtubules move around

chromosomes and various protein complexes according to the blueprints of differentiation. Kinetochore-mediated and polar ejection forces (PEF) move chromosomes toward the spindle equator. Kid and KIF-4 proteins are behind PEF (Brouhard GJ, Hunt AJ et al 2005 Proc Natl Acad Sci USA 102:13903). The nerve axon microtubules are oriented with the plus end (their growing point) away from the cell body whereas in epithelial cells they point toward the basement membrane. In fibroblasts and macrophage cells, the microtubules originate in the center of the cell and the plus end face the outer regions. The transport function requires the cooperation of motor proteins (kinesins, dynein) that push the protein complex organelles on the microtubule trails. Microtubules are somewhat unstable molecules and antimetabolic drugs such as colchicine or colcemid may block their growth. Taxol (an anticancer extract of yew plants) stabilizes the microtubules and arrests the cell cycle in mitosis. After polymerization the microtubules undergo modification, e.g., a particular lysine of α -tubulin may be acylated and tyrosine residues removed from the carboxyl end. Microtubule-associated proteins (MAP) mediate the “maturation” of microtubules. MAPs aid the differentiation of nerve axons and dendrites that are loaded with microtubules. Microtubules move various organelles such as the chromosomes during nuclear divisions in the cells with assistance of the proteins kinesin and dynein. The cortical protein Kar9 and the Bim1/EB1 microtubule stabilizing protein control the positioning of the microtubules. The EB1 is also a suppressor of the *adenomatous polyposis coli* tumors. The cilia and flagella involved in movements are built of bundles of microtubules. The microtubule protein complexes bind ATP at their “head” and associate with organelles by their “tail”. The “plus” end of microtubules where tubulin subunits are added rapidly and the “minus” end where the addition is more slow. The microtubules usually are in a dynamic instability, i.e., they alternate between extension and shortening but they may remain also in equilibrium. There are several protein factors that move the tubulins and associated structures. In prophase, the duplicated centrosomes are separated by the bimC, KAR3 and cytoplasmic dyneins (450–550-kDa, motility 75 $\mu\text{m}/\text{minute}$). The bimC family members (120–135-kDa and with 1–2 $\mu\text{m}/\text{min}$ motility) have different names in the different species (KLP61F and KRP₁₃₀ in *Drosophila*, Cin8 in *Saccharomyces*, cut7 in *Schizosaccharomyces*). The KAR3 family (65–85-kDa, motility 1–15 $\mu\text{m}/\text{min}$) is involved also in spindle stabilization during metaphase. Cdc14 mediates the localization of the microtubule-stabilizing proteins for successful anaphase separation (Higuchi T, Uhlmann F 2005 Nature [Lond] 433:171). During prometaphase, the

microtubules are captured by the kinetochore with the assistance of the MCAK (mitotic centromere associated kinesin). The chromosomes congregating at the metaphase plane are moved by KIF4 (140-kDa) and related proteins that are also involved in chromosome alignment during metaphase. During anaphase, CENP-E and the KAR3 family of proteins propel the movement of the chromosomes toward the poles. The MKLP, bimC and cytoplasmic dynein proteins mediate the elongation of the spindle fibers. ►actin, ►tubulin, ►Cdc14, ►kinesins, ►Pac-Man model, ►dynein, ►mitosis, ►meiosis, ►centrosome, ►spindle, ►centromere, ►tau, ►katanin, ►filaments, ►dynamic instability, ►treadmilling, ►polyposis adenomatous intestinal, ►colchicine, ►taxol, ►vinblastin; Nogales E 2000 Annu Rev Biochem 69:277; Downing KH 2000 Annu Rev Cell Dev Biol 16:89; Popov AV et al 2001 EMBO J 20:397; Schuyler SC, Pellman D 2001 Cell 105:421; Lloyd C, Hussey P 2001 Nature Rev Mol Cell Biol 2:40; McIntosh JR et al 2002 Annu Rev Cell Dev Biol 18:193; Howard J, Hyman AA 2003 Nature [Lond] 422:753; Westermann S, Weber K 2003 Nature Rev Mol Cell Biol 4:938; microtubule capture by kinetochore: Kotwaliwale C, Biggins S 2006 Cell 127:1105.

M

Microtubule Associated Proteins (MAP): It controls stability and organization of microtubules. ►microtubule, ►kinesin, ►dynein

Microtubule Organizing Center: The areas in the eukaryotic cells from where the microtubules emanate and grow such as the mitotic centers (poles) that give rise to the mitotic spindle (see Fig. M74). The microtubule-binding protein TPX2 binds Aurora A kinase and targets it to the mitotic spindle and this stabilizes microtubules connecting to the spindle pole (Özlü N 2005 Dev Cell 9:237). ►spindle, ►mitosis, ►MTOC, ►centrosome, ►Aurora

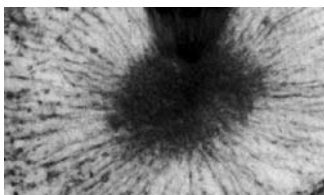


Figure M74. Microtubule organizing center

Microvilli: These are small emergences on the surface of various cells and increase the surface of the cells. The microvilli of the chorion may be sampled for amniocentesis in prenatal genetic examinations. ►amniocentesis

Microwave Radiation: Electromagnetic radiation in the $\sim 10^9$ to $\sim 10^{11}$ nm range. Genetic effects are difficult to separate from the heat effects. In the 2–3 Ghz range ambiguous mutagenic effects were reported and the mutagenicity of the radiations could not be confirmed. Microwave radiation can damage cell membranes.

MIDA1: A helix-loop-helix associated protein of mammals. It is inactive in erythroleukemic cells. ►erythroleukemia, ►zuotin, ►DNA-binding protein domains, ►helix-loop-helix

Midbody (midzone): After division, microtubule fragments (midbodies) may be detected in animal cells connecting the two daughter cells by a refringent structure (see Fig. M75). PRC1 is a midzone-associated microtubule bundling protein, a substrate of Cdk. Cdk-mediated phosphorylation of PRC1 keeps it in inactive, in monomeric state. During metaphase–anaphase transition, PRC1 is dephosphorylated and that promotes polymerization of PRC1 and lead to the formation of the midbody (Zhu C et al 2006 Proc Natl Acad Sci USA 103:6196). The proteins in the midbody are essential for chromosome segregation and cytokinesis. MudPIT analysis revealed the presence of 577 different proteins. Of the 172 proteins disrupted by RNAi analysis, 58% interfered with cytokinesis (Skop AR et al 2004 Science 305:610. ►microtubules; MudPIT, Piel M et al 2001 Science 291:1499; photomicrograph is the courtesy of Drs. Kevin Sullivan and D. W. Cleveland; red color indicates the centromeres of the blue HeLa chromosomes; green tubulins.

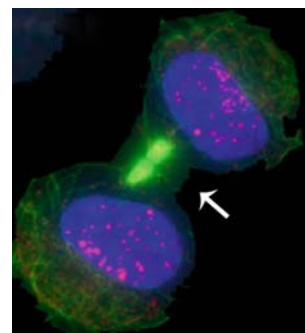


Figure M75. Midbody

Midbrain: The middle part of the brain. Degeneration of the motor neurons in this region may be responsible for Parkinson disease. ►brain human, ►Parkinson disease

Middle Lamella: The material (pectin mainly) that fills the intercellular space in plants.

Middle Repetitive DNA: It is made up of relatively short repeats dispersed throughout the genome of (higher) eukaryotes. ▶ [SINE](#), ▶ [LINE](#), ▶ [redundancy](#)

Midgut: The middle portion of the alimentary tract of insects and other invertebrates.

Midkine: ▶ [pleiotrophin](#)

Midparent Value: ▶ [breeding value \[midpoint\]](#)

Midpoint: ▶ [breeding value](#)

Midzone: A network of antiparallel, interdigitating, nonkinetochore microtubules, which initiate and complete cytokinesis. The PRC1 cyclin-dependent protein kinase is moved to the midzone by the Kif4 motor protein and both are essential for cytokinesis (Zhu C, Jiang W 2005 Proc Natl Acad Sci USA 102:343). ▶ [cytokinesis](#), ▶ [midbody](#), ▶ [PRC1](#), ▶ [Kif](#)

MIF (macrophage inhibitory factor): A pro-inflammatory pituitary factor; it may override glucocorticoid-mediated inhibition of cytokine secretion. MIF binds to cytoplasmic protein Jab1, which induces the phosphorylation of c-Jun and through it, the activity of AP-1. Jab1 also helps the degradation p27^{Kip1}. ▶ [cytokines](#), ▶ [glucocorticoid](#), ▶ [septic shock](#), ▶ [AP1](#), ▶ [Jun](#), ▶ [p27](#); Froidevaux C et al 2001 Crit Care Med 29 Suppl 7:S13.

Mifepristone (11-[44-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-(11 β ,17 β)-estra-4,9-dien-3-one): An antiprogesterin, targeted at the progesterone receptors. This receptor family includes the glucocorticoid, mineralocorticoid, androgen, estrogen and vitamin D receptors. It is used as a birth-control drug. ▶ [RU486](#) and the others mentioned, ▶ [hormone receptors](#), ▶ [breast cancer](#); Ho PC 2001 Expert Opin Pharmacother 2:1383; Zalányi S 2001 Eur J Obstet Gynecol Reprod Biol 98(2):152.

Mighty Mouse: ▶ [insulin-like growth factors](#)

Migraine: A neurological anomaly causing recurrent attacks of headaches, nausea, light and sound-avoidance. It may or may not be preceded by an aura (subjective sensation) and it appears to be controlled at chromosome 4q21 (Björnsson Á et al 2004 Am J Hum Genet 73:986). Migraine may be triggered by dietary factors (monosodium glutamate, tyramine and phenylethylamine occurring in chocolates, citrus fruits or certain cheeses) in persons with low levels of phenolsulphotransferase activity. (This enzyme catalyzes the conjugation of sulfate of catecholamines and phenolic drugs.) Its duration may be from minutes to days. The sexual migraine pops up during sexual activity, commonly at or near orgasm. It may affect females (18–24%) more frequently than males (6–12%) to a very variable degree. Migraine is

relatively rare in children (~4%) and its onset is usually begins after age 30. In males, it usually ceases after age 45 but in women it may continue well beyond menopause. It is generally attributed to multiple genes. Familial hemiplegic migraine (FHM) is however, a rare autosomal dominant condition coded in human chromosome 19p13 as is episodic ataxia type 2. CADASIL has been localized to the same chromosomal area and involves migraine. It appears that the basic defect is in a brain-specific Ca²⁺ ion channel α -1 subunit translated from 47 exons of the CACN1A4 gene. Spinocerebellar ataxia type 6 and episodic ataxia are allelic to the latter gene. Some migraines are associated with mtDNA-encoded MELAS syndrome. Another migraine susceptibility locus appears to be at Xq24. ▶ [ion channels](#), ▶ [spinocerebellar ataxia](#), ▶ [mitochondrial diseases in humans](#), ▶ [CADASIL](#), ▶ [CACN1A4](#), ▶ [serotonin](#); Guida S et al 2001 Am J Hum Genet 68:759; Wessman M et al 2002 Am J Hum Genet 70:652.

Migration: ▶ [gene flow](#)

Migration of DNA in Gels: It is affected by molecular size, configuration of the macro-molecule, concentration of the support medium (agarose, polyacrylamide), voltage, changing direction in the electric field, base composition, presence of intercalating dyes, buffer, etc.

Migration Inhibition Factor: MIF is a lymphokine. ▶ [lymphokines](#), ▶ [lymphocytes](#), ▶ [immune system](#)

Migration in Populations: ▶ [Gene flow](#)

Migration, Nuclear: Mediates polarization of cell division and provides direction for cell growth. (See Bloom K 2001 Curr Biol 11:R326)

Mik1: A mitotic kinase and an inhibitor of Cdc2. Mik1 accumulates in S phase and may mediate the transition from S phase to mitosis. ▶ [cell cycle](#), ▶ [Cdc2](#), ▶ [Wee1](#)

MIL Oncogene: The avian representative of the RAF murine oncogene, a protein serine kinase; it is also related to the murine leukemia virus (MOS). ▶ [oncogenes](#), ▶ [RAF](#), ▶ [MOS](#)

MILC (maximum identity length contrast): A statistical method for genetic analysis of multifactorial diseases. It looks for an excess of identity of parental haplotypes transmitted to the affected offspring as compared to non-transmitted haplotypes. ▶ [haplo-type](#); Bourgain C et al 2002 Ann Hum Genet 66:99.

Miliary: Minute lesions (resembling millet seeds)

Miller Units: ▶ [\$\beta\$ -galactosidase](#) (activity measurement)

Miller-Dieker Syndrome: Characterized by smooth brain (lissencephaly I, LIS1, AFAH1B1), more like in the early fetus, defects in other internal and external organs, mental retardation and death before age 20. Apparently, deletions in area 17p13.3 are responsible for the recessive phenotype. It is a cell-autonomous disease inhibiting neuronal migration. The LIS1 protein contains a C-terminal seven-blade- β -propeller domain whereas the N-terminal fragment includes the Lis homology (LisH) motif, which is widespread in more than 100 eukaryotic genes yet its function is not known (Kim MH et al 2004 Structure 12:987). The deletion always involves protein 14–3–3 ϵ and when two sites are simultaneously affected, the severity of the disease increases. (Toyo-oka K et al 2003 Nature Genet 34:274). Other genes also involving hydrocephaly and severe brain lesions may cause Lissencephaly II (DCX, Xq22.3-q23-linked doublecortin). The gene PAF (lipid platelet activating factor) encodes a subunit of brain platelet-activating acetylhydrolase. ►deletion, ►head/face/brain defects, ►malformations, ►Walker-Warburg syndrome, ►Walker-Wagner syndrome, ►lissencephaly, ►HIC; Cardoso C et al 2003 Am J Hum Genet 72:918.

Millets (*Eleusine*, *Pennisetum*): Arid climate grain crops (see Fig. M76). The cultivated *E. coracana* is $2n = 4x = 36$, tetraploid. *P. americanum* is $2n = 2x = 14$ diploid. The common millet (*Panicum miliaceum*) is an old grain crop; $2n = 4x = 36$. The foxtail millet (*Setaria italica*) is $2n = 2x = 18$ is mainly a hay crop.



Figure M76. Millet

Milroy Disease: ►lymphedema hereditary

MIM: ►mitochondrial import

MIME (Multipart Internet Mail Extensions): This was used before the Extensible Markup Language (XML) was developed ►XML

Mimicry: The process and result of protective change in the appearance of an organism that makes it resemble the immediate environment for better hiding or imitating the features of other organisms that are

distasteful or threatening to the common predators. The blister beetle *Meloe franciscanus*, which parasitize nests of the solitary bee *Habropoda pallida*, cooperate to exploit the sexual communication system of their hosts by producing a chemical cue that mimics the sex pheromone of the female bee. Male bees are lured to larval aggregations, and upon contact (pseudocopulation), the beetle larvae attach to the male bees. The larvae transfer to female bees during mating and subsequently are transported to the nests of their hosts. To mimic the chemical and visual signals of female bees effectively, the parasite larvae must cooperate, emphasizing the adaptive value of cooperation between larvae (Saul-Gershenz LS, Millar JG 2006 Proc Natl Acad Sci USA 103:14039). It has been observed that bats quickly learned to avoid the noxious tiger moths first offered to them and associated the warning sounds with bad taste. They then avoided a second sound-producing species regardless of whether it was chemically protected or not. A subset of the red bats subsequently discovered however, the palatability of the Batesian mimic (Barber JR, Conner WE 2007 Proc Natl Acad Sci USA 104:9331). ►Batesian mimicry, ►Biston betularia, ►industrial melanism, ►Müllerian mimicry, ►molecular mimics, ►pheromone; Mallet J 2001 Proc Natl Acad Sci USA 98:8928.

Mimicry, Macromolecular: Some proteins may mimic nucleic acids in shape, structure and, even to some extent, function. Such mimicry may protect a phage from the host restriction endonucleases. (See Nissen P et al 2000 EMBO J 19:489; Walkinshaw MD et al 2002 Mol Cell 9:187).

Mimicry, Structural: Pathogenic microorganisms produce virulence factors that are molecular mimics of host proteins. This way they may evade the host defense system. ►molecular mimics; Stebbins CE, Galán JE 2001 Nature [Lond] 412:701.

Mimics: Individuals that develop mimicry as a form of adaptation and evasion of predators. Also genes, which control practically the same phenotype yet they are not allelic.

Mimiotope (mimeotope): ►mimotope

Mimivirus: A very large double-stranded DNA virus (1,181,404 bp) in a 400-nanometer icosahedral particle. It contains 1,262 putative open reading frames; 10% of which encode proteins of known functions. Many of the genes are involved in protein synthesis-processing machinery. ►icosahedral, ►open reading frame, ►protein synthesis; Raoult D et al 2004 Science 306:1344; Suzan-Monti M et al 2005 Virus Res 117:145.

Mimotope: A conformational mimic of an epitope without great similarity in amino acid residues or as a response to microbial anti-DNA antibodies. ► [epitope](#); Wun HL et al 2001 *Int Immunol* 13(9):1099; Mullaney BP et al 2002 *Comp Funct Genomics* 3:254.

Mimulus sp: ($2n = 28$, $2n = 16$) are hermaphroditic/outcrossing species (~160) of plants with about two-months generation time and high (~2000) seed output (see Fig. M77). Its genome size is ~500 Mb; total map length ~2,000 cM in *M. guttatus* ($2n = 28$). (See <http://www.biology.duke.edu/mimulus/>).



Figure M77. *Mimulus luteus*

Mineral Corticoid Syndrome (ame): It causes hypertension without overproduction of aldosterone. This syndrome is activated by cortisol. 11β -hydroxysteroid dehydrogenase converts cortisol to cortisone and thus, activates the mineralcorticoid receptor. The patients are deficient in this enzyme, which is inhibited by glycyrrhetic acid (enoxolone [$C_{30}H_{46}O_4$], present in licorice). The mineral corticoid receptor and other steroid receptors regulate the activity of many genes. ► [nuclear receptor](#), ► [hypertension](#), ► [aldosteronism](#), ► [Liddle syndrome](#); Pearce D et al 2002 *J Biol Chem* 277:1451.

Mineral Requirements of Plants: The 9 macro elements (H, C, O, N, Ca, Mg, P, S) and 7 micro elements (Cl, B, Fe, Mn, Zn, Cu, Mo). Under some circumstances, other elements may also be beneficial. Using Inductively Couple Plasma (ICP) spectroscopy, 18 essential and nonessential macro- and microelements in plant tissues could be quantitatively determined. Mutations were also identified at about four dozen loci of *Arabidopsis* that control the metabolic role of these elements. It has been estimated that 2–4% of the genome of this plant involves the control of nutrient and trace element control, the “ionome” (Lahner B et al 2003 *Nature Biotechnol* 21:1215). ► [embryo culture](#)

Mini Mu: The deletion variants of phage Mu cloning vehicles that still carry the phage ends, a selectable marker and replicational origin. ► [Mu bacteriophage](#)

Miniaturization: The development of analytical tools and methods for the study of small samples, single cells, proteins or nucleotides, etc. (See Sauer S et al 2005 *Nature Rev Genet* 6:465, sequencing 25 million bases in four-hour run with 99% or better accuracy: Margulies M et al 2005 *Nature* 437:326).

Minicell: DNA-deficient bodies surrounded by cell wall (in bacteria). Since they have no DNA, they cannot incorporate labeled precursors either into RNA or protein. In case the mini-cells descended from parents with plasmids, they may contain DNA and can thus, make RNA and direct protein synthesis depending on the nature of the DNA they carry. ► [maxicells](#)

Minichromosome: In eukaryotic viruses (SV40, polyoma virus) it is the histone-containing, small nucleosome-like structure of genetic material; also in eukaryotes, an extra chromosome with extensive deletions. Such minichromosomes can be generated by the insertion of human telomeric sequences $(TTAGGG)_n$ between the centromere and the natural telomere and by eliminating the sequences distal to the insertion point. Human mini Y chromosomes have about 32.5 to 4 Mb compared with the normal Y chromosome of 50–75 Mb. Minichromosomes may also be generated by removal of non-essential distal genes from each arm. Neocentromeres may serve as well as regular centromeres for human artificial chromosomes. These minichromosomes permit the analysis of the role of different sections of the chromosomes and possibly, it may become feasible to extend the analysis of mammalian chromosomes in yeast cells. Artificial chromosomes may be exploited as large capacity cloning vectors. ► [human artificial chromosome](#), ► [neocentromere](#), ► [MCM1](#); Saffery R et al 2001 *Proc Natl Acad Sci USA* 98:5705.

Minichromosome Maintenance Factor: ► [MCM](#)

Mini-F: The basic replicon of the bacterial F plasmid. ► [F plasmid](#), ► [replicon](#)

Minigels: Minigels are used for the separation of small quantities (10 to 100 ng DNA), in small fragments (<3-kb) on about 5×7.5 cm slides (10 to 12 mL agarose), in a small gel box (ca. 6×12 cm) for 30 to 60 min at 5 to 20 V/cm. ► [electrophoresis](#)

Minigene: Some of its internal sequences are deleted in vitro before transfection. ► [transfection](#)

Minihelix of tRNA: It consists only of the T Ψ C arm and the amino acid acceptor arm and may be aminoacylated by some aminoacyl-tRNA synthetases according to the rule of the operational RNA code. The minihelix is considered to be the most ancestral part of the tRNA. ► [operational RNA code](#), ► [transfer](#)

RNA, ▶tRNA, ▶aminoacyl-tRNA synthetase; Nordin BE, Schimmel P 1999 J Biol Chem 274:6835.

Minimal Genome Size: The smallest number of genes required for survival (replication) in a specific milieu for a free-living organism. Based on transposon inactivation experiments of the genome *Mycoplasma genitalium*, the estimate was ~265–350 bp. Some viruses have only 4 genes but they are genetic parasites. Among free-living microorganisms, *Plagibacter ubique*, an abundant, heterotrophic marine proteobacterium has the smallest genome size of 1,308,799 bp (Giovannoni SJ et al 2005 Science 309:1242). ▶genome, ▶gene number, ▶*Mycoplasma*

Minimal Medium: Provides only the minimal (basal) menu of nutrients required for maintenance and growth of the wild type of the species. ▶complete medium

Minimal Promoter: It includes the most essential sequences to facilitate transcription of genes (basal promoter) without some other regulatory elements such as enhancer, transcriptional activator. ▶promoter, ▶basal promoter, ▶enhancer, ▶transcriptional activators

Minimal Residual Disease (MRD): Even after apparently successful chemotherapy of cancer, some residual cancerous cells may persist. Their detection is important to develop treatment for the prevention of relapse. Molecular techniques (PCR) are applicable for this goal. ▶PCR; Kim YJ et al 2002 Eur J Hematol 68:272.

Minimal Tiling Path: A tightly overlapping set of bacterial vector clones, suitable for sequencing eukaryotic genomes. ▶tiling

Minimization: ▶crossing over

Minimum Description Length (MDL): MDL is the principle frequently used in characterizing macromolecular sequence information. The best principle is that uses the least number of bits for the theory and the data. $L(T)$ indicates the complexity of the theory by the number of bits that encode the theory. $L(D/T)$ is the number of bits required to define the data in connection with the theory and reveals the consistency of the data with the theory. ▶bit

Minimum Evolution Methods: These methods use an estimate of a branch length of an evolutionary tree construct on the basis of pair-wise distance data calculated by various mathematical algorithms. The most plausible tree should be that which provides the smallest sum of total branch length. ▶evolutionary distance, ▶evolutionary tree, ▶least square methods, ▶four-cluster analysis, ▶neighbor joining method, ▶algorithm

Miniorgan (neo-organ) Therapy: The *ex vivo* genetically modified group of cells capable of synthesis of immunotoxins, angiogenesis inhibitors, hormones, ligands or other proteins and enzymes delivered to target cells/tissues in vivo with the purpose of correcting acquired or genetic disorders. In case the promoters can be regulated, the supply of the gene product(s) can be adjusted according to the need. ▶retroviral vectors, ▶immunotoxin, ▶angiogenesis, ▶promoter, ▶gene therapy, ▶cancer gene therapy, ▶*ex vivo*, Bohl D, Heard JM 1997 Hum Gene Ther 8:195; Rosenthal FM, Kohler G 1997 Anticancer Res 17(2A):1179.

Miniplasmid: ▶ π VX microplasmid, ▶recombinational probe

Miniprep: A small-scale quick preparation of DNA from plasmids or from other sources. (See Ferrus MA et al 1999 Int Microbiol 2(2):115).

Minireplicon: A vector consisting of a pBR322 replicon, a eukaryotic viral replicational origin (SV40, Polyoma) and a transcriptional unit. These vectors can be shuttled between *E. coli* and permissive mammalian cells. Also, deficient replicons containing only the replicational origin. ▶replicon, ▶shuttle vector; Roberts RC, Helinski DR 1992 J Bacteriol 174:8119.

Minisatellite: In eukaryotic genomes short (14–100-bp) tandem, highly polymorphic repeats occur at many locations with repeat arrays of 0.5–30 kb. In forensic work, the minisatellites are used for DNA fingerprinting. They are supposed to be products of replicational errors (slippage) and localized amplifications. Their high variability is probably due to frequent unequal crossing over and duplication-deficiency events. Gene conversion may also expand or contract minisatellites. These sequences are highly variable. The variations are associated with diabetes mellitus and various types of cancers. The minisatellite mutation rate in the human germline was estimated as ~5.2% although it may vary at different loci and may be different in the two sexes. They are used as RFLP or PCR probes in physical mapping or for characterization of populations. In contrast to humans mutations in general, minisatellite intra-allelic mutation rate is quite low at 5×10^{-6} per sperm (Bois PRJ et al 2002 Genomics 80:2). ▶microsatellite, ▶SINE, ▶VNTR, ▶DNA fingerprinting, ▶RFLP, ▶PCR, ▶small-pool PCR, ▶MVR, ▶unequal crossing over, ▶trinucleotide repeats, ▶MVR, ▶IAM, ▶SMM, ▶TPM, ▶gene conversion10:899; Vergnaud G, Denoeud F 2000 Genome Res 10:899.

Minisegregant: Bud-like extrusions of animal cells with pinched-off DNA.

MINK: MAP kinase kinase kinase; also represented as MAPKKK or Ste 11. ►Ste

MinK: A 15 K protein which in association with other proteins forms potassium ion channels.

Minocycline: A tetracycline type antibiotic capable of passing the blood-brain barrier and it is a neuroprotective by inhibition of caspases. It may delay the progression of neurodegenerative diseases (Zhu S et al 2002 Nature [Lond] 417:74).

Minor Allele Frequencies (MAF): These frequencies have a role in the susceptibility to a particular disease. Generally, the frequencies are less than 0.1 and because of their relatively small effect, the odds ratio is less than 1.3. Therefore, their identification—at an acceptable level of statistical significance—requires large populations ($>10^4$).

Minor Groove of DNA Double Helix: It is marked by an arrow in the Fig. M78.

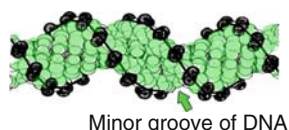


Figure M78. Minor groove of DNA double helix

Minor Histocompatibility Antigen: It has some role in immune reactions but it is not coded in the HLA region. ►HLA, ►MHC, Dazzi F et al 2001 Nature Med 7:769.

Minos: A 1,775-basepair transposable element of *Drosophila hydei* with 255-bp inverted terminal repeats and with two non-overlapping open reading frames. ►transposable elements animals; Zagoraiou L et al 2001 Proc Natl Acad Sci USA 98:11474.

Minus END: of microtubules or actin filaments is less liable for elongation. ►plus end

Minus Position of Nucleotides: It indicates the upstream distance from first translated triplet of the transcript of a gene. ►triplet code, ►RNA polymerase

Minutes: Approximately 60 dominant mutations in *Drosophila* that slow down the development of heterozygotes and is lethal when homozygous. The phenotypes vary but generally the bristles are reduced (see Fig. M79). Some mutants increase somatic crossing over. Minutes have several chromosomal locations. They are defective in ribosomal proteins. (See Lambertson A 1998 Adv Genet 38:69; Marygold SJ et al 2005 Genetics 169:683).

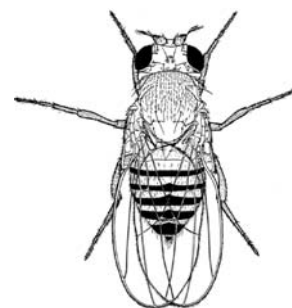


Figure M79. Minute (M1)n fly

MIP (methylation induced premeiotically): The mechanism of gene silencing by causing apparently a stall of the RNA polymerase before completing the transcription of fungal genes. ►RIP

MIP-1 α (macrophage inflammatory protein; CCL3L1/CC chemokine ligand 3-like): A chemokine mediating virus and other microbial induced inflammation protein related to RANTES. It belongs to the family of FK506-binding proteins. ►RANTES, ►blood cells, ►FK506, ►peptidyl-prolyl isomerases, ►acquired immunodeficiency syndrome; Matzer SP et al 2001 J Immunol 167:4635.

MIPS (Munich Information Center for Protein Analysis): A database of functional genomes and proteomes. (See Mewes HW et al 2002 Nucleic Acids Res 30:31; <http://mips.gsf.de>).

MIR: Mammalian-wide interspersed repeat, $\sim 12\text{--}30 \times 10^4$ copies/primate genome. They may regulate the expression of genes, alternative splicing, polyadenylation sites and evolution. ►redundancy; Matassi G et al 1998 FEBS Lett 439:63.

MIR: ►ILT

Mirabilis jalapa (four-o'clock): Ornamental plant and early object of inheritance, $2n = 58$ (see Fig. M80).



Figure M80. *Mirabilis*

miRE: MicroRNA responsive element ►microRNA

miRNA: ▶ [MicroRNA](#)

miRNP: A complex of ribonuclease containing miRNA and several proteins are involved in processing of interfering RNAs. ▶ [microRNA](#), ▶ [RNAi](#), ▶ [Dicer](#), ▶ [RISC](#); Morelato Z et al 2002 Genes Dev 16:720.

Mirtron (pre-microRNA intron): Debranched introns, which mimic the structural features of pre-miRNAs to enter the miRNA-processing pathway without Drosha-mediated cleavage. ▶ [microRNA](#), ▶ [Drosha](#), ▶ [intron](#); Ruby JG et al 2007 Nature [Lond] 448:83.

MIS (Müllerian inhibitory substance): ▶ [Müllerian duct](#), ▶ [gonads](#)

Mis12/Mtw1: A protein controlling kinetochore orientation in yeast. ▶ [kinetochore](#)

Miscall: ▶ [base-calling](#)

Miscarriage: The loss of pregnancy. It occurs spontaneously in about 15–20% of the pregnancies at least once during the life of human female. Repeated miscarriage before 20 weeks of pregnancy occurs in 0.5–2% of the women and it may be caused by environmental, extrinsic factors (infections) or by uterine anomalies, hormonal problems, chromosomal aberrations, autoimmune reactions or other immune problems (Rh), metabolic dysfunction (folic acid deficiency, hyperhomocystinemia, defects in nitric oxide synthase, etc.). Although most commonly genetic (chromosomal) anomalies of the fetus is responsible for the miscarriage, recent observations point to an essential role of mutation or deletion in the HLA-G (Ober C et al 2003 Am J Hum Genet 72:1425). (See terms under separate entries, ▶ [abortion spontaneous](#); Tempfer C et al 2001 Hum Reprod 16:1644).

Miscegenation: Sexual relations between partners of different human races. In the majority of human tribes, marriage was generally limited within the tribes, however, marriage by “capture” existed in ancient societies where the conquerors in war abducted females. Miscegenation was applied particularly to marriage between whites and blacks in the United States and in some South-American societies. There is no genetic justification against interracial

marriage. Although marriage between Blacks and Orientals was not prohibited by any law, marriage between Caucasians and Blacks was unlawful in about 15 states of the U.S. until 1967 when the Federal Court ruled that the choice to marry resides with the individual. Racial and social (cast) discrimination in marriage still exists in many underdeveloped countries and in backward communities. ▶ [mulatto](#), ▶ [mestizo](#), ▶ [racism](#), ▶ [marriage](#); Hulse FS 1969 J Biosoc Sci Suppl 1:31.

Mischarged tRNA: It is linked to wrong amino acids. ▶ [aminoacyl-tRNA synthetase](#), ▶ [protein synthesis](#)

Miscoding: ▶ [ambiguity in translation](#)

Misconduct, Scientific: The fabrication, falsification or embellishing of data, the use of inadequate statistics or techniques, making unjustified conclusions, plagiarism, omitting relevant facts concerning the experimental data or the literature, misrepresenting previous or competing publications, claiming undue credit or any other unethical behavior. A survey reported in 2005 (Martinson BC et al Nature [Lond] 435:737) indicates that 33% of the (several, thousands) scientists supported by National Institutes of Health USA anonymously admitted bad behavior although only 0.3% confessed falsifying data but 27.5% felt guilty of inadequate record keeping. The corrosive behavior was substantially (15.5%) promoted by inadequate institutional policies. ▶ [ethics](#), ▶ [publication ethics](#), ▶ [scientific misconduct](#)

Misdivision of the Centromere: A vertical rather than longitudinal division; generates two telochromosomes from one bi-armed chromosome. The telochromosomes may open up to isochromosomes and may undergo misdivision again forming telochromosome (see Fig. M81). ▶ [centromere](#), ▶ [heterochromatin](#); Darlington CD 1939 J Genet 37:341; photo at telochromosome.

Misexpression of a Gene: ▶ [ectopic expression](#)

Misincorporation: During DNA replication a normal nucleotide or an analog is placed into the growing strand, at a site where correct pairing (e.g., A = T, G = C) is not available. Such an event may lead to base substitution in the following step of replication, e.g.,

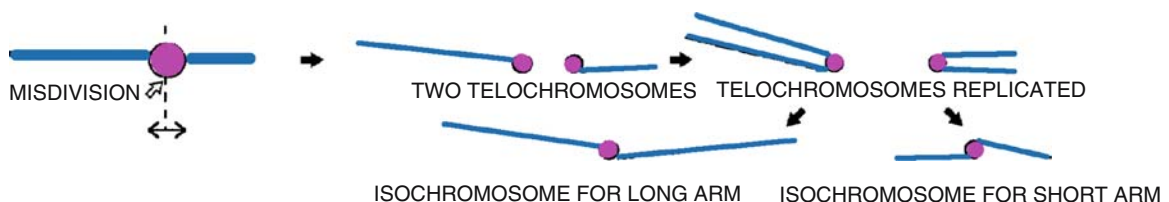


Figure M81. Misdivisional cycles

$A + T \rightarrow A:C \rightarrow G \equiv C$, resulting in mutation unless mismatch repair corrects it. Misincorporation can also occur during transcription of the DNA into RNA. ▶base substitution, ▶mismatch repair, ▶DNA repair, ▶error in transcription; Freese E 1963 p 207. In: Molecular Genetics. Taylor JH (Ed.) Academic Press, New York.

Misinsertion: DNA polymerase binds to a correctly matched 3' end of a primer where right and wrong dNTP substrates compete for insertion and occasionally the wrong may succeed resulting in misinsertion. ▶DNA editing, ▶dNTP

Mis-Localization: Gene products are normally localized according to a specific pattern within the tissues, cells or at subcellular sites. Deviations from the normal pattern may lead to disease. (See Sutherland HGE et al 2001 Hum Mol Genet 10:1995).

Mismatch: One or more wrong (non-complementary) base(s) in the paired nucleic acid strands. Mismatches are generally identified (localized) by the use of fluoro-chrome labeled probes or they can be labeled by nanoparticle gold and analyzed on the basis of reduction silver (in the presence of hydroquinone at pH 3.8) by ordinary flatbed scanners with high sensitivity. Chemical cleavage of mismatch (CCM) is a hydroxylamine/osmium tetroxide-based (HOT) analysis of sequence variability in DNA. This procedure has been improved by adapting fluorescence techniques.

A bulky rhodium (a platinum type metal) complex can bind to mismatched and matched sites in the DNA of the oligonucleotide 5'-(dCGGAATTCCCG)2-3'. At the AC mismatch site, the structure reveals ligand insertion from the minor groove with ejection of both mismatched bases and destabilized mispairs in DNA may be recognized. This unique binding mode contrasts with major groove intercalation, observed at a matched site, where doubling of the base pair rise accommodates stacking of the intercalator. Mass spectral analysis reveals different photocleavage products associated with the two binding modes in the crystal, with only products characteristic of mismatch binding in solution. This structure, illustrating two clearly distinct binding modes for a molecule with DNA, provides a rationale for the interrogation and detection of mismatches (see Fig. M82). DNA polymerases generate mismatches at the rate of 10^{-4} to 10^{-5} per base pair at the nucleotide insertion step. These mistakes are typically reduced to 10^{-7} per base pair per replication by exonucleases associated with the DNA polymerase and are further reduced to 50- to 1,000-fold by the mismatch repair machinery. Deficiencies in mismatch repair increase the rate of mutation and subsequently the risk of developing cancer (Pierre VC

et al 2007 Proc Natl Acad Sci USA 104:429). ▶transition mismatch, ▶transversion mismatch, ▶mismatch repair, ▶DNA grooves; Ellis TP et al 1998 Hum Mutat 11:345.



Figure M82. Mismatch

Mismatch Extension: DNA polymerase binds to either a matched or mismatched primer end, and the mismatch is extended in replication. ▶mismatch

Mismatch of Bases: Non-complementary bases in a (hetero)duplex DNA. ▶mismatch

Mismatch Repair (MMR): An excision repair that removes unpaired or mispaired bases and replaces them through unscheduled DNA synthesis with correct base pairs. The long-patch mismatch repair may have to correct tracts of hundreds of nucleotides. Mutations in *E. coli* gene *mutL* (homodimer, subunits ~68 kDa) and *mutS* (~95 kDa subunits) increase genetic instabilities and in yeast, defects in *PMS1*, *MLH1* and *MLH2* may increase genetic instability 100 to 700-fold because of deficient mismatch repair. In yeast Msh6 (S1036P) the mutant complex, which binds the mispaired base is defective in ATP-induced sliding clamp formation and assembly of the ternary complex with Mlh1-Pms1 and prevents the access of other repair systems to access to the defect. In another mutation of Msh6 (G1142D), which binds mispaired sequences and is defective in the ATP-induced sliding clamp formation but permits the assembly of the Mlh1-Pms1 complex yet either prevents the access of other repair system or hinders Mlh1-Pms1 to activate the other repair systems (Hess MT et al 2006 Proc Natl Acad Sci USA 103:558). *mutS* may also inhibit both homologous and homeologous recombination (Pinto AV et al 2005 Mol Cell 17:113). Mismatch repair deficiency may enhance mutation rate by 1–2 orders of magnitude, depending on the background (Ji HP, King M-C 2001 Hum Mol Genet 10:2737). The consequences of deletions of RTH1, encoding a 3'→5' exonuclease are similar. The G/T binding protein (GTBP, 100K) and hMSH2 (160 K, homolog of bacterial mismatch-binding protein) are essential for mismatch recognition in human cells. In fission yeast the mismatch repair enzyme, exonuclease I, reduces mutation rate. Defects in the bacterial methyl-directed mismatch repair system may also enhance mutability (Burdett V et al 2001 Proc Natl Acad Sci USA 98:6765). The repair system is directed to DNA strands by methylation of adenine

in the d(GATC) sequences. Since newly synthesized strands are not methylated, this is the criterion for recognition by the repair system (MutH, MutL, MutS, ATP). The mismatch may be located kilobases away from the d(GATC) tract. Interaction of this complex with heteroduplexes activates the MutH-associated endonuclease that responds to an initial sequence discontinuity or nick. Excision from the 5' side of the mismatch requires the RecJ exonuclease or exonuclease VII and digestion from the 3'-end needs exonuclease I and also a helicase to unwind the strands because these proteins hydrolyze only single strands. RecJ and exo VII require that the unmethylated GATC would be downstream from the defect. Exo I usually does not have this precondition. The replacement synthesis requires DNA polymerase III. Other polymerases do not work in this system. In the eukaryotic systems, the MutL homologs are PMS1 in yeast and PMS1, PMS2 in mammals. The yeast PMS1 system corrects G-T, A-C, G-G, A-A, T-T and T-C mismatches but C-C or long insertion/deletion sequences were barely repaired if at all. The human repair system fixes 8–12 pair mismatches and C-C. An MutS homolog in mammals is called GTBP (G-T binding protein). Defects in PMS1, MLH1, MSH2 and [MSH3] enhance mutation rate in the yeast mitochondria, increases somatic mutability up to three orders of magnitude at certain loci (e.g., canavanine resistance), destabilizes (GT)_n sequences. Mutations in the yeast Rth1 5'→3' exonuclease also increases mutability, particularly of plasmid-encoded genes. MutS function is required for the normal progression of meiosis and the maintenance of the female gonads. The yeast homologs of the bacterial MutS and MutL not only correct errors in replication but block recombination between not entirely homologous (homoeologous) sequences. Heterocomplexes of the mismatch repair genes have important role in meiotic recombination (Snowden T et al 2004 Mol Cell 15:437). Defects in mismatch repair result in increased frequency of recombination, mutation and indirectly on evolution. PCNA and related proteins mediating DNA replication are essential for repair synthesis. Cadmium is a potent inhibitor of mismatch repair and greatly increases mutation (Jin YH et al 2003 Nature Genet 34:326). Double-strand DNA breaks may be repaired by gene conversion. Mismatch repair deficiency may increase the susceptibility to methylating drugs but not for others (e.g., cisplatin) or ionizing radiation. ▶[unscheduled DNA synthesis](#), ▶[DNA repair](#), ▶[glycosylase](#), ▶[PCNA](#), ▶[MRD](#), ▶[incongruence](#), ▶[gene conversion](#), ▶[double-strand break](#), ▶[Walker boxes](#), ▶[mutator genes](#), ▶[microsatellite](#), ▶[homeologous recombination](#), ▶[hereditary non-polyposis colorectal cancer](#), ▶[Lynch cancer families](#), ▶[Muir-Torre syndrome](#), ▶[gonads](#), ▶[excision](#)

[repair](#), ▶[short patch repair](#), ▶[slippage](#), ▶[Huntington's chorea](#), ▶[cisplatin](#), ▶[morphogenic](#); Nakagawa T et al 1999 Proc Natl Acad Sci USA 96:14186; Oblomova G et al 2000 Nature [Lond] 407:703; Lamers MH et al 2000 *ibid* 701; Buermeier A et al 1999 Annu Rev Genet 33:533; Harfe BD, Jinks-Robertson S 2000 Annu Rev Genet 34:359; Evans E, Alani E 2000 Mol Cell Biol 20:7839; Junop MS et al 2001 Molecular Cell 7:1; Wang H, Hays JB 2002 J Biol Chem 277:26136, 26143; recombination: Sugawara N et al 2004 Proc Natl Acad Sci USA 101:9315; Kunkel TA, Erie DA 2005 Annu Rev Biochem 74:681.

Misoprostol (Misoprostol): A synthetic prostaglandin E₁ analog that inhibits secretion of gastric acid (as an antacid pill) but it also induces uterine contractions and can cause abortion. It is used also for non-surgical termination of pregnancy. ▶[prostaglandins](#), ▶[RU486](#)

Mispairing: Occurs when the homology between paired nucleotide sequences is imperfect and illicit binding takes place between nucleotides.

Misreading: A triplet is translated into an amino acid different from its standard coding role. ▶[ambiguity in translation](#)

Misrepair: ▶[DNA repair](#), ▶[SOS repair](#)

Misreplication: ▶[error in replication](#)

Missense Codon: Inserts an amino acid different from that encoded by the wild type codon at the site in the polypeptide chain. ▶[nonsense codon](#)

Missense Mutation: A change in DNA sequence that results in an amino acid substitution in contrast to mutations in synonymous codons where the change involves only the DNA but not the protein. ▶[nonsense mutation](#)

Missense Suppressor: Enables the original amino acid to be inserted at a site of the peptide in the presence of a missense mutation. ▶[suppressor tRNA](#); Benzer S, Weisblum B 1961 Proc Natl Acad Sci USA 47:1149.

Missing Genes: In the archaeobacterium, *Methanococcus janaschii*, four of the 20 aminoacyl-tRNA synthetases were not detected in the completely sequenced genome. It has been hypothesized that glutamine and asparagine are incorporated into polypeptides as transamidated derivatives of glutamate and aspartate. Furthermore, cysteine was assumed to be inserted as a trans-sulfurated serine and tRNA^{Lys} synthetase function was replaced by a protein quite dissimilar to known aminoacyl-tRNA synthetases. ▶[aminoacyl-tRNA synthetase](#); Bult CJ et al 1996 Science 273:1058.

Missing Link: The lack of transitional forms in evolution in between two species, of which one was/is supposed to have descended from the other. In 2006, a 385–359 million-year old fossil of a fish that lived in the Late Devonian period in Canada was reported to have been found. It had bony structures in the fins and other morphological features indicating a missing link to tetrapods (Daeschler EB et al 2006 Nature [Lond] 440:757). ▶tetrapod, ▶geological–evolutionary time periods

Missing Self Hypothesis: One of the functions of natural killer lymphocytes (NK) is to recognize and eliminate cells that do not express class I MHC (major histocompatibility complex) molecules. ▶killer cells, ▶MHC; Ljunggren HG, Karre K 1990 Immunology Today 11:237.

Missplicing: Incorrect splicing. ▶splicing

Mistranslation: ▶misreading, ▶ambiguity in translation

MIT.: The general designation of mitochondrial point mutations.

Mitchurin: A nineteenth-twentieth century Russian plant breeder who contributed a large number of improved varieties, mainly fruits, to the Russian and then to the Soviet agriculture. His career is often compared to that of the American Burbank. There was a very important difference, however, Burbank produced over 100 varieties to the USA agriculture without governmental pretensions that he made novel basic scientific discoveries. Mitchurin, on the other hand, published undigested and misunderstood theories and became the official forefather of lysenkoism, a state-supported charlatanism. He drew sweeping conclusions on the basis of tenuous experimental technology. ▶lysenkoism, ▶Burbank, ▶acquired characters inheritance, ▶graft hybridization

MITE (mariner insect transposon-like element, miniature inverted-repeat transposable element): A 1,457-bp DNA sequence in the vicinity of MLE containing a 24-bp tract with homology to Mos1 and supposedly responsible for the high frequency of unequal crossing over resulting in a duplication appearing as the Marie-Charcot-Tooth disease, and in the complementary deletion appearing as HNPP. Similar MITE elements occur also in rice, maize, sugarcane and other plants and control transcription. ▶Marie-Charcot-Tooth disease, ▶HNPP, ▶unequal crossing over, ▶hot spot, ▶Mos1, ▶mariner, ▶heartbreaker, ▶MLE; Casa AM et al 2000 Proc Natl Acad Sci USA 97:10083; Jiang N et al 2003 Nature (Lond) 421:163.

Mitochip: The mitochondria-specific oligonucleotide microarray that has potential to define mechanisms of

disease progression and drug toxicities involved in mitochondrial dysfunction (Desai VG, Fuscoe JC 2007 Mutation Res 616:210). ▶microarray; Zhou S et al 2006 J Mol Diagn 8:476.

Mitochondria: Cellular organelles 1–10 μm long and 0.5–1 μm wide, surrounded by double membranes. The outer membrane has a diameter of 50–75 and the inner 75–100 Å. The latter forms the structures, called cristae. Mitochondria are associated frequently with the cytoskeleton and the latter may control the distribution of this organelle within the cell and their transmission during cytokinesis.

The outer membrane is associated with monoamine oxidase and a NADH-cytochrome c reductase. Cardiolipin, phosphatidyl inositol, and cholesterol are major compounds associated with the inner membrane. Mitochondria have an important role in generation of ATP and in electron transport. ATP synthesis requires oxidative phosphorylation. The mitochondria generally encode cytochrome b, cytochrome oxidase (COX) subunits, ATPase and NADH dehydrogenase (see Fig. M83). Three protozoa (*Giardia*, *Trichomonas*, *Vairimorpha*) and *Entamoebas* are the only animals without mitochondria. All human cells, except the erythrocytes contain mitochondria. In human mitochondria 13 out of the 78 polypeptides involved in the electron transport are coded for by mitochondrial DNA.

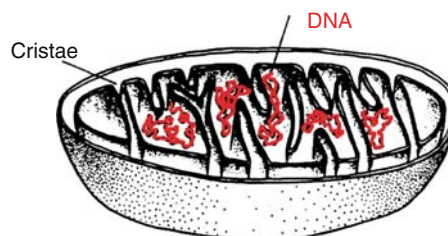


Figure M83. Diagram of a longitudinal section of a mitochondrion showing the cristae and the DNA strings in between them. according to electronmicroscopic view the cristae are tubular rather than lamellar structures

Mitochondria are the major source of reactive oxygen (ROS) in the body. In humans, about 300 nuclear genes control mitochondrial functions. The larger mitochondrial genomes of fungi and plants have larger coding capacity. The mitochondrial DNA and the prokaryotic type ribosomes in this organelle are capable of independent protein synthesis although they may not have all their necessary tRNA genes within the mt genome. The majority of the proteins within the mitochondria are synthesized in the cytosol and imported. This import depends also on the function of cytosolic chaperones such as Hsp70 and Hsp60. In yeast and some other organisms, under

some circumstances, a single giant mitochondrion is formed that spreads all over the cell and can break up into smaller organelles (see Fig. M84). Mitochondria are usually transmitted only through the eggs. Exceptions exist, however. In a human cell, about 100–1000 mitochondria may be found but a single mouse oocyte has $\sim 1 \times 10^5$. Each may contain 2–10 or more DNA molecules and about 1000 peptides of which only 13 are coded by mtDNA. In addition, the mtDNA genome (16.5×10^3 bp in higher animals) encodes two rRNAs and 22 tRNAs. (In other organisms, the number of genes in the mitochondria may vary between 5 and 60.) Mitochondria are involved in the production of $\sim 80\%$ of the cellular ATP, carry out respiration, synthesize amino acids, nucleotides, lipids, heme, regulate inorganic ion channels and apoptosis.

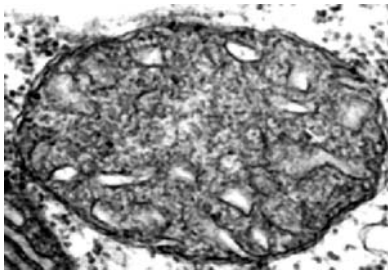


Figure M84. Plant mitochondrion

During mammalian oogenesis, the number of mitochondria may be 4,000–200,000 but their number may be reduced substantially during early development of the embryo. The number of mitochondria seems to be regulated by mtTFA and mtTFA is regulated by a nuclear regulatory factor (NRF-1). The large number of mitochondria within mammalian and other higher eukaryotic cells was probably necessitated by the limited capacity of DNA repair within the mitochondria. The large number can compensate for the defective organelles. There is apparently no nucleotide excision repair (NER) in the mammalian mitochondria but base excision repair (BER), by the use of glycosylases, has been detected. Mismatch repair (MMR) also exists in mitochondria. It is not clear whether recombinational repair has a role in mitochondria. The evolutionary origin of the mitochondria has been interpreted by syntrophic hypotheses assuming the fusion of a primitive amitochondrial eukaryote with a *Clostridium*-like eubacterium or a *Sulfolobus*-like archaeobacterium. Genome signatures, the selective advantage of expanded energy metabolism, and the possibility that *Clostridium* provided an opportunity for the development of the nucleus and the cytoplasm of the eukaryotic cell support the latter hypothesis. Mitochondrial DNA analysis (Finnilä S et al 2001 Am

J Hum Genet 68:1475) is a very important tool for evolutionary and demographic studies. Some anaerobic or near-anaerobic unicellular eukaryotes do not have typical mitochondria but hydrogenosomes. An integral membrane protein, mitofusin, mediates fusion of mitochondria (Koshiba T et al 2004 Science 305:858). ▶mtDNA, ▶paternal leakage, ▶doubly uniparental inheritance, ▶Eve foremother of mitochondrial DNA, ▶CSGE, ▶compatibility of organelles with the nuclear genome, ▶respiration, ▶photorespiration, ▶promitochondria, ▶mitochondrial genetics, ▶petite colony mutations, ▶organelle sequence transfer, ▶aspartate aminotransferase [glutamate oxaloacetate transaminase, ▶GOT2], ▶mitochondrial diseases in humans, ▶cytoplasmic male sterility, ▶mitochondrial abnormalities in plants, ▶mitochondrial genetics, ▶mitochondrial plasmids, ▶mitochondrial import, ▶polar granules, ▶*Neurospora*, ▶mitochondrial plasmids, ▶mtTFA, ▶sorting out, ▶endosymbiont theory, ▶Rickettsia, ▶evolution of organelles, ▶Tid50, ▶Hsp70, ▶Hsp60, ▶Ydj, ▶rho factor, ▶hydrogenosome, ▶apoptosis, ▶aging, ▶ROS, ▶signature genomic, ▶membrane proteins, ▶amitochondriate, mitosome, evolution of mitochondria: Gray MW et al 2004 Annu Rev Genet 38:477; MAVS, Chen XJ, Butow RA 2005 Nature Rev Genet 6:815; mitochondrial fusion and fission: Okamoto K, Shaw JM 2005 Annu Rev Genet 39:503; mitochondrial origins and evolution: Embley TM, Martin W 2006 Nature [Lond] 440:623; Mt DNA in human oocyte: Shoubridge EA, Wai T 2007 Curr Top Dev Biol 77:87; human mitochondrial database: <http://www.genpat.uu.se/mtDB/>; mitochondrial proteome: <http://www.mitop2.de/>; human mitochondria: <http://www.mitomap.org/>; *Arabidopsis* mitochondrial proteins: <http://www.ampdb.bcs.uwa.edu.au/>.

Mitochondria and Cancer: Dysfunction of apoptosis may lead to abnormal cell proliferation and thus to cancer. The apoptosis blocking Bcl-2 and other proteins are localized in the mitochondrial membrane. The oxidative processes in the mitochondria may cause mutagenic lesions leading to tumor initiation and progression. ▶apoptosis, ▶cancer

Mitochondria, Cryptic: Double-strand membrane-enclosed structures in microsporidia that were supposed to lack mitochondria. Microsporidia are intracellular parasites of some animals and protists. The cryptic mitochondria are about 1/10 in size of mitochondria of animals and contain only a few proteins. The majority of the mitochondrial functions were apparently lost in these parasites as a consequence of retrograde evolution. ▶retrograde evolution, ▶hydrogenosomes; Roger AJ, Silberman JD 2002 Nature [Lond] 418:827.

Mitochondrial Abnormalities in Plants: The cytoplasmic male sterility, widespread in many species of plants and the *non-chromosomal striped* mutations of maize have proven mitochondrial defects. The latter have deletions either in the cytochrome oxidase (*cox2*) or in NADH-dehydrogenase (*ndh2*) or in ribosomal protein (*rps3*) mitochondrial genes. The mtDNA defects apparently originate by recombination between repeats (6–36-bp) at different locations within the genome. Recombinations involving larger repeats may also give rise to normal mtDNA as well as duplication-deficiency molecules. The phenotype (green and bleached stripes on the leaves, stunted growth, etc.) might suggest as if the plastids would have been involved. A similar mt-coded enzyme causes mitochondrial defects in other plants as well as in animals. ▶cytoplasmic male sterility, ▶killer plasmids, ▶senescence, ▶mitochondrial diseases in humans, ▶mitochondrial genetics, ▶mitochondrial plasmids, ▶mitochondria; Newton KJ et al 1996 Dev Genet 19:277.

Mitochondrial Complementation: When mitochondria with long deletions (4696 bp), including the site of cytochrome oxidase c (COX) is lost, mice did not show any disease when COX⁺ mitochondria were introduced. Within single cells, apparently only normal mitochondrial function could then be detected, indicating genetic complementation. The results promise the possibility of gene therapy by mtDNA. ▶mitochondrial heterosis; Nakada K et al 2001 Nature Med 7:934.

Mitochondrial Control-Regions: They encompass the areas where replication of the heavy strand (control region I, bp 16040–16400 in humans) and light strand (control region II, bp 39–380 in humans) takes place. The control regions display greater variation than the rest of the molecule and therefore, these regions are frequently studied for base variations in evolutionary and population studies. ▶DNA replication mitochondria, ▶D loop, ▶mtDNA, ▶DNA 7 S, ▶mitochondrial genetics

Mitochondrial DNA Depletion Syndromes (MDDS): MDDS involve tissue-specific decrease of mtDNA copy number and organ failure. Mitochondrial DNA synthesis depends on import of deoxyribonucleotide phosphates from the cytosol or salvage from DNA inside mitochondria. Human deoxyguanosine kinase (dGK, 2p13) and thymidine kinase-2 (TK2, 16q12) are expressed in the mitochondria. These two enzymes phosphorylate purines (guanine, adenine) and pyrimidines (thymidine, cytidine) respectively. Mutations in TK2 can reduce its activity by 14–45% and involve devastating myopathy (Saada A et al 2001 Nature Genet 29:342). Similarly, mutation in the last step of the salvage pathway (ADP forming

succinyl-CoA ligase) resulted in mtDNA depletion and encephalomyopathy (Elpeleg O et al 2005 Am J Hum Genet 76:1081). A hepatocerebral mtDNA depletion locus (MPV17, 2p21-p23) affect the inner mitochondrial membrane and causes defects in (oxidative phosphorylation) OXPHOS (Spinazzola A et al 2006 Nature Genet 38:570). ▶Alpers progressive poliodystrophy, ▶oxidative phosphorylation myopathy, ▶mitochondrial diseases in humans, ▶hepatocerebral, ▶mtDNA

Mitochondrial Diseases in Humans: Up to the 1970s no human disease was attributed to mtDNA. Approximately 0.001 fraction of the newborns have a mitochondrial disease. The role of mitochondrial DNA was definitely proven only after molecular analysis became practical. The inheritance pattern is not always clear because of heteroplasmy. *Chloramphenicol* resistance in human cells is caused by several mutations in the mitochondrial DNA-encoded 16S ribosomal RNA genes. Leber hereditary optic atrophy (LHON), a progressive disease (caused most commonly by single base pair substitution [G(A(Arg→His))] resulting in wasting away of the eyes (optic atrophy), abnormal heart beat accompanied by neurological anomalies characterizes this disease (involving 5 NADH dehydrogenases at different sites in the mtDNA) that it appears a human X-chromosomal factor has a role in determining susceptibility to the mitochondrial defect (see Fig. M85). In mice, three nuclear quantitative gene loci appear to affect mitochondrial sorting out (Battersby BJ et al 2003 Nature Genet 33:183). In LHON models of mice and dogs adeno-associated virus vector carrying the gene for the retinal pigment epithelium photoreceptor successfully restored visual function by this gene therapy (Acland GM et al 2001 Nature Genet 28:92). *Kearns-Sayre syndrome* (KSS/ PEO) a progressive external ophthalmoplegia (paralysis of the eye muscles) is characterized by pigmentary degeneration of the retina and cardiomyopathy (inflammation of the heart muscles) and other less specific symptoms are caused either by deletion or base substitution mutation in nucleotide 8,993 in the mtDNA. Deletions—in 30–50% of the afflicted—are flanked by the 5'-ACCTCCCTCACCA direct repeats and show the loss of nucleotides 8,468–13,446 and a less frequent deletion between the repeats 5'-CATCAACAACCG at positions 8,468–16,084. The larger deletions may affect simultaneously also other mitochondrial genes. The KSS involves most commonly heteroplasmy and its occurrence is frequently sporadic. The basic defect is either in a protein phage T7 gene-4-like primase/helicase of DNA (Spellbrink JN et al 2001 Nature Genet 28:223) or in DNA polymerase γ , located at 15q22-q26 (Van Goethem G et al 2001 Nature Genet 28:211). In both cases, multiple

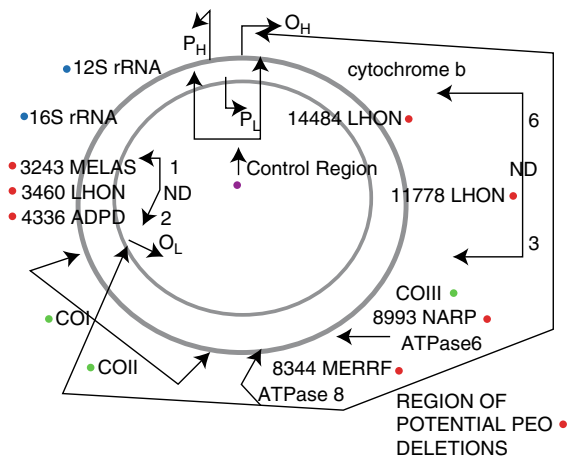


Figure M85. Incomplete Human mtDNA Map. O_H : Origin of heavy-chain replication, P_H : promoter of heavy chain replication, P_L : light strand promoter, ND: NADH-coenzyme Q oxidoreductase subunits, ADPD: Alzheimer disease late onset, CO: cytochrome oxidase subunits, NARP: neuropathy, ataxia, retinitis pigmentosa syndrome, MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like syndrome (associated mainly with mutation in the $tRNA^{Leu}$), LHON: Leber's hereditary optic neuropathy, MERRF: myoclonic epilepsy and ragged-red fibers, PEO: progressive external ophthalmoplegia (most commonly deletions)

mutation/deletions occur in the mtDNA. One form of *myoclonic epilepsy*, MERRF (shock-like convulsions and ragged red fibers [when stained with Gömöri's modified trichrome stain]) is caused by a point mutation in the mtDNA-coded $tRNA^{Lys}$. *Mitochondrial myopathy* (muscle/eye degeneration), *encephalopathy* (brain degeneration), *encephalomyopathy* (MTTL2) mutation in $tRNA^{Leu}$, *lactic acidosis* (accumulation of lactic acid in the blood), and *stroke-like episodes* (MELAS syndrome, *mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms*) are due to a mtDNA encoded $tRNA^{Leu}$ base substitution (A→G) at nucleotide 3,243 and at other sites and by mutation in $tRNA^{Cys}$ and $tRNA^{Val}$. The same $tRNA^{Leu}$ mutation occurs in about 20% of the patients with the recessive autosomal *Progressive external ophthalmoplegia* (PEO) and in some cases of diabetes mellitus ($tRNA^{Leu}$). Mutation in $tRNA^{Leu}$ A3243G leads to gradual pancreatic β -cell dysfunction upon aging and diabetes (*Mitochondrial diabetes*, Maassen JA et al 2004 Diabetes 53:S103). The *Pearson marrow-pancreas syndrome* is caused by mtDNA deletions affecting subunit 4 of NADH dehydrogenase, subunit 1 of cytochrome oxidase and subunit 1 of ATPase. This rare disease, usually heteroplasmic, is frequently fatal at infancy. *Oncocytoma*, responsible primarily for benign solid kidney

tumors, loaded densely with mitochondria, has deletions in subunit 1 of cytochrome oxidase.

In general, human males have more, or more are affected by mitochondrial mutations. About 85% of the *Leber's optic dystrophy* cases are found in males. Also, Alzheimer disease ($tRNA^{Gln}$), and Parkinson disease are associated with defective mitochondrial energy metabolism, reduced sperm motility and fertility. *Leigh syndrome* (an ATP synthase defect at nucleotide 8527–9207) is a progressive encephalopathy of children and it is accompanied by over 90% mutant mitochondria in the blood, muscle and nerve cells, although the inheritance appears autosomal. Several myopathies are associated with mutations also in various tRNAs of the mitochondria ($tRNA^{Phe}$, $tRNA^{Ile}$ [cardiomyopathy], $tRNA^{Glu}$ [cardiomyopathy], $tRNA^{Met}$, $tRNA^{Ala}$, $tRNA^{Asn}$, $tRNA^{Cys}$ [ophthalmoplegia], $tRNA^{Tyr}$, $tRNA^{Ser}$, $tRNA^{Asp}$, $tRNA^{Lys}$ [MERRF syndrome], $tRNA^{Gly}$, $tRNA^{Arg}$ [LHON], $tRNA^{Ser2}$, $tRNA^{Leu(CUN)}$ [skeletal myopathy], $tRNA^{Glu}$, $tRNA^{Thr}$ [cytochrome b subunits]). U → C transition mutation adjacent to the anticodon GAU of $tRNA^{Lys}$ may involve hypertension, dyslipidemia and atherosclerosis (Wilson FH et al 2004 Science 306:1190). In MELAS Leu^{UUR} tRNA five mutations (sites A3243G, G3244A, T3258C, T3271C and T3291C) lacked the normal taurine-containing modification (5-taurinomethyluridine) at the anticodon wobble position. Other mutations in $tRNA^{Leu^{UUR}}$ (G3242A, T3250C, C3254T and A3280G) display mitochondrial disease but not the MELAS symptoms (Kirino Y et al 2005 Proc Natl Acad Sci USA 102:7127).

Aminoglycoside-sensitivity (modest doses of streptomycin) may lead to hearing defects due to mutation in the 12S rRNA gene (Li R et al 2004 Am J Med Genet 124A:113; Li X et al 2004 Nucleic Acids Res 32:867). About 5×10^{-5} fraction of the human population is hypersensitive to chloramphenicol and may become anemic from the drug. Deletion of the COX (cytochrome oxidase) gene may result in *myoglobinuria*.

The human mitochondria harbors about 1,500 proteins and but most of them are encoded by nuclear genes. By computational technology, 1,080 gene products were allocated to mitochondria with an estimated false positive rate of 10%. The predicted number includes 8 genes implicated in disease (Calvo S et al 2006 Nature Genet 328:576). A decrease in the number of mitochondria, caused by nuclear genetic factors or drugs may lead also to disease.

The autosomal dominant progressive external ophthalmoplegia (adPEO, CPEO), a muscle weakness affecting the eyes primarily, is caused by a mutant gene in human chromosome 10q23.3-q24.3 that causes multiple deletions.

Hereditary spastic paraplegia is encoded by chromosome 16q but the 795 amino acid paraplegin protein is located in the mitochondria. Some of the late onset neurodegenerative diseases apparently have mitochondrial components. Human *colorectal tumors* frequently display purine transition mutations and appear homoplasmic. *Hereditary paraganglioma* is caused by mutation at 11q23 in the SHDS gene encoding a small subunit of cytochrome b involved in succinate-ubiquinone oxidoreductase (sybS). This disease shows vascularized benign tumors in the head and neck due to defects in the carotid body (the main artery to the head), which senses oxygen levels in the blood (Vanharanta S et al 2004 Am J Hum Genet 74:153).

The mtDNA contains 37 genes, most of them transcribed from the heavy chain, but 9 are read in opposite direction from the light chain of the DNA and they are thus somewhat overlapping. The human mitochondria encode only 13 respiratory chain proteins although it may harbor about ~1,500 proteins (see Fig. M86). Some human diseases or syndromes (hypotonia [reduced muscle tension], ptosis [dropping down eyelids], ophthalmoplegia [eye muscle paralysis], high level of lactate in the blood serum, liver defects) may be associated with a reduced level of mtDNA. Genetic counseling with mitochondrial disease is difficult because the transmission of the heteroplasmic conditions is irregular. Treatment of mitochondrial diseases so far appeared rather elusive. The mitochondrial respiratory chain involves the multisubunit complexes (I) NADH-UQ oxidoreductase, (II) succinate dehydrogenase, (III) UQ-cytochrome c oxidoreductase, (IV) cytochrome c oxidase, and (V) ATP synthase. Blocking complex I by 1-methyl-4-phenylpyridinium (MPP^+) mimicks Parkinson disease and LHON. Inhibition of complex II by 3-NPA (3-nitropropionic acid) causes the symptoms of Huntington's chorea. Cyanide and azide inhibition of complex IV resembles the expression of Alzheimer disease. The effect of oligomycin on complex V involves neuropathy, ataxia and retinitis pigmentosa-like symptoms. There are a number of diseases, which are not encoded by the mitochondrial DNA and neither are the proteins localized in the mitochondria yet they affect mitochondrial functions. Mitochondrially determined disease due to ATP

deficiency could be alleviated (Manfredi G et al 2002 Nature Genet 30:394) by introduction into the nucleus the functional mitochondrial gene. Also, the transplantation of nuclei from mitochondrial mutants into normal cytoplasm may restore normal health if the mutational defect was limited only to mitochondria (Sato A et al 2005 Proc Natl Acad Sci USA 102:16765). Dominant optic atrophy (Kjer type, 3q28-q29) causes serious vision defects in childhood and adulthood due to degeneration a mitochondrial intermembrane dynamin-like OPA1 protein (Kim JY et al 2005 Neurology 64:966). ▶mitochondria, ▶mitochondrial DNA depletion syndromes, ▶mtDNA, ▶mitochondrial genetics, ▶protoporphyrria, ▶aging, ▶senescence, ▶chondrome, ▶optic atrophy, ▶epilepsy, ▶spastic paraplegia, ▶antibiotics, ▶Leigh's encephalopathy, ▶diabetes mellitus, ▶ophthalmoplegia, ▶myoglobin, ▶Wolfram syndrome, ▶Friedreich ataxia, ▶Wilson disease, ▶Alzheimer disease, ▶Parkinson disease, ▶Charcot-Marie-Tooth disease, ▶spastic paraplegia, ▶MNGIE, ▶amyotrophic lateral sclerosis, ▶mitochondrial gene therapy, ▶homoplasmy, ▶heteroplasmy, ▶colorectal cancer, ▶apoptosis, ▶mtPTP, ▶mitochondrial abnormalities in plants, ▶atresia, ▶pleiotropy, ▶oxidative DNA damage, ▶transmitochondrial, ▶NARP syndrome, ▶myoneurogastrointestinal encephalopathy, ▶dimethylglycine dehydrogenase, ▶taurine, ▶wobble, ▶Gomori's stain; Wallace DC 1992 Annu Rev Biochem 61:1175; Smeitink J, van den Heuvel B 1999 Am J Hum Genet 64:1505; Acland GM et al 2001 Nature Genet 28:92; Thornburn DR, Dahl HH 2001 Am J Med Genet 106:102; Steinmetz LM et al 2002 Nature Genet 31:400; Taylor RW, Turnbull DM 2005 Nature Rev Genet 6:389; mtDNA – tRNA human disease: Florentz C et al 2003 Cell Mol Life Sci 60:1356; wobble site modification in tRNA leads to disease specificity: Kirino Y et al 2005 Proc Natl Acad Sci USA 102:7127; Wallace DC 2005 Annu Rev Genet 39:359; mitochondrial proteome: <http://www.mitop.de/>; human mitochondrial genome: <http://www.genpat.uu.se/mtDB/>; human mitochondrial variation database: <http://www.genomic.unimelb.edu.au/mdi/dblist/mito.html>.

Mitochondrial DNA: ▶mtDNA

Mitochondrial Export: ▶polar granules

Mitochondrial Gene Therapy: Several mitochondrial diseases became ascertained and studied since the 1970s. They may include (i) nuclearly encoded gene products imported to the mitochondria, (ii) strictly mitochondrially encoded defects, and (iii) gene products under dual control. Correcting the defect of proteins encoded by the nucleus and translated in the cytoplasm has about the same requisites as

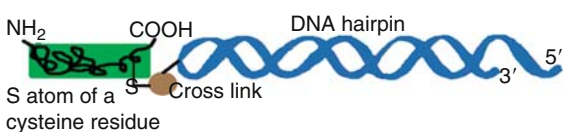


Figure M86. Targeting a transit peptide to DNA (Modified after Seibel P et al. 1998 in Mitochondrial DNA in Aging, Disease and Cancer. Singh KK ed. Springer, New York)

gene therapy in general. There are more hurdles to overcome when the therapeutic DNA sequences are intended for transport into the mitochondria with the aid of cytoplasm-located vectors. The first requirement is the construction of appropriate signal peptide, which would mediate the import. There is experimental evidence for the feasibility to targeting a hairpin-shape DNA into the mitochondrial matrix with the aid of an appropriate transit/signal peptide (Fig. M86). The transforming vector must use the coding system particular for the mitochondria that may be different in different organisms. The transcript and the translation product must be suitable for processing within the mitochondria by its own protein-synthesizing machinery. The mitochondrial ribosomes are also different from the cytosolic ones. The promoter must respond to the regulatory system of the mitochondria and the expression of the gene would be optimally modulated in that environment. The maintenance replication of the introduced transgene must be secured for both somatic divisions and for the maternal germline. Problems may arise if the defective, mutant polypeptide interferes with the assembly of the functional protein complex even in the presence of a correct product of the transgene. Since the majority of the mtDNA mutations involve deletions, duplications and rearrangement of the mitochondrial genome, some diseases may not be amenable to exogenously delivered corrections. The mitochondrial genome in higher organisms is present in “polyploid” forms and the rules of the mitochondrial segregation within the cells are not entirely known. There is evidence that in the relatively very simple yeast system the mitochondrial ATPase 8 defect could be corrected by a genetic vector product in the cytoplasm. It has been reported that the β subunit of the mitochondrial ATP synthase fused to the bacterial CAT (chloramphenicol acetyltransferase) and driven by the cauliflower mosaic virus CaMV 35 S promoter and introduced into tobacco (*Nicotiana glauca*) by an agrobacterial vector, was expressed mainly in the mitochondria but not in the chloroplasts. The introduction of transgenes by the biolistic methods to both mitochondria and chloroplasts has been achieved repeatedly. There may be ways to target therapeutic agents to the mitochondria by coupling, e.g., antioxidants to alkyltriphenylphosphonium cations (Smith RAJ et al 2003 Proc Natl Acad Sci USA 100:5407).

Defects of the mtDNA frequently result in faster replication of the mutation and this type of anomaly may be corrected by antisense technologies. Antisense technology may also silence a mitochondrial gene with harmful effect. Eventually gene replacement techniques may also become practical. ▶transit peptide, ▶signal peptide, ▶genetic code, ▶biolistic transformation, ▶ATPase, ▶transformation [plants], ▶antisense technologies, ▶gene replacement,

▶mitochondrial genetics, ▶mitochondrial diseases in humans, ▶mitochondrial anomalies in plants, ▶gene therapy, ▶mitochondrial complementation acid, ▶peptide nucleic acid; Murphy MP, Smith RA 2000 Adv Drug Deliv Rev 41:235.

Mitochondrial Genetics: The mitochondrial DNA is generally transmitted only by the egg cytoplasm. The failure of transmission of the mtDNA by the sperm in the majority of the species appears to be due to selective degradation. It appears that during spermatogenesis the mitochondrial nucleoid number is reduced and after fertilization the mtDNA is rapidly digested (Nishimura Y et al 2006 Proc Natl Acad Sci USA 103:1382). The wild type yeast mtDNA is inherited biparentally. The hypersuppressive petite mutants of yeast are transmitted, however, only uniparentally. In the bivalve molluscs a specific F (female) mitochondrial DNA is transmitted to both males and females whereas the M (male) mtDNA is transmitted only to the sons of males. These two types of mtDNAs recombine in the somatic tissues but the recombinant molecules are rarely transmitted (Passamonti M et al 2003 Genetics 164:603). In some species a low frequency of male transmission (paternal leakage) exists (Fig. M87).

Segregation of mitochondrial genes is followed by cell phenotype because individual mitochondria are not amenable to direct genetic analysis (see Fig. M88). (Molecular analysis can identify, however, differences among mitochondria.) Some of the genes are specific for the mitochondria and others, e.g., the cytochrome oxidase complex share subunit coding with the nucleus. This sharing may vary in different evolutionary groups, which seems to indicate interchanges between the nuclear, mitochondrial and chloroplast genomes. Despite the large number of mitochondria (>100/cell) and mtDNA molecules (4–6 per nucleoid), homoplasmic condition may be obtained at a much faster rate than expected on the basis of random sorting out. In mouse, it has been estimated that the number of segregating mitochondrial units is about 200 and the rapid sorting out was attributed to random genetic drift. (Some estimate the number of sorting mammalian mtDNAs >50,000.) The sorting out of the mitochondria—according to recent studies of yeast mutants of the MDM (mitochondrial distribution and morphology) group—is controlled by proteins of the cytoskeleton and integral proteins of the outer mitochondrial membrane, such as a dynamin-like protein. In fission yeast, mitochondrial distribution is mediated by microtubules tethered to the spindle pole bodies (Yaffe MP 11424). The ubiquitin-protein ligase suppressor, Rsp5p and the Ptc1p (serine/threonine phosphatase) seem also be involved in the regulation of mitochondrial transmission. In the mouse oocytes

mtDNA seems to be involved in neuron development and affect axonal and synaptic activity as well as cognitive functions of the brain (Roubertoux PL et al 2003 Nature Genet 35:65).

Recombinational mapping is generally useful within short distances (≈ 1 kb). Genetic maps of mtDNA are generally constructed by physical mapping procedures. Also, the relative position of the genes may be ascertained by co-deletion-co-retention analyses. These methods resemble the deletion mapping of nuclear genes. Genes simultaneously lost by deletion, or retained in case of deletion of other sequences, must be linked. Mitochondrial genes have been mapped also by polarity. It was assumed that the yeast mtDNA carried some sex-factor-like elements, ω^+ and ω^- , respectively. The omega plus (ω^+) cells appeared to be preferentially recovered in polar crosses ($[\omega^+] \times [\omega^-]$). In these so called *heterosexual crosses* the order of certain genes, single and double recombination and negative interference were observed. The exact mechanism of the recombination was not understood. The ω^+ factor turned out to be an intron within the 21S rRNA gene with a transposase-like function. Non-polar crosses have also been used to determine allelism. In the latter case all progeny was parental type and recombination was an indication of non-allelism. Linkage and recombination could also be detected in non-polar crosses but mapping was impractical. Complementation tests can be carried out in respiration deficient mutations on the basis that in "non-allelic" crosses respiration is almost completely restored within 5–8 hours whereas recombination may produce wild types only in 15–29 hours. Different loci are complementary and appear unlinked. Some loci may not complement each other. Mitochondrial fusion and complementation of mitochondrial genes in human cells has also been reported (Ono T et al 2001 Nature Genet 28:272; Westermann B 2002 EMBO Rep 3:527). Mitochondrial fusion requires the sequential interaction of the outer and inner mitochondrial membranes (Pfanner N et al 2004 Science 305:1723). The fusion of the outer membranes needs low levels of GTP (mediated by GTPase Fzo1) but the inner membrane fusion requires high GTP levels as well as inner-membrane electrical potential. Inner membrane fusion as well as the maintenance of the structure of the cristae requires the dynamin-related GTPase Mgm1 (Meeusen S et al 2006 Cell 127:383). Mutations in the genes controlling mitochondrial fusion (mitofusin, MFN2. 1p36.2) may account for the 2A type neuropathy of the Charcot-Marie-Tooth disease (Zuchner S et al 2004 Nature Genet 36:449) and optic atrophy (Zuchner S et al 2006 Ann Neurol 59:276). Primarily, dynamin-like proteins control mitochondrial fission. Mitochondrial fission

entails mitochondrial disintegration during apoptosis (Parone PA, Martinou JC 2006 Biochim Biophys Acta 1763:522). This protein is involved also in the control of cytokinesis (Chanez AL et al 2006 J Cell Science 119:2968).

Homologous recombination has been extensively studied in yeast by the Flp/FRT system. Recombination of mtDNA in vertebrate cybrids does not readily occur. In case of fusion of haploid cells, gene conversion may take place.

Transformation of mitochondria requires the biolistic method or by implantation of cell hybrids with mutant mitochondria. Unfortunately, only a fraction of the mutant mitochondria are transmitted and only through the female. Usually co-transformation by nuclear and mitochondrial DNA sequences is employed. The nuclear gene (*URA3*) is used for selection of transformant cells. The ρ^- cells cannot be selected because they are defective in respiration. They are crossed then with mt^+ cells that carry a lesion in the target gene and among the recombinants, the transformants may be recovered. It is possible that the wild type *URA3* gene is transferred from the mitochondrion into the *ura3* mutant nucleus whereas the cytochrome oxidase gene (*cox2*) is maintained in the nucleoid.

The large subunit of the mitochondrial ribosomal RNA may house a mobile element, ω^+ . This element (a Group I intron) may show polar transmission and can be used in a limited extent for recombination analysis as mentioned above. It encodes 235 amino acids and represents *SceI* endonuclease. A *Chlamydomonas smithii* intron (from the *cytb* mitochondrial gene) can move into the same but intronless gene in *C. reinhardtii*. Several other Group I introns have similar mobility and the introns usually share the peptide LAGLI-DADG, a consensus conserved also in some maturases. Other Group I introns display the GIY-10/11aa-YIG pattern. The VAR-1 yeast gene (ca. 90% A + T) encoding the small mt ribosomal subunit is also an insertion element. Other mobile elements with characteristic G + C clusters are common features of these insertion elements. Group II introns present in various fungi are also mobile. Splicing/respiration deficient mutants become revertible if the defective intron is removed. Similar mobile elements can be found in the cpDNA of *Chlamydomonas* algae. Mitochondrial plasmids may be circular or linear. Some of the circular mt plasmids display structural similarities to Group I introns and their transcripts are reminiscent of reverse transcriptases (resembling protein encoded by Group II introns).

In yeast, nuclear genes *MDM1* (involved in the formation of non-tubulin cytoplasmic filaments), *MDM2* (encodes $\Delta 9$ fatty acid desaturase) and *MDM10* (determines mitochondrial budding) control the transmission of mitochondria to progeny cells.

The subunit(s) of the mitochondrial transcriptase and the mtTFA transcription factor are coded in the yeast nucleus.

Nuclear and mitochondrial promoters share cis elements. It seems that mitochondrial signals regulate nuclear genes controlling mitochondrial functions. Partially reduced intermediates of NADH dehydrogenase and coenzyme Q (ubiquinone) are held responsible for the production of ROS. In human diseases such as cancer, ischemic heart diseases, Parkinson disease, Alzheimer disease, and diabetes ROS products have been implicated. The mitochondrial ROS activates mammalian transcription factors NF- κ B, AP and GLUT glucose transporters.

Majority of the prokaryotic mutagens are apparently effective in causing mutations in the mtDNA. The ROS molecules generated within the mitochondria may be responsible for a variety of alterations in the mtDNA.

Deletions and duplication, besides point mutations, may also occur spontaneously during the processes of aging. Mutation rates per mitochondrial D loop has been estimated to be 1/50 between mothers–offspring but other estimates used for evolutionary calculations are 1/300 per generation or 3.5×10^{-8} per site per year although the DNA polymerase γ appears to have low error rates. Some of the (recessive?) mitochondrial mutations are apparently non-detectable without molecular analysis because functionally the mitochondria are “polyploid” and their numbers in the cells are commonly very high. Due to the large number of cells, the large number of mitochondria per cell and the multiple copies of the mtDNA per mitochondria, chances for mutation are high within a multicellular organism. Also, within a single individual different mitochondrial mutations may occur and their spectrum may vary in the different tissues. By 1998, nearly 1000 mitochondrial point mutations were known and 65 were involved in human disease. Mutations in the mtDNA (5×10^{-7} /base/human generation) are much higher than in the nuclear DNA (8×10^{-8}). In the control region of human mtDNA mutation rate of 1/bp/ 10^6 years was reported (Howell N et al 2003 Am J Hum Genet 72:659). The estimates of mitochondrial mutations may be biased by genetic drift, selection, recurrent mutations, and hot spots in some hypervariable sequences.

The mutation rate/bp in both mtDNA and nuclear DNA varies substantially from region to region. About 40% of the mtDNA deletions involve 7000–9000 bp and 20% encompass 4000–5000. Their distribution is biased in as much as 95% of the deletions affect the region between bp 3300 to 12000.

Mitochondrial DNA frequently classified into macrohaplogroups including subhaplogroups on the basis of the mitochondrial protein sequence and

geographic origin. The African haplogroups (subhaplogroups) are L1, L2 and L3. The M and N haplogroups originated on L3 background in eastern Africa but migrated into Eurasia and also to the Americas from Siberia where additional variations, A, B, C, D and G accumulated (Mishmar D et al 2003 Proc Natl Acad Sci USA 100:171). Several additional haplogroups are distinguishable in Europe, Asia and the Americas facilitating the tracing of human migration (Pakendorf B, Stoneking M 2005 Annu Rev Genomics Hum Genet 6:165). High mutation rates, especially in the hypervariable sequences, may be an obstacle to definite conclusions regarding the populations’ origin. A further difficulty is that mtDNA sheds light only on maternal lineages. Another complication is the transfer of genes and gene fragments between organelles where their rate of mutation adjusts to that of the recipient organelle.

In plants, recombination repeats occur that may generate additional variation by interchanges. In somatic cell hybrids of plants, the mitochondria may recombine and non-parental sequences and duplications of genes may be generated. The pseudogenic sequences are also attributed to recombination. In maize, extensive intramolecular recombination occurs between/among the main mtDNA molecule or the subgenomic, smaller mtDNAs (Fauron C et al 1995 Trends Genet 11:228). These recombinational events may lead to variegation and other morphological alterations (Sakamoto W et al 1996 Plant Cell 8:1377). Early studies indicated an apparent lack of genetic repair systems in the mitochondria. Recent studies detected, however, several proteins (glycosylases, excinucleases, mismatch repair enzymes, Rec A like proteins, etc.) that may mediate genetic repair in the mitochondria. The *CHM* locus of *Arabidopsis* apparently encodes a mismatch repair protein, similar to the prokaryotic MutS. The protein is mitochondrially located and its mutations lead to variegation (Abdelnoor RV et al 2003 Proc Natl Acad Sci USA 100:5968). ▶physical mapping, ▶mapping function, ▶petite colony mutants, ▶deletion mapping, ▶rounds of matings, ▶interference, ▶mutations in cellular organelles, ▶homoplasmy, ▶sorting out, ▶biolistic transformation, ▶transformation of organelles, ▶chloroplast, ▶genetics, ▶mitochondria, ▶doubly uniparental inheritance, ▶transmitochondrial, ▶dynamin, ▶paternal leakage, ▶mtDNA, ▶mitochondrial import, ▶introns, ▶maturase, ▶mitochondrial plasmids, ▶mitochondrial diseases in humans, ▶killer plasmids, ▶senescence, ▶MSS, ▶mismatch repair, ▶Parkinson disease, ▶Alzheimer disease, ▶ischemic, ▶NF- κ B, ▶AP, ▶GLUT, ▶ROS, ▶mitochondrial plasmids, ▶mt, ▶bottleneck effects, ▶heteroplasmy, ▶mitochondrial recombination, ▶Romanovs, ▶sorting out, ▶RNA editing,

►endosymbiont theory, ►RU maize, ►conplastic, ►mitochondrial mutation, ►mitochondrial suppressor, ►recombination repeat, ►DNA repair, ►binomial probability, ►mitochondrial gene therapy, ►replicative segregation, ►spindle pole body, for an abbreviated human mtDNA map see ►mitochondrial diseases in humans, ►atresia, ►mutation spontaneous, ►Eve foremother, ►forensic genetics, ►out-of-Africa; Mutation Res 1999 Vol 434 issue 3; Elson JL et al 2001 Am J Hum Genet 68:145; Tully LA, Levin BC 2000 Biotechnol Genet Eng Rev 17:147; Pakendorf B, Stoneking M 2005 Annu Rev Genomics Hum Genet 6:165; division and fusion: Hoppins S et al 2007 Annu Rev Biochem 76: 751; <http://megasun.bch.umontreal.ca/ogmp/projects/projects.html>; <http://bighost.area.ba.cnr.it/mitochondriome>; human mitochondrial genome: <http://www.genpat.uu.se/mtDB/>.

Mitochondrial Heterosis: It was claimed that the presence of different mitochondria might lead to complementation and increased vigor. ►hybrid vigor, ►mitochondrial complementation; Sarkissian IV, Srivastava HK 1973 Basic Life Sci 2:53.

Mitochondrial Import: Transport into the mitochondria must pass through two cooperating membrane layers. The outer membrane carries four receptors (Tom37, -70, -20, and -22). The transmembrane import channel is built of at least six proteins; the transmembrane translocation system uses at least three proteins (Tom40, -6 -7). The Tom5 forms the link (a relay) between the outer and inner channel proteins. The inner membrane import channel proteins (Tim) are Mas6p (MIM23), Sms1p (MIM17), and Mpi1p (MIM44/ISP45). The mitochondrial heatshock 70 protein (Hsp70), the MIM44 complex, and ATP play a central role in import. It appears that MIM44 first binds the incoming unfolded polypeptide chain as it is passing the entry site, and it is then transferred to Hsp70 as ATP dissociates the complex. After this the polypeptide moves further and binds again to the complex and eventually traverses also the inner membrane. Tim10p and Tim12p mediate the import of the multispanning carriers into the inner membrane. Tim12 is bound to Tim22. Tim23 passes proteins through the inner membrane. Although the mitochondria contain their own protein-synthetic machinery (ribosomes, tRNAs), the majority of the mitochondrial proteins are encoded by the nucleus and translated in, or imported from, the cytosol. Imported cytosolic tRNAs may correct mutations of mitochondrial tRNAs. The import system is also nuclearly encoded. The general import factors include the Hsp proteins, cyclophilin 20, ADP/ATP carrier (AAC), and proteases. More specialized is the

role of the imported assembly facilitator proteins. Yeast genes *SCO1*, *PET 117*, *PET191*, *PET100*, *OXA1*, *COX14*, *COX11*, and *COX10* are such facilitators. The latter two are actually involved in heme biosynthesis. The COX10 product farnesylates protoheme b. Rescue of cells with defective mitochondria by transfer of normal mitochondria from adult stem cells or somatic cells has been reported without clarification of the mechanism involved (Spees JL et al 2006 Proc Natl Acad Sci USA 103:1283). ►mitochondria, ►mitochondrial genetics, ►mtDNA, ►chloroplast import, ►cyclophilin, ►heat-shock proteins, ►Hsp70, ►Ydj, ►Hsp, ►MSF, ►farnesyl, ►heme, ►Brownian ratchet, ►mitochondrial gene therapy; Annu Rev Biochem 66:863; Bauer MF et al 2000 Trends Cell Biol 10:25; Schneider A, Maréchal-Drouard L 2000 Trends Cell Biol 10:509; Wiedemann N et al 2001 EMBO J 20:951; Rehling P et al 2001 Crit Rev Biochem Mol Biol 36(3):291; Kovermann P et al 2002 Mol Cell 9:363; Pfanner N, Wiedemann N 2002 Current Opin Cell Biol 14:400; Neupert W, Brunner M 2002 Nature Rev Mol Cell Biol 3:555; Wiedemann N et al 2003 Nature [Lond] 424:565; Chacinska A et al 2005 Cell 120:817; Wilcox AJ et al 2005 Proc Natl Acad Sci USA 102:15435; protein import review: Dolezal P et al 2006 Science 313:314; Ryan MT, Hoogenraad NJ 2007 Annu Rev Biochem 76:701; ADP/ATP carriers: Nury H et al 2006 Annu Rev Biochem 75:713.

Mitochondrial Mapping: ►mitochondrial genetics

Mitochondrial Mutations: Mitochondrial mutations occur about ten times or more frequently than in the nuclear genes (Marcelino LA, Thilly WG 1999 Mutation Res 434:177). This may be due to inadequate DNA repair. The mtDNA is “naked” (free of histones) and there is relative abundance of free oxygen radicals in this organelle. Large deletions are common in the human mitochondrial DNA encompassing the “5-kb deletion” (mtDNA⁴⁹⁷⁷) between nucleotide positions 8470–8482 and 13447–13459, respectively. Some deletions may encompass even longer segments of the mtDNA and cover the position of more than a single mitochondrial gene. These deletions are most common in muscle tissues and the brain and frequently occur by aging. The average mutation rate in the elderly appeared to be 2×10^{-4} /bp in mtDNA (Lin MT et al 2002 Hum Mol Genet 11:133). Other deletions usually occur between direct repeats of 13 to 5 nucleotides. Some of the deletions may involve only single bases. Single base mutations Thymidine 7512Cytosine and Guanine 7497Adenine in the tRNA^{Ser(UCN)} reduced the amount of this tRNA below 10% and reduced protein synthesis by 45%.

Aminoacylation was not affected so it is supposed that a posttranslational structural alteration might be involved in the pathogenic condition (Möllers M et al 2005 *Nucleic Acids Res* 33:5647). The deletion mutants and their relative extent are characterized by various PCR procedures. The data on increased frequency of point mutations during aging are somewhat ambiguous. Apparently deletions and duplications, however, accumulate by aging. Sometimes it may be difficult to ascertain whether a particular mutation occurs in the nuclear or mitochondrial DNA. In cases of ambiguity, the problem may be resolved by transferring a new nucleus (karyoplast) into an enucleated cytoplasm (cytoplast). If the expression of the mutation is limited to the donated cytoplast, the mitochondrial origin of the mutation can be proved in animal cells. In plant cells, the plastids may complicate the identification. In cancer cells, the mtDNA mutations occurred 19 to 229 times as abundantly as in the nuclear p53 gene. Interestingly, the cancer cells were largely homoplasmic for the mtDNA mutations indicating that the mutation had selective advantage. With the techniques available, the complete sequence of the mtDNA can be determined in single cells. Deficiency for uracil-DNA glycosylase in yeast results in mitochondrial mutator phenotype. Although fidelity of DNA polymerase γ , responsible for the replication of mtDNA, is not poor ($<10^{-5}$ /base substitution) and the enzyme has 3' exonuclease function to correct defects, the relative mutation rate is elevated. One possible cause of the increased mutation frequency is the disproportionally increased deoxyguanidine nucleotide pool in the mitochondria of rats (Song S et al 2005 *Proc Natl Acad Sci USA* 102:4990). The Twinkle helicase and the accessory B subunit of DNA polymerase are absolutely essential for mtDNA replication pol γ . The duplex DNA binding activity of the B subunit is needed for coordination of POL γ holoenzyme and Twinkle helicase at the mtDNA replication fork. Mutations in Twinkle and the catalytic A and accessory B subunits of the POL γ holoenzyme may result in autosomal dominant progressive external ophthalmoplegia, which is associated with deletions in mtDNA (Farge G et al 2007 *Nucleic Acids Res* 35:902). ▶oxidative DNA damage, ▶oxygen effect, ▶aging, ▶mutation rate, ▶mitochondrial diseases in humans, ▶petite colony mutants, ▶PCR, ▶somatic cell hybrids, ▶homoplasmic, ▶p53; Inoue K et al 2000 *Nature Genet* 26:176; Taylor RW et al 2001 *Nucleic Acids Res* 29 (15):e74; Jacobs HT 2001 *Trends Genet* 17:653; Chatterjee A, Singh KK 2001 *Nucleic Acids Res* 29:4935; Taylor RW, Turnbull DM 2005 *Nature Rev Genet* 6:389; <http://www.mitomap.org>.

Mitochondrial Myopathy: ▶mitochondrial disease in human

Mitochondrial Plasmids: Plasmids are circular or linear and occur in the mitochondria of some cytoplasmically male sterile lines of maize plants and relatives. Their sizes vary between 1.4 to 7.4 kb. The main types are S, R, and D. S2, R2, and D2 are the same and R1 and D1 are apparently also identical with each other. S1 appears to have emerged as a recombinant between R1 and R2. The *cms*-S plants carry the S1 and S2 plasmids. During the formation of S1, a terminal part of R1 (R*) was lost and is inserted at two sites in the mtDNA. The S elements can be either integrated or free mitochondrial episomes. The S2 element encodes (*URF1*), a protein somewhat homologous to a viral RNA polymerase, whereas another (*URF3*) appears to be homologous to a DNA polymerase. The *cms*-C and *cms*-T nucleoids are free from these plasmids, whereas in the N-nucleoids the R1 and R2 sequences (from RU) are integrated. Another 2.3-kb plasmid (or a 2.15-kb derivative) is homologous to the tRNA^{Trp} and tRNA^{Pro} in the cpDNA, and also represents the only functional tRNA^{Trp} in the mitochondrion. ▶cytoplasmic male sterility, ▶mitochondrial genetics, ▶cpDNA, ▶mitochondria, ▶tRNA, ▶killer plasmids, ▶senescence, ▶episome, ▶cytoplasmic male sterility, ▶*Neurospora* mitochondrial plasmids, ▶endosymbiont theory, ▶RU maize; Bok JW, Griffith A 2000 *Plasmid* 43:176.

Mitochondrial Proteins: Most of the mitochondrial proteins are imported from the cytosol, but the ~17 kbp mammalian mitochondrial DNA transcribes 13 polypeptides, which are then translated by the organelle. The ~337 kbp *Arabidopsis* mtDNA encodes 32 proteins. In plants, many mitochondrial genes display multiple promoters (Tracy RL, Stern DB 1995 *Current Genet* 28:205; Kühn K et al 2005 *Nucleic Acids Res* 33:337) although two nuclear genes encode the transcriptase. The total number of proteins located in mitochondria may be about 1,500. The human heart mitochondria include more than 600 distinct proteins (Taylor SW et al 2003 *Nature Biotechnol* 21:281). The proteome of the yeast mitochondria includes >750 proteins (Sickmann A et al 2003 *Proc Natl Acad Sci USA* 100:13207). ▶mitochondrial diseases, ▶mitochondrial import; Kenmochi N et al 2001 *Genomics* 77:65; Taylor SW et al 2003 *Trends Biotechnol* 21:82; mitochondrial import of proteins: Neupert W, Hermann JM 2007 *Annu Rev Biochem* 76:723; human, yeast, mouse mitochondrial proteome: <http://www.mitop.de/>.

Mitochondrial Recombination: Mitochondrial recombination is generally inferred from observations of linkage disequilibrium. However, the problem is somewhat controversial. Paternal leakage is rare and reduces the chance for recombination. Furthermore,

the paternal mitochondria may be eliminated after fertilization even if they are transmitted. In different human tissue samples from the A8344G/A16182C (MERRF syndrome) and A3243G/G16428A (MELAS syndrome) double-heteroplasmic family, all four allelic combinations of the two heteroplasmic mutations were present in the family, although, as expected, the distribution showed significant differences between individuals. Two family members carried the double-mutant (and possibly recombinant) allelic combination; and high amounts of the possibly recombinant genotype, along with all other possible allelic combinations, were present in the fibroblast sample from one individual. The data indicate that recombinant mtDNA molecules can be inherited (Zsurka G et al 2007 *Am J Hum Genet* 80:298). ▶mitochondrial genetics, ▶paternal leakage, ▶mitochondrial diseases in humans; Wiuf C 2001 *Genetics* 159:749; Innan H, Nordborg M 2002 *Mol Biol Evol* 19:1122.

Mitochondrial Suppressor: Enzyme complexes involved in oxidative phosphorylation are encoded by cooperation among nuclear (*PET*) and mitochondrial genes (*oli/ATP9*). Mutation in, e.g., in *AEP2* nuclear gene regulating *oli1* mRNA stability may prevent the formation of a functional subunit 9 of ATP synthase. Mutation in the 5'-untranslated region of *oli1* may however suppress the mutation in *aep2*. ▶mitochondrial genetics; Chiang CS, Liaw GJ 2000 *Nucleic Acids Res* 28:1542; Alfonzo JD et al 1999 *EMBO J* 18:7056; Bennoun P, Delosme M 1999 *Mol Gen Genet* 262:85; Chen W et al 1999 *Genetics* 151:1315.

Mitochondrion: The singular form of mitochondria. ▶mitochondria

Mitochondriopathies: ▶mitochondrial diseases in humans

Mitogen: Collective name of substances stimulating mitosis and thus cell proliferation (such as growth factors).

Mitogen-Activated Protein Kinases: ▶MAPK

Mitogenesis: Processes leading to cell proliferation.

Mitokinesis: A hypothetical mechanism of orderly distribution of mitochondria between two cells during cell division possibly using the cytoskeleton as a vehicle.

Mitomap: (human mitochondrial genome database): <http://www.mitomap.org>.

Mito-Mice: Mice models of mitochondrial diseases. They display deletions in their mitochondrial DNA. (See Sato A et al 2005 *Proc Natl Acad Sci USA* 102:16765).

Mitomycin C ($C_{15}H_{18}N_4O_5$): Antibiotic, antineoplastic agent that after activation causes DNA crosslinks, enhances mitotic recombination, inhibits DNA synthesis, etc.

MitoNuc: A database of nuclear-encoded mitochondrial proteins. ▶mitochondrial genetics; <http://bighost.area.ba.cnr.it/mitochondriome>

MitoPark: Conditional knockout mice with Parkinsonism caused by mitochondrial malfunction due to dopamine neuron deficiency. ▶knockout, ▶Parkinson disease, ▶dopamine

Mitosenes: DNA cross-linking compounds (such as mitomycin), frequently with antitumor activity. ▶mitomycin

Mitosis: Nuclear division leading to identical sets of chromosomes in the daughter cells. Mitosis assures the genetic continuity of the ancestral cells in the daughter cells of the body. It involves one fully equational division preceded by a DNA synthetic phase. There is normally no (synapsis) pairing of the chromosomes. The centromeres split at metaphase separate at anaphase and the chromosomes relax after moving to the poles in telophase. The centromere-spindle association is regulated by a number of kinases (Mad1, Bub1, Msp1). Msp1 is essential for meiosis II but dispensable for mitosis. Before anaphase takes place, a number of proteins (Pds1, Scc1, Ase1) regulating sister chromatid cohesion are degraded by proteasomes under the control of the cyclosome (APC). The critical features of mitosis are diagrammed and comparable photomicrographs are also shown. Mitosis is thus, different from meiosis, in which there is one reductional and one numerically equational division. During meiotic prophase, the homologous chromosomes (bivalents) are synapsed and chiasmata may be observed. At the first meiotic division the centromeres do not split, and the undivided centromeres separate at anaphase I. Meiosis reduces the chromosome number to half, in contrast to mitosis, which preserves the number of chromosomes in the daughter cells. A comparison between mitosis and meiosis is also diagrammed. Mitosis and meiosis are the genetically most important processes of the eukaryotic cells (organisms).

Mitosis maintains genetic continuity in the development of an organism from conception to the end of its life. Somatic mutation may bring about changes in the exact continuity but this usually affects only a small fraction of the genes. The subsequent mitotic divisions provide the precise mechanism for the maintenance of such mutations. The mitotic and the meiotic cell cycles show some differences in the molecular mechanisms. In mitosis before the S phase, the two key cyclins, Clb5 and Clb6, are kept inactive

by the *cyclin-dependent kinase inhibitor protein* Sic1. Two cyclins (Cln1 and 2) along with Cdc28/Cdc2 degrade Sic. In case Clb5 and Clb6 are non-functional, the initiation of the S phase is delayed until cyclins CLB1–4 are activated at a subsequent stage. In meiosis, Cdc28/Cdc2 is not required and its role is taken over by a similar protein, SPF (S phase promoting factor) encoded by the yeast gene *IME2*. Note that only a single S phase is required for meiosis I, and meiosis II does not require the synthesis of new DNA because it involves only the segregation of the sister chromatids after reduction. The pre-replication complex in yeasts includes Cdc18/CDC6 and the minichromosome maintenance proteins (MCM). For meiosis in fission yeast, these proteins are apparently not mandated. Also the vegetative replication checkpoint genes are not active when there are problems

during the S-phase events. Cdc2 kinase and Cdc10 transcription factor and Cdc22 functions were also needed for meiosis. Mutation in DNA polymerases α and ϵ and ligase (Cdc17) functions delayed meiotic S phase. Mutation in DNA polymerase- δ (Cdc6) and in GEF (Cdc24), similarly to mitosis, reduced the number of divisions completed. ▶meiosis, ▶cell cycle, ▶nucleolus, ▶nucleolar organizer, ▶nucleolar reorganization, ▶CENP, ▶cyclosome, ▶proteosome, ▶condensin, ▶sister chromatid cohesion, ▶mitotic exit, ▶lamins, ▶Cdc18, ▶CDC6, ▶MCM, ▶cdc10, ▶cdc22, ▶Cdc2, ▶APC, ▶spindle fibers, ▶centromere, ▶kinetochore, ▶centrosome, ▶sister chromatid cohesion, ▶separin, ▶interphase, ▶CDC13, see Figs. M89 and M90; Forsburg SL, Hodson JA 2000 Nature Genet 25:263; Tóth A et al 2000 Cell 103:1155; Nasmyth K 2001 Annu Rev Genet 35:673; Georgi AB

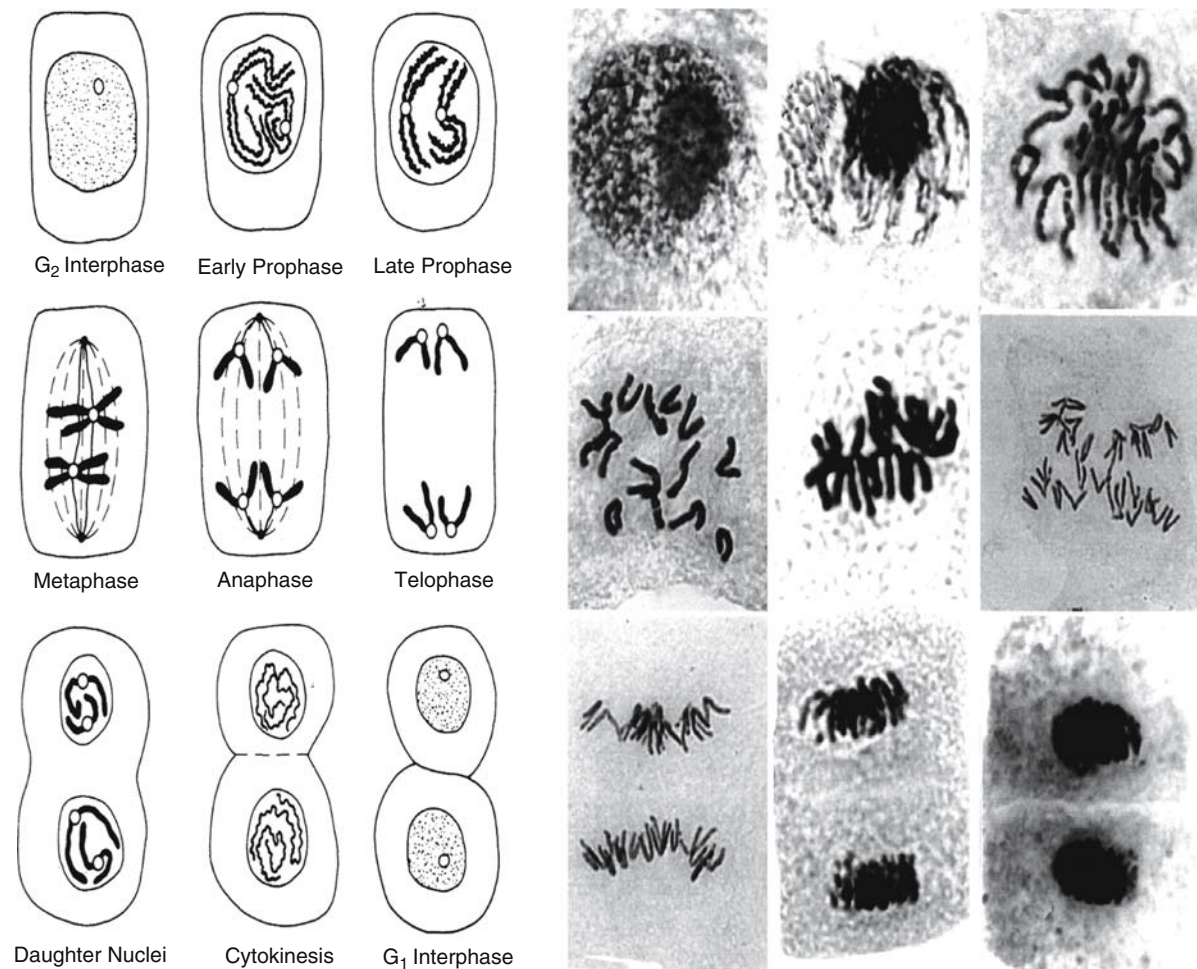


Figure M89. Mitosis. Left: The major steps of mitosis diagramed by only two chromosomes. Right: Photomicrographs of mitosis in barley $2n = 14$ (Courtesy of T. Tsuchiya). Top Right to Left: Interphase, early prophase, late prophase, middle; early metaphase, metaphase, early anaphase, Bottom: Early telophase, late telophase, two daughter nuclei in the two progeny cells

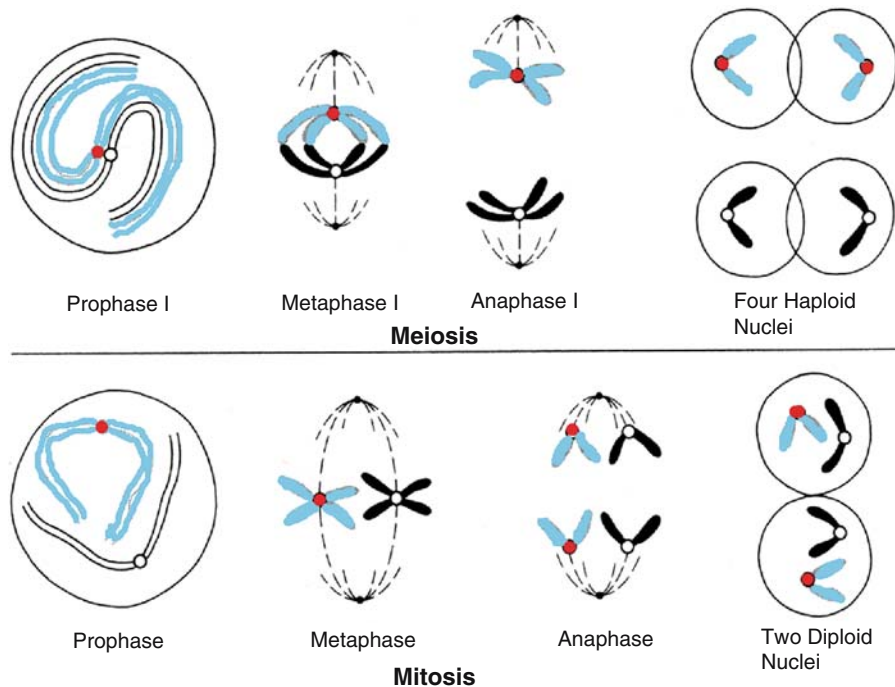


Figure M90. Meiosis and mitosis compared by cytological behavior. Meiosis: One numerical reduction & one numerically equational division synapsis & chiasma at prophase, centromeres do not split at metaphase and separate undivided at anaphase i chromosome number reduced. Mitosis: One fully equational division, no pairing & no chiasma, centromeres split in metaphase and separate at anaphase, chromosome number maintained in daughter cells

M

et al 2002 Curr Biol 12:105; Rieder CL, Kodjakov A 2003 Science 300:91; review of segregation of chromosomes by microtubules: Kline-Smith SL et al 2005 Current Opin Cell Biol 17:35.

Mitosome: A substantially reduced form of the mitochondrion. Mitosomes do not generate ATP but assemble iron-sulfur clusters, which are required for making ATP. Apparently, these organelles lost some of the mitochondrial functions during evolution (Tovar J et al 2003 Nature [Lond] 426:172), yet mitosomes seem to have some of the basic mitochondrial functions such as protein targeting (Dolezal P et al 2005 Proc Natl Acad Sci USA 102:10924). ▶mitochondria, ▶hydrogenosome, ▶protein targeting, ▶Giardia, ▶Trichomonas

Mitospore: Meiotic product of fungi ready for mitotic divisions.

Mitostatic: Stopping or blocking the mitotic process. Many anti-cancer agents are mito-static.

Mitotic Apparatus: Subcellular organelles involved in nuclear divisions. Mitotic apparatus include organelles such as the spindle (microtubules), centromere (kinetochore), centriole, poles, and CENP. In yeast cells, the mitotic apparatus is within the nucleus,

whereas in plants and animals the system is cytoplasmic and the nuclear membrane disappears, while the chromosomes are distributed to the poles and the membrane is reformed after completion of the process. In some organisms, the nuclear membrane does not disintegrate entirely during mitosis. ▶nuclear membrane

Mitotic Catastrophe: Mitotic catastrophe is caused by DNA damage resulting in chromosomal abnormalities, polyploidy, and formation of micronuclei. CDH1 and the slow breakdown of cyclin B1 interfere with the metaphase promoting complex. ▶CDH1, ▶cyclin B1, ▶micronucleus; Huang X et al 2005 Proc Natl Acad Sci USA 102:1065.

Mitotic Center: ▶centrosome

Mitotic Chromosomes: Chromosomes undergoing mitosis.

Mitotic Crossing Over: Recombination in somatic cells. Recombination is generally a meiotic event (▶crossing over) but in some organisms, the chromosomes may associate also during mitosis and this may be followed by genetic exchange of the linked markers. Although this may take place spontaneously, several agents capable of chromosome breakage (radiation,

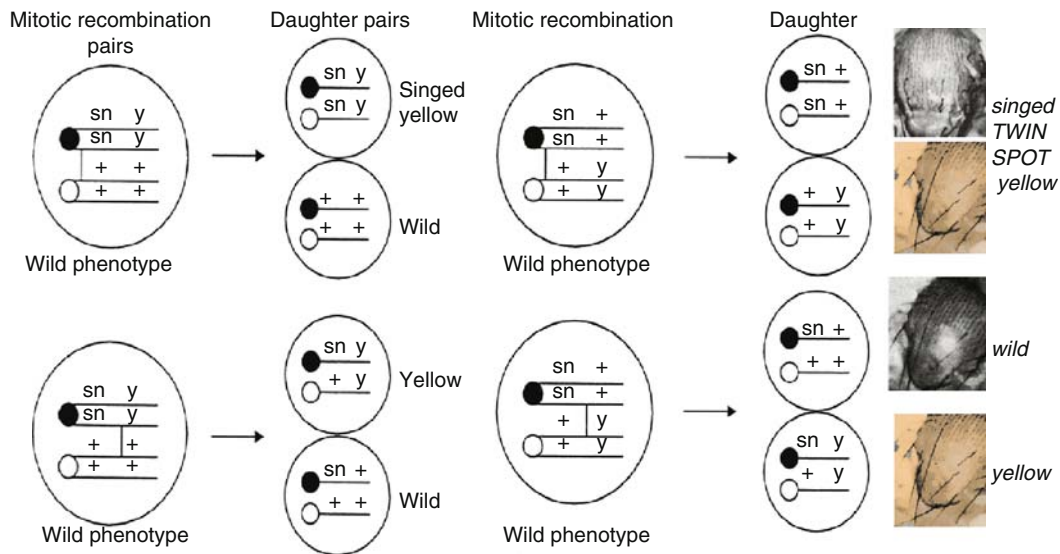


Figure M91. Mitotic crossing over (at sign I) with markers in coupling and repulsion and the consequences of recombination. (On the basis of experiments of Curt Stern, 1936. *Genetics* 21:625.)

chemicals) may enhance its frequency. For the detection of somatic recombination in higher eukaryotes, the markers must be cell and tissue autonomous, i.e., they should form sectors (spots) at the locations where such an event has taken place. In the first experiments with *Drosophila*, the chromosomal construct diagrammed here, was used. If an exchange has taken place between *sn* and *y*, then only a yellow sector (homozygous for *y*) was formed. *Twin spots* were observed only when in repulsion, the exchange took place between the proximal locus and the centromere (see Fig. M91).

Somatic recombination takes place in the *Drosophila* male too, although this usually does not happen in meiosis. The characteristics of somatic recombination are that exchange is between two chromatids at the four-strand stage, but instead of reductional division, as in meiosis, the centromeres are distributed equationally. Mitotic recombination is a relatively rare event in higher eukaryotes. Somatic recombination can be studied also in plants when the chromosomes are appropriately marked, and generative progeny can be isolated from the sectors, either from the sectorial branches or by tissue culture techniques. In fungi (lower eukaryotes), in which a longer diploid phase exists (*Aspergillus*), mitotic recombination can be used even for chromosomal mapping, because some of the parental and crossover products can selectively be isolated. The meiotic and mitotic maps are collinear, but the relative recombination frequencies in the different intervals vary.

Homologous mitotic recombination in mouse can easily be detected in a transgenic construct. Similar techniques are available also for plants. Two copies,

of a differently truncated vector cassette, containing the enhanced yellow fluorescent protein (EYFP), are introduced into the animal cells. The fluorescence is expressed only when the recombination, gene conversion, or repair of collapsed replication fork takes place within the coding sequence, shown in the diagram. Spontaneous recombination in primary fibroblasts from adult ear tissue occurred at 1.3 ± 0.1 per 10^6 per cell division. In embryonic fibroblasts, or if Mitomycin C was used, the rate was found to increase by an order of magnitude.

Homology of the chromosome is required in both meiotic and mitotic recombination (Shao C et al 2001 *Nature Genet* 28:169). A single nucleotide difference may reduce recombination frequency to a detectable extent. Larger sequence differences may reduce recombination by two-three orders of magnitude or eliminate it completely.

Some researchers assume that the mechanisms of the meiotic and mitotic recombination are the same. Several facts, however, cast some doubt about this view. Many proteins are involved in both meiotic and mitotic recombination. In yeast, e.g., both Rad51 and Dmcl are required for meiotic recombination, but Dmcl is not specific for the mitotic event (Shinohara M et al 2003 *Genetics* 164:855). In general, caution must be taken in interpreting genetic phenomena in somatic cells, unless classical progeny tests or molecular information can confirm the assumptions. (See Figs. M92 and M93, ►mitotic mapping, ►parasexual mechanisms, ►mitotic recombination as a bioassay in genetic toxicology, ►twin spot, ►recombination, ►GUS; Pontecorvo G 1958 *Trends*

in Genetic Analysis. Columbia University Press, New York; McKim KS et al 2002 Annu Rev Genet 36:205.

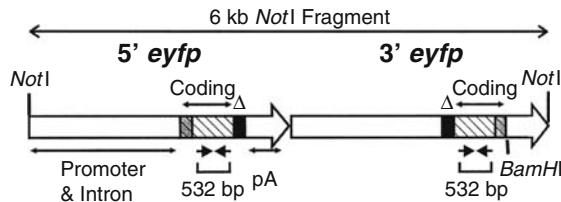


Figure M92. The tandem arrangements of the two deletion (Δ) constructs are represented by the arrows. The coding sequences are hatched. The chicken β-actin promoter and a cytomegalovirus enhancer drive the expression. NotI, BamHI are restriction enzymes, pA is polyadenylation signal. (By permission from CA Hendricks, KA Almeida, MS Stitt, VS Jonnalagedda, RE Rugo, GF Kerrison & BP Engeward 2003 Proc Natl Acad Sci USA 100:6325. Copyright 2003 National Academy of Sciences USA)

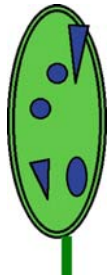


Figure M93. Plants heterozygous for transgenic constructs of the *uidA* (β-glucuronidase, GUS) alleles, which have not-overlapping defects upon spontaneous or induced (by DNA-damaging agents) recombination within the locus produce cells with restored enzyme function. By providing the appropriate substrates, the staining of the spots reveal the recombinational event at a frequency of 10^{-6} to 10^{-7} per cell. The size and shape of the spots or sectors are determined by the pattern of differentiation of the tissue. The recombination can be further verified by polymerase chain reaction at the site as well as by the presence of molecular markers flanking the gene. Schemating drawing based on the report by Swoboda P et al 1994 EMBO J 13:484)

Mitotic Drive: Stepwise expansion of trinucleotide repeats. ▶[trinucleotide repeats](#), ▶[anticipation](#), ▶[meiotic drive](#); Khajavi M et al 2001 Hum Mol Genet 10:855.

Mitotic Exit: In a mitotic exit, after metaphase the mitotic spindle moves the chromosomes during anaphase to the poles of the cell and eventually two daughter cells are formed. PDS and Clb5 protein components of the anaphase inhibitory complex inhibit the formation of the spindle apparatus. Both PDS and Clb5 need to be degraded by the activation of Cdc20 to prepare the path for exit from mitosis. PDS degradation activates the Cdc14 phosphatase. Clb5 kinase degradation facilitates the dephosphorylation of Sic1, Cdh1, and various cyclin kinases by Cdc14, and thus permits the transition from anaphase into G1 interphase. ▶[FEAR](#), ▶[PDS](#), ▶[Clb5](#), ▶[Cdc20](#), ▶[Cdc14](#), ▶[MEN](#), ▶[Sic1](#), ▶[Cdh1](#), ▶[mitosis](#); Bardin AJ, Amon A 2001 Nature Rev Mol Cell Biol 2:815; role of CDC14: Stegmeier F, Amon A 2004 Annu Rev Genet 38:203.

Mitotic Index: The fraction of cells involved in the process of mitosis at a particular time.

Mitotic Mapping: Genetic recombination during mitosis is generally a very rare event in the majority of organisms. In some diploid fungi, its frequency may reach 1 to 10% that of meiosis. As a consequence of ionizing irradiation and certain chemicals the frequency of mitotic exchange may increase and on the basis of mitotic recombination genetic maps can be constructed (see Fig. M94). Although the order of genes is the same in mitotic and meiotic maps, the recombination frequencies may be quite different. ▶[mitotic crossing over](#), ▶[parasexual mechanisms](#), ▶[mitotic recombination as a bioassay in genetic toxicology](#)

Mitotic Non-conformity: Genetic change in fungi due to chromosome translocations.

Mitotic Recombination: ▶[mitotic crossing over](#), ▶[mitotic mapping](#)

Mitotic Recombination as a Bioassay in Genetic Toxicology: Mitotic recombination has been used in



Figure M94. Comparison of a segment of the meiotic and mitotic maps of the fungus *Aspergillus nidulans* at identical scales. (Redrawn after Pritchard, RH 1963. Methodology in Basic Genetics, Burdette, WJ, ed., p. 228. Holden-Day, San Francisco.)

Saccharomyces cerevisiae yeast. In a diploid strain (D5) heterozygous for *ade2-40* and *ade2-119* alleles, twin spots are visually detectable in case of mitotic crossing over. Homozygosity for *ade2-40* has an absolute requirement for adenine and involves formation of red color; it is often called red adenine mutation. Homozygosity for *ade2-119*, a leaky mutation, results in pink coloration. Since the two genes are complementary, the heterozygous cells do not require adenine and the colonies are white. Any environmental or chemical factor that promotes mitotic recombination is thus detectable. This procedure has not been extensively used in genetic toxicology programs. ▶mitotic crossing over, ▶bioassays in genetic toxicology

Mitotic Spindle: ▶spindle, ▶spindle fibers

Mitoxantrone ($C_{12}H_{28}N_4O_6$): Antineoplastic drug with the ability to break DNA double strands.

Mitral Cells: Mitral cells can make junctions in a beveled fashion.

Mitral Prolapse: A buckling of the heart atrial leaflets as the heart contracts, resulting in backward flow (regurgitation) of the blood. It is caused by an autosomal (11p15.4) dominant allele and it is a common congenital heart anomaly affecting 4–8% of young adults, particularly females. It may accompany various other syndromes such as ▶Marfan syndrome, ▶Klinefelter syndrome, ▶osteogenesis imperfecta, ▶Ehlers-Danlos syndrome, ▶fragile X syndrome, and ▶muscular dystrophies. ▶Non-syndromic mitral valve prolapse has been mapped to 16p11.2-p12.1 and a similar disease is caused by mutation at Xq28. In an autosomal recessive form, ophtalmoplegia (paralysis of the eye muscles) is also involved. (See ▶heart disease and the other conditions named at separate entries, Towbin JA 1999 *Amer J Hum Genet* 65:1238; Freed LA et al 2003 *Am J Hum Genet* 72:1551).

Mixed Backbone Oligonucleotide (MBO): MBO is composed of a phosphorothionate backbone and 2'-O-methyloligoribonucleotides or methylphosphonate oligodeoxyribonucleotides. Such an antisense construct is resistant to nucleases and forms stable duplexes with RNA. ▶antisense technologies

Mixed Lymphocyte Reaction (MLR): MLR is used for the detection of histoincompatibility in vitro. The principle of the test is that lymphocytes of two individuals are mixed. One (donor) serves as *responder* and the other as *stimulator*. The proliferation of the antigen-presenting cells is blocked by irradiation or by mitomycin C. The CD4 T cells proliferate as they recognize foreign MHC II molecules, and the measure of their proliferation is assessed by the incorporation of

H^3 -thymidine. The cytotoxic CD8 T cells recognize differences primarily in MHC I molecules and the extent of the killing reaction is detected by using Cr^{51} (sodium dichromate)-labeled cells. In seven days, the reaction may detect histoincompatibility between two persons. ▶MHC, ▶lymphocytes, ▶HLA, ▶microcytotoxicity test

Mixed-Function Oxidases: Generally, flavoenzymes that oxidize NADH and NADPH, and in the process, may activate promutagens and procarcinogens. ▶promutagen, ▶procarcinogen, ▶P-450, ▶microsomes, ▶monooxygenases

Mixoploid: In a mixoploid, the chromosome numbers in the different cells of the same organism vary. (Bielanska M et al 2002 *Fertility & Sterility* 78:1248).

Miyoshi Myopathy (MM, 2p13.3-p13.1): ▶dysferlin

MKDOM: A protein domain analysis program (Gouzy J et al 1999 *Comput Chem* 23:333).

MKI: MAP kinase insertion factor. ▶MAPK

MKK: A homolog of MEK. ▶MEK

MKP-1: MKP-1 dephosphorylates Thr¹⁸³ and Tyr¹⁸⁵ residues, and thus regulates mitogen-activated MAP protein kinase involved in signal transduction. ▶MAP, ▶PAC

Mle (*maleless*): *mle* is located in *Drosophila* chromosome 2–55.2, *mle3* in *Drosophila* chromosome 3.25.8, and similar genes are also present in the X-chromosomes. The common characteristics are that homozygous females are viable but the homozygous males die. The underdeveloped imaginal discs of *mle3* may develop normally, if transplanted into wild type larvae. MLE protein appears to be an RNA helicase and its amino and carboxyl termini may bind double-stranded RNA. Ribonuclease releases MLE from the chromosomes without affecting MSL-1 and -2 and RNA. MLE and MSL proteins appear to control dosage compensation. ▶Msl, ▶dosage compensation

MLE (mariner-like element): A transposable element in *Drosophila* that is present also in the human genome where it is responsible for a recombinational hot spot in chromosome 17. ▶mariner, ▶Charcot-Marie-Tooth disease, ▶HNPP, ▶MITE

MLH (muscle enhancer factor, MLH2A): A MADS box protein inducing muscle cell development in cooperation with basic helix-loop-helix proteins. ▶MyoD, ▶MADS box, ▶bHLH

MLH2: ▶hereditary non-polyposis colorectal cancer

MLH3: A mismatch repair gene that occurs with frequent variation in hereditary nonpolyposis cancer.

►mismatch repair, ►hereditary non-polyposis colorectal cancer; Wu Y et al 2001 Nature Genet 29:137.

MLINK: A computer program for linkage analysis.

MLK (mixed lineage group kinases): Members of the MAP kinase family of phosphorylases mediating signal transduction. ►MAP kinase, ►signal transduction; Gallo KA, Johnson GL 2002 Nature Rev Mol Cell Biol 3:663.

MLL (mixed lineage leukemia, All-1, Htrx): The protein encoded in human chromosome 11q23 has four homology domains, the A-T hook region, DNA methyltransferase homology, Zinc fingers, and the *Drosophila trithorax* (*trx*, 3–54.2) homology. Overexpression of the MLL5 protein, encoded at 7q22, inhibits the cell cycle. In its vicinity at 7q36, MLL3 is situated. Loss of the long arm 7 leads to myeloid malignancies. Other MLL genes were located to chromosomes 12q12 and 19q13. ►leukemia, ►cancer stem cell, ►methyltransferase, ►SET, ►COMPASS; Deng L-W et al 2004 Proc Natl Acad Sci USA 101:757.

MLP1, MLP2: Proteins associated with the nuclear pore complex that suppress the export of unspliced mRNA (Galy V et al 2004 Cell 116:63). ►nuclear pores, ►PML39

MLS (maximum likelihood lod score, multipoint lod score): A method for the analysis of linkage (in human families). The MLS increases when the proportion of relatives carrying an allele identical by descent is higher than expected on the basis of the degree of relatedness and independent segregation. ►relatedness degree, ►maximum likelihood, ►lod score, ►maximum likelihood method applied to recombination

MLV: ►Moloney mouse leukemia virus

MLVA (multi-locus variable-length repeat analysis): Basically, the same as VNTR, used for the identification of related but different bacterial strains. ►VNTR

mm: Prefix for mouse (*Mus musculus*) protein or DNA, e.g., mmDNA.

MMP (microsatellite mutator phenotype): ►microsatellite mutator

MMP: Matrix metalloproteinase. ►metalloproteinases

MMR: ►mismatch repair

MMTV: Murine mammary tumor virus.

M-MuLV: Moloney murine leukemia virus.

MMTV: ►mouse mammary tumor virus (MTV)

MN Blood Group (MN): The human chromosomal location is 4q28-q31. α -sialoglycoprotein (glycophorin A) is responsible for the M blood type, while the δ peptide (glycophorin B) is responsible for the N type (see Fig. M95). Glycophorin deficient erythrocytes are resistant to *Plasmodium falciparum* (malaria). The En(a-) blood group variants also lack glycophorin A. The M and N alleles are closely linked to the S/s alleles and the complex is often mentioned as a MNS blood group. The frequencies of the allelic combinations in England were MS (0.247172), Ms (0.283131, NS (0.08028), and Ns (0.389489). ►blood groups

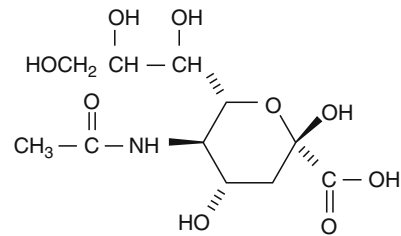


Figure M95. Sialic acid

MND2: An antagonist of the anaphase-promoting complex during meiotic prophase. ►anaphase-promoting complex; Penkner AM et al 2005 Cell 120:789.

MNEMONS: L. Cuénot's historical (early 1900s) term for genes.

MNGIE (mitochondrial neurogastrointestinal encephalopathy): An autosomal recessive disease involving myopathy with ragged-red fibers, reduced activity of the respiratory chain enzymes, etc. The basic defect is attributed to the deficiency of TK2 (a thymidine kinase), which phosphorylates normally also the deoxynucleosides of other pyrimidines. The reduction of the activity of the enzyme apparently affects the maintenance of mtDNA. The TK2 gene has been located to human chromosome 16q22 (earlier to chr. 17), and more recently MNGIE was assigned to 22q13.32-qter. ►mtDNA, ►mitochondrial diseases in humans

MNNG: *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine is a monofunctional alkylating agent and a very potent mutagen and carcinogen (see Fig. M96) (rapidly decomposing in light). It methylates the O⁶-position of guanine. Cell lines exist that are highly resistant to the cytotoxic effects of MNNG, but they are even more sensitive to the mutagenic effects. ►mutagens, ►alkylating agents

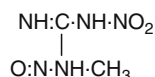


Figure M96. MethylNitrosoguanidine

MNU (*N*-methyl-*N*-nitrosourea): A monofunctional mutagen and carcinogen forming O⁶-methylguanine (see Fig. M97). ▶mutagens, ▶alkylating agents, ▶mono-functional

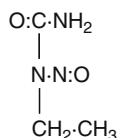


Figure M97. Ethylnitrosourea

MØ: ▶macrophage

MO15: A CDK-activating kinase, related to CAK. Association of MO15 with cyclin H greatly increases its kinase activity toward Cdk2. ▶cell cycle, ▶cyclin, ▶CDK, ▶CAK, ▶Cdk2

MoAb: ▶monoclonal antibody

mob: The *mob* bacterial gene facilitates the transfer of bacterial chromosome or plasmids into the recipient cell. In order to transfer the plasmids, there is a need for the cis-acting *nick* site and a *bom* site. At the former the plasmid is opened up (nicked) and the *bacterial origin of mobilization* (*bom*) makes possible the conjugative transfer. ▶Hfr, ▶conjugation

Mobile Genetic Elements: Mobile genetic elements occur in practically all organisms, represent different types of mechanisms, and serve diverse purposes. They share some common features. They are capable of integration and excision from the genome (like the temperate bacteriophages), or movement within the genome (like the insertion and transposable elements). These elements may fulfill general regulatory functions in normal cells (such as the switching of the mating type elements in yeast). Phase variation in *Salmonella*, antigenic variation as a defense system in bacteria (*Borrelia*) and protozoa (*Trypanosomas*), parasitizing plant genomes by agrobacteria, etc., may depend on such elements. They have a role in the generation of antibody diversity in vertebrates by transposition of immunoglobulin genes. They have played an important role in the evolution of the genomes (Kazazian HH Jr 2004 Science 303:1626). There is an apparent paucity of DNA transposon mobilization in mammals, and in amniotes in general in comparison with other organisms. (e.g., plants) This paucity may result from the relative difficulty in

horizontal transfer into animals' germ lines (Han K et al 2007 Science 316:238), although about 50% of the genome of simians consists of transposable elements. (See items under separate entries, ▶transposable elements, ▶SDR, ▶SINE, ▶LINE, ▶Alu, ▶organelle sequence transfers, ▶transposons, ▶retroposons, ▶retrotransposons, ▶pathogenicity islands; classification: <http://aclame.ulb.ac.be/>).

Mobility Shift Assay: When two molecules (DNA-protein, protein-protein) bind, upon electrophoretic separation the mobility is retarded. ▶gel retardation assay; Filee P et al 2001 Biotechniques 30:1944.

Mobilization: In mobilization, the binding of the ribosome to a mRNA initiates polysome formation. Mobilization also refers to the process of conjugative transfer; and to the release of a compound in the body for circulation.

Mobilization of Plasmids: The transfer of conjugative plasmids to another cell. ▶conjugation

Mobilome: Potentially mobile part of the genome, such as episomes, transposons, integrons, and genomic islands.

Möbius Syndrome: In this condition, congenital partial or full paralysis and dysfunction of a cranial nerve, face and limb malformations, and mental retardation also may occur. A dominant locus was found at 3q21-q22 and another dominant on the long arm of chromosome 10. Recessive and X-linked inheritance was also suspected.

Mod Score: A maximized lod score over recombination fractions (θ) and genetic models (φ). ▶lod score, ▶model genetic

Modal: Adjective of mode. ▶mode

Mode: The value of the variates (class of measurements) of a population that occurs at the highest frequency. ▶mean, ▶median

Model: A model represents the essential features of a concept with minimum detail. It assists in making predictions about an operation under different conditions and sheds light on the contribution of the components of the system. In the *procedural system* of modeling, the focus is on the steps from the data to the conclusion. An example: looking for binding sites of transcription factors in the promoter regions of genes to shed light on expression by searching for over-represented elements in the promoters of each gene cluster. Or we can test the genes with similar binding sites to determine whether they are co-expressed. In the *declarative approach*, the modeling extends to both binding sites in the promoter and to expression levels. In the next step, the validity of the

model is tested by the maximum likelihood estimation regarding its fit to the data available. The testing of the sequences may be evaluated by the hidden Markov chain procedure. ► [maximum likelihood](#), ► [hidden Markov chain model](#), ► [probabilistic graphical models of cellular networks](#), ► [small-world networks](#), ► [modeling](#); Friedman N 2004 *Science* 303:799.

Model, Genetic: In human genetic analysis, the genetic model is specified by the type of inheritance, e.g., dominant/recessive, autosomal/sex-linked, penetrance/expressivity, frequency of phenocopies, mutations, allelic frequencies, pattern of onset, etc.

Model, Molecular: Three-dimensional physical representation of molecules. (See molecular modeling for beginners: <http://www.usm.maine.edu/~rhodes/index.html>; <http://www.natsci.org/Science/Compchem/feature14b.html>).

Model Organisms: All organisms share basic molecular mechanisms. Relatively simple biological systems of common evolutionary descent facilitate rigorous experimental studies because of ease of manipulation, short lifecycle, small genomes, etc. “Model organisms” are frequently of no economic interest beyond making research efficient, fast and less demanding in labor and funds yet they make possible the understanding basic genetic and molecular mechanisms common in other biological systems. About 75% of the human disease genes have some counterparts in *Drosophila* and even particular genes of the plant *Arabidopsis* display about 40% similarity to a human disease gene, e.g., responsible for breast cancer. Such models are *E. coli* for prokaryotes, *Saccharomyces cerevisiae* for fungi and other eukaryotes, *Caenorhabditis elegans*, *Drosophila melanogaster*, zebrafish for lower animals and humans, mouse and rat for higher animals and humans, *Arabidopsis thaliana* for higher plants and can provide useful information for more complex systems. No single “model organism” is suitable for the study of all biological problems. Obviously dogs can be exploited better for the study of behavior than yeast. For the study of chromosomal mechanisms broad bean (*Vicia faba*) is better than *Arabidopsis*. The use of several types of research methods is immoral or otherwise objectionable in humans (e.g., controlled mating, testing of new drugs and mutagens, genetic engineering) and mouse models are indispensable and invaluable. Since DNA sequence and proteome information is becoming available generalizations on functions, development and evolution is much facilitated. Model organisms have provided useful means to study human disease, regulatory networks, development, behavior, comparative analysis of gene function and other basic and applied biological problems. The animal disease models

usually do not fully represent the human conditions. (See Reinke V, White KP 2002 *Annu Rev Genomics Hum Genet* 3:153, survey of recent genetic technologies: Nagy A et al 2003 *Nature Genet* 33 (Suppl): 276; Davis RH 2004 *Nature Rev Genet* 5:69; Neff MW, Rine J 2006 *Cell* 124:229; ► [Homophila](#); human disease *Drosophila* gene database: <http://superfly.ucsd.edu/homophila>; <http://www.nih.gov/science/models/>).

Model-Free Analysis: A term from human genetics indicating no need for a genetic model because the persons and ancestors have already been genotyped. ► [genotyping](#), ► [model genetic](#)

Modeling: Physical, mathematical, and/or hypothetical construction for the exploration of the reality or mechanism of theoretical concepts. In modeling a protein structure, it is assumed that the amino acid sequence specifies the three-dimensional structure. The normal structure represents most probably the global free-energy maxima. ► [simulation](#), ► [Monte Carlo method](#), ► [model](#); protein structure prediction: <http://predictioncenter.org>; protein modeling principles and tools: Schueler-Furman O et al 2005 *Science* 310:638; annotated mathematical models of biological systems: <http://www.ebi.ac.uk/biomodels/>.

Modem (modulator/demodulator): The modem either links the computer to another computer through a telephone line, e.g., fax modem (sends printed and graphic information), or a modem sends and retrieves information from a mainframe computer to other computer operators through information networks such as BITNET, INTERNET, and various online services.

Modification: Most commonly in molecular biology, methylation. ► [methylation of DNA](#), ► [methylase](#)

Modified Bases: Modified bases occur primarily in tRNA and are formed mainly by post-transcriptional alterations. More than 35 different modified nucleosides were known by the 1970s (Hall RH 1971 *The Modified Nucleosides in Nucleic Acids*. Columbia Univ. Press, New York), and over 100 became known later (<http://medlib.med.utah.edu/RNAmods/>). The most common modified nucleosides are ribothymidine, thiouridine, pseudouridine, isopentenyl adenosine, threonyl-carbamoyl adenosine, dihydrouridine, 7-methylguanidine, 3-methylcytidine, 5-methylcytidine, 6-methyladenosine, inosine, etc. These modified bases have important roles in the function of tRNA, e.g., 1-methyladenosine in the T ψ C loop at position 58 facilitates the translation from the tRNA_{1^{Met}} initiation codon of yeast. ► [transfer RNA](#), ► [ribosome](#), ► [initiation codon](#), ► [thiouracyl](#); Anderson J et al 2000 *Proc Natl Acad Sci USA* 97:5173; <http://genesilico.pl/modomics/index2.pt>; rRNA small subunit: <http://medlib.med.utah.edu/SSUmods/>.

Modifier Gene: A modifier gene affects the expression of another gene. ►epistasis; Nadeau J 2001 Nature Rev Genet 2:165; Burghes AHM et al 2001 Science 293:2213.

Modified Mendelian Ratios: These ratios are observed when the product(s) of genes interact. Such situations in case of two loci can be best represented by modified checkerboards using the zygotic rather than the gametic constitutions at the top and at the left side of the checkerboards.

At the top, a standard constitution is shown where for each locus the genotypes are $1AA, 2Aa, 1aa$, and $1BB, 2Bb, 1bb$, respectively, etc. Although in the boxes only the relative numbers of the phenotypes (genotypes) are shown (as a modification of the 9:3:3:1 Mendelian digenic ratio), their genetic constitution can be readily determined from the top left checkerboard. These schemes assume complete dominance. Additional variation in the phenotypic classes occurs in case of semidominance or codominance and the involvement of more than two allelic pairs. In common usage these modifications are mentioned as gene interactions but actually the products of the genes do interact.

Sometimes it is not quite easy to distinguish between two segregation ratios within small populations and statistical analysis may be required. Example: let us assume that we wish to ascertain whether the segregation is 3:1 or 9:7. With 3:1 the standard error of the recessives is $\sqrt{\frac{3n}{16}}$ and with 9:7 it is $\sqrt{\frac{63n}{256}}$. Since deviations from the expectation can be either + or -, the statistically acceptable misclassification of 0.025 can rely on the deviate of 0.05. From a table of the normal deviates (►normal deviate), the expected number of recessives must be or exceed 1.9599 times the standard error. Thus, for 9:7 ($7/16n$ - recessives) = $1.9599\sqrt{\frac{63n}{256}}$ and for the 3:1 segregation the expected is $r - 1/4(n) = 1.9599\sqrt{\frac{3n}{16}}$. By adding up, we get:

$$n([7/16] - [1/4]) = 1.9599\sqrt{n}\left(\sqrt{\frac{63}{256}} + \sqrt{\frac{3}{16}}\right)$$

$$\text{and } \sqrt{n} = \frac{16}{3} \left\{ 1.9599 \left[\left(\frac{7.9373}{16}\right) + \left(\frac{1.7321}{4}\right) \right] \right\}$$

$$= 937121.$$

Since $n = 9.7121^2 = 94.32$, about 95 individuals permit a distinction between the two hypothetical segregations at a level of 0.025 probability. In a similar way, other segregation ratios can also be tested. ►Mendelian segregation, ►Punnett square, ►semidominance, ►codominance, ►phenotype, ►genotype, ►normal deviate, see Fig. M98.

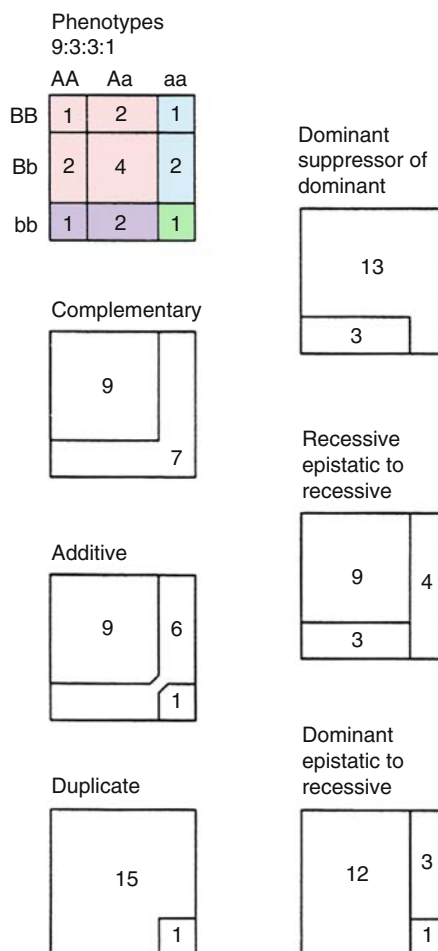


Figure M98. Modified Mendelian ratios

Modularity: Separability of a pattern into independently functionable units of a complex system. Developmental domains may be formed by specific transcription factors. These modules may subsequently affect other sets of transcription factors in a series of cascades of gene expression until the final differentiated structures arise. (See evolution of modularity: Kashtan N, Alon U 2005 Proc Natl Acad Sci USA 102:13773).

Modulation: Reversible alteration of a cellular function in response to intra- or extracellular factors.

Module: Single or multiple motif containing structural and functional units of macromolecules (proteins, DNA, RNA) and possibly small molecules. Their function is not a simple sum of that of the isolated components. Modules may be combined in alternative patterns and increase the functionality of the cell. Modules may be spatially isolated in the cell, e.g., as a ribosome, the complex site of polypeptide synthesis, or may only functionally be separated as, e.g., a particular signal transduction pathway. Modules

have the ability, however, for hierarchical interaction. One evolutionary advantage of the modular organization is that a mutation in a modular component may alter the function of that module without an upset in the whole system of the organism. Module components involved in a central role of the biology of the cell, e.g., histones, must be well conserved across phylogenetic ranges. Gene modules are coexpressed groups of genes within a genetic network. ►motif, ►genetic network, ►regulated gene, ►Williams syndrome; Bar-Joseph Z et al 2003 Nature Biotechnol 21:1337.

Modulon: ►origin

Modulins: Protein factors modulating bacterial infection. (See Neff L et al 2003 J Biol Chem 278:27721).

MODY (maturity-onset diabetes of the young): Apparently dominant, monogenic forms of familial diabetes with an onset at or after puberty but generally before age 25. Human chromosomal location is 20q11.2 (MODY1), 7p13 (MODY2), or 12q24 (MODY3), and it is a heterogeneous disease. MODYs are responsible for about 2–5% of non-insulin-dependent cases of diabetes. MODY1 is responsible for the coding of HNF-4 α , a hepatocyte nuclear transcription factor, a member of the steroid/thyroid hormone receptor family and an upstream regulator of HNF-1 α . MODY2 encodes the glycolytic glyco kinase, which generates the signal for insulin secretion. MODY3 displays defects in the hepatocyte nuclear factor HNF-1 α , a transcription factor that normally transactivates an insulin gene. SHP/NRPB2 (1p36.1) modulates the expression of HNF-4 α and contributes to obesity. ►diabetes mellitus, ►diabetes insipidus, ►GLUT; Barrio R et al 2002 J Clin Endocrinol Metab 87:P2532.

Moebius Syndrome: The major characteristics of the moebius syndrome are the facial paralysis of the sixth and seventh cranial nerves and often limb deformities and mental retardation. The dominant disorder was located to human chromosome 13q12.2-q13. The recurrence rate is below 1/50. ►neuro-muscular diseases, ►mental retardation, ►periodic paralysis, ►limb defects

Mohr Syndrome: ►orofacial digital syndrome II

Mohr-Tranebjaerg Syndrome (ddp): A recessive deafness encoded in xq21.3-qx22, involving poor muscle coordination, mental deterioration, but not blindness. In the same chromosomal region there is a transcribed region, DFN-1, which shows symptoms similar to DDP, but also blindness. ►deafness

MOI: ►multiplicity of infection

Molar Solution: 1 gram molecular weight compound dissolved in a final volume of 1 L.

Mole: *Talpa europaea*, 2n = 34, an insect-eating small underground mammal (see Fig. M99).



Figure M99. Mole

Mole: ►gram molecular weight; ►fleshy (placental) neoplasia

Mole: An abnormal mass of tissue in the uterus, developed from a degenerated oocyte. Alternatively, it may be of neoplastic nature. Hydatidiform moles may occur when one or two spermatozoa fertilize an enucleated egg. Moles frequently occur in the melanocytes of the skin and are generally benign and limited in growth. Mutations in the protein kinase BRAF, a downstream effector of the RAS oncogene, occasionally progress toward melanoma. Generally, the mutation induces cell cycle arrest and the induction of p16^{INK4a}, a tumor suppressor. In addition, the cells express a senescence-associated acidic β -galactosidase (SA- β -gal). The p16^{INK4a} and other factors apparently prevent proliferation and the cells and the mole remains senescent. This is an evidence of RAS oncogene induced senescence (Michaloglou C et al 2005 Nature [Lond] 436:720). ►nevus, ►tumor suppressor, ►galactosidase, ►senescence, ►RAS, ►melanoma, ►hydatidiform mole, ►p16^{INK4a}

Molecular Ancestry Network: <http://www.manet.uiuc.edu/>.

Molecular Beacon: A molecular tool for allele discrimination; it is a short hairpin oligonucleotide probe that binds to a specific oligonucleotide sequence and produces fluorescence signal. ►beacon molecular; Tyagi S et al 1998 Nature Biotechnol 16: 19; Rizzo J et al 2002 Mol Cell Probes 16(4):277.

Molecular Biology: The study of biological problems with physical and chemical techniques and interpretation of the functional phenomena on macromolecular bases. (See database: <http://nar.oupjournals.org>).

Molecular Breeding: The goal of molecular breeding is to develop highly efficient new vectors for genetic engineering. The procedure includes the reshuffling the coding regions of viral glycoprotein genes, which determine tropism of the proteins. This is followed by selection of vectors with exquisite specificity, improved gene transfer, etc. Molecular breeding may also mean application of molecular biology methods for the development of new crops or animal stocks. ►molecular pharming, ►plantibody, ►plant vaccine; Stöger E et al 2002 Mol Breeding 9(3):149, <http://www.phytome.org>.

Molecular Chaperone Heterocomplex (MCH): MCH includes heatshock proteins Hsp90 and Hsp70, chaperone interacting proteins Hop, Hip and p23, and peptidyl-prolyl isomerases, FKBP51, 52, and Cyp-40. ▶chaperones, ▶chaperonins, ▶heat-shock proteins, ▶cyclophilins, ▶FK506, ▶FKB; Bharadwaj S et al 1999 Mol Cell Biol 19:8033.

Molecular Clock: ▶evolutionary clock

Molecular Cloning: Reproduction of multiple copies of DNA with the aid of a vector(s). (See Sambrook J, MacCallum P 2006 Molecular Cloning. Cold Spring Harbor Lab, Press).

Molecular Combing: Spreading and aligning purified and extended DNA molecules on a glass plate and appropriate probes and optical tools reveal quantitatively at high resolution the amplification or losses of the genome. (See Allemand JF et al 1997 Biophys J 73:2064; Gueroui Z et al 2002 Proc Natl Acad Sci USA 99:6005).

Molecular Computation: Molecular computation could be called “reversed mathematics” because it uses DNA or protein sequence information in an attempt to solve complex mathematical problems. ▶DNA computer

Molecular Disease: The term “molecular disease” implies that the molecules involved in a disease have been identified, e.g., in sickle cell anemia, a valine replaces a glutamic acid residue in the hemoglobin β -chain. Since this first example, numerous diseases have been explained in molecular terms.

Molecular Drive: Copies of redundant DNA sequences are rather well conserved in the genomes although one would have expected divergence by repeated mutations. The force behind this tendency for uniformity within species has been named molecular drive or concerted evolution. The current literature uses mainly the latter term, which has priority. ▶concerted evolution

Molecular Evolution: Studies the relationship of the structure and function of macromolecules (DNA, RNA, protein) among taxonomic groups. ▶evolutionary distance, ▶evolutionary tree, ▶evolutionary clock, ▶evolution of the genetic code, ▶polymerase chain reaction. ▶ K_A/K_S , ▶RNA world, ▶origin of life, ▶phylogenomics; Nei M 1996 Annu Rev Genet 30:371; MANET, Wrenn SJ, Harbury PB 2007 Annu Rev Biochem 76:331; Phylemon: <http://phylemon.bioinfo.cipf.es/>.

Molecular Farming: The use of transgenic animals or plants for the production of substances needed for the pharmaceutical industry or for other economic activities. ▶transgenic, ▶pharming

Molecular Genetics: The application of molecular biology to genetics. It is a somewhat unwarranted distinction because genetics as a basic science must always use all the best integrated approaches.

Molecular Hybridization: Annealing two different but complementary macromolecules (DNA with DNA, DNA with RNA, etc.). ▶ C_{0t} curve, ▶probe

Molecular Imaging: A non-invasive imaging of targeted molecules in living organisms. The purpose is to identify a specific [altered] biological process with the aid of a molecular probe that is subject to alteration by the process and the alteration is detectable by light or near-infrared emission or by radioisotopes. An example is shown by the Fig. M100.

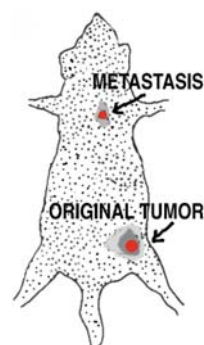


Figure M100. Using an appropriate vector firefly luciferase driven by a tissue-specific promoter is injected at the original tumor site. When metastasis takes place a new tumor site is detectable

Another example is that the dopamine receptor gene (D2R) in an adenovirus vector is injected into the tail of a mouse, and two days later the positron-labeled D2R ligand, (^{18}F) FESP (the dopamine analog 3-(2-(^{18}F) fluoroethyl)piperone, is injected into the mouse's bloodstream. MicroPET tomography then reveals the concentration of the molecular target by direct labeling. There are a wide variety of techniques for imaging other molecules. Direct-binding probes reveal the quantity of the target whereas indirect probes shed information on the activity status of the target. For the detection, one of the tomography or magnetic resonance imaging techniques or optical devices for luciferase activity are used. ▶tomography, ▶nuclear magnetic resonance spectroscopy, ▶luciferase, ▶GUS; Herschman H R 2003 Science 302:605.

Molecular Markers: ▶RFLP, ▶RAPD, ▶VNTR, ▶molecular weight, ▶ladder

Molecular Medicine: The integration of molecular, clinical and genomic information for developing improved therapy. (See Bellazzi R, Zupan B 2007 Int J Med Inform 40:787).

Molecular Mimics: Molecular mimics may trigger an autoimmune reaction because they have sequence homology to bacterial or viral pathogens. It is assumed that viral infection may lead to the synthesis of antigens structurally or functionally resembling self-proteins. Naïve T cells may be then activated by this antigen and may also mount an immune response to self-proteins. Some proteins appear to mimic the structure of nucleotides, e.g., domain 4 of EF2 peptide elongation factor mimicks the anticodon stem and loop of tRNA. Similarly, the eukaryotic release factors mimic tRNA. ▶autoimmune diseases, ▶bystander activation, ▶immune response, ▶immune tolerance, ▶tRNA, ▶structural mimics; Putnam WC et al 2001 Nucleic Acids Res 29:2199; Quin W et al 2007 Mol Immunol 44:2355.

Molecular Modeling: Aims to determine the three-dimensional atomic structure of macromolecules. Database and software information is available at <http://www.ncbi.nlm.nih.gov/Structure/>; <http://www.rcsb.org/pdb/home/home.do>.

Molecular Motor: ▶motor protein

Molecular Pharming: ▶pharming

Molecular Plant Breeding: This technique uses DNA markers to map agronomically desirable quantitative traits by employing the techniques of RFLP, RAPD, DAF, SCAR, SSCP, etc. The purpose is to incorporate advantageous traits into crops. (See separate entries, ▶QTL)

Molecular Plumbing: The generation of blood vessels by tissue culture techniques for the purpose of replacing defective organs.

Molecular Structure Database Tool: <http://bip.weizmann.ac.il/oca-bin/ocamain>.

Molecular Weight: The relative masses of the atoms of the elements are the atomic weights. The sum of the atomic weights of all atoms in a molecule determines the molecular weight of that molecule (MW). In the determination of the relative mass the mass of C^{12} is used, which is approximately 12.01 (earlier the mass of the hydrogen was used, 1.08 but the calculations with it were more difficult). The relative molecular weight is abbreviated usually as M_r . The molecular weight of macromolecules is generally expressed in daltons, $1 \text{ Da} = 1.661 \times 10^{-24}$ gram. Molecular weights are determined by a variety of physico-chemical techniques. In gel electrophoresis of DNA fragments are compared with sequenced (known base number) restriction fragments. For λ phage the fragments can be generated by *HinD* III [125 to 23,130 bp], by *HinD* III - *Eco* RI double digests [12 to 21,226 bp], or *Eco* RI [3,530 to 21,226 bp] or pUC18

plasmid cleaved by *Sau* 3AI [36 to 955 bp] or Φ X174 digested by *Hae* III [72 to 1,353 bp]. Alternatively, commercially available synthetic ladders containing 100-bp incremental increases from 100 to 1,600 bp or several other sizes are most frequently used. For the large chromosome-size DNAs studied by pulsed-field gel electrophoresis, T7 (40-kb), T2 (166-kb), phage G (758-kb), or even larger constructs obtained by ligation are used. For protein electrophoresis, bovine serum albumin (67,000 M_r), gamma globulin (53,000 and 25,000 M_r), ovalbumin (45,000 M_r), cytochrome C (12,400 M_r), and others can be employed. ▶ladder

Molecule: Atoms covalently bound into a unit.

Moloney Mouse Leukemia Oncogene (MLV): MLV integrates at several locations into the mouse genome; an integration site has been mapped to human chromosome 5p14. The Moloney leukemia virus-34 (Mov34) integration causes recessive lethal mutations in the mouse. Homolog to this locus is found in human chromosome 16q23-q24. The Mos oncogene encodes a protein serine/threonine kinase. It is a component of the cytotostatic factor CSF and regulates MAPK. ▶oncogenes, ▶CSF, ▶MAPK

Moloney Mouse Sarcoma Virus (MSV, MOS): The c-oncogene maps to the vicinity of the centromere of mouse chromosome 4. The human homolog MOS was assigned to chromosome 8q11-q12 in the vicinity of oncogene MYC (8–24). Break-point at human 8;21 trans-locations have been found to be associated with myeloblastic leukemia. It has been suspected that band 21q22, critical for the development of the Down syndrome, is responsible for the leukemia that frequently affects trisomic individuals for chromosome 21. The cellular mos protein (serine/threonine kinase) is also required for the meiotic maturation of frog oocytes. If the c-mos transcript is not polyadenylated maturation is prevented. Overexpression of c-mos causes precocious maturation, and after fertilization, cleavage is prevented but disruption of the gene may lead to parthenogenetic development of mouse eggs. This protein is active primarily in the germline, may cause ovarian cysts and teratomas, and oncogenic transformation also in somatic cells. ▶cell cycle, ▶teratoma, ▶polyadenylation, ▶leukemia, ▶Down syndrome, ▶c-oncogene

Moloney Murine Leukemia Virus: ▶MoMuLV

Molscrip: A computer program for plotting protein crystal structure. ▶protein structure; Kraulis PJ 1991 J Appl Crystallogr 24:946; Spock program manual: <http://quorum.tamu.edu/Manual/Manual/Manual.html>.

Molting: Shedding the exoskeleton (shell) by insects during metamorphosis (developmental transition stages). ▶Drosophila

Molybdenum: A cofactor of several enzymes in prokaryotes and eukaryotes. In mammals, it is required by xanthine dehydrogenase, aldehyde, and sulphite oxidase. An autosomal recessive molybdenum cofactor (molybdopterin) deficiency/sulphite oxidase deficiency involves neonatal seizures, neuronal damage, and is a rare lethal condition that manifests between ages two to six. Two open reading frames in human chromosome 6p encode the protein. ▶nitrate reductase, ▶gephyrin

Moments: The expectations of different powers of a variable or its deviations from the mean, e.g., the first moment is $E(X)$ = the mean, the second moment is $E(X^2)$, the third $E(X^3)$. The first *moment about the mean*: $E(X - E[X])^2$, the second $E(X - E[X])^3$. The third moment about the mean (if it is not 0) indicates skewness, the fourth moment reveals kurtosis. The moment of the joint distribution of X and Y is the covariance. ▶skewness, ▶kurtosis, ▶covariance, ▶correlation

MoMuLV (Moloney murine leukemia virus): A retrovirus with two copies of the genomic RNA in the capsid. The surface of the virus is decorated with trimeric transmembrane glycoprotein (Env). During infection, Env spikes mediate binding of the virus to the cell surface receptor, and structural rearrangements of Env enable the fusion with the cell membrane and entry of the virus into the cell. Cryo-electron tomography was found to reveal the structural basis of this process. The viral membrane is represented by purple and the green structure represents Env (see Fig. M101). The ~30 kDa receptor-binding domain fits into the Env.

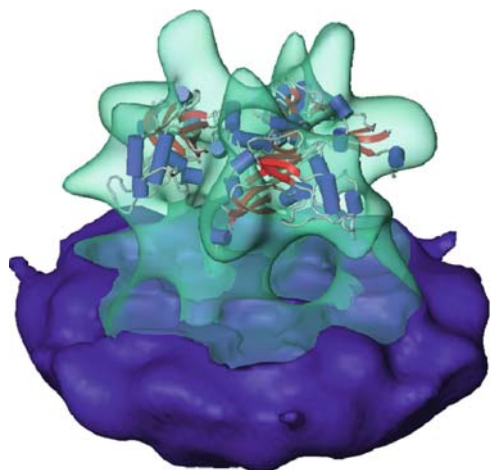


Figure M101. Envelope structure complex of MoMuLV *in situ* as mentioned in the text. For details see Förster F, Medalia O, Zauberman N, Baumeister W & Fass D 2005 Proc. Natl. Acad. Sci. USA 102:4729. (Courtesy of Dr. Friedrich Förster)

MoMuLV is frequently used for vector construction. It is potentially useful for transformation of both rodent and human cells. Integration is very efficient because the viral genome is retained in the reverse-transcribed DNA form of the virus. It can be targeted to rapidly dividing and not to post-mitotic cells. The *gag*, *pol*, and *env* protein genes are dispensable and also ensure that the virus is incapable of autonomous replication, but the ψ packaging signal is required. If the target cells do not have the ψ , the virus does not spread to other tissues. This is a particular advantage when tumor cells are targeted but normal cells are spared. For example, herpes simplex virus thymidine kinase (*HSV-tk*)-containing viral vectors thus convey ganciclovir-sensitivity only to tumor cells (which divide), and 10–70% may then be selectively killed by this cytotoxic drug. Similar vector designs can be applied to some degenerative diseases. (Parkinson disease, Huntington's chorea, Alzheimer disease and other neurodegenerative diseases). The protective gene can be transfected into cultured cells and then can be grafted back onto the target tissue of the same patient. ▶ganciclovir, ▶retroviral vectors, ▶gene therapy; D'Souza V, Summers MF 2004 Nature [Lond] 431:586; Förster F et al 2005 Proc Natl Acad Sci USA 102:4729.

MONA (Al Aqueel-Sewairi syndrome, 16q12-q21): Multicentric osteolysis with nodulosis and arthritis due to deficiency of matrix metalloproteinases.

Monarch Butterfly: ▶navigation, ▶*Bacillus thuringiensis*

Monastrol: A protein causing monopolar (rather than the normal bipolar) spindle in dividing cells. It blocks kinesin-related proteins (such as those in the bimC family, e.g., Eg5). ▶kinesin, ▶bimC; Kapoor TM et al 2000 J Cell Biol 150:975.

Mondrian: A type of representation of microarray of RNA transcripts resembling the “Broadway boogie-woogie” by the Dutch painter Piet Mondrian (1872–1944). It identifies open reading frames within the sequenced genomic DNA. (See Penn SG et al 2000 Nature Genet 26:315; art in science).

Mongolian Spot: A transient or long-lasting bluish birthmarks most commonly found upon the buttocks of infants. Its prevalence among Asians and East Africans 95–100%, Native Americans 85–90%, Hispanics 5–70%, and Caucasians 1–10%. It is caused by the entrapment of melanocytes during their migration from the neural crest into the epidermis during fetal development. (After Dr. Numabe, H., Tokyo University).

Mongolism (mongoloid idiocy): Now rejected name of Down's syndrome, human trisomy 21. Besides the epicanthal eyefold other—non-mongoloid—features

are more characteristics for the condition (see Fig. M102). ►Down syndrome, ►trisomy



Figure M102. Mongoloid eyefold

Monilethrix: Autosomal dominant (human chromosome 14q) and possibly autosomal recessive baldness (alopecia) due to defects of the keratin filaments of the hair. ►filaments, ►baldness, ►hair; Schweizer J 2006 J Invest Dermatol 126:1216.

Monitor: A video monitor receives and displays information directly received by a computer, while a television monitor accepts broadcast signals. Monitoring: keeping track of something.

Monoallelic Expression: In a diploid (or polysomic) cell or individual only one of the alleles is expressed such as the genes situated in one of the mammalian X chromosomes or as is the case of maternal or paternal imprinting. Besides X-chromosomal genes, imprinted autosomal genes display monoallelic expression. In addition several other autosomal genes (odorant receptors, pheromone receptors, immunoglobulins, T cell receptors, interleukins) are transcribed in random monoallelic manner. These alleles also show asynchronous replication, which may be responsible for their differences in expression. The asynchrony within a particular chromosome appears coordinated (Singh N et al 2003 Nature Genet 33:339). Monoallelically expressed autosomal genes of mammals display a substantially higher frequency of LINE1 sequences (Allen E et al 2003 Proc Natl Acad Sci USA 100:9940). Actually some lower organisms (*Plasmodium*, *Trypanosoma*) also express only one allele of some genes of the diploid. ►lyonization, ►imprinting, ►allelic exclusion, ►*Plasmodium*, ►*Trypanosoma*

Monoamine Oxidase: ►MAO, ►Norrie disease

Monobrachial Chromosome: A monobrachial chromosome has only one arm (see Fig. M103). ►telocentric, ►chromosome morphology

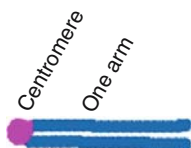


Figure M103. Monobrachial chromosome

Monocentric Chromosome: A monocentric chromosome has a single centromere, as is most common.

Monochromatic Light: Literally, light of a single color, practically light emission with a single peak within a very narrow wavelength band.

Monocistronic mRNA: A monocistronic mRNA codes for a single type of polypeptide. It is transcribed from a single separate cistron (not from an operon). Eukaryotic genes are usually monocistronic. The class I genes, 18, 5.8 and 28 S rRNAs, including spacers, are transcribed as a single unit containing one of each gene's pre-rRNAs and are cleaved subsequently into mature rRNA. The 5 S RNA genes are transcribed from separate promoters by pol III. ►ribosome, ►cistron

Monoclonal Antibody (MAB): The MAB is of a single type, produced by the descendants of one cell and specific for a single type of antigen. In case the epitome domains are highly conserved, the specificity of the monoclonal antibody is reduced. MABs are generated by injecting into mice, purified antigens (immunization), than by isolating spleen cells (splenocytes, B lymphocytes) from the immunized animals and fusing these cells, in the presence of polyethylene glycol (a fusing facilitator), with bone marrow cancer cells (myelomas) that are deficient in thymidine kinase (TK), or HGPRT. This process assures that the non-fused splenocytes rapidly senesce in culture and die. The unfused myeloma cells are also eliminated on a HAT medium because they cannot synthesize nucleic acids, either by the de novo or by the salvage pathway. The selected myelomas do not secrete their own immunoglobulins and thus, hybrid immunoglobulins are not produced. Single hybridoma cells are then cultured in multi-well culture vessels and screened for the production of specific MABs by the use of radioimmunoassays (RIA) or by enzyme-linked immunosorbent assay (ELISA). Most of the hybridomas will produce many types of cells and are of limited use; a few, however, may be more specific and these are re-screened for the specific type needed. E.g., animals immunized with melanoma cells produce HLA-DR (Human Leukocyte Antigen D-related) antibodies or melanotransferrin (a 95-kDa glycoprotein) or melanoma-associated chondroitin proteoglycan (heteropolysaccharides, glucosaminoglycans attached to extracellular proteins of the cartilage). Monoclonal antibodies have been used effectively for identification of tumor types in sera and histological assays. A human trial using humanized mouse monoclonal antibody in the hope to find an effective treatment for autoimmune conditions had a tragic outcome. Six healthy individuals in a London hospital were injected with anti-CD28 mAB that rather than suppressing regulatory T cells—as expected on the basis of experiment with mice and monkeys—turned ‘superagonist’ and activated all types of T cells,

and not just the regulatory T cells. The individuals in the trial developed serious organ failures and one fell into a coma for three weeks. Apparently, the mAb of TGN1312 caused an unexpected 'cytokine storm' indicating that there is still a lot to be learned before antibodies can be generally used for therapeutic purposes (Vitetta ESD, Ghetie VF 2006 Science 2006 313:308).

Some MABs have been successfully applied for direct tumoricidal effect. Radioactively labeled monoclonal antibodies of Melanoma Associated Antigens (MAA) have been used for imaging (immunoscintigraphy) and detecting melanoma cells in the body when other clinical and laboratory methods failed. The "magic bullet" approach of combining specific monoclonal antibodies (prepared from individual cancer patients) against a specific cancer tissue with Yttrium⁹⁰ isotope (emitting β rays of 2.24 MeV energy and 65 h half-life), or ricin (LD50 for mice by intravenous administration 3 ng/kg) or the deadly diphtheria toxin, or tumor necrosis protein (TNF) is expected to home in on cancer cells and destroy them. This attractive scheme has not been proven successful in clinical trials so far. (►abzymes). More recently, several monoclonal antibody drugs targeting tyrosine kinase (Gleevec, Trastuzumab) and antiangiogenesis Avastin have been approved for therapeutic use alone or in combination with other treatments. A newer approach is to clone separately cDNAs of a variety of light and heavy chains of the antibody and allowing them to combine in all possible ways, thus producing a combinatorial library of antibodies against all present and possible, and emerging and future epitopes. These antibodies can then be transformed into bacteria by using λ phage or filamentous phage such as M13. The phage plaques can then be screened with radioactive epitopes. The advantage of using filamentous phages is that they display the antibodies on their surface and permit screening in a liquid medium that enhances the efficiency by orders of magnitude. Although monoclonal antibodies did not completely fulfill all the (naïve) therapeutic expectations, they still remain a power-tool of biology and currently they represent more than 20% of the biopharmaceuticals being evaluated in clinical trials. Monoclonal antibodies cannot be produced against self-antigens or against less than about 1-kDa antigens. In the latter case, high molecular weight carrier proteins such as bovine serum albumin or limpet hemocyanin are used. Typical yield of MAb from hybridoma cells is 10–100 $\mu\text{g}/10^6$ cells/day. Currently, mammalian cells are used mainly to produce IgG and obtain post-translational modifications (e. g., glycosylation), which are essential for the maintenance of the conformation of the immunoglobulin effector function. For transient expression of antibody genes, most commonly COS cells are

employed. For stable-expression myeloma cell lines, SP2/0, NS0, and Chinese hamster ovary (CHO) cells are used. Antibodies can be produced in transgenic mammals, insects, and plants. Mouse adenocarcinoma-associated antigen (EpCAM [GA73302]) is a highly expressed target of mouse monoclonal antibody (mAb CO17–1 A) and it can be produced in transgenic *Nicotiana tabacum* plants after transformation by *Agrobacterium* vectors. Although the glycosylation pattern of the plant monoclonal antibody differs from that of the animals, it inhibited colon cancer cells in nude mice similarly to its mammalian counterpart (Ko K et al 2005 Proc Natl Acad Sci USA 102:7026). ►antibody, ►immunoglobulins, ►immune system, ►T cells, ►B cells, ►lymphocytes, ►somatic cell hybrids, ►hybridoma, ►MAB, ►TK, ►HGPRT, ►HAT medium, ►senescence, ►RIA, ►ELISA, ►hybridoma, ►heterohybridoma, ►melanoma, ►ricin, ►LD50, ►diphtheria toxin, ►epitope, ►combinatorial library, ►phage display, ►quasi-monoclonal, ►bispecific monoclonal antibody, ►keyhole limpet hemocyanin, ►humanized antibody, ►CD28, ►immunization genetic, ►phage display, ►HAMA, ►COS, ►transformation transient, ►CHO, ►plantibody, ►genetic engineering, ►antibody polyclonal, ►receptin, ►aptamer, ►genetic medicine; Ritter MA, Ladyman HM (Eds.) 1995 Monoclonal Antibodies. Production, Engineering and Clinical Application, Cambridge University Press, New York; Alkan SS 2004 Nature Rev Immunol 4:153; <http://www.antibodyresource.com/>; <http://bioresearch.ac.uk/browse/mesh/D000911.html>.

Monoclonal Antibody Therapies: Monoclonal antibody therapies open a variety of applications in medicine. Although at the moment they do not offer perfect solutions, they do have a lot of potential. Reocclusion of blood vessels after angioplasty—caused by unwanted aggregation of the platelets—may be alleviated by the 7E3 antibody fragments of the chimeric mouse-human Fab. Single- or two-chain fragments of the antibody variable region and the urokinase fusion protein (scFv-uPA) or tissue plasminogen activator (tPA) conjugated to anti-fibrin antibody have been designed for thrombolysis. Monoclonal antibodies may be generated against interleukins (IL-1), TNF, and cell adhesion molecules (selectins, integrins) to block inflammatory responses after wounding or autoimmune diseases (rheumatoid arthritis, septic shock), T cells, T cell receptors, etc. Monoclonal antibody-mediated cytotoxicity responses are activated or inhibited through the Fc γ receptors of the antibody. By computational design and engineering, the affinity of these receptors can be increased by two orders of magnitude and can broaden the therapeutic applicability to cancer (Lazar GA et al 2006

Proc Natl Acad Sci USA 103:4005). ▶magic bullet, ▶ADEPT, ▶vascular targeting, ▶immunotoxins, ▶antiviral antibodies, ▶tissue plasminogen activator, ▶thrombin, ▶platelet, ▶fibrin, ▶selectins, ▶integrin, ▶rheumatic fever, ▶septic shock, ▶auto-immune diseases, ▶T cell, ▶T cell receptor, ▶plantibody, ▶antibody, ▶antibodies intracellular, ▶abzymes, ▶gene therapy, ▶cancer gene therapy, ▶genetic medicine, ▶biomarkers; Baselga J 2001 Eur J Cancer 37 Suppl 4:16.

Monocotyledones: Plants that form only one cotyledon such as the grasses (cereals).

Monocytes: Mononuclear leukocytes that become macrophages when transported by the blood stream to the lung and the liver. ▶microglia, ▶atherosclerosis, ▶MCP-1, ▶leukocyte, ▶macrophage

Monoecious: Plants with separate male and female flowers on the same individual (see Fig. M104). ▶autogamous, ▶outcrossing, ▶protandry, ▶protogyny

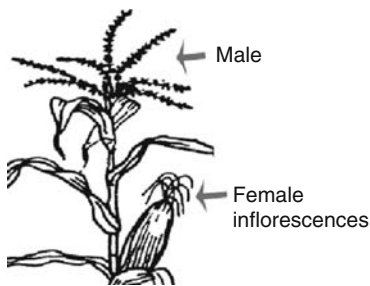


Figure M104. Monoecious plant

Monofactorial Inheritance: A single (dominant or recessive) gene (factor) determines the inheritance of a particular trait. Although this term has some value for classification of inheritance, in most of the case the phenotype is the function of a number of genes with different alleles that respond to a variety of internal and external factors at the same time. Thus, strictly monogenic inheritance may not exist. The so-called monogenic human diseases generally are expressed as syndromes. As of February 2006, 1,822 “monogenic” human allelic variants were identified by OMIM. Sequencing of the human disease genes and encoded proteins often reveals more than a single alteration even within the single gene. Also, environmental factors and the genetic background may modify the phenotypes substantially. ▶Mendelian laws, ▶reaction norm, ▶syndrome, ▶pleiotropy, ▶SNIPs, ▶epistasis, ▶digenic diseases, ▶QTL; Nadeau JH 2001 Nature Rev Genet 3:165.

Monofunctional Alkylating Agent: A monofunctional alkylating agent has only a single reactive group.

Monogenic Heterosis: Same as overdominance, superdominance.

Monogenic Inheritance: Same as monofactorial inheritance.

Monogerm Seed: A monogerm seed contains only a single embryo. The fruit of some plants (e.g., sugar beet) is frequently used for propagation and usually it contains multiple seeds. This fruit may, however, be genetically modified to contain a single seed or mechanically fragmented to become monogerm. The agronomic advantage of the monogerm seed is that the emerging seedlings are not crowded and the labor-consuming thinning may be avoided or is at least facilitated.

Monogyne: Social insects with single functional female (queen) in the colony. ▶polygyne

Monohybrid: A monohybrid is heterozygous for only one pair of alleles. ▶monofactorial inheritance

Monoisodisomic: In wheat, $20'' + i1''$, $2n = 42$, [“=disomic, i=isosomic].

Monoisosomic: In wheat, $20'' + i'$, $2n = 41$, [“=disomic, ‘=monosomic, i=isochromosome].

Monoisotrisomic: In wheat, $20'' + i2''$, $2n = 43$, [“=disomic, i=isosomic, “=trisomic].

Monokine: Lymphokine produced by monocytes and macrophages. ▶lymphokine

Monolayer: Non-cancerous animal cell cultures grow in a single layer in contact with a solid surface, i.e. in a monolayer. It also designates a single layer of lipid molecules. ▶tissue culture, ▶cell culture

Monolithic Substrate: Polymer or silicon substrate with microchannels or other functional elements.

Monomer: One unit of a molecule (which frequently has several in a complex); a subunit of a polymer ▶protein

Monomorphic Locus: In the population, a monomorphic locus is represented by one type of allele.

Monomorphic Trait: A monomorphic trait is represented by one phenotype in the population.

Mononucleosis: Caused by cytomegalovirus; infectious mononucleosis is the result of activation of the Epstein-Barr virus. ▶cytomegalovirus, ▶Epstein-Barr virus

Monooxygenases: Monooxygenases introduce one atom of oxygen into a hydrogen donor, e.g., P450 cytochromes, and have varied functions in cells in normal development, as detoxifiants, and in converting promutagens and procarcinogens into active compounds. ▶mixed-function oxidases, ▶P450

Monoparous: Species, which generally produce a single offspring at a time. ▶[multiparous](#)

Monophyletic: Monophyletic organisms have evolved from a single line of ancestry. ▶[polyphyletic](#)

Monoploid: A monoploid has only a single basic set of chromosomes. ▶[haploid](#)

Monopolar Spindle: A monopolar spindle pulls all chromosomes to one pole (see Fig. [M105](#)).

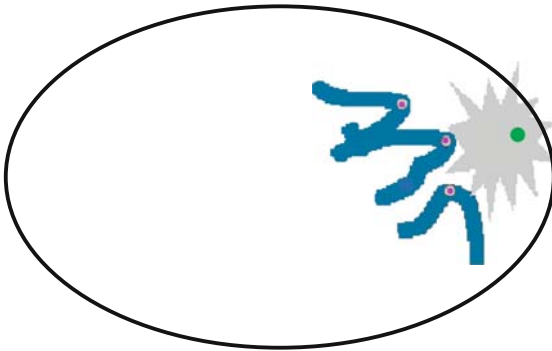


Figure M105. Monopolar spindle

Monoplin (Mam1): A kinetochore associated protein that assures that during meiosis I the homologous chromatids (held together by cohesin) are pulled to the same pole. The Csm1/Lrs4 proteins reside in the nucleolus and shortly before meiosis I they leave that location to associate with Mam1. ▶[meiosis](#), ▶[cohesin](#), ▶[co-orientation](#); Toth A et al 2000 Cell 103:1155; Rabitsch KP et al 2003 Dev Cell 4:535.

Monoprotic Acid: A monoprotic acid has only a single dissociable proton.

Monosaccharide: A carbohydrate that is only one sugar of basic units $C_nH_{2n}O_n$ and thus can be diose, triose, pentose, hexose, etc., depending on the number of C atoms; the sugars can also be aldose (e.g., glucose, ribose) or ketose sugars (e.g., fructose, deoxyribose).

Monosaccharide Malabsorption (22q13.1): Monosaccharide malabsorption is controlled by a sodium/glucose transporter at the intestinal brush border.

Glucose/galactose malabsorption may be remedied by fructose.

Monosodium Glutamate ($HOOCCH(NH_2)CH_2CH_2COONa \cdot H_2O$): Monosodium glutamate is used as a flavor enhancer (0.2–0.9%) in salted food or feed, for repressing the bitter taste of certain drugs, or as a medication for hepatic coma. ▶[Chinese restaurant syndrome](#)

Monosomic: In a monosomic, the homologous chromosome(s) is represented only once in a cell or all cells of an individual. The gametes of diploids are monosomic for all chromosomes. A monosomic individual of an allopolyploid has $2n - 1$ chromosomes. About 80% of the human $45 + X$ monosomics involve the loss of a paternal sex chromosome. Medical cytogeneticists frequently refer to deletions as “partial monosomy”, but this is a misnomer and should be avoided because such a condition is hemizygosity for a particular locus or chromosomal region. Monosomics can produce both monosomic and nullisomic gametes. ▶[nullisomics](#), ▶[chromosome substitution](#), ▶[monosomic analysis](#)

Monosomic Analysis: Monosomic analysis is very efficient in Mendelian analysis of allopolyploids, such as hexaploid wheats. Monosomic individuals can produce monosomic and nullisomic gametes and their proportions are different in males and in females (see Fig. [M106](#)). The proportion also depends on the individuality of the particular chromosomes. On the average, the gametic output and the zygotic proportion of selfed monosomics of wheat is as shown in the body of the table. Very few nullisomic sperms are functional, whereas the majority of the eggs are nullisomic because most of the monosomes (in the absence of a partner) remain and get lost in the meta-phase plane and the eggs receive only one representative from each chromosome that has paired during prophase I. The monosomics can be used to assign genes to chromosomes and if the proper genetic constitution is used cytological test may not be required. On the basis of the Fig. [M106](#) and the Table [M7](#) it is obvious that 75% of the F_1 will be of recessive phenotype if the genes are in the chromosome of the monosomic female. In case the recessive

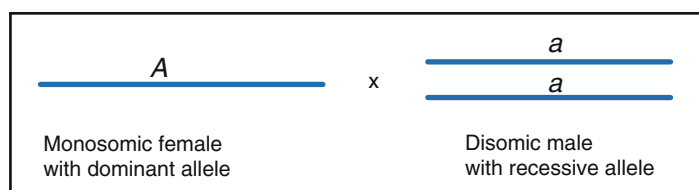


Figure M106. Gene localization to chromosome with monosomics

Table M7. Monosomic analysis

| | | |
|-----------------|--|----------------------------------|
| Eggs ↓ | <div>Monosomic (0.96) ← Sperms → Nullisomic (0.04)</div> | |
| Monosomic 0.25 | Disomic ≈ 24% (0.25 x 0.96) | Monosomic ≈ 1% (0.25 x 0.04) |
| Nullisomic 0.75 | Monosomic ≈ 72% (0.75 x 0.96) | Nullisomic ≈ 3% (0.75 x 0.04) |

is in the monosomic female, only 3% will be recessive in the F₂ offspring. ▶nullisomy; Morris R, Sears ER 1967 In Wheat and wheat improvement; Quisenberry KS, Reitz LP (Eds.) Am Soc Agron Madison WI Sears E R 1966 Hereditas Suppl 2:370; Tsujimoto H 2001 J Hered 92:254.

Monospermy: Fertilization by a single sperm.

Monotelodisomic: In wheat, 20” + t2”, 2n = 43, [“=disomic, t = telosomic, “=trisomic].

Monotelomonoisomic: In wheat, 20”+ t’+ i’, 2n= 42, [“=disomic, ‘=monosomic, t = telosomic, i = isosomic].

Monotelo-Monoisotrisomic: In wheat, 20”+ (t+ i)1”, 2n = 43, [“=disomic, “=trisomic, t = telosomic, i = isosomic].

Monotelosomic: In wheat, 20” + t’, 2n = 41, [“=disomic, ‘=monosomic, t = telosomic].

Monotocous Species: A monocotous species produces a single offspring by each gestation.

Monotrene: An animal belonging to the taxonomic order Monotremata, a primitive small mammalian group, including the spiny anteater and the duck-billed platypus (see Fig. M107). They lay eggs and nurse their offspring within a small pouch through a nipple-less mammary gland. They show other organizational similarities to marsupials. ▶marsupials, ▶sex determination



Figure M107. Platypus

Monotypic: A taxonomic category represented by one subgroup, e.g., a monotypic genus includes a single species.

Monoubiquitin: In a monoubiquitin, the surface of the ubiquitin may be ordained for separate multiple functions, e.g., for degradation or endocytosis. The various monoubiquitins are specialized to one function only although the function itself may vary, e.g., it may involve regulation of histones H2A and H2B, endocytosis, or budding of the retroviral Gag polyprotein. Monoubiquitins can be attached to separate sites, or *polyubiquitin* chains are attached at a single lysine⁴⁸. Polyubiquitin attachments at Lys⁶³ activates several proteins but this complex is not targeted to the proteasome. ▶ubiquitin, ▶sumo, ▶histones, ▶endocytosis, ▶retrovirus, ▶proteasome, ▶deubiquitinating enzymes; Hicke L 2001 Nature Rev Mol Cell Biol 2:195.

Monozygotic Twins: Monozygotic twins develop from a single egg fertilized by a single sperm, therefore they should be genetically identical, except mutations that occur subsequent to the separation of the zygote into two blastocytes after implantation into the wall of the uterus. Monozygous female twins may be phenotypically discordant in case of heterozygosity of X-linked genes. The difference may be caused by the inactivation of one or the other X chromosome. Although MZ twins are generally identical genetically, their birthweight may be different because of differences in intrauterine nutrition due the path of blood circulation. Developmental malformations may affect only one of the MZ twins. The concordance in susceptibility to infectious diseases has been investigated but the information is not entirely unequivocal. Multifactorial diseases are more concordant in MZ twins than among dizygotic twins. ▶twinning, ▶dizygotic twins, ▶heritability estimation in humans, ▶zygosis, ▶concordance, ▶discordance, ▶co-twin, ▶lyonization

Monte Carlo Method: A computer-assisted randomization of large sets of tabulated numbers that can be used for testing against experimentally obtained data to determine whether their distribution is random or not. It is used for simulation when the analysis is

intractable or too complex. ► [modeling](#), ► [simulation](#), ► [Markov chain](#); Roederer M et al 2001 Cytometry 45:47; Roederer M et al *ibid* 37.

Moolgavkar-Venzon Model: A revised version of Knudson's two-mutation model of carcinogenesis. It considers the possibility that after the first mutation not all the cells survive, and allows for differential growth of the cells before the occurrence of malignant transformation. ► [Knudson's two-mutation hypothesis](#); Armitage-Doll model, Holt PD 1997 Int J Radiat Res 71(2): 203.

Moore-Federman Syndrome: A dwarfism with stiff joints and eye anomaly. ► [dwarfism](#)

Mooring Sequence: An 11 nucleotide element anchored downstream to the base C to be RNA edited (CAAUUUGAUCAGUAUA). ► [RNA editing](#)

Moose, North American: (*Alces alces*), $2n = 70$.

Morality: Socially accepted principles and guidelines for the distinction of right from wrong in human behavior, usually based on customs and generally required to be abided by, by society. Moral standards are categorically binding principles independent of one's wishes or desires and therefore transcend all other kinds of potentially conflicting norms. Some moral rules are present in all human societies; these rules may have, however, distinct variations. ► [behavior genetics](#), ► [ethics](#), ► [ethology](#), ► [informed consent](#)

Morbidity: The diseased condition or the fraction of diseased individuals in a population. A wide range of biomarkers, reflecting activity in a number of biological systems (e.g., neuroendocrine, immune, cardiovascular, and metabolic), has been found to prospectively predict disability, morbidity, and mortality outcomes in older adult populations. Levels of these biomarkers, singly or in combination, may serve as an early warning system of risk for future adverse health outcomes. Markers for neuroendocrine functioning (epinephrine, norepinephrine, cortisol, and dehydroepiandrosterone), for immune activity (C-reactive protein [one of the acute phase proteins that increase during systemic inflammation], fibrinogen, IL-6, and albumin) is appropriate. For cardiovascular functioning (systolic and diastolic blood pressure), and for metabolic activity [high-density lipoprotein (HDL) cholesterol, total to HDL cholesterol ratio are being used. Glycosylated hemoglobin] over a 12-year period in a sample of men and women ($n = 1,189$) 70–79 years of age was informative cardiovascular problems. Almost all these markers entered into one or more high-risk pathways, although combinations of neuroendocrine and immune markers appeared frequently in high-risk

male pathways, and systolic blood pressure was present in combination with other biomarkers in all high-risk female pathways (Gruenewald TL et al 2006 Proc Natl Acad Sci USA 103:14158). ► [mortality](#); Petronis A 2001 Trends Genet 17:142.

Morgan: 100 units of recombination, 100 map units, usually the centiMorgan, 0.01 map unit is used. ► [map unit](#)

Morphactins: Various plant growth regulators.

Morphallaxis: ► [regeneration in animals](#), ► [epimorphosis](#)

Morpheins: Proteins in which one functional homooligomer can dissociate, change conformation, and reassociate into a different oligomer. ► [conformation](#)

Morphine: An opium-like analgesic and addictive alkaloid; methylation converts it to the lower potency codein. Noradrenergic signaling mediates opiate reward (Olson VG et al 2006 Science 311:1017). ► [alkaloids](#), ► [opiate](#), ► [animal hormones](#)

Morphoallele: Gene involved in morphogenesis. ► [morphogenesis](#)

Morphogen: A compound that can affect differentiation and/or development, and can correct the morphogenetic pattern of a mutant that cannot produce it if it is supplied by an extract from the wild type. In some sea algae (*Ulva*, *Enteromorpha*), marine bacteria (Cytophaga-Flavobacterium-Bacteroides), on the surface of the algae, control leaf-like morphology. The bacteria-produced thallusin (see Fig. M108) determines foliaceous morphology and spore germination (Matsuo Y et al 2005 Science 307:1598). In the higher plant *Cardamine hirsuta* (see Fig. M109), the KNOX (KNOTTED1-like homeobox) regulated by the asymmetric leaf 1 protein makes the leaves dissected, whereas in another crucifer, *Arabidopsis* leaves, KNOX is excluded making the leaves simple (Hay A, Tsiantis M 2006 Nature Genet 38:942). In tomato, the wildtype plant has compound leaves composed of several leaflets. The semidominant *lanceolate* (*LA*) mutation in chromosome 7 alters the leaf shape and structure. *LA* encodes the TCP transcription factor

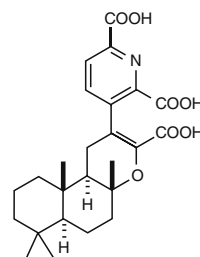


Figure M108. Thallusin

with miR319 (microRNA) binding site. Base substitution mutations in the binding site reduce or eliminate TCP inhibition required for the development of the wild type compound leaf (see Fig. M110).

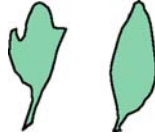


Figure M109. *C. hirsuta* *A. thaliana*

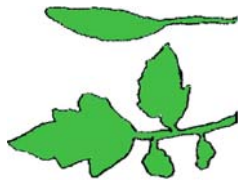


Figure M110. Wild type leaflet of tomato (Redrawn after Ori N et al. 2007 Nature Genet. 39:787)

M

The exact chemical nature of many morphogens is unknown, however, some hormones and proteins have these properties. There is some evidence that some morphogens (produced by Wingless and Hedgehog) are moved in the cell by association with glycosphosphatidylinositol (Panáková D et al 2005 Nature [Lond] 435:58). The morphogen is either a transcription factor or a type of transcriptional regulator. The slope of the *Decapentaplegic* gene expression acts as a morphogen on wing development and the expression gradient regulates growth (Rogulja D, Irvine KD 2005 Cell 123:449). Control by morphogens involves concentration gradients over a threshold level. Generally, the initial morphogen signal recruits other similar signals and signal receptors (encoded by genes) which act positive or negative manners and determine cell fates and bring about a differentiatonal event(s). Generally the production rate, the effective diffusion coefficient, the degradation rate, and the immobile fraction of the morphogen contribute to the pattern of the morphogenic differentiation (see Fig. M111) (Kicheva A et al 2007 Science 315:521). The activin signal (a member of the transforming growth factor- β family) spreads in a passive gradient about 300 μ m or 10 cells diameter within a few hours in the vegetal cells of animals. ►morphogenesis, ►vegetal pole, ►activin, ►cross-talk, ►signal transduction, ►selector genes, ►cue, ►wingless, ►hedgehog, ►TCP, ►microRNA; Pagès F, Kerridge S 2000 Trends Genet 16:40; Tabata T 2001

Nature Rev Genet 2:620; Gurdon JB, Bourillot P-Y 2001 Nature [Lond] 413:797; Nüslein-Volhard CN 2004 Cell 116:1; Lander AD 2007 Cell 128:245.

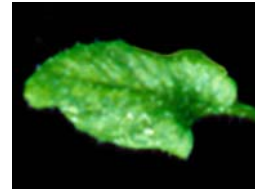


Figure M111. *Arabidopsis thaliana*: asymmetric leaf

Morphogenics: Morphogenics employs a dominant negative mismatch repair gene to create genetic diversity within defined cellular systems and results in a wide range of phenotypes. It has been used in immunology and drug development (Nicolaidis NC et al 2005 Ann NY Acad Sci 1059:86). ►mismatch, ►mismatch repair

Morphogenesis: The process of development of form and structure of cells or tissues and eventually the entire body of an organism beginning from the zygote to embryonic and adult shape. Morphogenesis is mediated through morphogens in response to inner and outer factors. Morphogenesis takes place in three phases: determination, differentiation, and development. Determination is a molecular change preparing the cell (or virus) to competence for differentiation. Differentiation is the realization of molecular and morphological structures that determines the differences among cells that are endowed with identical genetic potentials. The events of differentiation are coordinated in sequences of development. These steps generally occur in this order, yet may run in overlapping courses for different aspects of morphogenesis. The morphogenetic events vary in different organisms because this is the basis of their identity, yet some basic principles are common to all. The start point of morphogenesis is difficult to pinpoint because these events run in cycles of generations (what comes first: the egg or the hen?). The life of an individual begins with fertilization of the egg by the sperm and the formation of the zygote. The zygote has all the genes that it will ever have (*totipotency*) yet many of these genes are not expressed at this stage. (New genes may be acquired during life cycle by mutational conversion of existing ones or by transformation and transduction). Also, there are *maternal effect* genes that control oogenesis and affect the zygote from outside without being expressed at this stage within the embryo's own gene repertory. Morphogenesis cannot be explained by one general set of theory, e.g., *gradients of morphogens* or the *signal relay* system. Apparently, evidence for

either can be found in different morphogenetic pathways. Many structures in higher eukaryotes are under the control of partially redundant gene families. In different tissues different sets of transcription factors or transcriptional activators and enhancers may orchestrate in a combinatorial manner the expression of different cell types, adapted to a particular organ. The cytoskeleton and cell adhesion may determine cell shape. Signals originating outside or inside the cell may act as morphogens and by their concentration gradients along their distribution path may trigger morphogenetic changes. Alternatively, it has been suggested that signals induce a change in one type of cell that then through a relay of series of cells influences other cells to various types of changes. For example, signals transmitted to metalloproteinases, collagenase-1, and stromelysin-1 mediated by the RAS family (Rac) GTP-binding proteins are also involved in cell morphogenesis. ▶*Drosophila*, ▶homeotic genes, ▶morphogens, ▶signal transduction, ▶clonal analysis, ▶developmental genetics, ▶signal transduction, ▶RNA localization, ▶RAS, ▶Rac, ▶metalloproteinases, ▶cytoskeleton, ▶CAM, ▶imaginal disks, ▶oncogenes, ▶morphogenesis in *Drosophila*, ▶pattern formation, ▶RNA localization, ▶founder cells, ▶segregation asymmetric, ▶organizer, ▶anchor cell, ▶Hensen's node, ▶morphogenetic furrow, ▶development, ▶mRNA targeting, ▶compartmentalization, ▶primitive streak, ▶cue, ▶Notch, ▶left-right asymmetry, ▶selector genes; Madden K, Snider M 1998 Annu Rev Microbiol 52:687; Chase A 2001 Bioessays 23:972; high resolution X-ray computed tomography of animal morphology: <http://www.digimorph.org/>.

Morphogenesis in *Drosophila*: Morphogenesis in *Drosophila* has been the most extensively studied with

genetic techniques (see Fig. M112). Oogenesis requires four cell divisions within the oocyst (see illustration of maternal effect genes) resulting in the formation of 16 cells, one oocyte, and 15 nurse cells. The latter become polyploid and are surrounded by a single layer of somatic (diploid) follicle cells. The nurse cells are in communication with the egg through cytoplasmic channels. Both the nurse cell genes (somatic maternal genes) and the egg (germ-line maternal genes) influence the fate of the zygote through morphogens. The oocyte itself is transcriptionally not active. These maternal effect genes determine the polarity of the zygote (see Fig. M113). The anterior-posterior gradients of the morphogens account for the future position of the head and tail, respectively. Genes *gurken* (*grk*, 2–30) and *torpedo* (2–10) play an important role in anterior-posterior polarity and later during development also of dorso-ventral determination. The dorso-ventral determination is responsible for the sites of the back and belly, respectively. The medio-lateral polarities are involved in the determination of the left and right sides of the body. The larvae and the adults develop from 12 compartments, one for the head, three for the thorax, and nine for the abdomen, formed already during the blastoderm stage of the embryo.

Mutation of the maternal genes mentioned in the box below usually cause recessive embryo lethality although the homozygous mothers are generally normal. The males are usually normal and fertile. The molecular basis of their actions is known in a few cases. E.g., the amino terminal of the DL protein is homologous to the C-REL (avian reticuloendothelial viral oncogene homolog) protooncogene, which is present in human chromosome 2p13–2cen, and in mouse chromosome 11. The N terminus of *dorsal* is homologous to the product of gene *en* (*engrailed*,

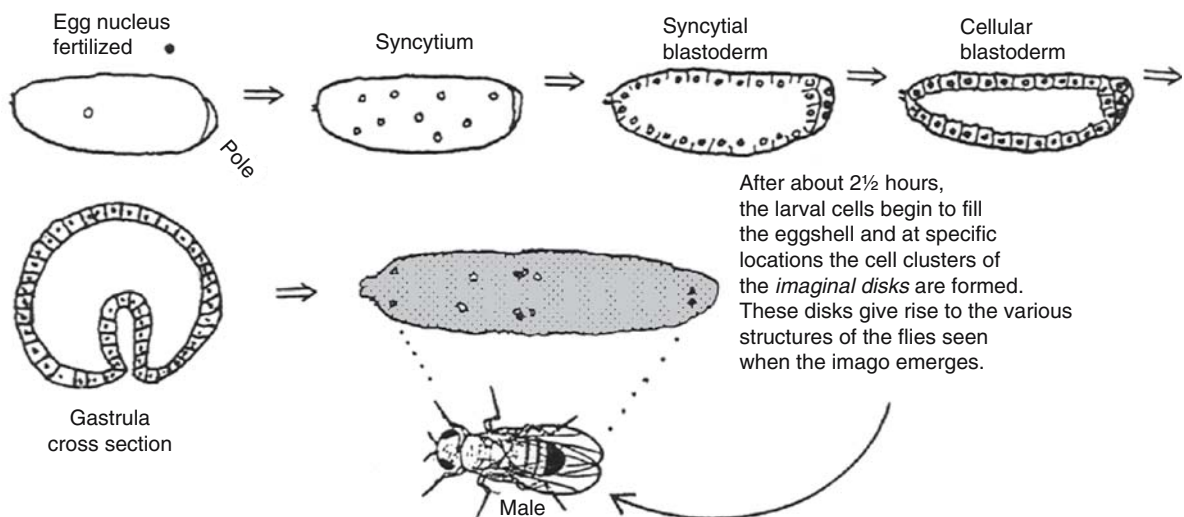


Figure M112. Embryogenesis in *Drosophila*

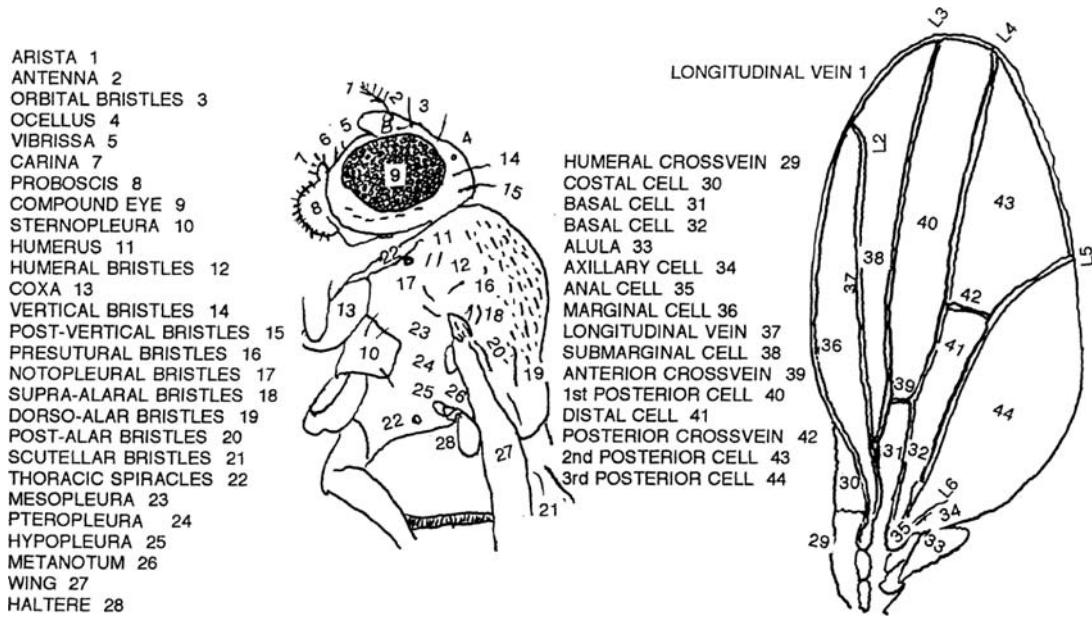


Figure M113. Head and wing landmarks of *Drosophila*

2–62) that is also expressed during gastrulation in stripe formation of the embryo. The carboxyl terminus of the *sna* gene product appears to contain five Zinc-finger motifs indicating a DNA binding mechanisms of transcription factors.

Somatic maternal effect lethal genes: in *Drosophila* {1} *tsl* (*torsolike*, chromosome 3–71) controls the anterior-posteriormost body structures (labrum, telson). Genes {2} *pip* (*pipe*, 3–47), {3} *dl* (*dorsal*, 2–52.9) eliminate ventral and lateral body elements, and their product is homologous to the *c-rel* proto-oncogene, a transcription factor homolog, NF-κB. {4} *ndl* (*nudel*, 3–17) exaggerates dorsal elements of the embryos, {5} *wbl* (*windbeutel*, 2–86) controls dorsal epidermis, and the {6} *sna* (*snail*, 2–51) strong alleles eliminate most mesodermal tissues. {7} The *gs* (*grandchildless*, 1–21), *gs(2)M* (chromosome 2) cause blockage of the embryos of normal-looking homozygous females before the blastoderm stage at temperature above 28.5 C°.

Maternal and germline genes (A very incomplete list. Numbers in parenthesis indicate map locations):

{8} *ANTC* (*Antennapedia Complex*, 3–47.5): This contains elements *lab* (*labial*), *pb* (*proboscipedia*) *Dfd* (*Deformed*), *Scr* (*Sex combs reduced*), and *Ant* affecting head structures in anterior-posterior relations. The *lab* and *pb* elements share cuticle protein genes. Elements (*ftz*) *fushi tarazu*, (*zen*) *zerknüllt*, and *z* (*zen-2* [*zpr*]) affect segment numbers and (*bcd*) *bicoid* functions as a maternal effect gene eliminating anterior structures (head) and duplicating posterior elements (telsons). The product of *bcd* also binds

RNA and acts as a translational suppressor of the *caudal* (*cad*) protein product. The *bcd* and *zen* genes are included in a 50-kb transcription unit called *Ama* (*Amalgam*). The latter four do not have homeotic functions. *Scr* regulates the segmental identity of the anterior thorax and the posterior part of the head is under the control of (*Scr*, *Dfd*, *pb* and *lab*). The entire complex encompasses 355-kb genomic DNA with multiple exons. Eight of the gene products are transcription factors and *Ant*, *Scr*, *Dfd*, *pb*, and *lab* have homeotic functions. The *Antp* (*Antennapedia*) gene has both lethal and viable loss-of-function and gain-of-function recessive and dominant alleles controlling structures anterior to the thorax and the thoracic segments. The first mutations observed converted the antennae of the adult into mesothoracic legs. The gene has two promoters and four transcripts that control differently the spatial expression, relying also on alternate splicing. The *bcd* gene is situated within *zen*, and *Ama* is a maternal lethal that affects head and thorax development. The strong alleles in the females replace the head and thorax of the embryos with duplicated telsons.

Injection of *bcd*⁺ cytoplasm into the embryo (partially) remedies the topical alterations brought about by mutant alleles. The RNA transcript sticks to the anterior pole of the embryo and forms a steeply decreasing gradient in the posterior direction. This *bcd* gradient is regulated by genes *exu*, *swa*, and *stau*, (see them below) and the gradient may be eliminated by mutations in these genes. In *bcd*[−] embryos, the anterior activity of *hb* is eliminated and replaced by

mirror image posterior *hb* stripes. The four exons are transcribed in either a long, complete RNA (2.6-kb) or a short one (1.6-kb) with exons 2 and 3 spliced out. The protein contains homologous tracts to the non-maternal effect genes *prd* (*paired*, 2–45, involved in the control of segmentation) and *opa* (*odd paired*, 3–48, that deletes alternate metasegments). Exon 3 contains the homeodomain with only 40% homology to other homeoboxes. The C-termini of the *bic* protein appears to be involved in transcription activation by binding to five high-affinity upstream sites of *hb* (TCTAATCCC). *Dfd* (*Deformed*) is a weak homeotic gene with recessive and dominant lethal alleles affecting the anterior ventral structures of the head; occasionally thoracic bristles may also appear on the dorsal part of the head. It is composed of five exons coding for a 586-residue protein. Gene *ftz* (*fushi tarazu* [segment deficient in Japanese]) has both recessive late embryo lethal and dominant and viable regulatory alleles affecting genes in the *BXC* (*Bithorax complex*), *Ubx* (*Ultrabithorax*, 3–58.8), involved in the control of the posterior thorax and abdominal segments. The general characteristics of *ftz* are the pair-rule feature, i.e., in the mutants the even numbered abdominal and nerve cord segments are deleted (or fused). The striped pattern of the abdomen is controlled within a 1-kb tract upstream of the beginning of transcription, whereas a more distal upstream element regulates the central nervous system and an even more distal tract is required for the maintenance of the striped pattern. The homeobox is within the second of the two exons of this gene. The *ftz Rpl* mutations may transform the posterior halteres into posterior wing, while the *ftz Ual* mutations convert patches of the first adult abdominal segment into a third abdominal segment-like structure. (The latter two types are not embryonic lethal as the others). The *lab* (*labial*) mutations are embryonic lethal because of the failure of head structures. The protein product of the gene contains *opa* (*odd paired*, 3–48; deletes alternate metasegments) as well as a homeodomain although it does not display homeotic transformations. Gene *pb* (*proboscipedia*) may convert labial (“lip”) portions into prothoracic leg structures or antennae. From the nine exons, #4 and #5 contain the homeobox and in exon 8 there are again *opa* sequences. The gene products (RNA and protein) are localized to the general area affected by the mutations. Null mutations in gene *Scr* (*Sex combs reduced*) are embryonic lethals. Homeotic transformations involve the labial and thoracic areas. Dominant mutation reduces the number of sex comb teeth. Gene *z2* (*zen-2*) has no detectable effects upon development. Gene *zen* (*zerknüllt*) mutations may involve embryo lethality and the products may be required for post-embryonic development.

{9} *arm* (*armadillo*, 1–1.2): Cell lethal at the imaginal disc stage because an anterior denticle belt replaces the posterior part of each segment. Transcripts have been found in all parts of the larva.

{10} *bcd* (*bicoid*): See *AntC*

{11} *bic* and *Bic* (*bicaudal*, 2–67, 2–52, 2–52.91): Genes affect the anterior poles of the embryo by replacing these segments with posterior ones in opposite orientation. *Bic* apparently encodes a protein homologous to actin, a part of the cytoskeletal system.

{12} *btd* (*buttonhead*, 1–31): Mutations fail to differentiate the head.

{13} *BXC* (*Bithorax complex*, 3–58): *BXC* is a cluster of genes that determine the morphogenetic fate of many of the thoracic and abdominal segments of the body. The second thoracic segment, which develops the second pair of legs and a pair of wings, is the most basic part of the complex. The genetic map appears as follows:

abx bx Cbx **Ubx** bxd pbx iab2 **abd-A** Hab iab3 iab4
Mcp iab5 iab6 iab7 **Abd-B** iab8 iab9

The entire complex is organized into three main integrated regions: *Ubx* (*Ultrabithorax*) is responsible for parasegments PS 5–6, *abd-A* (*abdominal-A*) defines the identity of PS7–13, and *Abd-B* (*Abdominal-B*) is expressed in PS10–14. In the *Ubx* domain, *anterobithorax-bithorax* (*abx-bx*) region specifies PS5 and *bithorax-postbithorax* (*bxd-pbx*) defines PS6. In the *abd-A* region are *iab2*, *iab3*, and *iab4*, and in *Abd-B* are *iab5* to *iab9* elements. Mutations in *iab* (*infra-abdominal*) tracts cause the homeotic transformation of an anterior segment to a more anterior abdominal (A) segment (e.g., A2→A1 or A3 [or more posterior ones]→A2, etc.) Mutation *abx* (*anterobithorax*) causes changes in thoracic (T) and abdominal (A) segments: T3 → T2, *bx* (*bithorax*): T3 → T2, *Cbx* (*Contrabithorax*): T2 → T3, *Ubx* (*Ultrabithorax*): A1+ T3 → T2 and T2+ T3→T1, *bxd* (*bithoraxoid*): A1 → T3, *pbx* (*postbithorax*): T3 → T2, *abd-A* (*abdominal-A*): A2 to A8 → A1, *Hab* (*Hyperabdominal*): A1+ T3 →A2, *Mcp* (*Miscadstral pigmentation*): A4 & A5 to an intermediate between A4 & A5, *Abd-B* (*Abdominal-B*): A5, A6, A7, which may be weakly transformed into anterior forms. Most of these changes involve only some structures in the segments but additional alterations may also occur.

{14} *cact* (*cactus*, 2–52) mutations reduce the dorsal elements and enhances ventral structures. This gene encodes a homolog of the I κ -B protein, which forms a complex with product of *dl*, a NF- κ B homolog transcription factor, which is released from the complex upon phosphorylation of the *cact* product. After entering the cell nucleus, it may participate in the activation of its cognate genes.

{15} *capu* (*cappucino*, 2–8) mutations may be lethal. It causes somewhat similar alterations as *stau* in addition to making pointed appendages on the head.

{16} *ci^P* (*cubitus interruptus^P*, Dominant, 4.0): The wing vein 4 is twice interrupted proximal and distal to anterior crossvein. In homozygotes, the anterior portions of the denticle belts are duplicated in a mirror image manner in place of the posterior parts, and they are lethal.

{17} *dpp* (*decapentaplegic*, 2–4.0, [old name was *ho*]) is a complex locus with multiple developmental functions (it is homologous to BMP, TGF- β). The haploid-insufficiency *Hin*/+ condition is dominant embryonic lethal because of defects in gastrulation. The *Hin-Df* (deficiency) and *hin-r* (recessive) are also lethal. The *hin-emb* is an embryonic lethal mutation. It is complementary to the *shv* (*shortvein*) and *disk* (*imaginal disk*) region genes in the same complex. The *shv-lc* recessive larva-lethal mutants complement all *disk* alleles but mutant *Hin* and *hin-r*. Mutants *shv-lnc* do not complement *disk*, *Hin* or *hin-r*, and *shv-p* alleles are viable and complement the disk mutants but not *Hin* or *hin-r*. Another mutation in the *shv* region, *Tg* (*Tegula*) causes the roof-like appearance of the wings. This mutation is complementary to all *dpp* genes. The *disk* group of mutations is either viable or lethal and may affect the eyes, wings, haltere, genitalia, head, imaginal disks, etc. The *dpp* gene apparently acts as regulator of mesodermal genes and it encodes a secreted protein of the TGF- β family transforming growth factor, involved in mammalian cancerous growth.

{18} *ea* (*easter*, 3–57) involves maternal effect lethal with loss- or gain-of-function effects on the dorsal, mesodermal, or lateral structures, depending on the alleles. The mutants may be rescued by injection of normal cytoplasm.

{19} *ems* (*empty spiracles*, 3–53): The interior of the breathing orifices are partially missing and it is embryo lethal.

{20} *en* (*engrailed*, 2–62): some point mutations and chromosome breaks are viable. Others display “pair rule” defects, adjacent thoracic and abdominal segments fuse.

{21} *eo* (*extra organs*, 1–[66]) in the homozygous lethal embryos causes head defects and ventral hole.

{22} *eve* (*even skipped*, 2–58), lethal segmentation and head defects, “pair rule” effects. Its expression is reduced in *h* mutants and *en* segments do not appear. The expression of *Ubx* protein is high in the odd-numbered parasegments 7 to 13 rather than in every segment from 6 to 12; the *ftz* segments are disrupted.

{23} *exu* (*exuperantia*, 2–93) replaces the anterior part of the head with an inverted posterior mid-gut and anal pit (proctodeum).

{24} *fs(1)K10* (*female sterile*, 1–0.5) and a whole series of other *fs* genes in chromosome 1 may have both specific and overlapping effects. Expression may depend on cues from the oocyte. Eggs of homozygous females are rarely fertilized but if they are, the gastrulation is abnormal, the anterior ends are dorsalized.

{25} *fu* (*fused*, 1–59.5): Veins L3 and L4 are fused beyond the anterior crossvein with the elimination of the latter. Heterozygous daughters of homozygous mothers have a temperature-sensitive segmentation problem that is not observed in reciprocal crosses.

{26} *ftz* (*fushi tarazu*): See *AntC* above (also in a separate entry).

{27} *gd* (*gastrulation defective*, 1–36.78) causes dorsal and ventral furrowing of the gastrula stage embryos.

{28} *gsb* (*goosberry*, 2–107.6) is homozygous lethal because the posterior part of segments are deleted and the anterior parts duplicated in mirror image fashion.

{29} *gt* (*giant*, 1–0.9): increased size larvae, pupae and imago based on increased cell size. DNA metabolism is abnormal and both viable and lethal alleles are known affecting many ways the entire embryo. The protein product appears similar to that of *opa*.

{30} *h* (*hairy*, 3–26.5) displays extra microchaetae along the wing veins, membranes, scutellum, and head. It is also a “pair rule” gene and affects the expression of *ftz*. It also regulates the expression of genes in the ASC (*achaete-scute* complex, 1–0.0) involved in the control of hairs and bristles. The major gene products are located in the posterior and adjacent anterior parts of segment primordia.

{31} *hb* (*hunchback*, 3–48) alleles have different effects; the class I alleles among other effects lack thoracic and labial segments, class II mutants retain the prothoracic segment, class III alleles retain also the labial parts, class IV mutations prevent the formation of the mesothoracic segments, class V alleles also cause various gaps as well as segment transformations. These alleles are transcribed from two different promoters and produce up to five different transcripts. The products of this locus interact with those of *kr* and *ftz*. The product of *nos* activates some of the *hb* alleles. The dMi-2 proteins in cooperation with *hb* repress *Polycomb* (see ► *Polycomb* under separate entry at P).

{32} *hh* (*hedgehog*, 3–81): in homozygous embryos a posterior-ventral portion of each segment is removed and the anterior denticle belt is substituted for in a mirror image. The embryos may not have demarcated segments. The gene has two activity peaks: during the first 3–6 hr and at 4–7 days of development (see more under separate entry).

{33} *kni* (*knirps*) [3–46]: these are lethal zygotic gap mutants. Its shorter transcript is expressed only

until the blastoderm stage but the longer one is expressed even after gastrulation. The NH₂ end of the protein is homologous to one of the vertebrate nuclear hormone receptors. The *kni* box, a Zn-finger domain, is homologous to parts of the products of genes *knrl* (*knirps-related*, 3–[46]) and *egon* (*embryonic gonad*, 3–[47]).

{34} *Kr* (*Krüppel*, 2–107.6) mutants show gaps in thoracic and abdominal segments and other anomalies, and are lethal when homozygous. The protein product has similarity to the Zn-finger domain of transcription factor TFIIB. It interacts with transcription factors TFIIB and TFIIE β . In monomeric form it is an activator, in the dimeric form at high concentration it represses transcription. This protein binds to the AAGGGGTAA motif upstream of *hb*. It also affects other maternal effect genes. The GLI oncogene is a homologue.

{35} *nkd* (*naked cuticle*, 3–47.3): Denticle bands are partially missing; germ bands are shortened and thus lethal.

{36} *nos* (*nanos*, 3–66.2) is active in the pole cells, and transport of its product in anterior direction is required for the normal abdominal pattern, and it is essential for the normal development of the germline. It is a maternal lethal gene. Its product represses that of *hb* in the posterior part of the embryo. Deficiency of both *hb* and *nos* is conducive, however, to normal development.

{37} *oc* (*ocelliless*, 1–23.1): Some alleles are viable although the ocelli are eliminated; others (*otd*) involve lethality because of neuronal defects.

{38} *odd* (*odd skipped*, 2–8): Embryonic lethal because posterior part of the denticle bands are replaced by the anterior parts in mirror image fashion in T2, A1, A1, A3, A5, and A7.

{39} *opa* (*odd paired*, 3–48): Alternate metasegments are genetically ablated. Denticle bands of T2, A1, A3, A5, A7, and naked cuticle of T3, A2, A4, and A6 are absent. The product of *en* is lost but that of *Ubx* increases in even-numbered parasegments.

{40} *osk* (*oskar*, 3–48): Homozygous females and males are fertile but the embryos produced by homozygous females are defective in the pole cells and consequently also in abdominal segments; IT affects also *BicD* and *hb* expression.

{41} *phl* (*pole hole*, 1–0.5) blocks the formation of anterior–posterior end structures as well as the entire 8th abdominal segment. The phenotype is similar to that caused by *tso*. It is the *raf* oncogene in *Drosophila*.

{42} *pll* (*pelle*, 3–92) gene causes maternal embryo lethality by preventing the formation of ventral and lateral structural elements.

{43} *prd* (*paired*, 2–45): In strong mutants the anterior parts of T1, T3, A2, A4, A6, and A8 and

posterior parts of T2, AS1, A3, A5, and A7 are absent.

{44} *run* (*runt*, 1–[65.8]; syn. *legless* [*leg*]): A “pair rule” embryo lethal; eliminates the central mesothoracic and the uneven numbered abdominal denticle belts. The deletions are accompanied by duplication of the more anterior structures. The wild type allele appears to regulate the expression of *eve* and *ftz*.

{45} *slp* (*sloppy paired*, 2.8): Parts of the naked cuticle are missing from T2, A1, A3, A5, and A7 in an irregular way and it causes lethality.

{46} *sna* (*snail*, 2–51): Embryonic lethals causes the dorsalization and reducing or eliminating of most of the mesodermal tissues. The C-terminus of the polypeptide encoded has five Zn-finger motifs.

{47} *snk* (*snake*, 3–52.1) is a maternal lethal gene with dorsalizing effects. The encoded polypeptide contains elements homologous to serine proteases.

{48} *spi* (*spitz*, [*spire*], 2–54) is embryonic lethal blocking the development of anterior mesodermal tissues.

{49} *spz* (*spätzle*, 3–92): Maternal lethal alleles accentuate dorsal structures.

{50} *stau* (*staußen*, 2–83.5) ablates pole cells and other anterior structures and some abdominal segments; causes the *grandchildless-knirps* syndrome. The Staufen protein binds RNA, and along with the Prospero RNA, is asymmetrically partitioned into the ganglion mother cells (GMC) and thus, they determine neuroblast cell fate. It functions also nonsense-mediated decay.

{51} *swa* (*swallow*, 1–15.9) is expressed in the nurse cells and the product is transported to the oocyte and into the blastoderm until gastrulation, leading to problems with nuclear divisions, head, and abdominal defects. In *swa* homozygotes the *bcd*⁺ products are disrupted.

{52} *tl* (*Toll*, 3–91): Females heterozygous for the dominant or homozygous for the recessive *tl* mutant alleles produce lethal embryos that are defective in gastrulation and dorsal or ventral structures. The gene product is an integral membrane protein. Toll-like proteins are receptors of interleukin signals in the innate immunity system of mammals.

{53} *tll* (*tailless*, 3–102) deletes several posterior structures (Malpighian tubules, hindgut, telson), but brain and other anterior structures are also missing. Its expression is required for the manifestation of “pair rule” genes, *h* and *ftz*, in the 7th abdominal segment and for site-specificities of *cad* (*caudal*, 2–[55]) involved with head, thorax, and abdominal structures and regulation of *ftz*, *hb* (see above), and *fkh* (*fork head*, 3–95, involved with homeosis in both anterior and posterior structures of this non-maternal embryonic lethal). Gene *tll* has negative effects on genes *kni*, *Kr*, *ftz* and *tor*.

{54} *tor* (*torso*, 2-[57]) locus has both loss-of-function and gain-of-function alleles. The former type of alleles eliminate anterior-most head structures and segments posterior to the 7th abdominal segment. The latter type alleles are responsible for defects in the middle segments and enlargement of the most posterior parts of the body. The gene is expressed in the nurse cells, oocytes, and early embryos. The expression of *ftz* is reduced in the gain-of-function *tor* mutants, whereas *phl* mutations are epistatic to *tor*. With the exception of the NH₂ terminus, the protein is homologous to the growth factor receptor kinases of other organisms. It is concentrated in both pole cells and at the surface cells. Apparently, the product of this gene receives and transmits maternal information into the interior of the embryo.

{55} *trk* (*trunk*, 2-36) mutants lack anterior head structures as well as segments posterior to the 7th abdominal band.

{56} *Tub* (*tubulin* multigene families, scattered in chromosome 2 and 3). The α *Tub* genes are responsible for the production of α -tubulin and are apparently active in the nurse cells; the transcripts accumulate in the early embryo and the ovaries and control mitotic and meiotic spindle and cytoskeleton. The β -tubulin genes are expressed in the nurse cell, early embryos, and various different structures and organs.

{57} *tud* (*tudor*, 2-[97]): The germline autonomous mutants display the “grandchildless-knirps” phenotype and lack pole cells, yet about 30% of the embryos survive into sterile adults.

{58} *tuf* (*tufted*, 2-59): Segment boundaries are duplicated in a mirror image and other parts deleted and neuronal pattern altered.

{59} *twi* (*twist*, 2-100): Mutants are embryo lethal with defects in mesodermal differentiation. The embryos are twisted in the egg case. Mutations at the *dl*, *ea*, *pll*, and *Tl* loci prevent the expression of *twi*. The *twi* polypeptides are homologous to DNA-binding myc proteins.

{60} *Ubx* (*Ultrabithorax*, 3-58.8): See *BXC*

{61} *vas* (*vasa*, 1-[64]) affects the pole region and segmentation (*grandchildless-knirp* syndrome). The protein product is homologous to murine peptide chain translation factor eIF-4A.

{62} *vls* (*valois*, 2-53): The phenotype is very similar to that caused by *vas*.

{63} *wg* (*wingless*, 2-30): Visible, viable, and lethal alleles control segmentation pattern and imaginal disk pattern (wings and halteres). Its protein product is homologous to the mouse mammary oncogene *int-1* (INT1/Wnt). It appears that *frizzled* (*fz*) is the receptor of *wg*. The signal then may be transmitted to *Dsh* and *Arm* (β -catenin) and transcription of *En* is turned on with the assistance of

other factors. (See more under ►*wingless* and ►*wnt* entries).

{64} *zen* (*zerknüllt*) is a segment of *ANTC* {8} affecting segmentation and dorsal structures of the early embryo.

The maternal germline mutations are genetically identical in the unfertilized egg and their gene products generally cause lethality in the egg or in the homozygous embryos. The heterozygous mothers are semi-sterile and the males are usually fairly normal in appearance and in function. The molecular bases of a few such lethal genes are known. E.g., the *phl* gene appears to be homologous to the *v-raf* protooncogene and *phl* gene is the *Drosophila raf* gene that encodes a serine-threonine kinase protein also in humans and mice. The *snk* locus encodes a protein that appears to have a calcium-binding site at the NH₂-end and with homology to several serine proteases at its C terminus. The product of the *ea* gene has some homology to an extracellular trypsin-like serine proteases. Specific cytoplasm extracted from some (e.g., *osk*, *tor*, *ea*, *bcd*) unfertilized normal eggs or from normal embryos when injected into the mutant cytoplasm end may rescue the embryos that develop into sterile adults. The 923-amino acid protein encoded by *tor* has no homology to other known proteins in the NH₂-end but the rest of it is similar to a growth factor receptor tyrosine kinases and a hydrophobic segment appears to be associated with the cell surface membrane. The product of the *Tl* locus is an integral membrane protein with both cytoplasmic and extracytoplasmic domains containing 15 repeats of leucine-rich residues resembling yeast and human membrane proteins. The cytoplasmic domain is homologous to the interleukin-1 receptor (IL1R), the heterodimeric platelet glycoprotein 1b, and coded in human chromosome 2q12 and mouse chromosome 1 near the centromere.

Although all of the mutants assigned to different chromosomal locations have different molecular functions, the phenotypic manifestation may not necessarily distinguish that. The majority of the morphogenetic-developmental mutations is pleiotropic (e.g., affects the pole cells and causes the *grandchildless-fushi tarazu* syndrome). Many display epistasis and indicate the complex interactions of the regulatory processes involved (e.g., the expression of *twi* may be prevented by mutations at *dl*, *ea*, *pll*, and *Tl*). The genes may be expressed at a particular position but their products form a diminishing gradient (e.g., *bcd*, *nos*). The DNA-binding protein encoded by *bcd*, depending on its quantitative level, then regulates qualitatively the transcription of, e.g., *hb*. Some of the genes display the so-called “gap” effect. They eliminate particular body segments, e.g., *kni*, *Kr*; and *hb*. The so-called “pair rule”

genes may eliminate certain body segments and replace them with others (e.g., *ftz*, *eve*) or eliminate half of the segments and fuse them together in pairs (e.g., *en*). Several of the genes, particularly those in the huge *BTC* and *ATC* clusters, may display homeotic effects. Although a great deal of information has been gathered on these genes primarily during the last decade, more specific knowledge is required for understanding the precise functions (especially the interacting circuits) of the morphogenetic processes. With the aid of microarray hybridization, information on the interacting systems will greatly expand. It appears that these genes are frequently preferentially expressed at a particular position. Their mRNA or protein product is then spread in a gradient to the sites of the required action. In some instances, only the RNA is spread and the protein is made locally. The position of morphogenetic function is controlled by a hierarchy of signals. These genes are expressed differently in different time frames and in coordinated sequences. The coordination is provided by the interaction of gene products. The same protein may turn on a set of genes and turn off others, depending also on the local concentration of the products.

According to their **main** effects, some of these genes may be classified into groups, others are more difficult to place in any of the groups because they all affect several stages and different structures. (The horizontal line stands for the embryo axis and the arrows or gaps illustrate the typical sites of action; the best representative genes are bracketed):

MATERNAL ANTERIOR GENES:→ ____ 1, 10 see [8] 23, 51,
 MATERNAL POSTERIOR GENES: ____← 6, 11, [36], 40, 50, 57, 61, 62
 MATERNAL END SEGMENT:— ←1, 24, [54], 55,
 MATERNAL DORSO-VENTRAL:—↓↑—2, [3] 4, 5, [14], 17, 18, 42, 46, 49, 52, 59, 63
 ZYGOTIC GAP:— ____ — ____ — ____ 29, [31], [33], [34], 53
 ZYGOTIC PAIR RULE:— - - - [22], 26, [30], 38, 39, [14], 45
 ZYGOTIC SEGMENT POLARITY:—→←—→←— 9, 16, [20], 25, 28, 32, 35, 43, [63]
 HOMEOTIC GENES: genes within the *Antennapedia Complex* (8), and the *Bithorax Complex* (13)

The development of wing veins is controlled by several genes. Locus *vn* (*vein*, 3–16.2, *Vein*, 3–19.6) disrupts longitudinal vein L4, posterior crossvein and sometimes L3, *ri* (*radius-incompletus* 3–46.8) interrupts L2, and mutations in *px* (*plexus*, 2–100.5) produce extra veins. *N* (*Notch*, 1–3.0) complex (*Ax*, *Co*, *fa*, *l(1)N*, *N*, *nd*, *spl*), with a very large number of (dominant and recessive) alleles, are homo- and hemizygous lethal and remove small portions of the ends of the wings and affect also hair and embryo morphogenesis, thickening of veins L3 and L5, and hypertrophied nervous system. *Notch* gene homologs are also present in vertebrates. The *N* complex codes for a protein with EGF-like repeats.

The *Ax* (*Abruptex*) homozygotes reduce the length of longitudinal vein L5 and commonly L4, L2, and sometimes L3. The various *Ax* alleles are either positive or negative regulators of *Notch*. The *Notch* signals are modulated by *fringe* and this gene determines the dorsal ventral boundaries. *Co* (*Confluens*) causes thickening of the veins. The *fa* alleles affect the eye facets and are non-complementary to the *spl* gene that also causes rough eyes and bristle anomalies. Gene *nd* (*notchoid facet*) is homozygous viable and displays some of the characteristics of the other genes within the complex. *E(spl)* (*Enhancer of split*, 3–89) mutation became known for exaggerating the expression of *spl* (enhancer in this context does not correspond to the term enhancer as used in molecular biology). This gene produces 11 similar transcripts. They share homologies with *c-myc* oncogene (a helix-loop-helix) protein and also with the β -transducin G protein subunit, known to involve signal transduction. *Dl* (*Delta*, 3–66.2) causes thickening of the veins (and a number of other developmental defects) and is responsible for a protein that has an extracellular element with nine repeats resembling the EGF, an apparent transmembrane and an intracellular domain with apparently five glycosylation residues. *Egfr* (*Epidermal growth factor receptor* [synonyms *top* {*Torpedo*}, *Elp* {*Ellipse*}, *fbl* {*faint little ball*}, 2–100) genes cause embryonic lethality and a number of other developmental effects including extra wing veins, eyes, etc.

The genes *wg* (see above {63} and *dpp* (see {17}) are involved in anteriorposterior specifications of the

embryo and thus, also in wing formation. Several other genes also affect wing and vein differentiation. Molecular evidence permits the assumptions that *Dsh* (dishevelled), a cytoplasmic protein is one of the receptors of the *Wg* protein signal. *Dsh* binds to *N* (*Notch*, a transmembrane protein) and inhibits its activity. When *N* binds to *Delta* it activates *Su(H)*, the suppressor of *hairless* (*H*). *Su(H)* then moves to the cell nucleus and operates as a transcription factor. The *Wg* signal can also activate the *Shaggy-Zeste white* (*Sgg-Za3*) serine- threonine kinase and the phosphorylation of *Armadillo* may lead the *Wg*-dependent gene expression. The level of *Armadillo* may be elevated also by binding *Wg* to a member of

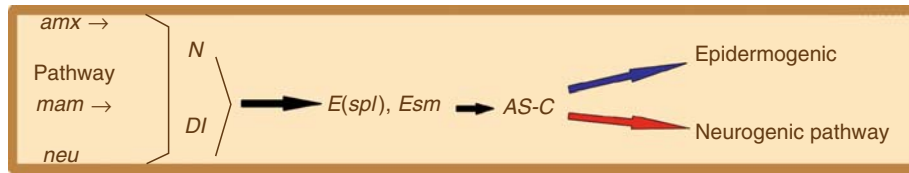


Figure M114. Epidermogenic and neurogenic pathways in *Drosophila*

the frizzled family (Dfz2). This *frizzled* (*fz*, 3–41.7) appears to be another receptor of Wg. Diffusible protein product of *optomotor-blind* (*omb*, 1–{7.5}), which was initially identified on the basis locomotor activity, is also required for the development of the distal parts of the wing within the *wg-dpp* system.

A general picture of neurogenesis is also emerging (see Fig. M114). (Modified after Campos-Ortega, Knust 1992 p. 347. In: Development. Russo VEA et al (Eds.) Springer Vlg., New York):

amx (*almondex*, 1–27.7) is a locus with multiple functions including eyes [some alleles complement the *lozenge* mutants]. Most relevantly, in the mutants there is hyperplasia of the central - peripheral nervous system and a concomitant reduction in epidermogenesis.

mam (*master mind*, 2–70.3) also affects the eyes but mutations lead to neural hyperplasia and epidermal hypoplasia.

neu (*neural*, 3–50) mutations also cause neural hyperplasia and epidermal hypoplasia.

N and *DI* have been briefly described above. Both have protein products with epidermal growth factors (EGF)-like repeats. EGF has growth promoting signals and has ability to bind appropriate ligands.

E(spl): The wildtype alleles encode a protein with helix-loop-helix motifs, characteristic for transcription factors and displays similarities also to one subunit of the trimeric G proteins, which have key roles in several signal transduction pathways.

ASC (*achaete-scute complex*, 1–0.0) controls sensilla and micro- and macrochaetae that are sensory organs of the flies and correspond to the peripheral nervous system. The ca. 100-kb region contains four major distinguishable areas *ac* (*achaete*), *sc* (*scute*), *l(1)* *s* (*lethal scute*) and *ase* (*asense*). All four reduce and alter the pattern of the sensory organs. The dominant components, the *Hw* (*Hairy wing*) mutations, increase hairiness. Another regulatory mutation has been named *sis-b* (*sisterless b*). The complex includes nine transcription units. Four of them appear to be transcription factors because of the helix-loop-helix motifs.

svr (*silver*), *elav* (*embryonic lethal abnormal vision*), and *vnd* (*ventral nervous system defective*) all are affected in the nervous system and located at 0 position of the X chromosome just like *ASC*. A large number of other genes at various locations are

also involved in the nervous system. One must remember that in even a relatively simple organism, such as *Drosophila* ~ 14,000 genes exist and their functions are too complex to be represented by simple models. ▶ *Drosophila*, ▶ *homeotic genes*, ▶ *morphogens*, ▶ *gap genes*, ▶ *clonal analysis*, ▶ *developmental genetics*, ▶ *signal transduction*, ▶ *imaginal disks*, ▶ *oncogenes*, ▶ *pattern formation*, ▶ *selector genes*, ▶ *RNA localization*, some genes are described with more details under separate entries, ▶ *selector genes*; Morisato D, Anderson KV 1995 Annu Rev Genet 29:371; Mann RS, Morata G 2000 Annu Rev Cell Dev Biol 16:243.

Morphogenetic Field: An embryonal compartment capable of self-regulation.

Morphogenetic Furrow: An embryonic tissue indentation marking the front line of the differentiation wave. Signal molecules mediate its progression. ▶ *morphogenesis*, ▶ *morphogenesis in Drosophila*, ▶ *daughter of sevenless*

Morpholinos: Antisense oligomers that block cell proliferation, interfere with normal splicing of pre-mRNAs, and generate aberrant splicing (see Fig. M115). They are highly specific and immune to nuclease (RNase H). They are suitable for the inactivation (knock-down) of targeted genes. (See Summerton J 1999 Biochim Biophys Acta 1489:141).

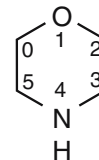


Figure M115. Morpholine

Morphology: Study of structure and forms.

Morphometry: Quantitative study of shape and size of a body or organ. ▶ *QTL*

Morphosis: A morphological alteration, a phenocopy rather than being a mutation.

▶ *phenocopy*, ▶ *epigenetic*

Morquio Disease: ▶ *gangliosidosis type I*

Morsier Syndrome: ▶septo-optic dysplasia

Morsus Diaboli (literally devil's bite): The fringe end of the oviduct (Fallopian tube) at the ovary. ▶uterus

Mortality: The condition of being mortal, i.e., subject to death. The rate of mortality is computed as the average number of deaths per a particular (mid-year) population. An important factor of (particularly) infant death rate is the coefficient of inbreeding. First cousin marriages (inbreeding coefficient 1/16) approximately double infant mortality. The rate of human mortality calculated as the number of deaths per 1000 population may vary substantially in different parts of the world. In the years 1955–59, in the USA it was 9.4, in England 11.6, in Japan 7.8. In some other parts of the world it was double or higher. *Extrinsic mortality* is an age and condition-independent concept. Infant mortality rate is highly correlated with the level of income in the world's 231 countries. In the 48 high-income countries, it is 0.8%, whereas in the lowest-income 67 countries, it was 79.2% by latest reports in 1999 (United Nations Demographic Yearbook, New York). In the same group of countries, birth was 7.9 and 55.8%, respectively. These figures indicate high birth rates and high infant and child mortality in the low-income countries. In the high-income countries the female literacy rate was 96, whereas in the low-income countries it was 68 and the health expenditure in dollars of purchasing power parity (PPP) was 2435 and 59 per capita, respectively. In the AIDS pandemic South Africa and Botswana, in the age group 15–49, mortality was 20.1 and 38.8%, respectively between 1997–1999. The median age in years in England, a high-economy country, was 40 and in the lower-resource-but-transitional country of Iran it was 20. More than 50/1000 births in developed countries are affected by genetically determined anomalies and almost 30% of them involve early mortality. Congenital heart disease involves more than 40% mortality and congenital malformation of the central nervous system is the second greatest cause of mortality at about 26%. In Western Europe, about 50% of the pregnancies with severe genetic/developmental defects are medically terminated. ▶inbreeding coefficient, ▶age-specific birth and death rates, ▶longevity, ▶aging, ▶juvenile mortality, ▶morbidity, ▶alcoholism substance abuse, ▶addiction, ▶smoking, ▶counseling genetic, ▶family planning, ▶prenatal diagnosis; Christianson A, Modell B 2004 Annu Rev Genomics Hum Genet 5:219; www.mortality.org.

Morula: A mass of blastomeres, containing 8–16 cells in the mouse (see Fig. M116) (the number of cells in humans is about twice or more) before implantation of the zygote onto the uterus by transfer the morula from the oviduct. ▶blastomeres, ▶blastocyst



Figure M116. Morula

Mos: ▶mariner

MOS (*mos*): ▶Moloney mouse sarcoma virus oncogene, ▶MITE

Mosaic: Mixture of genetically different cells or tissues. Mosaicism is generally the result of somatic mutation, change in chromosome number, deletion or duplication of chromosomal segments, mitotic recombination, nondisjunction, sister chromatid exchange, sorting out of mitochondrial or plastid genetic elements, infectious heredity, intragenomic reorganization by the movement of transposons or insertion elements, lyonization, gene conversion, lyonization etc.

A mosaic hybrid may be the result of co-dominance of the parental alleles (see Fig. M117). Some breeds, however, display homozygosity for mosaicism. Introduction of foreign DNA into the cells by transformation or gene therapy may also be the cause of mosaic tissues. Somatic mutation may be of medical importance and may lead to oncogenic transformation and the expression of cancer. Somatic reversion of recessive genes causing disease, e.g., reversion of adenosine deaminase (ADA) or the tyrosinemia (FAH) genes, followed by selective proliferation of the normalized sector, may alleviate the disease. Loss of the extra chromosome in trisomics or nondisjunction in monosomics may restore the normal chromosome number. When a mutation is induced only in a single strand of the DNA, its expression may be delayed, but in mice fur patches may occur in the heterozygotes



Figure M117. "Mosaic hybrid" rooster

and these animals are called *masked mosaics*. ▶[sex-chromosomal anomalies in humans](#), ▶[variegation](#), ▶[lyonization](#), ▶[allophenic](#), ▶[mosaic variegated aneuploidy](#); Extavour C, Garcia-Bellido A 2001 Proc Natl Acad Sci USA 98:11341; Yousouffian H, Pyeritz RE 2002 Nature Rev Genet 3:748.

Mosaic Analysis with Double Marker (MADM): Two reciprocally chimeric genes, each containing the N terminus of one marker and the C terminus of the other marker interrupted by a loxP-containing intron, are knocked in at identical locations on homologous chromosomes (see Fig. M118). Functional expression of markers requires Cre-mediated interchromosomal recombination. Such a system can generate loss of heterozygosity in tumor suppressor genes and their fate in cancer development can be followed (Zong H et al 2005 Cell 121:479; Mazumdar MD et al 2007 Proc Natl Acad Sci USA 104:4495). ▶[Cre/loxP](#), ▶[LOS](#), ▶[tumor suppressor gene](#)

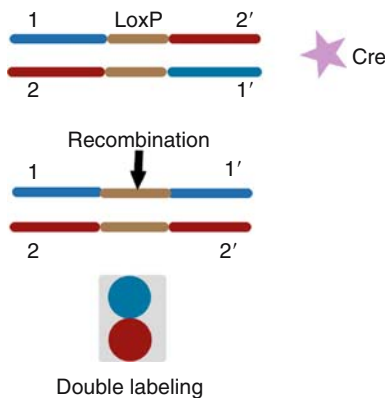


Figure M118. MADM

Mosaic genes: Mosaic genes contain exons and introns. Also some nuclear genes borrow from or loan exons to organelles or vice versa. Transposition can generate mosaics. Exon shuffling also generates mosaic genes. ▶[introns](#), ▶[exons](#), ▶[exon shuffling](#), ▶[organelle sequence transfer](#), ▶[transposition](#); mosaic genes in human chromosome 22: Bailey JA et al 2002 Am J Hum Genet 70:83.

Mosaic theory: ▶[suicide vectors](#)

Mosaic Variegated Aneuploidy (MVA, BUB1B/BUBR1, 15q15): MVA is characterized by somatic aneuploidy (trisomy, monosomy) of different chromosomes and in different tissues, apparently due to defects in the spindle checkpoints and nondisjunction. The premature termination of the transcript leads to the formation of a truncated protein. The recessive disorder causes reduced intrauterine growth, microcephaly, eye anomalies, and other morphological

defects (Hanks S et al 2004 Nature Genet 36:1159). The mutation leads to carcinogenesis, and the condition is frequently associated with rhabdomyosarcoma, Wilms tumors, leukemia, colorectal cancer, etc. The same defect occurs in yeast and various vertebrates. ▶[cancer](#), ▶[aneuploidy](#), ▶[Wilms tumor](#), ▶[leukemia](#), ▶[colorectal cancer](#)

Mosolov model: In the Mosolov model, an extremely long DNA fiber is tightly packed into a very compact eukaryotic chromosome (see Fig. M119). One of the many existing models is shown here. Each line represents an elementary chromosome fiber, including the nucleosomal structure at various stages of folding. E conceptualizes the chromomeres. The elementary fiber is about 25 Å in diameter and forms a tubular coil (solenoid). D signifies the tightly coiled coils of the metaphase chromosomes. ▶[packing ratio](#), ▶[nucleosome](#), ▶[chromosome structure](#), ▶[chromosome coiling](#), ▶[SMC](#), ▶[condensin](#)

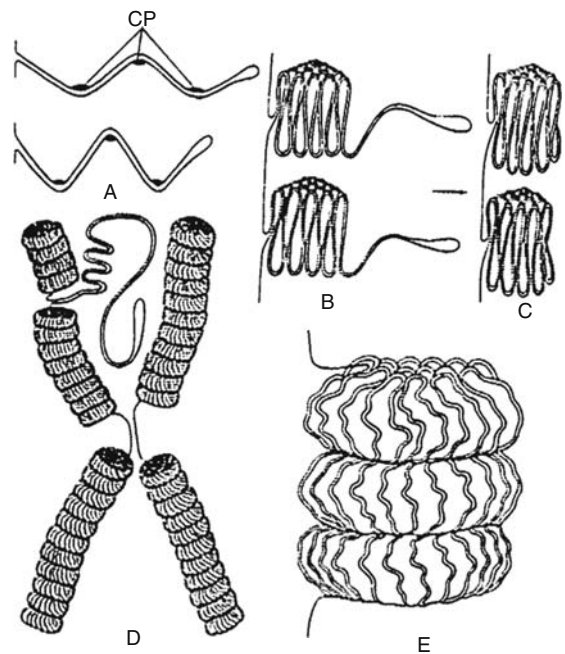


Figure M119. Mosolov model of chromosome structure. (Diagram from Kushev VV 1974 Mechanisms of Genetic Recombination. By permission of the Consultants Bureau, New York)

Mosquito: *Culex pipiens*, 2n = 6. ▶[malaria](#), ▶[Anopheles gambiae](#), ▶[Aedes aegypti](#); Atkinson P W, Michel K 2002 Genesis 32:42; <http://www.tigr.org/tdb/tgi/>.

MOST: is web tool for extraction of motifs in DNA sequences. (See Pizzi C et al 2005 Nucleic Acids Res. 33 (15):e135; <http://telethon.bio.unipd.it/bioinfo/MOST/>).

Mossy Fibers: Microtubules on nerve axons (see Fig. M120).



Figure M120. Mossy fiber

Most Recent Common Ancestor: ►MRCA, ►coalescent

Motheaten: Mutation in the SH2 domain of a tyrosine phosphatase of mice leading to autoimmune anomalies. ►tyrosine phosphatase, ►autoimmune disease, ►SH2; White ED et al 2001 J Leukoc Biol 69:825; Hsu HC et al 2001 J Immunol 166:772.

Mother-Fetus Compatibility: ►immune tolerance, ►Rh blood groups, ►incompatibility, ►mylotarg

Motif: A small, non-random assembly of structural domain or sequence of amino acids or nucleotides present in different macromolecules. Motifs are generally preserved during evolution and usually convey some functionality. The probability of a motif is matrix of probabilities. The column number in the matrix is the length (N) of the motif. The number of rows is four in DNA (the four kinds of nucleotides) and it is 20 in protein (the 20 common amino acids). Row number *i* and column number *j* specify the probability for finding a special appearance (instance) of a motif. ►protein domains, ►module, ►MP-score, ►matrix algebra, ►MOST; <http://www.bioinf.man.ac.uk/dbbrowser/PRINTS/>; motifs in different sets of genomic data: <http://fraenkel.mit.edu/webmotifs/>; new motif discovery: <http://genie.dartmouth.edu/scope/>.

Motif Ten EL6:47 PM (MTF): MTF promotes transcription by DNA-dependent RNA polymerase II when it is located in the core promoter at +18 to +22 from the initiator element (A+1). ►core promoter; Lim CY et al 2004 Genes Dev 18:1606.

Motif-Trap Technology: In motif-trap technology, random fragments of DNA fused to fluorescent protein are screened and their location in the cells is monitored. The procedure may facilitate the identification of the function of the unknown sequences. ►aequorin; Cutler SR et al 2000 Proc Natl Acad Sci USA 97:3718.

Motilin: A 22-amino acid, well-conserved, peptide hormone regulating motility of the intestinal tract. (See Coulie B et al 2001 J Biol Chem 276:35518).

Motor Proteins: Motor proteins can move along microtubules and actin filaments or macromolecules by deriving energy from the hydrolysis of energy-rich

phosphates such as ATP. They transport various molecules and vesicles within the cell. Motor proteins mediate some of the processes involved in establishing body plans, such as left-right, dorso-ventral, and anterior-posterior differentiation. Representatives include myosin, kinesin, dynein, helicases, bimC, etc. The MyoVa motor is involved in melanosome transport and organization of the endoplasmic reticulum in Purkinje cells. Motor protein defects are involved in several human diseases. ►microtubule, ►anaphase, ►duty ratio/duty cycle, ►myosins, ►actin, ►kinesin, ►dynein, ►Purkinje cells, ►albinism, ►cytoskeleton, ►caveolae; Karcher RL et al 2001 Science 293:1317; Schliwa M, Woehlke G 2003 Nature [Lond] 422:759; review: Mallik R, Gross SP 2004 Current Biol 14:R971; motor proteins in nanotechnology: van den Heuvel MGL, Dekker C 2007 Science 317:333.

Mountjack (*Muntiacus muntjack*): The male is $2n = 7$ and the female is $2n = 6$ but the *Muntiacus reevesi* is $2n = 46$ (see Fig. M121).

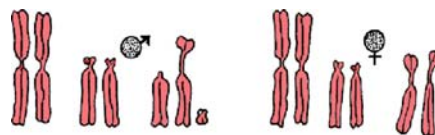


Figure M121. Mountjack chromosomes after Wurster & Bernischke

Mouse: The mouse of a computer is a pointer device.

Mouse (*Mus musculus*, $2n = 40$): Rodent belonging to the subfamily *Murinae*, including about 300 species of mice and rats (see Fig. M122). They are extensively used in genetics and physiological studies because of their small size (25–40 g), short lifecycle (10 weeks), life span of about two years, gestation ~19 days, having 5–10 pups/litter, and their practically continuous breeding. The genome is $\sim 1.8 \times 10^6$ kDa in $2n = 40$ chromosomes. The mouse genome is ~14% smaller than the human genome, yet about 40% of their genomes can be aligned. In one m² laboratory space up to 3,000 individuals can be studied annually. From embryonic stem cells, viable, fertile adults can be differentiated (Eggan K, Jaenisch R 2003 Methods Enzymol 365:25). Very detailed linkage information is available. According to the 1996 map the genetic length, based on 7,377 genetic markers including RFLP and other markers, is 1,360.9 units. The average spacing between markers then was 400 kb. A nucleotide sequence draft became available in 2002 and the final annotated sequence was expected by 2006. Transformation, gene targeting and other modern techniques of molecular genetic manipulations are well worked out. It is also very important

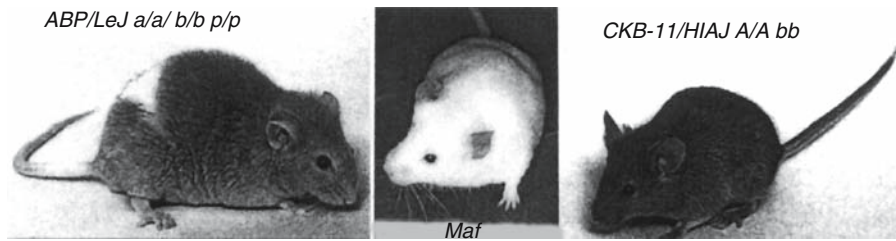


Figure M122. Mouse has a very large number of spontaneous and induced variations involving morphological, physiological, biochemical, and behavioral traits. Left: *pink-eyed dilution*, A/a *Typr*^{1^b}/*Typr*^{1^b} *bt/bt* *p/p*, chromosome 7–28.0. Middle: Kit ligand, *Mgf*^{S1-pan}/*Mgf*^{S1-pan}, chromosome 7 10–57.0. Right: tyrosine related, A/A *Typr*^{1^b}/*Typr*^{1^b}, chromosome 4–38. (Courtesy of Dr. Paul Szauter, <http://www.informatics.jax.org/mgihome/other/citation.shtml>).

that the mouse be used as a human genetic model for immunological, cancer, and other human diseases. About >85% of the autosomal gene repertory of the mouse displays conserved synteny with that in the human genome. The X chromosomal genetic structure is practically identical in man and mouse. *Mus spretus*, “a non-laboratory” relative, is similar in appearance to the laboratory mouse but it harbors many genetic differences and can form fertile female hybrids with the laboratory strains, which are inbred. Both of these species differ from the house mouse, *Mus domesticus*. In mice, Robertsonian translocations are common, and therefore the chromosome number may vary in different populations and in different individuals: <http://www.immunologylink.com/transgen.htm>. ►databases, ►animal models, ►ENU, ►MICER, ►IGTC, ►Encyclopedia of the Mouse Genome, ►Mouse Genome Database, ►Mouse Genome Informatics Group, ►Portable Dictionary of the Mouse Genome; Mapping information in *Nature* (Lond.) 380:149, knockout, radiation hybrid map: *Nature Genet* 1999 22:383; YAC-based physical map: *Nature Genet* 1999 22:388; Festing MFW 1979 *Inbred Strains in Biomedical Research*. Oxford Univ. Press, New York; origin of outbred strains, including genealogy of Swiss mice: Chia R et al 2005 *Nature Genet* 37:1181; large-scale gene expression information about mouse tissues and cells: Siddiqi AS et al 2005 *Proc Natl Acad Sci USA* 102:18485; Fox JG et al (Eds.) 2006 *The Mouse in Biomedical Research*. Academic Press, San Diego, California; <http://cgap.nci.nih.gov/SAGE#mouse>; electronic information sources: <http://www.informatics.jax.org>; <http://www.genome.wi.mit.edu> or by “help” to mailto:genome_database@genome.wi.mit.edu; <http://genome.rtc.riken.go.jp> BodyMap, nude mouse; <http://www.rodentia.com/wmc/index.html>; book: <http://www.informatics.jax.org/silver>; genetrapp: <http://www.genetrapp.org/>; transgenic and knockout: <http://www.immunologylink.com/transgen.htm>; Mouse Atlas: <http://genex.hgu.mrc.ac.uk>; genetic map: Dietrich WF et al 1996

Nature [Lond] 388:149; Mouse Sequence Consortium: <http://www.ensembl.org>; <http://www.ncbi.nlm.nih.gov/genome/seq/MmProgress.shtml>; transcript view: http://www.ensembl.org/Mus_musculus/transcriptsnpview; functional annotation; cDNA clones: <http://fantom.gsc.riken.go.jp/db/>; mouse gene expression pattern database: www.genepaint.org/; functional annotation: <http://mips.gsf.de/genre/proj/mfungd/>; embryo development: <http://genex.hgu.mrc.ac.uk/Emage/database/emageIntro.html>; Center for Rodent Genetics: <http://www.niehs.nih.gov/crg/cprc.htm>; gene expression database: http://www.informatics.jax.org/menus/expression_menu.shtml; mouse phenotypes: <http://www.jax.org/phenome>; GXD, *Adv Genet* 35:155; Joyner AL (Ed.) 2000 *Gene targeting. A practical approach*. Oxford University Press, Oxford, UK; mouse chromosome 16 versus human genome: Mural RJ et al 2002 *Science* 296:1661; physical map: Gregory SG et al 2002 *Nature* [Lond] 418:743; mouse genome: *Nature* [Lond] 420:509 2002, 15,000 cDNA sequences: Strausberg RL et al 2002 *Proc Natl Acad Sci USA* 99:16899; Paigen K 2003 *Genetics* 163:1; book with cDNA samples: Kawai J, Hayashizaki Y (Eds.) 2003 *RIKEN Mouse Genome Encyclopedia DNA Book*, RIKEN Genomic Sciences Center, Waco, Japan, genetic screens: Kile BT, Hilton DJ 2005 *Nature Rev Genet* 6:557; genome engineering: Glaser S et al 2005 *Nature Genet* 37:1187; genetic resources: Peters LL et al 2007 *Nature Rev Genet* 8:58.

Mouse Genome: A newsletter of Journal Subscriptions Department, Oxford University Press, Walton Str., Oxford, OX2 6DP, UK.

Mouse Genome Database (MGD): MGD integrates various types of information, mapping, molecular, phenotypes, etc. Contact: Mouse Genome Informatics, The Jackson Laboratory, 600 Main Str., Bar Harbor, ME 04609, USA, Phone: 207-288-3371, ext. 1900. Fax: 207-288-2516. INTERNET: mgi-help@infor

informatics.jax.org; for transgenic and knockout: <http://www.immunologylink.com/transgen.htm>.

Mouse Genome Informatics Group: An electronic bulletin board. Information: Mouse Genome Informatics User Support, Jackson Laboratory, 600 Main Str., Bar Harbor, ME 04609, USA. Phone: 207-288-3371, ext. 1900. Fax: 207-288-2516. INTERNET: mgi-help@informatics.jax.org.

Mouse Lymphoma Test for Genotoxicity (MLA): MLA employs thymidine kinase heterozygous (TK^{+/−}) and homozygous (TK^{−/−}) mouse lymphoma cells (L5178Y) and classifies the treated cultures for chromosomal aberrations and colony morphology. ▶ [bioassays in genetic toxicology](#); Hozier J et al 1981 Mutation Res 81:169; Clements J 2000 Mutation Res 455:97.

Mouse Mammary Tumor Virus (MMTV): MMTV causes mammary adenocarcinomas (see Fig. M123). The virus is transmitted to the offspring by breastfeeding. If the virus is transposed within 10-kb distance to the *Wnt-1* oncogene (homolog of the *Drosophila* locus *wingless* [*wg*]), the insertion may activate the oncogene because of the very strong enhancer in the viral terminal repeat. APOBEC3 proteins are packaged into virions and inhibit retroviral replication in newly infected cells, at least in part by deaminating cytidines on the negative strand DNA intermediates. A3 provides partial protection to mice against infection with MMTV (Okeoma CM et al 2007 Nature [Lond] 445:927). Retroviral insertion mutagenesis revealed 33 insertion sites as potential sources of tumor (Theodorou V et al 2007 Nature Genet 39:759). ▶ [DNA-PK](#), ▶ [pattern formation](#), ▶ [retroviruses](#), ▶ [APOBEC](#), ▶ [breast cancer](#)

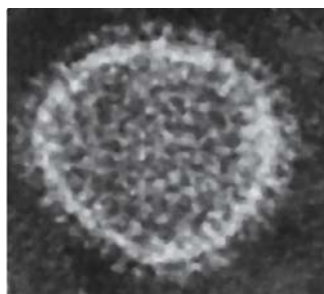


Figure M123. MMTV

Mouse Tumors, Spontaneous: <http://www.informatics.jax.org>.

Mov34: ▶ [Moloney mouse leukemia virus oncogene](#)

Movable Genetic Elements: ▶ [mobile genetic elements](#), ▶ [transposons](#), ▶ [transposable elements](#)

Movement Proteins: The synthesis of movement proteins is directed by plant viruses in order to spread the infectious particles through the plasmodesmata with the aid of microtubules. ▶ [microtubules](#), ▶ [plasmodesma](#), ▶ [motor proteins](#)

MOWSE (new name Gene Service): A peptide mass and molecular database <http://www.geneservice.co.uk/home/>.

MOZ (monocytic leukemia zinc finger domain): ▶ [CREB](#), ▶ [leukemia](#)

Mozart, Wolfgang Amadeus (1756–1791): Probably the greatest musical genius of all time, starting a musical career at age four and composition at six. His father was also a gifted violinist. Among his seven sibs, the only other survivor, Maria Anna, was also a very talented performer, although less renowned (see Fig. M124). ▶ [musical talent](#), ▶ [genius](#)



Figure M124. Mozart family portrait. Maria Anna (Nannerl), Amadeus, mother Anna Maria, father Leopold. (Coutesy of Steve Boerner)

M6P (mannose 6-phosphate): The M6P proteins are transmembrane proteins in the trans Golgi network. ▶ [endocytosis](#), ▶ [Golgi apparatus](#)

MP1 (MEK partner 1): MP1 is involved in the activation of MEK and ERK in the signal transduction pathway. ▶ [signal transduction](#), ▶ [MEK](#), ▶ [ERK](#); Schaeffer HJ et al 1998 Science 281:1668.

Mpl: A regulator of megakaryocyte formation. ▶ [megakaryocyte](#)

MPD: The maximal permitted dose. ▶ [radiation threshold](#), ▶ [radiation hazards](#), ▶ [radiation effects](#)

Mpd: A 36-kDa yeast protein in the endoplasmic reticulum with disulfide isomerase activity. ▶ [PDI](#), ▶ [Eug](#)

MPF (maturation protein factor/M-phase promoting factor): The MPF contains two subunits; a protein kinase (coded for by the *p34^{cdc2}* gene) and a B cyclin. Activation takes place (probably by phosphorylation at threonine 161 of the *p34^{cdc2}* protein) during M phase and deactivation is mediated by degradation of cyclin subunit during the rest of the cell cycle. MPF is deactivated also by phosphorylation at Thr-14 and Tyr-15 amino acid residues. These sites are dephosphorylated probably by the product of gene *p80^{cdc25}* or a homolog before the onset of mitosis. ▶protein kinases, ▶cyclin, ▶signal transduction, ▶*p34^{cdc2}*, ▶cell cycle, ▶APC; Frank-Vaillant M et al 2001 Dev Biol 231:279; Taieb FF et al 2001 Curr Biol 11:508.

MPF: Mating pair formation proteins of bacteria.

MPI (minimal protein identifier): The MPI serves as an index of protein identity on the basis of proteomics characteristics. ▶proteomics

MPK2: ▶p38

Mp1p: ▶See mitochondrial import

MPR: Mannose-6-phosphate receptor.

Mps: A kinetochore-associated kinase required for maintaining the anaphase checkpoint until the microtubules are attached to the kinetochore. It acts before the anaphase promoting complex. Mps1 participates also in the duplication of the centrosome in cooperation with Cdk2. ▶kinetochore, ▶checkpoint, ▶anaphase, ▶APC, ▶Cdk2, ▶centrosome; Abrieu A et al 2001 Cell 106:83; Fisk HA, Winey M 2001 Cell 106:95.

MP-Score: The mean sum of pairs score for a column in an alignment of motifs. In other words, the value of the SP-score divided by the total number of, e.g., amino acids. The SP-score is the sum of pair scores for a column in a multiple alignment. ▶motif

MPSS (multiple parallel signature sequencing): A system biology approach determining libraries of cDNAs from normal and diseased tissues. ▶cDNA, ▶massive parallel signature sequencing, ▶transcriptome; Brenner S et al 2000 Nature Biotechnol 18:630.

MPT (mitochondrial permeability transition): MPT indicates protein release from mitochondria and apoptosis and may be detected by ICAT. ▶apoptosis, ▶ICAT; Bruno S et al 2002 Carcinogenesis 23:447.

MQM: Marker-QTL-marker. ▶QTL

M_r (relative molecular weight): Relative molecular mass of a molecule compared to that of the mass of a C¹² carbon atom. This is different from the gram molecular weight, traditionally used in chemistry. ▶dalton

MR (*Male recombination*) factor of *Drosophila* (map location 2–54): Apparently, a defective P element (▶hybrid dysgenesis) that cannot move, yet it can facilitate the movement of other P elements. Besides causing recombination in the male, it induces many of the symptoms of hybrid dysgenesis, including chromosomal aberrations, high mutation rate, and mitotic exchange. ▶male recombination, ▶hybrid dysgenesis

MRCA (most recent common ancestor): An evolutionary concept for divergence or coalescence. If MRCA is old, many mutations could occur around a particular locus. However, if MRCA is young, the genetic background to the locus most likely did not change much during evolution. Also, if a mutation is young, the frequency of the allele may be low, because there was not yet enough time for it to diffuse (unless the selection coefficient was very large and positive). This would mean that rare mutations are young and young mutations are rare. On the bases of these three parameters, statistical procedures can be used to estimate the age of MRCAs (Patterson NJ 2005 Genetics 169:1093). ▶evolutionary tree, ▶coalescence, ▶diffusion genetic

MRD (mismatch repair detection): In MRD, DNA fragments are cloned and inserted into bacterial plasmids, and bacteria are transformed by the heteroduplex constructs. If there is a mismatch, the growing bacterial colonies become white, whereas in case of no mismatch the colonies are blue. The reporter gene is *LacZa*. The template for repair is a hemimethylated double-stranded DNA. Mismatches activate repair and the unmethylated strand is degraded, whereas the methylated strand becomes the template for repair. The method can scan up to 10-kb fragments for mismatches that are below five nucleotides in length. A revised procedure more suitable for high throughput analysis uses the Cre/lox recombinase, a tetracycline resistance (Tet^R), and a streptomycin sensitive (Str^S) marker. Two vectors are constructed and one of them carries a 5-bp deletion for the *Cre* gene. In other respects, the two vectors are identical. DNA fragments cloned in the active Cre⁺ vector are propagated in a bacterial strain, which is dam methylase free. The two clones are made only to be used as standard panels for testing human DNA samples. Human DNA fragments from each individual to be tested are first amplified and then pooled. Linearized methylated DNAs from the Cre-deletion and the Cre⁺ unmethylated DNA are combined in one vessel and single stranded PCR-amplified DNA is added. Subsequently, Taq ligase is added to generate hemimethylated, closed heteroduplex circles. The remaining linear strands are

removed by exonuclease III digestion. The heteroduplexes are cloned into an *E. coli* strain (carrying Str^R in its chromosome) carrying an F' plasmid with Tet^R and Str^S cassettes, each, flanked by two lox sites. The DNA strands, without mismatch, replicate normally in the bacterium and both types of plasmids survive. The Cre^+ protein mediates recombination between the two lox sites and as a consequence, the Tet^R as well as the Str^S genes are removed. The bacterial cell thus becomes tetracycline-sensitive but because of the presence of the chromosomal Str^R gene, it will thrive on streptomycin but not on tetracycline media. The mismatch in the heteroduplex will be repaired and the unmethylated Cre^+ strand will be degraded. The inactive Cre strand will, however, be used as a template for replication and thus, the intact Tet^R and Str^S cassettes will stay functional and cells carrying them will remain tetracycline-resistant and streptomycin-sensitive. The tetracycline and streptomycin resistant cells are propagated on Petri plates and their restricted DNA content can be assayed by gel electrophoresis. [▶ mismatch repair](#), [▶ lactose](#), [▶ Cre/lox](#), [▶ tetracycline](#), [▶ streptomycin](#), [▶ dam methylase](#), [▶ PCR](#), [▶ electrophoresis](#), [▶ restriction enzymes](#); Faham M, Cox DR 1995 *Genome Res* 5:474; Faham M et al 2001 *Hum Mol Genet* 10:1657.

MRE11: MRE11 mediates double-strand break repair in somatic cells in cooperation with Ku. In meiosis, it is expressed without Ku and apparently mediates repair of the recombined DNA strands. Its defects may cause symptoms of the Nijmegen breakage syndrome and ataxia telangiectasia. Mre11, Rad50, and Xrs2 complexes are important for DNA damage control, maintenance of telomere length, cell cycle checkpoint control, and meiotic recombination (Ghosal G, Muniyappa K 2005 *Nucleic Acids Res* 33:4692). [▶ Ku](#), [▶ DNA repair](#), [▶ PIK](#), [▶ Nijmegen breakage syndrome](#), [▶ ataxia telangiectasia](#), [▶ double-strand break](#), [▶ telomerase](#), [▶ MRE11](#), [▶ RAD50](#), [▶ XRS](#); Petrini JH 2000 *Curr Opin Cell Biol* 12:293; Costanzo V et al 2001 *Mol Cell* 8:137; Goldberg M et al 2003 *Nature [Lond]* 421:952.

MRF: A member of the family of muscle proteins. [▶ MEF](#), [▶ myogenin](#), [▶ MYF5](#), [▶ MYOD](#)

MRI: Magnetic resonance imaging. [▶ magnetic resonance](#)

MRN: A protein complex of Mre11, Rad50, and Nbs1/Xrs2, involved in chromosome breakage and telomeric fusion. [▶ MRE11](#), [▶ Rad50](#), [▶ Nijmegen breakage syndrome](#); Ciapponi L et al *Current Biol* 14:1360.

mRNA: Messenger RNA carries genetic information from DNA for the sequence of amino acids in protein. Its half-life in prokaryotes is about 2 min, in eukaryotes 6–24 hr, or it may survive for decades in trees. In individual cells, the life of the mRNA may vary by an order of magnitude (Grunberg-Manago M 1999 *Annu Rev Genet* 33:193). Unstable mRNAs even in eukaryotes may last only for a few minutes. The mRNA is produced by a DNA-dependent RNA polymerase enzyme, using the sense strand of the DNA as template, and it is complementary to the template. The mRNA is derived from the primary transcript by processing, including the removal of introns (in eukaryotes). The size of the mRNA molecules varies a great deal because the size of the genes encoding the polypeptides is quite variable. Upstream of the coding sequences of the mRNA there are several regulatory sequences (G box, CAAT or AGGA box, etc.), which are important for transcription but are not included in the mRNA. Transcription begins by the recognition and attachment of the transcriptase to a TATA box and the assembly of the transcription complex. The eukaryotic mRNA is capped with a methylated guanylic acid after transcription. Preceding the first amino acid codon (Met in eukaryotes and fMet prokaryotes), there is an untranslated leader sequence that helps in the recognition of the ribosome. In prokaryotes, the leader includes the Shine-Dalgarno sequence which assures a complementary sequence on the small ribosomal unit. In eukaryotes, such a sequence is not known; however, usually there is a AG—CCAUGG preferred box around the first codon and the ribosomal attachment is relegated to “scanning” for it in the leader. The structural genes then follow that in eukaryotes have been earlier spliced together from a highly variable number of exons. In the eukaryotic mRNA, there are untranslated sequences also at the 3' end that include a polyadenylation signal (most commonly AAUAAA) to improve stability of the mRNA by post-transcriptional addition of over hundred adenylic residues. This signal is used also for discontinuing transcription. In prokaryotes, either a rho protein-dependent palindrome or a rho-dependent GC-rich palindrome or a polyU sequence serves the same purpose. The number of mRNA molecules per cell varies according to the gene and the environment. In yeast cells, under good growing condition, 7 mRNA molecules were detected with a half-life of about 11 minutes, indicating that the formation of one mRNA molecule required about 140 seconds. The maximal transcription initiation rate for mRNA in yeast was found to be 6–8 second. The level of mRNA is frequently used for the assessment of proteins. The estimate so obtained may be biased, however, because

proteins may be in dynamic state subject maturation and degradation, and many proteins are regulated by alternative splicing of the mRNA and also by post-translational processing. The cellular distribution of mRNAs can be monitored by nuclease resistant molecular beacons used to monitor the path of the mRNA within the nucleus and its passing through the nuclear pores (Bratu DP et al 2003 Proc Natl Acad Sci USA 100:13308); (Bratu DP et al 2003 Proc Natl Acad Sci USA 100:13308). The movement of the mRNA and attached proteins may be stalled within the chromatin and to switch to the mobile phase requires ATP (Vargas D Y et al 2005 Proc Natl Acad Sci USA 102:17008). ►introns, ►RNA polymerase II, ►transcription factors, ►transcription complex, ►open promoter complex, ►Hogness box, ►Pribnow box, ►UAS, ►up promoter, ►G-box, ►GC box, ►enhancer, ►leader sequence, ►cap, ►Shine-Dalgarno box, ►mRNA tail, ►transcription termination in eukaryotes, ►decapping, ►transcription termination in prokaryotes, ►regulation of gene activity, ►monocistronic mRNA, ►operon, ►regulon, ►mRNA degradation, ►aminoacyl-tRNA synthetase, ►mRNA targeting, ►RNA non-coding, ►RNA surveillance, ►ribonuclease E, ►ribonuclease III, ►polynucleotide phosphorylase, ►degradosome, ►polyA polymerase, ►polyadenylation signal, ►beacon molecular, ►Mlp1, ►PML39, ►half-life, ►PMAGE; Brenner S et al 1961 Nature [Lond] 190:576; Maquat LE, Carmichael GG 2001 Cell 108:173; Moore MJ 2005 Science 309:1514; mRNA and small RNA of some plants: <http://mpss.udel.edu/>, coding potential of RNA transcripts: <http://cpc.cbi.pku.edu.cn/>.

mRNA CAP: ►cap

mRNA Circularization: The 5' and 3' ends of messenger RNA may be joined through the transcription initiation polypeptides eIF-4G, eIF-4E, and PABp, and this structure favorably modulates translation initiation and possibly prevents the truncation of the message and the polypeptide. The rotavirus mRNA, which has a GUGACC rather than a poly(A) tail, uses a special binding protein NSP3 and probably employs this structure to suppress host protein synthesis. ►PABp, ►polyadenylation signal; Mazumder B et al 2001 Mol Cell Biol 21:6440.

mRNA Degradation: mRNA degradation is not an incidental random process but it is under precise genetic control. The decay in eukaryotes may begin by the shortening or removal of the poly(A) tail, that is followed by removal of the Cap and digestion by 5'→3' exoribonucleases (encoded by *XRN1*, *HKE1*). The decay by 3'→5' exonuclease is of minor importance. The poly(A) tail is removed by the

PAN 3'→5' exonuclease but requires for activity the PABP (poly(A)-binding protein) and other proteins. The decapping is mediated by pyrophosphatases. The degradation is predominantly cytoplasmic although it may take place in the nucleus before the transfer to the cytoplasm. Most frequently, those mRNAs are attacked that have a termination codon 50–55 nucleotide upstream of the last exon–exon junction. AU-rich elements (AURE) and other factors in the downstream regions regulate the decay process. Decay regulatory purine-rich elements (180–320 base) reside also within the coding region. The histone mRNAs lack poly(A) tail and their stability depends on 6-base double stranded stem and a 4-base loop, and their stability depends also on the 50-kDa SLBP (stem-loop-binding protein) and other similar proteins. The destabilization of these mRNAs depends on the process of translation, and probably on the association of the stem-and-loop proteins with the ribosomes, and it appears to be auto-regulated also by histone(s). The degradation of the mRNA is initiated by defects in the process of the translation or by encountering nonsense codons, wrong splicing, upstream open reading frames (uORFs), and transacting protein factors in the cytoplasm and the nucleus. *RNA surveillance* (non-sense-mediated decay) disposes defective mRNAs. Similarly, if the mRNA is elongated beyond the normal stop signal, *non-stop decay* destroys it. If eukaryotic mRNA stalls during the process of translation, endonucleolytic cleavage takes place leading to *no-go decay*. The latter requires the presence of Dom34p and Hbs1p protein factors that resemble eRF1 and eRF3 translation termination factors (Doma MK, Parker R 2006 Nature [Lond] 440:561). Steroid hormones, growth factors, cytokines, calcium, and iron also affect mRNA stability. Cytokine and proto-oncogene mRNAs are degraded after binding the AUF1 protein to the 3' untranslated AU-rich sequences. This AU factor forms complexes with heatshock proteins, translation initiation factor eIF4G, and a polyA-binding protein. When the AUF1 is dissociated from eIF4G, AU-rich mRNA is degraded. Exo- and endoribonucleases, regulated by various factors, may also be involved in processing and also in protecting mRNA. Viral infections may rapidly destabilize host mRNAs without affecting the rRNAs and tRNAs. Premature termination of translation may account for Fanconi anemia Duchenne muscular dystrophy, Gardner syndrome, ataxia telangiectasia, breast cancer, polycystic kidney disease, desmoid disease, etc. A method exists for assessing the dynamics of the steady-state level and degradation of mRNA by the use of the cellular pyrimidine salvage pathway and affinity-chromatographic isolation of thiolated mRNA (Kenzelmann M et al 2007 Proc Natl

Acad Sci USA 104:6164). ►mRNA surveillance, ►non-stop decay, ►AMD, ►NMD, ►mRNA, ►polyA mRNA, ►exonuclease, ►endonuclease, ►nonsense codon, ►histones, ►Cap, ►transcription termination, ►mRNA tail, ►URS, ►transcription factors, ►eIF4G, ►heat-shock proteins, ►polyA mRNA, ►ubiquitin, ►RNAi, ►exosome; Ross J 1995 Microbiol Rev 59:423; Wilson GM et al 2001 J Biol Chem 276:8695; Wilusz CJ et al 2001 Nature Rev Mol Cell Biol 2:237; Chen C-Y et al 2001 Cell 107:451; van Hoof A, Parker R 2002 Current Biol 12:R285, degradation pathway in yeast: Kuai L et al 2005 Proc Natl Acad Sci USA 102:13962.

mRNA Display: An entirely in vitro technique for the selection of peptide aptamers to protein targets. The binding of the aptamers does not require disulphide bridges or special scaffold (e.g., antibody), yet the affinities are comparable to those of monoclonal antibody-antigen complexes. The polypeptides are linked to their mRNA in vitro, while stalling the translation on the ribosomes with the aid of puromycin, which attaches to the 3'-end of the mRNA. The mRNA-peptide fusions are then purified and selected in vitro. The procedure is highly efficient and permits selection in libraries of about 10^{13} peptides. It obviates the need for transformation, a disadvantage of phage display. ►aptamer, ►phage display, ►puromycin, ►RNA display; Wilson DS et al 2001 Proc Natl Acad Sci USA 98:3750.

mRNA Migration: After synthesis and release from the nucleus, the mRNA is not translated until it reaches its subcellular destination for translation. The localization is mediated by binding the onco-fetal protein ZBP1 (Zipcode binding protein 1) to a conserved 54-nucleotide element (Zip code) in the 3'-untranslated region of the β -actin mRNA. ZBP1 promotes translocation of actin to the periphery of the cell. Src protein kinase promotes translation by phosphorylating a key tyrosine residue (Tyr³⁹⁶) required for ZBP1 binding to mRNA (Hüttelmaier S et al 2005 Nature [Lond] 438:512). ►actin

mRNA Leader: ►leader sequence

mRNA Surveillance (nonsense-mediated decay, NMD): RNA transcripts containing premature stop codons or other defects are more liable to destruction by specific exonucleolytic proteins than normal ones. In yeast, the decay begins at the cap-binding protein or at the eIF4E translation initiation factor (Gao O et al 2005 Proc Natl Acad Sci USA 102:4258). The decay is generally initiated at the 5' or at the 3' end, but in *Drosophila* it starts in the vicinity of the nonsense codon (Gatfield D, Izaurralde E 2004 Nature [Lond] 429:575). Prematurely terminated mRNA molecules

may cause about 1/3 of the human hereditary diseases. In human cells, three proteins, hUpf1 (cytoplasmic ATP-dependent RNA helicase), hUpf2 (perinuclear), and hUpf3b (nuclear export-import signals shuttle between nucleus and cytoplasm), are involved. The NMD complex is formed apparently already in the nucleus at the exon-exon junctions, and triggers destruction of mRNA in the cytoplasm beginning downstream of the translation termination site. In *Caenorhabditis*, seven genes (*Smg*) are involved in NMD. Drugs (e.g., gentamycin) in cultured cells of the patients can inhibit the NMD pathway and the nonsense transcripts can be stabilized. The drug-induced changes are than revealed in normal and test systems with the aid of microarray hybridization. By identifying NMD inhibition, human disease genes can be recognized. This way, map location and biological function of the disease genes can be determined even when no *a priori* information is available. Some mutations causing NMD can be corrected by the application of appropriate drugs and the shortened polypeptide chain may be sufficient to alleviate defects normally causing hereditary disease. ►mRNA, ►mRNA degradation, ►alternative splicing, ►microarray hybridization, ►toeprinting, ►eIF-4E; Hilleren P, Parker R 1999 Annu Rev Genet 33:229; Lykke-Andersen J et al 2000 Cell 103:1121; Noensie EN, Dietz HC 2001 Nature Biotechnol 19:413; Amrani N et al 2004 Nature [Lond] 432:112; suppression of NMD for trapping mouse stem cells: Shigeoka T et al 2005 Nucleic Acids Res. 33(2):e20.

mRNA Tail: ca. 200 adenylate residues generally tails mature mRNAs of eukaryotes. This is not the end of the primary transcript; transcription may continue by a thousand or more nucleotides beyond the end of the gene. Polyadenylation requires that the transcript be cut by an endonuclease and then a poly-A RNA polymerase attaches to this poly-A tail, which is probably required for stabilization of the mRNA. Several of the histone protein genes do not have, however, a poly-A tail. Other histone mRNAs, which are not involved with the mammalian cell cycle and histone mRNAs of yeast and *Tetrahymena*, are polyadenylated. The common post-transcriptional polyadenylation is signaled generally by the presence near the 3'-end an AATAAA sequence, which is followed two dozen bases downstream by a short GT-rich element. Polyadenylation takes place within the tract bound by these two elements. Within most gene tracts, AATAAA occur at more upstream locations but they are not used for poly-A tailing. Several genes may have alternative polyadenylation sites, however, and thus can be used for the translation of different molecules, e.g., for membrane-bound or

secreted immunoglobulin, respectively. The polyadenylation signal may also have a role in signaling the termination of transcription, no matter how much further downstream that takes place. In the nonpolyadenylated histone genes, there is a 6-base pair palindrome that forms a stem for a 4 base loop near the 3'-end of the mRNA, and it is followed further downstream by a short polypurine sequence. The latter may pair with a U7 snRNP that facilitates termination. The U RNA transcripts of eukaryotic RNA polymerase II are not polyadenylated, either. The formation of an appropriate 3'-tail requires that it would be transcribed from a proper U RNA promoter and the transcript would have the 5' trimethyl guanine cap. The 3'-end of U1 and U2 RNAs is formed by the signal sequence GTTN₀₋₃AAAPUAGA [PU any purine, PY any pyrimidine] near the end. ▶transcription termination, ▶decapping, ▶polyadenylation signal, ▶polyA polymerase; Hilleren P et al 2001 Nature [Lond]:413:538.

mRNA Targeting: In order that proteins required for differentiation and morphogenesis would be available at the location needed, the mRNA generally carries a relatively long 3'-UTR (untranslated region). These long sequences appear to provide means for binding multiple proteins while being transported to the target sites. Additional 'zip codes' may be located in the 5'-untranslated sequences. During the process, the mRNA is bound and stabilized at the "ordained" sites from where the translated product may diffuse (in a gradient). ▶morphogenesis, ▶compartmentalization, ▶differentiation; Jansen R-P 2001 Nature Rev Mol Cell Biol 2:247.

mRNA, Transgenic: The result of trans-splicing of the transcripts. ▶trans-splicing; Finta C, Zaphiropoulos PG 2002 J Biol Chem 277:5882.

mRNA Turnover: ▶mRNA degradation

mRNP: The messenger ribonucleoprotein is a repressed mRNA. It is found in the eukaryotic cytoplasm and stored until later translation. In the female gametocyte of *Plasmodium*, this translational repression is mediated by an RNA helicase (DOZI, development of zygote inhibited) as a means of sexual development. Mutation in DOZI inhibits the formation of mRNAP and 370 transcripts are degraded. ▶mRNA, ▶gametocyte, ▶*Plasmodium*; Mair GR et al 2006 Science 313:667.

MRP (mitochondrial RNA processing): An RNase, which cleaves the RNA transcribed on the H strand of mtDNA at the CSB elements. MRP seems essential for normal exit from cell cycle at the end of mitosis

(Cai T et al 2002 Genetics 161:1029). MRP designates frequently also mitochondrial ribosome proteins. ▶CSB, ▶DNA replication mitochondria, ▶mtDNA, ▶ribosomal RNA, ▶ribosomal protein, ▶ribonuclease P, ▶Rex, ▶chondrodysplasia McKusick type; Ridanpaa M et al 2001 Cell 104:195.

MRP (matrix representation with parsimony): A method for constructing composite phylogenetic trees base on published data. The source phylogenetic information is encoded as a series of binary characters that represent the branching pattern of the original trees. The data matrix of the phylogenies is evaluated by parsimony and integrated into a composite tree. ▶evolutionary tree, ▶maximum parsimony; Bininda-Emonds OR 2000 Mol Phylogenet Evol 16:113.

mrr: ▶methylation of DNA

MRX: ▶mental retardation X-linked

MRX: A DNA double-strand break repair and telomerase complex. ▶DNA repair, ▶double-strand break, ▶telomerase

MS: ▶multiple sclerosis

MS2 Phage: A mainly single-stranded icosahedral RNA bacteriophage of about 3.6 kb with 4 genes, completely sequenced. The structure of phage RNA genetic material is represented in Fig. M125, M126.

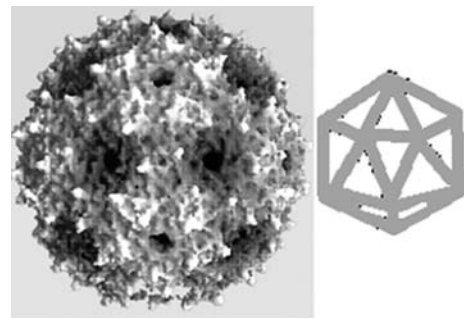
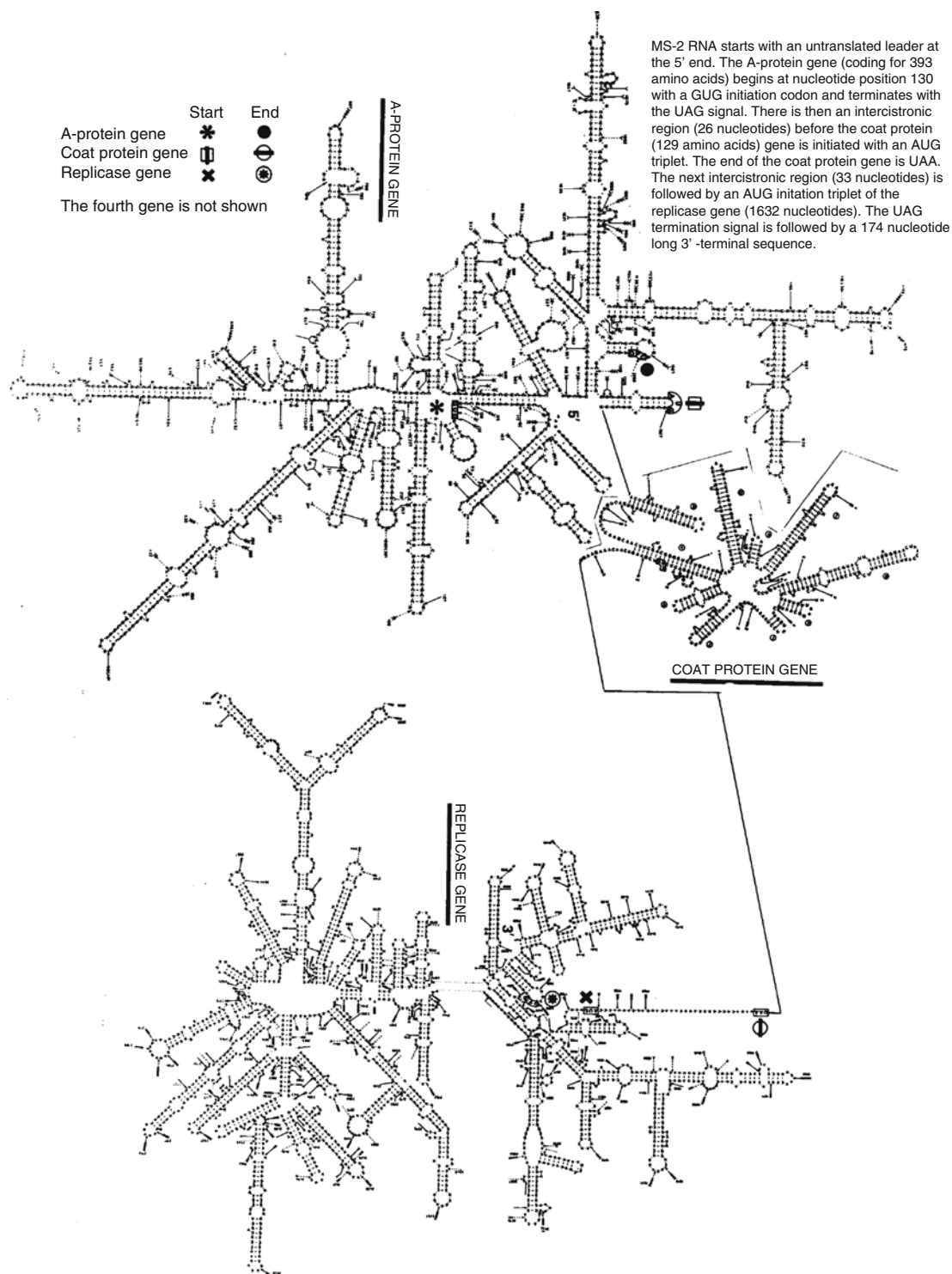


Figure M125. MS2 phage

The sequence is composed with permission on the basis of information provided by Min Jou W Ysebaert M et al 1972 Nature [Lond] 237:82; Fiers W 1975 In: Phages RNA, Zinder ND (ed) Cold Spring Harbor Laboratory, Cold Spring Harbor, N., pp353–396; Fiers W, Contreras R, et al 1976 Nature [Lond] 260:500. Gene 4 is not shown (see Fig. M126). ▶structure, ▶bacteriophages; Bollback JP, Huelsenbeck JP 2001 J Mol Evol 52:117.



M

Figure M126. The complete nucleotide sequence of the MS2 RNA phage. Composed according to Min Jou, W. et al. 1972 Nature 237:82; Fiers, W. 1975 in RNA Phages (Zinder ND ed), Cold Spring Harbor Lab. p.353; Fiers, W. et al. 1976 Nature 260:500.

MSAFP (maternal serum α -fetoprotein): MSAFP analysis may detect prenatally chromosomal aneuploidy, (trisomy), and open neural-tube defects between the first 15–20 weeks of pregnancy. Oxidation products of estradiol, estrone (estriol), and chorionic gonadotropin generally accompany the high level of this protein. ▶[fetoprotein](#), ▶[gonadotropin](#), ▶[trisomy](#), ▶[Turner syndrome](#), ▶[Down syndrome](#); Ochshorn Y et al 2001 *Prenat Diagn* 21:658; Miller R et al 2001 *Fetal Diagn* 16(2):120.

MSCI (meiotic sex chromosome inactivation): Silences unpaired (unsynapsed) chromosome regions in yeast and also in mouse during both male and female meiosis. The tumor suppressor protein BRCA1 is implicated in this silencing, mirroring its role in the meiotic silencing of the X and Y chromosomes in normal male meiosis. These findings impact the interpretation of the relationship between synaptic errors and sterility in mammals (Turner JM et al 2005 *Nature Genet* 37:11; Turner JM et al 2006 *Dev Cell* 10:521; MSUC).

MSCRAMM (microbial surface components recognizing adhesive matrix molecule): Microbial protein(s) recognizing host fibronectin-, fibrinogen-, collagen-, and heparin-related polysaccharides, important for host invasion, colonization, and as virulence factors. ▶[heparin](#), ▶[receptin](#); Patti JM et al 1994 *Annu Rev Microbiol* 48:585.

msDNA (multicopy single-stranded DNA): msDNA is formed in bacteria, which contain a reverse transcriptase and is associated with this enzyme. This DNA has a length of 162 to 86 bases and it may be repeated a few hundred times. The 5' end of the msDNA is covalently linked by a 2'-5'-phosphodiester bond to an internal G residue and thus forms a branched DNA-RNA copolymer of stem-and-loop structure. In some cases, because of processing, the msdRNA does not form a branched structure and exists only as a single-stranded DNA. The 5'-region of the msDNA is part of internal repeats within the copolymer. The system is transcribed from a single promoter and thus constitutes an operon. ▶[retron](#), ▶[reverse transcription](#); Lampson B et al 2001 *Progr Nucleic Acid Res Mol Biol* 67:69.

msdRNA: ▶[msDNA](#); Lima TM, Lim D 1997 *Plasmid* 38:25.

MSF (mitochondrial import stimulating factor): The MSF selectively binds mitochondrial precursor proteins and causes the hydrolysis of ATP. The MSF-bound precursor is made up of at least four proteins: Mas-20p, -22p, -70p, -37p. ▶[mitochondria](#), ▶[mitochondrial import](#); Hachiya N et al 1993 *EMBO J* 12:1579.

MSH: ▶[melanocyte stimulating hormone](#), ▶[hereditary non-polyposis colorectal cancer](#)

MSH2 (2p22-p21): A homolog of the bacterial MutS mismatch repair gene (Mazur DJ et al 2006 *Mol Cell* 22:39). ▶[mismatch repair](#)

MSH5/MSH4: MSH5/MSH4 are encoded in the central MHC class III region, and their obligate heterodimerization have a critical role in regulating meiotic homologous recombination and antibody gene switching (Sekine H et al 2007 *Proc Natl Acad Sci USA* 104:7193).

MSI: Microsatellite instability. ▶[microsatellite](#)

mSin: mSin proteins are transcriptional co-repressors. ▶[co-repressor](#), ▶[nuclear receptors](#); Ayer DE et al 1996 *Mol Biol Cell* 16:5772.

MSK: An enzyme of the MAPK family, closely related to RSK, and involved in phosphorylation of Histone 3 and thereby, in chromatin remodeling. ▶[chromatin remodeling](#), ▶[RSK](#)

Msl (male-specific lethal): At least five of the Msl genes exist in *Drosophila* that along with *Mle* (maleless) assure that a single X-chromosome in the male carries out all the functions at approximately the same level (dosage compensation) as two X-chromosomes in the female *Drosophila*. *Msl-1*, (2–53.3) and *Msl-2* (2–9.0) are located in the 2nd chromosome but similar genes are found also along the X-chromosome. Normally, the male chromatin is highly enriched in a histone 4 monoacetylated at lysine-16 (H4Ac16). Mutation at this lysine alters the transcription of several genes. Mutation in *Msl* genes prevents the accumulation of H4Ac16 in the male X-chromosome. Msl-2 protein by containing a Zinc-binding RING finger motif may specifically recognize X-chromosomal sequences and this way distinguishes between X and autosomes. The *Msl* complexes contain at least two RNAs on the X: roX1 (3.7 kb) and roX2 (0.6 kb). These RNAs, similarly to *Xist* RNAs in mammals, spread along over 1 Mbp of the chromosome although not as broadly as *Xist*, which may span over >100 Mbp. ▶[dosage compensation](#), ▶[Mle](#), ▶[ring finger](#), ▶[Xist](#), ▶[histone acetyltransferase](#); Larsson J et al 2001 *Proc Natl Acad Sci USA* 98:6273; Smith ER et al 2001 *J Biol Chem* 276:31483; Park Y et al 2002 *Science* 298:1620.

MS/MS: Tandem mass spectrometer. It can be used as an automatable tool for the diagnosis of amino acid sequence in proteins, etc. ▶[mass spectrometer](#), ▶[proteomics](#)

Msp I: Restriction endonuclease with recognition site C↓CGG.

MS-RDA (methylation-sensitive representational difference analysis): A subtractive hybridization method designed for the detection of differences in methylation

patterns among genes. ►methylation of DNA, ►subtractive cloning, ►differential hybridization mapping, ►RDA; Ushijima T et al 1997 Proc Natl Acad Sci USA 94:2284.

Mss (mammalian suppressor of Sec4): A guanosine-nucleotide exchange factor, regulating RAS GTPases. ►Ypt1, ►Rab, ►GTPase, ►RAS

MSUC (meiotic silencing of unsynapsed chromosomes): In MSUC, any chromosome region unsynapsed during pachytene of male and female mouse meiosis is subject to transcriptional silencing (Turner JM et al 2006 Dev Cell 10:521). Silencing seems to be due to extensive replacement of nucleosomes within unsynapsed chromatin and results in the exclusive incorporation of the histone H3.3 variant, which appears to be associated with transcriptional activity (van der Heijden GW et al 2007 Nature Genet 39:251). ►MSCI, ►silencer

MSUD (meiotic silencing by unpaired DNA): In MSUD, DNA unpaired in meiosis silences all homologous sequences including genes that are paired. MSUD requires the function of an RNA-dependent RNA polymerase. The mRNA is degraded after transcription. ►co-suppression, ►silencer, ►MSCI, ►quelling; Shiu PKT et al 2001 Cell 107:905; Shiu PKT et al 2006 Proc Natl Acad Sci USA 103:2243.

MSV (*msv*): ►Moloney mouse sarcoma virus

MSX (muscle segment homeobox, *msh*): Pleiotropic loci in humans (MSX1, 4p16.1) and MSX2 (5q34-q35) and homologous genes in mice control craniofacial (skull, teeth, etc.) development. ►pleiotropy, ►craniosynostosis, ►tooth-and-nail dysplasia; Milan M et al 2001 Development 128:3263; Cornell RA, Ohlen TV 2000 Curr Opin Neurobiol 10:63.

MTA: 5'-methylthioadenosine, one of the methyl donors in biological methylation.

MTA α : Yeast mating type α gene. ►mating type determination in yeast

MTA *a*: Yeast mating type *a* gene. ►mating type determination in yeast

MTD (maximum tolerated dose): The maximum tolerated dose of a treatment is that, which does not affect the longevity of the animal (except by cancer if the agent is a carcinogen) or does not decrease its weight under long exposure by more than 10%. MTD has been used in classification of carcinogens; in some instances at such high doses certain chemicals appear carcinogenic, however, under the conditions of normal use they may not pose a risk. Another potential problem is that genetic differences among test animals and humans may affect the sensitivity or susceptibility to the agents. ►bioassays in genetic toxicology; Leung DH, Wang YG 2002 Stat Med 21:51.

mtDNA (mitochondrial DNA): mtDNA in mammals consists of generally 5–6 small 16.5×10^3 bp mtDNA rings per organelle, but there are hundreds or thousands of mitochondria per cell. The yeast mtDNA genome is circular and 17–101-kb. In *Paramecium*, the mtDNA is linear and 40 kb. In about 1/3 of the yeasts and many other species (protozoa, fungi, algae), mtDNA may be linear. In plants, it varies in the range of 200 to 2,500-kbp, and occurs in variable size of mainly circular molecules, although smaller linear mtDNAs also exist and show inverted terminal repeats (Ward BL et al 1981 Cell 25:793). The mtDNA genome of *Plasmodium falciparum* is only 6-kbp, that of the plant *Arabidopsis* contains 366, 924-bp, and hexaploid wheat is 452,528 bp. More than 80% of the plant mtDNA is non-coding, whereas in protists only ~10% is non-coding. The human mtDNA genome contains 16,596 base pairs, is similar to that of other mammals, encodes 13 proteins, and transcribes two ribosomal genes and a minimal (22) set of tRNAs. The 13 proteins are: ATP synthetase subunits 6 and 8, cytochrome oxidase subunits I, II, III, apocytochrome b, and NADH dehydrogenase subunits 1–6 and 4L. A data set of 827 carefully selected sequences shows that modern humans contain extremely low levels of divergence from the mitochondrial consensus sequence, differing by a mere 21.6 nt sites on average. Fully 84.1% of the human mitochondrial genome was found to be invariant (Carter RW 2007 Nucleic Acids Res 35:3039).

Among the metazoan mtDNAs, some variations exist in gene number and the base composition of the coding strands also vary. *Reclinomonas* protozoons encode 97 genes by the mtDNA. Before the small (~16 kbp) metazoan mtDNAs have evolved, the unicellular protists had larger and genetically more complex mitochondria (Burger G et al 2003 Proc Natl Acad Sci USA 100:892).

Arabidopsis borrows two tRNAs from the chloroplasts. The wheat mtDNA includes 55 genes with exons, including 35 coding for protein, 3 rRNA, and 17 tRNA. Three percent of the wheat mtDNA genes are of chloroplast origin, ~16% of the total mtDNA is genic, and intramolecular recombination is evident (Ogihara Y et al 2005 Nucleic Acids Res 33:6235).

The number of mitochondria in the eukaryotic cells may run into hundreds to thousands. The buoyant density of the mtDNA is surprisingly uniform among many species; it varies between 1.705 to 1.707 g/mL.

In the marine mussels (*Mytilus*), there is an M (transmitted by the male to the sons) and an F (transmitted by the female to sons and daughters) mitochondrial DNA resulting in high degree of heteroplasmy among the males.

The replication of the mouse mtDNA proceeds generally from two origins of replication, thus

forming D loops, a tripartite structure of two DNA, and a nascent RNA strand. Replication of the heavy strand begins at the single origin (O_H) and continues until the origin of the light chain (O_L) is reached. Then the “lagging” strand replication is initiated in the opposite direction (for an overview of the human mtDNA map see p. 1,261). Another major D-loop originates at position 57 in several human cell lines. This replication type is responsible for the maintenance of mtDNA under steady-state conditions, whereas the other D-loop origin is more important for the recovery of mtDNA after depletion or for accelerating mtDNA replication in response to physiological demands (Fish J et al 2004 *Science* 306:2098). Restriction fragments including the replication forks when studied by 2-dimensional gels reveal structures that are called “Y arc”. In vertebrates, only a single DNA polymerase (polymerase γ) is involved in replication (Iyengar B et al 2002 *Proc Natl Acad Sci USA* 99:4483). This enzyme has two subunits; the larger (~125 to ~140-kDa) is involved in polymerization and the smaller (35–40-kDa) subunit may have a role in the recognition of the DNA replication primer and may function as a processivity clamp. The smaller, the accessory subunit, shares structural homology with the aminoacyl-tRNA synthetases. The large subunit also has a 3'→5'-exonuclease activity, assuring the high fidelity of DNA synthesis. Replication also in mitochondria requires a number of accessory proteins. The origin of replication of the light chain is at some distance from that of the heavy chain. The replication is regulated by the mtTFA protein, which also assures proper maintenance of the DNA and regulates transcription. The mutation rate of the mtDNA, despite the exonuclease function of polymerase γ , is an order of magnitude higher than that of the nuclear DNA. This higher rate has been attributed to oxygen, generated by oxidative phosphorylation. DNA repair may take place by nucleotide excision, mismatch repair, and alkyltransferase, but some aflatoxin B1, bleomycin, and cisplatin damage as well as pyrimidine dimers cannot be repaired efficiently.

In animals the heavy strand codes for 2 rRNAs, for 14 tRNAs, and for 12 polypeptides of the respiratory chain (ATP synthase, cytochrome b, cytochrome oxidase, 7 subunits of NADH dehydrogenase). In human mtDNA, the rRNA termination factor (mTERF) binds—by forming a loop—to both the termination and initiation sites of the two rRNA tracts and also drives mt rRNA synthesis (see Fig. M127) (Martin M et al 2005 *Cell* 123:1227; see diagram drawn after the electronmicrographs of Martin et al).

The plant mtDNA may encode three rRNAs and 15–20 tRNAs. The heavy chain of the mammalian mtDNA may be transcribed in a single polycistronic

unit and subsequently cleaved into smaller functional units. There are also abundant shorter transcripts of the heavy chain of the mtDNA. The light DNA strands of vertebrates are transcribed into eight tRNAs and into one NADH dehydrogenase subunit. The tRNA genes are scattered over the genome. The small mammalian mtDNA is almost entirely functional, and only a few (3–25) bases lie between the genes without introns, and some genes overlap. The promoter sequences are very short and are embedded in non-coding regions. The human mtDNA employs two forms of transcription factors that bear structural similarities to rRNA modifying enzymes (see Fig M128). These two factors (TFBM1 and TFBM2, the latter being much less efficient) bind to the core RNA polymerase (PolRMT), which can recognize the two promoter sites (LSP and HSP). TFAM is the protein that binds upstream to both promoters, unwinds the DNA template, and facilitates bidirectional transcription (Shoubridge EA 2002 *Nature Genet* 31:227). The upstream leader sequence is minimal and the typical eukaryotic cap is absent. In addition to the AUG initiator codon, AUA, AUU, and AUC may start translation as methionine codons. The genetic code dictionary of mammalian and fungal (yeast) mitochondria further differs somewhat from the “universal code”. The UGA stop codon means tryptophan, the AUA isoleucine codon represents methionine in both groups, whereas the CUA leucine

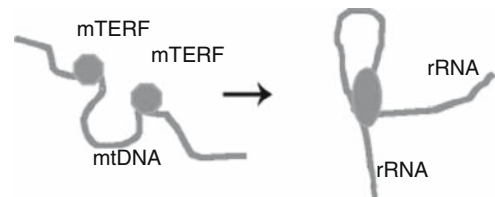


Figure M127. rRNA termination factor in mitochondria

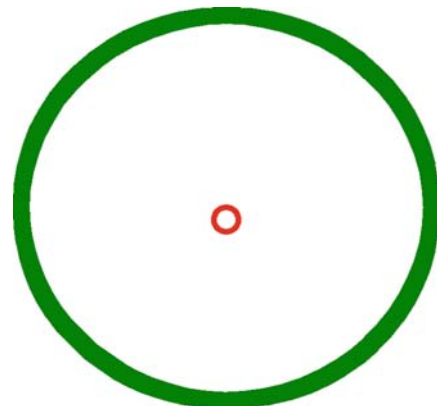


Figure M128. Arabidopsis mtDNA (outer circle) relative to mammalian mtDNA (inner circle)

codon in yeast mtDNA spells threonine (but in *Neurospora* mtDNA it is still leucine), and the AGA and AGG arginine codons are stop codons in mammalian mtDNA. Other coding differences may still occur in other species. Some mtDNA genes have no stop codons at the end of the reading frame but a U or UA terminate the transcripts after processing that may become, by polyadenylation, a UAA stop signal. Since mitochondria have only 22 tRNAs, the anticodons must use an unusual wobbling mechanism. The two-codon-recognizing tRNAs can also form a G*U pairing, and the four-amino-acid codon sets are base-paired either by two nucleotides only, or the 5' terminal U of the anticodon is compatible with any other of the 3' bases of the codon. Nuclear mRNA may not be translated in the mitochondria because of the differences in coding. Mitochondrial translation does not use the Shine-Dalgarno sequence for ribosome recognition in contrast to prokaryotes. Rather, it depends on translational activator proteins that connect the untranslated leader to the small ribosomal subunit. Plant mitochondria utilize the universal code.

The fission yeast and *Drosophila* mtDNAs are just slightly larger (19 kb) than that of mammals. The mtDNA of the budding yeast is about 80 kb, yet its coding capacity is about the same as that of the mammalian mtDNA. The large mitochondrial DNA is rich in AT sequences and contain introns. Some yeast strains have the same gene in the long form (with introns) while other strains in the shorter form (without intron). The introns may have maturase functions in processing the transcripts of the yeast genes that harbor them (cytochrome b) or they may be active in processing the transcripts of other genes (e.g., cytochrome oxidase). The 1.1-kb intron of the 21S rDNA gene contains coding sequences for a site-specific endonuclease that facilitates its insertion into some genes lacking this intron as long as they contain the specific target site (5'-GATAACAG-3'). Thus, this intron is also an insertion element.

For transcription of the vertebrate mtDNA the transcription factor mtTFA (a high-mobility group protein) must bind upstream (−12 to −39 bp) to the promoter to unwind the DNA for the mtRNA polymerase, which binds downstream. The distance between these two binding sites is important.

The *Saccharomyces* mtDNA genes are replicated from several (7 or more) scattered replicational origins, each containing 3 GC-rich segments separated by much longer AT tracts. Transcription is mediated by a mitochondrial RNA polymerase (similar to T-odd phage polymerases) that is coded, however, within the nuclear DNA. The conserved 5'-TTATAAGTAPuTA-3' promoter is positioned within nine bases upstream from the transcription initiation site. Unlike the much smaller mammalian mtDNA genes, yeast genes have more or

less usual upstream and 3' sequences. The much more compact mammalian or fission yeast genes do not use upstream regulatory sequences (UTRs). In the mtDNA, a 13-residue sequence embedded in the tRNA^{Leu(UUR)}, a 34-kDa protein, (mTERM) is bound and the complex is required for the termination of transcription. Transcription initiation also requires—besides sc-mtTFA—the protein sc-mtTFB. It seems that the primers for the heavy chain transcription are synthesized on the light chain of the mtDNA. Mammalian light chains contain three conserved sequence blocks (CSBs) serving apparently as primers for the transcription of the heavy chain. These seem to be analogous to the GC-rich segments of yeast. In yeast for the transcription of mtDNA heavy chain, a R loop is also formed. Near the origin of the heavy chain there is an RNase, specific (RNase MRP) for processing the 3'-OH ends of the origin-containing RNAs.

The rRNA genes, unlike in the nuclear genomes, are separated by other coding sequences. Yeast mtDNA encodes at least one ribosomal protein. In mammals, all mitochondrial ribosomal proteins are coded in the nucleus and imported into this organelle. The majority of the other proteins are also imported. Nuclear proteins mediate the translational control locus by specific or global manners.

The transport of proteins through the mitochondrial membrane takes place in several steps. The NH₂ terminus passes into the inner membrane through the protein import channel. The mitochondrial heatshock protein 70 (mtHsp70) stabilizes the translocation intermediate in an ATP-dependent process. The traffic may be in two ways, and it may be a passive transport.

The mtDNA of plants is much larger than that of other organisms, varying between 208 to 2,500 kbp. The mtDNA of *Arabidopsis* is 366,924 bp and contains 57 genes (Unsold M et al 1997 Nature Genet 15:57). The mtDNA of plants frequently exists in multiple size groups. This DNA is interspersed with large (several thousand kb) or smaller (200–300 kb) repeated sequences. Recombination between these direct repeats of a “master circle” may generate in stoichiometric proportion smaller, subgenomic DNA rings. In species without these repeats (e.g., *Brassica hirta*), subgenomic recombination does not occur. The very small mtDNA molecules are called plasmids. Plasmids, *S-1*, and *S-2* share 1.4-kb termini. These plasmids may integrate into the main mtDNA.

The variety and the number of repeats may vary in the different species and some species (*Brassica hirta*, *Marchantia*) may be free of recombination repeats. The recombination repeats may contain one or more genes. The repeats display recombination within and between the mtDNA molecules. These events then generate chimeric sequences, deficiencies, duplications, and a variety of rearrangements.

Recombination between direct repeats tosses out DNA sequences between them and generates smaller circular and possibly linear molecules. The 570-kb maize mtDNA “master circles” may have six sets of repeats, whereas in the T cytoplasm the repeats are quite complex. The size of the repeats may be 1 to 10-kb. Not all of them promote recombination and even the recombination repeats may vary in different species. Plant mitochondria may also contain single and double-stranded RNA plasmids. The latter may be up to 18-kb size. The single-stranded RNA plasmids may be replication intermediates of the double-stranded ones. The base composition of some is different from that of the main mtDNA and appears to be of foreign (viral) origin.

It has been reported that passage of cells thorough in vitro culturing (tissue culture) may incite rearrangements in the mtDNA genome. This phenomenon may be the result, however, of different amplification of preexisting alterations. Formation of cybrids may also result in new combinations of the mtDNAs (►somaclonal variation). The mitochondrial protein complexes may be organized by chaperone-like mitochondrial proteases.

Some of the DNA sequences in the plant mitochondria are classified as “promiscuous” because they occur in the nuclei and in the chloroplasts too. These promiscuous DNA sequences may contain tRNA (tRNA^{Pro}, tRNA^{Trp}) and 16S rRNA genes. Into the human nuclear DNA, mtDNA has been inserted several times during evolution and is detectable mostly as pseudogenes. It has been estimated that mtDNA sequences are translocated into the nuclear chromosomes at the high frequency of 1×10^{-5} per cell generation. With the aid of biolistic transformation any type of DNA sequence can be incorporated into organellar genetic material, including mtDNA. The plant mitochondrial tRNAs may be encoded by mtDNA, nuclear DNA, or plastid DNA directly, or by plastid DNA inserted into the mtDNA. Plant mitochondria may code for some mitochondrial ribosome proteins. These ribosomal proteins may be different in different plant species. The liverwort mtDNA genome is very large and contains at least 94 genes.

Human mtDNA was also used for evolutionary studies to trace the origin of the present-day human population to a common female ancestral line, the so-called phylogenetic Eve. Restriction fragment length polymorphism carried out on the mtDNA of 147 people, representing African, Asian, Australian, Caucasian, and New Guinean populations indicated an evolutionary tree by the maximal parsimony method. Accordingly, it appeared that Eve lived about 200,000 years ago in Africa because that population was the most homogeneous in modern times and other populations shared the most common mtDNA

sequences with these samples. The advantage of the mtDNA for these studies was that mitochondria are transmitted through the egg and thus recombination with males would not alter its sequences. Later studies have shown, however, that in mice (and probably in humans) a small number of mitochondria are transmitted also through the sperm. Therefore some of the conclusions of the original study regarding the time and population scales may require revision, although the basic ideas about the human origin may be correct. The unique descent of males can be traced through the Y chromosome. The original human mtDNA sequence (‘Cambridge reference’ Anderson S et al 1981 Nature [Lond] 290:457) has numerous errors because of variations particularly in the control region. These errors may affect demographic/population genetics conclusions and may lead to serious bias in forensic evaluations (Forster PM et al 2003 Ann Hum Genet 67:2).

In vitro in heteroplasmic cells, the mutant mtDNA replication could be inhibited by peptide nucleic acid, complementary to the mutant sequences. Mitochondria depend, either on the salvage pathway for deoxyribonucleotides or on special transporters to provide these DNA precursors. Human mitochondria have only two deoxyribonucleoside kinases. The thymidine kinase phosphorylates both deoxythymidine and deoxycytidine. The deoxyguanosine kinase phosphorylates both deoxypurine nucleosides.

Mutations can cause mtDNA depletion in humans and include: TP, which is associated with mitochondrial neurogastrointestinal encephalopathy (MNGIE, 22q13.32-pter); TK2 (16q22), encoding thymidine kinase, which causes mitochondrial myopathy2; DGUOK (2p13) that codes for a deoxyguanine kinase, associated with liver failure; POLG (5q25) that is responsible for Alpers progressive infantile poliodystrophy; MPV17 (2p23-p21) that can cause neurohepatopathy; and SUCLA2 (succinate-co-enzyme-A ligase, 13q12.2-q13), which causes encephalomyopathy (Ostergaard E et al 2007 Am J Hum Genet 81:383).

►mitochondria, ►introns, ►intron homing, ►spacers, ►kinetoplast, ►DNA replication mitochondrial, ►D loop, ►pan editing, ►RNA editing, ►mitochondrial import, ►numts, ►cryptogene, ►cytoplasmic male sterility, ►mitochondrial abnormalities in plants, ►RFLP, ►evolution by base substitution, ►DNA fingerprinting, ►chondrome, ►plastid male transmission, ►organelle sequence transfers, ►paternal leakage, ►Plasmodium, ►Eve foremother, ►mitochondrial genetics, ►petite colony mutations, ►maximal parsimony, ►MSF, ►ancient DNA, ►heat-shock proteins, ►chaperone, ►passive transport, ►heteroplasmy, ►peptide nucleic acid, ►mismatch repair, ►mtTFA, ►bottleneck effect,

►RU maize, ►mitochondrial disease in humans, ►sublimon, ►R loop, ►DNA 7S, ►RNA 7S, ►DNA repair, ►aflatoxin, ►bleomycin, ►cisplatin, ►methyltransferase, ►Y chromosome, ►polymerase chain reaction, ►mitochondrial-control regions, ►median-joining networks; Lang BF et al 1999 *Annu Rev Genet* 33:351; Richards M et al 2000 *Am J Hum Genet* 67:1251; Holt IJ et al 2000 *Cell* 100:515; Moraes CT 2001 *Trends Genet* 17:199; replication of mammalian mtDNA: Falkenberg M et al 2007 *Annu Rev Biochem* 76:679; for the evolutionary sequences of the mtDNA: <http://megasun.bch.umontréal.ca/gobase/>.

MTF (mouse tissue factor): A membrane protein initiating blood clotting.

mtFAM (mitochondrial transcription factor, Tfa, TCF6): A high mobility group nuclear gene product controlling transcription and replication in the mammalian mitochondria and possibly affecting transcription also in the nucleus. It is also indispensable for embryogenesis. Heart-specific local mutation (deletion) in mtFAM in mice leads the expression of heart anomalies appearing in Kearns-Sayre syndrome in humans. ►mtDNA, ►mitochondrial genetics, ►high mobility group proteins, ►mitochondrial diseases in humans

MTHF: ►photolyase

Mtj1: A transmembrane murine chaperone with homology to DnaJ and Sec63. ►DnaJ, ►Sec63

MTOC: microtubule organizing centers are formed early in the 16-cell stage within the cyst that gives rise to the primary oocyte and nurse cells. ►microtubule organizing center, ►centromere, ►spindle, ►spindle pole body, ►centrosome, ►maternal effect genes, ►oocyte; Rieder CL et al *Trends Cell Biol* 11:413.

MtODE: A mitochondrial AP lyase that cleaves double-stranded DNA at 8-oxoguanine sites and repair oxidative damage. ►oxidative DNA damage, ►AP lyase; Croteau DL et al 1997 *J Biol Chem* 272:27338.

mtPTP (mitochondrial transition pore): An opening on the mitochondrial inner membrane through which mitochondrial proteins can be released to the cytosol and may initiate, e.g., apoptosis. ►apoptosis, ►AIF

M-Tropic (e.g., virus): Homes on macrophages. ►tropic

MTS1 (multiple tumor suppressor): The *MTS1* gene encodes an inhibitor (p16) of the cyclin-dependent kinase 4 protein. When it is missing or inactivated by mutation, cell division may be out of control. *MTS1* is implicated in melanoma and pancreatic adenocarcinoma. ►p16, ►melanoma, ►tumor suppressor, ►pancreatic adenocarcinoma

MTT Dye Reduction Assay: The MTT dye reduction assay measures cell viability by spectrophotometry.

mtTF: The mitochondrial transcription factor. ►transcription factors, ►transcription complex, ►mtDNA

MtGENDO: mtGENDO refers to oxidative damage-specific mitochondrial AP lyases. It cleaves TG mismatches in double-stranded DNA. It does not recognize 8-oxodeoxyguanine or uracil sites. ►oxidative DNA damage, ►MtODE, ►AP lyase; Stierum RH et al 1999 *J Biol Chem* 274:7128.

Mu (*Mutator*): A transposable element system of maize increases the frequency of mutation of various loci by more than an order of magnitude (10^{-3} – 10^{-5}). About 90% of the mutations induced carry a *Mu* element. Their copy number in the genome may be 10–100. The element comes in various sizes but the longest are less than 2-kb. The shorter elements appear to have originated from the longer by internal deletions. There are relatively long (0.2-kb) inverted repeats at the termini, and 9-bp direct repeats are adjacent to them. The inverted terminal repeats are conserved among the at least five different classes of *Mu* elements, although the sequences in between them may be quite different. The *Mu* elements appear to transpose (in contrast to other maize transposable elements) by a replicative type of mechanism. The two best-studied forms, *Mu1* (1.4-kb) and *Mu1.7* (1.745-kb), were identified also in circular extrachromosomal states. When *Mu* is completely methylated, the mutations caused by it become stable. Less than complete methylation of the element and some other sequences (e.g., histone DNA) are associated with mutability. *Mu* is regulated by MuDR regulatory transposon (4.9-kb) carrying the *mudrA* and *mudrB* genes with transcripts of 2.8-kb and 1.0-kb, respectively. The MuDR element frequently suffers deletions limited to the MURB region. Mutator-like elements (MULEs) with substantial variations in structure and size have been discovered also in *Arabidopsis*. These 22 mutator elements are normally dormant in *Arabidopsis* but a mutation that decreases DNA methylation (DDM1) activates them. ►transposable elements, ►insertional mutation, ►controlling elements, ►hybrid dysgenesis, ►methylation of DNA; Singer T et al 2001 *Genes Dev* 15:591; Miura A et al 2001 *Nature [Lond]* 411:212; Yin Z, Harsdhey RM 2005 *Proc Natl Acad Sci USA* 102:18884.

Mu Bacteriophage: A 37-kbp temperate bacteriophage. Its linear double-strand DNA is flanked by 5-bp direct repeats. Transcription of the phage genome during the lytic phase requires the *E. coli* RNA polymerase holoenzyme. During replication, it may integrate into different target genes of the bacterial chromosome and thus, may cause mutations (as the name indicates). *Mu* may integrate in more than one copy

and if the orientation of the prophage is the same, it may cause deletion, or if the orientation of the two Mu DNAs is in reverse, inversion may take place by recombination between the transposons. The phage carries three terminal elements at both left and right ends where recombination with the host DNA takes place. There is a transpositional enhancer (internal activation sequence) of about 100-bp at 950 bp from the left end. This left-enhancer-right complex is called LER. The 75-kDa transposase binds to the two ends and to the enhancer. A complex of nucleoproteins, the transposome, mediates the transposition. The transposome includes four subunits of the MuA transposase and each contains a 22-base pair recognition site. These recognition sites—in case there is a shortage of Mu DNA—may recruit non-Mu DNA and then can transpose it too. In the presence of bacterial binding proteins (HU and IHF), a stable synaptic complex (SSC) is formed. Then at the 3'-ends, Mu is cleaved by the transposase and they form the Cleaved Donor Complex (CDC). Transesterification at the 3'-OH places Mu into the host DNA. In the Strand Transfer Complex (STC), the 5'-ends are still attached to the old flanking DNA but the 3'-ends are joined to the new target sequences and a cointegrate is generated by replication or nucleolytic cleavage separates Mu from the old flanks and then the gaps are repaired and the transposition is completed. ▶ **mini Mu**, ▶ **transposons**, ▶ **mutator phage**, ▶ **cointegrate**, ▶ **transposition site**; Bukhari AI 1976 *Annu Rev Genet* 10:389; Abbes C et al 2001 *Can J Microbiol* 47 (8):722; Goldhaber-Gordon I et al 2002 *J Biol Chem* 277:7694; Pathania S et al 2002 *Cell* 109:425.

Mucins: Glycosylated protein components of the mucosa that lubricate the intestinal tract. Mutation in the genes involved may lead to cancer. ▶ **D-amino acids**; Velcich A et al 2002 *Science* 295:1726; Hollingsworth MA, Swanson BJ 2004 *Nature Rev Cancer* 4:45.

Muckle-Wells Syndrome: Dominant (1q14) inflammatory disease accompanied by fever, abdominal pain, and urticaria (red or pale skin eruptions). Progressive nerve deafness and amyloidosis may follow. This, and two other diseases, involve mutations in the CIAS1 gene (cold autoinflammatory response) at the NALP locus. Cryopyrin (Nod family protein), along with CAIS1, regulates the inflammatory response (Dowds TA et al 2003 *Biochem Biophys Res Commun* 302:575; Sutterwala FS et al 2006 *Immunity* 24:317). ▶ **amyloidosis**, ▶ **deafness**, ▶ **urticaria familial cold**, ▶ **cold hypersensitivity**, ▶ **hydatiform mole**, ▶ **inflammasome**

Mucopolidoses (ML): ML include a variety of recessive diseases connected to defects in lysosomal enzymes.

ML I is a neuroaminidase deficiency and ML II is an N-acetylglucosamine-1-phosphotransferase deficiency (human chromosome 4q21-q23). This enzyme affects the targeting of several enzymes to the lysosomes. Congenital hip defects, chest abnormalities, hernia, and overgrown gums, but no excessive excretion of mucopolysaccharides are observed. ML III is apparently allelic to ML II although the mutant sites seem to be different. MP III (pseudo-Hurler polydystrophy) also has similarity to the Hurler syndrome (▶ **mucopolysaccharidosis**), although the basic defects are not identical. MP III A is a heparan sulfate sulfatase deficiency (▶ **mucopolysaccharidosis**, ▶ **Sanfilippo syndrome A**), whereas MP IIIB is basically the Sanfilippo syndrome B (▶ **mucopolysaccharidosis**). MP IV (19p13.2-p13.3) is a form of sialolipidosis with typical lamellar body inclusions in the endothelial cells that permit prenatal identification of this disease that may cause early death. ▶ **mucopolysaccharidosis**, ▶ **Hurler syndrome**

Mucopolysaccharidosis (MPS): Hurler syndrome (*MPS I*) recessive 22pter-q11 deficiency of α -L-iduronidase (IDUA) resulting in stiff joints, regurgitation in the aorta, clouding of the cornea, etc. The latest chromosomal assignment of MPS1 is 4p16.3. The IDUA protein (about 74 kDa) includes a 26-aminoacid signal-peptide. The *MPS II* (*Hunter syndrome*, I-cell disease) is very similar to *MPS I*, but it is located in human chromosome Xq27-q28. The symptoms in this iduronate sulfatase deficiency are somewhat milder and the clouding of the cornea is lacking. Dwarfism, distorted face, enlargement of the liver and spleen, deafness and excretion of chondroitin, and heparitin sulfate in the urine are additional characteristics. The following MPSs are controlled by autosomal recessive genes and the deficiencies involve: *MPS IIIA* (Sanfilippo syndrome A; human chromosome 17q 25.3) heparan sulfate sulfatase, in *MPS IIIB* (Sanfilippo syndrome B, in human chromosome 17q21) N-acetyl- α -D-glucosaminidase, in *MPS IIIC* acetylCoA: α -glucosaminide-N-acetyltransferase, *MPS IIID* (Sanfilippo syndrome D, 12q14) N-acetylglucosamine-6-sulfate sulfatase, in *MPS IVA* (Morquio syndrome A, 16q24.3) galactosamine-6-sulfatase, in *MPS IVB* (Morquio syndrome B) β -galactosidase, in *MPS VI* (Maroteaux-Lamy syndrome, 5q11-q13) N-acetylgalactosamine-4-sulfatase (arylsulfatase B), in *MPS VII* (Sly syndrome, 7q21.11) β -glucuronidase, and in *MPS VIII* (DiFerrante syndrome) glucosamine-3-6-sulfate sulfatase. The Hurler syndrome and Sly disease may be treated by implantation of neo-organs, tissues of skin fibroblasts secreting β -glucuronidase, or α -L-iduronidase, respectively. ▶ **mucopolidoses**, ▶ **iduronic acid**, ▶ **heparan sulfate**, ▶ **glucuronic acid**, ▶ **arylsulfates**, ▶ **hyaluronidase**

deficiency, ►coronary heart disease, ►eye diseases, ►deafness, ►miniorgan, ►geleophysic dysplasia, ►enzyme replacement therapy

Mucosal Immunity: The mucosal membranes (in the gastrointestinal tract, nasal, respiratory passages, and other surfaces that have lymphocytes) are supposed to trap 70% of the infectious agents. The mucosal cells rely on immunoglobulin A (IgA) rather than IgG used by the serum. In the gastrointestinal system are located the Peyer's patches that trap infectious agents and pass them to the antigen-presenting cells, T and B cells. The B cells generate the IgA anti-bodies. Concomitantly, the released antigen may stimulate the formation of IgG too. Providing attenuated forms of the pathogen (e.g., *Vibrio cholerae*) orally can trigger the mucosal immunity system. Another approach is to deliver the antigens by bacteria that more effectively stimulate simultaneously both IgA and IgG production. Other delivery systems may use a biodegradable poly (DL-lactide-co-glycolide), PLG, or liposomes. The oral polio vaccine has been quite successful because it provides lasting protection but most of oral vaccines are short in this respect. ►Peyer's patch, ►antigen-presenting cell, ►T cell, ►B cell, ►immunoglobulins, ►antigen, ►immune system, ►vaccines, ►plantibody; Simmons CP et al 2001 Semin Immunol 13(3):201.

Mucosulfatidosis: A multiple sulfatase deficiency with excessive amounts of mucopolysaccharides and sulfatides in the urine. Multiple sulfatase deficiency encoded by SUMF, causing a lysosomal storage disease, results from the lack or co- or post-translational replacement of cysteine by 2-amino-3-oxopropionic acid in several sulfatases (Schmidt B et al 1995 Cell 82:2712; Landgrebe J et al 2003 Gene 316:47). The numerous human sulfatases share common domains. The defect results in abnormal development and early childhood death because of abnormal signaling by gene WNT (Dhoot GK et al 2001 Science 293:1663). Another sulfatase (RsulfFP1) normally mediates proteoglycan signaling by desulfation (Ohto T et al 2002 Genes Cells 7:521). Some of the symptoms of sulfatase deficiency are shared by leukodystrophy, Maroteaux-Lamy, Hunter, Sanfilippo A, and Morquio syndromes, as well as by ichthyosis. Several sulfatase genes occur in bacteria to animals but few in plants. Heterologous bone transplantation, somatic cell gene transfer, and enzyme replacement offer therapeutic potentials in several sulfatase deficiency diseases. (See diseases mentioned in separate entries, ►genetic engineering; Diez-Roux G, Ballabio A 2005 Annu Rev Genomics Hum Genet 6:355).

Mud: A transposon modified (derived) from bacteriophage Mu. ►Mu bacteriophage

MudPIT (multidimensional protein identification technology): A method for the study of complex protein mixtures. Multidimensional liquid chromatography is followed by mass spectrometric analysis by digesting the cell lysate with the help of endoproteinase LysC, and then further purification. The databases are searched by SEQUEST algorithm. The peptide sequences can be used for the identification of proteins in a mixture. ►mass spectrum, ►MALDI-TOF, ►proteomics, ►SEQUEST; Washburn MP et al 2001 Nature Biotechnol 19:242; Smith RD et al 2002 Proteomics 2:513.

Muenke Syndrome (nonsyndromic coronal craniosynostosis): Primarily a skull bone fusion disorder that sometimes affects finger and toe development. It is generally caused by mutation affecting the proline²⁵⁰ site in the fibroblast growth factor receptor 3 (FGFR3) gene at 4p16.3. Its incidence is higher in women than in men. ►craniosynostosis syndromes

Muir-Torre Syndrome: A familial autosomal dominant disease involving skin neoplasias, apparently due to hereditary defects in the genetic (mismatch) repair system. ►mismatch repair, ►colorectal cancer, ►Gardner syndrome, ►polyposis hamartomatous, ►hereditary nonpolyposis colorectal cancer

Mulatto: Offspring of white and black parentage. ►miscegenation

Mulberry (*Morus* spp): fruit tree; $x = 14$. *M. alba* and *M. rubra* are $2n = 28$ whereas the Asian *M. nigra* is $2n = 38$.

Mulibrey Dwarfism: ►dwarfism [Mulibrey nanism]

Mule: ►hinny

MULE (Mcl ubiquitin ligase E3): Mcl-1 is an anti-apoptotic member of the Bcl protein family controlling DNA-damage-induced apoptosis (Zhong Q et al 2005 Cell 121:1085). ►apoptosis, ►BCL

Mulibrey Nanism (MUL, 17q22-q23): An autosomal anomaly causing small size. It involves all or some of the SE characteristics: low birth weight, small liver, brain, eye, growth, triangular face, yellow eye dots, etc. The basic defect is in a Zinc-finger protein (RBCC), containing a ring finger, a B box, and a coiled-coil region. It appears to be a peroxisomal disorder. ►stature in humans, ►Zinc finger, ►B box, ►ring finger, ►coiled coil, ►peroxisome; Kallijärvi J et al 2002 Am J Hum Genet 70:1215.

Muller 5 Technique: ►Base

Muller's Ratchet: Genetic drift can lead to the accumulation of deleterious mutations, particularly in asexual populations. By each mutation the ratchet (a toothed wheel) may click by one notch. The

expected time of losses of individuals with successive minimal number of mutations depends on the absolute number of individuals with minimal number of mutations: $N_m = q_m$ where q is their expected frequency and N = effective population size. Muller's ratchet may operate during the evolution of transposons and retroviruses and fix shorter sequences than the initial elements and establish elements that would depend on trans-acting elements for transposition. In case the number of non-deleterious mutations is small (n_0), the equilibrium value $n_0 = Ne^{-\mu/s}$ where N = effective population size, μ = expected number of deleterious mutations per genome, s = selection coefficient, e = base of natural logarithm. Conversely, the rapid mutations of retrotransposons may eliminate elements that would lose their transposase and thus can escape the Muller's ratchet. Deleterious mutations may be eliminated by reversions, by compensating new mutations, or by genetic recombination. The original hypothesis (Muller H J 1932 Amer Nature 66:118) suggested the advantage of the evolution of sex and recombination as a means to purify the population from deleterious mutations. ► **Y chromosome**, ► **genetic drift**, ► **transposable elements**, ► **retrovirus**; Gabriel W, Bürger R 2000 Evolution Int J Org Evolution 54:1116; Gordo I, Charlesworth B 2000 Genetics 156:2137.

M

Müllerian Ducts: Gonadal cells begin to develop before the mouse embryo is two-weeks old. From the unspecialized primordial cells in the male, the Wolffian ducts develop, and from those in the female, the Müllerian ducts. Initially, however, both sexes form both of these structures and appear bisexual but later, according to sex—one or the other—degenerates. The Müllerian inhibiting substance (MIS, Jost factor) causes the degeneration of the Müllerian ducts. This is a member of the TGF- β (transforming growth factor family of proteins) or is the AMH (anti-Müllerian hormone) and it is encoded in human chromosome 19p13-p13.2. Defect in the AMH receptor causes pseudohermaphroditism with uterine and oviductal tissues in males observed in PMDS (persistence of Müllerian duct syndrome). MIS regulates NF κ B signaling and breast cancer cell growth in vitro and can induce apoptosis in ovarian and cervical cancer cell lines (Renaud EJ et al 2005 Proc Natl Acad Sci USA 102:111). In mammals, the Wnt-4 signaling is required for ovarian morphogenesis. ► **gonad**, ► **Wolffian ducts**, ► **SRY**, ► **SF-1**, ► **sexual dimorphism**, ► **TGF**, ► **pseudohermaphroditism**; Segev DL et al 2001 J Biol Chem 276:26799; Bédécarrats G et al 2003 Proc Natl Acad Sci USA 100:9348.

Müllerian Inhibitory Substance (Jost factor): ► **Müllerian duct**

Müllerian Mimicry: In Mullerian mimicry, two monomorphic species share morphological similarities signaling a defense (e.g., distastefulness, poisonousness) to predators, and both benefit from the trait. Similar mimicry occurs in various species. A single gene locus may be shared among the different *Heliconius* species (see Fig. M129). ► **Batesian mimicry**; Kapan DD 2001 Nature [Lond] 409:338; Joron M et al 2006 PLoS Biol 4(10:e303).



Figure M129. *Heliconius* species of different geographical areas display Müllerian mimicry. From top to bottom: southern Ecuador, southern Brazil, northern Ecuador, western Brazil, Peru. (Courtesy of Fred Nijhout, Duke University)

Multibreed: A population including purebred and crossbred groups. ► **pure-breeding**, ► **cross breeding**

Multicase (multiple computer automated structure evaluation): Multicase relies on information of molecular fragments as descriptors of potential biological (carcinogenic) activity of chemicals. It compares the structure–activity relationship among many compounds in order to find commonality. ► **CASE**, ► **SAR**, ► **biophore**; Cunningham AR et al 1998 Mutation Res 405:9.

Multicellular Organisms: In a multicellular organism, the cells of an individual are coordinated for different function(s) and situated closely enough to ensure interaction. A bacterial colony is formed from many cells but these cells are not coordinated even when they display patterned growth. The multicellular condition apparently evolved repeatedly during evolution. The structural condition for evolution of a multicellular system was apparently the synthesis of

an adhesive polymer matrix needed for cell alignment (Vellicer GJ, Yu Y-t N 2003 Nature [Lond] 425:75). Evolution of multicellularity involved signal transmission, reception, and localized expression of specialized genes. Their main advantages are in feeding and dispersion. ►[quorum-sensing](#); Kaiser D 2001 Annu Rev Genet 35:103.

Multicompartment Virus: In a multicompartment virus, each individual viral particle may carry only part of the total genome and complementation between the particles can provide the full function. Such viral strategy permits a combinatorial advantage to the virus.

Multicomponent Virus: The genome of a multicomponent virus is segmented, i.e., its genetic material is in several pieces similarly to the chromosomes in eukaryotic nuclei. ►[bacteriophages](#)

Multicopy Plasmids: Multicopy plasmids have several copies per cell. ►[plasmid types](#)

Multidrug Resistance (MDR/ABCB1): Multidrug resistance is mediated by the multidrug transporter (MDT, 1,280 amino acids) phosphoglycoprotein that regulates the elimination (or uptake) of chemically quite different drugs from mammalian (cancer) cells in an ATP-dependent manner. MDR is generally carried by extrachromosomal elements in bacteria such as plasmids, transposons, and integrons. In cancer cells, the MDR gene is generally amplified as episomes and double-minutes. Intercellular transfer of phosphoglycoproteins can mediate acquired drug resistance (Levchenko A et al 2005 Proc Natl Acad Sci USA 102:1933). The MDR gene may be used for gene therapy by protecting the bone marrow from the effects of cytotoxic cancer drugs. The MDT gene controls a very broad base drug-resistance. The MRP (multidrug resistance associated protein) is a glutathione conjugate protein that belongs to the same family as MDR and may be expressed in cell lines where MDR function is usually limited. The bacterial multidrug resistance gene, *LmrA*, is very similar to the human gene and it is expressed in human cells when introduced by transformation. Besides gene mutation, MDR can be acquired also by rearrangement of the genome (aneuploidy) in cancer cells.

Whole-genome sequencing identified steps in the evolution of multidrug resistance in isogenic *S. aureus* isolates recovered periodically from the bloodstream of a patient undergoing chemotherapy with vancomycin and other antibiotics. After extensive therapy, the bacterium developed resistance, and treatment failed. Sequencing the first vancomycin susceptible isolate and the last vancomycin nonsusceptible isolate identified genome wide 35 point mutations in 31 loci (Mwangi MM et al 2007 Proc Natl Acad Sci USA 104:9451). ►[amplification](#), ►[multiple drug](#)

[resistance](#), ►[ABC transporters](#), ►[Emre](#), ►[episomes](#), ►[integron](#), ►[double-minute](#), ►[ABC transporters](#), ►[P-glycoprotein](#), ►[SOD](#), ►[MGMT](#), ►[DHFR](#), ►[aldehyde dehydrogenase](#), ►[glutathione-S-transferase](#), ►[chemosensitivity](#), ►[Crohn disease](#); Hipfner DR et al 1999 Biochim Biophys Acta 1461:359; Rosenberg MF et al 2001 J Biol Chem 276:16076; Duesberg P et al 2001 Proc Natl Acad Sci USA 98:11283; Yu EW et al 2003 Science 300:976; crystal structure of multidrug transporter: Murakami S et al 2006 Nature [Lond] 443:173; review: Alekshun MN, Levy SB 2007 Cell 128:1037.

Multifactorial Cross: In a multifactorial cross, the mating is between parents, which differ at multiple gene loci.

Multifactorial Disease: Multifactorial disease is caused or controlled by more than single genes. Generally, the number of factors involved cannot be determined in a straight forward manner and environmental influences may be significant. ►[QTL](#), ►[sporadic](#)

Multiforked Chromosomes: In bacteria, replication of the DNA may start again before the preceding cycles of DNA synthesis have been completed and thus display multiple replication forks (see Fig. M130). ►[replication fork](#), ►[replication bidirectional](#), ►[DNA replication](#); diagram from Sueoka N 1975 Stadler Symp 7:71.

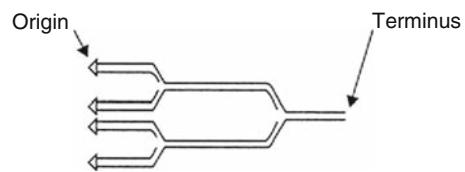


Figure M130. Multiforked chromosome of bacteria

Multifunctional Proteins: ►[one gene—one enzyme](#)

Multigene Family: In a multigene family, clusters of similar genes evolved through duplications and mutations and display structural and functional homologies. Some members of the families may be at different locations in the genome and some may be pseudogenes. ►[pseudogenes](#)

Multigenic: ►[polygenic inheritance](#)

Multi-Locus Probe (MLP): In a multi-locus probe, in DNA fingerprinting alleles of more than one locus are examined simultaneously. ►[DNA fingerprinting](#)

Multi-Locus Sequence Typing: Multi-locus sequence typing detects allelic variations (mutations and recombination) within about 450 bp internal sequences of seven bacterial housekeeping genes. Since the integrity

of housekeeping gene function is generally vital, most of the alterations detected are neutral. ▶[DNA typing](#), ▶[housekeeping genes](#); Feil EJ et al 2000 *Genetics* 154:1439.

Multimap: A computer program for linkage analysis using lod scores. ▶[lod score](#)

Multimeric Proteins: Multimeric proteins have more than two polypeptide subunits.

Multinomial Distribution: Multinomial distribution may be needed to predict the probability of proportions: $P = \frac{n!}{r_1!r_2!\dots r_z!} (a)_1^r (b)_2^r \dots (z)_z^r$ where P is the probability r_1, r_2, \dots, r_z stand for the expected numbers in case of a, b...z theoretical proportions and n = the total numbers. Example: in case of codominant inheritance and expected 0.25 AA, 0.50 AB, and 0.25 BB, the probability that in an AB x AB mating we would find in F2 among five progeny 2AA, 2AB, and 1 BB is: $P = \frac{5!}{2!2!1!} (0.25)^2 (0.50)^2 (0.25)^1 = \frac{120}{4} (0.0625) (0.25) (0.25) = 30(0.00391) \approx 0.117$. binomial distribution, distribution)

Multiparental Hybrid: A multiparental hybrid can be generated by fusion of two or more different embryos of different parentage at the (generally) 4 - 8 cell stage and then reimplantation at (generally) the blastocyst stage into the uterus of pseudo-pregnant foster mouse. Such hybrids may appear chimeric if the parents were genetically different and can be used advantageously for the study of development (see Fig. M131). ▶[allophenic](#), ▶[pseudo-pregnant](#), ▶[triparental human embryo](#)



Figure M131. Hexaparental mother mouse displaying yellow, black and white sectors (at right). It was obtained by aggregation of three strains in vitro that were implanted into a pseudopregnant female. Her offspring are at left. (Courtesy of RM Petters & CL Markert)

Multiparous: An animal species that usually gives birth to multiple offspring by each delivery; a human female that gives birth to twins at least twice.

Multipaternal Litter: A multipaternal litter is produced if the receptive multiparous female mates during estrus with several males. ▶[estrus](#), ▶[superfertilation](#), ▶[last-male sperm preference](#)

Multiphoton Microscopy: A non-invasive fluorescence microscopy for various tissues. Molecular excitation by two simultaneous absorptions of two photons provides intrinsic three-dimensional resolution of laser scanning fluorescence microscopy (Denk W et al 1990 *Science* 248:73). ▶[microscopy](#), ▶[laser scanning cytometry](#); Zipfel WR et al 2003 *Nature Biotechnol* 21:1369.

Multiple Alleles: More than two different alleles at a gene locus. The number of different combinations at a particular genetic locus can be determined by the formula $[n(n + 1)]/2$ where the number of different alleles at the locus is n . ▶[allelic combinations](#)

Multiple Birth: ▶[twinning](#)

Multiple Cloning Sites (MCS): ▶[polylinker](#)

Multiple Cross Mapping (MCM): A procedure for chromosomal localization of quantitative trait and complex loci using several inbred strains of mice. The technique can identify linked modifiers. ▶[QTL](#), ▶[modifier gene](#); Hitzemann R et al 2002 *Genes Brain & Behavior* 1(4):214; Park Y-G et al 2003 *Genome Res* 13:118.

Multiple Crossovers: Multiple crossovers are genetically detectable only when the chromosomes are densely marked. In the absence of interference, the frequency of multiple crossovers is expected to be equal to the products of single crossovers. ▶[coincidence](#), ▶[mapping](#), ▶[mapping function](#)

Multiple Drug Resistance (MDR): MDR is based on several mechanisms such as active detoxification system, improved DNA repair, altered target for the drugs, decreased uptake, increased efflux, and inhibition of apoptosis. The MDR genes control multiple drug resistance in mammals. The 27 exon MDR1 locus (human chromosome 7q21.1) encodes a phosphoglycoprotein and controls drug transport and drug removal ('hydrophobic vacuum cleaner' effect). A repressor binding to a -100 to -120 GC-rich sequence regulates the MDR1 gene. At -70 to -80 is a Y box (binding site of the NF-Y transcription factor). This area overlaps with the binding site of Sp1. There is also a 13-bp sequence (IN) surrounding the transcription initiation site and promoting the accuracy of transcription. If tumors have high expression of this gene, the prognosis for

chemotherapy is not good. Upon drug treatment, the activity of the MDR protein may increase several-fold. The MDR activity can be suppressed by some calcium channel blockers, antibiotics, steroids, detergents, antisense oligonucleotides, anti-MDR ribozymes, etc. Non-P-glycoprotein-mediated MDR has also been restricted by MRP (a multiple-drug-resistance-related glycoprotein), encoded in human chromosome 16p13.1. The MDR gene targeted to special tissues of transgenic animals by tissue-specific promoters may protect these tissues (e.g., bone marrow) during cancer chemotherapy. Also, the MDR transgenic cells may display selective advantage and thus be advantageous during the curing process. In mouse tumors like in human tumors, the response to drugs of individual tumors varies, but eventually they all become resistant to the maximum tolerable dose of doxorubicin or docetaxel. The tumors also respond well to cisplatin but do not become resistant, even after multiple treatments in which tumors appear to regrow from a small fraction of surviving cells. Classical biochemical resistance mechanisms, such as up-regulated drug transporters, appear to be responsible for doxorubicin resistance, rather than alterations in drug-damage effector pathways (Rottenberg S et al 2007 Proc Natl Acad Sci USA 104:12117). ▶ABC transporter, ▶cancer therapy, ▶chemotherapy, ▶multidrug resistance, ▶drug intersection, ▶transcription factors, ▶Sp1, ▶promoter, ▶epistasis; Gottesman MM et al 1995 Annu Rev Genet 29:607; Litman T et al 2001 Cell Mol Life Sci 58(7):931; review: Higgins CF 2007 Nature [Lond] 446:749.

Multiple Endocrine Neoplasia (MEN): ▶endocrine neoplasia

Multiple Epiphyseal Dysplasia (MED): An osteochondrodysplasia causing short stature and early onset osteoarthritis. Mutations in a cartilage oligomeric-matrix protein (a pentameric 524-kDa glycoprotein, COMP, 19p13.1), and in collagen IX (COL9A2, 1p33-p32.2, COL9A3, 20q13.3) cause MED. ▶osteochondromatosis, ▶osteoarthritis, ▶collagen, ▶Ehlers-Danlos syndrome, ▶pseudoachondroplasia, ▶COMP, ▶thrombospondin; Briggs MD et al 1995 Nature Genet 10:330.

Multiple Hamartoma Syndrome (MHAM, PTEN, MMAC1): Hamartomas are groups of proliferating, somewhat disorganized, mature cells—occurring under autosomal dominant control—on the skin, breast cancer, thyroid cancer, mucous membranes, and gum, but may be found also as polyps in the colon or other intestines. The lesions may become malignant. The symptoms may be associated with a number of other defects. The Cowden disease was assigned to human chromosome 10q22-q23. The Bannayan-Riley-Zonona syndrome resembles Cowden disease

and maps to the same location. The molecular basis is a dual function phosphatase with similarity of tensin. Another form involving megaloccephaly and epilepsy symptoms is the Lhermitte-Duclos disease. ▶cancer, ▶breast cancer, ▶tensin, ▶PTEN, ▶Bannayan-Riley-Zonona syndrome; Backman SA et al 2001 Nature Genet 29:396; Kwon C-H et al *ibid.* pp 404.

Multiple Hit: In a multiple hit, the mutagen causes mutation at more than one genomic site. ▶kinetics

Multiple Myeloma: A bone marrow tumor-causing anemia and decrease in immunoglobulin production, frequently accompanied by the secretion of the Bence-Jones proteins. Multiple myeloma may be genetically determined as it may appear in a familial manner. In some forms that have independent origin, within the same family or even within the same person, the protein may show some variations. It can be also induced in isogenic mice by injection of paraffin oil into the peritoneal cavity. Such animals may produce large quantities of the light chain immunoglobulin that can be subjected to molecular analysis. Such globulins are not necessarily monoclonal although from single transformation essentially similar molecules are expected. Multiple myeloma is also called amyloidosis encoded by a gene in human chromosome 11q13. Translocation of the IgH (14q32) immunoglobulin H gene to the amyloidosis locus or to the fibroblast growth factor receptor 3 (4p16.3) may also evoke multiple myeloma. The lymphocyte-specific interferon regulatory factor 4 (6p25-p23) may also be involved. The cyclin D1 protein mediating cell cycle events and the expression of oncogenes also occurs at the 11q13 location. ▶Bence-Jones proteins, ▶immunoglobulin, ▶monoclonal antibody, ▶macroglobulinemia, ▶cyclin D, ▶interferon; Kuehl WM, Bergsagel PL 2002 Nature Rev Cancer 2:175.

Multiple Regression: A continuous variable, say y regresses to other variables such as x_1, x_2, \dots, x_n . The expected value is: $E(y) = b_0 + b_1x_1 + \dots + b_nx_n$ where the b regression coefficients are generally estimated by least squares. ▶correlation, ▶least squares, ▶regression

Multiple Sclerosis (MS): a disease caused by loss of myelin from the nerve sheath or even defects of the gray matter. It is called multiple because it frequently is a relapsing type of condition involving incoordination, weakness, and abnormal touch sensation (paresthesia) expressed as a feeling of burning or prickling without an adequate cause. Myelin oligodendrocyte glycoprotein (MOG) is expressed in the central nervous system oligodendrocytes and in the outermost myelin lamellae. Anti-MOG antibodies have proven effective in destroying multiple sclerosis (demyelination) in some animal models. There is now

evidence that IgG binding to MOG can detect the disease at the preclinical early inflammatory stage in humans and marmoset monkeys (Lalive PH et al 2006 Proc Natl Acad Sci USA 103:2280).

The exact genetic basis is not clear. It may be determined polygenically or it may be recessive; in both cases with much reduced penetrance. It is associated with defects of the HLA-DQ and HLA-DR system in white as well as in American black populations (Oksenberg JR et al 2004 Am J Hum Genet 74:100). There is molecular evidence that in some forms α -B-crystalline, a small heatshock protein, is formed as an autoantigen. Viral initiation has also been considered. MS is basically an autoimmune disease. Encephalitogenic antigens and adjuvants induce *experimental allergic encephalomyelitis* in mice and the condition significantly modified autoimmune susceptibility in both females and males by the Y chromosome derived from the father and grandfather (Teuscher C et al 2006 Proc Natl Acad Sci USA 103:8024). In a rodent model, blocking cytosolic phospholipase A₂ (cPLA₂) may alleviate the condition if the disease has not progressed too far. The controls may reside in the thymus where the T lymphocytes develop. Also damage in the white matter of the central nervous system may be responsible. It appears that MS is induced by damage to the blood-brain barrier (BBB), caused by inflammatory cytokines (TFN, IFN- γ). Among close relatives the incidence may be 20 times higher than in the general population. The concordance between monozygotic twins is about 30%. HLA DR2 carriers have a four-fold increased relative risk. Females have almost twice the risk than males in the relapsing type but in the progressive MS male affliction is slightly more common. The prevalence in the USA is about 1/1,000 but it varies by geographical areas. The onset is between ages 20 to 40. Some of the symptoms may be shared with other diseases, and conclusive identification requires laboratory analysis of myelin. The synonym for MS is disseminated sclerosis. Several procedures have been suggested for the suppression or mitigation of the autoimmune reaction. Anti integrin $\alpha_4\beta_1$ agents (cognate antibodies, synthetic antagonists) may delay demyelination. In a mouse model, isolated neural precursor cells from the mouse brain was injected into the blood or the spinal fluid. These cells express the α_4 integrin protein, which may assist their movement from the blood to the brain where they differentiate into oligodendroglial cells and make myelin or may become neurons. As a consequence, the autoimmunological damage may be repaired (Pluchino S et al 2003 Nature [Lond] 422:688). Copaxone (Cop-1), and a synthetic copolymer of tyrosine, glutamate, alanine, and lysine may protect motor neurons against acute and chronic degeneration (Kipnis J, Schwartz M 2002 Trends Mol Med 8:319).

MS is under the control of several genes, yet linkage to 5p14-p12 with a lod score of 3.4 was found. The Pelizaeus-Merzbacher disease, a late onset multiple sclerosis-like disorder with an autosomal dominant expression, has been frequently confused with MS. Two principal regions in human chromosomes 17q22 and 6p21 (in the HLA area) control epistatically the susceptibility to MS. Besides these loci, chromosome 1 – centromere region also displays linkage with MS (lod score 4.9) or even stronger based on large African-European admixture populations (Reich D et al 2005 Nature Genet 37:1113). Genomewide association studies indicated linkage with the HLA region (6p21) and with interleukin receptor loci IL2RA (CD25, 10p15) and IL7RA (CD127, 5p13) and to a lesser degree with KIAA (multiple interacting proteins, 16p13) and CD58 (lymphocyte-associated antigen, 1p13) among other SNPs Ramagopalan SV et al 2007 New England J. Med. 357:2199. ▶myelin, ▶oligol, ▶epilepsy, ▶neuromuscular diseases, ▶autoimmune disease, ▶MHC, ▶HLA, ▶heatshock protein, ▶Pelizaeus-Merzbacher syndrome, ▶Addison-Schilder disease, ▶neurological diseases, ▶leukodystrophy, ▶HLA, ▶concordance, ▶twinning, ▶lod score, ▶TFN, ▶IFN, ▶BBB, ▶CD45; Klein L et al 2000 Nature Med 6:56; Smith T et al 2000 Nature Med 6:62; Barcellos LF et al 2001 Nature Genet 29:23; Schmidt S et al 2002 Am J Hum Genet 70:708; Keegan BM, Noseworthy JH 2002 Annu Rev Med 53:285.

Multiple Translocations: ▶translocation complex

Multiple Tumor Suppressor: ▶MTS1

Multiplex Amplifiable Probe Hybridization: Multiplex amplifiable hybridization uses PCR and electrophoresis for the detection of small deletions and duplications within genes. (See White S et al 2002 Am J Hum Genet 71:365).

Multiplexing: In multiplexing, several pooled DNA (or other) samples are sequenced/processed/analyzed simultaneously to expedite the process. ▶genome project

Multiplication Colony: Multiplication colony is an expansion by random mating of the foundation stock of inbred rodents for experimental use. ▶foundation stock, ▶inbred

Multiplication Rule: ▶joint probability

Multiplicative Effect: As per the multiplicative effect, alleles at more than one gene locus together have higher than simply additive contribution to the phenotype. In genetically determined disease, the relative risk with

two alleles is the square of the relative risk with only one allele. ►additive effects

Multiplicity of Infection: A single bacterial cell is infected by more than one phage particle. ►double infection

Multiplicity Reactivation: As per multiplicity reactivation, when bacterial cells are infected with more than one phage particle, each, that have been inactivated by heavy doses of DNA-damaging mutagens, the progeny may contain viable viruses because replication and/or recombination has restored functional DNA sequences. ►Weigle reactivation

Multipoint Cross: More than two genes are involved in a multipoint cross. (See <http://www.broad.mit.edu/ftp/distribution/software/>).

Multipolar Spindle: During mitosis, more than two poles exist under exceptional conditions, e.g., aneuploidy caused by fertilization by more than one sperm. Such a condition may be the result of centrosome defects in animals (see Fig. M132). Multiple centrosomes may be formed in case the tumor suppressor gene p53 is not functioning. ►mitosis, ►centrosome, ►p53, ►spindle

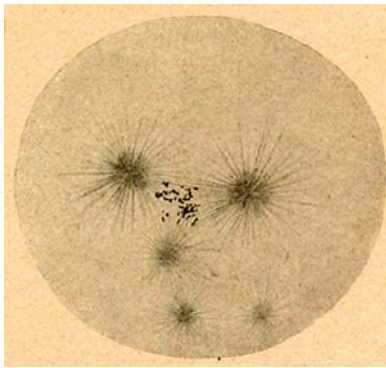


Figure M132. Multipolar spindle in a starfish egg

Multipotent: Multipotency is an ability to develop into more than one type of cell or tissue. ►pluripotency, ►totipotency, ►regeneration

Multi-Regional Origin: ►out-of-Africa hypothesis

Multisite Gateway Technology: Invitrogen Gateway technology exploits the integrase/*att* site-specific recombination system for directional cloning of PCR products and the subsequent subcloning into destination vectors. One or three DNA segments can be cloned using Gateway or MultiSite Gateway, respectively (Magnani E et al 2006 BMC Mol Biol 7:46; <http://www.invitrogen.com/content.cfm?pageid=8012&sku=12537023>).

Multisite Mutations: Multisite mutations occur generally when an excessively large dose of a mutagen(s) is applied. Frequently, deletions or other chromosomal aberrations are included. ►mutation, ►chromosomal aberration, ►deletion

Multistranded Chromosomes: Multistranded chromosomes contain more than two chromatids, such as in the polytenic chromosomes produced by repeated replication without separation of the newly formed strands. In the early period of electronmicroscopic studies of ordinary chromosomes, apparent multiple strands were observed, and it was assumed that each chromosome has many parallel strands of DNA (see Fig. M133). This assumption could not be validated by subsequent investigations. Each chromatid has only a single DNA double helix that is folded to assure proper packaging. ►packing ratio, ►polytenic chromosomes, ►Mosolov model

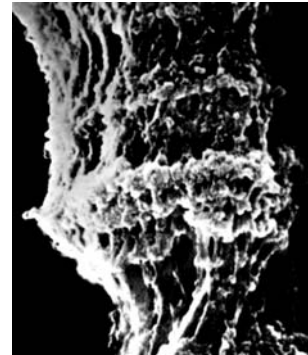


Figure M133. Scanning electronmicrograph of a segment of polytenic salivary gland chromosome. (Courtesy of Dr. Tom Brady)

Multitasking: The multitasking computer program performs more than a single operation simultaneously.

Multivalent: Multivalent refers to the association of more than two chromosomes in meiosis I. ►meiosis

Multivariate Analysis: Multivariate analysis has many uses in genetics when a decision is needed to classify syndromes with overlapping symptoms and when the diagnosis requires quantitation. It may be also used to classify populations with similar traits. The assumption is that the variates X_1, \dots, X_k are distributed according to a multivariate normal distribution. The variance of X_i , σ_{ii} and the covariance of X_i and X_j are presumed to be identical in the two populations, but σ_{ii} or σ_{ij} are not the same from one variate to another or one pair of variates to another pair, respectively. The difference between the two means for X_i is $\delta_i = \mu_{2i} - \mu_{1i}$. Hence the *linear discrimination function* $\Sigma L_i X_i$ provides the lowest probability of

incorrect classification. The L_i values will be determined according to the procedure shown. The δ/σ is maximalized for minimization of the chance of misclassification. The *generalized squared distance* is $\Delta^2 = (\sum L_i \delta_i)^2 / \sum \sum L_i L_j \sigma_{ij}$ and L_i is obtained by a set of equations: $\sigma_{11}L_1 + \sigma_{12}L_2 + \dots + \sigma_{1k}L_k = \delta_1$, $\sigma_{k1}L_1 + \sigma_{k2}L_2 + \dots + \sigma_{kk}L_k = \delta_k$. ▶[discriminant function](#), ▶[covariance](#) [[look up at correlation](#)], ▶[Euclidean distance](#))

Multivariate Normal Distribution:

$$f(x_1, x_2, \dots, x_q) = (2\pi)^{-q/2} \left| \sum \right|^{-1/2} \exp -1/2(x - \mu)' \sum^{-1} (x - \mu)$$

Multivesicular Body (MSB): Proteins or peptides covalently tagged with ubiquitin(s) are sorted through the MVB pathway and delivered to lysosome for breakdown. ▶[ubiquitin](#)

MUM (maximum unique match): Indicates the homology of the nucleotide sequences between two DNA single strands.

MUMmer: A genome sequence alignment algorithm. ▶[algorithm](#); Delcher AL et al 2002 Nucleic Acids Res 30:2478.

Mummies: Dried animal or human bodies, preserved by chemicals and/or desiccation. They may contain proteins (blood antigens), and DNA sequences to carry out limited molecular analysis using PCR technology. ▶[ice man](#), ▶[ancient DNA](#), ▶[ancient organisms](#); Buckley SA et al 2004 Nature [Lond] 431:294.

Mumps: An infectious disease caused by paramyxovirus. It is spread through contact, sneezing, saliva, or through other body fluids, and generally affects children under 15. Swelling of the parotid (salivary) glands situated in front and below the ears is its primary target, but it may affect other organs such the ovaries, testes, pancreas, and brain. In the majority of cases, clinical treatment is not required. Vaccination is available.

MUNC18: A mammalian homolog of the Unc18 protein of *Caenorhabditis*, and binds syntaxin. Sec1/Munc18 activate SNARE fusion and are required for neurotransmitter release (Shen J et al 2007 Cell 128:183). ▶[syntaxin](#), ▶[snare](#), ▶[neurotransmitter](#)

Mung Bean Nuclease: A single-strand specific endonuclease.

Munchausen Syndrome: Medically, a psychological disorder of simulating disease in order to get attention. It was so named by Batshaw ML et al (1985 in New England J Med 312:1437) for some

patients simulating Torsion Dystonia (9q34), a neurological disorder involving involuntary motions. Freiherr/Baron von Münchhausen, a German raconteur published his fancy, mendacious adventures in a *Vademecum for Happy People* in 1760, which appeared in different editions and languages and made him a legend of tall stories. ▶[dystonia](#)

Muprinting: Analysis of the pattern of integration sites of Mu phage in large populations of bacteria. ▶[Mu bacteriophage](#), ▶[insertional mutation](#)

Murashige & Skoog Medium (MS1): MS1 for plant tissue culture is suitable for growing callus and different plant organs. Composition mg/L: NH_4NO_3 1650, KNO_3 1900, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 440, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 370, KH_2PO_4 170, KI 0.83, H_3BO_3 6.2, $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$ 22.3, $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 8.6, $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ 0.25, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 0.02, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 0.025, Ferric-EDTA 43, sucrose 3%, pH 5.7, inositol 100, nicotinic acid 0.5, pyridoxine.HCl 0.5, thiamin.HCl 0.4, indoleacetic acid (IAA) 1 – 30, and kinetin 0.04 – 10. Microelements, vitamins, and hormones may be prepared in a stock solution and added before use. For kinetin, other cytokinins may be substituted such as 6-benzylamino purine (BAP) or isopentenyl adenine (or its nucleoside), for IAA, naphthalene acetic acid (NAA), or 2,4-D (dichlorophenoxy acetic acid) may be substituted or a combination of the hormones may be used in concentrations that are best suited for the plant and the purpose of the culture. For solid media, use agar or gellan gum. Heat labile components are sterilized by filtering through 0.45 μm syringe filters. Variations of this medium are commercially available as a dry powder ready to dissolve but the pH needs to be adjusted. ▶[agar](#), ▶[gellan gum](#), ▶[syringe filter](#), ▶[Gamborg medium](#); Murashige T, Skoog F 1962 Physiol Plant 15:473.

Murine: Pertaining to mice (or rats).

Murine Leukemia Virus (MuLV): ▶[viral vectors](#)

Muscarinic Acetylcholine Receptors: Muscarinic acetylcholine receptors are activated by the fungal alkaloid, muscarine, a highly toxic substance, causing excessive salivation (ptyalism, sialorrhea), lacrimation (shedding tears), nausea, vomiting, diarrhea, lower than 60 pulse rate, convulsions, etc. Deficiency of the M3 receptor decreases appetite in mice and the animals stay lean. Antidote: atropine sulfate. ▶[signal transduction](#)

Muscular Atrophy: Peroneal muscular atrophy (of the fibula) may be classified as (i) demyelinating form and sensory neuropathy, (ii) axonal motor and sensory neuropathy and (iii) distal hereditary neuropathy or distal spinal muscular dystrophy. ▶[Werdnig-Hoffmann disease](#), ▶[Kennedy disease](#), ▶[Charcot-Marie-Tooth](#)

disease, ►olivopontocerebellar atrophy, ►dentatorubral-pallidoluysian atrophy, ►Machado-Joseph syndrome, ►spinal muscular atrophy, ►trinucleotide repeats

Muscular Dystrophy: A collection of anomalies involving primarily the muscle, and controlled by X and autosomal recessive or dominant genes. The most severe form is the (DMD) *Duchenne muscular dystrophy* in human chromosome Xp21.2 (12q21). Its transmission is through the females because the males affected do not reach the reproductive stage. Similar defects were observed also in animals. The prevalence is about 3×10^{-4} . The frequency of female carriers is about twice as high as the affliction of males. The onset is around age 3 and within a few years, the affected persons fail to walk and usually die by age 20. Mental retardation is common in this disease. The earliest diagnosis may be made by an abnormally high serum creatine phosphokinase (CPK) level at birth. Prenatal diagnosis is feasible and successful in about 90% of the cases. The dystrophin gene is one of the largest human genes involving more than two megabases (about half of the size of the entire genome of *E. coli*). This gene includes many introns with an average size of about 16 kb, whereas in the about 79 exons average size is only about 50 kb. In a tissue specific manner, it may chose among eight promoters located at different positions. The full-length dystrophin is ~427-kDa but the R dystrophin is 260, the B 140, the S 114, and the G 71-kDa. The pertinent promoter used 5' downstream to determine the length of the protein. All have the same C-terminal domain, except the 40-kDa apodystrophin-3, which has a truncated C-terminal synthrophin-binding domain. The gene in the muscles appears to use a promoter other than in the brain. The majority of the cases are deletions and other chromosomal defects, yet gene mutations (predominantly frameshifts) are common too because of the large size of the gene. Intragenic recombination frequency was estimated to be 0.12. Dystrophin connects F-actin through its N-terminus, and its C-terminus binds to a complex of glycoproteins and through them to the extracellular matrix and the sarcolemma (Bassett DI et al 2003 Development 130:5851). In DMD, the dystrophin protein may be entirely missing, whereas in the milder form of the diseases, the *Becker type* (BMD), the dystrophin protein is just shorter. With antisense technology (in a mouse model, using 2'-O methyl oligoribonucleotides), skipping of exon 23 induction altered the reading frame and the mRNA was translated into a protein resembling that of the Becker type dystrophin. Such a gene therapy significantly mitigated the symptoms of the disease (Mann CJ et al 2001 Proc

Natl Acad Sci 98:42; Goyenvall A et al 2004 Science 306:1796). Adeno-associated virus vector can deliver an antisense sequence, through the tail vein to rodents had beneficial therapeutic effects (Denti MA et al 2006 Proc Natl Acad Sci USA 103:3758). The dog model of DMD responded favorable to intra-arterial delivery of blood vessel-associated stem cells making the wild type protein (Sampaolesi M et al 2006 Nature [Lond] 444:574). Combining the effects of nitric oxide with nonsteroidal anti-inflammatory activity by using HCT 1026, (a nitric oxide-releasing derivative of flurbiprofen) (see Fig. M134) in murine models for limb girdle and Duchenne muscular dystrophies, significantly ameliorated the morphological, biochemical, and functional phenotype in the absence of secondary effects and slowed down disease progression. In addition, HCT 1026 enhanced the therapeutic efficacy of arterially delivered donor stem cells, by increasing 4-fold their ability to migrate and reconstitute muscle fibers (Brunelli S et al 2007 Proc Natl Acad Sci USA 104:264).

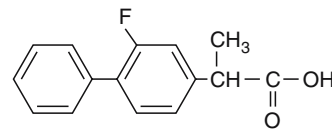


Figure M134. Flurbiprofen

The frequency of BMD is about 0.1 of that of DMD, and the patients may live until 35 and thus may have children. Apparently, allelic genes code for BMD and DMD. Deletions in the DMD gene may affect genes proximal to the centromere: CGD (chronic granulomatous disease), or the XK (McLeod syndrome) or the XP6 (retinitis pigmentosa) and distally GKD (glycerol kinase) or AHC (adrenal hyperplasia) may be affected. The two forms of the *Emery-Dreifuss dystrophy* affecting the shoulder muscles (scapulohumeral dystrophy) are autosomal (1q21-q23, encoding lamins A and C) and X-linked (Xq28, encoding emerin). In the *limb-girdle muscular dystrophy* (LGMD, 3 dominant, 8 recessive), the defects are in the sarcoglycan subunits; α -sarcoglycan is encoded in chromosome 17q12-q21, the β subunit is coded in chromosome 4q12, whereas the γ subunit was localized to 13q12. Mouse defective in α -sarcoglycan can be successfully treated by arterial delivery of mesangioblasts (stem cells) transduced by lentiviral vectors expressing the sarcoglycan gene (Sampaolesi M et al 2003 Science 3001:487). The human chromosome 4q35 region harbors the dominant genes, which are misregulated in FSHD (*facioscapulohumeral muscular dystrophy*). In FSHD, deletion is found in a 4q35 duplicated region (D4ZA) containing

a transcriptional silencer. Overexpression of FRG1 (but not the FRG2) gene in the region leads to the FSHD disease because of inappropriate alternative splicing of the pre-mRNA of mice (Gabellini D et al 2006 Nature 439:973). LGMD1A (human chromosome 5q) and LGMD2 (human chromosome 1q11-q21) are both the dominant forms. LGMDC (3q25) involves a defect in the plasma membrane protein caveolin-3. Chromosomes 2p13, 5q22.3–31.3, and 15q15 also encode LGMD subunits. The recessive (chromosome 9q31) *Fukuyama congenital muscular dystrophy* (FCMD) has a prevalence of $\sim 10^{-4}$ in Japan. It involves polymicrogyria (numerous small convolutions of the brain) due to defects of migration of the neurons and involves mental retardation. The mutation is caused by a ~ 3 -kbp insertion of a retrotransposal tandem repeat at the 3'-untranslated sequences of a gene encoding a secreted protein, fukutin. The recessive *Miyoshi myopathy* (2q13.2) has an early adulthood onset due to defect in the 6.9-kb cDNA encoding the dysferlin protein (named after dystrophy and fertility in *Caenorhabditis*). The *oculopharyngeal muscular dystrophy* (OPMD), a late adulthood onset disease of swallowing, dropping eye lids, and limb weakness is caused by 8–13 expansion of a (GCG)₆ tract specifying polyalanine encoded by the poly(a) binding protein 2 gene (PABP2) at human chromosome 14q11-q13. The symptoms of the muscular dystrophies display considerable variation in onset and severity of expression. The face and shoulder (fascioscapulohumeral) dystrophy is limited to the named body parts. The gene was assigned to human chromosome 4q35. The congenital dystrophy gene causing deficiency in the laminin $\alpha 2$ chain (merosin) around the muscle fibers was located to human chromosome 6q22-q23. Laminin- $\alpha 2$ -deficiency can be compensated for by agrin in mouse. Adeno-associated virus vector—introduced into multiple muscles—mediated overexpression of agrin and restored the structural integrity of the basal lamina of myofibers, inhibited interstitial fibrosis, and ameliorated the pathological symptoms by such somatic gene therapy in mice (Qiao C et al 2005 Proc Natl Acad Sci USA 102:11999). For improving plasmid-mediated integration of dystrophin, phage Φ C31 integrase was used in mouse model of gene therapy for Duchenne muscular dystrophy. Using luciferase expression vector, the integration can be modified in non-invasive manner (Bertoni C et al 2006 Proc Natl Acad Sci USA 103:419). The *Ullrich* (scleroatonic) *muscular dystrophy* is a recessive defect in collagen 6 (COL6A1, COL6A2, 21q22.3, COL6A3, 2q37). Mitochondria in cells from Ullrich patients, unlike those in myoblasts from healthy donors, depolarized upon addition of oligomycin and displayed ultrastructural alterations that were worsened by treatment with oligomycin. The increased apoptosis,

ultrastructural defects, and the anomalous response to oligomycin could be normalized by Ca^{2+} chelators, by plating cells on collagen VI, by treatment with cyclosporin A, or with the specific cyclophilin inhibitor methylAla3ethylVal4-cyclosporin, which does not affect calcineurin activity (Angelin A et al 2007 Proc Natl Acad Sci USA 104:991). Other types of muscular dystrophies may accompany symptoms of other human diseases. Dystrophin is a rod-like cytoskeletal protein, normally localized at the inner surface of the sarcolemma (the muscle fiber envelope). Dystrophin is attached within the cytoplasm to actin filaments and also to the membrane-passing β subunit of the dystroglycan (DG) protein while the α subunit of DG joins the basal lamina through the laminin protein (encoded in chromosome 6q22-q23). In the membrane, DG is associated with the β and γ subunits of sarcoglycan (SG); the α sarcoglycan is extracellularly attached to the other two subunits. In *Caenorhabditis*, the acetylcholine transporter SNF-6 mediates synaptic activity at the neuromuscular junctions. Improper clearing of acetylcholine in the mutants seems to contribute to muscular dystrophy pathogenesis (Kim H et al 2004 Nature [Lond] 430:891). In some LGMD patients, there is also a defect in the muscle-specific protease calpain-3, encoded in chromosome 15q15. [The LGMD disease is also called severe childhood autosomal recessive muscular dystrophy or SCARMMD]. In some of the SCARMMDs, the defect was associated with adhalin, a 50-kDa sarcolemma dystrophin-associated glycoprotein, encoded in human chromosome 17q. Bone marrow cells, which normally are precursors of cartilage, bone, and some parenchyma cells may differentiate into myotubes and have been considered as genetic therapeutic agents for the treatment of muscular dystrophy. Carriers of dystrophies can be *biochemically normalized* when from over-expressed positive cells the protein is diffused to the nearby negative cells. In case of *genetic normalization*, degenerated myonuclei are replaced by nuclei from dystrophin-positive *muscle satellite cells* (muscle stem cells). Gene therapy is possible by the injection of integrating vectors carrying the normal genes into muscle satellite cells that may fuse with the muscle fibers. Adenovirus vectors, however, do not integrate into the host nuclei and replicate only in extrachromosomal form. Therefore, after a variable period of time they may be lost. Retroviral vectors integrate and are stably expressed in the chromosomes. They can be introduced in vivo or ex vivo. Direct injection of supercoiled plasmid DNA may also be successful for transformation although such DNAs are not integrated into the host genome and frequently display variable expression. Another therapeutic approach is the injection of fusogenic, in vitro cultured myoblast cells that may cure in a mosaic pattern the host's defect.

Upregulation of the utrophin gene (6q24, its encoded protein is 65–80% homologous to dystrophin) has also been considered as a remedy. The utrophin gene is normally active only during embryonal development and then it falls dormant. ▶myotonic dystrophy, ▶Charcot-Marie-Tooth disease, ▶neuromuscular diseases, ▶muscular atrophy, ▶neuropathy, ▶lamins, ▶agrin, ▶RFLP, ▶apoptosis, ▶emerin, ▶myotubes, ▶gene therapy, ▶adenovirus, ▶viral vectors, ▶retroviral vectors, ▶myoblast, ▶sarcolemma, ▶dystrophin, ▶caveolin, ▶dysferlin, ▶mitochondrial diseases in humans, ▶contiguous gene syndrome, ▶antisense technologies, ▶readthrough, ▶Walker-Wagner syndrome, ▶collagen; Koenig M et al 1989 Am J Hum Genet 45:498; Arahata K 2000 Neuropathology Dystrophin S34-S41; Burton EA, Davies KE 2002 Cell 108:5; Durbeej M, Campbell KP 2002 Current Op Genet Dev 12:349; Chamberlain JS 2002 Hum Mol Genet 11:2355; Hauser MA et al 2002 Am J Hum Genet 71:1428, potential gene therapies: van Deutekom JCT, van Ommen G-JB 2003 Nature Rev Genet 4:774.

Mushroom: The fruit body of basidiomycete fungi. The mushroom is generally a genetic mosaic arising from mycelial fusion of two to several genetically compatible colonies. ▶basidiomycetes, ▶fungal life cycles

Mushroom Body: A central nerve (neuropil) complex in the insect brain and the pairs of mushroom bodies are implicated in olfactory memory recall and elementary cognitive functions. Mushroom bodies regulate sleep in *Drosophila* (Joiner WJ et al 2006 Nature [Lond] 441:757). ▶memory, ▶olfactogenetics; McGuire SE et al 2001 Science 293:1330.

Music of Macromolecules: <http://www.geneticmusic.com/dnamusic>; music of the genome: <http://www.pandora.com>.

Musical Talent: Pitch perception appears to be associated with an associative auditory area of the brain (asymmetry of the planum temporale). The immediate and correct recognition of the musical pitch, an auditory tone without an external reference, is rare autosomal dominant factor in the human populations and it is called the perfect or absolute pitch (AP). The heritability of musical ability appears high (70–80). The development of this ability is favored by early musical training. Whales and several species of birds use music somewhat similarly to humans (Gray PM et al 2001 Science 291:52). The neurobiological bases of human music perception and performance is discussed by Tramo MJ 2001 Science 291:54. ▶Bach, ▶Beethoven, ▶Mozart, ▶Strauss, ▶dysmelodia, ▶amusia, ▶prosody, ▶pitch; Baharloo S et al 1998 Am J Hum Genet 62:224 *ibid.* 67:755 2000; Peretz I et al 2002 Neuron

33:185; reviews on music faculty: 2003 Nature Neurosci 6:663–695.

Mustard Gas (dichloroethyl sulfide, $[\text{ClCH}_2\text{CH}_2]_2\text{S}$): A radiomimetic, vesicant poison gas, used for warfare in World War I. ▶nitrogen mustards, ▶radiomimetic

Mustards (family of cruciferous plants): The taxonomy of this family is not entirely clear. The white mustard (*Sinapis alba*) is $2n = 24$. The black mustard (*Brassica nigra*) is $2n = 2x = 16$ and supposedly the donor of its genome to the Ethiopian mustard (*B. carinata*) $2n = 34$, $(2 \times [8 + 9])$, an amphidiploid that received 9 chromosomes from *B. oleracea* ($2n = 18$). The brown mustard (*B. juncea*) $2n = 36$ ($2 \times [8 + 10]$) has one genome ($x = 8$) of the black mustard and another genome ($x = 10$) from *B. campestris* ($2n = 20$). The 38 ($2 \times (9 + 10)$) chromosomes of the rapes and swedes descended from *B. oleracea* ($2n = 18$) and *B. campestris* ($n = 20$). Sometimes *Arabidopsis* ($2n = 10$) is also called mustard since mustard also means crucifer. ▶*Brassica*

Mutatm Mouse: Commercially available transgenic strain with the *LacZ* insertion useful for testing mutagens/carcinogens. The transgene is extracted from mice and introduced into λ phage and subsequently into *E. coli* bacteria. In the presence of Xgal substrate, the mutant bacterial colonies appear colorless on a blue background because of the inactive galactosidase. Actually, mutations inside the mouse are ascertained outside the animals for convenience of detectability. ▶Big Blue, ▶Lac operon, ▶ β -galactosidase, ▶Xgal; Nohmi T et al 2000 Mutation Res 455:191.

Mutability: Mutability indicates how prone is a gene to mutate; it indicates a genetic instability. This may be an intrinsic property of the gene or due to the presence of transposable elements or it may depend on the functionality of the genetic repair systems.

Mutable Gene: A mutable gene has higher than usual rate of mutation. ▶mutator genes, ▶transposable elements, ▶mismatch repair, ▶DNA repair, ▶mutator

Mutagen: Physical, chemical, or biological agent capable of inducing mutation. ▶distal mutagen, ▶promutagen, ▶proximal mutagen, ▶ultimate mutagen, ▶activation of mutagen, ▶physical mutagens, ▶chemical mutagens, ▶biological mutagens, ▶effective mutagen, ▶efficient mutagen, ▶super-mutagen, ▶triple helix formation, ▶mutagen direct, ▶mutagen indirect, ▶environmental mutagens

Mutagen Assays: ▶bioassays in genetic toxicology, ▶Ames test, ▶C/B, ▶autosomal dominant assays, ▶autosomal recessive assays, ▶Basc

Mutagen Direct: A direct mutagen acts by modifying DNA (or RNA bases) by, e.g., alkylation or deamination, cross-linking DNA strands, and breaking the nucleic acid backbone.

Mutagen Indirect: An indirect mutagen damages DNA by its metabolic products (activation of promutagens), increase of reactive free radicals (ROS), affects (reduce) apoptosis, increases recombination, mutates oncogenic suppressors, etc.

Mutagen Information Center: ►databases

Mutagen Sensitivity: Mutagen sensitivity is determined by DNA repair and the metabolic enzymes degrading or activating mutagens/promutagens. ►DNA repair, ►promutagen; Tuimula J et al 2002 Carcinogenesis 23:1003.

Mutagenesis: Induction and procuring of mutations either by mutagenic agents in vivo or by the use of reversed genetics. Mutagenic agents usually inflict damage to the genetic material. The cell attempts to repair the lesions and uses transcription factors to meet this goal. By binding 30 damage-related transcription factors to the DNA, the DNA damage response pathway can be mapped (Workman CT et al 2006 Science 312:1054). ►mutation induction, ►cassette mutagenesis, ►transposable elements, ►insertion elements, ►insertional mutation, ►REMI, ►localized mutagenesis, ►directed mutation, ►oligonucleotide-directed mutagenesis, ►sequence saturation mutagenesis, ►RID, ►reversed genetics, ►genome-wide functional analysis, ►synthetic lethals, ►DNA repair; Jackson IJ 2001 Nature Genet 28:198.

Mutagenesis, Genome-Wide: ►insertional mutation; Spradling AC et al 1995 Proc Natl Acad Sci USA 92:10824; Szabados L et al 2002 Plant J 32:233.

Mutagenesis, Site-Selected: ►localized mutagenesis, ►directed mutation

Mutagenesis, Site-Specific: ►localized mutagenesis, ►directed mutation, ►targeting genes, ►site-specific mutation, ►RID, ►mutation locus-specific in humans

Mutagenic Potency: Mutagenic potency is difficult to determine for many agents that have low mutagenicity (see Table M8). Therefore, the genetic and carcinogenic hazard of many compounds is unknown, and possibly harmless agents may have been found mutagenic in some studies while other studies do not verify their harmful effect. There are other agents that may be definitely mutagenic and/or carcinogenic but may have escaped attention. Also, there is no perfect way to quantitate mutagenic effectiveness, particularly for human hazards because of the different quantities humans may be exposed to. As an example, the mutagenicity in the Ames *Salmonella* assay of a few compounds is listed in the table. It is interesting to note that ethylmethane sulfonate, the probably most widely used mutagen, is only the ninth on this list and nitrofurantoin, an erstwhile food preservative, exceeds its effectiveness as a mutagen on molar basis more than three thousand fold. ►environmental mutagens, ►Ames test, ►mutagen assays, ►bioassays in genetic toxicology

Mutagenic Specificity: As per mutagen specificity, base analogs (5-bromouracil, 2-aminopurine) affect primarily the corresponding natural bases. The target of hydroxylamine is cytosine. Alkylating agents preferentially affect guanine. There are no simple chemicals, however, that would selectively recognize a particular gene or genes, yet the frequency of mutation may vary according to the gene locus and the mutagen used. With the techniques of molecular biology, specifically altered genes can be produced by synthesis and introduced into the genetic material by transformation. Gene replacement by double crossing-over can substitute one allele for another (see Table M9).

Table M8. Mutagenic potency

| Compound | Mutations/nmole | Compound | Mutations/nmole |
|------------------------|-----------------|-----------------------|-----------------|
| Caffeine | 0.002 | Ethidium bromide | 80 |
| EDTA | 0.002 | Sodium azide | 150 |
| Sodium nitrite | 0.010 | Acridine ICR-170 | 260 |
| Ethylmethane sulfonate | 0.160 | Nitrosoguanidine | 1375 |
| Captan (fungicide) | 25.000 | Aflatoxin B-1 | 7057 |
| Proflavine | 38.000 | Nitrofurantoin (AF-2) | 20800 |

(After McCann, J. et al. 1975. *Proc. Natl. Acad. Sci. USA* 72:5135.)

Table M9. Mutations/ 10^{-6} bacterial cells induced by three different agents at 9 loci. (M. Demerec 1955 Amer. Nat. 89:5)

| MnCl ₂ | | UV | | X-rays | |
|-------------------|-----------|-------|-----------|--------|-----------|
| Gene | Mutations | Gene | Mutations | Gene | Mutations |
| phe-1 | 11 | hi-1 | 22 | leu-2 | 12 |
| leu-2 | 24 | phe-1 | 100 | hi-1 | 34 |
| ar-3 | 63 | ar-2 | 440 | ar-2 | 54 |
| hi-1 | 121 | leu-2 | 1,200 | try-3 | 113 |
| try-2 | 448 | try-3 | 1,800 | ar-3 | 468 |
| leu-3 | 1,050 | try-5 | 3,110 | try-2 | 1,160 |
| ar-2 | 1,720 | ar-3 | 4,600 | leu-3 | 1,380 |
| try-3 | 10,200 | leu-3 | 6,300 | try-5 | 1,563 |
| try-5 | 14,000 | try-2 | 10,700 | phe-1 | 2,460 |

►synthetic genes, ►frameshift, ►gene replacement, ►transformation, ►localized mutagenesis, ►TAB mutagenesis, ►Cre/Lox, ►knockout, ►knock in, ►targeting genes, ►chimeraplasty, ►triplex, ►homolog-scanning mutagenesis, ►TFO, ►Zinc-finger nuclease

Mutagenicity and Active Genes: Experimental data indicate that replicating or actively transcribed genes are preferred targets of mutagens, probably because of the decondensation of the genetic material. Spontaneous deleterious mutation does occur during the stationary phase of *E. coli* when replication is very low (Loewe L et al 2003 Science 302:1558).

Mutagenicity of Electric and Magnetic Fields: A large body of the published positive results lack rigorous experimental verification and reproducibility. Some newer data do not apparently suffer from these shortcomings. An electric field has electric charges at specific points and in the magnetic field magnetic force prevails. (See McCann J et al 1998 Mutation Res 411:45), ►mutagenicity of active genes

Mutagens-Carcinogens: A very large fraction of mutagens (genotoxic agents) are also carcinogens but not all carcinogens are mutagenic. The difference is based on the biology of the two events. Mutation is a single step alteration in the DNA/RNA and carcinogenesis is a multistep process. ►bioassays in genetic toxicology, ►environmental mutagens and carcinogens; Zeiger E 2001 Mutation Res 492:29; <http://potency.berkeley.edu/cpdb.html>.

Mutant: An individual with mutation.

Mutant Enrichment: ►screening, ►mutation detection, ►filtration enrichment

Mutant Frequency: The frequency of mutant individuals in a population, disregarding the time or event that produced the mutation. It is thus a concept different from mutation frequency. ►mutation rate, ►jackpot mutation

Mutant Hunt: Inducing/collecting/isolating particular mutants for a purpose.

Mutant Isolation: See Figs. M135 and M136 for the isolation of mutations. Basically similar procedures can be used in various microorganisms. The isolation of mutations is greatly facilitated if selective techniques are available.

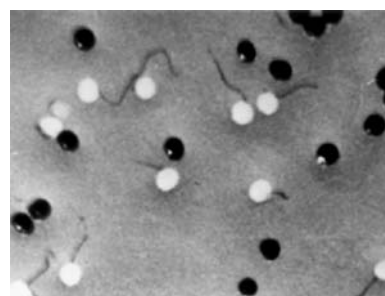
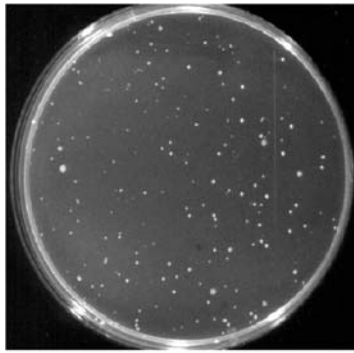
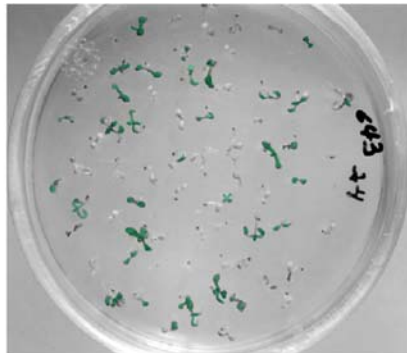


Figure M135. Allyl alcohol selection of alcohol dehydrogenase mutant maize pollen. The black is dead the germinating white pollen is resistant. (Courtesy of M. Freeling, photo by D.S.K. Cheng, see also Nature [Lond] 267:154)

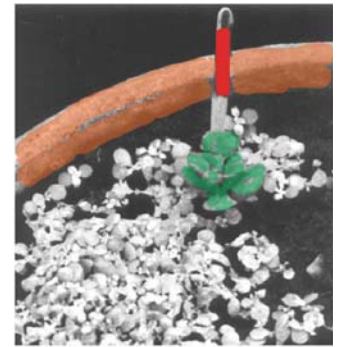
Revertants of auxotrophs can grow on minimal media whereas the resistants (to antibiotics, heavy metals, metabolite analogs, etc.) can be selectively isolated in the presence of the compound to what resistance is sought. Herbicide-resistant plants can be



Salmonella revertants
(G.P. Rédei, unpublished photos)



Kanamycin resistant *Arabidopsis* seedlings



Thiamine-revertant *Arabidopsis*

Figure M136. Selective isolation of mutants of bacteria and plants

selected in the presence of the herbicide. (►[mutation detection](#))

Auxotrophic animal cells could be isolated in the presence of 5-bromodeoxyuridine because the wild type cells that incorporated the nucleoside analog after exposure to visible light—because of breakage of the analog-containing DNA—are inactivated. The non-growing mutant cells fail to incorporate the analogs and thus stay alive and after transferring them to supplemented media they may resume growth. Feeding the cells allyl alcohol can isolate alcohol dehydrogenase mutations. The wild type cells convert this substance to the very toxic acrylaldehyde and are killed, whereas the alcohol dehydrogenase inactive mutants (microorganisms, plants) cannot metabolize allyl alcohol and selectively survive. ►[replica plating](#), ►[fluctuation test](#), ►[filtration enrichment](#), ►[penicillin screen](#), ►[selective medium](#), ►[Ames test](#), ►[reverse mutation](#), see Fig. [M137](#).

Mutarotation: A change in optical rotation of anomers (isomeric forms) until equilibrium is reached between the α and β forms.

Mutase: An enzyme mediating the transposition of functional groups.

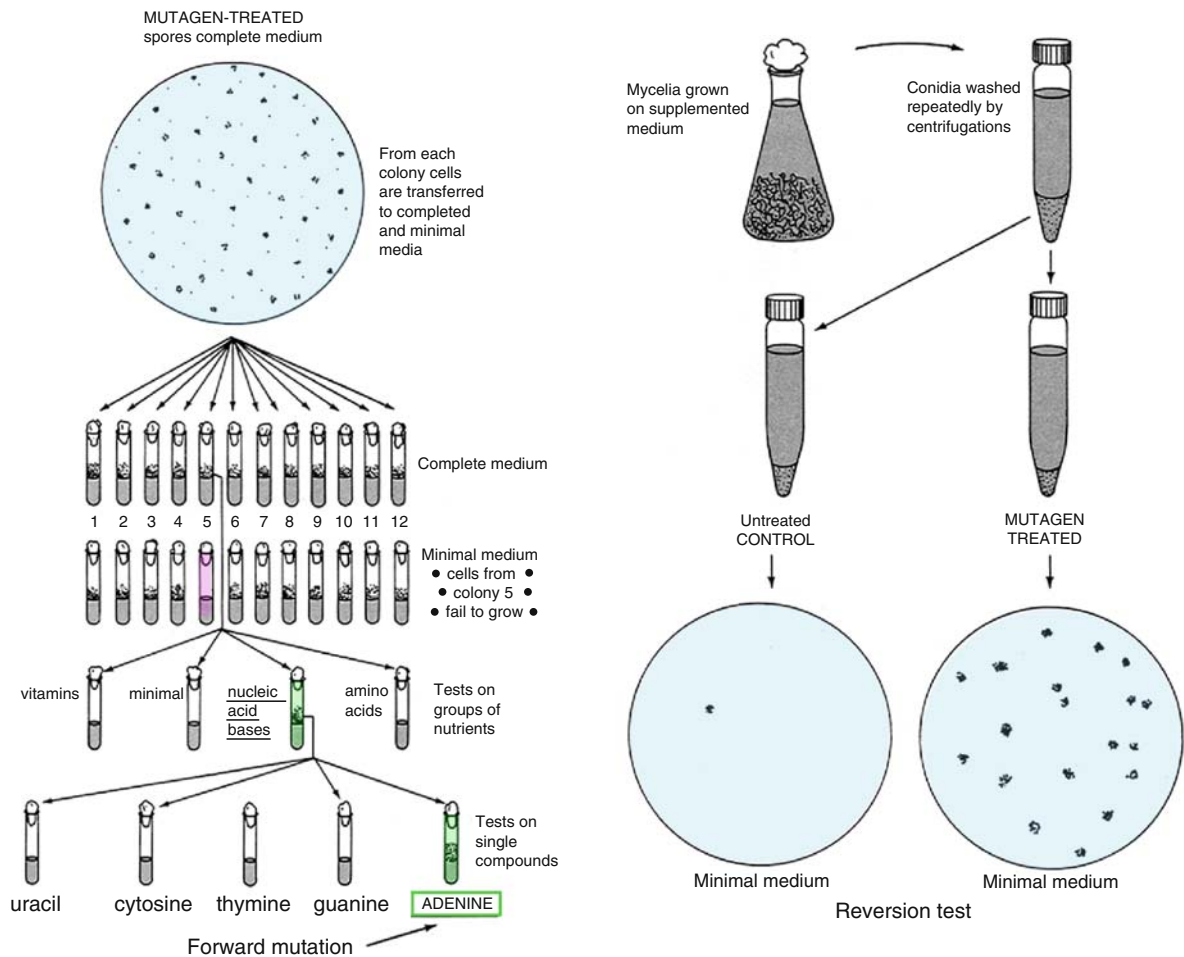
Mutosome: The enzyme complex (Rec A, UmuC-UmuD', pol III/pol V) involved in the error-prone DNA replication in translesion. In *E. coli*, the repair polymerase V and to some extent RecA are required. ►[DNA repair](#), ►[DNA polymerases](#), ►[RecA](#), ►[translesion pathway](#); Schlacher K et al 2005 Mol Cell 17:561.

Mutasynthesis: In mutasynthesis, a biochemically altered mutant of an microorganism may produce modified metabolites either directly or from a precursor analog; the new product (e.g., antibiotic) may be more useful as a drug.

Mutation: Heritable change in the genetic material; the process of genetic alteration (see Figs. [M138](#) and [M139](#)). ►[mutagen](#), ►[spontaneous mutation](#), ►[mutagenic potency](#), ►[mutagenic specificity](#), ►[mutagenicity in active genes](#), ►[mutant isolation](#), ►[mutagen assays](#), ►[mutation detection](#), ►[mutant frequency](#), ►[mutation rate](#), ►[mutation in multicellular germline](#), ►[somatic mutation](#), ►[mutation in cellular organelles](#), ►[mutator genes](#), ►[mutation chromosomal](#), ►[transposable elements](#), ►[mutation beneficial](#), ►[mutation neutral](#), ►[mutation pressure](#), ►[equilibrium mutations](#), ►[mutation useful](#), ►[mutation in human populations](#), ►[genetic load](#), ►[somatic hypermutation](#), ►[auxotrophy](#), ►[forward mutation](#), ►[reverse mutation](#), ►[polymorphism](#)

Mutation, Adaptive: ►[mutation beneficial](#)

Mutation, Age of: The age of a mutation may be inferred on the basis of breaking up the linkage disequilibrium of the ancestral haplotype by additional mutations and recombination. The task links the present haplotype to the haplotype of the coalescence. The identification of the ancestral haplotype is, however, problematic generally. There is no way to determine with certainty the constitution of the original haplotype. One approximation is the study of closely linked markers. The probability that the haplotype stays ancestral during the period elapsed since the mutation occurred can be statistically inferred. If we consider that p is the probability of the ancestral haplotype in a very large population in which all lineages are basically independent, then $G \sim -\ln(p)/r$ where G is the generations, and r is the frequency of mutations and recombination. ►[haplotype](#), ►[coalescent](#), ►[linkage disequilibrium](#), ►[genealogy](#); Reich DE, Goldstein DB p. 129 in Microsatellites, Goldstein DB, Schlötterer C (Eds.) 1999 Oxford University Press, Oxford, UK; Slatkin M, Rannala B 2000 Annu Rev Genomics Hum Genet 1:225.



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Figure M137. General procedures for the isolation of forward and reverse mutants in fungi or other haploid organisms. The chart (left) illustrates nonselective screening of forward mutants. Mutagen-treated haploid cells are propagated on a complete medium (containing vitamins, aminoacids, nucleic acid bases, etc.). Each colony on the Petri plate is the progeny of a single cell. Inocula are transferred both to minimal (without organic supplements) and to complete media to test the nutritional requirements of the colonies. Wild-type cells are expected to grow on both minimal and complete media. Auxotrophic mutants will grow on the complete medium (as shown in test tube 5) but not on the minimal. Then cells from the complete medium culture 5 are tested further for growth on groups of nutrients (vitamins, nucleic acid bases, amino acids, etc.). The mutant will grow only on the medium which contains the compound that cannot be synthesized because of the genetic defect. Then the response of the mutant is tested on media containing single compounds. An adenine mutant will grow only on adenine. For reverse mutant isolation (right chart), cells from an auxotroph are washed repeatedly to remove the needed compound. Then the cells are exposed to a mutagen or only to the solvent of the mutagen (control), and after washing they are spread onto minimal media. Only the revertants are expected to grow. The control plate provides information on spontaneous rate of reversion. The treated cells show the effect of the potential mutagen.

Mutation and Allelic Frequencies: ►equilibrium mutations

Mutation and DNA Replication: Most commonly, mutation is caused by base substitution as replicational error. In multicellular eukaryotes, the detection of the time of mutations is technically difficult or impossible although dormant seeds exposed to ionizing radiation regularly display mutations in

the progeny. These mutations are due, however, to chromosomal breakage or to the production of reactive chemicals that may act during subsequent cell divisions. In prokaryotes, tests can be devised for the detection of mutations occurring during the stationary phase. Using a conditional lethal system for selection, the cells may survive under both restrictive and permissive conditions. Mutations arising under restrictive growth conditions are not

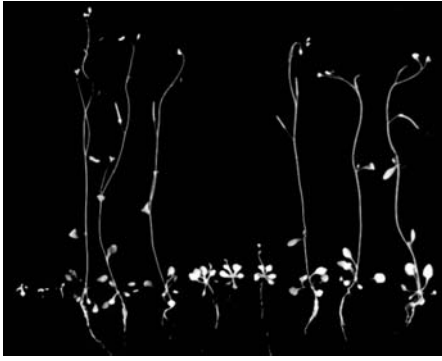


Figure M138. The thiazole-requiring mutants of *Arabidopsis* fail to grow on basal or pyrimidine media but display normal growth on thiazole or thiamine. (From left to right: Basal, Thiazole, Pyrimidine, Thiamine media)



Figure M139. The Thiamine biosynthetic pathway is controlled by single genes

expected to survive but may live under permissive conditions. Thus bacterial cultures in stationary phase are expected to lose all mutants, which occurred during the preceding exponential growth phase. Thus when the culture is shifted to permissive conditions, all the immediately detectable mutations must have their origin in mutations without replication.

►base substitution, ►mutagenicity in active genes, ►growth curve, ►conditional lethal, ►permissive condition; Freese E 1963 p 207. In: Molecular Genetics Pt. I. Taylor JH (Ed.) Acad. Press, New York.

Mutation Asymmetry: As per mutation asymmetry, the base substitution in the transcribed and non-transcribed strands is not equally frequent. It may be caused by transcription-coupled repair. ►DNA repair; Majewski J 2003 Am J Hum Genet 73:688.

Mutation Avoidance: Removal of potential mutations by DNA repair. ►DNA repair

Mutation, Beneficial: when a new mutant appears in the population with a reproductive success of 1.01 (selective advantage 0.01), the odds against its survival in the first generation, $e^{-1.01} \cong 0.364$. Its chances for elimination by the 127th generation will be reduced to 0.973 compared to the probability to a neutral mutation that has a 0.985 chance of extinction. Ultimately, at a selective advantage of 0.01, its chance of survival will be 0.0197. According to the mathematical argument, even mutations with twice as great fitness than the prevailing wild type, have a high (<13%) probability of being lost, $e^{-2} \cong 0.1353$, during

the first generation. Under normal conditions, the mutants' selective advantage (s) is generally very small and the probability of its ultimate survival is $(y) = 2s$. The chance of its extinction is $(l) = 1 - 2s$. In order that a mutant to have a better than random chance (0.5) for survival, the following conditions must prevail: $(1 - 2s)^n < 0.5$ or $(1 - 2s)^n > 2$, hence $-n \log_e (1 - 2s) > \log_e 2$ or approximately $-n(-2s) > \log_e 2$, and therefore $n > \log_e 2 / (2s)$, i.e., $0.6931 / (2s)$.

If $s = 0.01$ and $n =$ number of mutations, n must be larger than $0.6931 / (2 \times 0.01) = 34.655$.

In simple words, approximately 35 times must a mutation, with 0.01 selection coefficient, occur to be ultimately accepted and fixed. If the spontaneous rate of mutation at a locus is 1×10^{-6} , a population of 35 million is required for providing an adequate chance for the survival of a mutant of that type. Since the proportion of advantageous mutations is probably no more than 1 per 10,000 mutations, very few new mutations have a real chance of survival. The cause of this may be attributed to the fact that during the long history of evolution of the organisms, the majority of the possible mutations have been tried and the good ones were adopted by the species. The chances of new mutations is favored, however, when environmental conditions, such as agricultural practice, change in pests, pathogens, and predators, etc. take place for which historical adaptation does not exist.

A new study suggests that 1 in 150 newly arising mutations in bacteria is beneficial and that 1 in 10 fitness-affecting mutations increases the fitness of the individual carrying it. This high beneficial mutation rate is contingent of the relatively small size of the bacterial population ($\sim 10^4$) where clonal interference/competition among mutations would not eliminate many beneficial mutations. Hence, an enterobacterium has an enormous potential for adaptation and may help explain how antibiotic resistance and virulence evolve so quickly (Perfeito L et al 2007 Science 317:873).

►mutation neutral, ►fitness, ►selective advantage, ►selective sweep, ►mutation rate, ►adaptive evolution, ►genetic load, ►deleterious mutation

Mutation Bias: As per mutation bias, microsatellite sequences undergo frequent unequal recombination or replicational errors but the changes increase when the size of the tracts is short and decrease when it is longer than a particular size (~ 200) because the longer tracts are likely to include imperfections. This bias may be maintained in the population by selective forces. In various organisms, one type of base pair substitutions are more frequent than the others, presumable caused by differences of genetic repair. ►microsatellite, ►unequal crossing over; Udupa SM, Baum M 2001 Mol Genet Genomics 265:1097; Green P et al 2003 Nature Genet 33:514.

Mutation, Chromosomal: Partial chromosomal losses (deletion, deficiency), duplications, and rearrangements of the genetic material (inversion, translocation, transposition) are considered chromosomal mutations. The various types of aneuploids (nullisomy, monosomy, trisomy, polysomy, etc.) or increase in the number of genomic sets (polyploidy) can also be classified as chromosomal mutations. (See the specific entries for more details).

Mutation Clearance: The removal of disadvantageous mutations from a population. The emergence of sex and recombination facilitate the process.

Mutation, Compensatory: Compensatory mutation restores stability and/or functionality of another mutation.

Mutation, Cost of Production: The cost of production of mutations varies a great deal from organism to organism and also depends on the developmental stage when the mutagen is applied. Mutation induction at the gametic stage may be less expensive than at the multicellular (diploid) germline stage. In higher plants such as *Arabidopsis*, mutagens are generally applied to the mature seed and thus two generations are required for the isolation of mutants to be used for further experimental studies. The cost of raising these two generations may not be equal and both contribute to the final cost. Although in large M_2 families there is an increased probability for recovering the mutations induced, from the viewpoint of cost effectiveness large number of families with minimal size each are desirable. In case of recessive mutations, depending on the (n) number of individuals in M_2 families, the probability of recovery (P) of a mutant is at $n = 1$ ($P = 0.25$), $n = 2$ ($P = 0.437$), $n = 4$ ($P = 0.683$), $n = 8$ ($P = 0.899$), $n = 16$ ($P = 0.989$),

and $n = 24$ ($P = 0.998$) in case of heterozygosity of the M_1 generation, derived from a single cell. It is thus obvious that increasing the M_2 size from 1 to 24 involves the increase of probability of recovery only from 0.25 to 0.998. In the final cost, the cost of both generations must be included along with the effectiveness of recovery of the mutations induced. Table M10 indicates that M_2 family sizes larger than four individuals generally increase the labor and the cost. The recovery of mutations is most effective if selective techniques are applicable. Unfortunately, in some cases (morphological mutants) this may not be possible. (See Rédei GP et al 1984 In: Mutation, Cancer and Malformation, Chu EHY, Generoso WM (Eds.) Plenum, New York, pp 295).

Mutation, Dating of Origin: G (number of generations since the emergence of the mutation) can be determined in a population using the information of linkage disequilibrium (δ) concerning closely linked genetic or molecular markers and their known recombination frequencies (θ):

$$G = \frac{\log[1 - Q/(1 - pN)]}{\log(1 - \theta)} \times \frac{\log \delta}{\log(1 - \theta)}$$

where $\delta = (pD - pN)/(1 - pN)$ and pD and pN represent the two different linkage phases of the homologous chromosomes. Q (probability) = $(1 - [1 - \theta]^G)(1 - pN)$. (See Guo SW, Xiong M 1997 Hum Hered 47(6):315; Colombo R 2000 Genomics 69:131).

Mutation Detection: Detection of mutation depends on the general nature of the organisms. In haploid organisms (bacteria, algae, some fungi), in haploid cells (microspores, pollen, sperm), in hemizygous cells (e.g., Chinese hamster ovary cell cultures), or in heterozygotes for easily visible somatic markers, the mutations are readily detectable. In diploid or polyploid cells, only the dominant mutations can immediately be

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Table M10. Calculation of the cost of mutation

| M_2 family size → | 1 | 2 | 4 | 8 | 24 |
|---------------------|---|---------------|---------------|--------|--------|
| $M_1 + M_2$ size → | 24 + 24 | 12 + 24 | 6 + 24 | 3 + 24 | 1 + 24 |
| Mutant Expected → | 6 | 5.244 | 4.098 | 2.697 | 1 |
| Cost $M_1:M_2$ ↓ | Cost of 1 Mutation in Arbitrary Units Under the Conditions Shown Above and in the Left-Side Column of This Tabulation | | | | |
| 1:1 | 8 | 6.845 | 7.321 | 10.011 | 25 |
| 1:2 | 12 | 11.442 | 13.177 | 18.910 | 49 |
| 1:3 | 16 | 16.018 | 19.034 | 27.809 | 73 |
| 2:1 | 12 | 9.153 | 8.785 | 11.123 | 26 |
| 3:1 | 16 | 11.442 | 10.249 | 12.236 | 27 |
| 4:1 | 20 | 13.783 | 11.713 | 13.384 | 28 |

observed and for the detection of recessive mutations a more elaborate procedure is required (►mutation in the multicellular germline). The most effective methods involve selective screening. In diploid cell cultures, recessive mutation can be detected if mitotic recombination generates homozygosity at the mutant locus (Guo G et al 2004 Nature [Lond] 429:891; Yusa K et al ibid pp 896) or if the dominant wild type allele is deleted. Molecular methods are also available but these are generally not suitable for large-scale screening. When single-stranded DNA is subjected to electrophoresis in non-denaturing gel, changed pattern is detectable by SSCP. Heteroduplexes can be resolved by instability in non-denaturing gradient gels (DGGE). Also, heteroduplexes move differently in non-denaturing gels. Cleavage of heteroduplexes by chemicals or enzymes may detect mutant sites. Polymorphism at a single locus can be detected by automated analysis using PCR and fluorescent dyes coupled with a quencher (see more under ►polymorphism). Mutation may be detected by chemical modification of the mismatches. Carbodiimide generates electrophoretically slow moving DNA containing mismatched deoxyguanylate or deoxythymidylates. Hydroxylamine modifies deoxycytidylate and osmium tetroxide modifies deoxycytidylate and deoxythymidylate in such a way that the DNA at these residues becomes liable to cleavage by strong bases. Ribonuclease A cleaves at mismatches (depending on the context) in RNA-DNA hybrids. The Mut Y glycosylase of *E. coli* excises adenine from A-G and, with somewhat less efficiency, from A-C mispairs. In *E. coli*, methyl-directed mismatch system is working primarily up to 3-nucleotide insertions or deletions but longer sequences barely respond, if corrected at all, and C-C pairs are ignored. The MutH/L/S multi-enzyme complex misses only 1% of the G-T mispair-induced cuts at nearby GATC sequences. The repair is identified by PCR, which also may be a source of replicational error. The latter errors can be estimated as $f = 2/na$, where f is the estimated fraction of mutations within the sequence, l = the length of the amplified sequence, n = the PCR cycles, and a = the polymerase-specific error rate/nucleotides; (a for Taq polymerase is within the range of 10^{-6} to 10^{-7}). Direct sequencing may provide the most precise information at the highest investment of labor. ►selective screening, ►replica plating, ►sex-linked lethal tests, ►specific-locus tests, ►mutation in human populations, ►Ames test, ►host-mediated assays, ►EMC, ►SSCP, ►DGGE, ►DNA sequencing, ►gel electrophoresis, ►polymorphism, ►PCR, ►footprinting genetic, ►mutant isolation, ►bioassays in genetic toxicology, ►substitution mutation, ►padlock probe, ►SNIPS, ►Comet assay, ►heteroduplex analysis, ►allele-specific probe for mutation, ►ARMS, ►alanine-scanning mutagenesis, ►hemiclinal, ►cancer [INTER-SS PCR]

Mutation Equilibrium: ►equilibrium mutations

Mutation Frequency: The same as mutation rate; see also ►mutant frequency (that is different from mutation frequency).

Mutation, Implicit: A replication error rather than base substitution, insertion, deletion, or recombination. This term is used in genetic algorithms. ►algorithm genetic

Mutation in Cancer Cells: ►cancer, ►Knudson's two-mutation theory

Mutation in Cellular Organelles: Cellular organelles mitochondria and plastids are generally present in multiple copies per cell, and within individual organelles generally several copies of DNA molecules exist. Therefore, it generally is not expected that the mutations would be immediately revealed. For their visible manifestation they have to "sort out", i.e., the mutations may not be visible until single organelles become "homogeneous" regarding the mutation, and single cells would be "homoplasmonic" regarding that particular organelle. Although this process is frequently claimed to be stochastic, the direct observation does not seem to support the assumption. Organelles divide by fission, and the daughter organelles are expected to stay in the vicinity of the parental organelle within the viscous cytosol. Thus it is not mere chance where they are located, and the progeny organelles tend to remain clustered unless the plane of the cell division separates them. Therefore, sorting out may be a relatively fast process. Mutations in chloroplast gene generally do not affect the morphology of the plants, however, inactivation of the *clpP1* (caseinolytic protease P1) gene interferes with shoot development in tobacco (Kuroda H, Maliga P 2003 Nature [Lond] 425:86). Mutation in tRNA^{Leu} (MTTL1) in lung carcinoma cybrid cells may be higher than 95% and suppressor mutations in mitochondrial DNA have been identified in only about 10% of the total mtDNA. ►mitochondrial genetics, ►chloroplast genetics, ►mtDNA, ►chloroplasts, ►mitochondrial diseases in humans, ►suppressor gene, ►suppressor tRNA, ►sorting out

Mutation in Human Populations: Mutation in human populations is difficult to study directly because the random or assorted mating systems do not favor the identification of recessive mutations. Therefore, human geneticists generally rely on the relative increase of "sentinel phenotypes" such as new dominant mutations, hemophilia, muscular dystrophy, and cancer that may be used as "epidemiological indicators" for an increase of mutation. Also, sister chromatid exchange, chromosomal aberrations, and sperm motility assays may reveal mutations.

Molecular methods, such as RFLP, RAPD, and PCR have become more available recently and have changed the previously held view that was based on the fact that no transmitted genetic effects of radiation had been clearly detected by the traditional methods in human populations. Mutational hazard for humans is generally inferred from mouse data, which include induced mutations. The immature mouse oocytes are insensitive to radiation-induced mutation but quite likely to be killed by 60 rads of neutrons and 400 R of X-rays or γ rays. Maturing or mature mouse oocytes on the other hand are very susceptible to mutation by acute radiation, although the sensitivity to low-dose rate irradiation is 1/20 or less. In contrast, the immature human oocytes are not susceptible to killing but their susceptibility to mutation is not amenable to testing. The estimated mutational hazard of mouse oocytes at various stages ranged from 0.17 to 0.44 times that in spermatogonia, indicating lower hazard to females than to males. In industrialized societies, chemical mutagens constitute the major hazard, and because of their variety and potency, their effects are difficult to assess, especially at low levels of exposure. Mutation rates can be estimated also on the basis of base substitutions in synonymous and non-synonymous codons. It may be assumed that the majority of non-synonymous substitutions are more or less deleterious, whereas the synonymous substitutions are neutral. It has been estimated that a total of 100 new mutations occur in the genome of each human individual and that the rate of deleterious mutations per generation per diploid human genome is ~ 1.6 . (See more under individual entries, ►mutation rate [undetected mutation], ►doubling dose, ►bioassays in genetic toxicology, ►specific locus mutations test, ►RBE, ►atomic radiations, ►base substitution mutation, ►synonymous codon, ►mutation neutral, ►genetic load, ►diversity, ►human mutation assays, ►mutation locus-specific in humans; <http://mutview.dmb.med.keio.ac.jp>; <http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html>; <http://www.hgmd.cf.ac.uk/ac/index.php>; human gene mutation database: <http://www.hgmd.org/>).

Mutation in Multicellular Germline: Mutation in the multicellular germline reveals the numbers of cells in that germline at the time the mutation occurred (see Fig. M140). E.g., if a plant apical meristem is treated with a mutagen at the genetically effective 2-cell stage, in the second generation of this chimeric individual the segregation for a recessive allele will not be 3:1 but 7:1. This is so because one of the cells will produce four homozygous wild type individuals, the other cell will yield one homozygous wild type + 2 heterozygotes (=3 dominant phenotypes) and one homozygous recessive mutant ([4 + 3]:1). In case the

germline contains four cells, the segregation ratio is expected to be 15:1 (1/16). In case it consists of eight cells, the proportions are 31:1. ►mutation rate, ►GECN; Rédei GP et al 1984 In: Mutation, Cancer and Malformation, Chu EHY, Generoso WM (Eds.) Plenum, New York, pp 295.

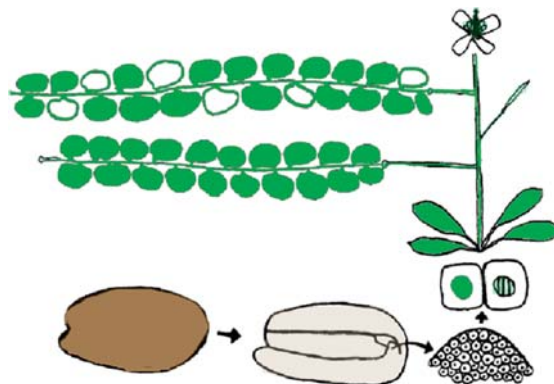


Figure M140. Mutation in multicellular diploid germline

Mutation Induction: See mutagen, directed mutation, localized mutagenesis, cassette mutagenesis, chemical mutagens, physical mutagens, environmental mutagens.

Mutation Load: ►genetic load

Mutation, Locus-Specific in Humans: Database of mutations specific for human genes: http://archive.uwcm.ac.uk/uwcm/mg/docs/oth_mut.html.

Mutation, Neutral: A neutral mutation is neither advantageous nor deleterious to the individual homo- or heterozygous for it. Its chance of immediate loss is determined by the first term of the Poisson series, $e^{-1} \cong 0.368$. (►evolution non-Darwinian). Consequently, its chance for survival is $1 - 0.362$. The chance for its extinction during the second generation is $e^{-0.632} \cong 0.532$, and by the third generation it is $e^{-(1 - 0.532)} \cong 0.626$ ($e = 2.71828$). In general terms, the extinction of any neutral mutation is e^{x-1} where x is the probability of its loss in the preceding generation. According to R.A Fisher, by the 127th generation the odds against the survival of a neutral mutation is 0.985 and may eventually reach 100%. Several evolutionists, notably M. Kimura, have argued statistically against the conclusion of Fisher (and the Darwinian theory of the necessity of selective advantage). Accordingly, if the rate of mutation for a locus is μ , the population size is N , and the organism is diploid, the number of new mutations occurring per generation per gene are $2N\mu$. The chance for random fixation is supposed to be $(1/2)N$ because the new allele is represented only

once among the total of $2N$. The probability of fixation, accordingly, is expected to be $(2N\mu) \times [(1/2)N] = \mu$, indicating that the rate of incorporation of a new neutral mutation into the population is equal to the mutation rate. The average number of generations required for fixation of a neutral mutation (according to Kimura and Ohta) is expected to be $4N_e$ where N_e = the effective population size. Thus, if the effective population size = 1,000 individuals, it takes 4,000 generations for a neutral mutation to be fixed in the population.

Sequencing 419 genes from 24 lines of *Drosophila melanogaster* and some related species, nearly 30% of the amino acid substitutions appeared to be adaptive (Shapiro JA et al 2007 Proc Natl Acad Sci USA 104:2271). In *Caenorhabditis elegans*, 65–80% of the mutations do not have a visible phenotype and thus do not seem to have much effect on fitness. In some human families, a 28-kb, apparently neutral, deletion was detected in chromosome 15q11-q13 area involved in imprinting (Buiting K et al 1999 Am J Hum Genet 65:1588). On the basis of nucleotide sequences, the neutrality can be statistically estimated by the HKA formula (Hudson RR et al 1987 Genetics 116:153) at the constant rate neutral model under specified conditions:

$$\chi^2 \sum_{i=1}^L (S_i^A - \hat{E}[S_i^A])^2 / \hat{Var}[S_i^A] + \sum_{i=1}^L (S_i^B - \hat{E}[S_i^B])^2 / \hat{Var}[S_i^B] + \sum_{i=1}^L (D_i - \hat{E}[D_i])^2 / \hat{Var}[D_i]$$

where L indicates the locus (loci, l) in species A and B sequenced. S_i^A and S_i^B stand for the number nucleotide sites that are polymorphic at locus i in the number of gametes of species A and B, respectively. D_i indicates the number of differences at locus i between a random sample of gametes of species A and B, respectively. \hat{E} and \hat{Var} stand for the estimates of expectation and variance, respectively. In the past, sequence variation in mitochondrial DNA has been considered as neutral but this assumption may not be generally valid. It is generally assumed the synonymous substitutions in the codons are neutral because these do not alter the amino acid sequence and composition of the proteins. This assumption may not be entirely valid because the codon usage is not stochastic and synonymous base substitutions may still affect RNA splicing and stability (Chamary JV et al 2006 Nature Rev Genet 7:98). The basic rate of neutral mutation can be detected in non-functional pseudogenes. ►effective population size, ►non-Darwinian evolution, ►adaptive evolution, ►neutral space, ►mutation beneficial, ►ultraconserved DNA elements, ►mutation rate, ►fitness, ►imprinting, ►radical amino acid substitution, ►McDonald-Kreitman hypothesis, ►Tajima's method,

►codon usage; Hudson RR et al 1987 Genetics 116:153; Kimura M, Ohta T 1977 J Mol Evol 9 (4):367; Gerber AS et al 2001 Annu Rev Genet 35:539; Clark AG et al 2003 Science 302:1960.

Mutation Pressure: Repeated occurrence of mutations in a population.

Mutation Pressure Opposed by Selection: Mutations are frequently prevented from fixation by chance alone (see mutation neutral, mutation beneficial, non-Darwinian evolution). An equilibrium of selection pressure and mutation pressure may be required for the new mutations to have a chance for survival. Mathematically, the frequency of homozygous mutants is $q^2 = \mu/s$ where μ is the mutation rate and s is the coefficient of selection. ►allelic fixation

Mutation-Preventive Concentration: A high concentration of a drug that does not permit the survival of even resistant mutant cells.

Mutation Rate: Frequency of mutation per locus (genome) per generation. This calculation is relatively simple if the cells population is haploid (prokaryotes, most of the fungi, or when the gametes are mutagenized). Mutation rate can be expressed also as alteration per nucleotide or as mutation per replicational cycle. If mutation takes place in the multicellular germline of higher eukaryotes, only indirect procedures can be used. First, the genetically effective cell number (GECN) in the germline must be determined (see genetically effective cell number). One must know also the level of ploidy. Thus mutation rate in these germline cells (R) is:

$$R = \frac{\text{number of independent mutational events}}{\text{survivors} \times \text{GECN} \times \text{ploidy}}$$

The standard error of mutation rates (s_m) can be computed as $\sqrt{\mu[1 - \mu]/n}$ where μ = the mutation rate observed, and n = the size of the population. The calculation of the mutation rate on the basis of survivors may pose problems if two different agents are compared. An example: if we use 10,000 haploid cells as a concurrent control and find 10 mutations, the spontaneous mutation rate would be $10/10,000 = 0.001$. If we expose another 10,000 cells to a mutagen that is lethal to 5,000 cells but again we obtain 10 mutations, the calculated apparent induced mutation rate is $10/5,000 = 0.002$, when actually the treatment may not have induced any mutation, it may have only reduced survival. In case the mutagen is very potent and in each genome or family multiple mutations occur, it may become very difficult to distinguish the multiple mutations from the single ones without further genetic analysis. Some information indicates that in bacteriophages, in case of high mutation rate (induced by mutator factors) more mutants contain more than a single (clustered) mutation as expected

by random distribution (Drake JW et al 2005 Proc Natl Acad Sci USA 102:12849). Since the distribution of mutations follows the Poisson distribution, in such a case the average mutation rate may be better determined on the basis of the size of the fraction of the population that shows no mutation at all. This is the zero class of the Poisson series, $e^{-\mu}$. If, e.g., the fraction of mutations of the population is 0.3, then zero class is $1 - 0.3 = 0.7 = e^{-\mu}$. Hence $-\mu = \ln 0.7 = -0.3566$ and $\cong 0.36$. In yeast for the determination of spontaneous backmutation rate, the formula of von Borstel may be used. Accordingly, $M = e^{(N_0/N)} - m_b/2C$, where N = the total number of compartments, N_0 = number of compartments without reversions, m_b = the average number of mutants in the inoculum, and C = the average number of cells in the compartment after the stoppage of growth. If no mutations are found at all in an experimental population, that does not necessarily mean that the mutation rate is zero. An approximation to the possible mutation frequency may be made. If we assume perfect penetrance and “normal distribution” of undetected mutations, we may further assume that in a population of n genomes the frequency of mutations is $(1 - q)$ at a probability of P . In order to obtain an estimate of q , we have to solve the equation: $(1 - q)^n = (1 - P)/2$, hence $\hat{q} = 1 - \sqrt[n]{[1 - P]/2}$. As an example, after arbitrary substitution of 10,000 for n and 0.99 for P , $\hat{q} \approx 1 - \sqrt[10000]{0.01/2} \approx 1 - 0.9995 \approx 5.3 \times 10^{-4}$. In simple words, this means that if we observed no mutations at all, there is a high probability that actually more than five may have occurred under these conditions but we have missed them by chance. It is also possible—of course—that the rate of mutation in this case is much below the 10^{-4} range or it may even be zero.

Mutation rate in human populations in case of dominance may be estimated:

$$\frac{\text{number of sporadic cases}}{2 \times \text{number of individuals}} = \mu.$$

The number of individuals stands for the number of total population studied and 2 is used to account for diploidy. Frequently, it may be necessary to use a correction factor for penetrance or viability. Recessive X-linked mutations can be estimated on the basis of the afflicted males and the formula becomes $\mu = (1/3)s(n/N)$, where n = the number of new mutations, N = the size of the population examined and s = the relative selective value and/or penetrance. (The 1/3 multiplier is used because the females have 2 and the males have 1 X chromosome). Estimation of the rate of recessive mutations is very difficult in human populations because the detection of homozygotes would require controlled mating (inbreeding). Mutation rate in mammals varies a great

deal (Ellegren H et al 2003 Curr Opin Genet Dev 13:562). The majority of the spontaneous mutations among humans occur in the males (achondroplasia, acrodyostosis, Marfan syndrome, oculodentaldigital syndrome, Pfeiffer syndrome) because more cell divisions take place in the male germline than in that of the female. Some analyses indicate four times higher mutation rates in males than in females and lower base substitutions in the human X-chromosomes than in the autosomes. Some other studies claim much smaller excess of mutations in the human males (Crow JF 2000 Trends Genet 16:525). On the basis of sequencing the human genome the male:female substitution rate $\alpha_m:\alpha_f = 2.1$. Mutability increases with paternal age. In some instances, the increased male mutation rate was attributed to a paradoxical selective advantage of the spermatogonia carrying the mutation (Goriely A et al 2003 Science 301:643). The number of indel mutations in the X and Y chromosomes is practically the same but in the Z chromosome of birds about twice as many indels were detected than in the W chromosome (Sundström H et al 2003 Genetics 164:259). In some human diseases, (e.g., Duchenne muscular dystrophy, neurofibromatosis) there is no large sex bias, however. Actually, deletions may be more frequent in females than in males (presumably because of the long dictyotene stage). In point mutation there is a reverse tendency. Human geneticists may also have great difficulty in identifying mutations that have symptoms overlapping several syndromes. For single cases, multivariate statistics may be used but for many this procedure may be arduous.

Precise calculation of mutation rate is almost intractable by classical techniques but may be solved by molecular methods. DNA sequencing indicates genetic variations in the range of about 1 per kb. Many of these are synonymous at the protein level or do not alter the visible phenotype. The rate of synonymous mutations is higher than that of the non-synonymous (Li WH et al 1985 Mol Biol Evol 2:150). Calculating mutation rate may not be accurate if the incidence of the mutation is considered at a particular age but potential loss of the mutations by abortus or neonate death is not considered. The mutation rate on the basis of single nucleotide polymorphism in a population for the Y chromosomes and autosomes has been estimated within the range 1.9×10^{-9} to 5.4×10^{-9} , and for mitochondria 3.5×10^{-8} per site per year. Other estimates for average nucleotide changes/human genome are higher (2.5×10^{-8} , ~ 175 /diploid genomes/generation). Single nucleotide replacements appear an order of magnitude higher than “length mutation”. Both transitions and transversions are most common at CpG sites. The average deleterious mutation rate (U) in humans appears 3 or less. In the HIV1 retrovirus,

mutation rate per nucleotide per generation was estimated to be as high as 1 per 10^{-5} to 10^{-4} .

Mutation rate in bacteria has been estimated by various means.

Rate = $\ln 2(M2 - M1)/(N2 - N1)$, alternatively $R = 2\ln 2(\frac{M2}{N2} - \frac{M1}{N1})/g$ where M1 and M2 are the number of mutant colonies at time 1 and 2, respectively; N1 and N2 are the corresponding bacterial counts, \ln = natural logarithm, g = number of generations. In order to obtain reliable estimates on the rates, the culture must be started by large inocula to avoid bias due to mutation at the early generations when the population is still small, and the experiments must be maintained over several generations under conditions of exponential growth. The majority of the *Caenorhabditis* genes do not mutate to visible, lethal, or sterile phenotypes. Some double mutants may display, however, mutant phenotype. In *Caenorhabditis*, by sequencing PCR-amplified genomes the spontaneous mutation rate per nucleotide per generation was found to be 2.1×10^{-8} , about an order higher than previous estimates for the organism (Denver DR et al 2004 Nature [Lond] 430:679) and for some of the figures given above for humans. More than half of the mutations were insertions or deletions. The rate of mitochondrial mutations was also higher (1.6×10^{-7}) than the neutral mutation rate in bacteria (Ochman H 2003 Mol Biol Evol 20:2091) or in human mitochondria as shown. The true mutation rate can be determined only by sequencing of the DNA. ▶mutation spontaneous, ▶fluctuation test, ▶multivariate analysis, ▶discriminant function, ▶F_{ST}, ▶polymorphism, ▶diversity, ▶chromosome replication, ▶synthetic lethal, ▶band-morph variants, ▶hemophilia, ▶SNIP, ▶substitution mutation, ▶base substitution, ▶error in replication, ▶DNA repair, ▶mitochondrial mutation, ▶indel, ▶mutator gene, ▶hot spot; Crow JF 2000 Nature Rev Genet 1:40; Nachman MW et al 2000 Genetics 156:297; Kumar S, Subramanian S 2002 Proc Natl Acad Sci USA 99:803.

Mutation Rate, Effective (w): The product of the mutation rate and the variance of mutational changes.

Mutation Rate, Evolution of: The evolution of the mutation rate is determined by the presence of mutator and antimutator factors. ▶mutator, ▶antimutator; Baer CF et al 2007 Nature Rev Genet 8:619.

Mutation Rate, Induced: Inducing N-ethyl-N-nitrosourea in mice at specific loci, 1.5×10^{-3} mutations per locus were observed. This rate may, however, be an overestimate for other eukaryotes, and the range appears to be about 10^{-4} or less. The induced mutation rate per cGy per locus in mouse was estimated to be 2.2×10^{-7} and in *Drosophila* $1.5\text{--}8 \times 10^{-8}$. It appeared also that in mouse the females had lower rates than the

males although the frequencies are much affected by the developmental stages. ▶mutation rate spontaneous, ▶supermutagens, ▶Gy, ▶MNU, ▶error in replication

Mutation Rate in Fitness: In *Drosophila*, about 0.3/ genome/generation was estimated as the frequency of deleterious mutations. In *E. coli*, the rate of deleterious mutations per cell was estimated to be 0.0002. This is larger than three orders of magnitude difference. The *Drosophila* genome is about 20 fold larger than that of *E. coli* and during a generation approximately 25 divisional cycles take place compared to one in the bacterium. If we take the liberty of making adjustments for these differences, $0.0002 \times 20 \times 25 = 0.1$, the deleterious mutation rate in the eukaryote and the prokaryote falls within close range. Mutation rate in fitness is very difficult to estimate and in *Caenorhabditis* it appears three order of magnitude lower than in *Drosophila*. (See Zeyl C et al 2001 Evolution Int J Org Evolution 55:909).

Mutation Scan: A system of mutation detection.

Mutation Screening: Selective isolation of mutation(s).

Mutation Shower: Chronocoordinate multiple mutations spanning multiple kilobases (Wang J et al 2007 Proc Natl Acad Sci USA 104:8403).

Mutation Spectrum: The mutation spectrum indicates the range of mutations observed in a population under natural conditions or after exposure to different types of mutagens (see Fig. M141). The theoretical expectations would be that the common genetic material would mutate at the same rate at identical nucleotides in different organisms or under different conditions. This expectation is not met because some mutagenic agents have specificities for certain bases. Others act by breaking the chromosomes, depending on their organization and the physical and biological factors present. Also, genes present in multiple copies per genome may suffer mutational alterations but this

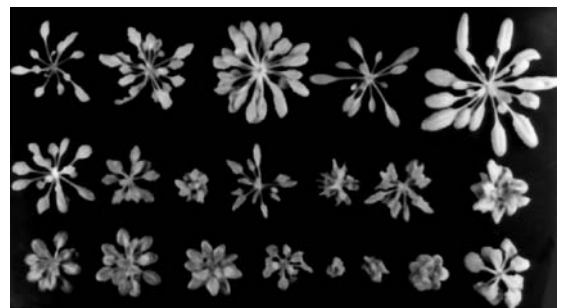


Figure M141. Sample of the spectrum of morphological mutations in *Arabidopsis* expressed at the rosette stage grown under 9 hours daily illumination. Columbia wild type is at the top right corner

may not be observed by classical genetic analysis although molecular methods may detect them. In general, obligate auxotrophic mutations are very limited in higher plants when the screening uses selective culture media. A range of morphological mutants of *Arabidopsis* (Figure M141); Li SL et al

1967 Mol Gen Genet 100:77; Reich DE, Lander ES 2001 Trends Genet 17:502.

Mutation, Spontaneous: Spontaneous mutation occurs at low frequency and its specific cause is unknown (Figure M142). The rate of spontaneous mutation per

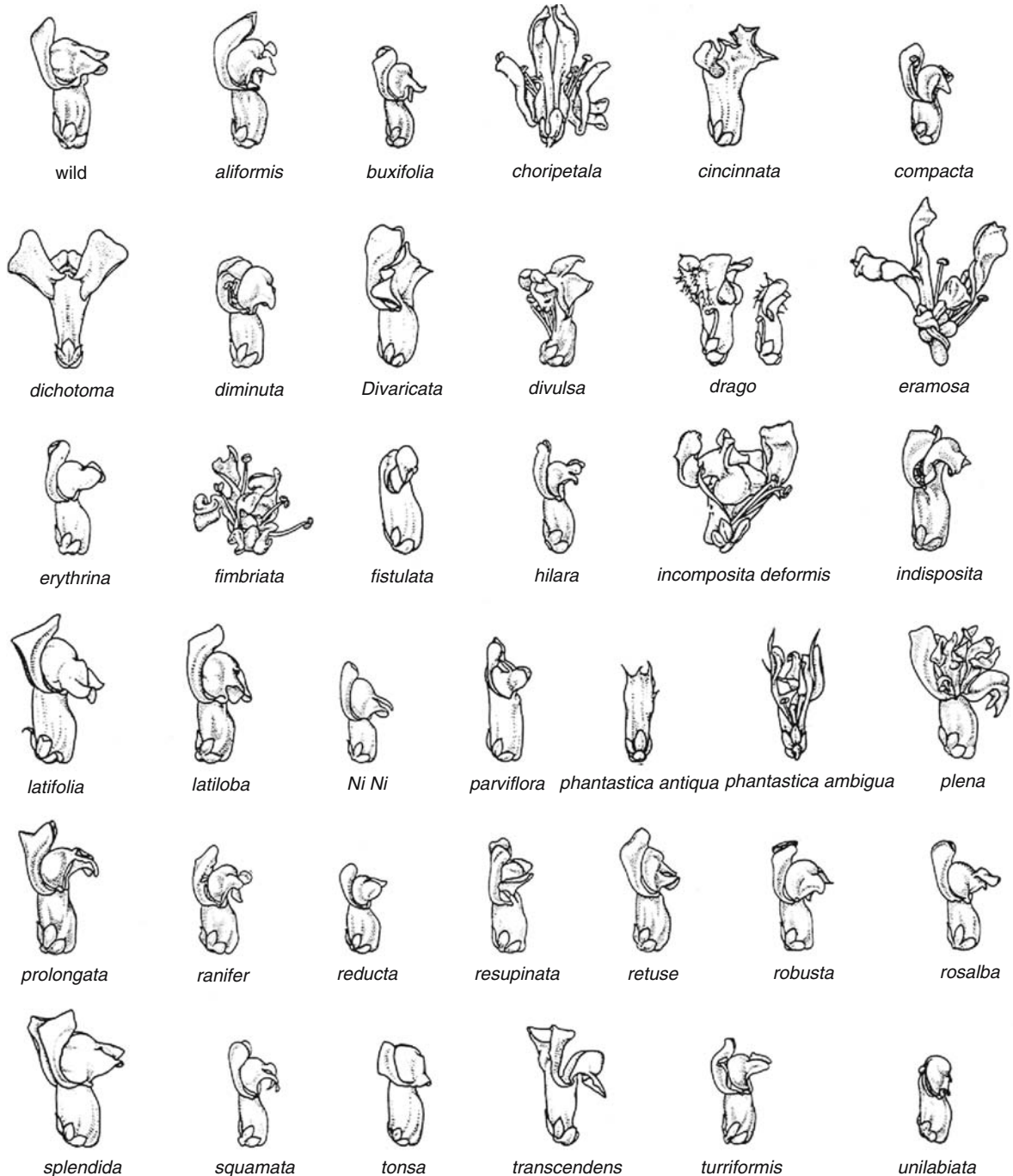


Figure M142. Mutations affecting the shape of the flower of snapdragon. The standard wild type is in the upper left corner. (Composed on the basis of H. Stubbe 1966 Genetik und Zytologie von *Antirrhinum* L. Sect. *Antirrhinum*. Fischer, Jena, Germany)

genome may vary. In bacteriophage DNA, it is 7×10^{-5} to 1×10^{-11} , in bacteria 2×10^{-6} to 4×10^{-10} , in fungi 2×10^{-4} to 3×10^{-9} , in plants 1×10^{-5} to 1×10^{-6} , in *Drosophila* 1×10^{-4} to 2×10^{-5} , in mice for seven standard loci is 6.6×10^{-6} per locus, in humans, 1×10^{-5} to 2×10^{-6} rates have been reported. The total number of detectable spontaneous mutations per live birth had been estimated as 10–3% but neither of these % estimates is very accurate because of the uncertainties of identifying very low levels of anomalies. In RNA viruses, the very high rates of 1×10^{-3} to 1×10^{-6} per base per replication have been estimated. The RNA viruses lack repair system. Amino acid substitutions in proteins may occur at the rate of 10^{-4} /residue. The error rate of the reverse transcriptase is extremely high because the enzyme does not have editing function. The induced rate of mutation may be three orders of magnitude higher but it varies a great deal depending on the locus, the nature of the mutagenic agent, the dose, etc. Mutation rates per mitochondrial D loop have been estimated to be 1/50 between mothers and offspring but other estimates used for evolutionary calculations are 1/300 per generation. Mutation rate in mitochondria on the basis of phylogenetic studies was estimated $\sim 0.17 \pm 0.15$ – 2.2 /site/Myr to 1.35 ± 0.72 – 1.98 /site/Myr at the 95% confidence level. Mutation rate per base in the human mitochondria has been estimated as 5×10^{-7} . ▶mutation rate induced, ▶mutation rate, ▶confidence interval, ▶Myr; for human diseases see Sankaranarayanan K 1998 Mutation Res 411:129; Maki H 2002 Annu Rev Genet 36:279.

Mutation, Useful: Although the majority of the new mutations have reduced fitness and are rarely useful for agricultural or industrial applications, some have obvious economic value.

Spontaneous and induced mutations have been incorporated into commercially grown crop varieties by improving disease and stress resistance, correcting amino acid composition of proteins, and eliminating deleterious chemical components (erucic acid, alkaloids, etc.).

Most of the natural variation in the species arose by mutation during their evolutionary history, and many have been added to the gene pool of animal herds and cultivated plants. Many of the floricultural novelties are induced mutants. Some of the animal stocks have accumulated single mutations, others such as the platinum fox are based on a single dominant mutation of rather recent occurrence (see Fig. M143).

Genetic alterations in industrial microorganisms have contributed very significantly to the production of antibiotics. (See Demain AL 1971 Adv Biochem Eng 1:113; Sakaguchi K, Okanishi M (Eds.) 1980 Molecular Breeding and Genetics of



Figure M143. Dark platinum fox mutant (From Mohr O, Tuff P 1939 J Heredity 30:227)

Applied Microorganisms, Academic Press, New York; Quesada V et al 2000 Genetics 154:421).

Mutational Bias: Microsatellites tend to change to longer repeats sequences, thus the bias is in favor of longer repeat tracts although long repeats may not recombine if mismatches are included that impede chromosome pairing. ▶microsatellite

Mutational Decay: Losing DNA sequences during evolution when their presence is no longer indispensable.

Mutational Delay: As per mutational delay, there is a time lag between the actual mutational event and the phenotypic expression because recessive mutations may show up only when they become homozygous. In organelles, the mutations must sort out before becoming visible, etc. ▶sorting out, ▶pre-mutation

Mutational Dissection: Analysis of a biochemical, physiological, or developmental process with the aid of mutations in the system.

Mutational Distance: The number of amino acid or nucleotide substitutions between (among) macromolecules that may indicate their time of divergence on the basis of a molecular clock. ▶evolutionary distance, ▶evolutionary clock

Mutational Envelope Scanning: As per mutational envelope scanning, functional similarities between proteins may be hidden because only a limited number of residues are critical for function, e.g., for ligand binding. Systematic mutations induced (e.g., by alanine scanning mutagenesis) at the critical side chains may reveal the hidden functional similarities. These hidden features may not be revealed by common biochemical, crystallographic, or nuclear magnetic resonance studies. ▶homologue-scanning mutagenesis; Christ D, Winter G 2003 Proc Natl Acad Sci USA 100:13202.

Mutational Load: ▶genetic load

Mutational Spectrum: The array and frequency of the different mutations that have been observed under certain conditions or in specific populations. The spectrum of auxotrophic mutations is much lower in most eukaryotes (except yeast and other fungi) than in lower and higher photoautotrophic organisms.

► [mutation spectrum](#)

Mutations Undetected: ► [mutations rate](#)

Mutator Genes: Mutator genes may be functioning on the basis of abnormal level of errors in DNA synthesis (error-prone DNA polymerase III) or abnormally low level of genetic repair due to defect of proofreading exonuclease in bacteria. The actual repair DNA polymerase in bacteria is pol I that also has 5'→3' polymerase and double and single-strand 3'→5' exonuclease capability. MutS protein recognizes DNA mismatches while MutL protein scans for nicks in the DNA and then through exonuclease action slices back the defective strand beyond the mismatch site and facilitates the replacement of the erroneous sequences with new and correct sequences. In bacteria, MutH protein recognizes mismatches not by the proofreading system of the exonucleases but by the distortion of the DNA molecules newly made. The recognition of the new strands depends on the not yet methylated A or C sites within GATC sequences in the new strands. Once the distortion is found, the mismatched base can be selectively excised. If either of these repairs fail, mutator action is observed.

Any defects in the bacterial gene *dam* (DNA methylase) may also result in high mutation rates because the correct base may be excised and replaced erroneously (see Fig. M144).

The active sites of DNA polymerases are highly mutable and the mutant enzymes may act as mutators of other genes (Patel PH, Loeb LA 2000 Proc Natl Acad Sci USA 97:5095).

Introducing point mutations in three structural domains of bacterial Pol I DNA polymerase resulted in $\sim 8 \times 10^4$ increase of transition mutations at random sites but with preference for plasmids DNA. The desired mutations can be selectively isolated and used for synthetic chemistry, gene therapy, and molecular biology (Camps M et al 2003 Proc Natl Acad Sci USA 100:9727).

Some of the so called mutator genes of the past were actually insertion elements that moved around in the genome and caused mutation by inactivation of genes through disrupting the coding or promoter sequences or altering specific bases in the gene(s). The mutator genes *mutA* and *mutC* of *E. coli* cause the A • T → T • A and G • C → T • A transversions in the anticodon of two different copies of tRNA genes, which normally recognize the GGU and GGC codons. As a consequence, Asp replaces Gly at a rate of 1 to 2%. Defective methyl-directed mismatch repair (gene MutS) occurs in 1–3% of *E. coli* and *Salmonella* raising the mutation rate to antibiotic resistance (Rif [rifampicin], Spc [spectinomycin] and Nal [nalidixic acid]) up to hundreds of fold, depending on the strain

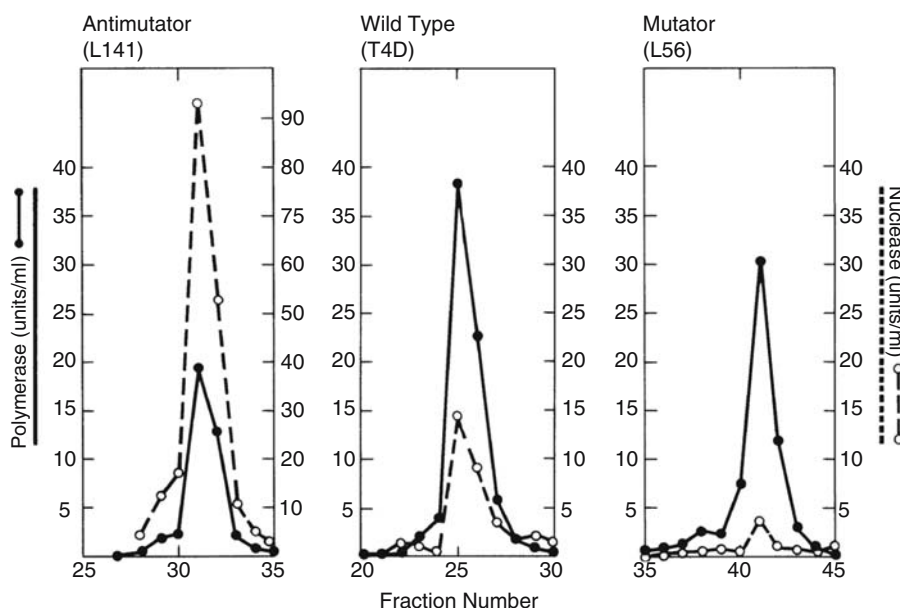


Figure M144. Mutator and antimutator activity may depend on the balance between DNA polymerase and nuclease functions. (From Muzyczka N et al. 1972 J. Biol. Chem, 247:7116)

of bacteria. Besides polymerase and repair defects, increase in mutation rate may be caused by anomalies of the replication accessory proteins such as RPA/RAF, PCNA, and RAD27/Rthp/Fen-1. Single-nucleotide substitutions in normal and neoplastic human tissues is two-hundred-fold different. In normal tissues, the frequency of spontaneous random mutation was exceedingly low, less than 1×10^{-8} per base pair. In contrast, tumors from the same individuals exhibited an average frequency of 210×10^{-8} per base (Bielas JH et al 2006 Proc Natl Acad Sci USA 103:18238).

High mutator activity may increase evolutionary adaptation in bacteria. Once the particular strain is well established, the high mutator activity is expected to decrease in that habitat. High mutator activity of a nuclear gene of *Arabidopsis*, *chm*, has been traced to mutation in mutS-like mismatch repair gene. The protein localized to the mitochondria and the mutations are manifested most obviously in the plastids (Abdelnoor RV et al 2003 Proc Natl Acad Sci USA 100:5968). The defect in *chm* apparently fails to correct the defects in substoichiometric shifting in the mtDNA. ▶insertional mutation, ▶transposable elements, ▶DNA replication prokaryotes, ▶DNA repair, ▶anti-mutators, ▶mutations in cellular organelles, ▶mismatch repair, ▶mutation detection, ▶RAD, ▶DNA polymerases, ▶anticodon, ▶tRNA, ▶substoichiometric shift, ▶transversion, ▶amino acids, ▶RPA, ▶PCNA, ▶RAD27, ▶Mu, ▶proofreading, ▶cancer, ▶mutation rate, ▶hot spot; Giraud A et al 2001 Science 291:2606; Shah AM et al 2001 J Biol Chem 276:10824; Shinkai A, Loeb LA 2001 J Biol Chem 276:46759; Shaver AC et al 2002 Genetics 162:557; Rédei GP 1973 Mutation Res 18:149.

Mutator Phage: The best characterized mutator phage is the Mu bacteriophage. The Mu particle includes a 60 nm isosahedral head and a 100 nm tail (in the extended form) containing also base plates, spikes, and fibers. The phage may infect Enterobacteria (*E. coli*, *Citrobacterium freundii*, *Erwinia*, *Salmonella typhimurium*). Its DNA genetic material consists of a 33-kb (α) and a 1.7-kb (β) double-stranded sequences separated by a 3-kb, essentially single-stranded, G-loop (specifies host range). It also has variable length (1.7-kb) single-strand “split ends” (SE). Besides the coat protein genes, the *c* gene is its repressor (prevents lysis). The other genes are *ner* (negative regulator of transcription), *A* (transposase), *B* (replicator), *cim* (controls superinfection [immunity]), *kil* (killer of host in the absence of replication), *gam* (protein protects its DNA from exonuclease V), *sot* (stimulates transfection), *arm* (amplifies replication), *lig* (ligase), *C* (positive regulator of the morphogenetic genes) and *lys* (lysis). Upon lysis,

50 to 100 page particles are liberated. The Mu chromosome may exist in linear and circular forms. Mu can integrate at about 60 locations in the host chromosome with some preference. At the position of integration, 5-bp target site duplications take place. The integration events cause insertional mutation in the host. Mu causes host chromosome deletions, duplications, inversions, and transpositions. These functions require gene *A*, the intact termini of the phage and replication of the phage DNA. A related other phage, D108, has several DNA regions that are non-homologous. Its host range is the same as that of Mu. ▶bacteriophages, ▶temperate phage, ▶Mu bacteriophage, ▶insertion elements; Nakai H et al 2001 Proc Natl Acad Sci USA 98:8247.

Mutein: Mutant protein.

Muton: An outdated term meaning the smallest unit of mutation. For three decades it is known that single nucleotides or nucleotide pairs are basic units of mutation. Benzer S 1957 In: The Chemical Basis of Heredity. McElroy WD, Glas B (Eds.) Johns Hopkins University Press, Baltimore, MD, pp 70).

MutS: ▶mismatch repair

Mutual-Best Blast Matches: Mutual-best BLAST matches use BLAST computer program for determining orthologous sequences in different species. ▶BLAST, ▶orthologous loci

Mutual Exclusiveness: An example of mutual exclusiveness is that alternative alleles at particular genetic sites in a haploid cannot exist simultaneously.

Mutualism: A mutually beneficial or alternatively a selective situation for increased exploitative association of organisms. ▶symbionts, ▶commensalism, ▶sociogenomics; Curie CR 2001 Annu Rev Microbiol 55:357.

MVR (minisatellite variant repeat): Within different-length minisatellite allele pairs of the same size different alterations may occur at different sites and generate isoalleles (see Fig. M145).

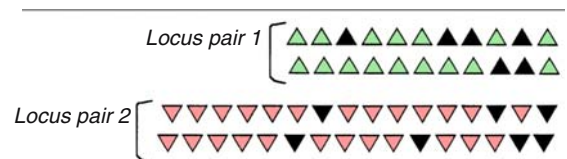


Figure M145. Minisatellite alleles

The hypervariable alterations (represented by the triangles) may be identified with aid of restriction enzyme digestion and electrophoresis and can yield profile of an individual. The majority of the mutations

show polarity, i.e., the alterations are most common at the end of the minisatellite site. Many of the mutations generate alleles of different lengths as a result of recombination of the parental alleles. Mutation rate is variable depending on alleles but apparently it is independent from the length of the repeat as long as homologies are not much violated. ▶[minisatellite](#), ▶[DNA fingerprinting](#); Junge A 2001 *Forensic Sci Int* 119:11.

Mx Proteins: 70–80-kDa interferon-inducible GTPases of the dynamin family that interfere with the replication and transcription of negative-strand RNA viruses. Mx1: myxovirus (influenza) resistance; it is located at human chromosome 21q22.3. ▶[dynamin](#), ▶[replicase](#); Regad T et al 2001 *EMBO J* 20:3495.

Mxi1: A tumor suppressor gene at human chromosome 10q24–26. ▶[prostate cancer](#), ▶[MYC](#); Wang DY et al 2000 *Pathol Int* 50(5):373.

Mxi/Max: Heterodimeric specific transcriptional repressors. ▶[Max](#), ▶[Mad/Max](#), ▶[E box](#); Billin AN et al 2000 *Mol Cell Biol* 20:9945.

My: A million years during the course of evolution; MYA means million years ago. ▶[KYA](#)

Myasis (myiasis): The infestation of a live body with fly larvae (maggots) such as occurs as a consequence of screw worm, a common pest of southern livestock (see Fig. M146). ▶[genetic sterilization](#)

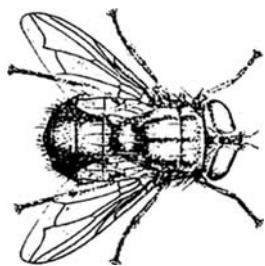


Figure M146. Adult screwworm fly. It has an average life span of three weeks and during the period of time it may travel 100 to 200 kilometers but it can survive only during the warm winters such as exist in Mexico or in the southern USA. (From Stefferud A (Ed.) 1952 *Insects. Yearbook of Agriculture*, USDA, Washington, DC)

Myasthenia (gravis, MG, 17p13): Generally involves muscular (eye, face, tongue, throat, neck) weakness, shortness of breath, fatigue, and the development of antibodies against the acetylcholine receptors. The genetic determination is ambiguous, generally it appears autosomal recessive. The infantile form lacks the autoimmune feature, although it also includes a defect in the acetylcholine receptor. Anticholinesterase therapy and immunosuppressive drugs may

be helpful. Newborns of afflicted mothers may be temporarily affected through placental transfer. In persons with “limb girdle,” pattern of muscle weakness may have small neuromuscular junction but normal acetylcholine receptor and acetylcholinesterase action (Beeson D et al 2006 *Science* 313:1975). ▶[neuromuscular diseases](#), ▶[epistaxis indirect](#), ▶[IVIG](#), ▶[rapsyn](#), ▶[acetylcholine](#)

Myb Oncogene: An avian myeloid leukemia (myeloblastosis) oncogene; its human homolog was assigned to chromosome 6q21–q23. Its product is a transcription factor. The same gene is also called AMV (*v-amv*). The MYB gene product is translated into ~75-kDa protein in immature myeloid cells and its activity is substantially reduced as differentiation proceeds.

The Myb protein (see Fig. M147), with a nuclear protein-binding leucine zipper in the regulatory domain, recognizes the 5'-PyAAC(G/Py)G-3' core sequence and in case the C- or N- terminus or both are deficient it becomes a potent activator of leukemia, although overexpression of the entire Myb may also be oncogenic. The Myb oncogene regulates hematopoiesis. The Myb A protein is required for normal spermatogenesis and mammary gland development. Using antisense oligodeoxynucleotides for codons 2–7 may reduce its transcription. The same treatment may be effective against chronic myelogenous leukemia. Recent data indicates that the Myc/Max/Mad proteins may regulate ~15% of all the genes (Orian A et al 2003 *Genes Dev* 17:1101). Myb homology domains occur in multiple copies in both monocotyledonous and dicotyledonous plants and are involved in various regulatory functions, such as in transcription factors. ▶[E box](#), ▶[oncogenes](#), ▶[leukemias](#), ▶[AMV](#), ▶[hematopoiesis](#), ▶[antisense technologies](#), ▶[incompatibility alleles](#)

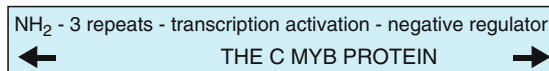


Figure M147. The C MYB protein

MYC (8q24.12–q24.13): An oncogene named after the myelocytomatosis retrovirus of birds from which its protein product was first isolated. It is a widely present DNA-binding nuclear helix-loop-helix phosphoprotein in eukaryotes. c-MYC is expressed only in dividing cells and it is an inhibitor of terminal differentiation. C-MYC induces the expression of the cell cycle activating kinase, CDK4. The MH-2 virus carries, besides the *v-myc* gene, also the *v-mil* gene, which encodes serine/threonine kinase activity and invariably causes monocytic leukemia. Most retroviruses in this group cause only the formation of non-immortalized macrophages requiring growth factors

for proliferation. The cellular forms of the oncogenes are specially named after the type of cells in which, they are found. NMYC occurs in neuroblastomas (and retinoblastomas). Homologues of this gene were assigned to human chromosome 2p24 and to mouse chromosomes 12 and 5. The LMYC genes are involved in human lung cancer where one was located to chromosome 1p32 and two to the mouse chromosomes 4 and 12. Alternative splicing and polyadenylation produce several distinct mRNAs from a single gene. Metastasis is favored by the presence of a 6-kb restriction fragment of the DNA. In human chromosome 7, another form, the MYC-like one gene was detected with a 28-bp near perfect homology to the avian virus. In both man and mouse, translocation sequences were identified between the Myc gene (human chromosome 8) and several immunoglobulin genes encoding the heavy, κ and λ chains. cMyc overexpression causes telomeric association of interphase chromosomes, which may result in breakage-bridge-fusion cycles and various types of chromosomal rearrangements (Louis SF et al 2005 Proc Natl Acad Sci USA 102:9613).

(PVT1) has an activation role in Burkitt's lymphomas (caused by the Epstein-Barr virus) and plasmacytomas (neoplasia). Myc/MAX heterodimer binds to the CDC25 gene and activates transcription after binding to the DNA sequence CACGTG. This binding site is recognized by a number of MYC-regulated genes. Frequent targets of activated Myc are the cycline genes as well as ornithine decarboxylase, lactate dehydrogenase and thymosine β 4. When cellular growth factors are depleted, Myc can induce apoptosis with the cooperation of CDC25. MYC in cooperation with RAS mediate also the progression of the cell cycle from G1 to the S phase through induction of the accumulation of active cyclin-dependent kinase and transcription factor E2F. MAD (Mxi1; 10q24–26) protein holds MYC in check. MAD forms a heterodimer with MAX (MAD-MAX), and this successfully competes with MYC-MAX heterodimers for transcription and thus can control malignancy. Down-regulation of the human ferritin gene by MYC leads to cellular proliferation. Myc expression may mediate Fas-FasL (Fas-ligand) interaction and an apoptosis pathway through FADD. The BIN1 protein interacts with MYC and serves as a tumor suppressor. Myc apparently affects the expression of thousands of genes and its effect can be detected by microarray hybridization and correlation analysis (Remondini D et al 2005 Proc Natl Acad Sci USA 102:6902). ▶oncogenes, ▶hepatoma, ▶cancer, ▶Burkitt's lymphoma, ▶Gardner syndrome, ▶PVT, ▶CDC25, ▶MAD, ▶BIN1, ▶apoptosis, ▶Fas, ▶FADD, ▶RAS, ▶CDK, ▶E2F, ▶CDF, ▶MAX, ▶ferritin, ▶immunoglobulins,

▶E box, ▶Id protein, ▶breakage-fusion-bridge cycles; Henriksson M, Lüscher B 1996 Adv Cancer Res 68:109.

Mycelium: a mass of fungal hyphae. ▶hypha

Mycobacteria: are Gram-positive bacteria and cause tuberculosis (killing 3 million people annually) and responsible for leprosy (*Mycobacterium leprae*, 3.27 Mb, 1604 genes), respectively. *M. leprae* is somewhat difficult to study because it does not grow in axenic cultures. The bacteria can be propagated to sufficient quantities for analysis in the nine-banded armadillo (*Dasypus novemcinctus*). About half of its genome is inactivated as pseudogenes. The populations have much lower variability than other bacteria. The bacterium probably originated in Eastern Africa and then spread to other parts of the world, primarily to India and Brazil and Western Africa (Monot M et al 2005 Science 308:1040). Their cell wall has low permeability and therefore they are rather resistant to therapeutic agents.

Mycobacterium tuberculosis (see Fig. M148) H37Rv genome is 4,411,529-bp and includes about 4,000 genes. (See Nature [Lond] 393:537 1998, see also corrections in Nature 396:190 1998). Through *mycobacterial protein fragment complementation* (in analogy to the yeast two-hybrid system) protein interaction network could be revealed that sheds light on virulence pathway of the tuberculosis bacterium (Singh A et al 2006 Proc Natl Acad Sci USA 103:11346). Envelope metalloprotease enzymes regulate the composition and virulence of the tuberculosis bacteria (Makinoshima H, Glickman MS 2005 Nature [Lond] 436:406). Worldwide about 2 billion people could be infected and 9 million have the active disease. The tuberculosis bacteria reside in the macrophages during latent infection and kept in check there by nitric oxide and other nitrogen intermediates (see Fig. M149). When the mycobacterial proteasome cleaves the inducible nitric oxide synthase, susceptibility to the disease increases



Figure M148. *M. tuberculosis*

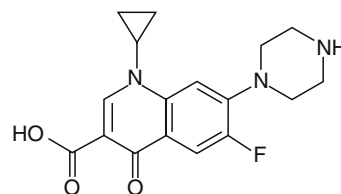


Figure M149. Cyproflaxacin (a fluoroquinolone)

(Darwin KH et al 2003 Science 302:1963). Mouse chromosome 1 harbors a gene (*sst*) for super susceptibility to tuberculosis and within the same locus there is a gene, *Intracellular pathogen resistance* (*Ipr1*). The closest human homolog to *Ipr1* is SP110 and there are three variants of it in West Africa (Gambia, Guinea-Bissau and Guinea) that convey resistance to tuberculosis. These variants lie within a 31-kb block and are in strong linkage disequilibrium (Tosh K et al 2006 Proc Natl Acad Sci USA 103:10364). The same gene conveys resistance also *Listeria monocytogenes* (Pan H et al 2005 Nature [Lond] 434:767). Infection by human immunodeficiency virus (AIDS) greatly increases the susceptibility to tuberculosis and antiretroviral drugs may provide protection thus against both diseases (Williams BG, Dye C 2003 Science 301:1535). Tuberculosis of cattle is caused by *M. bovis* and it can be transmitted also to humans and other animals. The transmission to humans is usually by not or improperly Pasteurized milk. *Mycobacterium avium* K-10 (paratuberculosis) genome has 4,829,781 bp and 4,350 open reading frames and more than 3,000 genes are homologous with the human tuberculosis bacterium but 161 sequences are unique to the bird bacterium (Li L et al 2005 Proc Natl Acad Sci USA 102:12344).

Tuberculosis is most commonly treated by isoniazid (INH) and as a result saturated hexacosanoic acid (C26:0) accumulates on a 12-kDa acyl protein carrier (see Fig. M150). This complex associates also with β -ketoacyl carrier protein synthase (KasA). Apparently INH acts by inhibiting KasA. When mutations occur in the latter, INH resistance develops. Apparently INH acts by inhibiting KasA. Nitroimidazopyran drugs are also promising against tuberculosis. The cure of tuberculosis generally requires strict multidrug therapy to avoid the emergence of drug-resistance, which is a very serious threat nowadays.

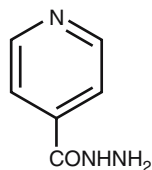


Figure M150. Isoniazid

Diarylquinoline (see Fig. M151), which apparently active on the proton pump of ATP synthase, at 0.06 $\mu\text{g/mL}$ in vitro, exceeded significantly the efficacy of isoniazid and rifampin and does not appear to have serious side effects (Andries K et al 2005 Science 307:223).

Fluoroquinolones (e.g., moxifloxacin and gatifloxacin) interact with DNA gyrase and DNA

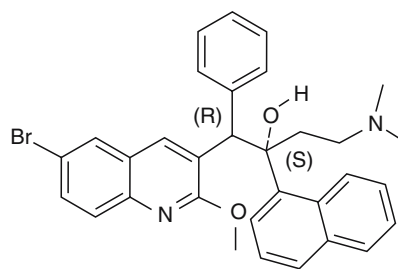


Figure M151. Diarylquinoline

topoisomerase are effective antibacterial agents yet the MfpA bacterial plasmid-encoded protein, which contains as every fifth amino acid either leucine or phenylalanine can convey resistance even against these newer fluoroquinolones. The MfpA protein forms a right-handed quadrilateral β helix (a DNA mimic), binds to DNA gyrase and inhibits its activity and conveys resistance to fluoroquinolone in vivo (Hegde SS et al 2005 Science 308:1480).

The mouse strain DBA/2 is very susceptible to tuberculosis whereas C57BL/5 is more resistant. The resistance is controlled by a QTL in chromosome 19 and 1. In humans natural resistance factors (controlling bacterial proliferation) have been found in chromosomes 2q, 15q and Xq (Mitsos L-M et al 2003 Proc Natl Acad Sci USA 100:6610). *Mycobacterium vaccae* and *Bacillus Calmette-Guérin* (BCG, also a mycobacterium) produce cross-reactive material against *M.l.*, and *M.v.* is suited for vaccine production against leprosis. *M.l.* cannot efficiently be propagated in vitro for vaccine production and only the nine-banded armadillo would be a suitable animal host. The virulence of mycobacteria seems to be controlled by the *erp* (exported repetitive protein) gene. Some major (2q32-q35, 15q11-q13) and apparently several minor genetic factors determine the susceptibility to tuberculosis and other diseases. Gene UBE3A, a ubiquitin ligase is located in the imprinted region of chromosome 15. Mycobacterial infection susceptibility genes encode the interferon- γ receptor (INFR-1, 6q23-q24; INFR-2, 6q23-q24), interleukin-12 β -1 chain receptor (9p13) and STAT1 (2q32). Some INFR-2 mutations gained new N-glycosylation sites (Vogt G et al 2005 Nature Genet 37:692).

The use of the BCG (bacillus Calmette-Guérin) vaccine is substantially effective for childhood treatment but much less efficient for adult infections. BCG primes T_H1 (helper T cells) and promotes the release of interferon (IFN- γ) by the macrophages. Newer vaccines incorporating antigen 85A of the bacterium with some adjuvants appear promising (Young D, Dye C 2006 Cell 124:683). ▶vaccine, ▶*Bacillus Calmette-Guérin*, ▶leprosy, ▶AIDS, ▶glycosylation, ▶PGRS, ▶interferon, ▶ T_H1 ;

Abel L, Casanova J-L 2000 *Am J Hum Genet* 67:274; Glickman MS, Jacobs WR Jr 2001 *Cell* 104:477; Russel DG 2001 *Nature Rev Mol Cell Biol* 2:569; Cervino ACL et al 2002 *Hum Mol Genet* 11:1599; *Mycobacterium bovis* genome sequence: Gernier T et al 2003 *Proc Natl Acad Sci USA* 100:7877; susceptibility: Fortin A et al 2007 *Annu Rev Genomics Hum Genet* 8:163; <http://genolist.pasteur.fr/>.

Mycology: the discipline of studying the entire range of mushrooms (fungi).

Mycophenolic Acid (MPA): ►IMPDH

Mycoplasma: Parasitic and/or pathogenic bacteria. They may also contaminate animal cell cultures. *Mycoplasma genitalium* was the first free-living organism to be completely sequenced by 1995, containing 580,070-bp DNA, 480 open reading frames, and 37 RNA transcribing genes; 31.8% of its known genes (127) is involved in translation.

The intact genomic DNA from *Mycoplasma mycoides* large colony (LC), virtually free of protein, was transplanted into *Mycoplasma capricolum* cells by polyethylene glycol-mediated transformation. Cells were selected for the tetracycline resistance marker of the donor, and proved that they contained the complete donor genome and were free of detectable recipient genomic sequences (Lartigue C et al 2007 *Science* 317:632).

Mycoplasma pneumoniae has $\sim 0.82 \times 10^6$ bp DNA genome and 679 genes. *Mycoplasma penetrans* sequenced circular genome is 2,358,633 bp and includes 1038 predicted coding sequences, one set of rRNA genes, and 30 tRNA genes (Sasaki Y et al 2002 *Nucleic Acids Res* 30:5293). ►phytoplasmas, ►gene number; Glass JI et al 2000 *Nature [Lond]* 407:757; Flynn JL, Chan J 2001 *Annu Rev Immunol* 19:93; <http://genolist.pasteur.fr/>.

Mycorrhiza: A symbiotic association between plant roots and certain fungi. Some of the mycorrhizal fungi are genetically quite peculiar in as much they are haploid but heterokaryotic with multiple nuclei and substantial differences among the nuclei (Hijri M, Sanders IR 2005 *Nature [Lond]* 433:160). ►nitrogen fixation, ►symbionts; Smith KP, Goodman RM 1999 *Annu Rev Phytopath* 37:473, nitrogen path: Govindarajulu M et al 2005 *Nature [Lond]* 435:819; arbuscular mycorrhiza: <http://www.ffp.csiro.au/research/mycorrhiza/intro.html>.

Mycosis: Infection or disease by fungi. The infection may be superficial, subcutaneous, and systemic by inhalation of the spores. Most commonly, fungi cause

skin diseases. Immune-compromised individuals are particularly susceptible to mycoses.

Mycotoxins: Fungal metabolites that damage DNA. The best known are: aflatoxins, sterigmatocystin, ochratoxin, zearalenone, and some penicillin toxins. ►aflatoxin

MyD88: (myeloid [bone marrow like] differentiation primary response factor, encoded in human chromosome 3p22-p21.3): An adaptor protein in the Toll — NF- κ B signaling pathway. ►NF- κ B, ►Toll/TRAF6, ►TIRAP

Myedema (hyperthyroidism): Myedema is also attributed to hypothyroidism caused by autosomal recessive/dominant conditions. It involves dry skin with wax-like deposits. Some HLA genes and autoimmune causes have been implicated. ►Graves disease

Myelencephalon: The part of the brain of the embryo that develops into the medulla oblongata (the connective part between the pons [brain stem]) and the spinal cord. ►brain

Myelin: A lipoprotein forming an insulating sheath around nerve tissues. ►Pelizaeus-Merzbacher disease, ►Marie-Charcot-Tooth disease, ►multiple sclerosis; Greer JM, Lees MB 2002 *Int J Biochem & Cell Biol* 34:211.

Myeloblast: A precursor (formed primarily in the bone marrow) of a promyelocyte and eventually a granular leukocyte. It contains usually multiple nucleoli. ►leukocyte, ►Wegener granulomatosis

Myeloblastin: A serine protease, specific for myeloblasts controlling growth and differentiation and myelogenous leukemia. ►leukemia

Myelocyte: A precursor of the granulocytes, neutrophils, basophils and eosinophils.

Myelocytoma: ►myeloma

Myelodysplasia (MDS): A recessive form of leukemia, generally associated with monosomy of human chromosome 7q. The critical deletion apparently involves chromosomal segment 7q22-q34. Peptide mass fingerprinting and quadrupole TOF MS identified two differential proteins: CXC chemokine ligands 4 (CXCL4) and 7 (CXCL7), both of which had significantly decreased serum levels in MDS, as confirmed with independent antibody assays (Aivado M et al 2007 *Proc Natl Acad Sci USA* 104:1307). ►leukemia, ►nucleophosmin, ►chemokine, ►CXCR, ►mass spectrum, ►proteomics, ►MALDI, ►quadrupole, ►TOFMS

Myeloma: Bone marrow cancer. CREB seems to promote myeloid transformation (Shankar DB et al 2005 Cancer Cell 7:351). Myeloma cells are used to produce hybridomas. ▶Bence Jones proteins, ▶monoclonal, ▶antibody, ▶hybridoma, ▶CREB

Myelomeningocele: ▶spina bifida

Myelopathy: Diseases involving the spinal cord and myelination of the nervous system. About 15 different human anomalies are involved. ▶Dejerine-Sottas neuropathy, ▶Charcot-Marie-Tooth disease

Myelopoiesis: The formation of granulocytic and monocytic cell lineages. ▶granulocyte, ▶monocyte

Myelosuppression: Myelosuppression interferes with bone marrow function and blood cell formation. It is the most common target of cancer chemotherapy drugs. These drugs are aimed at highly proliferative cells and the bone marrow produces 4×10^{11} cells daily for long periods of time.

MYF-3 (myogenic factor): MYF-3 was located to human chromosome 11-p14 and its mouse homolog, *MyoD* is in chromosome 7. MYF-3 controls muscle development, may be subject to imprinting, and may possibly be involved in the formation of embryonic tumors. The protein is a helix-loop-helix transcription factor (MASH2) and it is a mammalian member of the *achaete-scute* complex of *Drosophila*. ▶imprinting, ▶Mash-2, ▶morphogenesis in *Drosophila*.

Myhre Syndrome: ▶dwarfism

Myleran (1,4-di[methanesulphonoxy] butane): A clastogenic (causing chromosome breakage) alkylating mutagen. Also called busulfan.

Mylotarg: Monoclonal antibody used for targeting acute myeloid leukemia with the toxin calicheamycin. ▶leukemia, ▶monoclonal antibody, ▶magic bullet

Myoadenylate Deaminase: ▶adenosine monophosphate deaminase

Myoblast: Muscle cell precursor. Myoblasts can be well cultured in vitro and reintroduced into animals where they fuse into myofibers. They can be used also as gene or drug delivery vehicles. The paired-box proteins, Pax3 and Pax7, are essential for the formation of skeletal muscles (Relaix F et al 2005 Nature [Lond] 435:948). ▶vectors, ▶dermomyotome

Myocardial Infarction: Obstruction of blood circulation to the heart; it may be accompanied by tissue damage. Infarcted (dead/decaying) heart muscle cells may be replaced by transplantation of regenerating bone marrow cells. Arachidonat 5-lipoxygenase activating protein (encoded at 13q12-q13) confers

increased risk of myocardial infarction and stroke. This gene overlaps the ALOX5AP lipoxygenase activating-protein (FLAP) coding region and increases the risk for stroke almost two-fold in Icelandic populations. The effect is due to the over production of leukotrienes B and inflammation of the arterial walls (Helgadóttir A et al 2004 Nature Genet 36:233). Human haplotype HapK, spanning this region, confers an about three-fold greater risk of heart disease to Afro-Americans than to European-Americans (Helgadóttir A et al 2006 Nature Genet 38:68). Presence of variants of the proprotein convertase subtilisin/kexin type 9 serine protease gene (PCSK9) involved substantial reduction cholesterol. The low density lipoprotein cholesterol and myocardial infarction decreased by 88% among US blacks. In whites 15% reduction in cholesterol and 47% reduction in the heart disease risks were observed among several thousands of individuals examined during a period of 15 years (Cohen JC et al 2006 N Engl J Med 354:1264). Complement-reactive protein (CRP) increases myocardial and cerebral infarct size. 1,6-bis(phosphocholine)-hexane can abrogate the infarct size and protects from cardiac dysfunction by blocking CRP action (Pepys MB et al 2006 Nature [Lond] 440:1217). Delivery to the myocardium myocytes and biotinylated insulin-like growth factor, a cardiomyocyte growth and differentiation factor in biotinylated nanofibers, improved systolic function significantly. The delivery activated Akt, decreased caspase-3 activation, and improved the expression of troponin I (Davis ME et al 2006 Proc Natl Acad Sci USA 103:8155). ▶coronary heart disease, ▶heart disease, ▶MEF, ▶lipoxygenase, ▶leukotriene, ▶ethnicity, ▶haplotype, ▶LDL, ▶cholesterol coronary heart disease atherosclerosis, ▶insulin-like growth factor, ▶caspases, ▶troponin, ▶systole

Myocardium: The heavy muscles of the heart. ▶heart disease; Buckingham M et al 2005 Nature Rev Genet 6:826.

Myoclonic Epilepsy: Myoclonic epilepsy occurs in different forms. The recessive juvenile EJM gene is situated within the boundary of the HLA gene complex in the short arm of chromosome 6p21 (Janz syndrome). It is characterized by generalized epilepsy with onset in early adolescence. Mutations in a sub-unit of the sodium channel SCN1A gene (2q24) cause slow growth from the second year of life and often become ataxic and later suffer from speech problems. Myoclonous epilepsy associated with ragged-red fibers is characterized also by epileptic convulsions, ataxia, and myopathy (enlarged mitochondria with defects in respiration). The defect was attributed to an adenine → guanine transition mutation at position

8344 in the human mitochondrial DNA involving the tRNA^{Lys} gene. The recessive (EPM2A, 6q24; EPM2B, 6p22.3) myoclonous epilepsy (LaFora disease) shows up at about age 15 and results in death within ten years that after. The EPM2A disease involves defects in a protein tyrosine phosphatase (laforin protein). The EPM2B/NHLRC1 disease is due to deletions or various types of mutations in the 395 amino acid protein malin, which appears to be a single-subunit E3 ubiquitin ligase. Normally, malin ubiquitinates laforin but mutation in the gene leads to LaFora disease (Gentry MS et al 2005 Proc Natl Acad Sci USA 102:8501). Both of these proteins are associated with the endoplasmic reticulum and are normally involved in clearance of polyglucosans in dendrites and the defect disturbs neuronal synapsis (Chan EM et al 2003 Nature Genet 35:125).

The myoclonus epilepsy Unverricht and Lundborg (EPM1) is a 21q22.3 chromosome recessive with onset between ages six to 13, beginning with convulsions turning within a few years into shock-like seizures (myoclonus). The latter disease is caused by mutation in the cystatin B (cysteine protease inhibitor) gene. The EPM1 disease involves a large insertion (600–900 bp) consisting of 12-bp repeats (CCCCGCCCGCG). The cases appeared to be initiated by pre-mutational changes of 12–13 repeats and usually by maternal transmission the “alleles” appeared stable. In the majority of cases of paternal transmission, the repeats increased. In some cases, a 18mer repeat was observed at the 5′ region of the promoter and a 15mer repeat at the 3′ region. The 18 and 15mer repeats included also six and four T and A bases, respectively. Benign familial adult epilepsy maps to 8q23.3-q24.1. Some human myoclonus diseases are apparently under dominant control. A *myoclonus* disease in cattle has an apparent defect in glycine-strychnine receptors. In mouse, the spastic mutation in chromosome 3 affects the α -1 glycine receptors, whereas the α -2 receptor defect is X-linked. The incidence of epilepsy, especially in some breeds, is more common in dogs than in humans (Lohl H et al 2005 Science 307:81). ▶[epilepsy](#), ▶[trinucleotide repeats](#), ▶[mitochondrial disease in humans](#), ▶[pre-mutation](#), ▶[ion channels](#)

Myoclonus: Sudden, involuntary contractions of the muscle(s) like in seizures of epilepsy or sometimes as a normal event during sleep. Myoclonus-dystonia, a dominant disease, is located to 7q21 and the gene encodes ϵ -sarcoglycan (Müller B et al 2002 Am J Hum Genet 71:1303). ▶[myoclonic epilepsy](#), ▶[dystonia](#), ▶[sarcoglycan](#)

MyoD: Muscle-specific basic helix-loop-helix protein that regulates muscle differentiation and the cessation

of the cell cycle. Its DNA binding consensus is CANNTG in the promoter or enhancer of the genes controlled. MyoD may activate p21, and p16 and promotes muscle-specific gene expression. When MyoD is phosphorylated by cyclinD1 kinase (Cdk), it may fail to transactivate muscle-specific genes. ▶[p21](#), ▶[p16](#), ▶[cell cycle](#), ▶[helix-loop-helix](#), ▶[Myf3](#), ▶[cyclin](#), ▶[Cdk](#), ▶[myogenin](#), ▶[MEF](#), ▶[enhancer](#); Tedesco D, Vesco C 2001 Exp Cell Res 269:301.

Myofibril: Muscle fiber made of actin, myosin and other proteins (bundle of myofilaments). ▶[satellite cells](#)

Myofibromatosis, Juvenile: Multiple fibroblastic tumors on the skin, muscles bones, and viscera in young infants due to autosomal recessive or dominant mutation. Prognosis for survival in severe cases is low.

Myogenesis: Muscle development.

Myogenin: A protein involved in muscle development. MyoD activates myogenin and overcomes the inhibitor of DNA-binding (helix-loop-helix) gene *Id*, and other muscle gene transcription and differentiation is set on course. ▶[MyoD](#), ▶[MYF5](#), ▶[MRF](#), ▶[MEF](#); Sumariwalla VM, Klein VH 2001 Genesis 30(4):239.

Myoglobin: A single polypeptide chain of 153 amino acids, attached to a heme group and functions in the muscle cells to transport oxygen for oxidation in the mitochondria. Recurrent myoglobinuria may result by a microdeletion in the mitochondrially-encoded cytochrome C oxidase (COX) subunit III. Some Antarctic fishes do not have myoglobin, and homozygous myoglobin knockout mice function in a practically normal manner. ▶[hemoglobin](#), ▶[mitochondrial disease in humans](#)

Myo-Inositol: An active form of inositols. They are widely used as phospholipid head-groups (see Fig. M152). They are essential for signaling, membrane trafficking, etc. ▶[inositol](#), ▶[phosphoinositides](#), ▶[embryogenesis somatic](#), ▶[phytic acid](#)

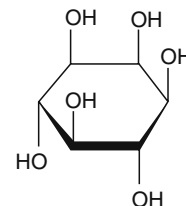


Figure M152. Myo-inositol

Myokymia: Hereditary spasmodic disorder of the muscles, caused by potassium channel defects. ► [ion channels](#)

Myoneurogastrointestinal Encephalopathy (mitochondrial myoneurogastrointestinal encephalopathy, MNGIE, 22q13.32-qter): A recessive defect in a nuclear gene, however, mitochondrial DNA aberrations may also accompany it. The onset usually sets in after the second decade of life and the clinical symptoms involve atrophy of the muscles (ophthalmoplegia), multiple neural disorders, lactic acidosis, etc. ► [ophthalmoplegia](#), ► [mitochondrial diseases in humans](#)

Myopathy: A collection of diseases affecting muscle function, controlled by autosomal dominant, autosomal recessive, X-linked, and mitochondrial DNA. Besides the weak skeletal muscles, ophthalmoplegia (paralysis of the eye muscles) usually accompanies it. The recessive homozygotes for myotonic myopathy are also dwarf and have cartilage defects and myopia. Two types are known with carnitine palmitoyl transferase deficiency (CPT1; mutation at 1pter-q12 (CPT2) involves myoglobinuria, especially after exercise or fasting. Another recessive myopathy is based on succinate dehydrogenase and aconitase. Phosphoglycerate mutase deficiencies (human chromosome 10q25 and 7p13-p12) also involve myoglobinuria. X-linked forms display autophagy (cytoplasmic material is sequestered into lysosome associated vacuoles) or slow maturing of the muscle fibers, or swelling and hypertrophy in the quadriceps muscles, respectively. Either insertion, deletion, or frameshift mutations in the ITGA7 integrin gene cause congenital myopathy (human chromosome 12q13). The Xq28-linked tubular myopathy is caused by defects in the myotubularin tyrosine phosphatase. The centronuclear myopathy is due to missense mutation in dynamin 2 and causes defect in centrosome function (19p13.2; Bitoun M et al 2006 Nature Genet 37:1207) and another similar myopathy due to anomalies of the myogenic factors (MYF5, MYF6) is encoded at 12q21 (Cupelli L et al 1996 Cytogenet Cell Genet 72:250). Dominant and recessive base substitution mutations in the skeletal muscle actin, ACTA1 gene (1q42), involve thin muscle fibers and severe, hypotonia, muscle weakness, feeding, and breathing difficulties and most commonly death during the first few months after birth. Occasionally, some afflicted individuals may survive to adulthood. ► [mitochondrial diseases in humans](#), ► [cartilage](#), ► [myopia](#), ► [carnitine](#), ► [Batten-Turner syndrome](#), ► [actin](#), ► [desmin](#), ► [integrin](#), ► [dynamin](#), ► [Sbfl](#), ► [troponin](#), ► [inclusion body myopathy](#), ► [myositis](#), ► [muscular](#)

[dystrophy](#), ► [cardiomyopathies](#), ► [adenosine monophosphate deaminase](#)

Myopia (nearsightedness): Myopia is caused by the increased length of the eye lens in the front-to-back dimension, and focusses the refracted light in front of the retina (nearsightedness). Most forms are under polygenic control with rather high heritability (around 0.6). Autosomal dominant, autosomal recessive (infantile), and X-linked forms have also been suggested. Some studies indicate significant positive correlation between myopia and intelligence. Myopia may be concomitant with various syndromes. ► [eye diseases](#), ► [farsighted](#), ► [human intelligence](#)

Myosins: Contractile proteins that form thick filaments in the cells, hydrolyze ATP, bind to actin, and account for the mechanics of muscle function, organelle movement, phagocytosis, pinocytosis, cell movement, RNA transport, phototransduction, signal transduction, etc. Myosins are activated by kinases (MLCK) and deactivated by phosphatases. MLCK is inhibited by PAK. Members of the 11 families of myosin are represented in amoebas, insects, mammals, and plants. The majority of myosin motors move in one direction toward the plus (+) end of actins. A conformational change at the actin-binding site (converter) of myosin class VI may facilitate movement of the lever in the minus (−) direction. This class of myosin has a 50-amino acid insertion at the converter region. The three-dimensional structure of myosin 5 has been determined (Liu J et al 2006 Nature [Lond] 442:209; Thirumurugan K et al 2006 Nature [Lond] 442:212). ► [filament](#), ► [microfilament](#), ► [myofibril](#), ► [phagocytosis](#), ► [pinocytosis](#), ► [Usher syndrome](#), ► [PAK](#), ► [RAC](#), ► [motor proteins](#), ► [kinesin](#), ► [deafness](#), ► [spindle](#); Homma K et al 2001 Nature [Lond] 412:831; crystal structure of myosin VI motor: Ménétrey J et al 2005 Nature [Lond] 435:779; <http://www.mrc-lmb.cam.ac.uk/myosin/myosin.html>.

Myositis: The name of some myopathies. ► [myopathy](#)

Myostatin Gene (human chromosome 2q32.1 recessive, GDF8): The inactivation (partial deletion) of the myostatin gene substantially increases muscle development in mammals. This mutation is found in the Belgian Blue and Piedmontese cattle breeds. Transforming growth factor- β is involved. The condition is also named 'double muscling' and 'growth/differentiation factor 8'. Inhibition of myostatin leads to robust muscle regeneration and this fact may mean therapeutic value for muscular dystrophy (Wagner KR et al 2005 Proc Natl Acad Sci USA 102: 2519). ► [insulin-like growth factors](#); Lee SJ, McPherron AC

2001 Proc Natl Acad Sci USA 98:93067; Schuelke M et al 2004 N Engl J Med 2004 350:2682.

Myotome: The area of the somites that forms involuntary muscles. ► [somites](#); Gros J et al 2004 Dev Cell 6:875.

Myotonia: The recessive myotonia congenita (chloride channel, CLCN1) is apparently in human chromosome 7q35 (Becker disease) and there is also a dominant form (Thomsen disease, 7q35). Both involve difficulties in relaxing the muscles. The various forms (M. fluctuans, M. permanens, paramyotonia congenita, K⁺-activated myotonia) may involve Na⁺ ion channel malfunctions. ► [periodic paralysis](#), ► [ion channels](#)

Myotonic Dystrophy (DM): A human disorder expressed as wasting of head and neck muscles, eye lens defects, testicular dystrophy, speech defects, frontal balding, frequently heart problems, and behavioral effects. It is controlled by a dominant gene (DMPK) at the centromere of human chromosome 19q13.2-q13.3 and it is caused by (CTG)_n expansion at the 3' untranslated region (Steinert disease). DM2 is a (CTG)_n expansion at 3q21 (Bachinski LL et al 2003 Am J Hum Genet 73:835). The DMPK related kinase, DK serine/threonine kinase, is at 1q41-q42. The prevalence is highly variable. It seems that DM may be a contiguous gene syndrome. In some isolated populations, it may occur in 1/500 to 1/600 proportion while in other populations the occurrence is about 1/25,000. The manifestation of the symptoms is enhanced in subsequent generations, and more are found in children of affected mothers than those of affected fathers. This observation may be due, however, to anticipation. The condition is dominant and it is quite polymorphic. Molecular evidence indicates that the DNA sequences concerned are unstable in the 3'-untranslated tracts downstream of the last exon of the protein kinase gene. The difficulties involving nucleosome assembly in DNA containing CTG triplet repeats in the 3'-untranslated region of a serine/threonine kinase gene seem to be concerned. It appears that the CUG repeats of the RNA transcript bind proteins (CUG-BP), which interfere with the proper splicing of the transcript. This toxic RNA can be silenced and DM can be normalized (Mahadevan MS et al 2006 Nature Genet 38:1066). The crystal structure of CUG repeats is known (Mooers BHM et al 2005 Proc Natl Acad Sci USA 102:16626). A troponin protein has been implicated with the binding. On the basis of linkage with chromosome 19 centromeric genes, prenatal

tests are feasible. Mutation frequency was estimated within the $1.1-0.8 \times 10^{-5}$ range. Ribozyme-mediated trans-splicing of the trinucleotide repeats have been tried to reduce the expansion. Mutation in the DM1 gene may result in the excessive binding of transcription factors to mRNA and mRNA is sequestered in the nucleus and thus the DM protein kinase gene is not translated sufficiently (Ebralidze A et al 2004 Science 303:383). A second myotonic dystrophy gene (DM2) was mapped to a 10-cM region of human chromosome 3q21 (ZNF9). The latter does not display CTG expansion (~15 kb) seen in DM1 but large expansion (~44 kb) of the tetranucleotide repeat (CCTG). Although the amplification involves untranslated sequences, neighboring genes (chloride channel subunit 1, insulin receptor, insulin intolerance) are spliced incorrectly in mammals (Houseley JM et al 2005 Hum Mol Genet 14:873). The expanded mRNAs are not distributed normally to the cytoplasm and are not translated into the needed protein in sufficient amounts nor do they interfere with the function of nuclear RNA-binding proteins. In the brain, hyperphosphorylated short tau protein may occur. ► [muscular dystrophy](#), ► [Pompe's disease](#), ► [Werdnig-Hoffmann disease](#), ► [Duchenne periodic paralysis](#), ► [Schwartz-Jampel syndrome](#), ► [Steinert disease](#), ► [anticipation](#), ► [prenatal diagnosis](#), ► [mental retardation](#), ► [imprinting](#), ► [fragile sites](#), ► [trinucleotide repeats](#), ► [troponin](#), ► [transsplicing](#), ► [contiguous gene syndrome](#), ► [tau](#); Liquori CL et al 2001 Science 293:864; Sergeant N et al 2001 Hum Mol Genet 10:2143.

Myotubes: Aggregate of myoblasts into a multinucleated muscle cell. ► [cadherin](#), ► [integrin](#), ► [fertilin](#), ► [meltrin](#), ► [acetylcholine](#)

Myristic Acid (tetradecanoic acid, CH₃(CH₂)₁₂COOH): A natural 14-carbon fatty acid without double bonds. Myristoylation are common in oncoproteins, protein serine/threonine and tyrosine kinases, and protein phosphatases in the α-subunit of heterotrimeric G proteins, transport proteins, etc. By myristoylation of nascent proteins, cell membranes can be targeted with the aid of myristoyl-CoA:protein N-myristoyltransferase enzyme. ► [fatty acids](#), ► [kinase](#), ► [G protein](#); Farazi TA et al 2001 J Biol Chem 276:39501.

Myt1: ► [Cdc2](#)

Myxobacteria: Slime-secreting bacteria, which may form cysts that contain lots of cells.

Myxococcus xanthus: The genome of myxococcus xanthus is a single circular chromosome with

9,139,763 bases of GC- rich DNA (69%) predicted to encode 7,331 coding sequences. ▶ [Myxobacteria](#); <http://www.xanthusbase.org>.

Myxoviruses: A group of RNA viruses. ▶ [RNA viruses](#)

m/z (m/e): Mass-to-charge. ▶ [mass spectrum](#)

MZ: Monozygotic twin. ▶ [twinning](#)

MZEf: A free, exon detection program based on quadratic discriminant function for multivariate statistical pattern recognition. ▶ [GENESCAN](#), ▶ [Genie](#), ▶ [FGENE](#); Zhang MQ 1997 Proc Natl Acad Sci USA 94:5495.

Historical vignettes

HJ Muller was the second geneticist recipient of the Nobel Prize, on 31 October 1946, for his research on the influence of X-rays on genes and chromosomes. At the Cold Spring Harbor Symposia on Quantitative Biology (9:163, in 1941) he stated:

“We are not presenting...negative results as an argument that mutations cannot be induced by chemical treatment.”

“...it is not expected that chemicals drastically affecting the mutation process while leaving the cell viable will readily be found by our rather hit-and-miss methods. But the search for such agents, as well as the study of the milder, ‘physiological’ influences that may affect the mutation process, must continue, in the expectation that it still has great possibilities before it for the furtherance both of our understanding and our control over the events within the gene”.

Timothy Taylor (archeologist) in 2001 in Nature (Lond) 411:419.

“Perhaps I have no business commenting on genetics, but what I am really interested in is an explanatory imperialism, which threatens to subsume even archeology.”

O

O: Refers to replicational origin. ►replication, ►replication fork, ►bidirectional replication

Ω (Omega): This is the insertion element present in 0 to 1 copy per mitochondrion in yeast. ►mitochondria, ►mtDNA, ►insertion elements

O Antigen: ►ABO blood group, see also O-type lipopolysaccharide-protein antigen of gram negative bacterial capsids

O Blood Group: ►ABO blood group

ω-Agatoxin: Refers to the ion channel blocking proteins present in the *Agelenopsis* spider.

Oak (*Quercus* spp.): This is a forest as well as an ornamental tree, which has many morphological varieties, $2n = 24$. The delineation of some of the numerous species may be difficult because of the not uncommon spontaneous hybridization.

Oats (*Avena* spp.): A major cereal crop with somewhat reduced acreage since farm mechanization has led to a decrease in the number of horses used in agriculture (see Fig. O1). The cultivated species (*A. sativa*) is an allohexaploid but diploid and tetraploid forms are also well known. Basic chromosome number, $x = 7$. (See <http://plants.usda.gov/java/profile?symbol=AVFA>; genes: <http://wheat.pw.usda.gov/GG2/index.shtml>).



Figure O1. *Avena*

Oaz (ornithine decarboxylase antizyme): A multi-Zn finger protein affecting both the BMP-Smad and olfactory Olf signaling pathways. ►BMP, ►Smad, ►Zinc finger, ►olfactogenetics; Hata A et al 2000 Cell 100:229.

OBA (Office of Biotechnology Activities): Information about regulations can be obtained from <http://www4.od.nih.gov/oba>.

Obesity: This condition is characterized by the accumulation of excessive body weight (primarily fat) beyond the physiologically normal range. Differences in predisposition to obesity have long been recognized by animal breeders and the different breeds of swine have large (over 100%) differences in fat content per body weight. Obesity is a health problem in humans because diabetes mellitus, hypertension, hyperlipidemia, heart disease and certain types of cancer appear to be associated with obesity. In mice obesity is regulated by a gene *ob* in chromosome 6, sequenced in 1994. It has been suggested that the 167 amino acid protein product synthesized in the adipose (fat) tissues is secreted into the bloodstream and regulates food intake by signaling to the hypothalamus. Reduction in this gene product or specific lesions in the ventromedial (basal-central) region of the hypothalamus stimulates food consumption and reduces the expenditure of energy. Mice lacking Nocturnin (a circadian deadenylase) remain lean on high fat diets, with lower body weight and reduced visceral fat. However, unlike lean lipodystrophic models, these mice do not have fatty livers and do not exhibit increased activity or reduced food intake. Data on gene expression have indicated that *Nocturnin* knockout mice have deficits in lipid metabolism or uptake, in addition to changes in glucose and insulin sensitivity (Green CB et al 2007 Proc Natl Acad Sci USA 104:9888).

It has been observed that in obese and normal mice the gut has different species of microbes (Ley RE et al 2005 Proc Natl Acad Sci USA 102:11070). Some experimental data point to the *db* (*diabetes*) gene (mouse chromosome 4) as a receptor for the *ob*-encoded factor, leptin. The *tubby* gene (mouse chromosome 7) also causes maturity-onset obesity, insulin resistance, vision and hearing deficit. Tubby is activated by signal transduction from G protein-linked receptors. Phospholipase C (PLC) releases Tubby from the phosphatidylinositol-4,5-bisphosphate of the plasma membrane and then triggers its movement to the cell nucleus where it functions as a transcription factor. The *fat* mutation in mice has a later onset than *ob*. In *ob/ob* mice the serum insulin level decreases with an increase of blood glucose level. In the *fat/fat* mice exogenously supplied insulin reduces the serum glucose level. Fat mice store 70% of their insulin as proinsulin. Apparently, the *fat* gene causes deficiency in carboxypeptidase, an enzyme that normally processes proinsulin. The protein tyrosine phosphatase-1B gene (PTP-1B) of mice is a negative regulator of insulin signaling. Mutational loss of PTP-1B activity results in

decreased phosphorylation of the insulin receptor. Insulin receptor knockout protects against obesity (Blücher M et al 2002 *Dev Cell* 3:25). Consequently, the mutant animals gain much less weight than those with the wild type allele. Phosphorylation of the insulin receptor apparently promotes glucose uptake and weight gain. In humans, obesity has been attributed to both dominant and recessive genetic factors with environmental (diet) factors accounting for about 40% of the variation in obesity. *Mahagony* (*mg*) locus has wide-ranging pleiotropic effects by suppressing obesity of the *agouti-lethal-yellow* locus. The *mg* gene encodes a transmembrane signaling receptor of 1,428 amino acids with homology to the human attractin protein produced by T lymphocytes and cross-talking between the immune system and melanocortin. Major genes in humans seem to determine 40% of the variation in body and fat mass. Heritability of increased body weight in humans may reach > 90% (Stunkard AJ 1991 *Res Publ Assoc Nerv Ment Dis* 69:205). There is a strong linkage between the growth hormone secretagogue receptor (ghrelin receptor, 3q26) and obesity (Baessler A et al 2005 *Diabetes* 54:259). Vaccination of rats with various forms of ghrelin slowed down weight gain and reduced obesity (Zorilla EP et al 2006 *Proc Natl Acad Sci USA* 103:13226). In humans, there is some indication of greater effect of either maternal or paternal body weight on the obesity of the progeny. The geneticist faces problems in measuring such a complex trait as obesity, e.g., in terms of body mass, fat mass, visceral adipose tissue amounts, metabolic rate, respiratory quotient and insulin sensitivity. Many human obesity factors have been implicated mainly on the basis of mice models and putative linkage of quantitative trait loci (QTL). A major susceptibility locus was detected in the short arm of human chromosome 10 (MLS 5.28) and minor quantitative factors appeared in chromosomes 2 (lod score 2.68) and 5 (lod score 2.93). Neuropeptide Y (NPY) appears to be a stimulant of food intake and an activator of a hypothalamic feeding receptor (Y5). A cAMP-dependent protein kinase (PKA) also plays an important role in obesity. This holoenzyme is a tetramer, containing two regulatory (R) and two catalytic (C) subunits. The catalytic function is phosphorylation of serine/threonine and the regulatory units slow down the enzyme when the level of cAMP is low. A knockout of the RII β regulatory subunit leads to the stimulation of energy expenditures in mice and they remain lean even on a diet that is normally conducive to obesity. In the inner membrane of the mammalian mitochondria, body heat is generated by uncoupling oxidative phosphorylation. Uncoupling proteins UCP1 (4q23), UCP2 (11q13) and UCP3 (11q13) also regulate obesity to some extent. UCP2 is associated with a slightly reduced tendency for obesity (Esterbauer H et al 2001 *Nature*

Genet 28:178). These proteins regulate energy balance and cold tolerance. Mice mutants in the uncoupling protein (ICP) have increased food intake but because of the increase in the rate of metabolism they do not become obese. Melanocyte regulatory factors (POMC, α -MSH, MC3-R, MC4-R) and bombesin receptor-3 (BRS-3) are modulators of energy balance and thus obesity and associated diseases. MC4-R regulates food intake and possibly energy use; MC3-R affects the efficiency of the feed and the storage of fat. Mice mutants for both these hormones eat excessively (because of MC4-R deficiency) and store fat excessively (because of MC3-R deficiency) and become quite obese. Systemic impairment of oxidative phosphorylation (OXPHOS) due to *Cre*-mediated targeted disruption, and unexpected ubiquitous reduction of mitochondrial frataxin protein expression lead to a significant reduction in total energy expenditure paralleled by increased expression of ATP citrate lyase, a rate-limiting step in de novo synthesis of fatty acids and triglycerides contributes to obesity (Pamplun D et al 2007 *Proc Natl Acad Sci USA* 104:6377). Perilipin (an adipocyte protein) modulates hormone-sensitive lipase (HSL) activity. HSL hydrolyses triacylglycerol, which stores energy in the cell. Deficiency of perilipin protects against obesity. The peptide motif CKGGRAKDC, which associates with prohibitin, a multifunctional membrane protein, targets angiogenesis in the adipose tissue and causes apoptosis. This results in resorption of white fat cells and normalizes metabolism without adverse effects (Kolonin MG et al 2004 *Nature Med* 10:625). Lymphocytic leakage – due to mutation at the mouse locus *Prox1* – also controls adult-onset obesity and lymphatic vascular disease (Harvey NL et al 2005 *Nature Genet* 37:1072). Close to 30 genetic sites are known to be involved in human obesity. Further, 16–22% of adults who are homozygous for FTO (fat mass and obesity, human chromosome 16q22.2 [mouse chromosome 8]) risk allele weighed about 3 kilograms more and had 1.67-fold increased odds of obesity when compared with those who did not inherit a risk allele (Frayling TM et al 2007 *Science* 316:889; Dina C et al 2007 *Nature Genet* 39:724).

Obesity may be controlled by appropriate exercise regimes as well as restricted food intake. Anti-obesity drugs may target appetite, intestinal fat absorption, increase energy expenditures, stimulate fat mobilization or decrease triglyceride synthesis. Some of the drugs of the dexfenfluramine family (Fen Phen, inhibit serotonin re-uptake and stimulate its release) may reduce obesity by 10% but may have life-threatening side effects in a few cases. The newer drug Sibutramine does not stimulate serotonin release and is considered safe. Current research has focused on the mechanism of action of leptin (response of the hypothalamus to it) and the level of leptin

biosynthesis or degradation. Cholecystokinin hormone receptor stimulants, glucagon-like peptide may reduce food intake. Fatty acid synthase (FAS) inhibitors may reduce food intake by inhibiting the removal of FAS from the cells and thus ensuring that the level of malonyl coenzyme A remains high. Malonyl-CoA (an appetite inhibitor) is generated from acetyl-CoA with the aid of acetyl-CoA carboxylase. During fasting lipid stores are mobilized from the adipose tissue in part by phosphorylation and inactivation of acetyl-coenzyme A carboxylase (ACC) involved in fatty acid synthesis. The pseudokinase Tribbles 3 (TRB3) also promotes lipolysis during fasting by degrading ACC by recruiting COP1 (ubiquitin ligase), a photomorphogenesis protein. Lipid metabolism and obesity may be controlled by both these pathways besides blocking or eliminating insulin signaling (Qi L et al 2006 Science 312:1763). Obesity in mice and humans may be promoted by an increase of Bacteroidetes and Firmicutes bacteria in the gut. These bacteria facilitate greater utilization of food energy resulting in increased body fat production (Tumbaugh PJ et al 2006 Nature [Lond] 444L1027). Germ-free animals – in contrast to mice with a gut microbiota – are protected against obesity that is a consequence of consuming a Western-style, high-fat, sugar-rich diet. Their persistently lean phenotype is associated with increased skeletal muscle and phosphorylated AMP-activated protein kinase (AMPK) in the liver and its downstream targets involved in fatty acid oxidation (acetyl-CoA carboxylase and carnitine-palmitoyltransferase). Moreover, germ-free knockout mice lacking fasting-induced adipose factor (Fiaf), a circulating lipoprotein lipase inhibitor whose expression is normally selectively suppressed in the gut epithelium by the microbiota, are not protected from diet-induced obesity (Bäckhed F et al 2007 Proc Natl Acad Sci USA 104:979).

Insects have developed a mechanism to avoid obesity. *Plutella xylostella* caterpillars reared for multiple generations on carbohydrate-rich foods (either a chemically defined artificial diet or a high-starch *Arabidopsis* mutant) progressively developed the ability to eat excess carbohydrate without storing it as fat, providing strong evidence that excess fat storage has a fitness cost. In contrast, caterpillars reared in carbohydrate-scarce environments (a chemically defined artificial diet or a low-starch *Arabidopsis* mutant) had a greater propensity to store ingested carbohydrate as fat. Moreover, insects reared on the low-starch *Arabidopsis* mutant evolved a preference for laying their eggs on this plant, whereas those reared on the high-starch *Arabidopsis* mutant showed no such preference. These observations provide an experimental example of metabolic adaptation in the face of changes in the nutritional

environment and suggest that changes in plant macronutrient profiles may promote host-associated population divergence (Warbrick J et al 2006 Proc Natl Acad Sci USA 103:14045).

In the twenty-first century obesity has become a serious human biological/social problem because of diabetes, heart disease and other ill effects on health. In the past centuries some degree of corpulence was regarded as a status symbol or opulence or beauty as revealed by many Renaissance Italian paintings and other masterpieces of art (see Fig. O2). In recent years there is an increased awareness and need for controlling obesity by all available means. Although the government is not supposed to intrude on personal free choice, it is becoming evident that some legislative controls are required. Precedents have been set by controlling the use of alcohol, tobacco and narcotics. Further legislative controls of food for schoolchildren, advertising high sugar- and fat-containing food for children seem to be warranted to curb the obesity epidemics. Also, schools should promote physical education and exercise for children (Mello MM et al 2006 N Engl J Med 354:2601). ▶leptin, ▶resistin, ▶histamine, ▶PYY₃₋₃₆, ▶neuropeptide Y, ▶orexin, ▶bombesin, ▶cholecystokinin, ▶frataxin, ▶melanocyte stimulating hormone, ▶melanocortin, ▶melanoma, ▶body mass index, ▶diabetes, ▶IL-6, ▶insulin, ▶insulin receptor, ▶secretagogue, ▶ghrelin, ▶obestatin, ▶adiponectin, ▶paternal transmission, ▶hypertension, ▶Prader-Willi syndrome, ▶Alström syndrome,



Figure O2. Tintoretto's *Suzanna with the Elders*; 16th century oil. By permission of the Kunsthistorisches Museum, Wien, Austria

►Bardet–Biedl syndrome, ►hypogonadism, ►QTL, ►triacylglycerols, ►serotonin, ►glucagon, ►bulimia, ►anorexia, ►lipodystrophy, ►lod score, ►MLS, ►MCH, ►ZAG, ►attractin, ►ciliary neurotrophic factor, ►GATA, ►muscarinic acetylcholine receptors, ►phosphoinositides, ►G proteins, ►cachexia, ►photomorphogenesis, ►COPI, ►acetyl-CoA carboxylase deficiency, ►fatty acids, ►JNK, ►microbiome; Barsh GS et al 2000 Nature [Lond] 404:644; Robinson SW et al 2000 Annu Rev Genet 34:255; Spiegelman BM, Flier JS 2001 Cell 104:531; Brockmann GA, Bevova MR 2002 Trends Genet 18:367; Unger RH 2002 Annu Rev Med 53:319; Czech MP 2002 Mol Cell 9:695; Phan J, Reue K 2005 Cell Metab 1:73; Bell CG et al 2005 Nature Rev Genet 6:221; Horvath TL 2005 Nature Neurosci 8:561; Morton GJ et al 2006 Nature [Lond] 443:289; Muoio DM, Newgard CB 2006 Annu Rev Biochem 75:367; Murphy KG, Bloom SR 2006 Nature [Lond] 444:854; Coll AP et al 2007 Cell 129:251; <http://obesitygene.pbrc.edu/>.

Obestatin: This is a peptide hormone transcribed from the ghrelin gene but its effects are opposite to those of ghrelin; it suppresses appetite, food intake and weight gain (Zhang JV et al 2005 Science 310:996). ►ghrelin, ►obesity

OBF (oct-binding factor; synonyms BOB.1, OCA-B): Regulates the lymphocyte-specific oct sequence in the promoter of the transcription of immunoglobulin genes; it is required for the development of the germinal centers. ►oct, ►immunoglobulins, ►germinal center

Objective Lens: Refers to the microscope lens next to the object to be studied. ►light microscopy

Obligate: This means restricted to a condition or necessarily of a type, e.g., obligate parasite, obligate anaerobe. The latter can thrive only in the absence of air.

Oblique Crossing Over: In the case of adjacent (tandem) duplications in homologous chromosomes pairing may take place in more than one register and crossing over may yield unequal products (see Fig. O3). ►unequal crossing over

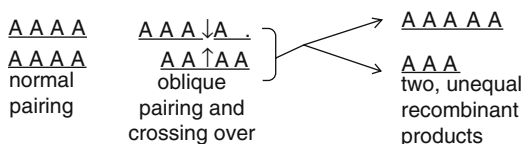


Figure O3. Oblique crossing over

Obsessive-Compulsive Disorder (OCD): This is a type of schizophrenic behavior bearing some resemblance to the Tourette syndrome (see Fig. O4).

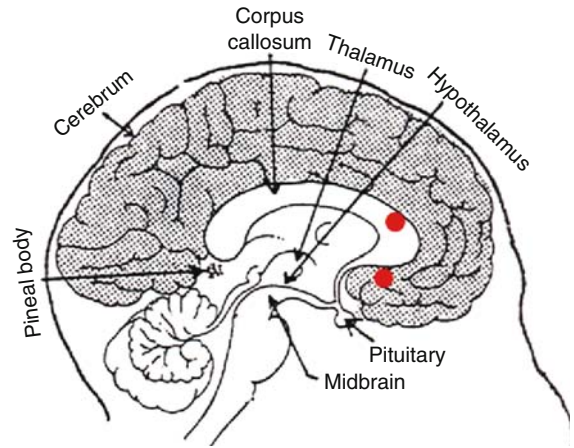


Figure O4. The red marked spots of the brain indicate some of the approximate areas of successful therapeutic stimulation. Other points (not shown here) were also used for the same purpose

A major dominant gene with minor modifiers determines this condition without difference in the two sexes. In some psychotherapy and electroconvulsive therapy resistant patients, who exhibit overactivity in the subgenual cingulate region of the brain (Brodmann area 25), electrical stimulation applied deep into the region was remarkably successful in reversing the condition in a limited trial (Mayberg HS et al 2005 Neuron 454:6512). ►schizophrenia, ►panic disorder, ►Tourette syndrome; Hanna GL et al 2002 Am J Med Genet 114:541.

OCA-B: This is the same as OBF or Bob. ►OBF

Occam's Razor (Ockham's razor): This is the philosophical precept of William Ockham [1280–1349], a rebellious clergyman and a venerabilis inceptor [= reverend innovator]: “*pluralites non est ponenda sine necessitate*”, meaning that multiple alternatives should not be offered in logical argumentation but the simplest yet adequate explanation should be chosen. ►maximal parsimony

Occipital Horn Syndrome (cutis laxa): ►Menkes syndrome, ►cutis laxa

Occluded Virus Particle: The virus is surrounded by proteinacious material that protects it from the adverse environment, e.g., when the insect host dies and decomposes. When the insect eats plant material the alkaline gut fluid dissolves the occlusion and the infectious (baculovirus) particles are released. The lipoprotein viral envelope fuses with the gut cell walls

and the nucleocapsids are transmitted to the cytoplasm and eventually to the cell nucleus. ▶[baculoviruses](#); Hu Z et al 1999 J Gen Virol 80(pt 4):1045; Braunagel SC et al 2003 Proc Natl Acad Sci USA 100:9797.

Occlusion: Transcription from one promoter reduces transcription from a downstream promoter. ▶[downstream](#), ▶[promoter](#), ▶[transcription](#)

Occupational Hazard: Refers to the presence of genotoxic (carcinogenic) agents at the workplace. Monitoring includes urine analysis for chemicals, sisterchromatid exchange, abnormal sperm count or deformed sperm or SNIPS, etc. ▶[mutation detection](#), ▶[epidemiology](#)

Occupational and Safety and Health Administration: ▶[OSHA](#)

Occurrence Risk: Refers to the chance that an offspring of a particular couple will express or become a carrier of a gene. ▶[genetic risk](#), ▶[recurrence risk](#)

Ocellus (plural ocelli): This is a simple light sensor (eyelet, eyespot) on the top of the head of insects (see tiny arrows in Fig. O5), behind the compound eyes (see Fig. O5). ▶[compound eyes](#), ▶[ommatidium](#), ▶[rhabdomere](#), ▶[morphogenesis in *Drosophila*](#)

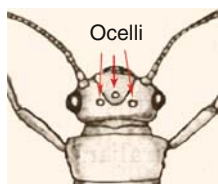


Figure O5. Ocelli in insects

Ochre: Denotes chain-terminator codon (UAA).

Ochre Suppressor: Refers to mutation in the anticodon of tRNA that permits the insertion of an amino acid at the position of a normally chain terminating UAA RNA codon; ochre suppressors frequently suppress amber (UAG) mutations. ▶[code genetic](#), ▶[nonsense codon](#), ▶[suppressor tRNA](#)

Ochronosis: This is the blue pigmentation in alkaptonuria. ▶[alkaptonuria](#)

ω-Conotoxins: These are *Conus* snail inhibitors of calcium ion channels. ▶[ion channels](#)

Oct: This is a mammalian gene regulatory protein (helix-turn-helix transcription factors) with octa recognition sequence: ATTTGCAT. Oct-1 and Oct-2 regulate B cell differentiation. Oct3/4 mediates differentiation and dedifferentiation of embryonic stem cells. The Oct-6 transcription factor regulates Schwann cell

differentiation. The presence of Oct-1 allele may lead to a fourfold increase in susceptibility to the cerebral form of malaria. ▶[Schwann cell](#), ▶[lymphocytes](#), ▶[OBF](#), ▶[B cell](#), ▶[immunoglobulins](#), ▶[Oct-2](#), ▶[Octa](#), ▶[malaria](#), ▶[octamer](#); Pesce M, Schöler HR 2001 Stem Cells 19:271.

Oct-2: A lymphoid transcription factor that is similar to Oct-1; both respond to BOB.1/OBF.1 activators. ▶[OBF](#), ▶[OCT](#)

Octa: This is an 8-base sequence (ATTTGCAT) in the promoter of H2B histone gene and some other genes. Several slightly different octa sequences are found in the promoter regions of various genes. (Octo in Latin, οκτώ in Greek: number 8, Oct-1). ▶[OCT](#)

Octad: This means comprising eight elements, e.g., the spores in an ascus if meiosis is followed by an immediate mitotic step as in *Neurospora*, *Ascobolus*, etc. ▶[tetrad analysis](#)

Octadecanoic Acid (stearic acid): This is an inducible plant defense molecule against insects. ▶[sphingolipids](#)

Octamers: These are conserved key elements in the promoter of immunoglobulin genes where several transcription factors bind. ▶[octa](#), ▶[OCT](#), ▶[immunoglobulins](#); Matthias P 1998 Semin Immunol 10:155.

Octaploid: This is a cell nucleus carrying eight genomes, 8x. ▶[polyloid](#)

Octopine: This derivative of arginine is synthesized by a Ti plasmid gene (*ocs*) in *Agrobacterium* strain Ach 5 (see Fig. O6). ▶[opines](#), ▶[Agrobacterium](#)

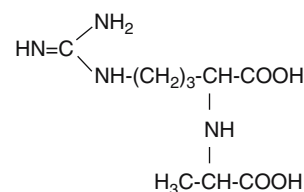


Figure O6. Octopine

Ocular: This refers to the microscope lens next to the viewer's eye. ▶[objective](#)

Ocular Albinism: ▶[albinism](#)

Ocular Cicatricial Pemphigoid: This is an autosomal dominant autoimmune disease of the eye and possibly of other mucous membranes. It may be associated with defects in the HLA system. ▶[eye diseases](#), ▶[autoimmune disease](#), ▶[HLA](#)

Oculocutaneous Albinism: Several forms of the recessive disease are known. Type I (11q14-q21) is

tyrosinase negative recessive whereas types II (15q11.2-q121) and III (9p23) are tyrosinase positive (brown). There is another brown type at 15q. The most prevalent is type II, its incidence is $\sim 1/1,100$ among the Ibos of Nigeria, $\sim 1/10,000$ among US blacks and $\sim 1/36,000$ among the general population of the US. ► [albinism](#)

Oculodentodigital Dysplasia: An autosomal dominant disorder characterized by defects in the eyes (microphthalmos), small teeth and polydactyly or syndactyly. Its mutation rate reveals a large paternal effect. The basic defect may be in the connexin 43 gene (6q22-q23) that may cause disturbance in the gap junctions that are required for the exchange of small ions and signaling molecules. ► [eye diseases](#), ► [microphthalmos](#), ► [polydactyly](#), ► [syndactyly](#), ► [connexins](#), ► [gap junction](#); Paznekas WA et al 2003 Am J Hum Genet 72:408.

O.D.: Optical density indicates the absorption of light at a particular wavelength by a compound in a spectrophotometer. O.D. can be used to characterize a molecule, e.g., pure nucleic acids have maximal absorption at 260 nm but contamination and the solvent may alter the absorption pattern. ► [DNA measurements](#), ► [extinction](#)

Odds Ratio (OR): A comparison of the effect of a treatment or exposure on a particular group (of a certain genotype) versus the same treatment or exposure on another different group. The OR may reveal the response of the organism of a certain genotype to the particular exposure. The OR can be estimated statistically by a two-by-two contingency table and as ad/bc . Greater differences from 1 (+/–) indicate stronger association. ► [association test](#), ► [lod score](#)

Odontoblast: Refers to the connective tissue cell that forms dentin and dental pulp of the teeth.

Odor-Sensing: ► [olfactogenetics](#), ► [pheromones](#); Hurst JL et al 2001 Nature [Lond] 414:631; Jacob S et al 2002 Nature Genet 30:175; Hallem EA, Carlson JR 2006 Cell 125:143.

ODP (origin decision point): This is a checkpoint for the initiation of replication. It precedes the restriction point. ► [R point](#); Wu JR, Gilbert DM 2000 FEBS Lett 484:108.

Oedipus Complex: According to Freudian theory, during adolescence a child may become more attached to the parent of the opposite sex, and if the condition persists it may lead to neurotic behavior.

Oenocytes: These insect organs accumulate lipid droplets during starvation and cooperate with fat

bodies in regulating lipid metabolism (Gutierrez E et al 2007 Nature [Lond] 445:275). ► [fat body](#)

Oenothera (Onagraceae, $x = 7$): Several species, diploid and polyploid have been used for the cytological study of multiple translocations and the nature and inheritance of plastid genes. ► [gaudens](#), ► [translocation](#), ► [complex heterozygote](#), ► [megaspore competition](#), ► [zygotic lethal](#); Cleland RE 1972 Oenothera: Cytogenetics and Evolution, Acad. Press, New York; Hupfer H et al 2000 Mol Gen Genet 263:581; Mracek J et al 2006 Genomics 2006 88:372.

Oestrogen (estrogen, estradiol): This is a steroid hormone. ► [animal hormones](#), ► [estradiol](#)

Oestrus (estrus): Refers to the periodically recurrent sexual receptivity, concomitant with sexual urge (heat) in mammals, except humans. In mice it lasts for ~ 3 –4 days, depending on crowding, exposure to male pheromones or hormone treatment and the daily light/dark cycles. ► [uterus](#)

OFAGE (orthogonal-field alternation gel electrophoresis): This device is used to isolate small chromosomal size DNA of lower eukaryotes. ► [pulsed field electrophoresis](#)

Offermann Hypothesis: Purported to provide a mechanism for recombination within a short chromosomal region that would appear to be intragenic. It was assumed that actually recombination separated two genes, which were involved in position effect. These loci were not supposed to have any detectable phenotype themselves, except the position effect on the neighbor. This idea emerged in 1935, years before pseudoallelism has been discovered in 1940 by C.P. Oliver. ► [pseudoallelism](#); Carlson EA 1966 The Gene: A Critical History. Saunders, Philadelphia, PA.

Offspring-Parent Regression: ► [correlation](#)

O-GlcNAc Transferase (OGT): This is an indispensable cellular enzyme mediating post-transcriptional glycosylation of many different proteins involved in regulatory functions. (See Hanover JA 2001 FASEB J 15:1865)

OGOD (one gene - one disorder): A hypothesis based on the analogy of the one gene - one poly-peptide (one enzyme) theorem. The majority of diseases in humans (and animals) cannot be reconciled with a single gene mutation, and most of the symptoms (syndromes) are under multigenic control although particular genes may have a major effect. ► [behavior in humans](#), ► [one gene—one enzyme theorem](#); Plomin R et al 1994 Science 264:1733.

Oguchi Disease: This condition is characterized by a recessive human chromosome-2q mutation or

deletion in the arrestin protein modulating light signal transduction to the eye or by defects in the arrestin and the rhodopsin kinase genes. Night vision is impaired but otherwise vision is normal. ►night blindness, ►arrestin, ►retinal dystrophy, ►eye diseases

Ohm ($\Omega = 1\text{V/A}$): A unit of resistance of a circuit in which 1 volt electric potential difference produces a current of 1 ampere.

OH[•] (hydroxyl radical): This is responsible for the oxidative damage of superoxide and hydrogen peroxide. ►superoxide, ►hydrogen peroxide, ►Fenton reaction, ►ROS

Ohno's Law: The gene content of the X chromosome is basically the same in all mammals. Some exceptions are seen in humans, marsupials and in the monotreme, *Platypus* where genes in the short arm of the X chromosome may be of autosomal origin. There are other exceptions such as the chloride channel gene (*Cln4*) is autosomal in the mouse *Mus musculus* but it is X-linked in *Mus spretus*. Similarly, the human steroid sulfatase (STS) gene is near the pseudo-autosomal region whereas in lower primates it is autosomal. The rationale of Ohno's Law is that translocations between autosomes and X chromosome would upset the sex determination gene balance. In the X chromosomes of various mammals sequence homologies are conserved. FISH probes have, however, revealed some rearrangements. ►sex determination, ►FISH; Ohno S 1993 Curr Opin Genet Dev 3:911; Palmer S et al 1995 Nature Genet 10:472.

Oidia: Asexual fungal spores produced by fragmentation of hyphae into single spores.

Oil Immersion Lens: This is the highest power objective lens of the light microscope. It is used with a special non-drying immersion oil, available at different viscosity with a refractive index of about 1.5150 for D line at 23°C, and it increases light-gathering power and improves resolution. ►light microscope, ►objective, ►resolution optical, ►numerical aperture

Oil Spills: It is known that around 22 bacterial genera have genetically determined ability to degrade petroleum hydrocarbons. Although a procedure invented by A.M. Chakrabarty did not involve molecular genetic engineering but only the introduction of two different plasmids into *Pseudomonas* (*P. aeruginosa* and *P. putida*) to degrade several harmful products, it was the first US patent (#4,259,444) issued in 1981 for unique microorganisms. ►patent, ►biodegradation; Díaz MP et al 2002 Biotechnol Bioeng 79:145.

OK Blood Group: This is encoded in human chromosome 19pter-p13. This antigen is present in the red cells of chimpanzees and gorillas but not in rhesus monkeys, baboons or marmosets. ►blood groups

Okadaic Acid ($\text{C}_{44}\text{H}_{68}\text{O}_{13}$): An inhibitor of PP1 and PP2a protein phosphatases. ►PP-1

Okayama & Berg PROCEDURE: This procedure permits cloning of full length mRNA genes. The mRNA is extracted from post-polysomal supernatant of reticulocyte lysate of rabbits, made anemic by phenylhydrazine injection. The globin mRNA is recovered in the alcohol-precipitate of phenol extract or with the aid of a guanidinium thiocyanate method. The poly-A tailed mRNA is annealed to plasmid pBR322 that is equipped with a poly-T attached to a SV40 fragment inserted into the vector. In the next step an oligo-G linker is constructed, separated, and purified by agarose gel electrophoresis. Now cloning of the mRNA can begin. The poly-A tail is annealed to the poly-T end of the vector. Using reverse transcriptase, a DNA strand, complementary to the mRNA strand, already in the plasmid, is generated. Using terminal transferase enzyme poly-C tails are added to one strand of the plasmid vector as well as to the DNA strand of the RNA-DNA double strand. Now the oligo-G linker is added to the oligo-C ends and the plasmid is made circular by DNA ligase. Then the mRNA strand is removed by RNase H and replaced by a complementary DNA strand, generated by DNA polymerase I and the construction is completed by ligation into a circular cloning vector. This new vector, containing the full length cDNA, is transformed into *E. coli* cells for propagation. ►cloning vectors, ►cDNA, ►ribonuclease H, ►linker, ►reverse transcriptase, ►terminal transferase, ►guanidinium thiocyanate, ►phenylhydrazine, ►RNA extraction; Okayama H Berg P 1982 Mol Cell Biol 2:161.

Okazaki Fragments: These are short (generally less than 1 kilobase in eukaryotes and about 2 kb in prokaryotes) DNA sequences formed during replication (of the lagging strand) and subsequently ligated into a continuous strand. Okazaki fragments are needed because nucleic acid chains can grow only by adding nucleotide to the 3' end and the lagging strand template would not allow continuous chain elongation like the leading strand of DNA. Six steps are involved in the generation of Okazaki fragments: (i) polymerase α and primase synthesize an RNA primer for 3' ← ← ← growth on the lagging strand template, (ii) RFC assists in binding the primer to the DNA and in the displacement of polymerase α , (iii) PCNA promotes the assembly of the replicator DNA polymerase δ complex, (iv) RNase H, Fen1 and Dna2 endonuclease digest off the RNA primer under the

control of replication protein RPA as DNA synthesis proceeds, (v) the gaps between the Okazaki fragments are filled by the DNA, and (vi) DNA ligase joins the fragment into a continuous strand of DNA. In eukaryotes the process is more complex than in prokaryotes. ▶DNA replication, ▶replication fork, ▶primosome, ▶RCF, ▶PCNA, ▶Rad27/Fen1, ▶ribonuclease H, ▶DNA ligase, ▶alpha accessory factor, ▶polymerase switching, ▶processivity; Bae S-H, Seo Y-S 2000 J Biol Chem 275:38022; Jin YH et al 2001 Proc Natl Acad Sci USA 98:5122; Bae S-H et al 2001 Nature [Lond] 412:456; Jin H Y et al 2003 J Biol Chem 278:1626.

Okihiro Syndrome: ▶Duane retraction syndrome

Okra (*Abelmoschus esculenta*): An annual vegetable of the Malvaceae with nearly 30–40 species having variable chromosome numbers, generally higher than $n = 34$ –36 as revealed by reports.

OKT3: A monoclonal antibody capable of blocking interleukin production. ▶Oct

Oleuropein: This complex substance is found in olive tree leaf extracts and it is used as a herbal medicine for various ailments.

Olig1: This is a basic helix-loop-helix transcription factor required for the repair of demyelinated lesions of the central nervous system. It is also needed for repairing the myelin sheath in multiple sclerosis. ▶multiple sclerosis, ▶helix-loop-helix; Arnett HA et al 2004 Science 306:2111.

2'-5'-Oligoadenylate: This is synthesized by 2–5A synthetases (2'5'AS), which are induced by interferons and they activate RNase L in defense of viral infection. ▶interferon, ▶ribonuclease L; Bonnevie-Nielsen V et al 2005 Am J Hum Genet 76:623.

Oligo-Capping: Refers to the replacement of the original cap of the mRNA by a short synthetic oligoribonucleotide. The removal is due to tobacco acid pyrophosphatase and the ligation by T4 RNA ligase. In uncapped mRNAs the 5' phosphate is first removed by alkaline phosphatase. The purpose is labeling prior to first-strand DNA synthesis. The 5' end of the mRNA is identified by reverse transcription-polymerase chain reaction. ▶cap, ▶RNA ligase, ▶RT-PCR; Maruyama K, Sugano S 1994 Gene 138:171.

Oligohydramnios: ▶renal tubular dysgenesis

Oligonucleotide: A short nucleotide tract (about 15 to 30 units). See <http://basic.northwestern.edu/biotools/OligoCalc.html>.

Oligopeptides: The natural oligopeptides are generally not more than 50 amino acids long and frequently have regulatory functions. (See database: <http://erop.inbi.ras.ru/>).

Oligostickiness: This is a measure of the binding affinity of 12-base (dodeca-) oligonucleotides to the genome of a species. The affinity is characteristic of genomes as well as of chromosomes of a species and hence facilitates identification. It is also known as chromosome texture. (See Nishigaki K and Saito A 2002 Bioinformatics 28:1153).

OL(1)p53: A phosphorothioate oligonucleotide sequence (5'-d[CCCTGCTCCCCCTGGCTCC]-3') used as antisense DNA to suppress p53 function to pass the checkpoint into the S phase of the cell cycle as a potential treatment for acute myeloblastic leukemia. ▶leukemia, ▶Myb oncogene, ▶antisense DNA, ▶phosphorothioate, ▶p53; Bishop MR et al 1997 J Hematother 6(5):441.

Oleuropein: A phenolic secoiridoid glycoside in the leaves of privet (*Ligustrum*) and when activated by herbivores becomes a protein cross-linking, lysine-decreasing glutaraldehyde-like structure, an α,β -unsaturated aldehyde as a means of self-protection (see Fig. O7). ▶plant defense, ▶host-pathogen relations; Konno K et al 1999 Proc Natl Acad Sci USA 96:9159.

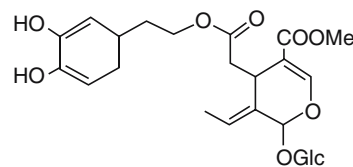


Figure O7. Oleuropein. The left side of the molecule represented here is a catechol and the right side is the secoiridoid moiety

Olfactogenetics: This is concerned with the genetically determined differences in (body) smell and the ability to recognize it. In the human brain the olfactory bulbs situated under the frontal lobes interpret the olfactory signals (see Fig. O8). The mouse olfactory bulbs contain ~two glomeruli for each olfactory receptor. The different olfactory receptors are segregated into groups of glomeruli. Scent is influenced by the chemical nature of secretions and to a large extent by the diet and the microflora of the body. Human polymorphism in olfactory responses is of concern for the cosmetics (perfume) industry. It has been

claimed that the ability to distinguish between various odors is determined by the *H2* locus of mice (an analog of the human *HLA* complex). Some people are incapable of smelling, anosmic for isobutyric acid or cyanide or urinary excretes of asparagus metabolites. The regulation of the olfactory responses involves cAMP or phosphoinositide (IP₃)-regulated ion channels and G protein (G_{olf}) coupled receptor kinases. The olfactory memory in sheep is triggered by nitric oxide that potentiates the release of glutamate and GABA neurotransmitters leading to an increase of cGMP in the mitral cells of the nose, the site of perception of smell. The olfactory memory formation has been localized in the mushroom body of the brain. In *Drosophila* cAMP phosphodiesterase, encoded by gene *dunce* (*dnc*, chromosome 1–3.9), calcium—calmodulin-dependent adenylyl cyclase (encoded by *rutabaga* [*rut*, 1–{46}]), the catalytic subunit of the cyclicAMP-dependent protein kinase A, and the α -integrin subunit encoded by *Volado* (*vol*, located in the X and the 2nd chromosomes) are involved in the control of olfactory memory. There are many other unidentified genes and proteins involved in different olfactory functions. It appears that each neuron of the olfactory epithelium expresses only one olfactory receptor. In the human genome ~900 olfactory receptor (OR) genes (encoding seven-transmembrane proteins) or pseudogenes (60%) have been identified. In humans, the non-functional, pseudogenic olfactory genes are twice as high as in non-human primates and in mice the proportion of pseudogenes of olfaction is only 20% (Gilad Y et al 2003 Proc Natl Acad Sci USA 100:3324). They are common in chromosomes 7 and 17 but are found in most other chromosomes as well, generally clustered as 6–138 genes. Of 856 olfactory receptors in the human genome, 40% is located in chromosome 11 in 28 single- and multi-gene clusters (Taylor TD et al 2006 Nature [Lond] 440:497). In each olfactory sensory neuron only one odorant receptor (MOR in mouse, HOR in humans) gene is expressed (Serizawa S et al 2003 Science 302:2088). A single transacting enhancer element may allow the stochastic activation of only one olfactory receptor allele in the olfactory sensory neurons of mice (Lomvardas S et al 2006 Cell 126:403). No olfactory receptor genes seem to be coded in human chromosomes 20 and Y. Different olfactory sensory neurons in the nose express a different complement of the ORs and transmit the information through their axons to the olfactory bulbs in the brain. In humans, mice and fishes there is another class of chemosensory receptors, TAARs (trace and amine-associated receptors). One group of TAARs recognizes volatile amines in the urine of mouse linked to stress and two groups are involved in sensing compounds enriched in the male urine (Liberles SD, Buck LB 2006 Nature [Lond] 442:645).



Figure O8. Olfactory bulbs in the human brain situated under the frontal lobes

In fishes approximately 100 genes are involved in olfactory functions whereas in rodents there are about 1,300 and humans have around 1,000. In humans many of the olfactory genes are not functional. In mammals only a single odor receptor gene is expressed per cell. Dogs and rats have a superior ability to smell. In dogs 1,094 and in rats 1,493 olfactory receptor genes were identified from shotgun sequences but nearly 20% were pseudogenes (Quignon P et al 2005 Genome Biol 6(10):R83). The *Drosophila* in general expresses two odor receptors per cell whereas the *Caenorhabditis* may express nine chemoreceptors per cell. The *Caenorhabditis* has around 1,500 G-protein-coupled odor receptors (GPCR). *Drosophila melanogaster* has about 60 genes for odorant receptors and an equal number but different gustatory receptor genes. These low numbers are characteristic of other insects as well. A combinatorial use of the olfactory receptors permits the distinction of an almost indefinite variety of odors. The ligands of the receptors also contribute to sensory specificity. Different glomeruli respond qualitatively and quantitatively to the types and intensities of the odors. According to some estimates olfactory receptors may represent 1% of all genes. It has been reported that the major histocompatibility complex is a main source of unique individual odors in animals and women can detect differences among male odor donors with different MHC genotypes. This ability is dependent on the HLA allele inherited by the human female from her father but not from her mother (Jacob S et al 2002 Nature Genet 30:175). In the vomeronasal organ—sensing pheromones—there are ~35 V1R and ~150 V2R receptor family members. The number of human OR genes exceed 1,000 and many of them are pseudogenes. In animals the major histocompatibility complex is a source of olfactory recognition of mating preferences and various other behavioral traits. The rodent ORs rarely, if at all, are pseudogenic. Natural odors are often a blend of several components present in specific ratios. Therefore, an enormous number of odor (fragrance) signals may exist. Several OR genes have been cloned. Pheromones are perceived by >240 proteins of the vomeronasal system including special 7-transmembrane proteins. The removal of the vomeronasal organ interferes with the pheromone

response but not with other odor perceptions. The olfactory pathway also mediates pheromone responses (Shepherd GM 2006 *Nature [Lond]* 439:149). The Ras-MAPK signal transduction pathway mediates odor perception and transmission of sensory signals to the *Caenorhabditis* olfactory neurons. Deficiencies in the olfactory system of the *Caenorhabditis* seem to prolong life. In 2004, Richard Axel and Linda Buck received the Nobel Prize for their work on olfaction. ▶bisexual, ▶cAMP, ▶cGMP, ▶neurotransmitter, ▶nitric oxide, ▶phosphoinositide, ▶IP₃, ▶MHC, ▶signal transduction, ▶*Asparagus officinalis*, ▶pheromones, ▶fragrances, ▶vomeronasal organ, ▶taste, ▶brain human, ▶Kallmann syndrome, ▶Bruce effect, ▶mushroom body, ▶odor-sensing; Pilpel Y et al 1999 In: Higgins SJ (ed) *Molecular Biology of the Brain*, Princeton Univ. Press, Princeton, NJ, pp 93; Buck LB 2000 *Cell* 100:611; Glusman G et al 2001 *Genome Res* 11:685; Firestein S 2001 *Nature [Lond]* 413:211; Mombaerts P 2001 *Annu Rev Genomics Hum Genet* 2:493; Young JM et al 2002 *Hum Mol Genet* 11:535; Nakagawa T et al 2005 *Science* 307:1638; Bargmann C 2006 *Nature [Lond]* 444:295; Shepherd GM 2006 *Nature [Lond]* 444:316; Jefferis GSXE et al 2007 *Cell* 128:1187; Lin H-H et al 2007 *Cell* 128:1205; <http://senselab.med.yale.edu/senselab/ordb/>; www.leffingwell.com.

Olfactory: This is related to the sense of smell. ▶olfactogenetics

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Oligodendrocyte: Refers to the non-neural cells that form the myelin sheath (neuroglia) of the central nervous system and they coil around the axons. They may become the stem cell of the central nervous system. ▶neurogenesis; Lu QR et al 2002 *Cell* 109:75.

Oligodeoxyribonucleotide Gated Channel: Composed of a 45-kDa protein, this is involved in Ca²⁺-dependent uptake of oligonucleotides through an approximately 5-μm pore. Protein kinase C and a few organic molecules are inhibitors. ▶protein kinases, ▶liposomes, ▶DNA uptake sequences; Salman H et al 2001 *Proc Natl Acad Sci USA* 98:7247.

Oligodontia: The lack of development of six or more permanent teeth is based on frameshift mutation in the PAX9 gene in human chromosome 14. ▶tooth agenesis, ▶hypodontia, ▶PAX; Heilig R et al 2003 *Nature [Lond]* 421:601.

Oligodynamic Action: Refers to the antimicrobial effect of trace amounts of heavy metals. ▶sterilization.

Oligogenes: This is a small group of genes responsible for a particular trait; usually one has a major role. ▶breast cancer, ▶prostate cancer, ▶polygenes, ▶QTL

Oligo-Labeling Probes: These are short (10–20 nucleotides), commonly radioactively or of fluorochrome labeled, synthetic probes for the identification of genes for isolation, labeling in gel retardation assays, screening of DNA libraries, etc. ▶label, ▶probe, ▶gel retardation assay, ▶variant detector assay

Oligomer: A polymer of relatively few units (amino acids, nucleotides, sugars, etc.). An oligomeric protein has a quaternary structure associated with non-covalent bonds.

Oligonucleotide-Directed Mutagenesis (Kunkel mutagenesis): Synthetic oligonucleotide with the mutation sought is annealed to a single-stranded M13 phage DNA template with a number of uracil residues in place of thymine in a strain *dut*⁻ (dUTPase) and *ung*⁻ (uracil-DNA-glycosidase). The *E. coli* transformation medium should contain the 4 deoxynucleotide triphosphates, T4 DNA polymerase and T4 DNA ligase to generate double-stranded circular DNA and M13 phages are selected with the mutation desired. The heteroduplex is introduced into a wild type *dut* and *ung* strain to maintain the mutation. ▶site-specific mutagenesis; Kunkel TA et al 1987 *Methods Enzymol* 154:367.

Oligophrenia Phenylpyruvica: Refers to mental retardation due to phenylketonuria. ▶phenylketonuria

Oligophrenin: This RAS-like GTPase protein (91-kDa) encoded in human chromosome Xq12 is responsible for cognitive impairment. Similar mental retardation genes are scattered in the genome and afflict about 0.15–0.3% of males. Its level is higher in several cancerous tissues. ▶mental retardation, ▶RAS; Pinheiro N A 2001 *Cancer Lett* 172:67.

Oligoribonucleotide Synthesis: ▶silyl-phosphite chemistry

Oligosaccharides: These consist of sugar residues, such as glycans, and they may be present in many metabolically, immunologically and structurally important molecules. Oligosaccharides may carry information for the folding of proteins in the endoplasmic reticulum. Their sequence can be determined by exoglycosidase mediated digestion or by sequencing the amino acids of the protein. In both procedures electrophoretic (MALDI) analysis may be used. ▶glycan, ▶electrophoresis, ▶protein folding, ▶folding, ▶endoplasmic reticulum; Billuart P et al 1998 *Nature [Lond]* 392:923; Lehrman MA 2001 *J Biol Chem* 276:8623.

Oligospermia: This condition is characterized by low sperm content in the semen. Chromosomal

rearrangement (translocations, inversions, ring chromosome, etc.) or aneuploidy may be responsible for this condition. ►sperm, ►semen, ►azoospermia, ►cytoplasmic male sterility

Oligozyme: Refers to nuclease resistant RNA oligomers (29–36 residues) that can cleave specific RNA sequences. ►ribozyme; Kitano M et al 2001 Nucleosides Nucleotides Nucleic Acids 20:719.

Olive (*Olea europea*): There are about 30 species of this oil-producing tree. The cultivated forms are $2n = 2x = 46$ although aneuploids have been identified. Because of its oleocanthal content freshly pressed oil is anti-inflammatory as it lowers cyclooxygenase enzymes COX-1 and COX-2 but has no substantial effect on lipoxygenase. ►cyclooxygenase, ►lipoxygenase; Beauchamp GK et al 2005 Nature [Lond] 437:45.

Olivopontocerebellar Atrophy (OPCAI): The autosomal dominant or recessive, variable types of expressions involve ataxia, paralysis, incoordination, speech defects, and brain and spine degeneration. In some forms eye defects and other anomalies have been observed. In several cases a linkage has been observed to the HLA complex in human chromosome 6p21.3–p21.2, but in others such a linkage was not evident. Patients with this disease exhibit 50% or less glutamate dehydrogenase activity. ►ataxia, ►palsy, ►glutamate dehydrogenase

Omega-3-Fatty Acids: This is a collective name for polyunsaturated fatty acids. The ω name is derived from the first double bond position. The early synthetic products with 1, 2 and 3 double bonds are shown. Mammals lack the enzymes (desaturases) to add double bonds beyond the 9th carbon atom of the fatty acid chain. Therefore, they cannot synthesize these *essential*, unsaturated fatty acids and depend on plants. Fish oil – because of feeding on algae – may also be rich in ω -3 fatty acids (see Fig. 09). In the absence of these fatty acids skin lesions, defects in the lipid membranes, kidney disease, reduced fertility, prostaglandin deficiency, etc. occur. Arachidonic acid, a ω -6-fatty acid, is the precursor of prostaglandins mediating anti-inflammatory responses. Omega-3 fatty acids are known to lower risks of cardiovascular diseases, to reduce depression, bipolar mental afflictions and other nerve disorders. On the other hand, these fatty acids may increase hemorrhages, lower immune responses, etc. According to the Federal Drug Administration, the intake of these fatty acids through food and supplements should be limited to 3mg/day. Some nutritionists have recommended higher doses. Since mammals lack the desaturase enzyme that can

convert ω -6 fatty acids to ω -3, it is of interest to introduce the gene for this enzyme from another animal such as *Caenorhabditis elegans*. Following the transfer of the *fat-1* gene to mice (Kang JX et al 2004 Nature [Lond] 427:504) and pigs (Lai L et al 2006 Nature Biotechnol 24:435) it was possible to produce a high ratio of n-6/n-3 of 0.7 in the muscles of transgenic mice compared to 49.0 in the wild type. In 8 transgenic pigs this ratio was variable but the average was 1.69 versus 8.52 in the wild type controls. For the experiments the humanized version of the pCAGGS-fat-1 expression vector was used with a cytomegalovirus enhancer and driven by the chicken β -actin promoter. The vector containing G418 selective marker was electroporated into fetal porcine fibroblasts. The transgenic cells were then used for nuclear transplantation into pig ova and cloned. A total of 1,633 engineered embryos was transferred to 14 females in estrus which resulted in pregnancies. Five of them were carried to term resulting in 10 live and two dead piglets of which six contained the *fat-1* transgene. Initially all the offspring were completely normal, however three piglets developed heart failure by the age of 3 weeks. This defect appeared to be due to the nuclear transfer procedure rather than to the *fat-1* gene. Although such transgenic pigs are not yet available for commercial meat production, the method appears very promising from the viewpoint of potential improvements in human diet and health. ►fatty acids, ►acetyl-CoA, ►syntxin, ►erucic acid, ►prostaglandins, ►arachidonic acid, ►desaturase, ►cardiovascular disease, ►enhancer, ►promoter, ►cytomegalovirus, ►G418, ►electroporation, ►nuclear transplantation

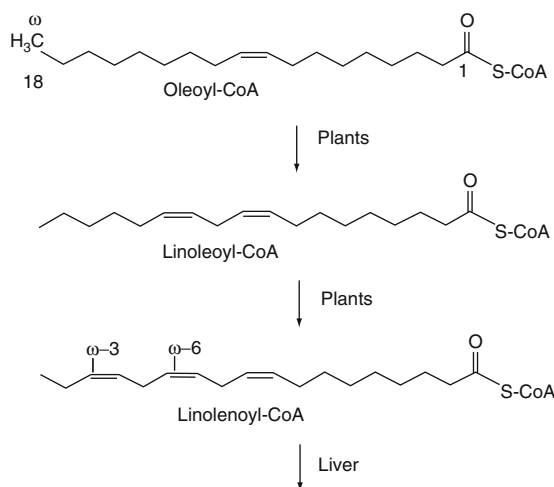


Figure 09. The ω numbering begins at the C of the methyl end; the n-3 or ω -3 indicate the double bond at the 3rd or 6th carbon from the methyl end. Chemists start the numbering (1) at the other end

Omega Sequence: This is the viral nucleotide sequence in the mRNA 5'-region of eukaryotic genes that enhances translation.

Omenn Syndrome: ►reticulosis familial histiocytic

OMIA (online Mendelian inheritance animals): This is a database for animal (excluding man and mouse) genes and hereditary diseases and disorders. (<http://omia.angis.org.au>).

Omics: Refers to genomics, transcriptomics, proteomics, etc.; the global information gathering and its tools in biology.

OMIM (online Mendelian inheritance man): This is an up-to-date catalog of autosomal dominant, autosomal recessive, X-linked and mitochondrial genes of humans available through the Internet (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>). The database provides information on relevant literature on ('morbid') genes and connections to other databases. As of May 1 2006 OMIM identified 1,871 genes in which at least one disease related mutation has been described and the number of phenotypes in these genes was 3,112 (McKusick V 2006 Annu Rev Hum Genet Genomics 7:1). By 2007 the number of entries totaled 17,370 (McKusick V 2007 Amer J Hum Genet 80:588). It is also available in book form: McKusick, Victor 1997 *Mendelian Inheritance in Man*. The Johns Hopkins University Press, Baltimore, MD. OMIM proteins are annotated at <http://www.hprd.org/>. ►BI-TOLA, ►OMIA; hereditary disease frequency: <http://www.findbase.org>.

Ommatidium (Plural ommatidia): A self-sufficient element (facet) of the compound eye of arthropods, such as *Drosophila* (see Fig. O10). E- and N-cadherins regulate the shape of the cells but the shapes are also controlled by the physical requirement to minimize surface (Hayashi T, Carthew RW 2004 Nature [Lond] 431:647). ►compound eye, ►rhabdomere, ►cadherins; Wernet MF et al Nature [Lond] 440:174.

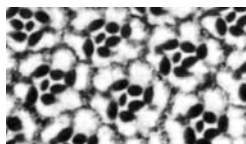


Figure O10. *Drosophila ommatidia* with eight photoreceptors inside each. There are about 800 ommatidia per eye

Ommochromes: These are insect eye pigments synthesized from tryptophan and the formation and condensation of hydroxykinurenine into xanthommatin

and complexing with other components into brown pigment granules. ►pteridines, ►w locus, ►pigmentation in animals

Omnibank (OST): A collection of 80–700-nucleotide long rapid amplification cDNA 3' ends by PCR (RACE), generated from mouse embryonic stem cells for the purpose of identification of sequence-tagged mutations. ►stem cell, ►PCR, ►RACE, ►sequenced-tagged sites; Zambrowicz BP et al 1998 Nature [Lond] 392:608.

Omnipotent: ►totipotent

Omp A: Refers to the outer membrane protein A of the bacterial cell. ►Rickettsia

OmpC, OmpF: Bacterial outer membrane proteins are regulated by kinase EnvZ in response to osmolarity (at low osmolarity by C and at high by F). OmpR is an outer membrane regulatory protein. OmpT is a serine protease which cleaves cyclin A. ►cell membrane, ►membrane proteins

Omphalocele: This refers to umbilical hernia. It is probably autosomal recessive with a prevalence of 1 to 2×10^{-4} . ►gastroschisis

OMSSA: The search engine for identifying MS/MS peptide spectra. ►mass spectrum; <http://pubchem.ncbi.nlm.nih.gov/omssa>; <http://pubchem.ncbi.nlm.nih.gov/omssa/download.htm>.

Oncocytoma: ►mitochondrial disease in humans, ►kidney diseases

Oncogene Antagonism Therapy: This therapy leads to transformation by vector constructs carrying tumor suppressor genes, dominant negative genes, suicide genes, antisense nucleotides, toxin genes that may prevent tumor formation or disable tumor cells. ►gene therapy, ►cancer gene therapy, ►suicide vectors, ►antisense technologies

Oncogene Collaboration: Some oncogenes do not transform cell cultures when applied single, e.g., rat embryo fibroblast requires the simultaneous presence of both RAS and MYC for complete transformation. ►oncogenes, ►transformation oncogenic

Oncogene-Induced Senescence: Certain oncogenes accelerate derepression of the *CDKN2a* locus by cooperation with the Polycomb group proteins. ►CDKN2, ►Polycomb; Collado M Serrano M 2006 Nature Rev Cancer 6:472.

Oncogenes: These genes of RNA viruses (v-oncogene) or similar genes in animal cells (c-oncogene) are responsible for the initiation of cancer. The c-oncogenes (proto-oncogenes) perform a normal function in animal cells but may cause abnormal

proliferation by activation or amplification or promoter/enhancer fusion (translocation), mutation, deletion or inactivation. The transforming genes of DNA viruses do not have cellular counterparts and they induce tumors by interacting with tumor suppressor genes. An allelic form of an oncogene represents such a gain-of-function that favors cancerous transformation. The primary target of the majority of oncogenes is the cell cycle and they deregulate the function of genes that normally control the initiation or progression of the cell cycle. The human genome contains about 30 recessive and over 100 known oncogenes. For details see ►**ABL**, ►**AKT1**, ►**AMV**, ►**ARAF**, ►**ARG**, ►**BLYM**, ►**BMYC**, ►**CBL**, ►**DBL**, ►**ELK**, ►**EPH**, ►**ERBB**, ►**ERG**, ►**ETS**, ►**EVI**, ►**FES**, ►**FGR**, ►**FLT**, ►**FMS**, ►**FOS**, ►**GLI**, ►**HIS**, ►**HKR**, ►**HLM**, ►**HST**, ►**INT**, ►**JUN**, ►**KIT**, ►**LCA**, ►**LCK**, ►**LYT**, ►**MAS**, ►**MCF**, ►**MEL**, ►**MET**, ►**MIL**, ►**MYB**, ►**MYC**, ►**NGL**, ►**NMYC**, ►**OVC**, ►**PIM**, ►**PKS**, ►**PVT**, ►**RAF**, ►**RAS**, ►**REL**, ►**RET**, ►**RHO**, ►**RIG**, ►**ROS**, ►**SPI1**, ►**SEA**, ►**SIS**, ►**SK**, ►**SNO**, ►**SRC**, ►**TRK**, ►**VAV**, ►**YES**, ►**YUASA**. Many of the oncogenic transformations are caused by cis-activation of proto-oncogenes by non-oncogenic viruses. ►**cancer**, ►**carcinogens**, ►**retroviruses**, ►**non-productive infection**, ►**proto-oncogene**, ►**CATR1**, ►**tumor suppressor**, ►**amplification**, ►**gene fusion**, ►**protein tyrosine kinases**; Kung HJ et al 1991 *Curr Top Microbiol Immunol* 171:1; Liu D, Wang LH 1994 *J Biomed Sci* 1:65; Dua K et al 2001 *Proteomics* 1:1191; <http://cgap.nci.nih.gov/>; <http://oncodb.hcc.ibms.sinica.edu.tw>.

Oncogenic Transformation: This refers to the development of a cancerous state. It may begin by the loss or suppression of tumor suppressor genes. ►**oncogenes**, ►**oncoproteins**, ►**oncogenic viruses**; Di Croce L et al 2002 *Science* 295:1079.

Oncogenic Viruses: These can integrate into mammalian cells and rather than destroying the host, they can induce cancerous proliferation of the target tissues by inhibiting the cellular tumor suppressor genes. Oncogenic viruses may have double-stranded DNA genetic material such as adenoviruses (genome size ca. 37-kbp), Epstein-Barr virus (ca. 160-kbp), human papilloma virus (ca. 8-kbp), polyoma virus (ca. 5–6-kbp) and the single-strand RNA viruses (retroviruses, 6–9-kb). ►**adenoviruses**, ►**SV40**, ►**papilloma virus**, ►**Epstein-Barr Virus**, ►**papova viruses**, ►**hepatitis B**, ►**retroviruses**, ►**acquired immunodeficiency**, ►**tumor viruses**, ►**Kaposi sarcoma**, ►**Moloney**, ►**Kirsten**, ►**Rous sarcoma**, ►**avian**

Oncolytic Viruses: Herpes simplex-1, Newcastle disease virus, reovirus and adenovirus may selectively

replicate and destroy tumor cells without the causing disease itself. Selectively targeting tumor cells may be accomplished by fusing antibody fragments or erythropoietin or heregulin to the viral envelope protein. Erythropoietin recognizes its receptor on erythroid precursor cells. Heregulin is a nerve growth factor required specifically for breast cancer and fibrosarcoma cells. Engineering tumor-specific promoter to the viral genes may enhance tumor-specific viral gene expression. The herpes simplex (HSV) or adenovirus may directly lyse the tumor cells. Cyclophosphamide enhances glioma therapy in rats by HSV by inhibiting immune responses (Fulci G et al 2006 *Proc Natl Acad Sci USA* 103:12873). Newcastle disease virus may increase sensitivity to tumor necrosis factor (TNF). The parvovirus may promote apoptosis of the cancer cells. The viral antigens bound to cellular MHC class I proteins may become targets for cytotoxic T lymphocytes (CTL). ►**cancer gene therapy**, ►**herpes**, ►**Newcastle disease**, ►**parvovirus**, ►**reovirus**, ►**adenovirus**, ►**heregulin**, ►**TNF**, ►**apoptosis**, ►**CTL**, ►**ONYX-015**, ►**cyclophosphamide**; Wildner O 2001 *Annals Med* 33 (5):291; Smith ER et al 2000 *J Neuro-Onc* 46(3):268.

Oncomine: This is a cancer microarray database and integrated data mining platform. (See <http://www.oncomine.org/>).

Oncomouse: This is the trade name for a mouse strain prone to breast cancer and suitable for this type of research. ►**breast cancer**; Kerbel RS 1998–99 *Cancer Metastasis Rev* 17(2):301.

Onconase: This is an anti-tumor protein with ribonuclease activity to tRNA. ►**tRNA**, ►**ribonuclease**; Notomista E et al 2001 *Biochemistry* 40:9097.

Oncoprotein: A product of an oncogene which is responsible for the initiation and/or maintenance of hyperplasia and malignant cell proliferation. ►**oncogenes**

Onco-Retroviral Vectors: These are engineered from onco-retroviruses such as murine leukemia virus and Rous sarcoma virus. The viral protein genes required for disease are removed and replaced by transgenes. Infectious particles are generated through packaging cells. ►**retroviruses**, ►**viral vectors**, ►**transgene**, ►**packaging cell lines**

Oncostatin M: ►**APRF**; Radtke S et al 2002 *J Biol Chem* 277:11297.

Index: Facilitates data acquisition from linked, integrated and visualized bases by graph analysis techniques. It can handle many hundreds of thousands of data and examine their potential relationships by identifying equivalent concepts and

filtering out unattached nodes. (See <http://ondex.sourceforge.net/>).

One Gene-One Enzyme Theorem: This theorem recognizes that one gene is generally responsible for one particular biosynthetic step, mediated through an enzyme. More precisely stated is the one gene (cistron)-one polypeptide rule because some enzymatically active protein aggregates may be encoded by more than a single gene. There are some other apparent exceptions, e.g., one mutation blocking the synthesis of homoserine may also prevent the synthesis of threonine and methionine because homoserine is a common precursor of these amino acids (see Fig. O11). Further, in the branched-chain amino acid (isoleucine-valine) pathway, ketoacid decarboxylase and ketoacid transaminase enzymes control the pathways leading to both isoleucine and valine. As data on genomics accumulate it becomes increasingly evident that the one nucleotide sequence (depending on the multiple promoters and processing of the transcript) may carry out different (pleiotropic) functions. Sequencing and proteomic information of the human genome indicates that the same gene (DNA tract) is spliced in three alternate ways and this may be construed as one gene—three functions. ▶homoserine, ▶isoleucine-valine biosynthetic pathway, ▶bifunctional enzymes, ▶overlapping genes, ▶contiguous gene syndrome, ▶pleiotropy, ▶genetic network; Beadle GW 1945 *Chem Rev* 37:15; Boguski MS 1999 *Science* 286:543; Venter JC et al 2001 *Science* 291:1304; Chen J et al 2002 *J Biol Chem* 277:22053; Kondrashov FA 2005 *Nature Genet* 37:9.

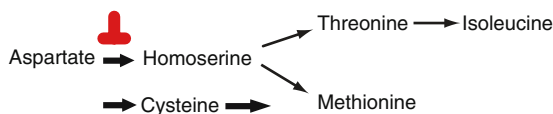


Figure O11. Block in homoserine biosynthesis generates requirements for threonine and methionine

One Gene-One Polypeptide: ▶one gene-one enzyme theorem

One-Hybrid Binding Assay: This is basically a gene fusion assay where a transcriptional activation domain is attached to a particular gene. The function of such a “hybrid” may be assessed by the expression of an easily monitored reporter gene (e.g., luciferase), depending on the signal received from the particular gene. ▶two-hybrid assay, ▶gene fusion, ▶luciferase, ▶split-hybrid system, ▶three-hybrid system; Wilhelm JE, Vale RD 1996 *Genes Cells* 1(3):317; Murakami A et al 2001 *Nucleic Acids Res* 29:3347.

One-Step Growth: Bacteriophages multiply within the bacterial cell and in one step, within less than 10 min, during the “rise” period, all the particles are released. The temperate phages may have a longer period preceding the rise after infection because the phage DNA may be integrated into the bacterial chromosome and then replicates synchronously with the bacterial genes (see Fig. O12). Upon induction the phage may switch to a lytic cycle, which begins with autonomous replication followed by liberation of the phage particles. The number of phage particles released is called the burst size. See Fig O12, ▶bacteriophages, ▶phage lifecycles; Hayes W 1965 *The Genetics of Bacteria and Their Viruses*. Wiley, New York.

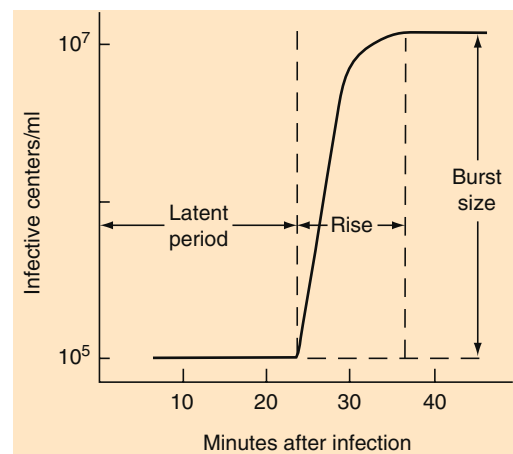


Figure O12. One-step growth

Onion (*Allium* spp.): The *Alloideae* subfamily of lilies has 600 species. *A. cepa*, $2n = 2x = 16$. Most of the North American species have $x = 8$ (see Fig. O13). Polyploid species occur in different parts of the world with somatic chromosome numbers 24, 32, 40, 48. The eye-irritating lachrymatory factor (propanal S-oxide) is generated from 1-propenyl-L-cysteine sulfoxide by the enzyme lachrymatory factor synthase. It may be possible to develop a variety of onion that retains its full flavor without the pungent characteristics [Imai S et al 2002 *Nature [Lond]* 419:685]. ▶garlic



Figure O13. *Allium* $x = 8$

One-Tailed Test: The deviation is measured in one direction of the null hypothesis.

Onozuka R-10: ►cellulase

Onset: Denotes stage (time) of expression of a genetically determined trait.

Onto Tools: Function analysis of protein-coding genes from microarray data. <http://vortex.cs.wayne.edu/Projects.html>.

Ontogeny: Describes the developmental course of an organism. ►phylogeny

Ontology, Genetic: This seeks out the function and meaning of genes and genetic elements; e.g., the gene is a functional unit that can be either a DNA or a RNA but it is not a protein or other macromolecule. ►gene ontology; <http://bcl.med.harvard.edu/proj/gopart>.

Ontos: Refers to *E. coli* computer data sets organized into object-oriented database management system.

Onyx-015: This is a genetically modified adenoviral vector which lacks E1B-55K. It was earlier believed that the absence inactivates p53 tumor suppressor protein and facilitates oncolytic viral replication and selectively destroys cancer cells. However, it now known that the loss of E1B-55K leads to the induction rather than the inactivation of p53 by selective RNA export function (O'Shea CC et al 2004 Cancer Cell 6:611). ►adenovirus, ►oncolytic viruses, ►p53; Galanis E et al 2001 Crit Rev Oncol Hematol 38 (3):177.

Oocyte Donation: This is a means to overcome infertility in women who for some reason (older age, genetic risks, etc.) do not want or cannot conceive in the normal manner but can serve as a recipient of either their own ovum obtained earlier and preserved or of an ovum from a donor. These women can thus carry to term a normal baby. From a genetic viewpoint it is important that the ovum implanted is carefully analyzed to ensure that there is no risk involved. ►artificial insemination, ►surrogate mother, ►ART, ►micromanipulation of the oocyte; Noyes N et al 2001 Fertil Steril 76:92.

Oocyte, Primary: This has the same chromosome number as other common body cells (2n, 4C) but upon meiotic division each gives rise to two haploid *secondary oocytes* (n, 2C). The smaller of the two is called the 1st polar body. By another division the egg and three polar bodies (n, 1C) are formed. The egg may become fertilized but the polar bodies do not contribute to the progeny and fade away. In human females meiosis begins in the four month old fetus and proceeds to the diakinesis (dictyotene) stage until sexual maturity. After puberty in each four-week cycle one oocyte reaches the stage of the secondary oocyte and after completing the equational phase of meiosis (meiosis II), an egg is released during

ovulation. Each of the two human ovaries contains about 200,000 primary oocytes (see Fig. O14). On an average around 400 eggs are produced during the entire fertile period of the human female, spanning a period of 30 to 40 years, i.e., beginning at puberty and terminating with the onset of menopause. Apoptosis leads to the loss of oocytes. The exhaustion of oocytes nutrients and the inability to generate NADPH may be contributing factors. It has been observed that pentose-phosphate-mediated inhibition of cell death is due to inhibitory phosphorylation of caspase 2 by calcium-dependent protein kinase II (Nutt LK et al 2005 Cell 123:89). In vitro differentiation of oocytes from embryonic stem cells can be studied experimentally. According to some reports, bone marrow and peripheral blood stem cells can repopulate the ovaries and can reinitiate the ovulation of oocytes after the loss of this capacity due to radiation injury or disease (Johnson J et al 2005 Cell 122:303). These findings have significance for post-menopausal women or those who suffered from cured ovarian cancer. A recent study did not confirm these observations and concluded that parabiosis, allowing efficient circulation of humoral and cellular factors, did not contribute to ovulated oocytes in mice but only to previously committed blood cells (Eggen K et al 2006 Nature [Lond] 441:1109).

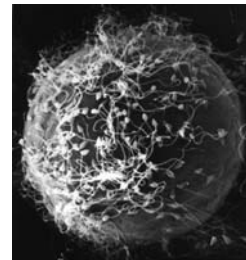


Figure O14. Human oocyte with about 1,500 spermatozoa (Courtesy of Dr. Mia Tegner)

In the human metaphase II oocytes, compared with reference samples from other tissues, 5,331 transcripts were significantly upregulated and 7,074 transcripts significantly down regulated. Of the oocyte upregulated probe sets, 1,430 had unknown function. A core group of 66 transcripts was identified by intersecting significantly upregulated genes of the human oocyte with those from the mouse oocyte and from human and mouse embryonic stem cells. GeneChip array results were validated using RT-PCR in a selected set of oocyte-specific genes. Within the upregulated probe sets, the top overrepresented categories were related to RNA and protein metabolism, followed by DNA metabolism and chromatin modification (Kocabas AM et al 2006 Proc Natl Acad Sci USA 103:14027).

Mouse embryonic stem cells in culture can develop into oögonia that enter meiosis, recruit adjacent cells to form follicle-like structures, and later develop into blastocysts (Hübner K et al 2003 Science 300:1251). Stem cells isolated from the skin of porcine fetuses have the intrinsic ability to differentiate into oocyte-like cells. When differentiation was induced, a subpopulation of these cells expressed markers such as Oct4, growth differentiation factor 9b (GDF9b), the Deleted in Azoospermia-like (*DAZL*) gene and Vasa (a germ line-specific protein) — all consistent with germ cell formation. On further differentiation, these cells formed follicle-like aggregates that secreted estradiol and progesterone and responded to gonadotropin stimulation. Some of these aggregates extruded large oocyte-like cells that expressed oocyte markers, such as zona pellucida, and the meiosis marker, synaptonemal complex protein 3 (SCP3). Some of these oocyte-like cells spontaneously developed into parthenogenetic embryo-like structures (Dyce PW et al 2006 Nature Cell Biol 8:384). These developments may eventually obviate the need for embryonic stem cells in therapeutic cloning. ▶egg, ▶spermatocyte, ▶meiosis, ▶C amount of DNA, ▶menopause, ▶gametogenesis, ▶*Xenopus* oocyte culture, ▶oögonium, ▶oospore, ▶oocyte translation system, ▶nurse cell, ▶fertilization, ▶spermatozoon, ▶stem cells, ▶NADP, ▶protein kinase, ▶caspase, ▶parabiosis, ▶azoospermia, ▶therapeutic cloning; Johnstone O Lasko P 2001 Annu Rev Genet 35:365.

0

Oocyte, Secondary: ▶oocyte primary

Oocyte Translation System: mRNAs injected into the amphibian oocyte (*Xenopus*) nucleus (germinal vesicle) may be transcribed, and in the cytoplasm these exogenous messengers are translated, the proteins may be correctly processed, assembled, glycosylated, phosphorylated, and delivered (targeted) to the proper location, etc. Similarly, injections of foreign DNA into the fertilized embryos may be replicated and inserted into the chromosomes. ▶translation in vitro; Skerrett IM et al 2001 Methods Mol Biol 154:225.

Oogamy: Refers to the fertilization of a (generally) larger egg with a (smaller) sperm. ▶oocyte.

Oögenesis: Refers to the formation of the egg. Meiosis in the mammalian oocyte begins much before fertilization but it is arrested at late prophase (dictyotene stage). The G_s protein-linked receptor (GPR3) maintains the pause (Mehlmann LM et al 2004 Science 306:1947). Shortly before ovulation meiosis is resumed. In vertebrates, the luteinizing hormone of the pituitary acts on the surrounding somatic cells and the continuation of meiosis is

mediated by CDK1. ▶gametogenesis, ▶dictyotene stage, ▶ G_s protein, ▶luteinizing hormone, ▶CDK1; Navarro C et al 2001 Curr Biol 11:R162; Matzuk MM et al 2002 Science 296:2178; Schmitt A, Nebreda AR 2002 J Cell Sci 115:2457.

Oögonium: This is the female sex organ of fungi fertilized by the male gametes. It is also called a zygote.

Oögonium in Animals: Refers to the primordial female germ cell that is enclosed in a follicle by the term of birth of the individual and becomes the oocyte. ▶gametangium, ▶gametogenesis

Ookinete: This is the protozoan zygote at a motile stage within the malaria host mosquito.

Oophorectomy: The surgical removal of the ovary is also known ovariectomy, neutering, or spaying. ▶castration

Ooplasm: This is an egg cytoplasm. The transfer of 5–15% of ooplasm from a donor may facilitate pregnancy in certain cases of in vitro fertilization. The transfer involves mitochondria and mRNA. ▶ART; Brenner CA et al 2000 FertilSteril 74:573.

Oospore: A fertilized egg in (fungi) which is either dikaryotic or diploid and is frequently covered by a thick wall (see Fig. O15). ▶oögonium



Figure O15. Oospore

Oözing: The binding of a protein at one site facilitates the adjacent binding of additional proteins until the resulting multimeric protein complex extends to the site of transcription initiation (Talbert PB, Henikoff S 2006 Nature Rev Genet 7:793).

Opal: This is the chain-terminator codon (UGA). ▶code genetic

Opaque (o): Refers to genes in maize (several loci); *o-2* in particular attracted attention because its presence reduces the levels of prolamins and zein type proteins and increases the lysine content of the kernels. This improves the nutritional value significantly which is of concern to people in some parts of the world where corn is the main staple food. ▶floury, ▶kwashiorkor

Open-Label Trial: In contrast to the double-blind tests both subjects and experimenters are aware of the prospective medicine tested and the dose used.
▶ [double-blind trial](#)

Open Promoter Complex: Refers to a partially unwound promoter (the DNA strands separated) to facilitate the operation of the RNA polymerase. This separation is thought to be the result of the attachment of the transcriptase to the promoter. The TATA box of the promoter is a logical place for the attachment of the pol enzyme because there are only two hydrogen bonds between A and T in contrast to the three bonds between G and C and thus the separation of the double helix is easier. This is followed by initiation of transcription. After the attachment of the RNA elongation proteins, the σ subunit of the bacterial pol enzyme is evicted and transcription proceeds. Transcription factor TFIIB has a 7-bp recognition element immediately upstream of the TATA box and TFIIB and TBP are required for the formation of the preinitiation complex for RNA polymerase II. Several protein elements are important for forming an open complex. ▶ [closed promoter complex](#), ▶ [promoter melting](#), ▶ [PIC](#), ▶ [pol](#), ▶ [Pribnow box](#), ▶ [Hogness box](#), ▶ [TBP](#), ▶ [TAF](#), ▶ [transcription factors](#), ▶ [RAD25](#), ▶ [regulation of gene activity](#), ▶ [nucleosome](#), ▶ [reinitiation](#), ▶ [PSE](#), ▶ [IHF](#), ▶ [FIS](#), ▶ [CAP](#); Uptain SM et al 1997 Annu Rev Biochem 66:117; Ranish JA et al 1999 Genes Dev 13:49; Davis C A et al 2005 Proc Natl Acad Sci USA 102:285.

Open Reading Frame (ORF): This is a nucleotide sequence between an initiation and a terminator codon. In higher organisms one of the two DNA strands is usually transcribed into functional products although there are open reading frames in both strands. ▶ [initiation codon](#), ▶ [nonsense codon](#), ▶ [coding sequence](#), human and mouse ORF database: <http://orf.invitrogen.com/>.

Open System: This system exchanges material and energy within its environment.

Operand: Refers to what is supposed to be operated (worked) on.

Operational Concepts: These concepts were frequently used in genetics for providing an explanation when the underlying mechanism was not fully understood but from the manifest behavior a conceptualization was possible in agreement with what was known. For example: T.H. Morgan defined the gene as the unit of function, mutation and recombination before the nature of the genetic material was discovered. F.H.C. Crick concluded on the basis of frameshift mutagenesis—before the genetic code was experimentally determined—that the genetic code probably used nucleotide triplets.

Operational RNA Code: This is a sequence/structure-dependent aminoacylation of RNA oligonucleotides that are devoid of an anticodon. The specificity and efficiency is determined by a few nucleotides near the amino acid acceptor arm. ▶ [aminoacylation](#), ▶ [aminoacyl-tRNA synthetase](#), ▶ [transfer RNA](#), ▶ [mini-helix of tRNA](#); Schimmel P et al 1993 Proc Natl Acad Sci USA 90:8763; de Pouplana LR, Schimmel P 2001 J Biol Chem 276:6881.

Operational Taxonomic Unit (OTU): ▶ [character matrix](#)

Operator: This is the recognition site of the regulatory protein in an operon or possibly in other systems such as suggested for controlling elements (transposable elements) of maize. ▶ [transposable elements](#), ▶ [operon](#), ▶ [Lac operon](#), ▶ [Ara operon](#)

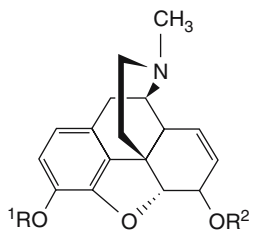
Operon: This is a functionally coordinated group of genes producing polycistronic transcripts (co-transcription). Operons have been discovered in prokaryotes but are exceptional in eukaryotes. Similar organization occurs in the homeotic gene complexes of eukaryotic organisms, such as *ANTP-C* and *BX-C* of *Drosophila*. Many genes of the nematode (ca. 15%), *Caenorhabditis* seem to be coordinately regulated and transcribed into polycistronic RNA that is processed into monocistronic mRNA by transsplicing (Blumenthal T et al 2002 Nature [Lond] 417:851). ▶ [Lac operon](#), ▶ [Arabinoase operon](#), ▶ [Tryptophan operon](#), ▶ [His operon](#), ▶ [dual-gene operons](#), ▶ [supraoperon](#), ▶ [morphogenesis in Drosophila](#), ▶ [homeotic genes](#), ▶ [coordinate regulation](#), ▶ [überoperon](#), ▶ [transsplicing](#), ▶ [SL1](#), ▶ [SL2](#); Hodgman TC 2000 Bioinformatics 16:10; Blumenthal T, Seggerson Gleason K 2003 Nature Rev Genet 4:119; Ben-Shahar Y et al 2007 Proc Natl Acad Sci USA 104:222; <http://regulondb.ccg.unam.mx:80/index.html>; operon database: <http://odb.kuicr.kyoto-u.ac.jp/>.

Operon, Selfish: Clustered genes are more likely to be transmitted as a group. This is a selfish evolutionary feature because the clustering itself may not have any physiological benefit for the host, except the joint transmission. ▶ [lateral transmission](#); Lawrence JG, Roth JR 1996 Genetics 143:1843; Lawrence J 1999 Curr Opin Genet Dev 9:642.

Ophthalmoplegia: Autosomal dominant phenotypes (incidence $\sim 1 \times 10^{-5}$, encoded at 10q23.3-q24.3, 3p14.1-p21.2, 4q34-q35) involve defects in moving the eyes and the head as well as some other variable symptoms. The 4q locus encodes a tissue-specific adenine nucleotide (ADP/ATP) translocator (ANT) and also controls mtDNA integrity. The autosomal recessive ophthalmoplegic sphingomyelin lipidosis appears to be allelic to the Niemann–Pick syndrome gene and it is associated with mitochondrial DNA

mutations. ▶mitochondrial diseases in humans, ▶neurogastrointestinal encephalomyopathy, ▶Kearns–Sayre syndrome, ▶Niemann–Pick syndrome, ▶eye disease, ▶myopathy, ▶inclusion body myopathy, ▶horizontal gaze palsy

Opiate: An opium-like substance which regulates pain perception and pain signaling pathways and mood (see Fig. O16). *Endogenous opiates*, enkephalins and endorphins, were isolated from the brain and the pituitary gland, respectively. They contain a common 4-amino acid sequence and bind to the same cell surface receptors as morphine (and similar alkaloids). Nociceptins (orphanin) are 17 amino acid antagonists of the opioid receptor-like receptor. Opioids are opiate-like, but they are not derived from opium. Nocistatin with an evolutionarily conserved C-terminal hexapeptide blocks pain transmission in mammals. Opioids activate the expression of FAS which upon binding its ligand (FasL) promotes apoptosis of lymphocytes and thereby the immune system. Opioids may affect the immune system by suppressing cytokine synthesis. Opioids modulate stress responses, learning and memory, metabolism, and may lead to addiction, etc. A region of chromosome 14q with a non-parametric lod 3.3 is responsible for opioid addiction (Lachman HM et al 2007 Human Mol Genet 16:1327). The major types of opiates are plant alkaloids. ▶enkephalin, ▶endorphin, ▶dynorphin, ▶morphine, ▶FAS, ▶apoptosis, ▶immune system, ▶cytokines, ▶nociceptor; formula after Massotte D, Kieffer BL 1998 Essays Biochem 33:65.



Morphine: $R^1 = R^2 = H$
 Codeine: $R^1 = CH_3$, $R^2 = H$
 Heroin: $R^1 = R^2 = CH_3 - CO$

Figure O16. Opiates

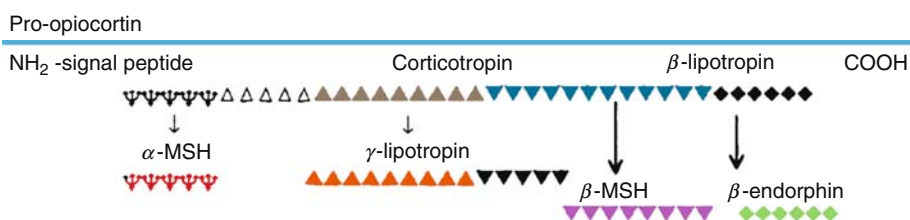


Figure O17. Pro-opiocortin

Opines: These are synthesized in crown-gall tumors of dicotyledonous plants under the direction of agrobacterial plasmid genes. The bacteria use these opines as carbon and nitrogen sources. The octopine family of opines comprises octopine, lysopine, histopine, methiopine and octopinic acid. The nopaline group includes nopaline and nopalinic acid. Agropines are agropine, agropinic acid, mannopine, mannopinic acid and agrocinosines. ▶*Agrobacteria*, ▶T-DNA octopine, ▶nopaline; Petit A et al 1970 Physiol Vég 8:205.

Opiocortin: This is a prohormone (pro-opiocortin) translated as a precursor of several corticoid hormones and cut by proteases and processed into corticotropin, β -lipotropin, γ -lipotropin, α -MSH (melanin-stimulating hormone), β -MSH and β -endorphin as shown here (see Fig. O17) ▶animal hormones, ▶POMC, ▶individual peptide hormones under separate entries, ▶pigmentation of animals; Lowry PJ 1984 Biosci Rep 4(6):467; De Wied D, Jolles J 1982 Physiol Rev 62:976; Challis BG et al 2002 Hum Mol Genet 11:1997.

Opisthotonus: A motor protein (myosin) dysfunction resulting in spasms and backward pulling of the head and heels while the body seems to move forward. ▶Usher syndrome

Opitz Syndrome (G syndrome, BBB syndrome, 22q11.2): An apparently autosomal dominant anomaly with complex features such as hypertelorism (the distance between paired organs is abnormally increased), defects in the esophagus (the passageway from the throat to the stomach), hypospadias (the urinary channel opens in the underside of the penis in the vicinity of the scrotum), etc. In an autosomal recessive form it is characterized by polydactyly, heart anomaly, triangular head, failure of the testes to descend into the scrotum and suspected deficiency of the mineralocorticoid receptor. An Xp22 gene encodes the 667-amino acid Mid1 (midline) Ring finger protein and its mutant forms may interfere with microtubule function. ▶corticosteroid, ▶head/face/brain defects, ▶Opitz-Kaveggia syndrome; Liu J et al 2001 Proc Natl Acad Sci USA 98:6650.

Opitz-Kaveggia Syndrome: This is a Xp22-linked phenotype characterized by a large head, short stature, imperforate anus, heart defect, muscle weakness, defect in the white matter of the brain (corpus callosum) and mental retardation. A recent report noted that *MED12* (Xq13) encodes a subunit of the macromolecular complex of Mediator, which is required for thyroid hormone-dependent activation and repression of transcription by RNA polymerase II. The MED12 protein is not part of the Mediator core complex but is a member of a Mediator module that may act as an adaptor for specific transcription factors and a defect in it leads to the syndrome (Risheg H et al 2007 Nature Genet 39:451). ▶stature in humans, ▶heart disease, ▶mental retardation, ▶head/face/brain defects, ▶Opitz syndrome

Opossum (Metatherians/Marsupials): *Caluromys derbianus* 2n = 14, *Chironectes panamensis* 2n = 22, *Monodelphis domestica* 2n = 18. The latter is a South American species, closely related to the North American Virginia opossum. A draft sequence of its genome is available which contains 3,475 Mb comprising about 18,000 to 20,000 protein-coding genes. The autosomes of opossum are extremely large whereas the X chromosome is much smaller than in most eutherians. The average rate of autosomal recombination is lower ($0.2\text{--}0.3\text{ cM Mb}^{-1}$) compared to other amniotes ($0.5\text{--}3\text{ cM Mb}^{-1}$) but in the X chromosome it is larger than in the autosomes. The G + C content is about 2% lower than in other amniotes. Segmental duplications are much shorter and lower in frequency than the sequenced amniotes and shorter sequences separate them. The stability of the genome is greater. Conserved non-coding elements in opossum evolved from transposons. The eutherian protein-coding sequences are largely conserved in this species (Mikkelsen TS et al 2007 Nature [Lond] 447:167; Goodstadt L et al 2007 Genome Res 17:969; Belov K et al 2007 Genome Res 17:982; Gentles AJ et al 2007 Genome Res 17:992).

Opsins: These are photoreceptor proteins of the retina but non-visual photoinduction opsin is found in the pineal gland. The chromophore of opsins is either 11-cis-retinal or 3-dehydroretinal. Red-green color vision depends on these molecules. The red- and green-sensitive pigments differ mainly in amino acids at sites 180, 277 and 28 respectively. In red sensitives alanine and phenylalanine, and in green sensitives serine, tyrosine and threonine, respectively are most common. In hominids and Old World monkeys two X chromosomal genes encode these pigments. In all mammals (with the exception of the New World monkeys) there is only one locus encoding either red or green opsins. In humans, additional sites have minor effects. In pigeons five retinal opsin genes have

been distinguished. ▶pineal gland, ▶rhodopsin, ▶retinoic acid, ▶color vision, ▶color blindness, ▶navigation; Yokoyama S, Radlwimmer FB 1999 Genetics 153:919.

Opsonins: These trigger phagocytosis by the scavenger macrophages and neutrophils. These substances bind to antigens associated with immunoglobulins IgG and IgM and facilitate the recognition of the antigen-antibody complexes by the defensive scavenger cells. Also, they may bind to the activated complement of the antibody and assist in the recognition of the cell surface antigens and thus mediate their destruction. ▶antibody, ▶complement, ▶immunoglobulins, ▶macrophage, ▶neutrophil; Moghimi SM, Patel HM 1988 FEBS Lett 233:143.

Opsonization: Foreign invaders of the cells are coated by opsonins to facilitate their destruction by phagocytosis. ▶opsonin, ▶phagocytosis; Mevorach D 2000 Ann NY Acad Sci 926:226.

Optic Atrophy: This is determined either by autosomal dominant, recessive (early onset types) or X-linked or mitochondrial defects of the eye, the ear and other peripheral nerve anomalies. OPA1 gene in 28 exons encodes a dominant optic atrophy at human chromosome 3q28-q29. Its product is a 960-amino acid dynamin-like protein localized in the mitochondria. The prevalence of OPA1 is 5×10^{-4} . ▶Behr's syndrome, ▶night blindness, ▶Leber optic atrophy, ▶Kearn-Sayre syndrome, ▶Wolfram syndrome, ▶mitochondrial disease in humans, ▶myoclonic dystrophy, ▶eye diseases, ▶color blindness, ▶dynammin, ▶methylglutaconic aciduria; Pesch UEA et al 2001 Hum Mol Genet 10:1359.

Optical Density: ▶O.D.

Optical Mapping: This may be used for ordering restriction fragments of single DNA molecules. The fragments are stained by fluorochrome(s) and the restriction enzyme-generated gaps can be visualized. The contigs are assembled automatically by using the Gent algorithm. Most of the optical mapping procedures are useful only for mapping small genomes. An adaptation of these principles for the assembly of very large genomes is also available (Valuev A et al 2006 Proc Natl Acad Sci USA 103:15770). ▶physical mapping, ▶mapping genetic, ▶FISH, ▶Gent algorithm; Lin J et al 1999 Science 285:1558; Aston C et al 1999 Trends Biotechnol 17:297.

Optical Rotatory Dispersion: Denotes a variation of optical rotation by the wavelength of polarized light; it depends on the difference in refractive index between left-handed and right-handed polarized light. The rotation is measured as an angle. It is similar to circular dichroism. ▶base stacking, ▶circular dichroism

Optical Scanner: A device that generates signals from texts, diagrams, pictures, electrophoretic patterns, autoradiograms, etc. that can be then read or printed out with the assistance of a computer.

Optical Tweezer: This consists of a special laser beam linked to a microscope system. It facilitates the manipulation of cell membranes, protein folding, DNA condensation, structure of chromosomes, etc. ▶ [scanning force spectroscopy](#); Hayes JJ, Hansen JC 2002 Proc Natl Acad Sci USA 99:1752; Grier DG 2003 Nature [Lond] 424:810.

Optimon: This DNA unit avoids recombination and is preserved as such during evolution.

Opus: ▶ [copia](#)

OR: ▶ [odds ratio](#), ▶ [lod score](#)

Oral Bacterial Films: The human oral cavity and the gut may be inhabited by more than 500 different taxa. These microorganisms cause tooth decay, gingival bleeding and other health problems. ▶ [microbiome](#), ▶ [gut](#), ▶ [Helicobacter](#); Kolenbrander PE 2000 Annu Rev Microbiol 54:413; Hooper LV, Gordon J I 2001 Science 292:1115.

Oral-Facial-Digital Syndrome: ▶ [orofacial-digital syndrome](#)

Orange (*Citrus aurantium*, $2n = 18$): This is a common fruit tree. Botanically, the peel of the fruit is the pericarp, containing at the lower face the fragrant oil glands. The juice sacs are enclosed by the carpels, containing the seeds. ▶ [navel orange](#)

ORC (origin recognition complex): This six subunit complex (including Rap1 and Abf1 silencers) is required before DNA replication can begin in the eukaryotic cell. The N-terminal domain of Orc1 protein (the largest subunit) interacts with Sir1 and Sir1 mediates the recruitment of the other Sir proteins. Sir2 is a NAD-dependent histone deacetylase and Sir3 and Sir4 play structural roles. Sir3 and Sir4 interact with Rap1 and bind the N-terminal ends of histones H3 and H4 and control the epigenetic mechanism of sex determination in yeast and chromatin remodeling (Hsu H-C et al 2005 Proc Natl Acad Sci USA 102:8519). In yeast the ORC binds to the autonomously replicating sequence (ARS). During a cell cycle replication can be initiated only once but hundreds of sites of replicational origin exist. The ORC may place the nucleosomes at the DNA replication initiation site to facilitate the process. The ORC also mediates sister chromatid cohesion in yeast (Shimada K, Gasser SM 2007 Cell 128:85). In budding yeast the ORC complex and Cdc6 in the presence of a tandem array of GAL4 binding site in a plasmid is sufficient for the initiation of replication

from this artificial construct (Takeda DY et al 2005 Genes Dev 19:2827).

The replication cannot begin before the *origin of licensing* is created in the M phase with the participation of the MCM protein(s). This is followed by the *origin of activation* in the S phase. Both these steps are controlled by the ORC. Protein subunit ORC2 (Orp2 in fission yeast) apparently interacts with Cdc2, Cdc6 and Cdc18 proteins that regulate replication. The ORC is required for silencing the *HMRa* and *HMLa* loci of yeast, involved in mating type determination. The ORC homolog of *Drosophila* is DmORC2. Budding yeast genome appears to have ~429 replication origins. The replication origins in *Schizosaccharomyces pombe* are quite different from the same functional elements in budding yeast. They are mainly in intergenic regions, rich in AT (~70%) sequences (Dai J et al 2005 Proc Natl Acad Sci USA 102:337). ▶ [replication](#), ▶ [Cdc2](#), ▶ [Cdc18](#), ▶ [mating type determination in yeast](#), ▶ [HML](#), ▶ [HMR](#), ▶ [ARS](#), ▶ [MCM](#), ▶ [replication licensing factor](#), ▶ [ARS](#), ▶ [cell cycle](#), ▶ [Rap1](#), ▶ [Abf1](#), ▶ [histone deacetylase](#), ▶ [nucleosomes](#), ▶ [cohesin](#), ▶ [sister chromatid cohesion](#); Lipford JR, Bell SP 2001 Mol Cell 7:21; Vashee S et al 2001 J Biol Chem 276: 26666; Dhar SK et al 2001 J Biol Chem 276:29067; Gilbert DM 2001 Science 294:96; Wyrick JJ et al 2001 Science 294:2357; Fujita M et al 2002 J Biol Chem 277:10345.

Orchard Grass (*Dactylis glomerata*): A shade and drought-tolerant forage crop, $2n = 28$.

Orchids (*Orchideaceae*, $2n = 20, 22, 34, 40$): These are monocotyledonous tropical ornamentals.

Ord: 55-kDa chromosomal protein with a role in chromatid cohesion. ▶ [sister chromatid cohesion](#); Bickel SE et al 1998 Genetics 150:1467.

Order: A taxonomic category above *family* and below *class*, e.g., order of primates within the class of mammals.

Ordered Tetrad: The spores in the ascus represent the first and second meiotic divisions in a linear sequence such as A A a a . ▶ [tetrad analysis](#)

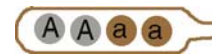


Figure O18. Ordered tetrad

Orestes: Contraction of the words open reading frames + EST (expressed sequence tags). The procedure is aimed at sequencing mid-portions of the genes in contrast to ESTs which deal with either 5' or 3' ends. ORESTES may help in the annotation of the genomes. By 2001 700,000 ORF tags were available for the definition of the human proteome. ▶ [ORF](#),

►EST, ►proteome; de Souza SJ et al 2000 Proc Natl Acad Sci USA 97:12690; Camargo AA et al 2001 Proc Natl Acad Sci USA 98:12103.

Orexin A and B (hypocretin): Appetite-boosting peptides synthesized in the lateral hypothalamus area of the brain. Their aberrant splicing (caused by insertional mutation) may lead to narcolepsy. Their G-protein coupled receptors are Hcrtr-1 and -2. Hcrtr-2 was assigned to human chromosome 17q21. Orexins also regulate the sleep-wake cycles in neurodegenerative diseases, and drug (e.g., cocaine) and food reward. ►leptin, ►obesity, ►narcolepsy; Scammell TE 2001 Curr Biol 11:R769; Petersen A et al 2005 Hum Mol Genet 14:39; Harris GC et al 2005 Nature [Lond] 437:556.

ORF: Denotes open reading frame, i.e., the nucleotide sequences between the translation initiator and the translation terminator codons, e.g., AUG →→→→→→→→ UAG. ►cORF, ►hORF, ►kORF, ►qORF, ►sORF, ►tORF, ►OST, ►Gateway cloning; Snyder M Gerstein M 2003 Science 300:248.

Orfome (ORFeome): The collection of all defined open reading frames of an organism (Harrison PM et al 2002 Nucleic Acids Res 30:1083). ►Gateway cloning

Organ: A body structure destined to a function.

Organ Culture: Refers to growing organs in vitro to gain insight into function, differentiation and development. Plant organ cultures, such as propagating roots, stem tips and embryos under axenic conditions on synthetic media are known for decades. More recently, research has focused on generating human tissues and organs as replacements in case of injury or disease. The organs generated from the patients' own tissues avoid some of the problems of graft rejection. Since 1997 the US Food and Drug Administration has approved the clinical use of cultured cartilage. Laboratory production of blood vessels, bladder, cardiovascular tissues and even kidneys and livers is expected. Usually, researchers employ biodegradable polymer scaffolds (polyglycolic acid, polylactide) to permit the development of thicker cell layers permeable to nutrients. ►tissue culture, ►grafting in medicine, ►stem cells

Organelle: Refers to intracellular bodies, such as the nucleus, mitochondria and plastids. The division of plastids requires – among other proteins – FtsZ and DRP. The division of the mitochondria does not require an ancestral prokaryotic system but relies on DRP and other proteins. Both these organelles universally require dynamin-related guanosine triphosphatases for division (Osteryoung KW, Nunnari J 2003 Science 302:1698).

The term organelle is also used for specialized protein complexes. Earlier no bacterial organelles were detected. Recently, membrane-enclosed acidocalcisomes have been identified in *Agrobacterium tumefaciens* (Seufferheld M et al 2003 J Biol Chem 278:29971) that are similar to the acidic calcium storage compartments of some unicellular eukaryotes (trypanosomas, apicomplexan parasites, algae and slime molds). In *Arabidopsis* the number of proteins localized in different organisms was as follows: endoplasmic reticulum 182, Golgi apparatus 89, plasma membrane 92, vacuoles 24, mitochondria and plastids 140 and 162 to unknown sites (Dunkley TPJ et al 2006 Proc Natl Acad Sci USA 103:6518). These numbers are probably much lower than the actually figures. A map of the mouse liver reveals 10 subcellular locations of 1,404 proteins (Foster LJ et al 2006 Cell 125:187). ►nucleus, ►mitochondria, ►chloroplast, ►apicoplast, ►FtsZ, ►DRP, ►dynamin, ►*Agrobacterium*, ►*Trypanosoma*, ►slime mold, ►evolution of organelles, ►tissue-specificity; origin of organelles: Dyall SD et al 2004 Science 304:253; genomes: <http://megasun.bch.umontreal.ca/gobase/>; protein database: <http://organelledb.lsi.umich.edu/>; protein map in organelles: <http://proteome.biochem.mpg.de/ormd.htm>; mitochondrial and chloroplast genome database: <http://gobase.bcm.umontreal.ca/>.

Organelle Genetics: ►mitochondrial genetics, ►chloroplast genetics, ►sorting out, ►Golgi, ►gobase

Organelle Sequence Transfers: During evolution sequences homologous among the major organelles were transferred in the direction shown (see Fig. O19). In budding yeast mtDNA sequences may be regularly transferred to the nucleus during double-strand break repair. In the 2nd chromosome of *Arabidopsis* 135 genes appear to be of chloroplast origin. In the centromeric region of the same chromosome of one *Arabidopsis* ecotype ~618-kb appears identical to part of the mitochondrial genome (Stupar RM et al 2001 Proc Natl Acad Sci USA 98:5099). The organelle genomes (mitochondrial, plastidic) are adopted by initial symbiosis. The complete genomes of the originally free-living organisms were not retained during evolution, some were lost and others were redistributed among the organelles. Some of the genes were apparently sequestered into the organelles in order to assure a homeostatic balance in the redox potential. Approximately 18% of the nuclear protein-coding genes of *Arabidopsis* appear to be acquired from the cyanobacterial ancestors of the plastids (Martin W et al 2002 Proc Natl Acad Sci USA 99:12246). Enhanced production of reactive oxygen—by metabolic accident—may kill the sensitive cells unless the damage is readily corrected at the origin. A survey

277 genera of angiosperm plants indicated that the ribosomal protein gene, *rps10*, has been transferred from the mitochondrion to the nucleus at a very high rate during evolution and this probably still continues in plants but not in animals. The transfer of functional genes from the mitochondria to the nucleus seems to be more common in selfing or clonal plants than in outcrossing plants. It has been suggested that selfing and vegetative reproduction conserve adaptive mitochondrial – nuclear gene combinations, allowing functional transfer, whereas outcrossing prevents transfer by breaking up these combinations (Brandwain Y et al 2007 Science 315:1685).

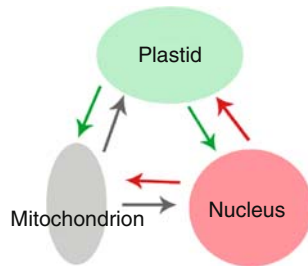


Figure O19. Organelle sequence transfer

Nuclear mutations in yeast control the escape of mitochondrial DNA into the nucleus (Thorsness PE Fox TD 1993 Genetics 134:21). The process is mediated by zinc-dependent mitochondrial protease (Weber ER et al 1996 Mol Biol Cell 7:307). There are interactions between organellar and nuclear functions without the actual transfer of genetic material (Traven A et al 2001 J Biol Chem 276:4020). Microarray hybridization revealed that in the petite strains of yeast (devoid of mitochondrial DNA), the expression of several nuclear genes (citrate synthase, lactate dehydrogenase, etc.) is altered. The petite strains exhibited increased resistance to heatshock and pleiotropic drug resistance. The rate of transfer of genes from the mitochondria to the nucleus appears to be within the range of 2×10^{-5} and from the plastid to the nucleus is about 6×10^{-5} per cell generations. The potential expression of organellar genes within the nucleus depends of the nature of the promoters. Prokaryotic type organelle promoters may not function at nuclear locations. Some of the aminoacyl-tRNA synthases (24 known) can be shared between mitochondria and chloroplasts (~15) and 5 are shared between the cytosol and mitochondria and one also present in the chloroplasts (Duchène A-M et al 2005 Proc Natl Acad Sci USA 102:16484). The phototrophic unicellular ciliate protozoan *Myrionecta rubra*/*Mesodinium rubrum* can intake chloroplasts, mitochondria and nuclei from the cryptomonad alga *Geminigera cryophila* and these organelles can

survive and function up to 30 days within the predator (Johnson MD et al 2007 Nature [Lond] 455:426). ▶mobile genetic elements, ▶chloroplasts, ▶mtDNA, ▶double-strand break, ▶nupt, ▶numts; Race HL et al 1999 Trends Genet 15:364; Adams KL et al 2000 Nature [Lond] 408:354; Blanchard JL, Lynch M 2000 Trends Genet 16:315; Hedtke B et al 1999 Plant J 19:635; Adams KL et al 2002 Plant Cell 14:931; Huang CY et al 2003 Nature [Lond] 422:72; Martin W 2003 Proc Natl Acad Sci USA 100:8612; Timmis JN et al 2004 Nature Rev Genet 5:123; <http://megasun.bch.umontreal.ca/gobase/gobase.html>.

Organelles: These are membrane-enclosed cytoplasmic bodies such as the nucleus, mitochondrion, plastid, Golgi and lysosome. See under separate entries, ▶organelle, ▶organelle sequence transfer; organelle protein database of several eukaryotes: <http://organelledb.lsi.umich.edu/>.

Organic: A carbon containing compound or something associated with a metabolic function.

Organic Evolution: Refers to the historical development of living beings in the past and present times. ▶geological time periods

Organismal Genetics: Studies inheritance in complete animals and plants by biological means and does not employ molecular methods or the tools of reversed genetics. ▶reversed genetics, ▶inter-organismal genetics

Organizer (Spemann organizer): The dorsal lip of the blastopore (an invagination that encircles the vegetal pole of the embryo) becomes a signaling center for differentiation (see Fig. O20). The formation of the organizer is preceded by induction of the mesoderm cell layer, resulting in the expression of organizer-specific homeobox genes and transcription of genes coding for signal molecules. This is followed by recruitment of the neighboring cells into the axial mesoderm and neural tissues. Several of the nuclear genes responsible for the component of the organizer have been identified by genetic and molecular means. The organization is controlled by proteins such as Wnt that determine the body axis and anterior posterior development. Activin and fibroblast growth factor (FGF) involve signal reception to organize the formation of the mesoderm or by noggin that controls dorsal/ventral differentiation. Chordin affects the development of the notochord, and follistatin is an antagonist of activin, etc. Chordin and noggin are also required for the development of the forebrain. These proteins apparently bind to and antagonize the BMP protein of vertebrates (homologous to decapentaplegic of *Drosophila*). The organizer may show some

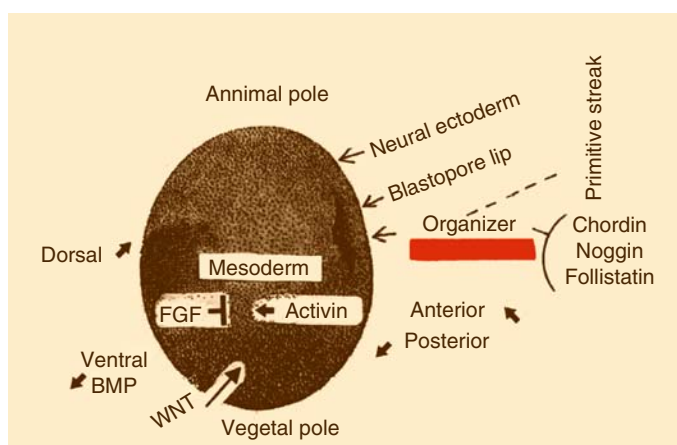


Figure O20. Organizer

additional variations in different species. It is diagrammatically not possible to represent correctly the complexity of the embryonal differentiation, which involves thousands of genes directly and indirectly. The discovery of the organizer by Hans Spemann and co-workers in the 1920s is considered a major milestone in experimental embryology and in recognition of his work Spemann was awarded the Nobel Prize in 1935. This line of research initiated a new series of inquiries in “chemical embryology” and became the focus of contemporary molecular biology. Many of the genes involved in embryonic induction, regulation of differentiation and development have now been cloned. The discovery of new techniques based on genetics, immunology, radioactive tracers, fluorochromes, microarray hybridization, scanning electron microscopy, etc., coupled with genetic transformation will provide the answer to the most basic problems of development and the nature of disease, cancer, etc. The *Gooseoid* homeobox transcription factor of the organizer promotes tumor cell malignancy and indicates that other conserved organizer genes may function similarly in metastasis of human cancer (Hartwell KA et al 2006 Proc Natl Acad Sci USA 103:18969). ▶vegetal pole, ▶animal pole, ▶morphogenesis, ▶gastrula, ▶epiblast, ▶homeobox, ▶homeotic genes, ▶signal transduction, ▶LIM, ▶BMP, ▶FGF, ▶decapentaplegic, ▶activin, ▶follistatin, ▶bone morphogenetic protein, ▶noggin, ▶pattern formation, ▶induction, ▶signal transduction, ▶primitive streak, ▶left-right asymmetry, ▶Spemann organizer, ▶self-regulation, ▶metastasis; Harland R Gerhart J 1997 Annu Rev Cell Dev Biol 13:611; De Robertis EM et al 2000 Nature Revs Genet 1:171; Shilo B-Z 2001 Cell 106:17; Lee HX et al 2006 Cell 124:147; Yu J-K et al 2007 Nature [Lond]445:613.

Organogenesis: The development of organs from cells differentiated for special purposes.

Organophosphates: These are common ingredients of insecticides and biological warfare agents such as sarin, soman and paraoxon. Their acute toxicity is due to irreversible inhibition of acetylcholinesterase, an enzyme that inactivates the neurotransmitter acetylcholine. Galanthamine (see Fig. O21), a reversible inhibitor, when administered in combination with atropin to guinea pigs provides effective protection soon after exposure to organophosphates (Albuquerque EX et al 2006 Proc Natl Acad Sci USA 103:13220). Goats transgenic for recombinant butyrylcholinesterase produced active rBChE in milk, sufficient for prophylaxis of humans at risk for exposure to organophosphate agents (Huang Y-J et al 2007 Proc Natl Acad Sci USA 104:13603). ▶acetylcholinesterase, ▶acetylcholine, ▶sarin, ▶insecticide resistance

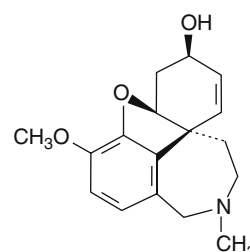


Figure O21. Galanthamine

ori: Refers to origin of replication. ▶DNA replication, ▶replication, ▶plasmid ori_T, ▶ori_V

oriC: This gene controls the origin of replication in *E. coli* and binds the replication proteins DnaA and

DnaB. ►DNA replication in prokaryotes, ►DnaA, ►DnaB; Margulies C, Kaguni JM 1996 J Biol Chem 271:17035.

Orientation, Magnetic: Determines the light-dependent migration of birds during autumn and spring. Photon absorption leads to the formation of radical pairs and the avian compass responds to the intensity of light. However, the fixed direction in migratory orientation depends on another mechanism (Wiltschko R et al 2005 Current Biol 15:1518)

Orientation Selectivity: The majority of transposases work well only in one orientation. Accessory proteins associated with the transposases choose this orientation. It is synonymous with the directionality of transposons. ►transposable elements, ►transposons

Origin of Life: The prebiotic evolution laid down the foundations for the origin of life ►evolution prebiotic, ►evolution of the genetic code. The following steps may have been involved in this process: 1. generation of organic molecules, 2. polymerization of RNA, capable of self-replication and heterocatalysis (cf. ribozymes), 3. peptide synthesis with the assistance of RNA, 4. the evolution of translation and polypeptide assisted replication and transcription, 5. reverse transcription of RNA into DNA, 6. the development of DNA-RNA-Protein auto- and heterocatalytic systems, 7. the sequestration of this complex into organic micellae formed by fatty acid - protein membrane-like structures, 8. the appearance of the first cellular organisms about 3–4 billion years ago, and 9. the development of photosynthesis and autonomous metabolism. According to some estimates, the starter functions of life may have been carried out by as few as 20–100 proteins. The extensive duplications in all genomes may be an indication that the early enzymes did not have strong substrate specificity. The minimal cellular genome size may have been comparable to that of *Mycoplasma genitalium*, 580-kb long and coding 482 genes. The time required to develop from the 100-kb genome to a primitive heterotroph cyanobacterium with 7,000 genes may have taken about 7 million years. Life originated on earth about 3.2 billion years ago (Nofke N et al 2006 Geology 34:253). ►spontaneous generation unique or repeated, ►exobiology, ►geological time periods, ►evolution of the genetic code; Nisbet EG, Sleep NH 2001 Nature [Lond] 409:1083; Rotschild LJ, Mancinelli RL 2001 ibid:1092; Carroll SB 2001 ibid. 1102; Hanczyc MM et al 2003 Science 302:618.

Origin of Replication: This is the starting point of replication during cell proliferation. ►replication

Origin of Species: This is the title of a book by Charles Darwin, first published in 1859. The book is one of the most influential works on human cultural history. Darwin recognized the role of natural selection in evolution. Although he did not understand the principles of heredity (this book was published 7 years prior to the paper of Mendel). With the development of modern concepts of heredity, cytogenetics, population genetics and molecular biology, the seminal role of this book became generally recognized and appreciated even from a sesquicentennial distance. ►Darwinism, ►evolution

Origin Recognition Element (ORE): This is the DNA site where proteins that initiate replication bind. ►replication fork

Origins: These are the processors of environmental perturbations in transcriptional networks. Origins are sub-networks originating in a single transcription regulatory network. A pleiotropic regulator controls all nodes in *modulons*. *Simulons* include all nodes affected by an environmental signal and are composed of all origins rooted in transcription factors sensitive to the signal. ►networks, ►genetic networks, ►modulon; Balázs G et al 2005 Proc Natl Acad Sci USA 102:7841.

ori_T: This refers to the origin of transfer of the bacterial plasmid. Its A=T content is higher than the surrounding DNA. It has recognition sites for a number of conjugation proteins. It contains promoters for the *tra* genes that are localized in such a way that only after the complete transfer of the plasmid can all of them be transferred. The transfer of the single strand proceeds in 5'→3' direction in all known cases, including the transfer of T-DNA to plant chromosomes. The 3' end can accept added nucleotides. After the transfer has terminated, the plasmid re-circularizes. All these processes require specific proteins. ►bom, ►conjugation, ►T-DNA

Ori_v: Refers to the origin of vegetative replication that is used during cell proliferation of bacteria.

Ornithine (NH₂[CH₂]₃CH[NH₂]COOH): A non-essential amino acid for mammals. It is synthesized through the urea cycle. ►urea cycle

Ornithine Aminotransferase Deficiency (hyperornithinemia, OAT): Ornithine is derived either from arginine or *N*-acetyl glutamic semialdehyde or glutamic semialdehyde, and carbamoylphosphate synthetase converts it to citrulline. The decarboxylation of ornithine (a pyridoxalphosphate [vitamin B₆] requiring reaction) yields polyamines such as spermine and spermidine. OAT deficiency causes ornithinemia, 10–20 times increase of ornithine in blood plasma, urine and other body fluids. It also leads to

the degeneration of eye tissue and tunnel vision and night blindness by late childhood. Restricted ornithine diet may prevent eye defects due to deficiency of the γ -chain. The OAT locus (21-kb, 11 exons) is in human chromosome 10q23qter and its mutation blocks the metabolic path between pyrroline-5-carboxylate and ornithine. Pseudogenes are at Xp11.3-p11.23 and at Xp11.22-p11.21. ▶amino acid metabolism, ▶urea cycle, ▶ornithine transcarbamylase deficiency, ▶ornithine decarboxylase, ▶ornithine transcarbamylase deficiency, ▶pseudogene, ▶hyperornithinemia, ▶nicotine

Ornithine Decarboxylase (ODC): The dominant allele (human chromosome 2p25, mouse chromosome 12, in *E. coli* 63 min) controls the ornithine→putrescine reaction and its activity is very sensitive to hormone levels. There is a second ODC locus in human chromosome 7 but the latter has a reduced function. Elevated levels of ODC may be indicative of skin tumorigenesis. ▶amino acid metabolism, ▶ornithine aminotransferase deficiency, ▶antizyme

Ornithine Transcarbamylase Deficiency (OTC): This X-linked (Xp21.1) enzyme normally expressed primarily in the liver mitochondria, catalyzes the transfer of a carbamoyl group from carbamoyl phosphate to citrulline and ornithine is made while inorganic phosphate is released (see Fig. O22). The defect may lead to an accumulation of ammonia (hyperammonemia) because carbamoyl phosphate is generated from NH_4^{4+} and HCO_3^- (in the presence of 2 ATP). The high level of ammonia may cause emotional problems, irritability, lethargy, periodic vomiting, protein avoidance and other anomalies. Na-benzoate, Na-phenylacetate and arginine may mediate the plasma ammonium level. The incidence of OTC deficiency in Japan was found to be about 1.3×10^{-3} . In mice an OTC deficiency mutation is responsible for the *spf* (sparse fur) phenotype. This single gene metabolic defect may be corrected by somatic gene therapy. Unfortunately, one of the initial attempts using a very high dose of adenoviral vector (6×10^{14} particles/kg) ended in an unexpected fatal immune reaction in Jesse Gelsinger in 1999. ▶amino acid metabolism, ▶ornithine aminotransferase, ▶ornithine decarboxylase, ▶channeling, ▶hyperammonemia

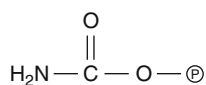


Figure O22. Carbamoyl phosphate

Ornithine Transporter: ▶urea cycle

Orofacial-Digital Syndrome (OFD): OFD I is a dominant Xp22-linked or a recessive autosomal syndrome. The

dominant form is lethal in males. OFD I is characterized by loss of hearing and polydactyly of the great toe, mental retardation, face and skull malformation, cleft palate, brachydactyly (short fingers and toes), defective kidney cysts, etc. (Ferrante MI et al 2006 Nature Genet 38:112). OFD II (Mohr syndrome) is characterized by polysyndactyly, brachydactyly [short digits] and lobate tongue. OFD III and OFD IV include mental retardation, eye defects, teeth anomalies, incomplete cleft palate, hexadactyly, hunchback features, etc. OFD IV is distinguished on the basis of tibial dysplasia (shinbone defects). OFD V (Váradí-Papp syndrome) also includes a nodule on the tongue and neural defects, etc. ▶polydactyly, ▶limb defects, ▶mental retardation, ▶Majewski syndrome; Ferrante MI et al 2001 Am J Hum Genet 58:569.

Orosomucoid: There are two orosomucoid (serum glycoprotein) genes in humans, ORM1 and ORM2 in 9q31-q32. (See Yuasa I et al 2001 J Hum Genet 46(10):572).

Orotic Acid:

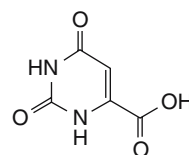


Figure O23. Orotic acid monohydrate

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Oroticaciduria: This is a recessive deficiency of the enzyme orotidylate decarboxylase, encoded at human chromosome 3q13 or a deficiency of orotate phosphoribosyl transferase. Rare human diseases have their counterparts in other higher eukaryotes. The clinical symptoms include anemia with large immature erythrocytes and urinary excretion of orotic acid (see Fig. O24). The administration of uridylate and cytidylate alleviates the symptoms. Homologous mutations have been detected in cattle. ▶orotic acid

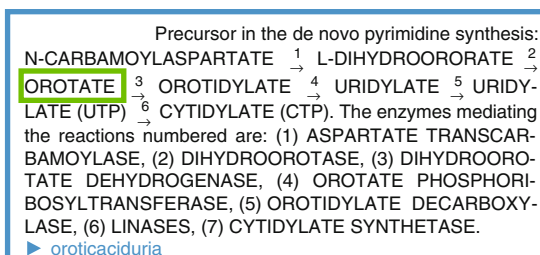


Figure O24. Orotate in the pyrimidine pathway

Orphan Genes: These are open reading frames in yeast (about 1/3 of the ORFs) that cannot be associated with known functions (FUN genes) and do not seem to have homologs in other organisms. With advancing information their number is expected to decline. ▶ORF, ▶*Saccharomyces*, ▶fun genes; Enmark E Gustafsson JA 1996 Mol Endocrinol 10:1293; Brenner S 1999 Trends Genet 15:132.

Orphan Receptor: This has either no known ligand or it has the ligand-binding domain but lacks the conserved DNA binding site. ▶nuclear receptors, ▶receptor; Xie W Evans RM 2001 J Biol Chem 276:37739.

Orphanin: ▶opiate

Orphon: This is a former member of a multigene family, but at a site separate from the cluster, and contains one coding region or they are pseudogenes. ▶gene family, ▶pseudogene

Orthogenesis: Evolution follows a straight line toward a goal or proceeds along a predetermined path rather than being influenced by Darwinian selection.

Orthogonal-Field Alternation Gel Electrophoresis: ▶OFAGE

Orthogonal Functions: These can be employed for comparisons between observed data which have not affected each other.

Orthogonal mRNAs: The suppressor tRNA is not a substrate for endogenous aminoacyl-tRNA synthetases, and the mutant aminoacyl-tRNA synthetase aminoacylates only the suppressor tRNA with an unnatural amino acid but no other tRNA. Such a system facilitates the incorporation of unnatural amino acids into peptides. ▶unnatural amino acids

Orthologous Loci: These genes are in the direct line of evolutionary descent from an ancestral locus, e.g., 1,000 genes in *Bacillus subtilis* are similar to those in *Escherichia coli*, indicating the common ancestry. Among the eukaryotes, *Saccharomyces cerevisiae* and *Caenorhabditis elegans* ~57% of the protein pairs of the two organisms are represented by just one from each of these organisms. Intermediary metabolism (in 28%), DNA and RNA synthesis and function (in 18%), protein folding and degradation (in 13%), transport and secretion (in 11%) and signal transduction (in 11%) are carried out by genes preserved through evolution from a common origin in these two eukaryotes. ▶paralogous loci, ▶duplications, ▶evolution of proteins, ▶non-orthologous gene displacement, ▶xenology, ▶homolog, ▶orthologous proteins, ▶genome projects, ▶comparative genomics, ▶constrained elements; Koonin EV 2005 Annu Rev Genet 39:309; <http://www.ncbi.nlm.nih.gov/COG>; orthologous groups of 17 eukaryotes: <http://inparanoid.cgb.ki.se/>; human-mouse orthologous miRNA gene homologies <ftp://ftp.ncbi.nih.gov/pub/HomoloGene/>; http://www.informatics.jax.org/searches/homology_form.shtml; orthologs in 9 eukaryotes: http://www.sanger.ac.uk/PostGenomics/S_pombe/YOGY/; ortholog server: <http://oxytricha.princeton.edu/BlastO/>.

Orthology: Refers to common ancestry in evolution. ▶orthologous loci, ▶paralogy

Orthostitchies: ▶phyllotaxis

Orthotopic: This means in normal position. ▶ectopic

Oscillator: This molecular mechanism generates the circadian rhythm, heart, neuronal and other cellular functions. The bursts of cell divisions oscillate between pauses and transcription of genes within the entire genome displays temporal clusters. In baker's yeast cell suspensions with billions of cells show synchronized metabolic oscillations in NADH fluorescence with a period of duration around one half minute (see Fig. O25). Acetaldehyde and glucose (if the glucose transporters are open) are oscillators. The oscillation indicates that the cells are in communication (Danø S et al 2007 Proc Natl Acad Sci USA 104:12732). ▶circadian rhythm, ▶quantized, ▶repressilator, ▶entrainment, ▶gene-switch cassette, ▶gene circuits; Goldbeter A 2002 Nature [Lond] 420:238; Klevecz RR et al 2004 Proc Natl Acad Sci USA 101:1200, Farré EM et al 2005 Current Biol 15:47; Fung E et al 2005 Nature [Lond] 435:118.

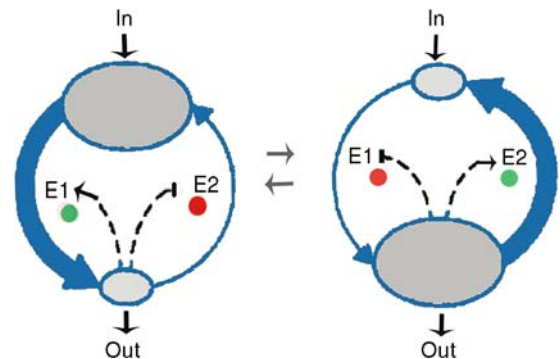


Figure O25. Schematic representation of metabolic oscillations. Enzymes E1 and E2, respectively turned on (arrow) or off (bar). The substrates and products are represented by shaded ovals

Oscillin: This is a protein formed in the egg after penetration by the sperm, and it is involved with the oscillation of the level of Ca^{2+} . It is apparently involved in triggering the early development of the embryo. (See Nakamura Y et al 2000 Genomics 68(2):179).

Osha: This is the acronym for Occupational Safety and Health Administration which is based in the USA. It provides information about and protects against potential hazards involved in laboratory and industrial operations.

Oskar (*osk*, 3–48): *Drosophila* homozygous females and males are normally viable and fertile. The embryos produced by the homozygous females lack pole plasm, the abdominal segments do not form and the embryos die (see Fig. O26). The *osk* mRNA appears in the posterior of the embryo. Kinesin I facilitates the transport of *oskar* and *Staufen* mRNAs along the microtubules and the Mago Nashi (Kataoka N et al 2001 EMBO J 20:6424) and Y14 proteins (Hachet O, Ephrussi A 2001 Curr Biol 11:1666) are involved in the splicing of the pre-mRNA (Palacios IM 2002 Curr Biol 12:R50). Translation initiation factor eIF4E-binding protein Cup interacts with silencing protein Bruno and inhibits translation. The large (50S-80S) silencing particle involving the oligomerized mRNA cannot be accessed by the ribosomes although it may be advantageous for mRNA transport (Chekuleava M et al 2006 Cell 124:521). ▶eIF-4E



Figure O26. Oskar

Osler-Rendu-Weber Syndrome: ▶telangiectasia hereditary hemorrhagic

Osmiophilic: This readily stains by osmium or osmium tetroxide.

Osmium Tetroxide (OsO_4): This is a fixative for electron microscopic specimens. ▶fixatives, ▶microscopy

Osmolarity: Refers to the osmotic pressure of a solution as the molarity of dissociated particles.

Osmosis: This is a process by which water passes through a semipermeable membrane toward another compartment (cell) where the concentration of solutes is higher. The osmo-sensing signal seems to be mediated by the Jnk protein kinase, a member of the mitogen-activated large family of proteins in mammals. In bacteria, a histidine kinase sensor (EnvZ) and a transcriptional regulator (OmpR) are involved. In yeast a similar mechanism is implicated, also involving HOG-1. ▶HOG-1, ▶histidine kinase, ▶HSP

Osmotic Pressure: In two compartments separated by a semipermeable membrane the solvent molecules pass toward the higher concentration of solutes. This

flow may be prevented by applying high pressure to the compartment toward which the flow is directed. Osmotic stress may regulate the expression of genes as a homeostatic control. (See Xiong L et al 2002 J Biol Chem 277:8588)

Osmotin: Refers to protein in plants that may accumulate at high concentrations of salts. It is a homolog of mammalian adiponectin, which regulates lipid and sugar metabolism. ▶adiponectin; Narasimhan M L et al 2005 Mol Cell 17:171.

O-Some: A nucleosome-like structure of lambda phage involved in DNA replication. It is formed from dimeric λO (lambda origin) protein-coding sequences and four inverted repeats. During the beginning of replication the dimer of λP (λ promoter) and a hexamer of DnaB forms $\text{ori}\lambda\sim\lambda\text{O}\sim(\lambda\text{P}\sim\text{DnaB})_2$ which gives rise to the pre-primosomal complex. ▶lambda phage, ▶nucleosome, ▶DNA replication prokaryotes, ▶primosome; Zyllicz M et al 1998 Proc Natl Acad Sci USA 95:15259.

OSP: ▶allele-specific probe for mutation

OSP94: ▶HSP

Ossification of the Longitudinal Filaments of the Spine:

This common disorder in humans (over 3% above the age of 50) is caused by ectopic bony development of the spinal muscles. In mice, defects in the nucleotide pyrophosphatase (*Npps*, chromosome 10), which regulates soft tissue calcification and bone mineralization by producing inorganic phosphate, seem to be a major factor.

OST: This is an open reading frame tagged by EST. ▶EST, ▶Gateway cloning

Osteoarthritis: A common human affliction involving degeneration of the cartilage, caused by the replacement of the $[\alpha 1(\text{II})]$ collagen by αII chains with reduced glycosylation. Several gene loci at 4q26, 7p15, 2q12, 11q and others are involved. More than 70% of the US population over 65 years of age may be afflicted to varying degrees. GDF5 (growth and differentiation factor) or CDMP1 (cartilage-derived morphogenetic protein 1) is a member of the transforming growth factor (TGF) superfamily and is closely related to bone morphogenetic proteins (BMPs). GDF5 is expressed in the regions of future joints during early development, and mutations in both mouse and human *GDF5* cause abnormal joint development and is a factor in the development of osteoarthritis (Myamoto Y et al 2007 Nature Genet 39:529). ▶collagen, ▶arthritis; Stefánson SE et al 2003 Am J Hum Genet 72:1448.

Osteoblast: This is a cell involved in bone production from mesenchymal progenitor and is positively

controlled in the mouse mainly by genes CBFA-1. Gene Hoxa-2 and leptin are negative regulators. Osteoblast and skeletal differentiation are mediated by Runx2 and ATF4 transcription factors, controlled by SATB2 (Dobrev G et al 2006 Cell 125: 971). ▶osteoclast, ▶ATF, ▶RUNX, ▶mesenchyma, ▶ITAM; Olsen BR et al 2000 Annu Rev Cell Dev Biol 16:191; Science 2000 Vol. 289:1501–1514.

Osteocalcin (1q25-q31, three γ -carboxyglutamic acid, 5.9 kDa): This is an abundant, non-collagen type protein in the bones dependent on Ca^{2+} . It is involved in blood coagulation. In Neanderthal relics osteocalcin residues have been found which are similar to that observed in modern humans and modern primates (Nielsen-Marsh CM et al 2005 Proc Natl Acad Sci USA 102:4409).

Osteochondromatosis (dyschondroplasia, osteochondrodysplasia): An inhomogeneous group of autosomal dominant bone and cartilage defects encoded at 8q24 and 11p11-p12 and possibly at other sites. ▶spondyloepimetaphyseal dysplasia, ▶spondyloepiphyseal dysplasia, ▶Dyggve-Melchior-Clausen dysplasia

Osteochondroplasias (osteochondrodysplasias): These cartilage disorders are caused by defects in different collagen genes. ▶collagen, ▶chondrodysplasias

Osteoclastogenesis Inhibitory Factor (OCIF): ▶osteoprotegerin

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Osteoclasts: These multinucleate cells mediate bone resorption. The osteoclast differentiation factor (ODF) receptor is TRANCE/RANK. The ITAM motif plus RANK ligand and macrophage colony stimulating factor are required for maintenance between bone formation and resorption (Koga T et al 2004 Nature [Lond] 428:758). ▶Paget disease, ▶TRANCE, ▶osteoblast, ▶bone morphogenetic protein, ▶RANK, ▶ITAM, ▶macrophage colony stimulating factor, ▶osteoporosis; Karsenty G 1999 Genes & Development 13:3037; Väänänen KH et al 2000 J Cell Sci 113:377; Motickova G et al 2001 Proc Natl Acad Sci USA 98:5798; Feder ME, Mitchell-Olds T 2003 Nature Rev Genet 4:649.

Osteogenesis Imperfecta (OI, 11q12-q13, [neonatal lethal] 17q21.3, [perinatal] 7q22.1): These are rare (prevalence 1/5,000 – 1/10,000) autosomal dominant or recessive disorders of collagen, resulting in abnormal bone formation due to mutation at numerous loci (ca. 17) that replace, e.g., a glycine residue by a cysteine. Such a substitution disrupts the Gly - X - Pro tripeptide repeats in collagen that assures the helical structure of the molecules. Type I (chromosome 17) is characterized by postnatal bone fragility, blue coloring of the eye white (sclera) and

ear problems. Type II (Vrolik type) generally involves dominant negative lethality at about birth time due to a variety of bone defects. Most of the cases are considered new dominant mutations. Type III may lead to prenatal bone deformities and the survivors are crippled. The symptoms may also include hearing loss. This may be either recessive or dominant. Type IV is characterized by a milder expression (17q21.3) of the similar symptoms than the other classes and may not prevent survival. The four types have defects in collagen genes COL1A1 or COL1A2. OI types V – VII have no mutations in collagen; the *fragilitas osseum* mutation of mouse leads to severe osteogenesis and dentinogenesis imperfecta because of deletion of sphingomyelin phosphodiesterase 3 (Aubin I et al 2005 Nature Genet 37:803). Cartilage associated protein (CRTAP) is required for prolyl 3-hydroxylation and its mutation causes OI (Morello R et al 2006 Cell 127:291). ▶collagen, ▶sphingomyelin, ▶dentinogenesis imperfecta, ▶hydrocephalus, ▶mitral prolapse, ▶connective tissue disorders, ▶dominant negative; Millington-Ward S et al 2002 Hum Mol Genet 11:2201.

Osteolysis: This group of diseases is characterized by bone resorption and osteoporosis controlled by several different loci. ▶bone diseases

Osteolysis, Familial Expansile: ▶Paget disease

Osteomalacia: ▶hypophosphatemia; Feng JQ et al 2006 Nature Genet 38:1310.

Osteonectin (5q31.3-q32): This is a glycine-rich protein involved in bone proliferation, formation of the extracellular cell matrix, repair, morphogenesis, etc.

Osteopenia: This condition is characterized by reduced bone mass. It may be due to defects in zinc transporter, ZNT5 resulting in defective maturation of osteoblasts to osteocytes (Inoue K et al 2002 Hum Mol Genet 11:1775)

Osteopetrosis: This condition is manifested in different forms and is controlled by autosomal dominant or recessive genes in humans. The recessive form at 11q13 may be due to defects in a 3-subunit osteoclast-specific proton pump encoded by ATP6i. Osteopetrosis (increased bone mass) with renal tubular acidosis is based on deficiencies in the carbonic anhydrase B or CA2 enzyme. The disease makes the calcified bones brittle. It generally involves mental retardation, visual problems, reduced growth, elevated serum acid phosphatase levels, and higher pH of the urine because of the excretion of bicarbonates and less acids in the urine. In the recessive Albers-Schönberg disease (16p13.3, 1p21), osteopetrosis causes reduction in the size of the head, deafness, blindness, increased liver size and anemia. Defects in

a colony stimulating factor (CSF) have been inferred from mouse experiments. A mild form of osteopetrosis is also known. A severe lethal form affects the fetus by the 24th week and may cause stillbirth. In mice and humans the loss of chloride ion channel (CIC-7, 16p13.3) leads to dominant osteopetrosis, i.e., Albers-Schönberg disease. ▶carbonic anhydrase, ▶osteoporosis, ▶TRANCE, ▶colony stimulating factor, ▶ion channels, ▶cathepsins; Lazner F et al 1999 Hum Mol Genet 8:1839; Kornak U et al 2001 Cell 104:205; Bénichou O et al 2001 Am J Hum Genet 69:647; Sobachi C et al 2001 Hum Mol Genet 10:1767; Lange PF et al 2006 Nature [Lond] 440:220.

Osteopoikilosis (BOS, Buschke–Ollendorf syndrome, 12q14): Refers to dominant, spotty (sclerotic) areas at the ends of bones and skin, as well as connective tissue lesions. (See Hellemans J et al 2004 Nature Genet 36:1213)

Osteopontin: This glycoprotein is produced by osteoblasts and is encoded in human chromosome 4q21–q25 at the SPP1 locus. Its expression is repressed by Hoxc-8 but Smad1 prevents Hoxc-8 from binding to the osteopontin promoter and facilitates its transcription. Osteopontin is also called Eta-1 (early T lymphocyte activation factor 1) because it is a ligand of CD44 and plays a role in cell-mediated immunity. Its deficiency severely impairs the immunity of mice to Herpes simplex virus 1 and bacterial (*Listeria monocytogenes*) infection. Osteopontin deficiency interacting with CD44 reduces the expression of IL-10. A phosphorylation-dependent interaction of Eta-1 and its integrin receptor stimulates IL-12. Osteopontin normally affects cell migration, calcification, immunity and tumor cell phenotype. Milk production in cattle is affected by six quantitative trait locus (QTL) scattered in the genome. BTA6 QTL controls the milk protein level. The osteopontin gene aids in the characterization of the neighboring QTL (Schnabel RD et al 2005 Proc Natl Acad Sci USA 102:6896). ▶osteoblast, ▶homeotic genes, ▶Smad, ▶integrin, ▶CD44, ▶L-10, ▶IL-12, ▶Herpes, ▶QTL; Agnihotri R et al 2001 J Biol Chem 276:28261.

Osteoporosis (17q21.31–q22.05, 7q22.1, 7q21.3): This condition is characterized by abnormal thinning of the bone structure because of reduced activity of the osteoblasts to manufacture bone matrix from calcium and phosphates. The frequency of fracture of the vertebrae may increase up to ~30 times in post-menopausal women. Steroids and other hormones and vitamin D can regulate this condition. The autosomal recessive juvenile form (IJO) may be caused by defects in bone formation and the symptoms may be alleviated spontaneously by adolescence or may be treated successfully with steroid hormones. Another

autosomal recessive form in infancy involves eye defects (pseudoglioma) and possibly problems of the nervous system. The collagen genes COL1A1 and COL1A2 have been implicated. An extracellular non-collagen proteoglycan (biglycan) deficiency in mice may lead to an osteoporosis-like phenotype. A vegetable rich diet may retard bone resorption. Osteoporosis is caused by bone resorption mediated through the osteoclasts. Inactivation of the cannabinoid type 1 receptors results in increased bone mass and protects ovariectomized rodents from bone loss. Also, cannabinoid receptor antagonists protect against bone loss after ovariectomy (Idris AI et al 2005 Nature Med 11:774). Osteoclasts mediating bone resorption in osteoporosis when inhibited by the antibiotic reveromycin A (see Fig. 027) caused apoptosis of these cells and thus attenuated osteoporosis (Woo J-T et al 2006 Proc Natl Acad Sci USA 103:4729). ▶aging, ▶LDL, ▶hormone-receptor elements, ▶estradiol, ▶Cbl, ▶Src, ▶collagen, ▶ABL oncogene, ▶osteoblast, ▶osteoclasts, ▶apoptosis, ▶ovariectomy, ▶TNF, ▶Paget disease

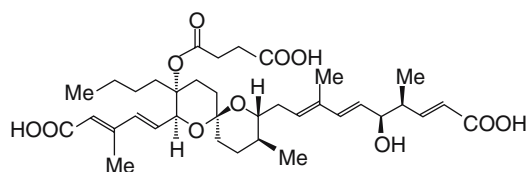


Figure 027. Reveromycin A (from Woo, JT et al 2006)

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Osteoprotegrin (osteoclastogenesis inhibitory factor, OPG/OCIF): This is a receptor of the TNF family of proteins. The ~29-kb human gene encodes an inhibitor of TRAIL and other TNF ligands. It regulates bone formation and the mutant form may lead to the early onset of osteoporosis and arterial calcification, i.e., calcium deposits in the veins. ▶TNF, ▶TRAIL, ▶osteoporosis; Bucay N et al 1998 Genes Dev 12:1260.

Osteosarcoma: This autosomal recessive, usually malignant bone tumor has an onset in early adulthood. It is normally part of a complex disease. People affected by bilateral (but not those afflicted by unilateral) retinoblastoma are at a high risk to develop bone cancer. Circulating monocytes mediate the inflammation in osteosarcoma. These cells can be used as reporters for the disease by the genetic markers carried (Patino WD et al 2005 Proc Natl Acad Sci USA 102:3423). ▶retinoblastoma, ▶sarcoma

Osteosclerosis: This condition is characterized by abnormal hardening of the bones. ▶cathepsins, ▶osteopetrosis

Ostiole (ostium): This is a small (mouth-like) opening on various structures such as fungal fruiting bodies or internal organs.

Ostrich (*Struthio camelus*): The zoological name reflects the ancient belief that this huge bird descended from a misalliance between the sparrow and the camel. It differs from other birds because it has only two toes. Also, while other birds copulate by bringing together their cloacas (the combined opening for urine, faeces and reproductive cells), the male ostrich everts a penis-like structure from the cloaca during the process.

OTC: The expanded form of this acronym is over-the-counter drug, i.e., available without prescription.

OTF-1, OTF-2: These binding proteins recognize the consensus octamer 5'-ATGCAAAT-3' and facilitate transcription in several eukaryotic genes. OTF-1 is identical to NF-3 replication factor of adenovirus. ▶[NF](#), ▶[binding proteins](#)

Otopalatodigital Syndrome (OPD): This condition involves human chromosome Xq28, semidominant, variable expression deafness, cleft palate, broad thumbs and big toes. ▶[cranioorodigital syndrome](#), ▶[deafness](#), ▶[cleft palate](#)

Otosclerosis: This is an autosomal dominant hardening of the bony labyrinth of the ear resulting in lack of mobility of the structures and thus conductive hearing defect. It may be a progressive disease starting in childhood and fully expressed in adults. The incidence of otosclerosis leading to loss of hearing is about 0.003 among US whites and among blacks its frequency is of a lower magnitude. OTSC1 is at 15q25-q26 and OTSC2 at 7q34-q36. ▶[deafness](#)

Otter: *Amblonyx cinerea*, 2n = 38; *Enhydra lutris*, 2n = 38 (see Fig. [O28](#)).



Figure O28. Otter

Otto: This is a gene predictor program based on integrated multiple evidence such as homology, EST, mRNA, and RefSeq. ▶[EST](#), ▶[mRNA](#), ▶[RefSeq](#)

OTU (operational taxonomic unit): Refers to an entity such as a particular population or a species which is used in evolutionary tree construction. ▶[evolutionary tree](#), ▶[character matrix](#)

Ötzi: ▶[ice man](#) (named after the Ötztal where the mummy was found)

Ouabain (3[6-deoxy- α -L-mannopyranosyl]oxy]1,5,11 α , 11,19-pentahydroxy-card-20(22)-enolide): A cardiotonic steroid capable of blocking potassium and sodium transport through the cell membranes; a selective agent for animal cell cultures. Ouabain regulates cell adhesion, differentiation, migration and metastasis through hormone-like action (Larre I et al 2006 Proc Natl Acad Sci USA 103:10911). ▶[steroids](#); Aizman O et al 2001 Proc Natl Acad Sci USA 98:13420.

Ouchterlony Assay: ▶[antibody detection](#)

Outbreeding: This is the opposite of inbreeding; mating is between unrelated individuals (crossbreeding, allogamy). ▶[allogamy](#), ▶[autogamy](#), ▶[inbreeding](#), ▶[protogyny](#), ▶[protandry](#)

Outbreeding Depression: Co-adapted and different subpopulations can no longer interbreed successfully because of divergence. ▶[speciation](#), ▶[co-adapted genes](#)

Outcome Space: Denotes all possible genotypic constitutions in a specific pedigree compatible with Mendelian inheritance and parental genotypes.

Outcrossing: Refers to pollination of an autogamous plant by a different individual or strain or mating between animals of different genetic constitution. ▶[protandry](#), ▶[protogyny](#), ▶[incross](#)

Outgroup: This means that at least two species can be used to distinguish an ancestral from a derived species and for the rooting of phylogenetic trees. Characters (physical or molecular) shared between the ingroup and the outgroup are considered to be ancestral. ▶[evolutionary tree](#), ▶[PAUP](#)

Outlier: Refers to a gene or genes which is/are more divergent from the typical members of a gene family than expected. These represent highly specialized function(s). In statistical treatment of data, the extreme values that appear inconsistent with the bulk of the data are called outliers. ▶[gene family](#)

Out-of-Africa: A hypothesis proposes that the origins of the human race are in Africa. The human race diverged from chimpanzee-like ancestors 4.5 million years ago according to DNA information (Takahata N, Satta Y 1977 Proc Natl Acad Sci USA 94:4811). The first human fossil records date back to ~3.6 million years and 2.5 million years ago humans were found only in Africa (Stringer C 2003 Philos Trans Roy Soc London

B 357:563). The African origin thesis is supported by mtDNA composition showing that more differences exist in this respect in Africa than other parts of the world, supposedly because a few founders (highly conserved mtDNA) emigrated, spread and evolved relatively recently into the majority of the existing human racial groups. However, insufficient number and quality of archeological and paleontological relics plague the current concepts of hominine dispersion. It is also difficult to distinguish between the various early species such as *Homo erectus* (*Pithecanthropus erectus*) and *Homo ergaster* and the many other primitive taxonomic categories (Dennell R, Roebroeks W 2005 Nature [Lond] 438:1099).

At the niche of origin longer evolutionary period permitted greater divergence. This hypothesis has been further substantiated by linkage disequilibrium between an Alu deletion at the CD4 locus in chromosome 12 and short tandem repeat polymorphisms (STRP) used as nuclear chromosomal markers. The two markers are separated by only 9.8 kb. The mapping data indicate that 1 cM of the human genome corresponds to about 800 kb. The Alu deletion was mainly associated with a single STRP in Northeast Africa and non-African populations sampled from 1,600 individuals from European, Asian, Pacific and the Amerindian groups. In contrast in the sub-Saharan Africa a wide range of STRP markers were with the Alu deletion. These data also indicate that migration from Africa took place relatively recently, i.e., an estimated 102,000 to 313,000 years

ago. This estimate is in relatively close agreement with the age of the first human fossil records in the Middle East (90,000–120,000 years old). Other information has indicated that dispersion from Africa began about 1.7 million years ago (Gabunia L et al 2000 Science 288:1019). Recent information based primarily on mitochondrial DNA evidence of the oldest isolated human populations, e.g., the Andaman people in the island between India and Burma and the Orang Asli people of Malaysia, has revealed other possible routes of migration as shown on the map (see Forster P Matsumura S 2005 Science 308:965). *Homo sapiens* diverged from *H. erectus* around 800,000 or more years ago. The European continent was settled from the Levant nearly 40,000 years ago in several waves during the paleolithic, mesolithic and neolithic eras. In 2005, Paleolithic flint artifacts dated to about 750,000 (700 kyr) years ago were found in the Suffolk area of England, indicating very old human activity in northern Europe (Parfitt SA et al 2005 Nature [Lond] 438:1008). An analysis of the mtDNA of Paleolithic central European human remains (7500 years old) revealed that mtDNA sequences that were present in 25% of the ancient populations were present in only 0.2% of the present populations (see Fig. O29). This finding suggests that the Paleolithic people made a minimal contribution to the current gene pool (Haak W et al 2005 Science 310:1016). More recent analysis of mtDNA suggests that the Levant area was populated by a migration from Southeast Asia toward the Levant and from the

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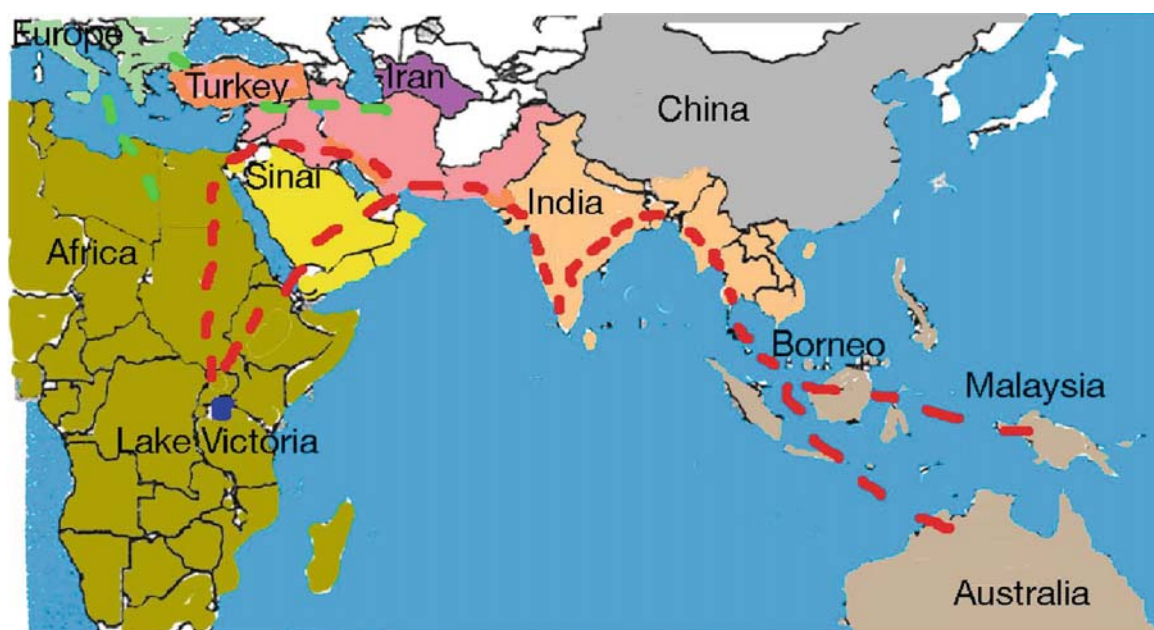


Figure O29. One of the most plausible routes (red path) of human migration from Africa about 85,000 years ago, based on mtDNA and archeological evidence. From Asia Minor and North Africa migration to Europe (green path) also took place

Levant they re-entered North Africa (Olivieri A et al 2006 Science 314:1767). Near the Don River of Russia 45,000–42,000 years old human remains were unearthed (Anikovich MV et al 2007 Science 315:223). In South Africa 36,000–33,000 years old human skulls were found (Grine FE et al 2007 Science 315:226).

The subsequent waves of migration were expected to replace the preceding ones (*replacement theory*). Some anthropologists, however, do not accept this theory of human evolution and have suggested *multiregional origin* of modern humans. An analysis of the human Y chromosome lends support not only to the African origin thesis of male descent, but also to the same general region as proposed by the Eve foremother theory in the case of females. Some genetic variations exist among the major continents and –to a smaller extent – within continents. If appropriate and sufficiently large number of loci are selected, the majority of human groups exhibit differences, especially in regions of limited migration. Even such small differences may be of significance from a medical point of view and for social policy (e.g., lactose intolerance and school lunch programs). Some of the European populations migrated to that continent from Asia as the gradient of gene flow from the Mid-East toward Northern and Western Europe decreased. Patterns of gene differences among the groups indicate population expansion and demography (Harpending HC et al 1998 Proc Natl Acad Sci USA 95:1961). The effective population sizes of males appeared to be lower than those of females indicating polygyny and elimination of males but not females during wars and conquests (Dupaloup I et al 2003 J Mol Evol 57:85). Such studies mandate appropriate case controls in stratification. ▶mtDNA, ▶Eve foremother of mitochondrial DNA, ▶Y chromosome, ▶founder principle, ▶Garden of Eden, ▶CD4, ▶Alu, ▶hominids, ▶ancient DNA, ▶demography, ▶case control, ▶stratification, ▶ethnicity, ▶radiocarbon dating; Quintana-Murci L et al 1999 Nature Genet 23:437; Harpending H Rogers A 2000 Annu Rev Genomics Hum Genet 1:3611; Barbujani G Bertorelle G 2001 Proc Natl Acad Sci USA 98:22; Adcock GJ et al 2001 Proc Natl Acad Sci USA 98:537; Templeton AR 2002 Nature [Lond] 416:45; Tishkoff SA Williams SM 2002 Nature Rev Genet 3:611; Barbujani G Goldstein DB 2004 Annu Rev Genomics Hum Genet 5:119.

Outparalog: This means evolved through ancient duplications. ▶paralogous loci, ▶inparalog

Output Trait: ▶input trait

Outside-in Signaling: ▶inside-out signaling

Ovalbumin: This is a nutritive protein of the egg white of chickens ($M_r \approx 4,500$); each molecule carries a carbohydrate chain. The gene is split by 7 introns into

8 exons and its transcription is induced by estrogen or progesterone. In the presence of the effector hormone the mRNA has a half-life of about a day but in the absence of it, its half-life may be reduced to 20%. The gene is part of a family of 3. ▶oviduct, ▶intron

Ovalocytosis: ▶elliptocytosis, ▶acanthocytosis

Ovarian Cancer: This is probably due to mutation of the OVC oncogene (9p24). In 2004 it accounted for approximately 26,000 new cases and around 16,000 deaths in the USA. The expression of several other genes is altered. The same genes affect a large variety of other cancers too. Ovarian cancer may be associated with breast cancer and may increase following the administration of tamoxifen medication. Mutation in the so-called ovarian cancer cluster region (OCCR, nucleotides 3059–4075 and 6503–6629) of the BRCA2 increases the relative risk of ovarian cancer by 0.46–0.84. Ovarian germ cell cancer involves the germ cells in the ovaries and ~5% of the cases are due to genetic causes. OPCML (opioid binding protein/cell adhesion-like molecule, encoded at 11q25) appears to be a tumor suppressor of ovarian cancer (Sellar GC et al 2003 Nature Genet 34:337). Hormone (estradiol family) replacement therapy of menopausal women may increase the risk. It has been suggested that the use of oral contraceptives may lower the risk. Apparently microarray hybridization profile provides an early diagnosis. Bombesin, somatostatin and luteinizing hormone releasing hormone coupled with 2-pyrrolinodoxorubicin can be targeted to the receptors of these substances in the ovary and may block ovarian cancer (Buchholz S et al 2006 Proc Natl Acad Sci USA 103:1043). ▶breast cancer, ▶tamoxifen, ▶sex hormones, ▶mesothelin, ▶bombesin, ▶somatostatin LRF, ▶doxorubicin; Welsh JB et al 2001 Proc Natl Acad Sci USA 98:1176; Thompson D, Easton D (Breast Cancer Linkage Consortium) 2001 Am J Hum Genet 68:410; Cannistra SA 2004 New Engl J Med 351:2519.

Ovariectomy (oophorectomy): Surgical removal of the ovary. ▶castration, ▶spaying, ▶neutering

Ovariole: ▶ovary

Ovary (ovarium): This contains the ovules of plants, the egg-producing organ of animals, and a female gonad. The ovaries of *Drosophila* contain *ovarioles*, each with 2–3 germ line stem cells at the tip and associated with the *terminal filament cells* with the duty of somatic signaling (see Fig. O30). In the *Caenorhabditis* asymmetric differentiation of the germ cell lineage is not observed rather the distal mitotic stem cells undergo meiosis through adulthood. In humans the pre-implantation development is mediated through the brain-derived neurotrophic factors (BDNF) through TrkB and some low-affinity receptors.

BDNF enhances exclusion of the first polar body and oocytes development (Kawamura K et al 2005 Proc Natl Acad Sci USA 102:9206). Ovary transplantation (in the case of developmental failure) from one monozygotic twin to the other can be successful and can lead to the restoration of fertility (Silber SJ et al 2005 N Engl J Med 353:58). ▶gonad, ▶uterus, ▶gametogenesis, ▶germarium, ▶pole cells, ▶germ line, ▶cytoblast, ▶ovary genes, ▶functions, ▶mutations, ▶TRK, ▶BDNF, ▶polar body, ▶twinning; biomedical relevance: <http://ovary.stanford.edu>.

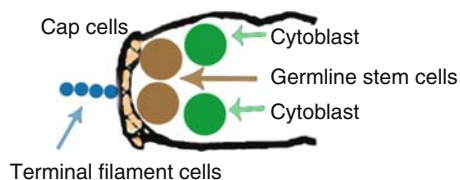


Figure O30. Ovary of *Drosophila*

OVC Oncogene: This was discovered in an ovarian cancer in a fusion of human chromosomes 8–9. ▶oncogenes

Overdispersion: The empirically observed variance of the data exceeds expectation for a certain model, e.g., the variation is not compatible with the binomial distribution or with the Poisson distribution because of the numbers of outliers encountered or specifications used. ▶binomial distribution, ▶Poisson distribution, ▶outlier

Overdominance: The *Aa* heterozygote surpasses both *AA* and *aa* homozygotes. Deleterious recessive genes may occur in heterozygotes at a higher frequency (at linkage disequilibrium) than expected because of the association with neutral genes; this is called *associative overdominance* (see Fig. O31).

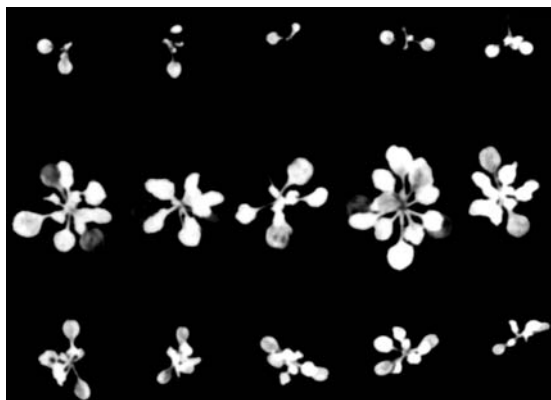


Figure O31. Allelic complementation (= overdominance) of temperature-sensitive pyrimidine mutants of *Arabidopsis*. Top and bottom rows are homozygous mutants, in the middle row: the F_1 hybrids. (From Li, S.L. & Rédei, G.P)

Pseudo-overdominance occurs when two genes are closely linked and the *aB* and *Ab* combinations simulate overdominance whereas the increased performance is actually due to dominance. Polar overdominance characterizes the non-Mendelian inheritance of the callipyge genes in sheep and cattle. Callipyge (*CLPG1*) is expressed as a muscular hypertrophy in the buttock due to a single nucleotide substitution ($A \rightarrow G$) in the heterozygotes but not in the homozygotes in the intergenic region of the imprinted genes *Delta-like (DLK1)* and the maternally *Expressed Gene 3 (MEG3)*. These two genes are at the distal end of bovine chromosome 18. The CLPG gene is expressed biallelically during the prenatal stage but only monoallelically in adults. During prenatal development CpG sites flanking the mutation is normal but postnatally it increases, except when two alleles are present. In the CLPG sheep *DLK1* expression is enhanced because of the reduction in chromatin condensation at the location. Imprinting is not affected by callipyge (Murphy SK et al 2006 Genome Res 16:3430; Takeda H et al 2006 Proc Natl Acad Sci USA 103:8119). ▶hybrid vigor, ▶superdominance, ▶heterosis, ▶overdominance and fitness, ▶polar overdominance

Overdominance and Fitness: It is assumed that in the case of overdominance the selection against the two homozygotes at a locus is 0.05. Thus, instead of the Hardy-Weinberg proportions, the population will be *AA* 95, *Aa* 200 and *aa* 95. The proportion of the surviving zygotes will be $390/400 = 0.975$. This means 2.5% reduction in the size of the population in a single reproductive phase. This may not be very serious in the case of a single locus and large populations, but in the case of 10, 100 and 500 loci it would be $0.975^{10} \cong 0.776$, $0.975^{100} \cong 0.0795$ and $0.975^{500} \cong 0.0000032$, respectively.

It is likely that such a large reduction in population size would not be tolerated. Thus, overdominance may be advantageous only at 1 or very small number of loci. ▶heterosis, ▶fitness, ▶hybrid vigor, ▶allelic complementation, ▶monogenic heterosis; Rédei GP 1982 Cereal Res Commun 10:5.

Overdrive: A consensus of 5'-TAAAPuTPyNCTGT-PuTNTGTTTTGTTTG-3' in the vicinity of the T-DNA right border of some octopine plasmids facilitating the transfer of the T-DNA into the plant chromosomes. The VirC1 protein binds this region. In the *overdrive mode* of the RNA polymerase the system does not respond to protein signals of transcription termination or pause. ▶*Agrobacterium*, ▶T-DNA, ▶virulence genes of *Agrobacterium*, ▶antitermination, ▶terminator, ▶transcription factors, ▶RNA polymerase; DeVos G Zambryski P 1989 Mol Plant-Microbe Interact 2:43.

Overepistasis: This is an archaic term for overdominance.

Overgrowth: Denotes increase of cell size and/or number in the neighboring tissues.

Overhang: A double-stranded nucleic acid has a protruding single strand end (see Fig. O32)

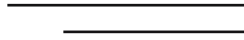


Figure O32. Single-strand overhang

Overlapping Code: This is a historical idea about how neighboring codons may share nucleotides. ▶overlapping genes; Yčas M 1969 The Biological Code. North-Holland, Amsterdam.

Overlapping Genes: These occur in the small genomes of viruses, eukaryotic mitochondria and rarely in eukaryotic nuclear genes. In *Drosophila* 3,152 (~22%), in humans more than 1,000 protein coding (~1,600) and in the mouse 2,481 protein coding and non-protein coding gene pairs appeared overlapping in either a parallel or an antiparallel fashion or in a nested arrangement (Boi S et al 2004 Curr Genomics 5:509). In human chromosome 11 one-quarter of the protein coding genes overlaps other genes (Taylor TD et al 2006 Nature [Lond] 440:497). In *Arabidopsis* 1,340 potential overlapping (cis-natural) gene sequences have been identified and evidence has been obtained for 957 cis-nat-pair transcription (Wang X-J et al 2005 Genome Biol 6(4):r30). Earlier, a multitude of sense and antisense transcripts was detected in rice (Osato N 2003 Genome Biol 5:R5). Sequences of the genetic material may be read in different registers; thus the same sequences may represent two or more genes in a complete or partial overlap because they do not need equal amounts of proteins from the overlapping genes. The means for achieving this goal is either stop codon read-through or translational frame shifting on the ribosome. The murine leukemia virus (MLV) and the feline leukemia virus (FeLV) use the first alternative. In

the HIV virus the RNA transcript makes a small loop and in the sequence 5' UUUUUUA]GGGAAGAU-LOOP-GGAU a one base slippage (framed) takes place. This allows the normally UUA recognizing tRNA^{Leu} to pair with UUA (leucine) and in place of GGG (glycine) an AGG (arginine) was inserted, and thus the stop codon was thrown out of frame which permitted the synthesis of a fusion protein (*gag* + *pol*, i.e., envelop + reverse transcriptase). This frameshift translation is generally stimulated by a pseudoknot located 5–9 nucleotides (3') from the shift site. After the translation the pseudoknot unfolds and the RNA returns to a linear shape. Such a ribosomal frameshifting occurred only in a fraction (11%) of the ribosomes but as a consequence instead of a 10–20 envelope:1 reverse transcriptase protein, the proportion changed to 8 envelope:1 reverse transcriptase (*gag* + *pol*) production. After the completion of sequencing of the genome, of the 879 nested genes found in *Drosophila* 574 were transcribed from the opposite polarity strands (Misra S et al 2002 Genome Biol 3(12):res0083). Within a ~3-Mb region of the long arm of chromosome 2 of *Drosophila* 12/17 were transcribed from the antiparallel strand. Deletions encompassing overlapping genes usually result in sterile or lethal phenotypes. In compact eukaryotes such as cryptomonads (e.g., microsporidia, *Guillardia*) single RNA molecules encode more than one gene but the phenomenon is not due to operons (Williams BAP et al 2005 Proc Natl Acad Sci USA 102:10936). ▶gene, ▶transcription, ▶frameshift, ▶decoding, ▶wobble, ▶recoding, ▶tRNA, ▶deletion, ▶knockout, ▶contiguous gene syndrome, ▶translational hopping, ▶φX174, ▶pseudoknot, ▶fuzzy logic; Pedersen AM, Jensen JL 2001 Mol Biol Evol 18:763; Besemer J et al 2001 Nucleic Acids Res 29:2607; Barrette IH et al 2001 Gene 270:181.

Overlapping Inversions: A part of one chromosomal inversion is included in another inversion (see Fig. O33). ▶inversion, ▶figure, ▶salivary gland chromosomes



Figure O33. Two overlapping inversions in a heterozygous salivary gland cell of *Drosophila*. The salivary gland chromosomes display somatic pairing. (From Dobzhansky T and Sturtevant AH 1938. Genetics 23:28)

Overlay Binding Assay: This is used to determine interactions between protein subunits (on a membrane) after labeling of the SDS-PAGE separated proteins still retaining the critical conformation. ▶[SDS-polyacrylamide gels](#); Kumar R et al 2001 J Biosci 26(3):325.

Overproduction Inhibition: A highly active promoter of a transposase may actually reduce the rate of transposition of a transposable element. ▶[transposable elements](#)

Overwinding: This generates supercoiling in the DNA. ▶[supercoil](#)

Oviduct: This is the passageway through which externally laid eggs are released (e.g., in birds), the channel through which the egg travels from the ovary to the uterus (e.g., mammals). In mammals fertilization takes place in the oviduct. ▶[ovary](#), ▶[uterus](#), ▶[ovalbumin](#), ▶[morula](#)

Ovis aries (sheep, 2n = 54): This forms a fertile hybrid with the wild mouflons but the sheep x goat (*Capra hircus*, 2n = 60) embryos rarely develop in a normal way although some hybrid animals have been produced. ▶[nuclear transplantation](#)

Ovist: ▶[preformation](#)

Ovotestis: Refers to a gonad that abnormally contains both testicular and ovarian functions. ▶[hermaphrodite](#); Sato A et al 2002 Genetics 162:1791.

Ovulation: This involves the release of the secondary oocyte from the follicle of the ovary that is eventually followed by the formation of the egg and the second polar body. Bone morphogenetic protein 15 (BMP15, Xp11.2-p11.4), a member of the TGFβ family of proteins, is expressed specifically in the oocytes and is essential for normal follicular development and ovulation. Heterozygosity for a mutation (in sheep) in the gene may lead to twinning but homozygosity for the mutation impairs follicular growth beyond the primary stage and results in female sterility. The number of oocytes released in a cycle is called the ovulation quota that varies among multiparous and monoparous species. ▶[gametogenesis](#), ▶[twinning](#), ▶[fertility](#), ▶[luteinizing hormone-releasing factor](#), ▶[multiparous](#); Richards JS et al 2002 Annu Rev Physiol 64:69.

Ovule: This is the megasporangium of plants in which a seed develops; the animal egg enclosed within the Graafian follicle. ▶[Graafian follicle](#), ▶[nucellus](#)

Ovulin: A seminal fluid protein which stimulates egg laying and the release of oocytes.

Ovum (plural ova): This is an egg(s) ready for fertilization under normal conditions.

Ox (plural oxen): Refers to a castrated male cattle. ▶[cattle](#)

Ox40: This is a member of the tumor necrosis factor receptor family. ▶[TNF](#); Rogers PR et al 2001 Immunity 15:445.

Oxalosis (hyperoxaluria): Autosomal recessive forms involve the excretion of large amounts of oxalate and/or glycolate through the urine caused either by a deficiency of 2-oxoglutarate (α-ketoglutarate): glyoxylate carboligase or a failure of alanine:glyoxylate aminotransferase or serine:pyruvate aminotransferase. The accumulated crystals may cause disease of the kidney and liver. The glycerate dehydrogenase defects also increase urinary oxalates and hydroxypyruvate. Hydroxypyruvate accumulates because the dehydrogenase does not convert it to phosphoenolpyruvate. It is also called peroxisomal alanine: glyoxylate aminotransferase deficiency (AGXT) traced to human chromosome 2q36-q37. Hyperoxaluria II (9cen) is a deficiency of glyoxylate reductase/hydroxypyruvate reductase. ▶[glycolysis](#), ▶[peroxisome](#)

oxi3: Denotes the mitochondrial DNA gene responsible for cytochrome oxidase.

Oxidation: Refers to loss of electrons from a molecule.

Oxidation–Reduction: This is a reaction transferring electrons from a donor to a recipient.

Oxidative Burst: In plants resistance to microbial infection may be mediated by the production of reactive oxygen species (ROS) such as superoxide anion (O^{•−}), OH[−], H₂O₂. The oxidative burst may induce the transcription of defense genes in the plant tissue infected by even avirulent or non-pathogenic agents. The reactive oxygen may kill the cells along with the invader and may modify the cell wall proteins, which then reinforce the barrier to the infectious microbes. Several genes encoding proteins with functional similarity to RAC, a RAS family of proteins involved in signal transduction, mediate these reactions. ▶[host–pathogen relations](#), ▶[RAC](#), ▶[ROS](#); Martinez C et al 2001 Plant Physiol 127:334; Siddiqi M et al 2001 Cytometry 46(4):243.

Oxidative Deamination: For example, O replaces a NH₂ group of cytosine (C) resulting in the conversion of C → Uracil. ▶[nitrous acid mutagenesis](#), ▶[chemical mutagens II](#)

Oxidative Decarboxylation: ▶[pyruvate decarboxylation complex](#)

Oxidative DNA Damages: These occur when ionizing radiation or oxidative compounds hit cells. The major class of damages includes the formation of thymine

glycol (isomers of 5,6-dihydroxy-5,6-dihydrothymine), 5-hydroxymethyluracil, 5,6-hydrated cytosine, 8-oxo-7,8-di-hydroguanine, 2,2-diamino-4-[(2-deoxy- β -D-erythripenofuranosyl)amino]5(2H)-oxazolone and its precursor, cross-linking between the DNA and protein, elimination of the ribose. 8-oxoguanine represents about 10^{-5} of the mammalian guanine in the DNA. A minor oxidative damage product is 2-hydroxyadenine, which can also pair with guanine. These two purines are regularly generated within the cells and cause mutation or death unless repaired by glycosylases (Ushijima Y et al 2005 Nucleic Acids Res 33:672). 8-oxoguanine can be incorporated and paired in the DNA with A and C residues. DNA polymerases λ and η with the assistance of proliferating cell nuclear antigen (PCNA) and replication protein-A (RP-A) permit the correct incorporation of dCTP (compared to the incorrect dATP) opposite an 8-oxo-G template 1,200-fold and 68-fold better, respectively (Maga G et al 2007 Nature [Lond] 447:606). If 8-oxoguanine is not repaired A \rightarrow T \rightarrow G \rightarrow C transitions or G \rightarrow C \rightarrow T = A transversions occur. The oxidative damages are usually repaired by exonucleases, endonucleases, glycosylases and other repair enzymes in prokaryotes and eukaryotes (Fromme JC et al 2004 Nature [Lond] 427:652). 8-oxoguanine-DNA glycosylase OGG1 excises 8-oxoguanine from the DNA. Defects in OGG1 have been associated with cancer in humans; enhanced mutagenesis and accelerated senescence have been observed in a mouse strain with thermolabile OGG1 (Kuznetsov NA et al 2007 J Biol Chem 282:1029). OGG1 initiates age-dependent CAG trinucleotide expansions in somatic cells resulting in Huntington's chorea (Kovtun IV et al 2007 Nature [Lond] 447:447). In mice mutation of the MMH (MutM homolog) repair enzyme results in a threefold to sevenfold increase in 8-hydroxyguanine. In prokaryotes MutY and in humans hMYH glycosylases normally remove oxoguanine from the DNA. MutY oxidation mediated by guanine radicals with the aid of charge transport of the DNA duplex is the first step in signaling to DNA repair upon oxidative damage (Yavin E et al 2005 Proc Natl Acad Sci USA 102:3546). Oxidation of mRNA leads to premature termination of the translation process and the proteolytic degradation of the modified full length polypeptide resulting from translation errors induced by oxidation (Tanaka M et al 2007 Proc Natl Acad Sci USA 104:66).

A method has been developed for the genome-wide identification of functional polymorphisms in the antioxidant response element (ARE), a *cis*-acting enhancer sequence found in the promoter region of many genes that encode antioxidant and detoxification enzymes/proteins. In response to oxidative stress, transcription factor NRF2 (nuclear factor erythroid-derived 2-like 2) binds to AREs, mediating transcriptional activation of its responsive genes and

modulating in vivo defense mechanisms against oxidative damage (Wang X et al 2007 Hum Mol Genet 16:1188). [▶DNA repair](#), [▶oxidative deamination](#), [▶ROS](#), [▶abasic site](#), [▶photosensitizer](#), [▶transition mutation](#), [▶transversion mutation](#), [▶MtODE](#), [▶MtGendo](#), [▶glycosylases](#), [▶deoxyoxoguanine](#); Nunez ME et al 2001 Biochemistry 40:12465; Kaneko T et al 2001 Mutat Res 487:19; Vance JR Wilson TE 2001 Mol Cell Biol 21:7191; Aitken RJ, Krausz C 2001 Reproduction 122(4):497; Sartori AA et al 2004 Nucleic Acids Res 32:6531; Banerjee A et al 2005 Nature [Lond] 434:612; David SS et al 2007 Nature [Lond] 447:941.

Oxidative Phosphorylation (OXPHOS): ATP is formed from ADP as electrons are transferred from NADH or FADH₂ to O₂ by a series of electron carriers. Such processes take place in the inner membrane of the mitochondria with the assistance of cytochromes as electron carriers. This is the main mechanism of ATP formation. OXPHOS minus yeast mutants are petite and fail to grow on a non-fermentable carbon source and cannot convert into a red pigment, an intermediate of the adenine (*ade*⁻) biosynthetic path. Nearly 20 different mutations in nuclear genes are now known, which control various functions of the mtDNA. Also, 82 structural subunits of mitochondrial genes are encoded in the nucleus versus the 13 coded by the mtDNA. mtDNA haplotypes from NIH3T3 and NZB/B1NJ mice induce significantly different OXPHOS performance as compared with those from C57BL/6J, BALB/cJ and CBA/J mice. In addition, a single nucleotide polymorphism (SNP) in the *mt-Tr* gene (mitochondrial tRNA^{Arg}) is the sequence variation responsible for the phenotypes observed. The differences in OXPHOS performance are masked by a specific upregulation in mitochondrial biogenesis, triggered by an increase in the generation of reactive oxygen species (ROS) in cells carrying NIH3T3 or NZB/B1NJ mtDNA (Moreno-Loshuertos R et al 2006 Nature Genet 38:1261). [▶mitochondria](#), [▶mitochondrial DNA depletion syndromes](#), [▶ATP](#), [▶NADH](#), [▶FAD](#), [▶petite colony mutants](#), [▶mitochondrial diseases in humans](#); ROS, Saraste M 1999 Science 283:1428; Shoubridge EA 2001 Hum Mol Genet 10:2277.

Oxidative Stress: Such stress is exerted by free radicals (reactive oxygen species, ROS, singlet oxygen, nitric oxide) and peroxides and hydroxyl species through the action of enzymes involved in mixed-function oxidation and auto-oxidation (P450 cytochrome complex, xanthine oxidase, phospholipase A₂). These reactions play an important role in mutagenesis, aging, mitochondrial functions, signal transduction, etc., and are thought to affect neuronal degeneration in Alzheimer's and Parkinson's diseases

and in amyotrophic lateral sclerosis. The transcription of protooncogenes may be regulated by redox systems. Glutathione and thioredoxin-dependent enzymes provide some protection. See diseases mentioned under separate entries, ►ROS, ►superoxide dismutase, ►catalase, ►redox reaction, ►glutathione, ►thioredoxins, ►peroxidase, ►Yap1, ►vitellogenin, ►FOX; Carmel-Harel O, Storz G 2000 *Annu Rev Microbiol* 54:439; Rabilloud T et al 2002 *J Biol Chem* 277:19396.

Oxidizing Agent: Refers to an acceptor of electrons.

Oxindoles: These are protein tyrosine kinase inhibitors. They inhibit the fibroblast growth factor and other receptor tyrosine kinases. For example, chemically they are 3-[4-(formylpiperazine-4-yl)benzyl-idenyl]-2-indolinone and 3-[(3-(carboxyethyl)-4-methylpyrrol-2-yl)methylene]-2-indolinone. (See Cane A et al 2000 *Biochem Biophys Res Commun* 276:379).

8-Oxodeoxyguanine: ►oxidative DNA damage, ►abasic site

Oxoguanine: ►8-oxodeoxyguanine (see Fig. O34).

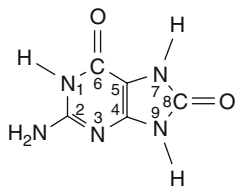


Figure O34. 8-Oxoguanine

Oxoprolinuria: ►glutathione synthetase deficiency

Oxphos (oxidative phosphorylation): A mitochondrial process by which molecular oxygen is combined with the electron carriers NADH and FADH₂ by the enzymes of the respiratory chain and mediate the ADP + P_i → ATP conversion. ►oxidative phosphorylation

Oxygen Effect: In the presence of air or oxygen the frequency of chromosomal aberrations induced by ionizing radiation increases in comparison to conditions of anoxia (lack of air in the atmosphere). Bacterial irradiation experiments have indicated that oxygen must be present before or at the radiation pulse for reducing survival but after the pulse its effect rapidly decreases. Glutathione level in the cells protects against oxygen effect. Exogenous thiols (cysteine, cysteamine, WR2721, Amifostil, [2-(3-amino propyl)aminoethyl-phosphorothioic acid])

also have a protective role. Nitroaromatic compounds (e.g., antiprotozoan metronizadol) and 5'-halogen-substituted pyrimidines (bromouracil) are sensitizers under anoxia. The higher mutability of the mtDNA relative to that of the nucleus is attributed to the presence of reactive oxygen in this organelle. The ambient atmospheric oxygen level has almost doubled during the last 205 million years (beginning in early Jurassic and Eocene periods) and has contributed to the evolution of large placental mammals (Falkowski PG et al 2005 *Science* 309:2202). Deprivation of oxygen may lead to human death within seconds. ►physical mutagens, ►radiation effects, ►mtDNA; Thoday JM, Read JM 1947 *Nature [Lond]* 160:608; Schulte-Frohlinde D 1986 *Adv Space Res* 6(11):89; Hsieh MM et al 2001 *Nucleic Acids Res* 29:3116; Ragu S et al 2007 *Proc Natl Acad Sci USA* 104:9747.

Oxygenases: ►mixed function oxidases

Oxyntic Cells: These cells secrete HCl acid in the lining of the stomach.

Oxyntomodulin: The small intestine secretes oxyntomodulin which reduces appetite and body weight; it suppresses ghrelin. ►ghrelin, ►obesity

Oxysterols: These are derivatives of cholesterol with extra hydroxyl or keto groups, usually at the 7 position on the B ring or at the 24, 25, or 27 positions on the side chain. Oxysterols are synthesized in various tissues by specific hydroxylases and play a role in the export of excess cholesterol from the brain, lung and other organs. They are intermediates in bile acid synthesis. Oxysterols are potent feedback regulators of cholesterol homeostasis despite the fact that their concentration is lower by several orders of magnitude (Rhadhakrishnan A et al 2007 *Proc Natl Acad Sci USA* 104:6511). ►sterol, ►SREBP, ►cholesterol, ►statins

Oxytocin: This is an octapeptide stored in the pituitary that regulates uterine contraction and lactation. During delivery in rats, oxytocin triggers an inhibitory switch in GBA signaling in the brain (Tyzio R et al 2006 *Science* 324:1788). It is synthesized in the hypothalamus with other associated proteins. They are assembled in the neurosecretory vesicles and transported to the nerve ends in the neurohypophysis (posterior lobe of the pituitary) and may eventually be secreted into the bloodstream. Vasopressin and oxytocin (12-kb between them) and neurophysin genes are linked within the arm of human chromosome 20pterp12.21. They are transcribed from the opposite strands of the DNA. It appears that pre-proarginine - vasopressin - neurophysin are transcribed jointly and

post-translationally separated by proteolysis. Oxytocin favorably affects the social behavior of animals and humans (Kosfeld M et al 2005 Nature [Lond] 435:673).
 ▶ vasopressin [antidiuretic hormone], ▶ neurophysin, ▶ animal hormones, ▶ memory, ▶ behavior genetics, ▶ microsatellite, ▶ GABA; Breton C et al 2001 J Biol Chem 276:26931.

Oxytricha: This is a group of ciliate protozoa with a germ line micronucleus and a somatic macronucleus (see Fig. O35). During conversion of the micronucleus to macronucleus about 150,000 internal DNA segments are routinely eliminated by recombinational events. The processes permit shuffling of the ca. 30,000 genes at reconstitution and high rates of mutation. ▶ protozoa; Prescott DM 1999 Nucleic Acids Res 27:1243; <http://oxytricha.princeton.edu/dimorphism/database.htm>.

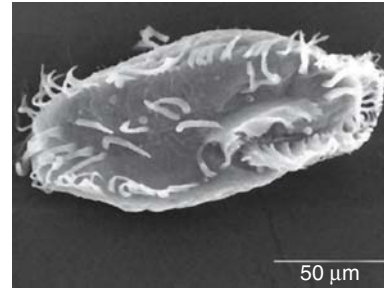


Figure O35. *Oxytricha*. (Courtesy of National Human Genome Research Institute)

Ozone (O₃): This is a bluish, highly reactive form of oxygen. It is a disinfectant and its presence in the atmosphere acts as a screen protecting the earth from excessive ultraviolet radiation coming from the sun.

Historical vignettes

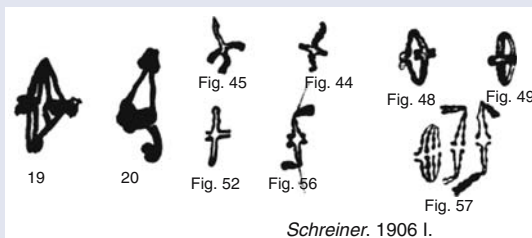
“First your opponents say it can’t be true. Next they say if it is true it can’t be very important. Finally they say well, we’ve known it all along.”

Jeffrey Kluger (2004) citing Jonas Salk in his book *Splendid Solution. Jonas Salk and the Conquest Polio*. Putnam, New York.

On July 9, 1909 (more than two decades earlier than the Neurospora work), FA Janssens, Professor at the University of Louvain, presented his theory of chiasmotypy in the journal *La Cellule* (25:389–411):

“In the spermatocytes II, we have in the nuclei chromosomes which show one segment of two clearly parallel filaments, whereas the two distal parts diverge... The first division is therefore reductional for segment A and a and it is equational for segment B and b ... The 4 spermatids contain chromosomes 1st AB, 2nd Ab, 3rd ab, and 4th aB. The four gametes of a tetrad will thus be different...

“The reason behind the two divisions of maturation is thus explained... The field is opened up for a much wider application of cytology to the theory of Mendel.”



P

P: Parental generation.

P: ►probability

P (Polyoma): A regulatory DNA element in the viral basal promoter. ►Simian virus 40, ►polyoma

³²**P:** Phosphorus isotope. ►isotopes

P1: Double-stranded DNA, temperate *E. coli* phage. It is also a vector used DNA sequencing with a load capacity of ~80 kb.

P₁, P₂: Designations of the parents, homozygous for different alleles, at the critical locus (loci) in a Mendelian cross. ►Mendelian laws, ►gametic arrays, ►genotypic segregation, ►allelic combinations

p (petit): Short arm of chromosomes, also denote frequencies. ►q

π: ►diversity

π: $22/7 \approx 3.132857$, Ludolf number, indicates the ratio of the circumference to the diameter of a circle.

Φ (phi): The symbol of some phages.

ψ (psi): ►pseudouridine (see Fig. P1), formula. Also, packaging signal for virions. The packaging signal is located at the 5' LTR repeat and reaches over into the upstream end of the gag gene. It is not translated. ►retroviruses

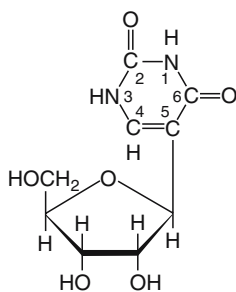


Figure P1. Pseudouridine

p13suc1: The yeast cell cycle activating enzyme binding to the cyclosome. ►cyclosome, ►cell cycle; Simeoni F et al 2001 Biochemistry 40:8030.

p14: ►ARF

p15^{INK4B}: An inhibitor of CDK4 (encoded in human chromosome 9p21) appears to be an effector of TGF-β, a protein known to control the progression

from G1 phase of the cell cycle to S phase. ►cell cycle, ►TGF, ►p16^{INK4}, ►p18, ►p19, ►cancer; Seoane J et al 2001 Nature Cell Biol 3:400.

p16 (*MTS1* [multiple tumor suppressor], CDKN2): A cell cycle gene (in human chromosome 9p21) that has a major role in tumorigenesis. In 50% of the melanoma cells, it is deleted and in 25%, it is mutated. Over 70% of the bladder cancer cases are associated with deletions of 9p21 in both homologous chromosomes, in head and neck tumors 33%, in renal and other cells usually this tumor suppressor gene is lost. It normally restrains CDK4 and CDK6. ►melanoma, ►pancreatic adenocarcinoma, ►CDK4, ►CDK6, ►cell cycle, ►ARF; Serrano M et al 1993 Nature [Lond] 366:704.

p16: A weak ATPase and a packaging protein of φ29 bacteriophage. It interacts with the viral packaging RNA (pRNA) and the phage portal protein and assists in pumping the double-stranded DNA into the phage head. p16 and other packaging components are not found within the head. ►packaging of DNA; Ibarra B et al 2001 Nucleic Acids Res 29:4264.

p16^{INK4} (CDKN2A): A protein inhibitory to CDK4/CDK6 and thus appears to be a tumor suppressor because it inhibits the progression of the cell cycle from G¹ to S. Thus, it may also direct the cell toward senescence rather than neoplasia. p16^{INK4a} induces age-dependent decline in cell regenerative capacity (Krishnamurthy J et al 2006 Nature [Lond] 443:453). Absence of p16^{INK4a} may reduce aging of hematopoietic stem cells and acts similarly to ARF in tumor suppression. The two proteins share coding sequences but ARF does not seem to affect stem cell aging (Janzen V et al 2006 Nature [Lond] 443:421). Both p16^{INK4} and p19^{INK4} are transcribed from the same 9p21 locus but from alternative alleles. ►CDK4, ►tumor suppressor, ►PHO81, ►cell cycle, ►cancer, ►p18, ►p19, ►Ets oncogene, ►Id protein, ►senescence, ►mole, ►centrosome; Quelle DE et al 1995 Cell 83:993; Wang W et al 2001 J Biol Chem 276:48655; Reynolds PA et al 2006 J Biol Chem 281:24790.

p18^{INKC}: Cell cycle inhibitors that block cell cycle kinases CDK4 and CDK6. ►cell cycle, ►cancer, ►p15, ►p16, ►p19; Blais A et al 2002 J Biol Chem 277:31679.

p19^{Arf}: ►Arf, ►p16^{INK4}

p19^{INK4d}: Cell cycle inhibitor of CDKs. ►p15, ►p16, ►p18, ►cell cycle, ►cancer, ►ARF

p21: A transforming protein of the Harvey murine sarcoma virus. A Ras-gene encoded 21 kDa protein binds GDP/GTP and hydrolyzes bound nucleotides

and inorganic phosphate. This protein is involved in signal transduction, cell proliferation and differentiation and p21 controls the cyclin-dependent kinases (Cdk4, Cdk6, Cdk2), and binds to DNA polymerase δ processivity factor and it inhibits in vitro PCNA-dependent DNA replication but not DNA repair. In the absence of p21, cells with damaged DNA are arrested temporarily at the G2 phase and that is followed by S phases without mitoses. Consequently hyperploidy arises and apoptosis follows. Gene *p21* is under the control of p53 protein and the retinoblastoma tumor suppressor gene RB. MyoD regulates expression of the p21 Cdk inhibitors (p21^{Cip/Waf1}, 6p21.2) during differentiation of muscle cells and non-muscle cells, and then withdrawal from the cell cycle does not require the participation of p53. Experimental evidence indicates that telomere dysfunction induces p21-dependent checkpoints in vivo that can limit longevity at the organismal level (Choudhury AR et al 2007 Nature Genet 39:99). RAF and RHO activate protein p21^{Cip/Waf}, leading to inhibition of the transition of the cell cycle into the S phase. Actually, RAS activates the serine/threonine kinase Raf that may facilitate the transition to the S phase but upon excessive stimulation by RAF and RHO, p21^{Cip/Waf} has the opposite effect. Also, p53 is an independent activator of p21^{Cip/Waf}. After mitosis, p21 is expressed at the onset of differentiation but it may again be down-regulated at later stages of differentiation due to proteasome activity. In addition, p21 may not have an absolute requirement for induction by MyoD. The N terminal domains of p27 and p57 provide other antimitogenic signals. P21^{SNFT} is a 21 kDa nuclear factor of T lymphocytes. Its overexpression represses transcription from the interleukin-2 and AP1-driven promoters. [▶cell cycle](#), [▶Cdk](#), [▶mitosis](#), [▶cancer](#), [▶hyperploidy](#), [▶apoptosis](#), [▶p53](#), [▶PCNA](#), [▶p27](#), [▶p57](#), [▶MyoD](#), [▶cell cycle](#), [▶RAS](#), [▶RASA](#), [▶proteasome](#), [▶interleukin](#), [▶AP1](#), [▶NF-AT](#), [▶epigenesis](#); Prall OWJ et al 2001 J Biol Chem 276:45433; Wu Q et al 2002 J Biol Chem 277:36329; Bower KE et al 2002 J Biol Chem 277:34967.

p23: A component of the steroid receptor complex with Hsp90. [▶Hsp](#), [▶steroid hormones](#), [▶molecular chaperone interacting complex](#), [▶telomerase](#); Knoblauch R, Garabedian MJ 1999 Mol Cell Biol 19:3748; Munoz MJ et al 1999 Genetics 153:1561.

p24: A family of evolutionarily conserved small integral membrane proteins, which form parts of the COP transport vesicles or regulate the entry of cargo into the vesicles. It also mediates viral infection. [▶protein sorting](#), [▶COP transport vesicles](#); Blum R et al 1999 J Cell Sci 112(pt 4):537; Hernandez M et al 2001 Biochem Biophys Res Commun 282:1.

p27 (p27^{Kip1}): A haplo insufficient tumor suppressor protein, which inactivates cyclin-dependent protein kinase 2. Its mutation (homo- or heterozygous) results in increased body and organ size and neoplasia in mouse. p27 in cooperation with RAS controls metastasis (Bessom A et al 2004 Genes Dev 18:862). The wild type allele as a transgene may retard cancerous proliferation. Germ-line mutations in p27^{Kip1} can predispose to the development of multiple endocrine tumors in both rats and humans (Pellegata NS et al 2006 Proc Natl Acad Sci USA 103:15558). Inactivation of p27^{Kip1} is triggered by phosphorylation and mediated by the proteasome complex. Non-receptor tyrosine kinases phosphorylate p27^{Kip1} and decrease its stability leading to entry into the cell cycle (Kaldis P 2007 Cell 128:241). [▶Cdk2](#), [▶p21](#), [▶cell cycle](#), [▶cancer](#), [▶KIP](#), [▶Knudson's two-mutation theory of cancer](#), [▶cancer gene therapy](#), [▶metastasis](#), [▶RAS](#), [▶transgene](#), [▶proteasome](#), [▶p38](#), [▶SKP](#), [▶dyskeratosis](#), [▶MEN](#); Mohapatra S et al 2001 J Biol Chem 276:21976; Malek NP et al 2001 Nature [Lond] 413:323.

p27^{BBP}: [▶eIF-6](#)

p34^{cdc2-2}: The gene coding for the catalytic subunit of MPF in *Schizosaccharomyces pombe* (counterparts, *CDC28* in *Saccharomyces cerevisiae*, *CDCHs* in humans have 63% identity with *cdc2*; these genes are present in all eukaryotes). The gene product is a serine/tyrosine kinase and its function is required for the entry into M phase of the cell cycle. If prematurely activated, it may cause apoptosis. [▶cell cycle](#), [▶MPF](#); Shimada M et al 2001 Biol Reprod 65:442; Nigg EA 2001 Nature Rev Mol Cell Biol 2:21.

p35 (Cdk5 regulatory subunit): A homolog of the baculoviral (survival) protein and cyclin-dependent regulator of neural migration and growth and which blocks apoptosis in a variety of eukaryotic cells. It colocalizes in the cells with RAC and Pac-1. Truncation of p35 results in a very stable p25 protein that is present in Alzheimer disease tangles. [▶baculoviruses](#), [▶RAC](#), [▶Pac-1](#), [▶Alzheimer disease](#), [▶CDK](#); Tarricone C et al 2001 Mol Cell 8:657; Lin G et al 2001 In Vitro Cell Dev Biol Anim 37(5):293.

p38 (MPK2/CSBP/HOG1): A stress-activated protein kinase of the MEK family. It accelerates the degradation of p27^{Kip1}, and it phosphorylates H3 histone. p38 is one of the factors required for the initiation of G2/M checkpoint after UV radiation. The down-regulation of E-cadherin during mouse gastrulation requires p38 and a p38-interacting protein (Zohn IE et al 2006 Cell 125:957). The p38-activated protein (PRAK) is essential for RAS-induced senescence and tumor suppression (Sun P et al 2007 Cell 128:295). The mitogen-activated protein kinase

(MAPK) p38 controls inflammatory responses and cell proliferation. Using mice carrying conditional *Mapk14* (also known as *p38α*) alleles, when specifically deleted in the mouse embryo, fetuses developed to term but died shortly after birth, probably owing to lung dysfunction. Fetal hematopoietic cells and embryonic fibroblasts deficient in p38 showed increased proliferation resulting from sustained activation of the c-Jun N-terminal kinase (JNK) pathway (Hui L et al 2007 Nat Genet 39:741). p38 is a lung tumor suppressor (Ventura JJ et al 2007 Nat Genet 39:750). ►MEK, ►MEF, ►MAP kinase, ►JNK, ►cadherins, ►gastrula, ►checkpoint, ►UV; Schrantz N et al 2001 Mol Biol Cell 12:3139; Bulavin DV et al 2002 Curr Opin Genet Dev 12:92.

p40: A tumor suppressor encoded in human chromosome 3q, produced by alternative splicing of p51. Also an L1 RNA transcript (of ORF II) binding protein required of retrotransposon movement. ►p51, ►p53, ►L1, ►retrotransposon, ►ORF; Hess SD et al 2001 Cancer Gene Ther 8(5):371; Henning D, Valdez BC 2001 Biochem Biophys Res Commun 283:430.

p42: ►MAPK

p50: The N-terminus of the p105 light chain of NF-κB encoded at 4q23-q24. ►NF-κB; Yamada H et al 2001 Infect Immun 69:7100.

p51: A cell proliferation inhibitor protein related to p73 and encoded at 3q28. p51A is 50.9 kDa and p51B is 71.9 kDa. ►p73, ►p40, ►p53; Guttieri MC, Buran JP 2001 Virus Genes 23:17.

p52^{SHC}: A RAS G-protein regulator protein; it is regulated through CTLA-4–SYP associated phosphatase. ►CTLA-4, ►SYP, ►RAS; Joyce D et al 2001 Cytokine Growth Factor Rev 12:73.

p53 (TP3, 17p13.1): A tumor suppressor gene when the wild type allele is present but single base substitutions may eliminate suppressor activity and the tumorigenesis process may be initiated.

p53 is a tetramer with separate domains for DNA binding, transactivation and tetramerization (see Fig. P2).

The transcriptional coactivator p300 binds to and mediates the transcriptional functions of the tetrameric tumor suppressor p53. In the four domains of

the complex between tetrameric p53 and p300, the latter wraps around the four transactivation domains of p53 (see Fig. P3) (Teufel DP et al 2007 Proc Natl Acad Sci USA 104:7009). Protein p53 as tetramers of tetramers binds to different DNA sites and in case of stress activates the expression of genes involved in apoptosis. Wild type alleles of oncogenes and DNA damage, both activate tumor suppressor activities of p53 although through separate metabolic routes (Efeyan A et al 2006 Nature [Lond] 443:159; Christophorou MA et al 2006 Nature [Lond] 443:214). New information is available for the structural framework in interpreting mechanisms of specificity, affinity and cooperativity of DNA binding as well as regulation by regions outside the sequence-specific DNA-binding domain (Kitayner M et al 2006 Mol Cell 22:741). Protein p53 recognizes specific DNA sequences, activates transcription from promoters with p53 protein binding sites and represses transcription from promoters lacking p53-binding sites; p53 regulates more than 160 genes. Recent data based on chromatin immunoprecipitation and paired end ditag sequencing identified 542 binding sites for p53 (Wei CL et al 2006 Cell 124:207). After DNA damage, the level of p53 increases by new translation and increased half-life of its mRNA. Ribosomal protein L26 binds to the 5'-untranslated region of mRNA and enhances its translation. Protein nucleolin binds to the same region and decreases translation (Takagi M et al 2005 Cell 123:49). Tumor suppressors p53, p63 and p73 express multiple splice variants and can use different promoters, thereby determine tissue-specificity of their expression (Bourdon J-C et al 2005 Genes Dev 9:2122; Murray-Zmijewski F et al 2006 Cell Death Differ 13:962). It promotes annealing of DNAs, inhibits replication, controls G1 and G2 phase checkpoints, leads to apoptosis or just blocks cytokinesis if the DNA is damaged, interferes with tumorous growth, maintains genetic stability, reduces radiation hazards by its regulatory role in the cell cycle. For the maintenance of G2 arrest after DNA damage it also requires the presence of p21. Protein p53 binds to a somewhat conserved consensus and it is phosphorylated at serine 315 residues by CDK proteins during S, G2 and M phases of the cell cycle but not at G1 although p53 controls an important G1

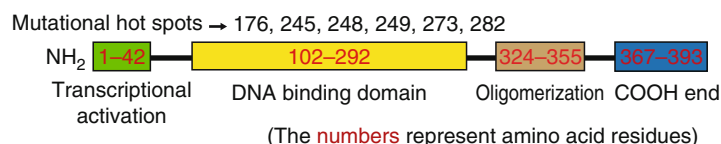


Figure P2. Structure of the p53 protein

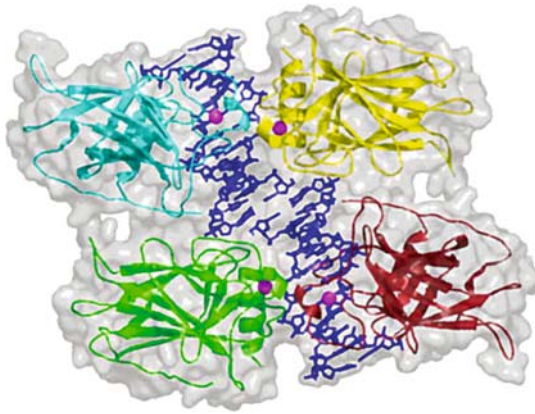


Figure P3. Ribbon diagram of the four core domains of p53 (light blue, green, yellow, maroon) interacting with DNA (dark blue). The Van der Waals surface is shown in gray; the four Zn ions are represented by magenta spheres. (Courtesy of Professor Z. Shakked, Weizmann Institute of Science)

checkpoint. Binding subunits may have ubiquitin-conjugating role. Histone H3, methylated at lysine 79, targets 53BP1 to DNA double-strand breaks (Huyen Y et al 2004 Nature [Lond] 432:406). p53 also controls proteins p21, p27 and p57. The p53 protein binds to the four copies of its consensus in DNA (5'-PuPuPuGA/T-3'). The C-terminal domain controls tetramerization and the N-terminal domain is responsible for transcriptional activation and for the regulation of down-stream genes. Small-angle x-ray scattering information in solution defined its shape, and NMR identified the core domain interfaces and showed that the folded domains had the same structure in the intact protein as in fragments. The combined solution data with electron microscopy on immobilized samples provided medium resolution 3D maps (Tidow H et al 2007 Proc Natl Acad Sci USA 104:12324).

One study indicated that at least 34 different transcripts were induced by p53 more than ten-fold although there was heterogeneity in the response. Co-activators TAFII40, TAFII 60 and other TATA box binding factors mediate its transcriptional activation. When the first six exons of the gene are deleted, the mRNA is still translated into a C-terminal protein fragment. Such a mutation enhances tumor suppression but leads to premature aging in mice (Tyner SD et al 2002 Nature [Lond] 415:45). p53 is encoded in human chromosome 17p13.105-p12; in about half of the human tumors the normal allele is altered. p53 regulates mitochondrial respiration through cytochrome oxidase c (SCO2) and may account for glycolysis in cancer cells and aging versus the

respiratory pathway in normal cells (Matoba S et al 2006 Science 312:1650). Protein 53 plays a central role in cellular metabolism and its expression is induced by many factors such as oncogene expression, chemotherapy, oxidative stress, hypoxia, etc. Topoisomerase I is a p53-dependent protein. A p53-induced apoptosis may require transcriptional activation or it may occur in the absence of RNA or protein synthesis. The activation of p53 may be followed by FAS transport from Golgi intracellular stores without a need for synthesis of FAS. Tumor suppressor p53 product in the nucleus regulates pro-apoptotic genes such as *FAS*, *BAX*, *Bid*, *Noxa* and *PUMA*. In the cytoplasm, the p53 protein activates Bcl-2 and facilitates the permeability of the mitochondria for the release of pro-apoptotic molecules such as cytochrome c. In the cytoplasm, p53 is dislodged from Bcl-2 by PUMA to act on the mitochondrial permeability and apoptosis; thus PUMA interconnects the nuclear and cytoplasmic functions of p53 (Chipuk JE et al 2005 Science 309:1732).

The activity of p53 is also regulated by methylation of lysine 4 residues of histone-3 by Set9 methyltransferase and thereby the protein is better stabilized (Chuikov S et al 2004 Nature [Lond] 432:353). The Smyd2 protein mediates methylation of Lys370 in p53 and represses its activity; Set9 mediated methylation at Lys372 reduces methylation at Lys370 (Huang J et al 2006 Nature [Lond] 444:629). Acetylation of lysines 373 and 382 increases its DNA binding (Luo J et al 2004 Proc Natl Acad Sci 101:2259). Single nucleotide polymorphism in the promoter of MDM2 increases the affinity of the Sp21 transcriptional activator and attenuation of the p53 resulting in accelerated tumorigenesis (Bond GL et al 2004 Cell 119:591).

The ASPP family member regulatory proteins bind to the proline-rich region of p53, which contains the most common p53 polymorphism at codon 72. iASPP (inhibitory ASPP) binds to and regulates the activity of p53Pro72 more efficiently than the alternative amino codon p53Arg72. Hence, escape from negative regulation by iASPP is a newly identified mechanism by which p53Arg72 activates apoptosis more efficiently than p53Pro72 (Bergamaschi D et al 2006 Nature Genet 38:1133).

The calcium-binding proteins S100B and S100A4 bind preferentially to the tetramerization domain at lower oligomerization states, disrupt tetramerization and control intracellular movement of the p53 protein (Fernandez-Fernandez, M.R. et al. 2005 Proc Natl Acad Sci USA 102:4735).

Protein p73 has functions similar to those of p53. p33^{ING1}, encoded at human chromosome 13q34, cooperates with p53 by protein-protein interaction in

repressing cellular proliferation and the promotion of apoptosis.

The DNA-dependent protein kinase (DNA-PK) activates p53 in case the DNA is damaged. When amino acid site 376 is dephosphorylated by ionizing radiation protein 14-3-3 binds to p53 and increases its ability for DNA binding (see Fig. P4). Still other proteins such as IRF may be involved with p53 and other cooperating proteins. p53 activity may also be affected by oncoproteins RAS and MYC. Chemotherapeutic agents, UV light and protein kinase inhibitors may also activate p53. p53 is reversibly blocked by pifithrin- α (2[2-imino-4,5,6,7-tetrahydro-benzothiazol-3-yl]-1-polyethanone) and may protect from the undesirable side effect of anticancer therapy without causing new tumors in the absence of p53 function. When 33,615 human unique genes were tested by cDNA microarrays, 1,501 genes responded one way or another to p53 (Wang L et al 2001 J Biol Chem 276:43604).

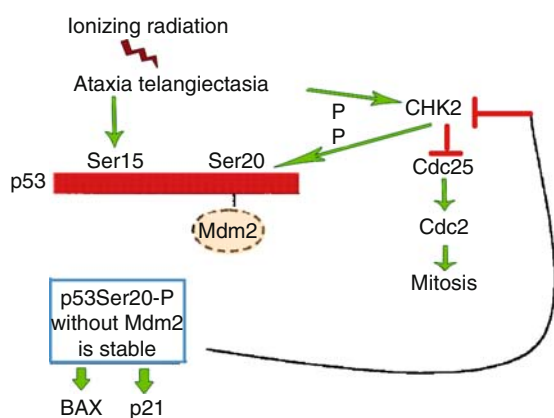


Figure P4. Some of the circuits of p53. Ionizing radiation damage to the ataxia telangiectasia protein results in the phosphorylation of the serine 15 residue of p53 and checkpoint 2 (CHK2), which in turn phosphorylates residue 20. The latter point is normally occupied by Mdm2/HDM2 a negative regulator of p53 that is now dislodged by the phosphorylation of site 20. The p53 ser20-p protein is now stabilized, despite the radiation and can induce BAX (a porin with anti-apoptosis function) and p21, a suppressor of mitosis. The blocking of CHK2 then prevents its inhibition of cell division cycle proteins (Cdc25 and Cdc2). The process to mitosis is then facilitated

Pharmacological compounds (CP-31398, CP-257042, etc.) have been selected by large-scale screening that could stabilize the DNA-binding domain of mutant p53 and activate its transcription as well as to slow tumor development in mice. In some cancers, p53 may increase sensitivity to chemotherapeutic agents but in others, it does not affect them.

NADH quinone oxidoreductase may stabilize the p53 protein. Synthetic siRNA with single base difference may suppress the expression of mutation in p53 and may selectively block tumorigenesis by restoring wild type function (Martinez LA et al 2002 Proc Natl Acad Sci USA 99:14849). Using RNAi technology p53 function can be reactivated in murine liver carcinomas by triggering cellular senescence and innate immunity and consequently leading to tumor clearance (Xue W et al 2007 Nature [Lond] 445:656). Blocking p53 expression by introducing a stop cassette into the gene or removing it by the use of the Cre/loxP system, lymphomas and sarcomas of mice could be induced and then regressed after restoration of p53 function (Ventura A et al 2007 Nature [Lond] 455:661). The antiviral and anticancer effects of p53 is mediated by interferons (α and β), which boost the response to stress signals and thus promote apoptosis (Takaoka A et al 2003 Nature [Lond] 424:516).

Germline mutations occur in about 1×10^3 of the Caucasian populations but in about half of the sporadic cancers, it is somatically mutated. (Science magazine declared p53 the molecule of year 1993). **p53** tumor suppressor gene, **p53** annealing, **p53** apoptosis, **p53** PUMA, **p53** BCL, **p53** TAF, **p53** TBP, **p53** transactivator, **p53** nucleolin, **p53** cancer, **p53** Sp1, **p53** cell cycle, **p53** p21, **p53** p27, **p53** p40, **p53** p51, **p53** p57, **p53** p63, **p53** p73 substitution mutation, **p53** DAP kinase, **p53** MDM2, **p53** lactacystin, **p53** ARF, **p53** IRF, **p53** papilloma virus, **p53** DNA-PK, **p53** protein 14-3-3, **p53** E2F, **p53** ribonucleotide reductase, **p53** ataxia telangiectasia, **p53** CHK, **p53** Cdc, **p53** porin, **p53** p21, **p53** GADD45, **p53** RNAi, **p53** interferon, **p53** paired-end diTAG; Vogelstein B et al 2000 Nature [Lond] 408:307; Vousden KH 2000 Cell 103:691; Asher G et al 2001 Proc Natl Acad Sci USA 98:1183; Johnson RA et al 2001 J Biol Chem 276:27716; Olivier M et al 2002 Hum Mut 19:607; minireview: Kastan MB 2007 Cell 128:837; p53 mutation database: <http://www-p53.iarc.fr/index.html>; <http://p53.free.fr>.

p55 (TNFR1): A tumor necrosis factor receptor of Fas. **p55** Fas, **p55** TNF; Dybedal I et al 2001 Blood 98:1782; Longley MJ et al 2001 J Biol Chem 276:38555.

p56^{chk1}: A protein kinase and a checkpoint for mitotic arrest after mutagenic damage inflicted by UV, ionizing radiation or alkylating agents. The DNA damage results then in the phosphorylation of this protein in yeasts. The phosphorylation may prevent the mitotic arrest yet the cells may die later; p56 is not involved in DNA repair. Phosphorylation is required so that other checkpoint genes become/stay functional. **p56^{chk1}** cell cycle, **p56^{chk1}** DNA repair; Feigelson SW et al 2001 J Biol Chem 276:13891.

- p57** (p57^{Kip2}): An antimitogenic protein; its carboxyl end assures nuclear localization and the amino end is involved in the inhibition of CDK proteins. ►**CDK**, ►**p21**, ►**p27**, ►**cell cycle**, ►**KIP**; Thomas M et al 2001 *Exp Cell Res* 266:103.
- p58^{IPK}**: A heatshock protein 40 family member that inhibits interferon-induced, double-stranded RNA-activated eukaryotic translation initiation factor eIF2 α protein kinase, PERK. Stress in the endoplasmic reticulum (ER) caused by unfolded proteins activates the translation of the gene and thereby reduces protein overload in the ER. ►**heat-shock proteins**, ►**eIF2**; Yan W et al 2002 *Proc Natl Acad Sci USA* 99:15920.
- p60**: Binds to Hsp70 and Hsp90 and chaperones the assembly of the progesterone complex. ►**Hsp70**, ►**Hsp**, ►**progesterone**, ►**animal hormones**, ►**chaperone**; Mukhopadhyay A et al 2001 *J Biol Chem* 276:31906.
- p63**: A member of the p53 tumor suppressor gene family, encoded at 3q27-q29. The gene expresses at least 6 transcripts, involved with transactivation of p53 and p73, DNA binding and oligomerization. It controls ectodermal (limb, craniofacial and epithelial) differentiation. Protein p63 regulates also the commitment to prostate cell lineage development (Signoretti S et al 2005 *Proc Natl Acad Sci USA* 102:11355). The first direct target of p63 appears to be the Perp protein localized in the desmosomes. Absence of Perp leads to post-natal death in mice (Ihrie RA et al 2005 *Cell* 120:843). Although p63 belongs to the p53 tumor suppressor family, its function seems to be different. Mouse heterozygotes for p63 were not prone chemically induced tumorigenesis (Keyes WM et al 2006 *Proc Natl Acad Sci USA* 103:8435). p63 protects female germ line—by apoptosis—during meiotic arrest (Suh E-K et al 2006 *Nature [Lond]* 444:624). Epithelial stem cells require p63 for proliferation (Senoo M et al 2007 *Cell* 129:523). ►**p53**, ►**p73**, ►**desmosome**, ►**EEC syndrome**, ►**Hay-Wells syndrome**; van Bokhoven H et al 2001 *Am J Hum Genet* 69:481; van Bokhoven, Brunner HG 2002 *Am J Hum Genet* 71:1.
- p65**: A component of the NF- κ B complex. It can be exploited advantageously for gene activation in a chimeric construct with a mutant progesterone-receptor-ligand binding domain of gene GAL4. ►**NF- κ B**, ►**GAL4**, ►**gene-switch**, Burcin MM et al 1999 *Proc Natl Acad Sci USA* 97:355.
- p70/p86**: The Ku autoantigen. ►**DNA-PK**, ►**Ku**
- p70^{S6k}**: Phosphorylates S6 ribosomal protein at serine/threonine residues before translation. Also called S6 kinase. ►**translation initiation**, ►**p85^{S6k}**, ►**S6 kinase**, ►**signaling to translation**; Harada H et al 2001 *Proc Natl Acad Sci USA* 98:9666.
- p73**: It has homology in amino acid sequence to p53 protein and is encoded in human chromosome 1p36.3. Similarly to p53, it regulates apoptosis and anti-tumor activity (upon E2F1 induction), hippocampal dysgenesis, hydrocephalus, immune reactions and pheromone sensory pathways. It affects proliferation, although in a somewhat different manner, but its loss does not lead to tumorigenesis in mice. p73 may compete with p53. This protein may have antiapoptotic effect in neurons. ►**p53**, ►**apoptosis**, ►**p63**, ►**E2F**; Sasaki Y et al 2001 *Gene Ther* 8:1401; Stiewe T, Putzer BM 2001 *Apoptosis* 6:447; Melino G et al 2002 *Nature Rev Cancer* 2:605.
- p75**: A non-tyrosine kinase receptor protein, TNFR 2 (tumor necrosis factor receptor 2). It is a Fas receptor. ►**Fas**, ►**TNF**; Hutson LD, Bothwell M 2001 *J Neurobiol* 49(2):79; Wang X et al 2001 *J Biol Chem* 276:33812.
- p80^{Sdc25}**: A protein phosphatase that activates p34^{cdc2}-cyclin protein kinase complex by dephosphorylating Thr¹⁴ and Tyr¹⁵. ►**cell cycle**, ►**Ku**; McNally KP et al 2000 *J Cell Sci* 113[pt 9]:1623.
- p85^{S6k}**: Phosphorylates S6 ribosomal protein before translation at serine/threonine sites; also called S6 kinase. p85 protein is also involved in a p53-dependent apoptotic response to oxidative damage and activation of natural killer. p85 phosphoinositide 3-kinase also mediates developmental and metabolic functions. ►**translation initiation**, ►**p70^{S6k}**, ►**S6 kinase**, ►**phosphoinositides**; Fruman DA et al 2000 *Nat Genet* 26:379.
- p95**: is Fas and is involved in apoptosis; its mutation leads to the Nijmegen breakage syndrome and other double breakage of the chromosomes. ►**acrosomal process**, ►**Fas**, ►**APO**, ►**Nijmegen breakage syndrome**, ►**apoptosis**
- p97** (Cdc48): About M_r 600 ATPase and mediates membrane fusion. ►**endoplasmic reticulum-associated degradation**; Hirabayashi M et al 2001 *Cell Death Differ* 8(10):977.
- p105**: ►**p50**
- p107**: A retinoblastoma protein-like regulator of the G1 restriction point of the cell cycle. ►**restriction point**, ►**tumor suppressor**, ►**retinoblastoma**, ►**cell cycle**, ►**pocket**; Charles A et al 2001 *J Cell Biochem* 83:414.
- p110 α** : The catalytic subunit of PIK. It has a critical role in insulin signaling and with TOR it controls the

development of gliomas. ►PIK/PI(3)K, ►insulin, ►glioma

p110^{Rb}: The protein encoded by the retinoblastoma (Rb) gene. When not fully phosphorylated it interferes with the G₀ and G₁ phases of the cell cycle by inhibition of the E2F transcription factor. ►retinoblastoma, ►cell cycle, ►tumor suppressor, ►E2F, ►killer cells; DeCaprio JA et al 1988 Cell 54:275.

p115: A monomeric GTPase with a specific guanine exchange factor (GEF) for RHO (p115 Rho GEF). ►GTPase, ►RHO, ►GEF; Wells CD et al 2001 J Biol Chem 276:28897.

p125^{FAK} (focal adhesion kinase): A non-receptor tyrosine kinase. ►CAM; Yurko MA et al 2001 J Cell Physiol 188:24.

p130: A retinoblastoma protein-like regulator of the G1 restriction point of the cell cycle. p130^{Cas} is involved in the organization of myofibrils, actin fibers, anchorage-dependence of cultured cells. ►restriction point, ►tumor suppressor, ►retinoblastoma, ►CAS, ►pocket; Tanaka N et al 2001 Cancer 92:2117.

p160: A family of transcriptional co-activators such as SRC-1, GRIP1/TIF2 and pCIP. They modify chromatin structure by methylating some of the histones. ►chromatin remodeling, ►nuclear receptors, ►pCIP; Mak HY 2001 Mol Cell Biol 21:4379.

p300 (CBP): A cellular adaptor protein preventing the G₀/G₁ transition of the cell cycle, it may activate some enhancers and stimulate differentiation. It is also a target of the adenoviral E1A oncoprotein. Its amino acid sequences are related to CBP, a CREB-binding protein. Nuclear hormone-receptors interact with CBP/p300 and participate in gene transactivation. PCAF is a p300/CBP-associated factor in mammals, and it is the equivalent of the yeast Gcn5p (general controlled nonrepressed protein), an acetyltransferase working on histones 3, 4 (HAT A) and thus regulating gene expression. p300 functions also as a co-activator of NF-κB. p300 also binds PCNA. In several human cancers, p300 mutations were identified indicating that the protein is a tumor suppressor. p300 may show ubiquitin ligase activity for p53. ►adenovirus, ►CREB, ►NF-κB, ►PCNA, ►histone acetyl-transferase, ►E1A, ►bromodomain, ►chromatin remodeling, ►histone methyltransferases, ►p53; Lin CH et al 2001 Mol Cell 8:581; ►CARM

p350: A DNA-dependent kinase, it is a likely basic factor in severe combined immunodeficiency and it may also be responsible for DNA double-strand repair, radiosensitivity and the immunoglobulin V(D)J rearrangements. In association with the KU protein,

it forms a DNA-dependent protein kinase. ►severe combined immunodeficiency, ►kinase, ►KU, ►DNA-dependent protein kinase, ►immunoglobulins; Chan DW 1996 Biochem Cell Biol 74:67.

P450 (CYP): A family of genes coding for cytochrome enzymes involved in oxidative metabolism. They are widely present in eukaryotes and scattered around several chromosomes. All mammalian species have at least eight subfamilies. The homologies among the subfamilies are over 30% whereas the homologies among members of a subfamily may approach 70%. These cytochromes possess monooxygenase, oxidative deaminase, hydroxylation, sulfoxide forming, etc., activities. *Aspergillus oryzae* has ~149 cytochrome P450 genes in multiple copies. The proteins are generally attached to the microsomal components of homogenized cells (endoplasmic reticulum [fragments]), often called S9 fraction. Some of these enzymes (subfamily IIB) are inducible by phenobarbital. Their expression may be tissue-specific, predominant in the liver, kidney or intestinal cells. Mammalian P450 cytochrome fraction is generally added to the *Salmonella* assay media of the Ames test in order to activate promutagens. The pregnane X receptor (PXR) is activated by a variety of compounds and is thus responsible for the activation of different drugs involved in mutation, cancer and interaction with other drugs. One member of the P450 series is involved in the regulation of the synthesis of the 6th class of plant hormones, brassinosteroids. P450 enzymes require the cofactor NAD or NADPH and their activity is favored by the presence of peroxides as oxygen donors. By mutagenesis, industrially more useful P450 variants are being produced. The P-450 (CYP1A1) dioxin and aromatic compound-inducible P450 maps to human chromosome 15q22-qter. CYP1A2 is phenacetin O-deethylase. Phenacetin is an analgesic and antipyretic carcinogen. CYP2D (22q13.1) is a debrisoquin 4-hydroxylase. Debrisoquine is a toxic anti-hypertensive drug. CYP51 (7q21.2-q21.3) is lanosterol 14-α-demethylase is a sterol biosynthetic protein. ►Ames test, ►cytochromes, ►hypoaldosteronism, ►steroid hormones, ►brassinosteroids, ►peroxide, ►NAD, ►analgesic, ►antipyretic, ►cyclophilin; Fujita K, Kamataki T 2001 Mutat Res 483:35; Ingelman-Sundberg M 2001 Mutat Res 482:11; crystal structure of p450 3A4: Williams PA et al 2004 Science 305:683.

P Blood Group: Controlled by two non-allelic loci. The non-polymorphic P blood group is located in human chromosome 6 and it is encoding globoside whereas the polymorphic P1 locus in human chromosome 22 encodes paragloboside. The frequency of the P gene in Sweden was found to be 0.5401 and that of P1 0.4599. According to other studies, the frequency of

P among caucasoids is about 0.75. The P1 blood type facilitates bacterial attachment to the epithelial cells of the urinary tract and kidney. Therefore, infections are more common. Some P alleles raise the risk of abortions, and others may increase the chances of stomach carcinomas. Some of the literature calls P as P1 and P1 as P2. ►blood groups, ►globoside; Stroud MR 1998 *Biochemistry* 37:17420.

P Body (processing bodies, cytoplasmic body): A small number of specific sites in the cytoplasm involved in the decapping of mRNA after deadenylation of the polyA tail. At this location, mRNAs occur at various stages of degradation mediated by several proteins. Argonaute 2 of the RISC complex of RNAi is also localized in the P bodies (Sen GL, Blau HM 2005 *Nat Cell Biol* 7:633). The mammalian protein elongation factor eIF4E, its transporter (eIF4E-T) as well as the DEAD-box helicase rck/p54 are also located at these cytoplasmic sites (Andrei MA et al 2005 *RNA* 11:717). P bodies can recycle to the polysomes and when conditions are favorable can be translated (Brenques M et al 2005 *Science* 310:486). ►decapping, ►mRNA, ►RNAi, ►microRNA, ►eIF-4E, ►DEAD-box, ►RNA surveillance; Sheth U, Parker R 2003 *Science* 300:805; review: Parker R, Sheth U 2007 *Mol Cell* 25:635.

P1 Cloning Vectors: They have a carrying capacity up 100 kbp DNA; thus they fall between Lambda and YAC vectors. ►vectors, Park K, Chatteraj DK 2001 *J Mol Biol* 310:69; Grez M, Melchner H 1998 *Stem Cells* 16(Suppl. 1):235.

P

P Cytotype: ►hybrid dysgenesis

P Element: ►hybrid dysgenesis

P Element Vector: Constructed from the 2.9 kb transposable element P of *Drosophila* equipped with 31 bp inverted terminal repeats. The gene to be transferred is inserted into the element but in order to generate stable transformants the transposase function located in the terminal repeats is disabled. Functional transposase is provided in a separate helper plasmid (p π 25.7wc). Such a binary system permits the separation of the two plasmids and the screening of the permanent transgenes if a selectable marker is included. Both plasmids are mixed in an injection buffer and delivered into pre-blastoderm embryos. The various P vectors have been widely used in for gene tagging, induction of insertional mutation and for exploration of functional genetic elements in *Drosophila* and in some other insects. A newer type of vector, Pacman contains the P transposase and the phage ϕ C31 integration site. The ϕ C31 integrase mediates recombination between the engineered phage *attP* in the *Drosophila* genome

and a bacterial *attB* site in an injected plasmid. Such a system permits integration of large tracts of DNA (up to 133 kb) at specific sites. Such a targeted transgenesis can rescue much larger lethal mutations than it would be possible with only P element (Venken KJT et al 2006 *Science* 314:1744). ►hybrid dysgenesis, ►transposon vector, ►att sites; Sullivan W et al 2000 *Drosophila* Protocols, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

P Granule: Serologically definable elements in the cytoplasm of animal cells at fertilization that segregate to the posterior part of the embryo where stem cell determination takes place. During embryogenesis, the P granules (RNA) may segregate asymmetrically into the blastomeres that produce the germline. (See Harris AN, Macdonald PM 2001 *Development* 128:2823).

P Nucleotides: ►immunoglobulins

P1 Phage: An *E. coli* transducing phage and vector with near 100 kb carrying capacity. (See Lehnher H et al 2001 *J Bacteriol* 183:4105).

P22 Phage: The temperate bacteriophage of *Salmonella typhimurium*; its genome is about 41,800 bp. (See Vander Byl C, Kropinski AM 2000 *J Bacteriol* 182:6472).

P1 Plasmid: A cloning vector with a carrying capacity of about 100 kb. ►vectors, ►P1 phage; Bogan JA et al 2001 *Plasmid* 45(3):200.

P Region of GTP-Binding Proteins: Shares the G-X-X-X-X-G-K-(S/T) motif (►amino acid symbols) and is suspected to involve the hydrolytic process of GTP-binding and several nucleotide triphosphate-utilizing proteins. ►GTP binding protein superfamily

P Site: The peptidyl site on the ribosome where the first aminoacylated tRNA moves before the second charged tRNA lands at the A site as the translation moves on. The binding of the tRNA to the 30S ribosomal subunit appears to be controlled by guanine residues at the 966, 1401 and 926 positions in the 16S rRNA. ►A site, ►protein synthesis, ►ribosome; Feinberg JS, Joseph S 2001 *Proc Natl Acad Sci USA* 98:11120; Schäfer MA et al 2002 *J Biol Chem* 277:19095.

PABp: The poly(A) binding protein (~72 kDa) is the major protein that binds to the poly A tail of eukaryotic mRNA and converts it to mRNAP. Pab1p connects the mRNA end to the eIF-4H subunit of the eukaryotic peptide initiation factors eIF-4G and eIF-4F. It contains four RRM motifs. PABp also interacts with PAIP a translational co-activator protein in mammals. ►binding proteins, ►mRNAP, ►mRNA

tail, ►polyadenylation signal, ►mRNA decay, ►eIF-4F, ►eIF-4G, ►Xrn1p, ►ribosome scanning, ►translation initiation, ►translational termination, ►RRM, ►mRNA circularization; Kozlov G et al 2001 Proc Natl Acad Sci USA 98:4409.

PAC (phage artificial chromosome): P1 phage PAC carries about 100–300 kb DNA segments. Most PAC vectors lack selectable markers suitable for mammalian cell selection but can be retrofitted by employing the Cre/loxP site-specific recombination system. ►BAC, ►YAC; Poorkaj P et al 2000 Genomics 68:106.

pac: A site in the phage genome where terminases bind and cut during maturation of the DNA before packing it into the capsid. ►terminase, ►packaging of the DNA

PAC-1: Dephosphorylates Thr¹⁸³ and Tyr¹⁸⁵ residues and thus regulates mitogen-activated MAP protein kinase involved in signal transduction. The Pac1 nuclease removes the 3' external transcribed spacers from the nascent rRNAs in cooperation with RAC. PAC1 is activated by p53 protein during apoptosis and suppresses carcinogenesis. ►MAP, ►MKP-1, ►apoptosis, ►p53; Boschert U et al 1997 Neuroreport 8:3077; Spasov K et al 2002 Mol Cell 9:433.

PACAP (pituitary adenylyl cyclase-activating polypeptide-like neuropeptide): A neurotransmitter at the body-wall neuromuscular junction of *Drosophila* larvae. It mediates the cAMP-RAS signal transduction path. ►signal transduction, ►RAS, ►RAF; Kopp MD et al 2001 J Neurochem 79:161.

Pacemaker: Maintains rhythmic balance like the pulse of the heart or circadian rhythm.

Pachynema: Literally “thick thread” of chromosomes at early meiosis when the double-stranded structure of the chromosomes is not distinguishable by light microscopy because the chromatids are tightly appositioned (see Fig. P5). Also, the two homologous chromosomes are closely associated, unless structural differences prevent perfect synapsis. If a pair of chromosome is not completely synapsed by pachytene, they will not pair later either. In pachytene the chromosomal knobs and chromomeric structure is visible and can be used for identification of individual chromosomes. After pachytene, the synaptonemal complex is dismantled and the chromosomes progressively condense. In case the chromosomes are defective at this stage the Red1 (required for chromosome segregation) and Mek1 proteins serve as checkpoint control by preventing further progress of meiosis. Normally MEK kinase phosphorylates Red. Phosphatase Glc7 dephosphorylates Red. More than two dozens of other proteins (named differently in

different organisms) are also involved in pachytene controls. ►meiosis, ►pachytene analysis, ►synapsis, ►chiasma, ►chromomere, ►MEK; Bailis JM, Roeder GS 2000 Cell 101:211; Roeder GS, Bailis JM 2000 Trends Genet 16:395.

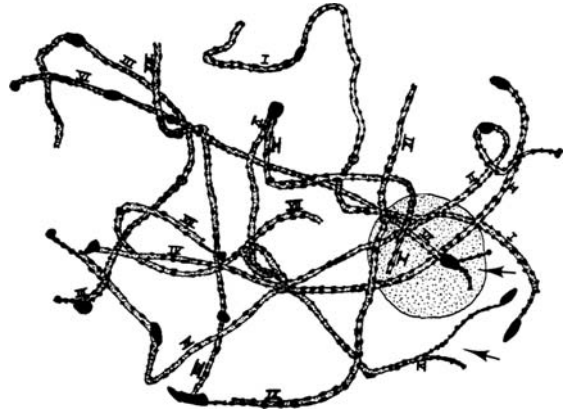


Figure P5. Naturalistic drawing of the 10 pachytene chromosome pair of a teosinte x maize hybrid. Note (←) unpaired ends of chromosomes V, VII. And some terminal and near-terminal knobs (Courtesy of Dr. A. E. Longley, see also 1937 J Agric Res 54:835)

Pachyonychia: A rare autosomal dominant keratosis of the nails and skin. ►keratosis

Pachytene Analysis: The study of meiotic chromosomes at the pachynema stage when cytological landmarks, chromomeres, and knobs are distinguishable by the light microscope, and chromosomal aberrations (deletions, duplications, inversions, translocations, etc.) can cytologically be identified and correlated with genetic segregation information. The pachytene analysis of plants is analogous to the study of giant chromosomes in dipteran flies and other lower animals. The bands of the (somatic) salivary chromosomes are tightly appositioned chromomeres in these endomitotic chromosomes. ►meiosis, ►salivary gland, ►chromomere, ►endomitosis, ►recombination nodule; McClintock B 1931 Missouri Agric Exp Sta Bull 163; Carlson WR 1988 In: Corn and Corn Improvement, Agricultural Monograph 18, ASA-CS-SSA, Madison, Wisconsin, p 259.

Pachytene Stage: The chromosomes form pachynema. pachynema.

Packaging Cell Lines (For Retroviral Vectors): For the replication of the vector the viral proteins gag, pol, env are required but these are deleted from the vectors to prevent the production of disease-causing virions. The packaging signal ψ is however retained in the vector. Another solution is to insert these viral genes

into host chromosomes or remove from the helper virus the packaging signal (Ψ [psi]) and delete the 3'-LTR. In neither case could the production (by two recombinations) of replication-competent virions be completely eliminated. Thus, the nucleic acid (with the transgene) can be packaged although the virions are defective. An improved construct removed LTRs from the structural genes and replaced them with heterologous promoters and polyadenylation signals. The *gag* and *pol* genes are placed on a plasmid different from the one that carries the *env* gene. Thus, in the packaging cell lines, these two are inserted at different chromosomal sites. Also, if the number of cell divisions is limited, the chance of recombination between vector and helper is reduced. In an improved packaging system, a stop codon is engineered into *gag* reading frame to prevent the assembly of a fully competent virus. In the packaging cell lines, the appropriate envelope protein for the intended target (ecotropic or amphotropic) should be present in the helper virus (pseudotyping) to insure optimal transfection. The envelope protein may need modification in order to ensure the proper targeting to the intended types of cells. Antibodies, specific for certain cell surface antigens or against particular receptors may be employed. Although some of these procedures appear very attractive, they may not always be equally efficient. These technical problems are obviously attracting serious research efforts. ▶retroviral vectors, ▶ecotropic retrovirus, ▶amphotropic retrovirus, ▶pseudotyping, ▶viral vectors; Thaler S, Schnierle BS 2001 Mol Ther 4(3):273.

P

Packaging of Phage DNA: λ phage gene A recognizes the cos sites, gene D assists in filling the head (capsid) and genes W, F, V ILK and GMH assemble the phage from prefabricated elements and act in the processes shown diagrammatically in Fig. P6.

The DNA that first enters the phage capsid has the Nu end and the opposite end (the last) is the R end. The organization of the DNA in the phage head is not random; the geometry of the arrangement is determined by writhe of the DNA (Arsuaga J et al 2005 Proc Natl Acad Sci USA 102:9165). ▶lambda phage, ▶p16, ▶development, ▶writhe number, ▶heedful rule; Smith DE et al 2001 Nature [Lond] 413:748, Kindt J et al 2001 Proc Natl Acad Sci USA 98:13671.

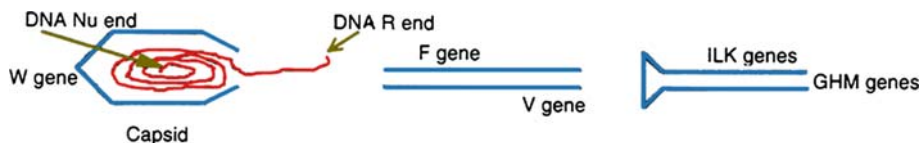


Figure P6. Packaging of phage DNA

Packaging Signal (ψ): Allows the stuffing of the viral genome into the viral capsid.

Packing Ratio: The DNA molecule is much-much longer than the most extended chromosomes fibers. The packing ratio was defined as the proportion of the DNA double helix and the length of the chromosome fibers. In the human chromosome complement, the packing ratio was estimated to be more than 100:1 at metaphase. The length of the *Drosophila* genome at meiotic metaphase was estimated to be 7.8 μm and the length of a chain of 3000 nucleotides is approximately 1 μm . The *Drosophila* genome contains about 9×10^7 bp, hence the total length of DNA within the *Drosophila* genome is about 30,000 μm and that would indicate a packing ratio of 3846:1. The packing ratio indicates some of the problems the eukaryotic chromosomes encounter in condensing an enormous length of DNA to a small space and still replicating, transcribing and recombining it in an orderly manner. To illustrate the problems in a trivial way: many eukaryotes have the same packing problem as folding a 2.5 km (1.6 mi) long thread into a 2.5 cm (1") skein. Prokaryotic type DNA—such as without nucleosomal structure—the excessive amount of plasmid DNA forms liquid crystalline molecular supercoils. ▶Mosolov model, ▶supercoiled DNA; see photo of bacterial chromosome at lysis, p. 1,150; DuPrav EJ 1970 DNA and Chromosomes. Holt, Rinehart and Winston, New York; Holmes VF, Cozzarelli NR 2000 Proc Natl Acad Sci USA 97:1322; Cook PR 2002 Nature Genet 32:347.

Pack-MULEs: The abundant (3000/rice genome) transposable elements in different plant species that carry fragments of cellular genes (~ 1000 in rice) derived from all chromosomes. These fragments can have multiple chromosomal origins, and can be functional. During millions of years, the fragments could be rearranged, amplified and contributed to evolution of plant genes. ▶transposable elements plants; Jiang N et al 2004 Nature [Lond] 431:569.

Paclitaxel: ▶taxol

Pac-Man Model: Kinetochores induce depolymerization of the microtubules of the kinetochore at their plus end and that allows the sister-chromatids to move toward the poles during mitosis by, so to say, chewing

up spindle fiber tracks. ►anaphase, ►spindle fibers, ►microtubules, ►kinetochore; Rogers GC et al 2004 Nature [Lond] 327:364; Liu J, Onuchic JN 2006 Proc Natl Acad Sci USA 103:18432.

PACT (p53 associated cellular protein): A negative regulator of p53. ►p53

Pactamycin: An inhibitor of eukaryotic peptide chain initiation (see Fig. P7).

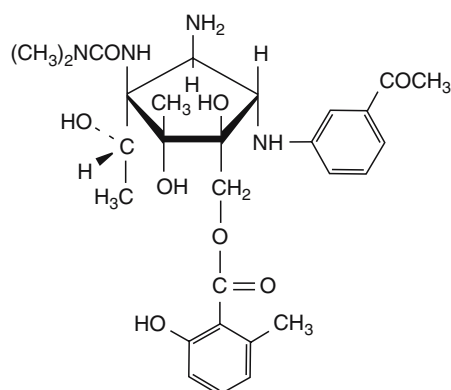


Figure P7. Pactamycin

PAD4: peptidylarginine deiminase. It converts methyl-arginine to citrulline and releases methylamine. It targets also multiple sites in histones H3 and H4. ►arginine, ►citrulline, ►methylation of DNA, ►histones, ►epigenesis; Wang Y et al 2004 Science 306:279.

Padlock Probe: Contains two target-complementary segments connected by linker sequences (see Fig. P8). Hybridization to target sequences brings the two ends close to each other and can be covalently ligated. The so circularized probes are thus catenated to the DNA (\approx) like a padlock (OO). Such probes permit high-specificity detection and distinction among similar target sequences and can be manipulated without alterations or loss. By using circularizable or circularized allele-specific probe, primers and rolling circle, amplification can detect mutations in short genomic sequences (see Fig. P9). The principle of the procedure is shown modified after Lizardi PM et al 1998 Nature Genet 19:225.



Figure P8. Padlock

Alternatively, for the rolling circle amplification two primers were used (see Fig. P10). After the first primer (P1) initiated the replication the second (P2) primer is bound to the tandem repeats and both primers generate repeats in opposite directions \rightarrow or \leftarrow using either the (+) or (−) strands, respectively. In 90 min, at least 10^9 copies of the circles are generated making it possible to detect very rare somatic mutations. Rolling circle amplification can detect gene copy number single base mutations and can quantify the transcribed mRNA (Christian AT et al

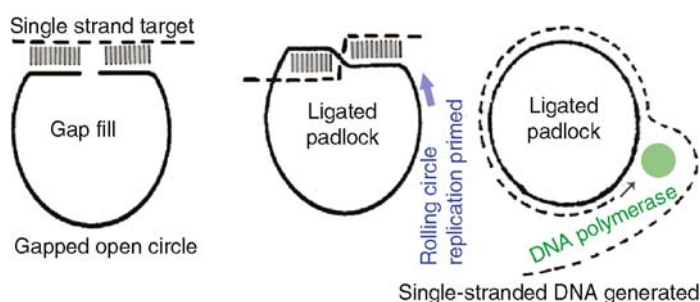


Figure P9. The probe at left, interrupted by a 6- to 10-base gap, hybridizes to the target DNA. The gap is filled with an allele-specific or DNA polymerase-generated sequence. After ligation, it generate a closed duplex padlock. A complementary (18-base) primer was then employed with a DNA polymerase. The original target DNA is not shown

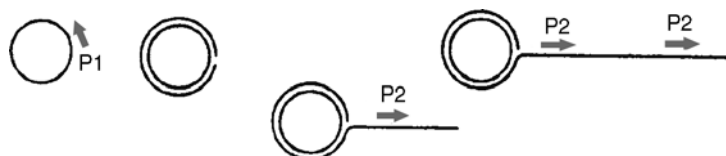


Figure P10. Padlock primers

2001 Proc Natl Acad Sci USA 98:14238). The procedure generated replication products, which were hybridized to either fluorescein- or Cy3-labeled deoxyribonucleoprotein-oligonucleotide (DNP) tags, respectively. The tag was anti-DNP immunoglobulin M (IgM). This process of condensation of amplification circles after hybridization of encoding tags is called CACHET. The procedure permits also the identification of single-copy genes by epifluorescence microscopy. ▶[probe](#), ▶[rolling circle](#), ▶[fluorochromes](#), ▶[immuno-globulins](#), ▶[DNA polymerases](#), ▶[microscopy](#), ▶[mutation detection](#); Baner J et al 2001 Curr Opin Biotechnol 12:11; Roulon Tet al 2002 Nucleic Acids Res 30 (3):e12.

Padumnal Allele: Derived from the male. ▶[madumnal allele](#)

PAF (population attributable fraction): PAF represents the fraction of the disease that would be eliminated if the risk factor were removed. High risk alleles generally show PAF > 50% whereas in rare alleles in common diseases it is generally <10%. The common modest-risk alleles account for greater PAF in common diseases than the rare high-risk alleles. This hypothesis is called the common disease/common variant (CDCV). ▶[complex disease](#), ▶[QTL](#), ▶[correlation](#), ▶[association](#), ▶[HapMap](#); Carlson CS et al 2004 Nature [Lond] 429:446.

PAF: A positive and negative regulator of RNA polymerase II mediated transcription (Shi X et al 1996 Mol Cell Biol 16:669). The Paf complex has a role also in polyadenylation of mRNA.

PAF-AH: platelet activating factor acetylhydrolase coupled with dynein affects neural migration in lissencephaly. ▶[lissencephaly](#), ▶[dynein](#); Tarricone C et al 2004 Neuron 44:809.

Page: An acronym for polyacrylamide gel electrophoresis. ▶[gel electrophoresis](#)

Paget Disease: Two autosomal dominant forms have been described involving cancer of the bones or of the anogenital region (the region of the anus and genitalia) or the breast. The disease is an anomaly of osteoclastogenesis. BDB1 gene was located to 6p21.3 and PDB2 (also called familial expansile osteolysis, FEO) to 18q21-q22. Mutations in the tumor necrosis factor receptor, TNFR seem to be involved and affect the signaling by NF-κB (RANK, receptor activator of nuclear factor κB). Additional loci mapped to 5q35-qter (PDB3), to 5q31 (PDB4), to 2q36 (PDB5) and 10p13 (PDB6). ▶[osteoclast](#), ▶[osteoporosis](#), ▶[NF-κB](#), ▶[TNFR](#); Laurin N et al 2001 Am J Hum Genet 69:528.

PAH (polyaromatic hydrocarbon): The majority of PAH are carcinogenic (see Fig. P11).

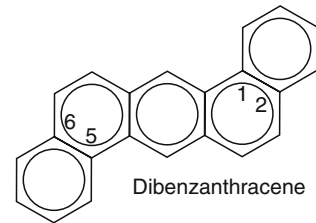


Figure P11. PAH

PAH (paired amphipathic helix motif): It may mediate protein-protein interactions in regulating enzyme functions. ▶[amphipathic](#)

PAI: plasminogen activation inhibitor. ▶[plasminogen activator](#); Eilers AL et al 1999 J Biol Chem 274:32750.

Pain-Insensitivity: Controlled by defects causing hereditary sensory neuropathies. In the dominant form, the dorsal ganglia are degenerated. In the recessive neuropathy, the loss of myelinated A-fibers cause touch insensitivity. The congenital pain insensitivity with anhidrosis (CIPA, 1q21-q22) involves a defect of the nerve growth factor receptor (TRKA), and in the congenital insensitivity to pain without anhidrosis, the small myelinated A-delta fibers are defective. Mutation in the Na-channel subunit (SCN9A, encoded at 2q24.3) leads to pain-insensitivity (Cox JJ et al 2006 Nature [Lond] 444:894). The apparent insensitivity to the self-torture of the fakirs (Hindu ascetics) may be based on such genetic condition. ▶[neuropathy](#), ▶[Riley-Day syndrome](#), ▶[TRK](#), ▶[sensory neuropathy 1](#), ▶[anhidrosis](#); Mardy S et al 2001 Hum Mol Genet 10:179; Cheng H-YM et al 2002 Cell 108:31.

Pain-Sensitivity: May be traditionally treated with analgesics. Gene therapy by introduction of genes producing analgesic substances (catecholamines, enkephalins) or antinociceptive peptides are potential molecular approaches. The capsaicin or vanilloid receptor (VR1) control heat-gated ion channel with response to low temperature (~43°C) stimuli whereas the VRL-1 receptor responds to about 52°C. The vanilloid channel receptor is induced by protein kinase C. The transcriptional repressor DREAM constitutively suppresses prodynorphin in the neurons of the spinal cord. When DREAM is knocked out, there is still sufficient expression of dynorphin but there is a strong reduction in pain-sensitivity. Single amino acid substitutions (val¹⁵⁸/met) in catechol-O-methyltransferase (COMT) may modulate pain sensitivity/insensitivity. Simultaneous, two synonymous and one

non-synonymous, divergence in the human haplotype of the gene modulate COMT protein expression by altering mRNAs secondary structure (Nackley AG et al 2006 Science 314:1930). Prostaglandin E^2 is a mediator of inflammatory pain-sensitization via glycine receptor $\alpha 3$ (Harvey RJ et al 2004 Science 304:884). Expectation of pain reduced the subjective feeling of pain as well as activation of pain-related areas of the brain (Koyama T et al 2005 Proc Natl Acad Sci USA 102: 12950). Covalent modification of reactive cysteines within TRPA1 (Transient Receptor Potential family of ion channels) by noxious compounds causes channel activation, rapidly signaling potential tissue

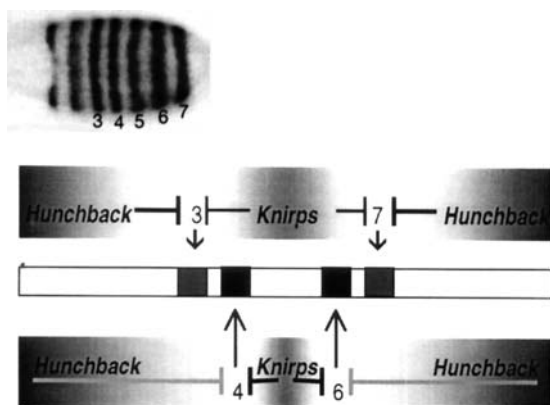


Figure P12. Pair rule genes. The banding pattern on the body of the *Drosophila* embryo is under the control of several regulatory genes. In the case of the *even-skipped* gene (chromosome 2.58) the seven stripes in the syncytial blastoderm are under the control of five enhancers. Three of them #1, #2, #3 drive the expression of single stripes and the remaining two control the expression of pairs of stripes (3 + 7 and 4 + 6). The stripes are formed at the boundary of interactions of the suppressor gradients of genes *Hunchback* (encoded at 3.48) and *Knirps* (encoded at 3.46) and the *even-skipped* enhancers. It is assumed that binding-site affinity and distribution on the enhancers determine the sensitivity to the repressors as illustrated on the diagram. The four bands in the middle represent body stripes (not chromosome bands!) brought about by the interactions of the suppressor gradients. (Modified after Clyde DE et al 2003 Nature [Lond] 426:849)

damage through the pain pathway (Macpherson LJ et al 2007 Nature [Lond] 445:541). ▶analgesic, ▶nociceptor, ▶catecholamines, ▶enkephalins, ▶endorphin, ▶dynorphin, ▶DREAM, ▶protein kinase, ▶prostaglandins, ▶allodynia, ▶temperature-sensitive mutation; Samad TA et al 20001 Nature [Lond] 410:471; Costigan M, Woolf CJ 2002 Cell 108:297; Mantyh PW et al 2002 Nature Rev Cancer 2:201; Zubieta J-K et al 2003 Science 299:1240.

Pair Rule Genes: Determine the formation of alternating segments in the developing embryo as shown in Figure P12. Similar segment pattern, although with variations, occurs in other insects too. ▶morphogenesis in *Drosophila*, ▶metamerism, ▶*fushi tarazu*, ▶*knirps*, ▶*engrailed*, ▶*Runt*

Paired Box Genes: ▶PAX

Paired t-Test: ▶matched pairs test, ▶Student's *t* distribution, ▶*t* value

Paired-End dTAG (PET): PET uses chromatin immunoprecipitation to enrich DNA fragments for the mapping transcription factors across the genome. It separates signature sequences from the 5' and 3' ends of the fragments, concatenates them and maps them (Ng P et al 2005 Nat Methods 2:105). ▶immunoprecipitation, ▶transcriptome, ▶transcription factor map

Paired-End Sequence: The product of the first sequencing of both ends of a cloned DNA tract. (See Zhao S et al 2000 Genomics 63:321).

Paired-End Sequence Method: The method used to identify structural alterations in the DNA. The standard genome sequence is compared with another genome represented by fosmid paired-end sequences (see Fig. P13). The procedure detects fine-scale variations in the genome that may be important for disease. ▶fosmid; Tuzun E et al 2005 Nature Genet 37:727.

Pairing (synapsis): The intimate association of the meiotic chromosomes mediated by several protein factors. In prokaryotes, the RecA and the RecT protein have important role and in yeast and humans, the Rad52 protein carries out similar functions. ▶meiosis, ▶zygotene, ▶pachytene analysis, ▶somatic pairing, ▶hydrogen pairing, ▶base pair, ▶tautomeric shift, ▶synapsis,

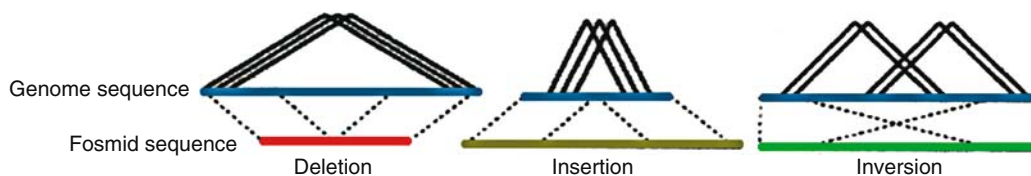


Figure P13. Paired-end sequence method

►*RecA*, ►*RecT*, ►*Rad*, ►*Ph* gene; Kagawa W et al 2001 J Biol Chem 276:35201.

Pairing Alkylated Bases: ►alkylation

Pairing Centers: The cis-acting sites required for accurate segregation of homologous chromosomes during meiosis of *Caenorhabditis elegans* (MacQueen AJ et al 2005 Cell 123:1037). The *HIM-8* gene, encoding a zinc-finger protein, concentrates at the pairing centers on the X chromosome mediates chromosome-specific synapsis (Phillips CM et al 2005 Cell 123:1051).

Pairing-Sensitive Repression: Polycomb (PC) proteins bind to Polycomb-response elements (PREs) and thus cause repression. Repression is enhanced when two such elements are present. There are other similar elements like Mcp. ►*Polycomb*

Pair-wise Likelihood Score: Estimates the potential relationship between pairs of individuals on the basis of allele sharing. (See Smith BR et al 2001 Genetics 158:1329).

PAK (p21 activated kinase): The serine/threonine kinases activated by GTPases, Rac and Cdc42. Pak3 regulates Raf-1 by phosphorylating serine 338 in rats. Paks regulate the actin cytoskeleton, cell motility, neurogenesis, angiogenesis, signal transduction, apoptosis, metastasis, etc. A non-syndromic mental retardation (human chromosome Xq22, yeast homolog is *STE20*) prematurely terminates PAK3 transcription. ►*GTPase*, ►*Rac*, ►*raf*, ►*Cdc42*, ►*p21*, ►*p35*, ►*PDK*, ►*actin*, ►*cytoskeleton*, ►*apoptosis*, ►*mental retardation*, ►*non-syndromic*; Xia C et al 2001 Proc Natl Acad Sci USA 98:6174; Bokoch GM 2003 Annu Rev Biochem 72:743.

PAL: Phenylalanine ammonia lyase.

Palea: The inner, frequently translucent, bract around the grass flower (see Fig. P14).

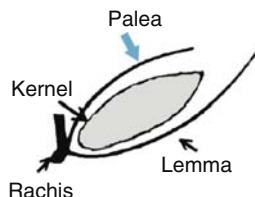


Figure P14. Palea

Paleogenomics: ►ancient DNA

Paleolithic Age (Old Stone Age): More than 20,000 years ago it marked the beginning of human tool formation and cave artistry by the Cro-Magnon

humans. ►*neolithic*, ►*mesolithic*, ►*geological time periods*, ►*Lascaux*, ►*Neanderthal*

Paleologous Loci: Include ancient duplications.

Paleontology: Deals with the relics of past geological periods. Its methods and materials are used for the study of the evolution of biological forms. ►*paleolithic age*, ►*geological time periods*; Eurasian Miocene and Pleistocene land mammals and excavation sites: <http://www.helsinki.fi/science/now/>.

Paleozoic: The geological period between about 225 to 570 million years ago. During the later part of this period land plants, amphibians and reptile appeared. ►*geological time periods*

Palindrome: The region of a DNA strand where complementary bases are in opposite sequence, such as ATGCAC*GTGCAT (see Fig. P15). Palindromes may come about by inverted repeats of sections of the double-stranded DNA where these sequences of the opposite strands read the same forward and backward. Upon folding of these sequences in a single strand, they can assume structures with paired bases.

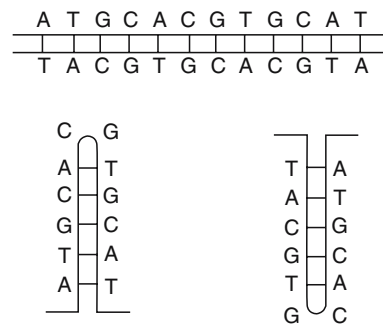


Figure P15. Palindromic DNA and possible pairing within single strands of it. (From Flavell RB, Smith DB 1975 Stadler Symp 7:47)

Palindromic sequences in the DNA reassociate very rapidly because of the complementary bases are in close vicinity. A simple palindromic word is MADAM, it reads the same from left to right or from right to left. Palindromic sequences are often unstable; recombination within palindromes results in deletions and duplications. The restriction enzyme recognition sites are palindromic. Palindromes are common in cancer cells and provide a platform for gene amplification and chromosomal aberrations (Tanaka H et al 2005 Nature Genet 37:320). ►*stem and loop*, ►*inverted repeats*, ►*insertion elements*, ►*restriction enzyme*, ►*RecA independent recombination*; Leach DR 1994 Bioessays 16:893; Nasar F et al 2000 Mol Cell Biol 20:3449; Zhu Z-H et al 2001 Proc Natl Acad Sci USA 98:8326; short

palindromic repeat detection: <http://crispr.u-psud.fr/Server/CRISPRfinder.php>.

Palingenesis: The regeneration of lost organs and parts or the reappearance of evolutionarily ancestral traits during ontogeny. According to Ernst Haeckel (1834–1914) the ontogeny recapitulates the phylogeny. ▶ontogeny, ▶phylogeny

Palisade Cells: Oblong cells and arranged in a row; the large palisade parenchyma cells are below the upper epidermis of plant leaves and loaded with chloroplasts (see Fig. P16).

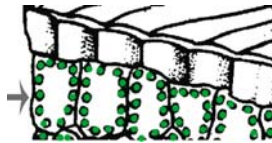


Figure P16. Palisade cells in a leaf

Pallister-Hall Syndrome: postaxial polysyndactyly (PA-PA1), encoded in human chromosome 7q13, at the same location as the Greig syndrome. The gene is also called GLI3 and its product has a homology to the *Drosophila* Krüppel Zn-finger protein. The clinically distinct phenotypes of the two diseases are due to different allelic mutations of the same gene (Johnston JJ et al 2005 Am J Hum Genet 76:609). A similar syndactyly was recorded by French scientist, Maupertuis, in the Prussian royal court in Berlin in 1756. ▶polydactyly, ▶Greig cephalopolysyndactyly, ▶DNA-binding protein domains, ▶EEC syndrome, ▶Smith-Lemli-Opitz syndrome

Palmitoylation: The covalent attachment of fatty acids (mainly palmitate) to cysteine residues to membrane proteins by creating a thioester link. This process tethers protein reversibly to cellular membrane surfaces. The enzymes involved belong to the protein acetyltransferase (PAT) family (e.g., Akr1, Erf2) and share a common domain of DHHC (aspartate-histidine-histidine-cysteine; see Mitchell DA et al 2006 J Lipid Res 47:1118). Palmitoylated proteins play key roles in cell signaling, membrane traffic, cancer and synaptic transmission, heterotrimeric G proteins and many non-receptor tyrosine kinases (Fyn, Lck, Yes) and the epithelial nitric oxide synthase are palmitoylated. By proteomic analysis, 35 new PAT proteins have been identified in budding yeast (Roth AF et al 2006 Cell 125:1003). ▶fatty acids, ▶G proteins, ▶Fyn, ▶Lck, ▶Yes, ▶nitric oxide

Palmprint: ▶fingerprint, ▶Down's syndrome, ▶simian crease

Palomino: A horse with light tan color fur and flaxen mane and tail. The genetic constitution is *AAbbCCDd* (see Fig. P17).



Figure P17. Palomino

PALS: ▶alternative splicing

Palsy (paralysis): Cerebral palsy may be caused by physical injuries or may be part of the symptoms of diverse genetic syndromes. ▶syndrome, ▶tau

PAM: ▶evolutionary clock

PAMAM (polyamidoamine): The dendrimers can carry chemotherapy compounds (methotrexate) to the cancer cell, especially if connected with folate hooks that attach preferentially to the abundant folate receptors of cancer cells. ▶dendrimer, ▶methotrexate, ▶nanotechnology; Najlah M et al 2007 Bioconjug Chem 18:937.

PAMP: pathogen-associated molecular pattern recognition is an important step in developing reaction in animals and plants against infection. ▶vaccine

PAN: The genus of chimpanzees. ▶primates, ▶hominidae; Gagneux P 2002 Trends Genet 18:327.

PAN Editing: Adding of U residues to the primary transcripts of mtDNA and thus causing extensive post-transcriptional changes in RNA. ▶kinetoplast, ▶RNA editing

Pancreas: A large gland behind the stomach, between the spleen and the duodenum. It secretes insulin, glucagons, and protein-digesting enzymes. ▶spleen, ▶duodenum, ▶insulin, ▶glucagons, ▶diabetes, ▶Langerhans islets, diabetes: <http://www.cbil.upenn.edu/EPConDB>.

Pancreatic Adenocarcinoma: The cancer of the pancreas is frequently associated with loss or defect of DCC, or p53 or MTS1 oncogene suppressors. One study revealed an average of 15 annotated gene alterations (amplifications, deletions, tumor suppressors) in 24 adenocarcinoma lines (Aguirre AJ et al 2004 Proc Natl Acad Sci USA 101:9067). It was also attributed to mutations in codon 12 of the c-K-ras

(Kirsten RAS) gene encoded at human chromosome 12p12. A dominant susceptibility locus was assigned to 4q32-q34. Chromosomal aberrations, telomere shortening, methylation of CpG islands and point mutation may be the underlying cause. Silencing of cancer suppressors by hypermethylation at multiple genes may be involved. HER2/NEU overexpression is also a frequent cause. Tyrosine-kinase growth factor receptors may be involved. It may be associated with the Peutz-Jeghers syndrome (66%) and other syndromes such as hereditary pancreatitis (40%), BRCA2 (5–10%), etc. Its prevalence in the USA is $\sim 3 \times 10^{-5}$, and its prognosis is bad. ▶DCC, ▶p53, ▶p16, ▶Kirsten-Ras, ▶p21, ▶Peutz-Jeghers syndrome, ▶HER2, ▶NEU; Eberle MA et al 2002 Am J Hum Genet 70:1044; Hansel DE et al 2003 Annu Rev Genomics Hum Genet 4:237.

Pancreatitis, Hereditary: Autosomal dominant (7q35) gene (80% penetrance and variable expressivity) has an onset before the teen years, appearing as abdominal pain and other anomalies. The basic defect is in a cationic trypsinogen. ▶trypsin, ▶Johanson-Blizzard syndrome

Pancytopenia: Low blood cell number.

Panda (*Ailurus fulgens*): $2n = 36$.

Pandemic: The infection by a microbe or virus spread over large areas (countries, continents).

Paneth's Cells: The secretory intestinal epithelial cells expressing defensin and other antimicrobial peptides. In the Paneth cells of mice, 149 transcripts expressed 2 to 45-fold by microbial colonization. Among them was very abundant (31-fold increase) a bactericidal lectin (RegIIIγ) that may represent a primitive evolutionary form of innate immunity (Cash HL et al 2006 Science 313:1126). ▶defensin, ▶microbiome; Ghosh D et al 2002 Nature Immunol 3:583.

Pangenesis: An ancient misconception about heredity that originated in the Aristotelian epoch and periodically revived during the centuries. Charles Darwin has also interpreted inheritance as pangenesis. Accordingly, all the information expressed during the life of the individuals is transported to the gametes from all parts of the body. Thus, pangenesis is the means of the inheritance of all, including the acquired characters. ▶lysenkoism, ▶acquired characters

Pangenome: The essential, shared sequences among all representatives of a species (Tettelin H et al 2005 Proc Natl Acad Sci USA 102:13950).

Panic Disorder (PD): Episodic panic attacks involving palpitations, sweating, shortness of breath, feeling of choking, chest pain, false touch sensations usually in the absence of physical contact (such as burning, prickling), nausea, etc. The heritability appeared

0.48. Panic disorder may be associated with a number of physical diseases. Chromosome 13q appears to harbor several genes responsible for PD and chromosome 22 may carry some susceptibility factors. ▶psychoses, ▶panic obsessive disorder, ▶anxiety; Hamilton SP et al 2003 Proc Natl Acad Sci USA 100:2550.

Panicle: An inflorescence of a compound raceme structure such as of oats. ▶raceme

Panmictic Index: ▶fixation index, ▶panmixis

Panmixis (panmixia): Random mating; in a population there is equal chance for each individual to mate with any other of the opposite sex. ▶Hardy-Weinberg theorem

Panning: The use of antibody affinity chromatography or ELISA for the separation of specific molecules (in analogy to the gold-washing pans of the gold hunters). ▶affinity chromatography, ▶ELISA, ▶phage display; Chen G et al 2001 Nature Biotechnol 19:537.

Panspermia: The theory claiming that life has originated at several places in the universe and spread to earth by meteorites or by other means. ▶origin of life

Panther (*Panthera pardus*, leopard): $2n = 38$: A feline species; in captivity may be crossed with lion but no mating is known to take place in the wild where conspecific sexual partners are available.

Panther: The database for functionally related proteins, signaling pathways. <http://panther.appliedbiosystems.com>.

Pantothenic Acid: A precursor of Coenzyme A (see Fig. P18).

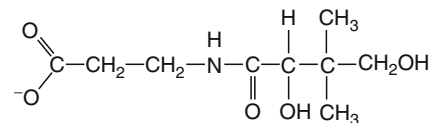


Figure P18. Panthotenate

Pantropic: Can affiliate with many different types of tissues.

PAP (purple acid phosphatases): Ubiquitous metallo-phosphoesterase proteins with phosphatase, exonuclease, 5'-nucleotidase, etc. functions. (See Li D et al 2002 J Biol Chem 277:27772).

Pap (Papanicolaou) Test: A cytological test for pre-malignant or malignant conditions (used primarily on smears obtained from the female urogenital tract). It detects also papilloma virus infections. ▶malignant growth, ▶papilloma virus

PAPA Syndrome (pyogenic sterile arthritis and acne and familial recurrent arthritis, 15p): It may involve also ulcerative skin lesions (pyoderma gangrenosum). It may be caused by defects in the 15-exon CD2-binding protein1 (CD2BP1). ▶CD2; Wise CA et al 2002 Hum Mol Genet 11:961; Shoham NG et al 2003 Proc Natl Acad Sci USA 100:13501.

Papain: A member of a family of proteolytic enzymes with an imidazole group near the nucleophilic SH group, and the former plays a role as a proton donor to the cleaved-off part. Papain cleaves immunoglobulin G into three near equal size fragments and this helped in clarifying the structure of antibodies. ▶proteolytic, ▶calpain, ▶immunoglobulins, ▶antibody

Papanicolaou Test: ▶PAP test

Papaver: ▶poppy

Papaya (*Carica papaya*): A melon-like, edible fruit, latex-producing small tree with four genera and all $2n = 2x = 18$; it is the source of the proteolytic enzyme papain. ▶papain

PapD: Gram-negative bacterial chaperone (28.5 kDa) delivers the components of the pilus from the periplasm. ▶periplasma, ▶chaperones, ▶pilus, ▶Gram negative/Gram positive

Paper Chromatography: A technique for the separation of (organic) molecules in filter paper by applying the mixture in a spot or band at the bottom of the paper and allowing an appropriate solvent to be sucked up and thus carry the components at different speed (to different height) so they can be separated (see Fig. P19). The components become visible by their

natural color or by the application of specific reagents. A large variety of different modifications were worked out in one or two dimensions, in ascending and descending ways. Nowadays paper chromatography is not used very much. ▶chromatography, ▶thin layer chromatography, ▶Rf value, ▶column chromatography, ▶high performance liquid chromatography, ▶affinity chromatography, ▶ion-exchange chromatography

Papillary Renal Cancer, Hereditary: Based on the MET oncogene at human chromosome 7q31, encoding a hepatocyte growth factor receptor. ▶MET, ▶HGF, ▶receptor tyrosine kinase

Papillary Thyroid Carcinoma: Caused by the RET oncogene. It accounts for about 80% of the thyroid cancers that have prevalence in the 10^{-5} range. Its incidence is higher in females than males. ▶RET

Papillation, Bacterial: Secondary colonies develop on the colonies of bacteria.

Papilloma: Pre-malignant neoplasia displaying epithelial and dermal finger-like projections.

Papilloma Virus (HPV, human papilloma virus): A double-stranded DNA ($\approx 5.3 \times 10^6$ Da or ~ 8 kb) virus causing animal and human warts and squamous carcinomas in mice. The HPV-16 and 18 are frequently present in cervical cancer. The E6 viral protein of HPV-16—through a ubiquitin path—is prone to degrade the p53 tumor suppressor if at amino acid position 72 there is an arginine rather than a proline. The E7 protein of strain HPV-18 degrades another tumor suppressor protein RB. The E1 protein is a hexameric helicase (Enemark EJ, Joshua-Tor L 2006 Nature [Lond] 442:270). Apparently, highly effective vaccines have been developed against HPV strains 16 and 18 that most commonly cause viral cervical cancer. HPV is a critical factor in the majority of cases of cervical cancer that which allowed development of strategies to prevent this form of oncogenesis. It is important to note that several other cancers are also associated with HPV infection, including head and neck cancers. Cancer prevention will require the long-term observation of a large number of treated women and it is necessary in the meantime to monitor for unintended adverse consequences of vaccination (Baden LR et al 2007 N Engl J Med 356:1990). There is also an unresolved moral and ethical problem regarding the age of vaccination of adolescent, sexually not active girls. HPV has about 100 different strains and some pose cancer risk whereas some others do not seem to be carcinogenic. HPV is one of the most common causes of sexually transmitted disease and condom use does not offer perfect protection because the transmission is through

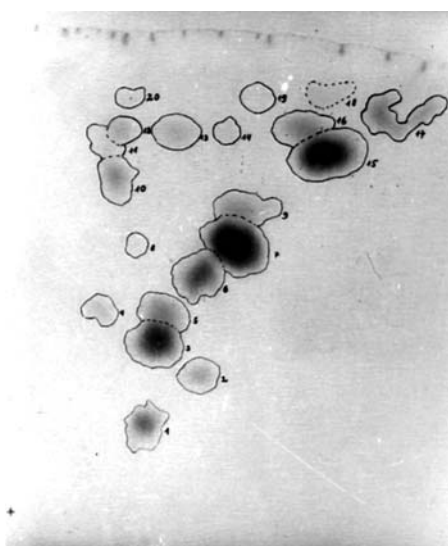


Figure P19. Two-dimensional separation of 20 amino acids in a plant extract

the skin. HPV has been used as a genetic vector. ▶papova viruses, ▶p53, ▶retinoblastoma, ▶tumor suppressor, ▶cervical cancer, ▶Pap test, ▶condom, ▶helicases; Wolf JK, Ramirez PT 2001 *Cancer Invest* 19:621.

Papillon-Lefèvre Syndrome: ▶periodontitis

Papova Viruses: A large class of (oncogenic) animal viruses of double-stranded, circular DNA includes the polyoma viruses, the bovine papilloma virus and simian virus 40 (SV40), etc. that have been used as genetic vectors for transformation of animal cells. Also, they have been extensively studied by molecular techniques to gain information on structure and function. ▶polyoma, ▶Simian virus 40, ▶papilloma virus; Soeda E, Maruyama T 1982 *Adv Biophys* 15:1.

PAPS: 3'-phosphoadenosine-5'-phosphosulfate is a sulfate donor in several biochemical reactions, involving cerebroside, glycosaminoglycans and steroids. It is generated by the pathway: ATP + sulfate → adenosine-3'-phosphosulfate (APS) + pyrophosphate, APS + ATP → PAPS + ADP. Mutations at 10q23-q24 (spondyloepimetaphyseal dysplasia, SEMD) locus encoding the PAPSS2 cause short bowed limbs, large knee joints, brachydactyly, curved spinal column (kyphoscoliosis). ▶bone diseases

PAR (pseudoautosomal region): Where recombination may take place between the X and Y chromosomes. The ends of both of the short arm (PAR1) and the long arm (PAR2) have pseudoautosomal regions. ▶pseudoautosomal, ▶X chromosome, ▶Y chromosome, ▶lyonization; Dupuis J, Van Eerdewegh P 2000 *Am J Hum Genet* 67:462.

PAR (protease-activated receptors): The seven-transmembrane G protein-coupled receptors that mediate thrombin-triggered phosphoinositide hydrolysis. Pars are involved in thrombosis, inflammation and vascular biology. Matrix metalloprotease (MMP-1) is an agonist of Par1 (Boire A et al 2005 *Cell* 120:303). Pars may also activate proteases and protect the airways. Par1 has a role in invasive and metastatic cancers. PAR is a cofactor of PAR4. Binding and phosphorylation of PAR4 by Akt is essential for the survival of cancer cells. Inhibition of the PI3K-Akt pathway leads Par4-dependent apoptosis (Goswami A et al 2005 *Mol Cell* 20:33). Par2 is a trypsin receptor. ▶thrombin, ▶phosphoinositides, ▶metalloproteinases, ▶AKT, ▶apoptosis; Kamath L et al 2001 *Cancer Res* 61:5933.

Parabiosis: Two animals joined together naturally such as Siamese twins or by surgical methods and can be used to study the interaction of hormones, transduction signals, etc., in-between two different

individuals. Intrauterine parabiosis develops immune tolerance.

Paracellular Space: The intercellular space in the tissues.

Paracentric Inversion: ▶inversion paracentric

Paracentrotus lividus: Sea urchin; extensively studied by embryologists. ▶sea urchins

Paracrine Effect: A ligand (e.g., hormone) is released by a gland and affects neighboring cells.

Paracrine Stimulation: When one type of cell affects the function (such as proliferation) of another (nearby) cell. ▶autocrine; Janowska-Wieczorek A et al 2001 *Stem Cells* 19:99.

Paracytosis: Passing bacteria through cell layers without disruption of the cells (See van Schilfgaarde M et al 1995 *Infect Immun* 63:4729).

Paradigm: A model or an example to be followed.

Paradox: A statement or phenomenon, which is apparently contradictory to current knowledge but may actually be true.

Paraesthesia (paresthesia): Peripheral nerve damage, disease-caused itching, burning and tickling sensation.

Paraganglioma: ▶mitochondrial diseases in humans

Paraganglion: Cells originating from the nerve ectoderm flanking the adrenal medulla, and darkly stained by chromium salts. These cells may form a type of pheochromocytoma tumors that secrete excessive amounts of epinephrine and norepinephrine. ▶SHC oncogene

Paragenetic: phenotypic alterations not involving hereditary mutation.

Parahemophilia: Determined by homozygosity of semi-dominant autosomal genes. The symptoms involve bleeding similar to the conditions observed in hemophiliacs, bleeding from the uterus (menorrhagia) several days following childbirth. The physiological basis is a deficiency of proaccelerin, a protein factor (V) involved in the stimulation of the synthesis of prothrombin. The therapy requires blood or plasma. ▶antihemophilia factors, ▶hemophilia, ▶pro-thrombin deficiency, ▶hemostasis

Parahox Genes: The hox-like genes in clusters, separate from the hox genes, and has originated by duplication from an ancestral protohox gene. ▶homeotic genes

Parainfluenza Viruses: A group of immunologically related but distinguishable pathogens responsible for some respiratory diseases. ▶Sendai virus

Paralinin: ▶karyolymph

Parallel Cascade Identification: Non-linear systems modeling approach. In biology, it can be used to predict long-term treatment response for cancer on the basis of small differences of gene expression levels. (See Korenberg MJ 2002 J Proteome Res 1:55).

Parallel Substitution: Various organismal lineages may display similar or different nucleotides at a number of sites. The chance of these substitutions at a site (p) in (n) lineages can be predicted on the basis of the binomial distribution, $(p + [1 - p])^n$ and upon expansion, e.g., for $n = 5$ it becomes $p^5 + 5p^4(1 - p) + 10p^3(1 - p)^2 + 10p^2(1 - p)^3 + 5p(1 - p)^4 + (1 - p)^5$ and the same change per any two lines is p^2 . ▶evolution and base substitutions, ▶evolutionary substitution rate, ▶evolutionary tree, ▶parallel variation

Parallel Synthesis: An approach commonly applied in drug development. Several similar compounds are generated simultaneously rather in a sequence, one after the other in order to speed up the process of discovery of effective drugs. ▶combinatorial chemistry

Parallel Variation: Within taxonomically closely or even distantly related groups of organisms similar mutations may occur during evolution. Mutation in regulatory switches may be the basic cause of these alterations. ▶parallel substitution; Vavilov NI 1922 J Genet 12:47; Pagel M 2000 Brief Bioinform 1(2):117.

Paraloci: They have the same properties as pseudoalleles. ▶pseudoalleles

Paralogon: A pair of genes evolutionarily derived from common ancestral sequences.

Paralogous Loci: Originated by duplication that was followed by divergence. However, Paralogs may provide backup in case of defect or damage of one of the pairs (Kafri R et al 2005 Nature Genet 37:295). ▶orthologous loci, ▶isolocus, ▶evolution of proteins, ▶non-orthologous gene displacement, ▶gene family, ▶duplication, ▶subfunctionalization, ▶tetralogue, ▶outparalog, ▶inparalog; Yamamoto E, Knap HT 2001 Mol Biol Evol 18:1522.

Paralogy: Evolution by duplication of a locus. ▶orthologous loci, ▶orthology, ▶homolog

Paramecium: Unicellular Protozoan. Normally reproduces by binary fission, i.e., a single individual splits into two. Each cell has two diploid micronuclei and a polyploid macronucleus. At fission, the micronuclei divide by mitosis while the macronucleus is simply halved. These animals also have sexual processes (*conjugation*). Two of the slipper-shaped cells of opposite mating type attach to each other and proceed

with meiosis of the micronuclei (see Fig. P20). Only one of the four products of meiosis survives in each of the conjugants. Each of these haploid cells divides into four cells (gametes). One of these gametes (male) is passed on into the other conjugating partner through a *conjugation bridge* and fuses with a haploid gamete (female).

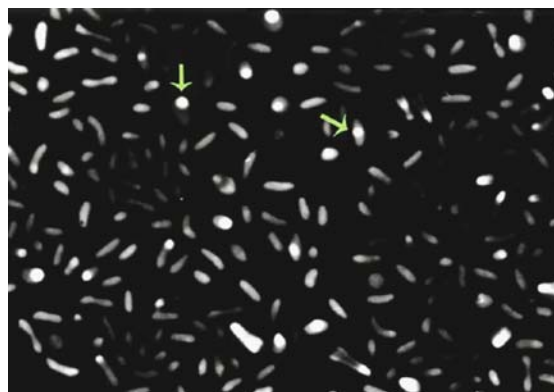


Figure P20. *Paramecium aurelia* (500 X) cells with bright and non-bright kappa particles symbionts (1,650X). The symbionts are bacteria. The bright particles contain the so-called R (refractive) bodies, which are bacteriophages. The non-bright kappa can give rise to bright indicating lysogeny. The kappa-free (*kk*) paramecia are sensitive to the toxin produced by the bright particles and may be killed. The K, killer stocks are immune to the toxin. (From Preer JR et al 1974 Bacteriol Rev 38:113 [Photo by C. Kung]; courtesy of Dr. J. R. Preer)

This is a reciprocal fertilization, resulting in diploid nuclei in the conjugants. Subsequently the pair separates into two *exconjugants*. The macronucleus disintegrates then in both. The diploid zygotic nuclei undergo two mitoses and form four diploid nuclei each. Two of the four nuclei function as separate micronuclei of the cells whereas the other two fuses into a macronucleus that become polyploid, and that is responsible for all metabolic functions and for the phenotype. Besides this sexual reproduction (*conjugation*), *Paramecia* may practice self-fertilization (*autogamy*).

Meiosis takes place and the one surviving product divides twice by mitoses. Two of these identical cells then fuse and form two diploid, isogenic micronuclei.

If the conjugation lasts longer, cytoplasmic particles may also be transferred through the conjugation bridge. Chromosome numbers may be 63–123; in the macronuclei there may be 800 or more chromosomes. *P. tetraurelia* genome includes 39,642 genes and 80% carry introns of mean 25 bp. The large gene number is apparently the result of whole genome duplication (Aury J-M et al 2006 Nature [Lond] 444:171). ▶killer

strains, ►symbionts hereditary, ►*Ascaris*, ►macro-nucleus, ►chromosome diminution, ►duplication, ►polyploidy, ►internally eliminated sequences, ►cortical inheritance, ►conjugation paramecia; Sonneborn TM 1974 In: King RC (Ed.) Handbook of Genetics, vol. 2, Plenum, New York, p. 469; Prescott DM 2000 Nature Rev Genet 1:191; *Paramecium tetraurelia* database: <http://paramecium.cgm.cnrs-gif.fr>.

Parameter: A quantity that specifies a hypothetical population in some respect or a variable to which a constant value is attributed for a specific purpose or process. Statistics usually denotes parameters by Greek letters and Latin letters indicates the computed values.

Parameter Alpha: ►alpha parameter

Parametric Methods in Statistics: Involves explicit assumptions about population distribution and parameters such as the mean, standard deviation of the normal distribution, the p parameter of the *Bernoulli process*, etc. ►Bernoulli process, ►normal distribution, ►non-parametric statistics, ►robustness

Parameter Space: In a dynamic system the values of the various parameters of a model are constrained within this limit.

Paramyxoviruses: Negative-sense retroviruses of 15–19 kb RNA containing 6–10 genes. They are infectious to a wide range of mammals. In humans, they cause influenza-like respiratory diseases. (See Gotoh B et al 2002 Rev Med Virol 12:337).

P

Paramutation: A *paramutable* allele becomes a *paramutant* (paramutated) in response to a *paramutagenic* allele if the two are in heterozygous condition. The alteration is similar but not identical to the paramutagenic allele. Both *paramutability* and paramutagenic functions are allele-specific. In contrast to gene conversion, paramutation may take place at low frequency and also in the absence of a paramutagenic allele. At the R locus of maize partial reversion of the paramutant may happen but this has not been observed at the B locus of maize. The paramutant phenotype at the R locus may vary but at the B locus, the phenotype appears to be uniform. The exact mechanism of this heritable alteration is not fully understood.

Apparently at the R locus of maize hypermethylation is involved, at the B locus involvement of methylation has not been detected. Distant upstream sequences play regulatory role in the expression and paramutation of the B' locus (Stam M et al 2002 Genetics 162:917). At the pl locus the paramutation seems to results in a genetic alteration of the chromatin structure, which affects the regulation of the expression of the gene during development. It appears that the level of

transcription is reduced at the paramutant allele compared to that in the paramutable one.

Although paramutation has been considered an endogenous mechanism, it appears that in the promoter region of the two r alleles in the homozygotes the *doppia* (CACTA) transposable elements are present within the 387 bp σ region that is intercalated between the two S elements in opposite orientation. (These elements are called S because they are responsible for anthocyanin coloration of the seed by this complex locus. The elements responsible for coloration of the plant were named P). Paramutation of the bl locus of maize depends on an RNA polymerase encoded by the *mop1* gene (*mediator of paramutation*). Paramutation at the bl locus involves the presence of non-coding tandem repeats of an

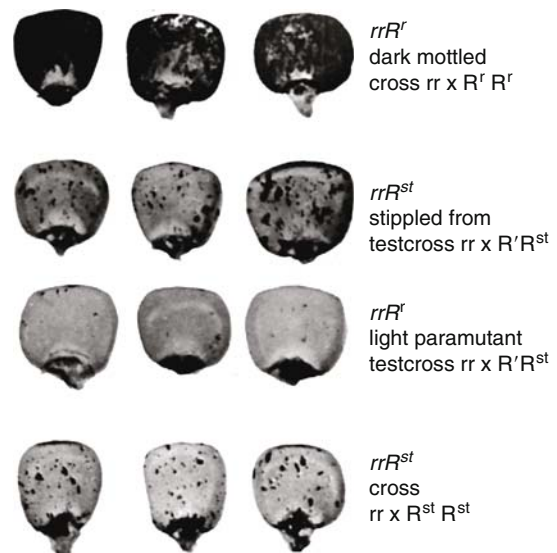


Figure P21. Paramutation results in reduced pigmentation in the triploid aleurone of maize. The R^r homozygotes are fully colored (when all other color-determining alleles are present). The r homozygotes are colorless. The rr genotype is responsible for the dark mottled aleurone. R^{st} causes paramutation (stippling) of the R^r paramutable allele that may be manifested in different grades. In the crosses the pistillate parents are shown first, left. (Courtesy of Brink RA see also 1956 Genetics 41:872)

853 bp sequence 100 kb upstream. The number of repeats may be 7 to 1. The strength of the paramutation is correlated with the number of these repeats and a single copy is not sufficient for paramutation. The RNA polymerase transcribes both strands of the repeats (Alleman M et al 2006 Nature [Lond] 442:295).

Paramutation is not a general property of all genes although similar phenomena have been observed at

a few other genes in maize and other plants. This phenomenon seems to violate the Mendelian principle that alleles segregate during meiosis independently and during the process, no “contamination” takes place. Paramutation in the broad sense involves several types of gene silencing in various organisms. Paramutation-like phenomenon attributed to transmethylation was observed in mouse (Herman H et al 2004 Nature Genet 34:199). A new mechanism of paramutation was reported in mouse. Insertion of a 3 kilobase *LacZ-neomycin* cassette into the *Kit* gene downstream of initiator ATG site resulted in mutation involving white spots in the animals because inactivation of a tyrosine kinase receptor and defect in melanogenesis (►phenotype on the reconstructed image of an animal). Although the homozygotes were lethal, the heterozygotes expressed the phenotype as illustrated. The proven wild type individuals (lacking the insertion) among the progeny of heterozygotes displayed the white patches on the tail and feet as did the heterozygous mutants. This phenotype was transmitted by male and female to the offspring and there was a reduced level of *Kit* mRNA and an accumulation of abnormal size non-polyadenylated RNA molecules. The paramutant condition was transmitted through meiosis for several generations but eventually it was diluted out. Injection into fertilized eggs either the total RNA from *Kit^{tm1Alf/+}* or *Kit*-specific microRNA also induced the white tail (see Fig. P22). The observations indicate a particular type of epigenetic inheritance of RNA molecules (Rassoulzadegan M et al 2006 Nature [Lond] 441:469). This phenomenon bears similarities to the case in the plant *Arabidopsis* claiming that a cache of RNA can be maintained in the nuclei and cause the reappearance of an atavistic trait (Lolle S et al 2005 Nature [Lond] 434:505). Newer information indicates, however, that the apparent “atavism” is due to contamination by pollen of the *Arabidopsis* mutant *HOTHEAD*, which has protruding stigma making unexpected cross-pollination easier (Pennisi E 2006 Science 313:1864). ►gene conversion, ►copy choice, ►directed mutation, ►localized mutagenesis, ►pan-genesis, ►blending inheritance, ►presence-absence hypothesis, ►graft hybrid, ►co-suppression, ►RIP, ►epigenesis, ►position effect, ►transvection, ►tissue specificity, ►atavism; Brink RA 1960 Quart Rev Biol 35:120; Hagemann R, Berg W 1978 Theor Appl Genet

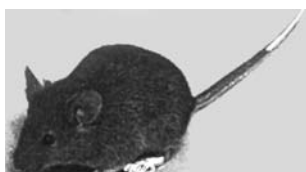


Figure P22. *Kit^{tm1Alf}*

53:113; Chandler VL 2000 Plant Mol Biol 43 (2–3):121; Lisch D et al 2002 Proc Natl Acad Sci USA 99:6130; Chandler VL, Stam M 2004 Nature Rev Genet 5:532; Chandler VL 2007 Cell 128:641.

Paramyotonia: Periodic paralysis (gene located in human chromosome 17). ►myotonia

Paramyxovirus: Single-stranded RNA viruses with a genome of 16–20 kb. Members of this group cause human mumps, respiratory diseases in human and other animals, including birds and reptiles. ►RNA viruses

Paranemic Coils: The two components of the coil can be separated from each other without any entanglement as one can easily pull apart two spirals that were pushed together after they were wound separately, i.e., they are not interlocked. ►plectonemic coils

Paraneoplastic Neurodegenerative Syndrome: ►auto-immune diseases

Paranoia: A psychological disorder in more (paranoia) or less severe (paranoid) state. The major characteristics are delusions of persecution (delusional jealousy, erotic delusions) or less frequently by feeling of grandiosity. It differs from schizophrenia in that, the rest of the personality and mental capacity may remain normal. Frequently, however, paranoid schizophrenia may occur. The precipitating factors are insecurity, frustration, physical illness, drug effects, etc. There is also an apparently undefined genetic component. ►schizophrenia, ►affective disorders

Paranome: Genes within gene families; the entire sets of duplicated genes. ►gene family

Paranormal: Beyond the normal biological expectation, e.g., extrasensory perception. It has been reported (Cha KY et al 2001 J Reprod Med) that prayer for success of in vitro fertilization approximately doubled the success of pregnancy in an international, randomized, double-blind clinical trial involving 219 women. More recently, experts questioned the outcome of this study and suspected inappropriate handling of the experiment (Nature [2004] 429:796). In the nineteenth century, Francis Galton, the father of biometrics, concluded that prayer has unlikely influence on worldly events because the number of shipwrecks was not effected by the fact that praying missionaries were aboard or royalties, for whom their subjects regularly prayed, did not live longer than other citizens. In some instances, when prayer provides comfort, beneficial psychological effects may result (Handzo G et al 2004 N Engl J Med 351:192; ►creationism

Paraoxonase (PON1, 7q21.3): May be associated with high-density lipoprotein in the blood plasma. It may

protect against coronary heart disease by destroying oxidized lipids, responsible for inflammation. It may detoxify organophosphate pesticides (parathion, chlorpyrifos [Dursban]). ▶ **arylesterase**, ▶ **cholinesterase**, ▶ **pseudocholinesterase**, ▶ **HDL**, ▶ **Kupffer cell**; Brophy VH et al 2001 *Am J Hum Genet* 68:1428.

Parapatric Speciation: Groups of organisms inhabiting an overlapping region become sexually isolated. ▶ **allopatric**, ▶ **sympatric**

Paraphyletic Group: Does not include all descendants of the latest common ancestor.

Paraplegia: The paralysis of the lower part of the body; it may be hereditary. ▶ **Pelizaeus-Merzbacher disease**, ▶ **Silver syndrome**, ▶ **spastic paraplegia**, ▶ **Mast syndrome**, ▶ **ALS**

Paraplegin: ▶ **mitochondrial disease in humans**

Paraptosis: A programmed neuronal cell death different from apoptosis in as much it is mediated by a caspase-9, which is independent of Apaf-1 and it does not respond to Bcl-X. ▶ **apoptosis**, ▶ **Apaf-1**, ▶ **BCL**; Sperandio S et al 2000 *Proc Natl Acad Sci USA* 97:14376.

Paraprotein: An abnormally secreted normal or abnormal protein, e.g., the Bence-Jones protein in myelogenous myeloma. It is also called M component. ▶ **Bence-Jones protein**

Paraquat: An artificial electron acceptor of photosystem I and a lung toxicant. It may produce oxidative stress by indirect production (through cellular diaphorases) of superoxide radicals. ▶ **diquat**, ▶ **photosystem I**, ▶ **diaphorase**, ▶ **superoxide**, ▶ **ROS**

Pararetrovirus: The genetic material is double-stranded DNA but it is replicated with the aid of an RNA molecule, e.g., in hepadnaviruses and caulimoviruses. They may occur in many copies in higher eukaryote genomes. ▶ **animal viruses**, ▶ **plant viruses**, ▶ **retroviruses**, ▶ **hepatitis B virus**, ▶ **cauliflower mosaic virus**; Richert-Poggeler KR, Shepherd RJ 1997 *Virology* 236:137; Gozuacik D et al 2001 *Oncogene* 20:6233.

Parascaris: A group of nematodes. ▶ **Ascaris**

Parasegment: The unit of a metamer complex consisting of the posterior part of one segment and the anterior part of another in insect larval and subsequent stages. ▶ **morphogenesis**

Paraselectivity: An apparent (but not real) selectivity in pollination among plants.

Parasexual Mechanism of Reproduction: The somatic-cell fusion and mitotic genetic recombination. The processes bear similarities to those common at sexual reproduction but do not involve sexual mechanisms.

▶ **mitotic recombination**, ▶ **cell fusion**, ▶ **somatic cell genetics**; Pontecorvo G 1956 *Annu Rev Microbiol* 10:393.

Parasitemia: The blood contains parasites, e.g., *Plasmodium*. ▶ **thalassemia**, ▶ *Plasmodium*

Parasitic: That which lives on and takes advantage of another live organism. ▶ **biotrophic**, ▶ **parasitoid**; <http://www.ebi.ac.uk/parasites/parasite-genome.html>; various parasites' database: <http://fullmal.ims.utokyo.ac.jp>.

Parasitic DNA: same as DNA selfish.

Parasitoid: Lives on another organism and eventually destroys it like some wasps and viruses. Some plants—upon attack and wounding by some insects—synthesize and emit host and parasite specific volatile compounds that attract parasitoid wasps that in turn may destroy the insects. The parasitoid wasp *Cotesia congregata* of the lepidopteran host *Manduca sexta* harbors Polydnavirus. The virus is injected into the host along with the parasitoid egg. The viral genome controls the host immune system and protects the wasp progeny development inside the host. The virus genome is 567,670 bp contained by 30 DNA circles of 5–40 kb, including 156 coding sequences of 66% AT; 69% of the viral genes has introns. The rest of the viral DNA is non-coding (Espagne E et al 2004 *Science* 306:286). ▶ **parasitic**, ▶ **biological control**, ▶ **aphid**

Paraspeckles: Formed from RNA-binding proteins in the cell nucleus within the interchromatin nucleoplasmic space, usually at the periphery of the nucleolus and in the vicinity of the nuclear speckles. ▶ **speckles**; Fox AH et al 2002 *Curr Biol* 12:13.

Parasterility: Caused by incompatibility between genotypes that may be fertile in other combinations. ▶ **self-incompatibility alleles**, ▶ **Rh blood group**

Parastichies: The imaginary helical line in phyllotaxis. ▶ **phyllotaxis**

Parathormone (parathyroid hormone, 11p15.3-p15.1): Produced by the parathyroid gland next to the thyroid gland. It is a regulator of calcium and phosphate metabolism (mediated by cAMP) primarily in the bones, kidneys and the digestive tract. A recessive hypoparathyroidism was mapped to Xp27. ▶ **hypercalcemia-hypocalciuria**, ▶ **hyperparathyroidism**, ▶ **enchondromatosis**; Healy KD et al 2005 *Proc Natl Acad Sci USA* 102:4724.

Parathyroid Hormone: Regulates Ca^{2+} level in animals. ▶ **parathormone**

Paratope: The epitope-binding site of the antibody Fab domain. ▶ **antibody**, ▶ **epitope**

Paratransgenic: An insect, which has transgenic symbionts inhabiting its gut. *Rhodnius prolixus* carries the actinomycete bacterium *Rhodococcus rhodnii* with which it has a symbiotic relationship. *R. prolixus* is a blood-sucking arthropod, vector of *Trypanosoma cruzi*, responsible for Chagas disease. When *R. rhodnii* is transformed by cecropin A, a 38-amino acid antimicrobial peptide derived from the moth *Hyalophora cecropia*, the peptide diffuses into the insect and lyses *Trypanosoma cruzi* within the insect without serious damage to *R. rhodnii* and thus effectively curtails the propagation of the protozoan. This is a more attractive defense than using chemical pesticides. ▶transgenic, ▶*Trypanosoma*, ▶Chagas disease, ▶CRUZIGARD; Beard CB et al 2001 Int J Parasitol 31:621.

Parcelation: The relative lack of pleiotropic effects between two sets of non-overlapping traits.

Parenchyma: In plant biology it means storage cells, either near isodiametric, *spongy parenchyma*, closer to the lower surface of the leaves or the *palisade parenchyma* consisting of one or two layers of columnar cells with their long axis perpendicular to the upper epidermis. Both types of tissues contain conspicuous intercellular space. In zoology, the parenchyma cells mean the functional units, rather than the network of an organ or tissue. ▶palisade cells

Parens Patriae: The state or community right to intervene against individual rights or beliefs and protect the interest of a person against potentially serious or actually life-threatening conditions, e.g., compulsory immunization, genetic screening, prohibition of incest, etc.

Parental Ditype: ▶tetrad analysis

Parental Histone Segregation: In front of the DNA replication fork the existing nucleosome structure is temporarily and reversibly disrupted to make nascent

DNA readily accessible to the replication protein machinery (see Fig. P23).

Parenteral: The application of a substance by injection rather than by oral means.

Parent-of-Origin Effect: May be due to the differences in the cytoplasm, differential transmission of defective chromosomes through the two sexes, differences in trinucleotide-repeat expansions, endosperm: embryo chromosomal differences in the reciprocal crosses in case of polyploids and imprinting. ▶imprinting, ▶trinucleotide repeats, ▶uniparental disomy, ▶uniparental inheritance; Morrison IM, Reeve AE 1998 Hum Mol Genet 7:1599; Haghighi F, Hodge SE 2002 Am J Hum Genet 70:142.

Pareto Distribution: $f(x) = \frac{\gamma \alpha^\gamma}{x^{\gamma+1}}$ Applicable for the gene expression profiles. Some genes are expressed at very high level other transcripts occur once or even less per cell thus the distribution is highly skewed by the low-abundance transcripts (see Fig. P24). The Pareto probability distribution is: $\alpha \leq x < \infty, \alpha > 0, \gamma > 0$, mean = $\gamma \alpha / (\gamma - 1, \gamma > 1$ and variance = $\gamma \alpha^2 [(\gamma - 1)^2 (\gamma - 2), \gamma > 2$ (See Kuznetsov VA et al 2002 Genetics 161:1321).

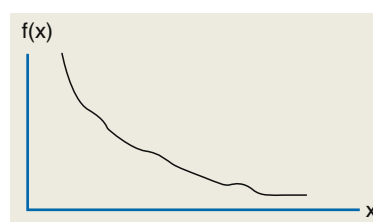


Figure P24. A hypothetical Pareto distribution

Parietal: Situated on the wall or attached to the wall of a hollow organ.

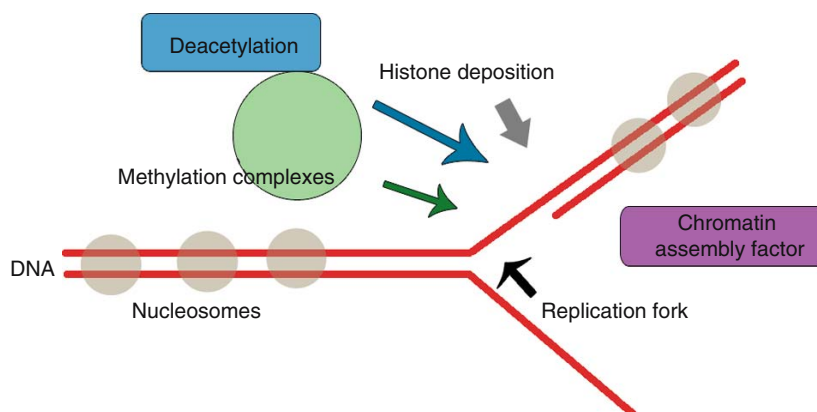


Figure P23. Nucleosome remodeling—Parental histone segregation

Periodontal Disease: Involves inflammation of the tissues surrounding teeth such as gingiva, ligaments, gum, etc. ► [point-of-care test](#)

Paris Classification: Paris classification of human chromosomes standardized (in 1971) the banding patterns and classified them by size groups; it is very similar to what is used today. Current maps show, however, only one of the two chromatids. ► [human chromosomes](#), ► [Denver classification](#), ► [Chicago classification](#)

Parity: Parity in gene conversion the process can go equally frequently in the direction of one or the other allele. ► [gene conversion](#); Fogel S et al 1971 Stadler Symp 1–2:89.

Parity: In human biology, it is the condition that a woman had borne offspring. Natural selection does not necessarily favor maximal reproduction because reproduction imposes fitness costs, reducing parental survival, and offspring quality. Parents in a pre-industrial population in North America incurred fitness costs from reproduction, and women incurred greater costs than men. The survivorship and reproductive success (Darwinian fitness) of 21,684 couples, married between 1860 and 1895, identified in the Utah Population Database showed that increasing number of offspring (parity) and rates of reproduction were associated with reduced parental survivorship, and significantly more for mothers than fathers. Parental mortality resulted in reduced survival and reproduction of offspring, and the mothers' mortality was more detrimental to offspring than the fathers' were. Increasing family size was associated with lower offspring survival, primarily for later-born children, indicating a tradeoff between offspring quantity versus quality (Penn DJ, Smith KR 2007 Proc Natl Acad Sci USA 104:553). ► [fitness](#), ► [reproductive rate](#), ► [fecundity](#), ► [fertility](#)

Parity Check: In a digital system it reveals whether the number of ones and zeros is odd or even.

Parkin: ► [Parkinson's disease](#)

Parking: A set of rules for seeding in which no seed overlaps with any other seedings. It is an iterative procedure that may be used at the early phase in genome sequencing. Each iteration sequences a new portion of non-overlapping piece of the DNA. Aside for non-overlaps, the sequences are chose at random. ► [seeding](#), ► [genome projects](#); Roach JC et al 2000 Genome Res 10:1020.

Parkinsonism: A secondary symptom caused either by drugs, or inflammation of the brain (encephalitis), or Alzheimer's disease, or Wilson's disease, or Huntington's chorea, etc. ► [Parkinson's disease](#) and the conditions named above, ► [tau](#)

Parkinson Disease (PD, PARK): A shaking palsy (bradykinesia) generally with late onset, however juvenile forms also exist. PD may include mental depression, dementia, reduced olfactory abilities and deficiency of several different substances, notably dopamine, from the nervous system. The genetic determination of the heterogeneous symptoms is unclear; autosomal dominant, recessive, X-linked, polygenic and apparently only environmentally caused phenotypes have been observed. The prevalence of PD is 0.001 and it may be 0.01 over age 50 but perhaps no more than 10% of the cases are familial.

Defects in the mitochondrial complex I resulting in oxidative stress favor the development of PD (Canet-Avilés RM et al 2004 Proc Natl Acad Sci 101:9103). Conditional knockout mice (termed MitoPark mice), with disruption of the gene for mitochondrial transcription factor A (*Tfam*) and in progressive degeneration of the nigrostriatal dopamine system (DA) neurons have reduced mtDNA expression and respiratory chain deficiency in midbrain DA neurons, which, in turn, leads to a parkinsonism phenotype with adult onset of slowly progressive impairment of motor function, accompanied by formation of intraneuronal inclusions and dopamine nerve cell death. Confocal and electron microscopy show that the inclusions contain both mitochondrial protein and membrane components demonstrating that respiratory chain dysfunction in DA neurons may be of pathophysiological importance in PD (Ekstrand MI et al 2007 Proc Natl Acad Sci USA 104:1325). Endocannabinoids may have beneficial effects on motor deficits in PD and Huntington chorea (Kreitzer AC, Malenka RC 2007 Nature [Lond] 445:643).

A PTEN-induced putative kinase (*PINK1*) mutation in *Drosophila* that has high similarity to human PINK1 also encodes a mitochondrially located protein and it is complemented by parkin (Park J et al 2006 Nature [Lond] 441:1157; Clark IE et al 2006 Nature [Lond] 441:1162). Loss-of-function mutations in a previously uncharacterized, predominantly neuronal P-type ATPase gene, *ATP13A2*, underlying an autosomal recessive form of early-onset Parkinsonism with pyramidal degeneration and dementia (PARK9, Kufor-Rakeb syndrome) were observed. The pyramidal cells are excitatory neurons in cerebral cortex. The wild-type protein was located in the lysosome of transiently transfected cells; the unstable truncated mutants were retained in the endoplasmic reticulum and degraded by the proteasome (Ramirez A et al 2006 Nature Genet 38:1184).

The herbicide paraquat, the fungicide maneb, the insecticide rotenone and other environmental toxins may contribute to PD by inhibiting complex I (Dawson TM, Dawson VL 2003 Science 302:819).

Mitochondrially coded nicotinamide adenine dinucleotide dehydrogenase complex plays a role in reduced susceptibility (van der Walt JM et al 2003 *Am J Hum Genet* 72:804).

An early onset PD was located to human chromosome Xq28 and another (PARK6) to 1p35-p36. Mitochondrially localized PTEN-induced kinase 1 (PINK1, 1p35) mutations are involved in PARK6 (Valente EM et al 2004 *Science* 304:1158). PINK contains a serine-threonine protein kinase domain; it localized in mitochondria. An autosomal dominant form is in chromosome 22. Another locus encoding spheres of protofibrils of α -synuclein was assigned to human chromosome 4q21-q23. The α -synuclein gene is apparently responsible for only a minor fraction of Parkinsonism. A susceptibility gene (SNCA) has been located also to human chromosome 17q21. Multiple copies of SNCA may occur in a single nucleus. A low penetrance (40%), late onset (~60 years) gene is at 2p13. Autosomal dominant juvenile Parkinsonism gene (1395 bp ORF) encoding the 465-amino acid *parkin* protein was located to 6q25.2-q27. Parkin is an E3 ubiquitin protein ligase and ubiquitin-proteasome deficit favors the development of PD and its S-nitrosylation inhibits its normal protective action (Kung KKK et al 2004 *Science* 304:1328). Parkinson disease is Parkinsonism without the formation of Lewy bodies. Several other loci are also involved with the development of this disease. Protein DJ-1 (1p36)—situated in the mitochondria—is a protein regulating mRNA stability and its defect can cause Parkinsonism.

The parkin gene appears to be a suppressor of ovarian cancer and adenocarcinoma (Cesari R et al 2003 *Proc Natl Acad Sci USA* 100:5956). In some cases a missense mutation in the carboxy terminal hydrolase L1 (UCH-L1, 4p14), component of the ubiquitin complex, localized in the Lewy bodies, is responsible for PD. Not all forms of PD shows Lewy bodies. Loss of dopaminergic neurons in the substantia nigra is usually associated with the disease. Glial cell line-derived neurotrophic factor (GDNF) has nutritive effects on the dopaminergic nigral neurons. In an autosomal recessive juvenile PD parkin-associated endothelin receptor-like (Pael-R) accumulates apparently because a misfolded Pael-R is not degraded if there is a defect in parkin. LRRK2 (PARK8, 12p12) is a leucine-rich repeat kinase gene involving Lewy body disease of advanced adult age.

Parkin has several other substrates and that explains the complicated etiology of the different forms of PD (Imai Y et al 2001 *Cell* 105:891; Shimura H et al 2001 *Science* 293:263).

Various tomography techniques facilitate detection of susceptibility to PD before the appearance of clinical symptoms. The imaging can measure the

integrity of dopamine in the substantia nigra of the brain. The procedure is based on the conversion of 18F-DOPA into 18F-dopamine or by the use of DOPA transporter (DAT) ligands. The reduction in DAT ligand uptake correlates with the loss of dopamine in the corpus striatum (the striped gray substance in front and beside the thalamus in the brain) and this is characteristic for aging and particularly for incipient PD. Also, loss of fluorodeoxyglucose distinguishes PD from other neurodegenerative diseases. Dopamine dysfunction may be indicated also by olfactory impairment (see DeKosky ST, Marek K 2003 *Science* 302:830).

Gene therapy using lentivirus vector carrying the GDF gene, injected into the brain (striatum and substantia nigra) of old monkeys or young monkeys pretreated with a nigrostriatal degeneration inducing agent (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]) reversed the functional deficits and prevented degeneration, respectively. Anticholinergics (blocking choline) and dopamine, glial-cell-derived neurotrophic factor (GDNF) treatments may be somewhat beneficial. An alternative approach may be using gene therapy by expressing transfected tyrosine hydroxylase or aromatic amino acid decarboxylase in the striated muscle cells. These enzymes can produce dopamine yet the response is below expectation. New approaches appear more promising ([▶ gene therapy](#)). Transplantation of fibroblasts equipped for secretion of BDNF and GDNF into the brain appears promising in animal models. Inhibition of cyclooxygenase (COX-2) seems to prevent the formation of the oxidant dopamine-kinone, which has been implicated in Parkinsonism (Teismann P et al 2003 *Proc Natl Acad Sci USA* 100:5473). Electric shocks localized to the globus pallidus (a medial part of the brain) had beneficial effects in some cases. Caspase-3 may be a conditioning factor in the apoptotic death of dopaminergic neurons in PD. Embryonic stem cells may develop into dopamine-producing neurons in the brain of the mouse and seem to be promising for cell-replacement therapy of PD (Kim J-H et al 2002 *Nature [Lond]* 418:50; Barberi T et al 2003 *Nature Biotechnol* 21:1200). Midbrain proteins Lmx1a and Msx1 mediate dopamine neuron differentiation of proneural protein NGN2 and seem important for cell replacement therapy in PD (Andersson E et al 2006 *Cell* 124:393). Activation of intracellular neurotrophic signaling pathways by vector transfer is a feasible approach to neuroprotection and restorative treatment of neurodegenerative disease. Adeno-associated virus 1 transduction with a gene encoding a myristoylated, constitutively active form of the oncoprotein Akt/PKB had pronounced trophic effects on dopamine neurons of adult and aged mice, including increases in neuron size, phenotypic markers, and sprouting. Transduction confers almost complete

protection against apoptotic cell death in a highly destructive neurotoxin model (Ries V et al 2006 Proc Natl Acad Sci USA 103:18757). Nix, a pro-apoptotic BH3-only protein, promotes apoptosis of non-neuronal cells. Using a yeast two-hybrid screen with POSH (plenty of SH3 domains, a scaffold involved in activation of the apoptotic JNK/c-Jun pathway) as the bait, identified an interaction between POSH and Nix and contributed to cell death in a cellular model of Parkinson disease (Wilhelm M et al 2007 J Biol Chem 282:1288). The disease-linked processes are detectable in peripheral blood by 22 unique genes differentially expressed in patients with PD versus healthy individuals. Such an approach may provide biomarkers for early clinical detection of the disease (Scherzer CR et al 2007 Proc Natl Acad Sci USA 104:955). Multiple axon-guidance pathway genes may predispose to PD (Lesnick TG et al 2007 PloS Genet 3(6):e98). ▶parkinsonism, ▶neuromuscular diseases, ▶dopamine, ▶adeno-associated virus, ▶Akt, ▶tyrosine hydroxyls, ▶Lewy body, ▶Kufor-Rakeb syndrome, ▶GDNF, ▶BDNF, ▶dopamine, ▶mitochondrial disease in humans, ▶substantia nigra, ▶synuclein, ▶caspase, ▶ubiquitin, ▶tau, ▶stem cells, ▶brain human, ▶tomography, ▶PTEN, ▶argyrophilic grains, ▶BAK, ▶cannabinoids, ▶axon guidance; Dawson TM 2000 Cell 101:115; Kordower JH et al 2000 Science 290:767; Valente EM et al 2001 Am J Hum Genet 68:895; Vaughan JR et al 2001 Ann Hum Genet 65:111; Lansbury PT Jr, Brice A 2002 Curr Opin Genet Dev 12:299; Betarbet R et al 2002 BioEssays 24:308; Cookson MR 2005 Annu Rev Biochem 74:29; Farrer MJ 2006 Nature Rev Genet 7:306.

Paromomycin (C₂₃H₄₅O₁₄N₅): An aminoglycoside antibiotic. It may cause translational errors by increasing the initial binding affinity of tRNA. Oral LD₅₀ in mice is 1625 mg/kg. ▶phenotypic reversion, ▶aminoglycoside antibiotics, ▶LD50

Parotid Gland: The salivary gland; the proline-rich parotid glycoprotein is encoded in human chromosome 12p13.2.

Parexysm: Recurring events such as convulsions (but most commonly normal conditions in between), sudden outbreak of disease.

Parexysmal Nocturnal Hemoglobinuria: A dominant human chromosome 11p14-p13 susceptibility of the erythrocytes to destruction by the complement because of a deficiency in protectin (HRF20/CD59) and DAF. ▶complement, ▶membrane attack complex, ▶DAF, ▶angioneuritic edema, ▶CD59, ▶protectin, ▶hemoglobin

PARP (poly[ADP-ribose] polymerase): An enzyme involved in surveillance and base excision repair of

DNA and NAD⁺-dependent chromatin remodeling (Kim MY et al 2004 Cell 119:803). PARP is involved in puff formation of *Drosophila* gene loci (Tulin A, Spradling A 2003 Science 299:560). It is cleaved by an ICE-like proteinase. Its deficiency increases the sensitivity to radiation damage, recombination and sister chromatid exchange. PARP is required also for the assembly and structure of the spindle (Chang P et al 2004 Nature [Lond] 432:645). PARP-deficient mice are viable and free of tumors and inhibitors of PARP/DNA repair activity can selectively kill BRCA2 defective tumor cells (Bryant HE et al 2005 Nature [Lond] 434:913). PARP deficiency prevents homologous recombination repair of damaged BRCA1 and BRCA2 eventually apoptosis eliminates the mutant cells (Farmer H et al 2005 Nature [Lond] 434:917). ▶ICE, ▶apoptosis, ▶puff, ▶tankyrase, ▶telomeres, ▶spindle, ▶DNA repair, ▶breast cancer, ▶Kif; Bauer PI et al 2001 FEBS Lett 506(3):239; Lavrik OI et al 2001 J Biol Chem 276:25541.

PARS (poly[ADP-ribose] synthetase): PARS attaches ADP-ribose units to histones and to other nuclear proteins. It is activated when DNA is damaged by nitric oxide.

Parser: A software for reading flat files for further processing. ▶flat file

Parsimony: ▶maximal parsimony, ▶evolutionary tree

Parsing: Resolve it to parts or components. ▶exon parsing, ▶pars means part in Latin

Parsley (*Petroselinum crispum*): The roots and leaves of parsley are used for flavoring; 2n = 2x = 22 (see Fig. P25).



Figure P25. Parsley

Parsnip (*Pastinaca sativa*): A root vegetable; $2n = 2x = 22$ (see Fig. P26).



Figure P26. Parsnip

Parsonage–Turner Syndrome (Feinberg syndrome/Tinel syndrome/Kiloh–Nevin syndrome): The syndrome is most likely to be identical with hereditary amyotrophic neuralgia; it is also very similar to the Guillain–Barré syndrome. ▶[amyotrophy hereditary neuralgic](#), ▶[Guillain–Barré syndrome](#)

Parthenocarp: The development of fruit without fertilization. It may have horticultural application by producing seedless apple varieties such as Spencer Seedless or Wellington Bloomless. The gene responsible in these apples is homologous to *pistillata* of *Arabidopsis*. ▶[parthenogenesis](#), ▶[apomixia](#), ▶[seedless fruits](#), ▶[flower differentiation in Arabidopsis](#); Yao J et al 2001 Proc Natl Acad Sci USA 98:1306.

Parthenogenesis: Embryo production from an egg without fertilization. Parthenogenesis may be induced in sea urchins by hypotonic media or in some amphibia by mechanical or electric stimulation of the egg. In some fish, lizards and birds (turkey) it occurs spontaneously. Parthenogenesis in animals is most common among polyploid species. Parthenogenetic individuals produce only female offspring. On theoretical grounds, parthenogenesis may be disadvantageous because it deprives the species of elimination of disadvantageous mutations on account of the lack of recombination available in bisexual reproduction. Parthenogenesis may cause embryonic lethality in mouse if the imprinted paternal genes are not expressed. Parthenogenesis is not known to occur in humans (or generally in mammals but deletion of

imprinting may yield viable parthenogenetic mouse), however it may exist as a chimera when after fertilization, the male pronucleus is displaced to one of the blastomeres and then the maternal chromosome set in the other blastomere is diploidized. The failure of parthenogenetic development of mammalian offspring is due to the requirement for imprinting (Kono T et al 2004 Nature [Lond] 428:860). Fusion of two oocyte nuclei can produce, however, viable, fertile mouse. Many plant species successfully survive by asexual reproduction as an evolutionary mechanism. Parthenogenesis in plants is called apomixis or apomixia. Asexually reproducing plant populations appear to be preponderant under conditions marginally suitable for the species is called *geographic parthenogenesis*. ▶[apomixia](#), ▶[gynogenesis](#), ▶[parthenocarp](#), ▶[RSK](#), ▶[imprinting](#), ▶[oocyte](#); Mittwoch U 1978 J Med Genet 15:165; Cibelli JB et al 2002 Science 295:819; Krawetz SA 2005 Nature Rev Genet 6:633.

Parthenote: An egg stimulated to divide and develop to some extent in the absence of fertilization by sperm. Parthenotes may offer possibilities for stem cell production for therapeutic purposes when embryonic stem cells are prohibited. ▶[parthenogenesis](#), ▶[apomixia](#); Kiessling AA 2005 Nature [Lond] 434:145.

Partial Digest: The reaction is stopped before completion of nuclease action and thus the DNA is cut into various size fragments some of which may be relatively long because some of the recognition sites were not cleaved. ▶[restriction enzyme](#)

Partial Diploid: ▶[merozygote](#)

Partial Dominance: An incomplete dominance, semi-dominance.

Partial Linkage: The genes are less than 50 map units apart in the chromosome and can recombine at a frequency proportional to their distance. ▶[crossing over](#), ▶[recombination](#)

Partial Trisomy: Only part of a chromosome is present in triplicate. ▶[trisomy](#)

Particulate Inheritance: The modern genetic theory that inheritance is based on discrete particulate material (written in nucleic acid sequences) transmitted conservatively rather than according to the pre-Mendelian theory of pangenesis, which claimed that the hereditary material is a miscible liquid subject to continuous changes under environmental effects. According to the particulate theory of genetics, genes are discrete physical entities that are transmitted from parents to offspring without blending or any environmental influence, except when mutation or gene conversion

or imprinting occurs. ►pangenesis, ►gene conversion, ►mutation, ►imprinting, ►blending inheritance

Particulate Radiation: ►physical mutagens

Partington Syndrome (Xp22.13): Primarily mild or moderate mental retardation accompanied by developmental anomalies caused by polyalanine expansion in the *aristaless-like* homeobox gene. (*al*, *aristaless* alleles were discovered early in *Drosophila* and mapped to chromosome 2.4; some involved cytologically detectable inversions. Mammalian homologs exist.) At this chromosomal area several other similar mental retardation genes occur. Some have recessive expression others are dominant. ►homeotic genes, ►mental retardation, ►mental retardation X-linked

Partitioning (segregation): The distribution of plasmids and/or the bacterial chromosome(s) into dividing bacterial cells. It may be a passive process mediated by the attachment of the DNAs to the cell membrane. The partition depends on ParA and ParB proteins by the P1 plasmid. ParB recognizes at the partition site a dimeric B box and at the opposite ends two A boxes with helix-turn-helix (HTH) domains (see Fig. P27). The HTH domains emanate from the dimerized DNA-binding modules composed of a six-stranded β -sheet coiled coil that binds the B boxes (Schumacher MA, Funnell BE 2005 Nature [Lond] 438:516). A bacterial tubulin-like protein FtsZ may carry out the separation. Plasmid and bacterial genes control the process. The bacterial chromosome or some of the plasmids seem to have a centromere-like protein that may bind to the cell poles and to 10 copies of a sequence situated along a 200 kb region near the replicational origin. The loss of the chromosome in the new cells is less frequent than 0.003. The segregation of plasmids present in multiple copies is more complex. Mechanisms (“addiction” system) exist to resolve plasmid dimers and to ensure that each cell would have at least one copy of a plasmid. The two-component addiction module include a stable toxin and a labile antitoxin. The plasmid-free cells may be eliminated (Engelberg-Kulka H, Glaser G 1999 Annu Rev Microbiol 53:43). ►segregation, ►cell division, ►addiction module, ►plasmid maintenance; Hiraga S

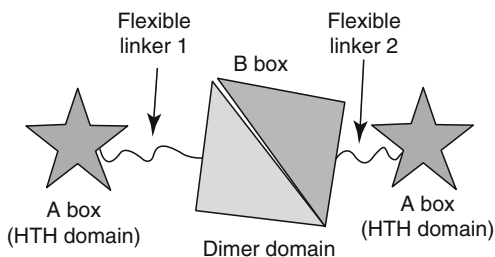


Figure P27. Partitioning

2000 Annu Rev Genet 34:21; Gordon GS, Wright A 2000 Annu Rev Microbiol 54:681; Draper GC, Guber JW 2002 Annu Rev Microbiol 56:567.

Partitioning: In statistics, breaking down the variances among the identifiable experimental components or in a compound chi square to reduce the quantity of the residual or error variance. ►analysis of variance

Parturition: The labor of child delivery.

Parvoviruses: Non-enveloped, icosahedral (18–25 nm), single-stranded DNA (~5.5 kb) viruses. The group includes the densovirus of arthropods, the autonomous, lytic parvoviruses and the adeno-associated viruses. ►icosahedral, ►adeno-associated virus, ►autonomous parvovirus, ►oncolytic viruses; Lukashov VV, Goudsmit J 2001 J Virol 75:2729.

Parvulin: A very small monomeric 92-amino acid prolyl isomerase of *E. coli* involved in protein maturation. Similar proteins occur in yeast (Ess1, 19.2 kDa) and humans (Pin1, 18 kDa) and *Drosophila* (dodo, 18.3 kDa). Ess1 may not have isomerase activity, but Pin1 does. In the absence of Ess1 the nuclei fragment and growth ceases, dodo has apparently similar function as Ess1 and it is interchangeable. Pin regulates mitotic progression by interacting with CDC25 and NIMA. ►PPI, ►peptidyl-prolyl isomerases, ►CDC25, ►NIMA; Rulten S et al 1999 Biochem Biophys Res Commun 259:557.

PAS Domain (Per-Arnt-Sim): A shared motif of proteins involved in the regulation of the circadian rhythm of the majority of eukaryotes. PAS domain serine/threonine kinases also regulate several different signaling pathways including drug response. ►circadian rhythm; Rutter J et al 2001 Proc Natl Acad Sci USA 98:8991.

PASA: A special PCR procedure by which chosen allele(s) can be amplified if the primers match the end of that allele. ►PCR; Smith EJ, Cheng HH 1998 Microb Comp Genomics 3:13; Shitaye H et al 1999 Hum Immunol 60:1289.

Pascal Triangle: Represents the coefficients of individual terms of expanded binomials: $(p + q)^n$:

$$1p^n + \frac{n}{1!(n-1)!}p^{n-1}q + \frac{n!}{2!(n-2)!}p^{n-2}q^2 + \dots + \frac{n!}{(n-1)!1!}p^{n-(n-1)}q^{n-1} + 1q^n$$

Since genetic segregation is expected to comply with the binomial distribution, the coefficients indicate the frequencies of the individual phenotypic (or in case of trinomial distribution) genotypic frequencies. ►binomial distribution, ►trinomial distribution, see Table P1.

Table P1. The Pascal triangle represents the coefficients of individual terms of expanded binomials. The exponent of the binomial is n . The figures display a symmetrical hierarchy. The frequency of a particular class can be readily calculated because the sum of the coefficients is displayed at the bottom of the columns. Mendelian segregation follows the binomial distribution

| $n \rightarrow$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-----------------|------|------|------|-------|-------|-------|--------|--------|--------|---------|
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | 1 | 3 | 6 | 10 | 15 | 21 | 28 | 36 | 45 |
| | | | 1 | 4 | 10 | 20 | 35 | 56 | 84 | 126 |
| | | | | 1 | 5 | 15 | 35 | 70 | 126 | 210 |
| | | | | | 1 | 6 | 21 | 56 | 126 | 252 |
| | | | | | | 1 | 7 | 28 | 84 | 210 |
| | | | | | | | 1 | 8 | 36 | 120 |
| | | | | | | | | 1 | 9 | 45 |
| | | | | | | | | | 1 | 10 |
| | | | | | | | | | | 1 |
| SUMS | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1024 |
| $n \rightarrow$ | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 11 | | 12 | 13 | 14 | 15 | 15 | 17 | 18 | 18 | 20 |
| 55 | | 66 | 78 | 91 | 105 | 120 | 136 | 153 | 171 | 190 |
| 165 | | 220 | 286 | 364 | 455 | 560 | 680 | 816 | 969 | 1140 |
| 330 | | 495 | 715 | 1001 | 1365 | 1820 | 2380 | 3060 | 3876 | 4845 |
| 462 | | 792 | 1287 | 2002 | 3003 | 4368 | 6188 | 8568 | 11682 | 15504 |
| 462 | | 904 | 1716 | 3003 | 5005 | 8008 | 12376 | 18564 | 27132 | 38760 |
| 330 | | 792 | 1716 | 3432 | 6435 | 11440 | 19448 | 31824 | 50388 | 77520 |
| 165 | | 495 | 1287 | 3003 | 6435 | 12870 | 24310 | 43758 | 75582 | 125970 |
| 55 | | 220 | 715 | 2002 | 5005 | 11440 | 24310 | 48620 | 92378 | 167960 |
| 11 | | 66 | 286 | 1001 | 3003 | 8008 | 19448 | 43758 | 92378 | 184756 |
| 1 | | 12 | 78 | 364 | 1365 | 4368 | 12376 | 31824 | 75582 | 167960 |
| | | 1 | 13 | 91 | 455 | 1820 | 6188 | 18564 | 50388 | 125970 |
| | | | 1 | 14 | 105 | 560 | 2380 | 8568 | 27132 | 77520 |
| | | | | 1 | 15 | 120 | 680 | 3060 | 11628 | 38760 |
| | | | | | 1 | 16 | 136 | 816 | 3876 | 15504 |
| | | | | | | 1 | 17 | 153 | 969 | 4845 |
| | | | | | | | 1 | 18 | 171 | 1140 |
| | | | | | | | | 1 | 19 | 190 |
| | | | | | | | | | 1 | 20 |
| | | | | | | | | | | 1 |
| SUMS | 2048 | 4096 | 8192 | 16384 | 32768 | 65536 | 131072 | 262144 | 524288 | 1048576 |

Passage: The transfer of cells from one medium to another.

Passenger DNA: A DNA inserted into a genetic vector.

Passenger Proteins: Include the inner centromeric protein (INCENP), which is a substrate for Aurora, the Aurora B kinase, the TD-60 autoimmune antigen, the inhibitor-of-apoptosis protein Survivin/BIR-1. These proteins are situated at the centromeres and move the spindle at late metaphase and anaphase. ▶centromere, ▶mitosis, ▶Aurora, ▶Survivin; Bishop JD, Schumacher JM 2002 J Biol Chem 277:27577.

Passive Immunity: Acquired by the transfer of antibodies or lymphocytes

Passive Transport: Does not require special energy donor for the process. ▶active transport

Pasteur Effect: The fast reduction of respiration (glycolysis) if O₂ is added to fermenting cells.

Pasteurella multocida: A pathogenic bacterium causing cholera in birds, bovine hemorrhagic septicemia, atrophic rhinitis (inflammation of the nasal mucosa) in pigs, and humans may be infected by it through cat or dog bites. The sequenced genome of 2,257,487 bp contains ~2014 coding sequences. ▶Yersinia; May BJ et al 2001 Proc Natl Acad Sci USA 98:3460.

Pasteurization: Reducing (killing) the microbe population in a material by heating at a defined temperature for a specified period of time. ▶aseptic, ▶axenic, ▶autoclaving

PAT1 (Ran1): A protein kinase required for the continuation of mitotic division in fission yeast. Its inactivation triggers the switch to meiosis. ▶meiosis, ▶Ran1

Patatin: A glycoprotein like storage protein in potato with lipid acid hydrolase and esterase activity. It inhibits pests' larvae. It constitutes ~40% of the soluble proteins in the tubers. ▶potato; Hirschberg HJ et al 2001 Eur J Biochem 268:5037.

Patau's Syndrome: Caused by trisomy for human chromosome 13. This is one of the few (X, Y, 8, 18, 21, 22) trisomies that can be carried to term but it generally leads to death within six months because of severe defects in growth, heart, kidney and brain failures. It is accompanied by face deformities (severe hare lip, cleft palate), polydactyly, clubfoot, defects of the genital systems, etc. (see Fig. P28). Definite identification is carried out by cytological analysis, including FISH with the available

chromosome-13-specific probes. An old designation of trisomy 13 was trisomy D because chromosome 13 belonged to the D group of human chromosomes. ▶trisomy, ▶aneuploidy, ▶polydactyly, ▶hare lip, ▶clubfoot



Figure P28. Patau syndrome. (Courtesy of Dr. Judith Miles)

Patch (Ptc): ▶sonic hedgehog, ▶hedgehog

Patch (patched duplex): The resolution of a recombination intermediate (Holliday junction) without an exchange of the flanking markers (can be gene conversion). ▶Holliday model L

Patch Clamp Technique: The method to measure the flow of current through a voltage gated ion channel by tightly pressing an electrode against the plasma membrane. It is used also for the sensitive in situ study of neurotransmitters. ▶ion channels

Patch Mating: Actin patches of the cytoskeleton can be used in yeast to quantify the number of viable diploid cells in the presence of silencer genes, which regulate the expression of mating types. Actin patches are detectable for duration about 10 seconds at sites of polarized growth and then rapidly disappear. ▶mating type determination in yeast; Smith MG et al 2001 J Cell Sci 114(pt 8):1505.

Patella Aplasia-Hypoplasia (PTLAH, 17q21-q22): The absence or reduction of the size of the knee cap. The symptoms occur also in various syndromes such as the Coffin-Siris syndrome, trisomy 8 syndrome. ▶Coffin-Siris syndrome, ▶nail-patella syndrome

Patent: The so-called gene patents do not protect the DNA (or ESTs) sequence itself, rather the process of manipulation is the object. The gene "ownership" only prevents the use or selling a particular sequence without permission. In general, according to US patent laws, the patent is protected for 17 years from date of issue. A requisite for patenting is that the

subject of the patent application would be new and non-obvious and practically useful, e.g., a probe for a gene. Natural DNA sequences are not patentable, but purified or isolated recombinant molecules or parts of a vector are patentable. Legal patentability requirements: (i) usefulness, (ii) novelty, (iii) being non-obvious, and (iv) definiteness of description. A further requirement is “enablement,” i.e., a trained person after reading the patent description can use the “invention” without further research. In October 1998, USA, the first patent was awarded to an EST. Once a patent is issued, even further, originally undisclosed applications are protected. Also, another person after isolating a full-length open reading frame using an STS may obtain a patent but not without the permission of the “inventor” of the patented STS. During the period of patent, the patent-holder can prevent anybody from using it, including those who invented the same independently or even those who improved on the procedure to such an extent that the second invention meets the requirements for patenting. However, the inventor is obligated by law to disclose the invention in sufficient technical detail so that anybody with proper expertise can use it. The fact that an invention was arrived at under federal financial support does not exclude patentability but the inventor must report the patentable invention to the sponsoring agency. The intention of the government is that the invention would be used at maximum benefit to the public that can be achieved most effectively by commercial private enterprises. Laboratory assays, reagents and procedures, including computer programs may also be patentable. By 2005, more than 4000 genes were patented and three-fourths of them by single individuals. Presenilin gene (PSN2) has 8 patent owners for 9 patents and breast cancer gene (BRCA1) has 12 owners for 14 patents. Of the 292 cancer genes reported by 2004, 131 are patented (Jensen K, Murray F 2005 Science 310:239).

The patenting of the outcome of genetic research may be harmful to science if the investigators keep the ongoing work a secret until it becomes patentable. Patenting basic research products (upstream inventions) is detrimental to society because it may prevent the development of new useful (commercial) products. The Bayh–Dole Act allows the “exemption for research” to facilitate the use of the results of basic research. Unfortunately, this exemption is difficult to define and is subject to controversy (Holman C 2006 Cell 125:629). The exemption can be applied to the patent (effectiveness, usefulness) itself but does not permit application of the patent (Kaye J et al 2007 Nature Biotechnol 25:739). If the discovery is published through proper means of scientific communications prior to the patent application, it is disqualified from

patenting. It is generally easier to patent a product than a process. Natural products (e.g., proteins) are usually not patentable unless they are modified in some way and are different from the natural product in structure or function and these properties were not generally known. A DNA sequence, identified as the coding unit for a genetic disease or a genetic marker in its vicinity, may be patentable but a cloned gene that may be used for translating a protein may be not. DNA markers are patentable only if their direct use can be determined. The concept of patenting biological material raises several moral objections but it is defended by the biotechnology industry because it takes 100s of millions of dollars for the completion of such projects, and without the financial means, these investigations cannot be maintained. Between 1981 and 1995, a total of 1175 human DNA sequences were patented. If the subject of the patent has been published or in use for more than one year prior to the date of the patent application, it will not be approved. If another person can prove that he/she invented the object before the date of publication by others, the person may still be entitled to a patent. The patent laws vary in different countries, and new legislation may take place any time. The European Union is now approving patents for human genes and transgenic animals and plants. An alternative to patenting is Trade Secret Protection. One way of preventing another person from patenting an invention is public disclosure, e.g., publication in sufficient details (e.g., in a scientific journal). This ensures that another party would not be able to claim priority for the invention, which is one of the requisites for patenting. Publications may not necessarily provide an effective and lasting protection. Patent infringement usually does not entitle the patentee for more financial compensation than the reasonably calculated loss of royalty or profit caused by the infringement. It must also be verified that the original patent description do not include deceptive assertions.

The justification of an existing patent may be challenged administratively by *inter partes* re-examination request to the US Patent and Trademark Office (USPTO, Washington DC, USA). The claim must prove substantial new question of patentability based on a “prior art” document and requires a fee of \$8800. This procedure has monetary advantages vis-à-vis litigation (Derzko NM, Behringer JW 2003 Nature Biotechnol 21:823). The patent regulations are subject to changes and it is advisable to seek consent from the owners of the patent even when the invention is used only for laboratory research. A recent analysis revealed many problems with patents granted by USPTO. The patents examined had problems with description (37.5%), enablement/utility (42.4%) novelty/non-obviousness (6.9%) and

definiteness (13.1%). The conclusion faulted insufficient educational background of the examiners with most of the problems (Paradise J et al 2005 Science 307:1566). ▶STS, ▶EST, ▶SNP, ▶Herfindahl index, ▶presenilin, ▶breast cancer, ▶cancer, ▶Cohen-Boyer patent on recombinant DNA; Eisenberg RS 1992 p 226. In: Annas GJ, Elis S (Eds.) Gene Mapping, Oxford University Press, New York, DNA-based patents: Robertson D 2002 Nat Biotechnol 20:639; Arnold BE, Ogielska-Zei E 2002 Annu Rev Genomics Hum Genet 3:415; patented genetic sequence information retrieval: Dufresne G et al 2002 Nature Biotechnol 20:1269; ethical issues of DNA patenting: Resnik DB 2004 Owning the Genome: A Moral Analysis of DNA Patenting, State University New York Press, Albany, New York; Eisenberg RS 2003 Science 299:1018; Robertson JA 2003 Nature Rev Genet 4:162; property rights in plant breeding: Fleck B, Baldock C 2003 Nature Rev Genet 4:834; Paradise J, Janson C 2006 Nature Rev Genet 7:148; Van Overwalle G et al 2006 Nature Rev Genet 7:143; stem cell lines: Loring JF, Campbell C 2006 Science 311:1716; <http://geneticmedicine.org> or patents in general: <http://www.uspto.gov>; <http://scientific.thomson.com/derwent>; <http://www.bioforge.org>; <http://www.bustPATENTS.COM/>; gene and sequence patents for various organisms: <http://www.patome.org/>; <ftp://ftp.ebi.ac.uk/pub/databases/embl/patent>; ftp://ftp.wipo.int/pub/published_pct_sequences.

Patent Ductus Arteriosus (6p12): The ductus arteriosus connects the lung artery and the aorta and shunts away blood from the lung of the fetus. Normally it fades away after birth. In ~1/2000 cases, this does not happen and the duct stays open and causes heart defect. The disease may be caused by fetal rubella infection and apparently by autosomal dominant gene(s). The 6p12-p21 dominant *Char syndrome* involves patent ductus, facial anomalies and abnormal fifth digit of the hand (see Fig. P29).



Figure P29. Char syndrome. In the Char syndrome the middle phalanx of the fifth digit is missing

The basic problem is traced to TFAP2B neural crest-related transcription factor that does not bind properly to its target. Risk of recurrence in an affected family is about 1–2%. General incidence is less than 10% of that. ▶risk, ▶aneurysm; Zhao F et al 2001 Am J Hum Genet 69:695.

Paternal Leakage: The transmission of mitochondrial DNA through the males. Generally, mitochondria are not transmitted through the animal sperm because mitochondrial DNA of spermatozoon is destroyed by ubiquitination in the oocytes (Sutovsky P et al 2000 Biol Reprod 63:582). In mice, apparently the male transmission of mitochondria is within the range of 10^{-5} . In interspecific mouse crosses, paternal mitochondria are transmitted but they are eliminated during early embryogenesis or later during development (Kaneda H et al 1995 Proc Natl Acad Sci USA 92:4542). Heteroplasmy is rare. The role of transmission of mitochondria in humans is not clear. Some cytological observations may indicate the incorporation of the midpiece of the sperm (containing mitochondria) into the egg. Genetic evidence for human paternal transmission of mitochondria is rare (Schwartz M, Vissing J 2002 N Engl J Med 347:576).

In some molluscs (mussel), there is a strong biparental inheritance of mtDNA. In *Mytilus* the paternal and maternal mtDNA displays 10–20% nucleotide divergence. The females transmit just one type of mitochondria to sons and daughters whereas the males transmit a second type of mtDNA genome to the sons. Biparental transmission of mtDNA may also occur in interspecific crosses of *Drosophila*. In *Paramecia*, mitochondria may be transmitted through a cytoplasmic bridge. In fungi, the transfer is maternal although in some heterokaryons cytoplasmic mixing may take place. In some slime molds, mtDNA transmission is also mating type dependent. In *Physarum polycephalum* different *matA* alleles regulate the mtDNA transmission but a plasmid gene may also be involved and recombination can take place between mtDNAs. In *Chlamydomonas* algae, several genes around the mating type factors were implicated. In the contact zone of hybridizing conifers (*Picea*) recombinant mtDNA was observed as apparent result of paternal leakage (Jaramillo-Correa JP, Bousquet J 2005 Genetics 171:1951). ▶mtDNA, ▶plastid male transmission, ▶Eve foremother, ▶mitochondrial disease in humans, ▶mitochondrial genetics, ▶plastid genetics, ▶doubly uniparental inheritance, ▶*Paramecium*, ▶heteroplasmy; Eyre-Walker A 2000 Philos Trans R Soc Lond B Biol Sci 355:1573; Shitara H et al 1998 Genetics 148:851; Yang X, Griffith AJ 1993 Genetics 134:1055; Meusel MS, Moritz RF 1993 Curr Genet 24:539.

Paternal Transmission: Imprinting causes paternal transmission of certain genes. Some of the human insulin and the insulin-like growth factor alleles may be preferentially inherited through the paternal chromosome and cause early-onset obesity. ▶imprinting, ▶obesity, ▶paternal leakage; Le Stunff C et al 2001 Nature Genet 29:96.

Paternity Exclusion: Based on genetic paternity tests.

►paternity testing, ►DNA fingerprinting, ►Y chromosome, ►alternate paternity

Paternity Testing: Frequently required in civil litigation suits, it might have significance for medical, population, immigration, archeological and other cases. The laboratory procedures are generally the same as used for DNA fingerprinting. Here, as in DNA fingerprinting in general, the exclusion of paternity is simple and straightforward. However, the determination of identity may pose more difficulties because in the multilocus tests more than 10% of the offspring may show one band difference and 1% may show two, due to mutation. Therefore, Penas and Chakraborty (Trends Genet 10:204 [1994]) recommended the formula shown in Figure P30.

$$PI = \frac{\binom{N}{U} \mu^U (1 - \mu)^{N-U}}{\binom{n}{U} X^{n-U} (1 - X)^U}$$

Figure P30. Penas-Chakraborty formula

PI = paternity index, μ = mutation rate, X = band-sharing parameter, N = total number of bands per individual, n = number of test bands, U = number of bands not present in the alleged father. In rare instances (mistakes at maternity wards) similar test may be necessary to test maternity. The biological father of a child—even if the paternity can be accurately proven—cannot assert paternal rights against the will of the mother if she was/is married to another man (Hill JL 1991 N Y Univ Law Rev 66:353). When “the child is born to a mother who is single or part of a lesbian couple, law does permit the biological father to assert his paternal rights, even if he clearly stated his intention prior to conception to have no relation” (Charo RA 1994 In: Frankel MS, Teich A (Eds.) The Genetic Frontier. Ethics, Law and Policy, American Association of Advance Science, Washington DC). ►Y chromosome, ►forensic genetics, ►DNA fingerprinting, ►forensic index, ►utility index, ►surrogate mother, ►microsatellite typing

Path Coefficient: This method of Sewall Wright was worked out for studying mathematically and by diagrams, the paths of genes in populations and genetic events determining multiple correlations. Here it is not possible to discuss meaningfully the mathematical foundations but one type of graphic application for determining some relations between

offspring and parents can be found under F and inbreeding coefficient. ►inbreeding coefficient, ►correlation; Wright S 1923 Genetics 8:239; Wright S 1934 Ann Math Stat 5:161.

Pathogen: An organism (microorganism) capable of causing disease on another. (See pathogen database: <http://www.nmpdr.org>; ►vectors for pathogens, ►Brucella, ►Rickettsia, ►Coxiella and viruses: <https://patric.vbi.vt.edu>).

Pathogen Identification: The food industry may need rapid and highly sensitive methods for the detection of live pathogens in various products. In case of viable *E. coli* cells, this is feasible by infection with compatible bacteriophages carrying bacterial luciferase inserts. The genes in the phages are expressed only in live bacteria and if such are present, with a high-powered luminometer or by a microchannel plate enhanced image analyzer, even a single bacterial cell emitting light may be detected. Immunoassays and PCR are also useful for the detection of the presence of pathogens. An apparently very fast procedure is based on B lymphocyte sensors (CANARY: cellular analysis and notification of antigen risks and yields), which are engineered with the potential to express green fluorescent protein (GFP, aequorin) and membrane-bound antibodies specific for the pathogen of interest. GFP is a calcium-activated light emitter. When the antibody binds the pathogen, the intracellular calcium concentration is elevated within seconds and fluorescence is readily detectable. A bio-conjugated nanoparticle-based fluorescence immunoassay for in situ pathogen quantification detects single bacteria within 20 min (Zhao X et al 2004 Proc Natl Acad Sci USA 101:15027). For epidemic surveillance of respiratory pathogens, identification and strain typing can employ electrospray ionization mass spectrometry and polymerase chain reaction amplification from highly conserved genomic regions even from polymicrobial mixtures (Ecker DJ et al 2005 Proc Natl Acad Sci USA 102:8012). ►luciferase bacterial, ►immunological test, ►B lymphocytes, ►bioterrorism, ►PCR, ►aequorin, ►electrospray MS, ►polymerase chain reaction, ►quenched autoligation probe, ►quantum dot; Rider TH et al 2003 Science 301:213; GeneDB, bacterial, protozoa, fungal gene sequences: <http://www.genedb.org/>.

Pathogen-Derived Resistance: The protection of plants against certain pathogens by the transgenic expression of viral coat proteins, other proteins, antisense sequences, satellite and defective viral sequences. ►host-pathogen relations, ►plantibody

Pathogenesis Related Proteins (PR): A variety of acidic or basic proteins synthesized in plants upon infection

with pathogens. The chitinases and glucanases apparently act by damaging the cell wall of fungi, insects or even bacteria. ►[host–pathogen relations](#), ►[SAR](#)

Pathogenic: Capable of causing disease. (See Hill, A.V. S. 2001 *Annu Rev Genome Hum Genet* 2:373).

Pathogenicity Island (PAI): A group of genes in a pathogen involved in the determination and regulation of pathogenicity. In *Helicobacter pylori*, these islands are delineated by 31 bp direct repeats (DR), and indicate that horizontal transfer acquired these. Commonly the same genes are present between the ends of this large insert and the chromosomal genes in both pathogenic and non-pathogenic species of the same group of bacteria. Frequently, the insert is adjacent to a tRNA 3' sequence or a codon for an unusual amino acid. The DNA inserts encode a rather specific secretory system (type III) and elements of transport and bacterial surface effectors located then next to host cell receptors. The PAI may carry insertion elements, integrases and transposases and their sequences may be unstable. Their location may change within the same bacterium. This organization is conducive to effective subversion the host defense system. The size of the pathogenicity islands may vary from 10 to 200 kb or more. The base composition of the islands and the codon usage may differ from that of the core DNA. In some bacteria only a single PAI occurs, in others there are several. Similar mechanisms operate in both animals and plants. ►[transmission](#), ►[cholera toxin](#), ►[host–pathogen relations](#), ►[integrase](#), ►[transposase](#), ►[secretion system](#), ►[codon usage](#), ►[Helicobacter pylori](#), ►[symbionts](#); Hacker J, Kaper JB 2000 *Annu Rev Microbiol* 54:641; <http://www.gem.re.kr/paidb>.

Pathogenicity Islet: These are similar in some functions to pathogenicity islands but their size is much smaller, 1–10 kb.

Pathovar: Plant varieties or species, which share disease susceptibility/resistance genes. Alternatively, a plant pathogen that is specific for a taxonomic group of plants.

Pathway Tools (<http://bioinformatics.ai.sri.com/ptools/>): Software for determining metabolic and signaling pathways and database. ►[EcoCyc](#), ►[MetaCyc](#), ►[BioCyc](#)

Pathways: Guide to metabolic, molecular, immunological and many other processes and interactions: <http://www.pathguide.org/>; network tools: <http://visant.bu.edu/>.

Patrilocality: An anthropological term indicating that males more frequently bring in mates from outside

their location than moving to the location of the females.

Patristic Distance: The sum of the length of all branches connecting two species in an evolutionary tree. ►[evolutionary tree](#)

Patroclinous: Inheritance through the male such as the Y chromosome, androgenesis, fertilization of a nullisomic female with a normal male, through non-disjunction the chromosome to be contributed by the female is eliminated, some of the gynandromorphs, sons of attached-X female *Drosophila*, etc. ►[gynandromorph](#), ►[nondisjunction](#), ►[attached-X](#)

Patronymic: A designation indicating the descent from a particular male ancestor, e.g., Johnson, son of John or O'Malley descendant of Malley. Common family names may assist in isolated populations to establish relationships. This analysis may be improved by studies of Y-chromosomal molecular markers. ►[isonymy](#), ►[Y chromosome](#)

Pattern Formation during Development: Pattern formation specifies the arrangement of the cells in three dimensions. Developmental patterns may begin by intracellular differentiation (animal pole, vegetal pole, yolk), positional signals between cells and intracellular distribution of the receptors to various signals. Fibroblast growth factor and transforming growth factor- β have apparently major roles as epithelial and mesoderm induction signals. The *Drosophila* gene *fringe* (*fng*) is involved with mesoderm induction and in wing embryonal disc formation. Juxtaposition of *fng*-expressing and non-expressing genes is required for establishing the dorsal ventral boundary of wing discs. The gene *fng* is expressed in the dorsal half of the wing disc whereas *wingless* (*wg*, 2-30) is limited to the dorsal-ventral boundary. Gene *hedgehog* (*hh*, 3-81) is expressed in the posterior half, and *decapentaplegic* (*dpp*, 2-40) is detected in the anterior-posterior boundary. Anterior-posterior patterning in *Drosophila* is affected by the *trithorax* (*trx*), *Polycom* (*Pc-G*) family members such as *extra sex combs* (*esc*). The homolog of the latter, *eed* (embryonic ectoderm development) controls anterior-posterior differentiation in mouse. Homologs to these genes have been identified in other animals and humans as well. In *Xenopus*, it appears that the FNG protein is translated with a signal peptide (indicating that it is secreted), in the proFNG, peptide is terminated with a tetrabasic site for proteolytic cleavage and after this processing it is ready for the normal function. *Wingless* of *Drosophila* is homologous to *Wnt1* mouse mammary tumor gene. The branching pattern of trachea and lung, respectively in *Drosophila* and mammals is controlled primarily by the fibroblast growth factor

signaling pathway. This is used reiteratively in repeated sequences of a branching. At each stage different feedback and other control signals provide the specifications (Metzger RJ, Krasnow MA 1999 Science 284:1635). In mice, mutation of the *Foxn1* gene causes follicular development to terminate just after it starts accumulating pigments. Then the immature follicles restart the developmental process and the skin color of the animal displays the striped pattern (Suzuki N et al 2003 Proc Natl Acad Sci USA 100:9680). Vascular mesenchymal cells can differentiate into specific embryonic structures and in adult diseases the process may be restarted again and bone osteoblasts may arise in the walls of the arteries or in the cardiac walls under the influence of morphogens. The process may be mathematically modeled (Garfinkel A et al 2004 Proc Natl Acad Sci USA 101:9247). In bacteria pattern formation can be programmed in a synthetic system by acyl-homoserine chemical signals emitted by labeled “sender” cells to “receiver” cells in Petri plate cultures (see Fig. P31).



Figure P31. Pattern formation induced by the sender cells (darker color) in the receiver cells (lighter color) lawn of bacteria. In the experiments the two types of cells were distinguished by fluorescence. (Redrawn after Basu, S. et al. 2005 Nature [Lond] 434: 1130)

A newer idea posits that the mechanical control of form precedes pattern formation (Ingber DE 2005 Proc Natl Acad Sci USA 102:11571). Using micro-fabrication for controlling the organization of sheets of cells revealed the emergence of stable patterns of proliferative foci. Concentrated growth corresponded to regions of high tractional stress and could be measured by micromechanical force sensor. Inhibiting actomyosin-based tension or cadherin-mediated connections between cells disrupted spatial pattern of proliferation. The conclusion is that contraction of cells, an existence of pattern of mechanical forces, is due to multicellular organization and the tissue form is an active regulator of tissue growth (Nelson CM et al 2005 Proc Natl Acad Sci USA 102:11594).

Developmental pattern formation is under genetic control also in plants (Lee MM, Schiefelbein J 1999 Cell 99:473). The progress has been much slower, however, because the plant tissues and cells are more liable to dedifferentiation and redifferentiation. Mutants have been obtained with clear differences

in morphogenesis, with the exception of flower differentiation and photomorphogenesis, much less is known about the molecular mechanisms involved. Down-regulation of the MYB transcription factor gene (*PHANTASTICA*) changes compound pinnate (left) leaves into palmate compound (right) leaves (see Fig. P32) (Kim M et al 2003 Nature [Lond] 424:438). ▶morphogenesis, ▶morphogenesis in *Drosophila*, ▶RNA localization, ▶flower differentiation, ▶photomorphogenesis, ▶MADS box, ▶signal transduction, ▶homeotic genes, ▶cell lineages, ▶fibroblast growth factor, ▶actomyosin, ▶cadherin; reaction–diffusion model of leaf venation as a mechanism of pattern formation: Dimitrov P, Zucker SW 2006 Proc Natl Acad Sci USA 103:9363; Malakinski G, Bryant P (Eds.) 1984 Pattern Formation: A Primer in developmental biology, Macmillan, New York; Comparative Pattern Formation in Plants and Animals: Willemsen V, Scheres B 2004 Annu Rev Genet 38:587.

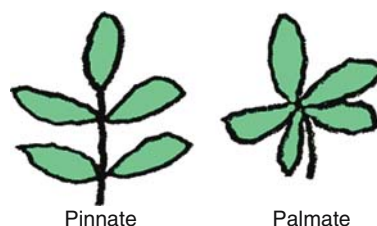


Figure P32. Pinnate (left); palmate (right)

Pattern Recognition Receptors (PRR): These are tools of the innate immunity system. They recognize pathogen-associated molecular patterns (PAMPs) that are essential for the survival of the pathogen and are therefore stable. PRRs are hereditary, are conserved across phylogenetic categories, expressed constitutively and do not require immunological memory. PRRs recognize pathogen-associated molecular patterns such as exist in lipopolysaccharides, proteoglycans or double-stranded RNA. (See Qkira S et al 2006 Cell 1214:763; innate immunity, Toll, host–pathogen relationship, downstream pathways: Lee MS, Kim Y-J 2007 Annu Rev Biochem 76:447.

PAU Genes: ▶seripauperines

pauling: ▶evolutionary clock

PAUP (phylogenetic analysis using parsimony): A computer program for the analysis of evolutionary descent on the basis of molecular data. ▶evolutionary distance, ▶evolutionary tree

Pause: RNA polymerase, I, II and III do not operate continuously at the same rate but due to various causes, their transcription may hesitate and then

resume synthesis. A minimal functional element of PAUSE-1 is TCTN_xAGAN₃T₄ where $x = 0, 2$ or 4 . Various elongation proteins such as ELL, Elongin, and transcription factor TFIIF may mediate pausing. The pause may facilitate the binding of regulatory factors. Pausing and backtracking allows the binding of the RfaH suppressor factor of early termination (Artsimovich I, Landick R 2002 Cell 109:193). Pausing may allow for proofreading and elimination of misincorporated bases (Shaevitz JW et al 2003 Nature [Lond] 426:684). Sequence-specific pause sites have been revealed (Herbert KM et al 2006 Cell 125:1083). ▶attenuator region, ▶Nus [▶lambda phage], ▶σ; Ogbourne SM, Antalis TM 2001 Nucleic Acids Res 29:3919.

Pausing, Transcriptional (hesitation): The discontinuity of the transcriptional process by all RNA polymerases. As a consequence there is a heterogeneity of the transcripts because of the differences in recognition of modulating factors such as attenuation, transcription factors TFIIF, ELL, silencers, nus (λ phage), antitermination signal, etc. Paucity of a nucleotide(s) or too high concentration of it may slow down transcription. RNA polymerase often pauses before a GTP is incorporated. Pause signals have been detected in both the template and the non-template DNA strands. Generally, hairpin structures (RNA base-pairing) favor pausing although secondary structure may not be the sole cause of it. DNA sequences 16–17 bp downstream of the pause may alter the conformation of the polymerase and the pause. Even the non-template strand may have an effect. ▶arrest transcriptional, terms named under separate entries; Davenport RJ et al 2000 Science 287:2497.

PAX (paired box homeodomains): They are so called because they include two helix-turn-helix DNA-binding units. Several PAX proteins are known to be encoded in at least five different chromosomes and they mediate the development of the components of the eyes in insects (compound eyes) and humans, teeth, the central nervous system, the vertebrae, the pancreas and tumorigenesis. The 130-residue paired domain binds DNA and functions as a transcription factor for B cells, histones and thyroglobulin genes. The *Pax5* gene encodes the BSAP transcription factor. Mutation in *Pax5* arrests B cells at the pro-B stage. BSAP may also promote the expression of CD19 and indirectly IgE synthesis. BSAP may block the immunoglobulin heavy chain 3'-enhancer and isotype switching and the formation of the pentameric IgM antibody. The activator motifs of BSAP display about 20 times higher binding affinity to the DNA than the repressor motif yet the activator or repressor function depends primarily on the context of the

motif. The level of BASP is high in the pre-B and immature B cell stages and after the antigen signal has arrived its level greatly diminished by signals from IL-2 and IL-5. Overexpression of BSAP results in its repressor activity. PAX6 (11p13) mutations cause absence of the iris of the eye (aniridia) without elimination of vision but other general neurodevelopmental problems. ▶Waardenburg syndrome, ▶DiGeorge syndrome, ▶aniridia, ▶Wilms tumor, ▶renal-coloboma syndrome, ▶hypodontia, ▶rhabdomyosarcoma, ▶animal models, ▶B cell, ▶immunoglobulins, ▶histones, ▶thyroglobulin, ▶hox, ▶homeotic genes, ▶isotype switching, ▶FKP, ▶goiter familial, ▶helix-turn-helix motif, ▶integrin, ▶PTIP, ▶myoblast, ▶neural crest; Balczarek KA et al 1997 Mol Biol Evol 14:829; Chi N, Epstein JA 2002 Trends Genet 18:41; Pichaud F, Desplan C 2002 Curr Opin Genet Dev 12:430; <http://pax2.hgu.mrc.ac.uk/>; <http://pax6.hgu.mrc.ac.uk/>.

PAZ Domain (Piwi/Argonaute/Zwille): In Argonaute 1 protein it consists of a left-handed, six-stranded β-barrel capped at one end by two α-helices and wrapped on one side by a distinctive appendage, which comprises a long β-hairpin and a short α-helix. The PAZ domain binds a 5-nucleotide RNA with 1:1 stoichiometry. It plays a role in RNAi function and it is present in both Argonaute and Dicer proteins. ▶Argonaute, ▶Dicer, ▶RNAi; Yan KS et al 2003 Nature [Lond] 426:469; Lingel A et al 2003 Nature [Lond] 426:465; Ma J-B et al 2004 Nature [Lond] 429:318; PIWI domain structure: Parker JS et al 2005 Nature [Lond] 434:663; Ma J-B et al 2005 Nature [Lond] 434:666.

PBAF: An ATP-dependent chromatin remodeling complex. ▶chromatin remodeling; structure of PBAF: Leschziner AE et al 2005 Structure 13:267.

Pbp74: ▶Hsp70

pBR322: A non-conjugative plasmid (constructed by Bolivar & Rodriguez) of 4.3 kb, can be mobilized by helper plasmids because (although it lost its mobility gene) it retained the origin of conjugal transfer (see Fig. P33). It is one of the most versatile cloning vectors with completely known nucleotide sequence and over 30 cloning sites. It carries the selectable markers ampicillin resistance and tetracycline resistance. Insertion into these antibiotic resistance sites permit the detection of the success of insertion because of the inactivation of these target genes results in either ampicillin or tetracycline sensitivity. Although its direct use of this 20-year old plasmid has diminished during the last years, pBR322 components are present in many currently used vectors. ▶plasmid, ▶vectors, ▶Amp, ▶tetracycline; Bolivar, F., Rodriguez RL et al 1977 Gene 2:95.

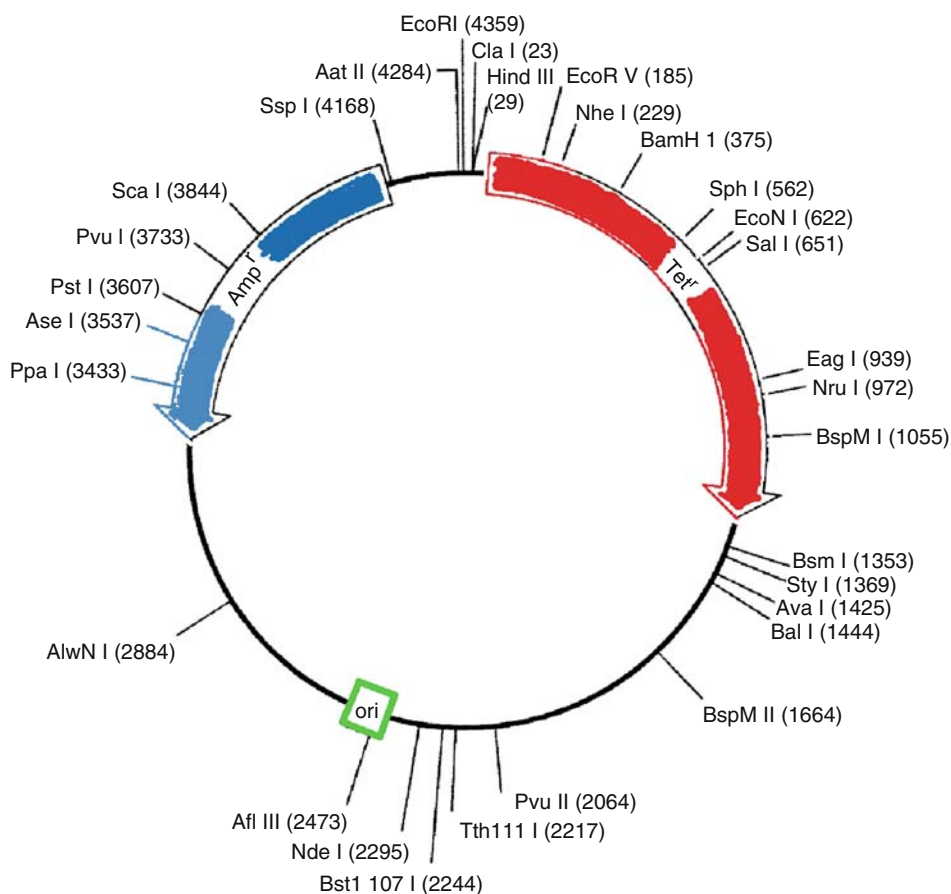


Figure P33. pBR vector (4361 bp), From Pharmacia Biotech Inc., by permission

PBS: Phosphate buffered saline. ►saline

PBSF (pre-B cell growth-stimulating factor): A ligand of CXCR controlling B cell development and vascularization of the gastrointestinal system. ►CXCR, ►lymphocytes; Egawa T et al 2001 Immunity 15:323.

PBX1, PBX2: Transcription factors involved in B cell leukemias, encoded in human chromosomes 1q23 and 3q222, respectively. ►leukemia

p. c.: ►post coitum

PC4 (positive co-activator of transcription): PC4 interacts with activator protein-1 (AP-2) and facilitates transcription, and may relieve the self-interference of AP-2. ►transcription, ►AP1; Zhong L et al 2003 Gene 320:155.

PCA (principal component analysis): A multivariate statistical method that separates the original variables into independent variables and associated variances. It may be useful for the interpretation of microarray data. (See Méndez MA et al 2002 FEBS Lett 522:24).

PCAF: A human acetyltransferase of histones 3 and 4. ►p300, ►TAF_{II}230/250, ►histone acetyltransferases,

►nucleosome, ►signal transduction, ►chromatin remodeling, ►bromodomain, ►INHAT; Blanco JC et al 1998 Genes Dev 12:1638.

PCB: Polychlorinated biphenyl is an obnoxious industrially employed carcinogen. A *Pseudomonas* enzyme may break it down. ►environmental carcinogens, ►sperm

PCD: ►apoptosis

pCIP: A co-activator protein, interacting with p300 (CREB) and regulates transcription and somatic growth of mammals. ►signal transduction, ►nuclear receptors; Wang Z et al 2000 Proc Natl Acad Sci USA 97:13549.

PCL: Putative cyclin. ►cyclin

PCNA (proliferating cell nuclear antigen): An auxiliary protein (a processivity factor) in pol δ and pol ϵ functions in eukaryotes. It has a similar role in DNA replication in general, and in the cell cycle and repair. Its function is similar to that of the β subunit of the prokaryotic pol III, it provides a "sliding clamp" on the DNA to be replicated. Binding to p21 may inhibit

PCNA replicative function. PCNA also binds other proteins such as cyclin D, FEN1/Rad27/MF1, DNA ligase 1, GADD, DNA methyltransferase, DNA repair proteins XPG, MLH and MSH. The protein interaction (PIP-box) provides a dock for interaction with replication and repair proteins (Bruning JB, Shamoo Y 2004 Structure 12:2209). The PCNA-interacting mutations in PCNA alter the conditions for nucleosomal assembly by interacting with CAF. Under such conditions, silencing by heterochromatin is reduced or lost. Some mutations in RFC may compensate for defects in PCNA. If the DNA is damaged, PCNA is modified by mono-ubiquitination at lysine residue 164 or a lysine 63-linked multi-ubiquitin chain to allow error-free or error-prone replication bypass of the damaged site. Ubiquitination of PCNA at lysine 164 specifically activates DNA polymerase η and Rev1, a deoxycytidyl-transferase in mutagenic replication of DNA (Garg P, Burgers PM 2005 Proc Natl Acad Sci USA 102:18361). In addition, SUMO-modified PCNA may recruit Srs2 helicase, which disrupts recombination by affecting Rad51 protein (Pfander B et al 2005 Nature [Lond] 436:428). ▶DNA replication, ▶eukaryotes, ▶cell cycle, ▶DNA polymerases, ▶ligase DNA, ▶p21, ▶cyclins, ▶ABC excinuclease, ▶excision repair, ▶mismatch repair, ▶sliding-clamp, ▶methylation of DNA, ▶Rad27/Fen1, ▶RFC, ▶CAF, ▶heterochromatin, ▶ubiquitin, ▶SUMO, ▶Srs, ▶Rad51; Karmakar P et al 2001 Mutagenesis 16:225; Ola A et al 2001 J Biol Chem 276:10168; López de Saro FJ, O'Donnell M 2001 Proc Natl Acad Sci USA 98:8376; Lau PJ, Kolodner RD 2003 J Biol Chem 278:14; crystal structure of binding domains: Kontopidis G et al 2005 Proc Natl Acad Sci USA 102:1871; review: Moldovan G-L et al 2007 Cell 129:665.

PCR: ▶polymerase chain reaction

PCR, Asymmetric: By using unequal amounts of amplification primers, an excess of single-strand copies of DNA can be obtained (Gyllensten UB, Erlich HA 1988 Proc Natl Acad Sci USA 85:7682). ▶polymerase chain reaction, an improved procedure: Pierce KE et al 2005 Proc Natl Acad Sci USA 102:8609.

PCR, Allele-Specific: Used to screen a population for a particular allele-specific mutation, e.g., mutations responsible for MELAS in the aging human mitochondrial DNA. One of the most common mutations in this anomaly involves the transition A→G at site 3243. If the primer containing the complementary base C is used, the mutant sequence from appropriate tissues is successfully amplified and can be detected by gel electrophoresis. The same C primer does not generate substantial quantity of the fragment using

the wild type template. Thus, by this procedure, the approximate frequency of this allele-specific mutation or recombination can be determined. ▶polymerase chain reaction, ▶mitochondrial disease in humans, ▶transition mutation, ▶hot-start PCR; Ugozzoli L, Wallace RB 1992 Genomics 12:670.

PCR, Broad-Based: Uses primers, which amplify a broad base of genes, e.g., the microbial rRNA genes or a group of viral genes common to the majority of related species in order to facilitate molecular identification of same pathogens. RDA and other procedures may supplement the analysis. ▶RDA

PCR, Competitive: Used for quantifying DNA or RNA. The competitor nucleic acid fragment of known concentrations in serial dilutions is co-amplified with another (the experimental) nucleic acid of interest using a single set of primers. The beginning quantity of the experimental molecules is estimated from the ratio of the competitor and experimental amplicons obtained during the PCR procedure that are supposedly amplified equally. The quantity of the unknown DNA is determined by the equivalence-point (EQP) where the experimental and the competitor show the same signal intensity indicating that their amounts is the same. A simplified new version is described by Watzinger F et al 2001 Nucleic Acids Res 29(11):e52.

PCR, Discriminatory: A method to detect small mismatches or point mutations (see Fig. P34). It is a much easier method than sequencing larger sequences to distinguish, e.g., phylogenetic differences within taxonomic groups. (See Picard FJ et al 2004 J Clin Microbiol 42:3686).

| Wildtype | Mismatch mutant |
|-----------------|-----------------|
| GGCGTGTGAAC TG | GGCGTGTGTG TCTG |
| | |
| CCGCACACTTGAC | CCGCACAC CAGAC |
| PCR ↓ | PCR ↓ |
| primer TGTGAA → | primer TGTGAA → |
| CCGCACACTTGAC | CCGCACAC CAGAC |
| Product made | No product made |

Figure P34. Discriminatory PCR

PCR, DOC (degenerate oligonucleotide-primed polymerase chain reaction and capillary electrophoresis of DNA): A random amplification technique combined with analysis on microchips. ▶capillary electrophoresis, ▶PCR, ▶DOP-PCR; Cheng J et al 1998 Anal Biochem 257:101.

PCR, Electronic: ▶electronic PCR

PCR, Methylation-Specific: ►methylation-specific PCR

PCR, Multiplex: Employs multiple sets of primers for amplification in a single reaction batch. (See Broude NE et al 2001 Proc Natl Acad Sci USA 98:206).

PCR, Nested: The use of two different internal primers to thus identify overlapping transcripts.

PCR, Overlapping: The use of two sets of primers; each has complementary sequences at the 5'-end. Two separate PCRs are carried out and then the products purified by gel to remove the unincorporated primers. A second PCR process uses only the outside primer pairs and the two primary products are joined. ►PCR

PCR, Quantitative: Determine gene expression quantitatively by optimized primers: <http://primerdepot.nci.nih.gov/>; <http://mouseprimerdepot.nci.nih.gov/>.

PCR, Real-Time Reverse Transcription: see Seeger K et al 2001 Cancer Res 61:2517.

PCR, Single Molecule: ►polony

PCR Targeting: ►targeting genes

PCR, Transcriptionally Active (TAP): 1. Specific primers amplify the gene of interest. 2. Mixtures of DNA fragments are equipped with promoter and terminator elements and then can be used for transfection in a suitable plasmid. They can be inserted into plasmids also by homologous recombination. TAP products can be used as DNA vaccines and generate antibodies against the encoded genes. The procedure is suitable for the generation of hundreds or thousands of transcriptionally active genes for genomic/proteomic studies. (Liang X et al 2002 J Biol Chem 277:3593).

PCR-Based Mutagenesis: Any base difference between the amplification primer will be incorporated in the future template through polymerase chain reaction. Actually only half of the new DNA molecules would contain the alteration present in the original amplification primer unless a device is used, e.g., the undesired strand would be made unsuitable for amplification and therefore lost from the reaction mixture. The method may include multiple point mutations, small insertions or deletions too. The amplification may also result in other nucleotide alterations as a result of the error-prone Taq polymerase. ►local mutagenesis, ►primer extension, ►polymerase chain reaction, ►DNA shuffling, ►VENT, ►small-pool PCR; Nelson RM, Long GL 1989 Anal Biochem 180:147.

PCR-LSA (polymerase chain reaction amplification): A method for the localization of SNIPS. ►SNIPS, ►RRS

PCR-Mediated Gene Replacement: The procedure replaces—by mitotic recombination—particular genes with an identifiable marker of a neutral phenotype. A 20 bp unique sequence tract tags each of these lines. On the basis of hybridization of the PCR products to a tag sequence, it is possible to quantitate the altered cell lines in a population. When one of the target genes is deleted in diploid yeast, the other is still expected to be functional. Some of them, however, due to haplo-insufficiency, will display a defective phenotype. These “heterozygotes” may also display increased sensitivity to drugs and may be used for pharmaceutical research. ►haplo-insufficiency; Giaever G et al 1999 Nature Genet 21:279.

PC-TP: phosphatidylcholine transfer protein mediating transfer of phospholipids between organelles within cell.

PD-1: An inhibitory immune receptor (2q37.3) on B, T lymphocytes and natural killer cells.

PDB (Protein Data Bank): <http://www.rcsb.org/pdb/cgi/explore.cgi?pdbld>.

PDECGF: Platelet-derived endothelial cell growth factor.

pDelta: γδ

PDF: An electronic publishing software readable with the aid of Adobe Acrobat reader. Frequently used by journals available through the Internet.

PDGF: ►platelet derived growth factor

PDGFR: Platelet derived growth factor receptor

PDI (protein disulfide isomerase): A co-factor of protein folding mediated by chaperones. ►chaperone, ►PPI, ►Eug, ►Mpd, ►Erp61

PKD (phosphoinositide-dependent kinase): A part of the MAPK, RSK signaling pathway. ►MAPK, ►RSK, ►phosphoinositides, ►PIK, ►Akt; Toker A, Newton AC 2000 Cell 103:185.

PDS: An anaphase inhibitory protein that must be degraded with the assistance of CDC20 component of APC before the cell cycle can exit from mitosis regulated also by the activity of the Cdc14 phosphatase. ►cell cycle, ►APC, ►Esp1, ►sister chromatid cohesion, ►checkpoint, ►mitotic exit, ►Cdc14, ►Cdc20; Salah SM, Nasmyth K 2000 Chromosoma 109:27.

pDUAL: γδ

PDZ Domains (post-synaptic density, disc-large, zo-1): Approximately 90 amino acid repeats involved in ion-channel and receptor clustering, and linking effectors and receptors. PDZ domain proteins are involved in the regulation of the Jun N-terminal

kinase pathway, in the post-synaptic density (PSD) proteins at glutamatergic synapses, Rho-activated citron protein function, visual signaling, etc. The *Drosophila* gene, *scribble* (*scrib*) encodes a multi PDZ domain protein and in cooperation with a leucine-rich protein controls apical polarization of the embryo. ▶ion channels, ▶tight junction, ▶protein folding, ▶Van Gogh, ▶receptor, ▶effector, ▶signal transduction, ▶AMPA, ▶HOMER, ▶citron, ▶Jun, ▶Rho, ▶NMDAR, ▶mesenchyma, ▶Fraser syndrome; Harris BZ, Lim WA 2001 J Cell Sci 114(pt 18):3219; Hung AY, Sheng M 2002 J Biol Chem 277:5699.

Pea (*Pisum* spp): Several self-pollinating vegetable and feed crops: the Mendel's pea is *P. sativum*, and others are $2n = 2x = 14$ (see Fig. P35). *Pisum*, photograph shows normal Mendelian segregation for smooth and wrinkled within a pod.

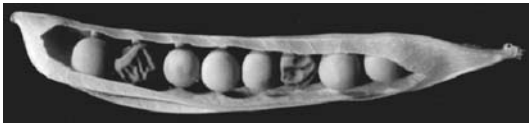


Figure P35. Pea

PEA: Death effector domain proteins.

Pea Comb: Comb characteristic of poultry of *rrP(P/p)* genetic constitution. ▶walnut comb

Peach (*Prunus persica*): $x = 7$, the true peaches are diploid.

P

Peacock's Tail: An evolutionary paradigm when a clear disadvantage (like the awkward tail) turns into a mating advantage because of the females' preference for the fancy trait and thus increasing the fitness of the males that display it. ▶fitness, ▶selection, ▶sexual selection

Peanut: ▶groundnut

Pear (*Pyrus* spp): About 15 species; $x = 17$ and mainly diploid, triploid or tetraploids. It is very difficult to hybridize it with apples but can be crossed with some *Sorbus*. ▶apple

Pearson Marrow Pancreas Syndrome: ▶mitochondrial disease in humans

Pearson's Product Moment Correlation Coefficient: ▶correlation

Pebble: ▶scaffolds in genome sequencing

Pectin: The polygalacturonate sequences alternated by rhamnose and may contain galactose, arabinose,

xylose and fucose side chains. Molecular weight varies from 20,000 to 400,000. Its role is intercellular cementing of plant cells. Acids and alkali may cause its depolymerization.

Pedicel: The stalk of flowers in an inflorescence. ▶peduncle

PEDANT (protein extraction, description and analysis tool): See <http://pedant.gsf.de/>.

Pedigree Analysis: Generally carried out by examination of pedigree charts used in human and animal genetics where the family sizes are frequently too small to conduct meaningful direct segregation studies (see Fig. P36). The pedigree chart displays the lines of descent among close natural relatives. Females are represented by circles, males by squares and if the sex is unknown a diamond (◇) is used (see Fig. P37). The same but smaller symbols or by a vertical or slanted line indicates abortion or still birth over the symbol. For spontaneous abortions, triangles (q) may be used. Individuals expressing a particular trait are represented by a shaded or black symbol, and in case they are heterozygous for the trait, half of the symbol is shaded.

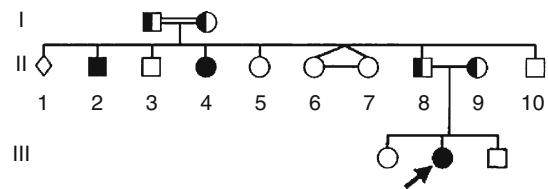


Figure P36. Pedigree chart

When an unaffected female is the carrier of a particular gene, there is a dot within the circle. In case segregation for traits needs to be illustrated in the pedigree, the individual displaying both traits may be marked by a horizontal and vertical line within the symbol or only by a horizontal or vertical line, respectively. Horizontal lines connect the parents and if the parents are close relatives, the line is doubled. The progeny is connected to the parental line with a vertical line and the subsequent generations are marked by Roman numerals at the left side of the chart, I (parents), II children, III (grandchildren), and so on. Twins are connected to the same point of the generation line and if they are identical, a horizontal line connects them to each other. The order of birth of the offspring is from left to right and may be numbered accordingly below their symbol. An arrow to a particular symbol indicates the proband, the individual who first became known to the geneticist as expressing the trait. The appropriate symbols of

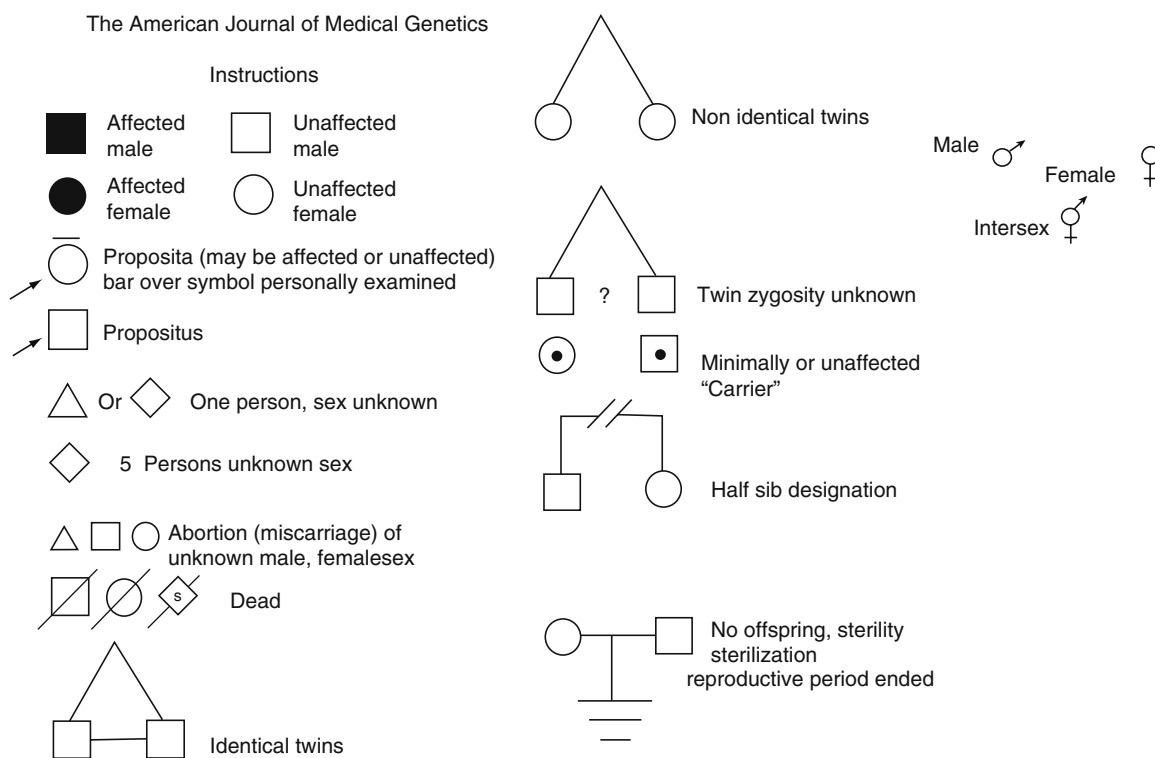


Figure P37. Pedigree symbols

adopted children may be bracketed. If a prospective offspring is considered at risk, broken lines draw the symbol. A horizontal line connected by a vertical line to the "parental" line may indicate lack of offspring by a couple.

Infertility may be represented by doubling a horizontal line under and connected to the male or female symbol, respectively. Egg or sperm donors (in case of assisted reproductive technologies [ART]) are indicated by a D and surrogate mothers by S within the symbols. *Mars shield* represents males and a *Venus mirror* represents females, and the sign in the box shown above at right indicates intersexes. ▶ART; Bennett RL et al 1995 Am J Hum Genet 56:745; Am J Med Genet pedigree chart is reprinted by permission of John Wiley & Sons, Inc.

Pedogenesis: Egg production by immature individuals such as larvae.

PEDro (Proteomics Experiment Data Repository): A model for the collection of information in proteomics. ▶proteomics; Taylor CF et al 2003 Nat Biotechnol 21:247.

Peduncle: The stalk of single standing flowers (→); bundle of nerve cells (see Fig. P38). ▶pedicel

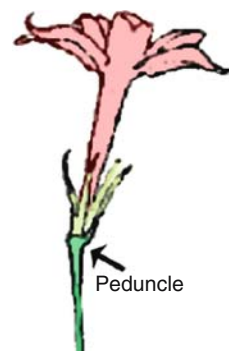


Figure P38. Peduncle

PEG (polyethylene glycol): May be liquid or solid and comes in a range of different viscosities (200, 400, 600, 1500, etc.). It facilitates fusion of protoplasts, uptake of organelles, precipitation of bacteriophages, plasmids and DNA, promoting end-labeling, ligation of linkers, reduction of immunogenicity when attached to humanized antibody, etc.

PEG-3 (progression elevated gene-3): In nude mice up-regulates carcinogenesis in progress via activation of VEGF. It can be blocked by antisense technology. ▶VEGF, ▶antisense technology

PEG (paternally expressed gene): ► [imprinting](#)

PEGylation: Attaches polyethylene glycol (PEG) to the polypeptide backbone of a protein drug, and renders it less liable to clearance from the body, and thus does not have to be supplied so frequently. PEGylated interferons have about 24 h half-life in the plasma whereas native interferons display only 4 h half-life. Interferon- α -2b (a recombinant product) when PEGylated is administered only once a week whereas without PEGylation it needs three dosing per week. ► [interferon](#); Walsh G 2003 Nat Biotechnol 21:865.

PEK: ► [HRI](#)

Pelargonidine: ► [anthocyanin](#)

Pelargonium zonale (geranium): An ornamental plant. Some variegated forms transmit the non-nuclear genes also through the sperm whereas in the majority of plants the plastids are transmitted only through the egg. ► [uniparental inheritance](#), ► [chloroplasts](#), ► [chloroplast genetics](#)

Pelger(-Huet) Anomaly: An autosomal dominant condition in humans as well as in rabbits, cats, etc., characterized by fewer (1.1–1.6) than normal (2.8) nuclear lobes in the granulocytic leukocytes. Mutations may involve the lamin B receptor. It may be a mild anomaly but it may be associated with other more serious ailments. The prevalence varies from 1×10^{-3} to 4×10^{-4} . Similar phenotypes were described also as autosomal recessive or X-linked. ► [laminopathies](#); Shultz LD et al 2003 Hum Mol Genet 12:61.

P

Pelizaeus-Merzbacher Disease: An Xq22 chromosomal recessive leukodystrophy that accumulates a proteolipoprotein (PLP, a 276-amino acid integral membrane protein) of the endoplasmic reticulum and the surface protein DM20 (26.5 kDa). The defect involves alternative splicing of the same mRNA. Duplications and deletion may be responsible for the disorder. The clinical symptoms are defective myelination (dysmyelination) of the nerves and defective interaction between oligodendrocytes and neurons, pathogenesis of the central nervous system and impaired motor development with an onset before age one. Mutation in the same gene encoding PLP is responsible also for X-linked spastic paraplegia type 2 (SPG-2) and the difference is in the degree of hypomyelination and motor dysfunction. Hereditary spastic paraplegia alleles were assigned to 8p, 16p, 15q and 3q27-q28. The corresponding defect in mouse displays *jimpy* and the myelin deficient (*msd*) phenotype. ► [myelin](#), ► [Charcot-Marie-Tooth disease](#), ► [leukodystrophy](#), ► [spastic paraplegia](#)

Pelle: Serine/threonine kinase, involved in dorsal signal transduction. ► [IRAK](#)

Peloric: The circular symmetry of the flower in contrast to the bilateral symmetry of the wild type first described in *Linaria* by Linnaeus. Homologous mutations occur in *Antirrhinum* as shown in Figure P39. This variation of floral symmetry of *Linaria* is due to the different methylation of a gene, *Lcyc* (Cubas P et al 1999 Nature [Lond] 401:157). It is thus an epimutation. The first figure is the wild type *Antirrhinum* flower of bilateral symmetry. The second figure is the *cycloidea* mutant with radial symmetry (pelory). (Illustration is the courtesy of Professor Hans Stubbe; ► [methylation of DNA](#), ► [epigenesis](#), ► [superman](#), ► [snapdragon](#), ► [cycloidea](#))

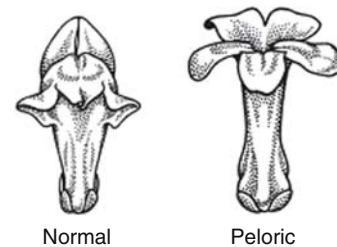


Figure P39. Normal and peloric snapdragon flowers

pelota: *Drosophila* gene involved in sperm function. ► [azoospermia](#)

Pemphigus: A collection of skin diseases with the general features of developing smaller or larger vesicles of the skin that may or may not heal and in extreme cases may result in death. The autosomal dominant familial pemphigus vulgaris is an autoimmune disease of the skin and mucous membranes. In the majority of cases, HLA-DR4 is involved. This anomaly is particularly common among Jews in Israel. In mice pemphigus vulgaris, inhibitor of MAPK (p38) can reduce the autoimmune blisters (Berkowitz P et al 2006 Proc Natl Acad Sci USA 103:12855). ► [Hailey-Hailey disease](#), ► [HLA](#), ► [skin diseases](#), ► [desmosome](#), ► [autoimmune disease](#)

Pena-Shokeir Syndrome: A fetal akinesia caused by brain malformations; X-chromosomal inheritance is suspected. ► [akinesia](#)

Pendred Syndrome: A recessive (7q31, PDS) thyroid anomaly and neurosensory deafness. The locus encodes *pendrin* an anion transporter, a presumed sulfate transporter localized in the cell membrane and a bicarbonate secretion in the kidney. Recent evidence indicates chloride and iodide transport too. This locus is responsible for about 1–10% of the genetically determined hearing loss. ► [deafness](#), ► [goiter](#); Royaux IE et al 2001 Proc Natl Acad Sci USA 98:4221.

Penetrance: The percentage of individuals in a family that express a trait determined by gene(s) they contain. The genetic basis of this phenomenon is poorly understood, and may cause serious problems in genetic counseling. ► [expressivity](#)

Penicillin: An antibiotic originally obtained from *Penicillium* fungi (see Fig. P40). The arrow points to the reactive bond of the β -lactam ring. ► [antibiotics](#), ► [Penicillium](#), ► [lactam](#), ► [\$\beta\$ -lactamase](#)

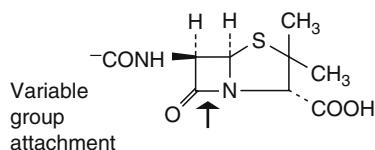


Figure P40. Basic structure of penicillins

Penicillin Enrichment: ► [penicillin screen](#)

Penicillin Screen: Used for mass isolation of auxotrophic microbial mutations that failed to grow in basal media (in contrast to the wild type) and the presence of the antibiotic therefore did not lead to their death (in contrast to the wild type). After transfer to complete (or appropriately supplemented) media the auxotrophs grew and thus were selectively isolated. ► [selective medium](#), ► [replica plating](#), ► [mutant isolation](#); Davis BD 1948 J Am Chem Soc 70:4267; Lederberg J, Zinder N 1948 J Am Chem Soc 70:4267.

Penicillinase: β -lactamase

Penicillin Binding Proteins: ► [PBP](#)

Penicillium notatum (fungus): $x = 5$ (see Fig. P41).



Figure P41. *Penicillium* conidiophore with conidia

Penis: The male organ of urinary excretion and insemination (homologous to the female clitoris). It contains the *corpus spongiosum* through which the urethra and sperm passes. Above that are the *corpora cavernosa* that become extended when erection takes place due to enhanced blood supply to this elastic tissue as a consequence of NO (nitrogen-monoxide) gas flows to the muscles of the blood vessel wall, initiated by acetylcholine. The

release of acetylcholine is controlled by steroid hormones. Cyclic GMP-dependent kinase is an essential enzyme for the maintenance of the extended state of the *corpus cavernosum*. Injection of prostaglandin E1 blocks cGMP-degrading phosphodiesterase and facilitates erection. The penis of canines (and most other mammals including primates except humans and spider monkeys) contains a small bone (*baculum* or *os penis*). In all humans, the gulonolactone oxidase (EC 1.1.3.8) gene on chromosome 8p21 is defective and no baculum is formed. The lack of this enzyme also makes humans dependent on dietary ascorbic acid. (It has been suggested that God created Eve not from a rib but from the baculum of Adam.) The baculum of mammals assists quick penetration of the vagina. During sexual intercourse of dogs, the male first penetrates the vulva of the female and erection takes place only in a second phase. At the base of the dog's penis the oval *bulbus glandis* then expands and locks the penis in position and the mating pair cannot separate until the ejaculation is terminated. Some animals (snakes, lizards, crustaceans and insects) have two penises (*virgae*). In *Euborellia plebeja* (Dermaptera) both are functional. ► [animal hormones](#), ► [acetylcholine](#), ► [acetylcholine receptors](#), ► [hypospadias](#), ► [nitric oxide](#), ► [cGMP](#), ► [prostaglandin](#), ► [baculum](#), ► [erectile dysfunction](#), ► [clitoris](#); Kamimura Y, Matsuo Y 2001 Naturwiss 88:447; insect penis evolution review: Palmer AR 2006 Nature [Lond] 444:689.

Pentaglycines: ► [bacteria](#)

Pentaploid: Its cell nucleus contains five genomes (5x). Pentaploids are obtained when hexaploids (6x) are crossed with tetraploids (4x). The pentaploids are generally sterile or semi-fertile because the gametes generally have unbalanced number of chromosomes. ► [polyploids](#), ► [Rosa canina](#)

Pentatrico: A ~35 unit sequence of amino acids, generally repeated several times in some proteins. Pentatricopeptide repeat (PPR) proteins form one of the largest families in higher plants and are believed to be involved in the posttranscriptional processes of gene expression in plant organelles and RNA editing in the chloroplasts (Okuda K et al 2007 Proc Natl Acad Sci USA 104:8178). ► [RNA editing](#), ► [retrograde regulation](#)

Penton: Capsomer with five neighbors in the viral capsid. ► [capsomer](#), ► [hexon](#); Zubieta C et al 2005 Mol Cell 17:121.

Pentose: A sugar with 5-carbon-atom backbone, such as ribose, deoxyribose, arabinose, xylose.

Pentose Phosphate Pathway: glucose-6-phosphate + 2 NADP + H₂O → ribose-5-phosphate + 2 NADPH +

2 H + + CO₂, i.e., the conversion of hexoses to pentoses generates NADPH, a molecule that serves as a hydrogen and electron donor in reductive biosynthesis. ► **Embden-Meyerhof pathway**, ► **Krebs-Szentgyörgyi cycle**

Pentose Shunt: Same as pentose phosphate pathway.

Pentosuria: An autosomal recessive non-debilitating condition characterized by excretion of increased amounts of L-xylulose (1–4 g) in the urine because of a deficiency of the NADP-linked xylitol dehydrogenase enzyme. In Jewish and Lebanese populations, the frequency of the gene was about 0.013–0.03. ► **gene frequency**, ► **allelic frequencies**

PEPCK (phosphoenolpyruvate carboxykinase): A regulator of energy metabolism.

Pepper (*Capsicum* spp): It exists in a great variety of forms but all have 2n = 2x = 24 chromosomes. Some wild species are self-incompatible and the cultivated varieties yield better if they have a chance for xenogamy. ► **self-incompatibility**, ► **xenogamy**

Pepsin: An acid protease, formed from pepsinogens. It has preference for COOH side of phenylalanine and leucine amino acids.

Pepstatin (C₃₄H₆₃N₅O₉): A protease (pepsin, cathepsin D) inhibitor.

Peptamer: The exposed loop on the surface of a carrier protein; it is thus protected from degradation and its conformational stability is improved.

Peptidase (protease): Hydrolyzes peptide bonds. In humans, the peptidase gene PEPA is in chromosome 18q23, PEPB in 12q21, PEPC in 1q42, PEPD in 19cen-q13.11, PEPE in 17q23-qter, PEPS in 4p11-q12, and the tripeptidyl peptidase II (TPP2), a serine exopeptidase is in 13q32-q33. (See <http://merops.sanger.ac.uk>).

Peptide Bond: Amino acids are joined into peptides by their amino and carboxyl ends ↑ (and they lose one molecule of water) (see Fig. P42).

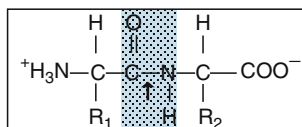


Figure P42. Peptide bond

Peptide Elongation: ► **protein synthesis**, ► **aminoacylation**, ► **aminoacyl-tRNA synthetase**, ► **elongation factors** (eIF), ► **ribosome**, ► **tmRNA**, ► **cycloheximide**

Peptide Initiation: ► **protein synthesis**, ► **pactamycin**

Peptide Mapping: The separation of (in)complete hydrolysates of proteins by two-dimensional paper chromatography or by two-dimensional gel electrophoresis for the purpose of characterization. The distribution pattern is the map or fingerprint, characteristic for each protein.

Peptide Mass Fingerprints: The protein is first cleaved by a sequence-specific protease such as trypsin and analyzed by MALDI-TOF and compared with protein sequences with similar lysyl or arginyl residues of the same mass. On this basis matching proteins even in a mixture can be identified. Modified proteins are detectable on the basis of peptide sequence with an incremental mass due to, e.g., a phosphogroup. ► **proteomics**, ► **MALDI**, ► **trypsin**; Mann M et al 2001 Annu Rev Biochem 70:437; Pratt JM et al 2002 Proteomics 2:157; Giddings MC et al 2003 Proc Natl Acad Sci USA 100:20; <http://www.peptideatlas.org/>.

Peptide Nucleic Acid (PNA): A nucleic acid base (generally thymine) is attached to the nitrogen of a glycine (or other amino acids) by a methylene carboxamide linkage in a backbone of aminoethyl-glycine units (see Fig. P43). Such a structure can displace one of the DNA strands and binds to the other strand.

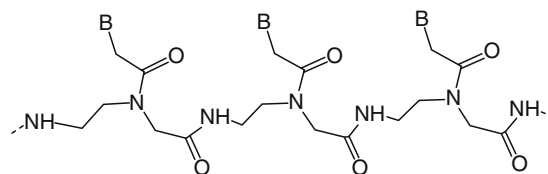


Figure P43. PNA backbone resembles that of DNA. The letter B stands for nucleic acid bases

They are DNA mimics. This highly stable complex has similar uses as the antisense RNA technology. PNA may be used to inhibit excessive telomerase activity in cancer cells. Homopyrimidine PNA may invade homopurine tracts in double-stranded DNA and may form triplex DNA and interfere with transcription. Peptide nucleic acid can target the polyguanine tract of HIV-1 and can arrest translation elongation (Boutiah-Hamoudi F et al 2007 Nucleic Acids Res 35:3907). PNA may also be used to screen for base mismatches and small deletions or base substitution mutations. Peptide nucleic acid complementary to mutant mtDNA selectively inhibits the replication of mutant mtDNA in vitro. PNA has been suggested to be the first pre-biotic genetic molecule rather than RNA. PNA may be useful for delivering genes to the mitochondria. PNA-DNA hybrids may be identified by binding of the dye 3,3'-diethylthiadicarbocyanine and used for the rapid detection of

mutations of clinical importance. Site-specific recombination may be substantially enhanced by PNA. ▶antisense RNA, ▶antisense DNA, ▶TFO, ▶mtDNA, ▶Hoogsteen pairing, ▶RNA world, ▶mitochondrial gene therapy, ▶acquired immunodeficiency; Corey DR 1997 Trends Biotechnol 15:224; Chinnery PF et al 1999 Gene Ther 6:1909; Wilhelmsson LM et al 2002 Nucleic Acids Res 30(2): e3; Rogers FA et al 2002 Proc Natl Acad Sci USA 99:16695.

Peptide Processing: ▶post-translational processing

Peptide Sequence Tag: ▶electrospray MS

Peptide Transporters: ▶TAP, ▶ABC transporters

Peptide Vaccination: Synthetic polypeptides corresponding to CTL epitopes may result in cytotoxic T cell-mediated immunity but in some instances, it may enhance the elimination of anti-tumor CTL response. ▶vaccination, ▶CTL, ▶epitope, ▶cancer prevention, ▶immunological surveillance; Vandenbark AA et al 2001 Neurochem Res 26:713.

Peptidoglycan: The heteropolysaccharides cross-linked with peptides constituting the bulk of the bacterial cell wall, especially in the Gram-positive strains. ▶Gram negative; see chemical formula in Fig. P44.

Peptidomimetics: These are polymer analogs containing unnatural amino acids. The non-natural amino acids are incorporated by the translation machinery using suppressor amino acid-transfer RNAs or nonsuppressor tRNA in a modified system. Peptidomimetics may facilitate the study of translation, enable directed evolution of small molecules with desirable catalytic and pharmacological properties, and are potential blocking agents of carcinogenesis by promotion of apoptosis. ▶translation, ▶aminoacyl-tRNA synthetase, ▶suppressor tRNA, ▶genetic code, ▶alloproteins; Forster AC et al 2003 Proc Natl Acad Sci USA 100:6353.

Peptidyl Site: ▶P site, ▶ribosome, ▶protein synthesis

Peptidyl Transferase: Generates the peptide bond between the preceding amino acid carboxyl end (at the P ribosomal site) and the amino end of the incoming amino acid (at the A site of the ribosome). It is a ribozyme and the catalytic function resides in the 23S ribosomal RNA. Essential function is attributed to adenine 2451. ▶ribosome, ▶protein synthesis, ▶macrolide

Peptidyl-Prolyl Isomerases (PPI): PPI mediate the interconversion of the cis and trans forms of peptide bonds preceding proline. PPI genes are in human chromosomes 4q31.3, 6p21.1, 7p13 and the mitochondrially located at 10q22-q23. This family includes cyclophilins, FKBs and parvulins. ▶FK506, ▶cyclophilins, ▶parvulin; Shaw PE 2002 EMBO Rep 3:521; Wu X et al 2003 Genetics 165:1687.

Peptoid: A peptide-like molecule that results from the oligomeric assembly of N-substituted glycines. Peptoids have various biological applications.

per (period) locus: In *Drosophila* (map location 1-1.4, 3B1-2), *per* locus controls the circadian and ultradian rhythm, thus affecting eclosion, general locomotor activity, courtship, intercellular communication, etc. The mutations do not seem to affect the viability of the individuals involved, only the behavior is altered. When *per^S* (caused by a base substitution mutation in exon 5) in the brain is transplanted into *per⁰¹* mutants (nonsense mutation in exon 4) causing short ultradian rhythm and multiple periods, some flies may be somewhat normalized. The locus has been cloned and sequenced and seems to code for a proteoglycan. Gene NONO of mammalian cells apparently positively modulates PER and gene WDR5 (involving a histone-methyltransferase subunit) controls methylation/expression of PER (Brown SA et al 2005 Science 308:693). The Per protein forms a heterodimeric complex with the Tim (*timeless* gene) protein

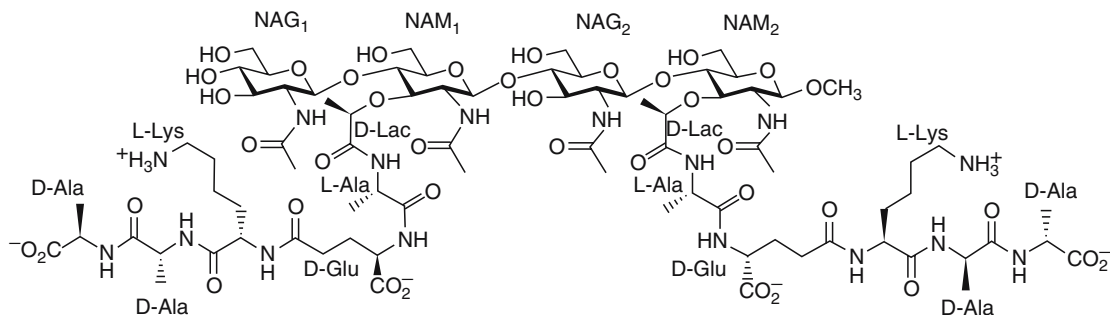


Figure P44. Chemical structure of a segment of peptidoglycan. (NAG): N-acetylglucosamine-N-acetyl muramic acid disaccharide (NAM) and attached pentapeptide. See Meroueh SO et al. 2006 Proc Natl. Acad. Sci. USA 103:4404

and jointly autoregulate transcription. Tim is degraded in the morning in response to light and that results in the disintegration of the complex that is reformed again in dark in a circadian oscillation. In mammals, three *mPer* loci have been identified controlling the circadian clock. ▶circadian, ▶ultradian, ▶proteoglycan

Percent Identity Plot (PIP): A macromolecular sequence map displaying the percentage of identity between two sequences. (See <http://bio.cse.psu.edu>).

Percentile: The percentage of the distribution of variates. More than 50 percentile indicates a value higher than 50% of the variates.

Perdurance: The persistence and expression of the product of the wild type gene even after the gene itself is no longer there.

Perennial: Lasts through more than one year.

Perfect Flower: Has both male and female sexual organs, i.e., it is hermaphroditic (see Fig. P45). ▶hermaphrodite, ▶flower differentiation

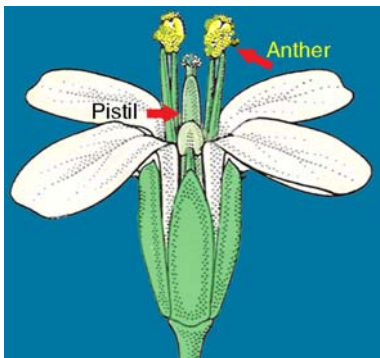


Figure P45. Perfect flower

Perforin (encoded at 10q22): Pore-forming protein (homologous to component 9 of the complement) that establishes transmembrane channels; it is stored in vesicles within the CD8⁺ cytotoxic T cells (CTL). These vesicles contain also serine proteases. Perforin mediates apoptosis by permitting killer substances (granzyme) slowly enter the cell. Perforin may have a role in T cell-mediated destruction of pancreatic β -cell in diabetes mellitus type I. ▶apoptosis, ▶complement, ▶T cells, ▶fragmentin-2, ▶granzymes, ▶caspase, ▶histiocytosis, ▶diabetes mellitus; Keefe D et al 2005 Immunity 23:249.

Perfusion: Adding liquid to an organ through its internal vessels in vitro or in vivo.

Perianth: Designates both sepals and petals of the flowers. ▶flower differentiation

Pericarp: The fruit wall (maternal tissue), developed from the ovary wall such as the pea pod, the outer layer of the wheat or maize kernels. The *Arabidopsis* silique, the peel of the citrus, and the skin of apple, the shell of the nuts, etc., are also similar but are exocarps. The outer layer of the common barley “seed” is not part of the fruit wall but it is a bract of the flower.

Pericentric Inversion: ▶inversion pericentric

Pericentromeric Region: A highly redundant tract (<1 kb to ~85 kb), a transition zone, between the genic region of the chromosomes and the satellite heterochromatin. ▶heterochromatin, ▶centromere, ▶satellite DNA; Horvath JE et al 2001 Hum Mol Genet 10:2215.

Perichromatin Fibers: Active genes occupy the surface of specific compartments in the interphase nucleus (chromosome territories) and represent the perichromatin fibers. ▶SR motif, ▶chromatin, ▶chromosome territories; Cmarko D et al 1999 Mol Biol Cell 10:211.

Periclinal Chimera: Contains genetically different tissues in different cell layers. ▶mericlinal chimera, ▶chimera

Pericycle: The (root) tissue between the endodermis and phloem. ▶root, ▶endodermis, ▶phloem

Peridium: The covering of the hymenium or the hard cover of the sporangium of some fungi. ▶hymenium, ▶sporangium

Perinatal: The period after 28 weeks of human gestation⇔four weeks after birth.

Perinuclear Space: A ~20 to 40 nm space between the two layers of the nuclear membrane. ▶nucleus

Periodic Acid-Schiff Reagent (PAP): The tests for glycogen, polysaccharides, mucins, and glycoproteins. It breaks C-C bonds by oxidizing near hydroxyl groups and forms dialdehydes and generates red or purple color.

Periodic Paralysis (PP, KCNE): A group of autosomal dominant human diseases manifested in periodically recurring weakness accompanied by low blood potassium level (hypokalemic periodic paralysis, defect in the α subunits of Ca²⁺ channel) or in other forms with high blood potassium level (hyperkalemic periodic paralysis, paramyotonia). The latter types were attributed to base substitution mutations in a highly conserved region of the α subunit of a transmembrane sodium channel protein. In another type of the disease, the blood potassium level appeared normal and the patients responded favorably to sodium chloride. The MiRP2 potassium

channel defect is also associated with PP. ►ion channel, ►Moebius syndrome, ►myotonia, ►hyperkalemic periodic paralysis; Abbott GW et al 2001 Cell 104:217.

Periodicity: The number of base pairs per turn of the DNA or the number of amino acids per turn of an α -helix of a polypeptide chain. ►protein structure, ►Watson and Crick model

Periodontitis: Several diseases involving inflammation of the gingiva, especially at the base of the teeth and the alveolae, the bone support of the teeth. It is usually associated with keratosis of the palms and soles. About 30% of the human population is affected by it. In the juvenile form (encoded at 4q11-q13) both milk and permanent teeth may be lost in early childhood. The disease is the result of bacterial infections (~500 different species may inhabit the human mouth). The Papillon-Lefèvre syndrome (11q14, prevalence $1-4 \times 10^{-6}$) is based on deficiency of cathepsin C, a dipeptidyl peptidase I. In the similar autosomal recessive periodontitis deficiency of IL-1 is suspected. Similar symptoms may occur also in the Ehlers-Danlos syndrome Type VIII. ►keratosis, ►cathepsin, ►IL-1, ►Ehlers-Danlos syndrome, ►dentinogenesis imperfecta; Travis J et al 2000 Adv Exp Med Biol 477:455.

Peripheral Nervous System: Resides outside the brain and the spinal chord.

Peripheral Proteins: These are bound to the membrane surface by hydrogen bonds or by electrostatic forces. ►membrane proteins

Peripherin (retinal degeneration slow protein): ►retinal dystrophy

Periplasma: The cell compartment between cell wall and cell membrane. In *E. coli* the Sec family of proteins mediate the translocation across the periplasmic and the outer membrane. The extracellular stress response factor σ^E regulates the assembly of the outer membrane. The two-component Cpx seems to be involved in the assembly of the pilus. ►Sec, ►two-component regulatory system, ►pilus; Danese PN, Silhavy TJ 1998 Annu Rev Genet 32:59; Raivio TL, Silhavy TJ 2001 Annu Rev Microbiol 55:591.

Peristalsis: The contraction of muscles of a tubular structures (e.g., intestines) propelling the content.

Peristome: A fringe of teeth at the opening of the sporangium of mosses or the buccal (mouth) area of ciliates.

Perithecium: A fungal fruiting body of disk or flask shape with an opening (ostiole) for releasing the spores (see Fig. P46). A perithecium of *Neurospora*

contains about 200 asci. Its primordium is called protoperithecium. ►ascogonium, ►apothecium, ►cleistothecium, ►gymnothecium, ►*Neurospora*, ►ascus, ►tetrad analysis

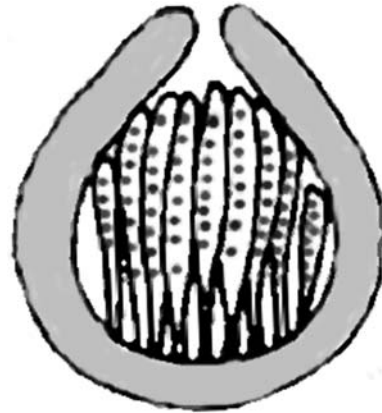


Figure P46. Perithecium

Periventricular Heterotopia: A human X-chromosomal mental retardation and seizures caused by anomalies of the brain cortex. The neurons destined for the cerebral cortex fail to migrate. The mutation involves the filamin gene (FLN1, Xq28) encoding an actin-cross-linking phosphoprotein. ►double cortex; Sheen VL et al 2001 Hum Mol Genet 10:1775.

PERK (PKR-like ER kinase): A phosphorylating enzyme in the endoplasmic reticulum, similar to the mammalian RNA-dependent protein kinase (PKR). It is interferon-inducible and activated by double-stranded RNA. PERK and the phosphorylation of eIF2 α inhibit the initiation of translation. ►PKR, ►eIF2 α , ►Ire, ►unfolded protein response, ►S6; Kumar R et al 2001 J Neurochem 77:1418.

Perl Script: Assembles and merges sequences from different DNA libraries. ►DNA library, ►PHRAP

Perlecan: Heparan sulfate proteoglycan that interacts with the extracellular matrix, growth factor receptors and affects signal transduction. ►proteoglycan, ►heparan sulfate, ►Schwartz-Jampel syndrome; Knox S et al 2002 J Biol Chem 277:14657.

Perlegen Sciences: Perlegen sciences have genotyped over 1.5 million unique genetic variants (SNPs), in 71 individuals of European American, African American, or Han Chinese ancestry. In total, more than 112 million individual genotypes were determined, with an average distance between adjacent SNPs of 1871 base pairs. The genotype browser permits accession to virtually all the SNP, linkage disequilibrium, and haplotype data reported in the study. ►SNIPs, ►linkage disequilibrium, ►haplotype;

expanded data: Hinds DA et al 2005 Science 307:1072; <http://genome.perlegen.com/>.

Permafrost: The soil layer in cold regions that remains permanently frozen even when the top may thaw.

Permanent Hybrid: ►complex heterozygote

Permease: The enzymes involved in the transport of substances through cell membranes. ►membrane transport, ►membrane channels, ►membrane potential, ►ion channels; Abramson J et al 2003 Science 301:610.

Permissible Dose: ►radiation hazard assessment

Permissive Condition: The condition at which a conditional mutant can survive or reproduce. ►conditional mutation

Permissive Host: A cell permits (viral) infection and/or development.

Permutation: Generating all possible orders of n numbers, and it can be obtained by the factorial: $n!$, e.g., the factorial of 4, $4! = 4 \times 3 \times 2 \times 1 = 24$. ►combination, ►variation

Permutation Test (randomization test): The test used to assess the association of QTLs with multiple (molecular) markers in a randomized array. ►QTL, Edington ES 1995 Randomization tests, Marcel Dekker, New York.

Permuted Redundancy: At the termini of phage DNA a collection of redundant sequences occur in the phage population that start and end with permuted sequences of the same nucleotide sequence, e.g., 1234...1234, 2341...2341, 3412...3412, etc. This arrangement is characteristic for T-uniform phages, e.g., T1, T3, T5, etc. ►non-permuted redundancy

Perodictus: ►*Lorisidae*

Peroxidase: Heme protein enzymes, which catalyze the oxidation of organic substances by peroxides. Glutathione peroxidase (and selenium) deficiency may cause hemolytic disease. Several peroxidase genes have been located in the human genome: GPX1 in 3q11-q12, GPX2 in 14q24.1, GPX3 in 5q32-q33, GPX4 (in testes) in chromosome 19, a rare eosinophil peroxidase (EPX) may compromise the immune system, a thyroid peroxidase deficiency (2p25) interferes with thyroid function. ►immune system, ►eosinophil, ►hemolytic disease, ►oxidative stress

Peroxidase and Phospholipid Deficiency: An autosomal recessive anomaly of the eosinophils involving the enzyme defects named. ►microbody, ►Refsum disease, ►Zellweger syndrome

Peroxides: They display the — O — O — linkage. Organic peroxides participate in activation and deactivation of promutagens, mutagens, procarcinogens

and carcinogens and in many other physiological reactions. Peroxides are formed by the breakdown of amino acids and fatty material in the cell and may inflict serious damage. According to some views, spontaneous mutation may be caused to a great extent by these regular components of the diet. Therefore, eating rancid food may pose substantial risk. ►environmental mutagens, ►peroxidase, ►catalase peroxisomes, ►promutagen, ►ROS, ►P450

Peroxins: Peroxisome proteins. PEX1 (7q21-q22), PEX10, human chromosome 1) is a peroxisome biogenesis protein, PEX13 (2p15) in another peroxisome biogenesis protein. ►peroxisome, ►PEX, ►Zellweger syndrome, ►Refsum disease, ►microbodies; Walter C et al 2001 Am Hum Genet 69:35.

Peroxiredoxins: Antioxidant enzymes present in prokaryotes and eukaryotes and control signal transduction, apoptosis, tumor formation, HIV infection, etc. (See Wood ZA et al 2003 Science 300:650; Neumann CA et al 2003 Nature [Lond] 424:561).

Peroxisomal 3-Oxoacylcoenzyme A Thiolase Deficiency (pseudo-Zellweger syndrome): Autosomal recessive disease assigned to human chromosome 3p23-p22. ►microbody, ►Zellweger syndrome, ►adrenoleukodystrophy

Peroxisome: Peroxisome are ~0.15–0.5 μm diameter bodies, surrounded by single-layer membrane, in eukaryotic cells containing about 50 proteins, including oxidase and catalase enzymes. The peroxisomes synthesize ether phospholipids by dihydroxyacetonephosphate acetyltransferase (DHAPAT, human chromosome 1q42) and alkyl dihydroxyacetonephosphate synthase (ADHAPS, 2q31). In a human cell, the number of peroxisomes vary from less than 100 to more than 1000. In yeast either over expression or lacking the Inp 1 protein (inheritance of peroxisome protein 1) are detrimental for the right amount and the proper distribution of peroxisome. Inp binds several proteins involved in peroxisome division (Fagarasanu M et al 2005 J Cell Biol 169:765). The peroxisomes have indispensable roles in fatty acid β oxidation, phospholipid and cholesterol metabolism. Fatty acid granules are also named microbodies. The peroxisome biogenesis disorders (PBD) are recessive lethal diseases in variable forms. The extreme form is the Zellweger syndrome, the Refsum disease and the adrenoleukodystrophy are milder and the rhizomelic chondrodysplasia punctata (RCDP) involves bone defects. Peroxisome mutations have been identified also in yeast (PAS). Some rodent carcinogens increase the number of peroxisomes but in humans, these agents did not appear to be carcinogenic. Peroxisomal protein Pex2 controls photomorphogenesis in *Arabidopsis*. ►glyoxisome,

►microbodies, ►PPAR, ►peroxin, ►Zellweger syndrome, ►Refsum disease, ►adrenoleukodystrophy, ►chondrodysplasia, ►oxalosis, ►peroxidase and phospholipid deficiency, ►peroxisomal 3-oxo-acyl-coenzyme A thiolase deficiency, ►PPAR, ►micro-pexophagy, ►pexophagy, ►PEX; Gould SJ, Valle D 2000 Trends Genet 16:340; Sacksteder KA, Gould SJ 2000 Annu Rev Genet 34:623; Titorenko VI, Rachubinski RA 2001 Trends Cell Biol 11:22; Thai T-P et al 2001 Hum Mol Genet 10:127; Titorenko VI, Rachubinski RA 2001 Nat Rev Mol Cell Biol 2:357; Purdue PE, Lazarow PB 2001 Annu Rev Cell Dev Biol 17:701; Hu J et al 2002 Science 297:405; Matsumoto N et al 2003 Am J Hum Genet 73:233; Weller S et al 2003 Annu Rev Genomics Hum Genet 4:165; Wanders RJA, Waterham HR 2006 Annu Rev Biochem 75:295; <http://www.peroxisomeDB.org>.

Peroxynitrite (ONOO⁻/ONOOH): The diffusion-limited product of nitric oxide with superoxide. It is strongly oxidizing and toxic. ►nitric oxide, ►super-oxide, ►peroxides; García-Nogales P et al 2003 J Biol Chem 278:864.

Perp: ►p63

Persistence, Bacterial: A phenocopy-like phenomenon in bacteria. When the culture is exposed to strong stress (e.g., antibiotics), the majority of the cells die but a small fraction survives although without a heritable resistance. When they re grow the population become sensitive to the antibiotic. ►phenocopy; Balaban NQ et al 2004 Science 305:1622.

Personal Genomics: ►DNA fingerprinting, ►DNA sequencing

Personality: Can be characterized by five main groups of features: (1) *extraversion* (being outgoing) or the lack of it, ability to lead and sell their ideas versus reticent and avoiding company [heritability about 0.71]; (2) *neuroticism* (emotional versus stable) worrisome or self-assured, [heritability about 0.21]; (3) *conscientiousness* (well-organized versus impulsive) responsible or irresponsible, reliable or undependable, [heritability 0.38–0.32]; (4) *agreeableness* (empathic or unfriendly) warm versus cold, cooperative versus quarrelsome, forgiving versus vindictive, [heritability about 0.49], and (5) *openness* (insightful or lacking intelligence) imaginative versus imitative, inquisitive or superficial). These heritability estimates vary a great deal, however, and may be very different in some populations. Based on twin studies, several investigators concluded that overall close to 50% of the variance could be attributed to additive or non-additive genetic determination. ►behavior in humans, ►behavior genetics, ►human intelligence, ►affective disorders, ►heritability in humans

Person/Year: Used as, for e.g., incidence of an event a (symptoms of a disease) per person per year.

Persyn: ►synuclein-γ

Perturbogen: Short peptides or protein fragments that can disrupt specific biochemical function in the cell.

Pertussis Toxin: Produced by the Gram-negative *Bordetella* bacteria, responsible for whooping cough. The toxin stimulates ADP-ribosylation of the Gα_i subunit of a G-protein in the presence of ARF and thus GDP stays bound to the G-protein and adenylate cyclase is not inhibited and K⁺ ion channels do not open. As a consequence, histamine hypersensitivity and reduction of blood glucose level follows. ►whooping cough, ►signal transduction, ►ARF, ►G-protein, ►ADP, ►GDP, ►cholera toxin, ►adenylate cyclase; Alonso S et al 2001 Infect Immun 69:6038.

PERV (porcine endogenous retrovirus): Exists in >50 copies/pig chromosome complement and has been feared to endanger humans with xenotransplantation of pig organs. So far, the limited information indicates minimal risk relative to the potential benefits. PERVs can be transferred to mice by xenotransplantation. ►xenograft, ►xenotransplantation, ►nuclear transplantation; Specke V et al 2001 Virology 285:177.

PEST (proline [P]-glutamate [E]-serine [S]-threonine [T]-rich motif): PEST in the carboxyl domain of IκB and other proteins (Ubc) is involved in the stimulation of proteolysis. ►IκB, ►NF-κB, ►proteasome, ►Ubc, ►ubiquitin

Pest Eradication by Genetic Means: ►genetic sterilization, ►*Bacillus thuringiensis*, ►host–pathogen relations (see Fig. P47).



Figure P47. *Bacillus thuringiensis* toxin transgene is lethal to worms (right) but the wild type plants (left) were destroyed. (Courtesy of Professor Marc Van Montagu, Rijksuniversiteit, Gent)

Pesticide Mutagens: ►environmental mutagens

Pesticin: The toxin of *Pasteurella* bacteria

Pestilence: An infectious epidemic of disease.

PET: ►tomography

PET: ►transcriptome, ►paired-end diTAG

Petaflop Computer: An extremely powerful supercomputer. “Peta” comes from the Latin word *peto* (I move forward) and in computer jargon, “flops” designate floating operations. This new hardware may be capable of performing one quadrillion flops/second, that are more than 10^6 times the efficiency of the best desktop computers.

Petals: Generally the second whorl of modified leaves from the bottom of the flower (see Fig. P48).

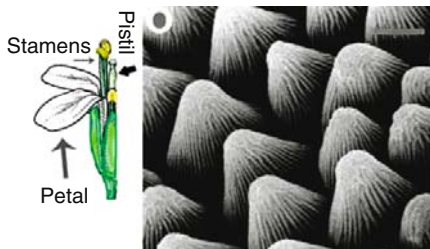


Figure P48. Petals of *Arabidopsis* are shown at left. At right: The adaxial ridge of the petal as viewed by scanning electronmicrography and reveal the beauty, which the naked eye cannot see. (From Bowman JL, Smyth DR 1994 In: Bowman JL (ed) *Arabidopsis: An Atlas of Morphology and Development*. By permission of Springer-Verlag, New York)

Frequently, they are quite showy because of their anthocyanin or flavonoid pigmentation. The petal number is a taxonomic characteristic, although petal number may be altered by homeotic mutations converting the anthers and/or pistils into petals and appearing as sterile double flowers of floricultural advantage. MicroRNA may have a role in the regulation of petal number (Baker CC et al 2005 *Curr Biol* 15:303). ►flower differentiation, ►flower pigments, ►homeotic mutants; Roeder AHK, Yanofsky MF 2001 *Dev Cell* 1:4.

PETCM (α -[trichloromethyl]-4-pyridineethanol): Stimulates caspase-3 activity and thereby apoptosis. ►caspase, ►apoptosis; Jiuang X et al 2003 *Science* 299:223.

Petiole: The stalk of a leaf (see Fig. P49).

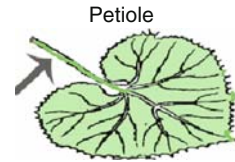


Figure P49. Petiole

Petite Colony Mutants: Petite colony mutants of yeast forms small colonies because they are deficient in respiration (OXPHOS minus) and lethal under aerobic conditions. The *vegetative petites* (ρ^-) are caused by (large) deletions in the mitochondrial DNA, the *segregational petites* are controlled by nuclear genes at over 200 loci. The mitochondrial mutations occur at high (0.1 to 10%) frequency and using ethidium bromide as a mutagen their frequency may become as high as 100%. The mitochondrial petites fail to transmit this character in crosses with the wild type except one special group the *suppressive petites* that may be transmitted at a low frequency in outcrosses with the wild type. In yeast, the A + T content of the normal mitochondrial DNA is about 83%, in some of the mitochondrial mutants the A + T content may reach 96% because the coding sequences were lost and only the redundant A + T sequences were retained and amplified so the mtDNA content is not reduced. The *hypersuppressive petite* mutants have short (400–900 bp) repeats that share 300 bp (*ori* and *rep*) sequences with the wild type, necessary for replication. *Neutral petites* produce wild type progeny when outcrossed to the wild type. Yeast cells that have normal mitochondrial function make large colonies and are called *grande*. Cells that can dispense with mitochondrial functions are sometimes called petite-positive whereas that absolutely need mitochondria are called petite-negative. Inactivation of an ATP and metal-dependent protease (Yme1p) associated with the inner membrane of the mitochondrion can convert the “positives” to “negatives” and the presence of the Yme1p function may have the opposite effect. Yme is not universally present in all yeasts. ►mitochondria, ►mtDNA, ►mitochondrial mutations, ►oxidative phosphorylation; Sager R 1972 *Cytoplasmic Genes and Organelles*, Academic Press, New York; MacAlpine DM et al 2001 *EMBO J* 20:1807; Chen XJ, Clark-Walker GD 2000 *Int Rev Cytol* 194:197.

Petri Plate: A (flat) glass or disposable plastic culture dish for microbes or eukaryotic cells (see Fig. P50).



Figure P50. Petri plate

Petunia hybrida (2n = 28): *Solanaceae*; predominantly self-pollinating but allogamy also occurs. It has been used extensively for cell, protoplast and embryo culture, intergeneric and inter-specific cell fusion, genetic transformation and the genetic control of pigment biosynthesis. It has a good number of related species.

Peutz-Jeghers Syndrome: ▶polyposis hamartomatous

PEV (position effect variegation): ▶position effect, ▶heterochromatin, ▶RPD3

PEX: Proteins import the peroxisome-targeting signals (PTS) to the peroxisomes. The various PEXs play roles in peroxisome biogenesis. ▶peroxisome; Braverman N et al 1988 Hum Mol Genet 7:1195.

Pexophagy: Sequestration to and engulfing peroxisomes into vesicles and their destruction. ▶peroxisome

Peyer's Patches: Aggregated lymphatic nodes. The Peyer's patches mediate the uptake of macromolecules, antigens and microorganisms through the epithelium of the gut. These plaques are instruments of mucosal immunity. B cells are required for the normal functions of the Peyer's patches. *Salmonella typhi* infection may cause perforation of the Peyer's patches. Tyrosine kinase receptor RET is a regulator of Peyer's patch formation (Veiga-Fernandes H et al 2007 Nature [Lond] 446:547). ▶mucosal immunity, ▶RET oncogene

Peyronie Disease: An apparently dominant autosomal disorder, it may be caused by a variety of acquired and genetic conditions. Its exact prevalence has not been determined but it may occur at ~1 to 8% of the human males. It involves fibrous, thickened collagen plaques on most commonly on the dorsal part of the penis and causes its curvature under painful conditions of erection. The condition may be transient. It occurs generally after age 40. Several drugs and in severe conditions surgical intervention have been used for treatment. (See Usta MF, Hellstrom WJG 2004 In: Seftel AD et al (Eds.) Male and Female Sexual Dysfunction, Mosby, St. Louis, Missouri, p 191).

PFAM: A database of over 3000 protein families and domains, multiple sequence alignments and profile hidden Markov models. ▶alignment; Bateman A et al

2002 Nucleic Acids Res 30:276; <http://pfam.wustl.edu>; <http://www.sanger.ac.uk/Software/Pfam/>; <http://pfam.jouy.inra.fr>; <http://pfam.cgb.ki.se/>.

Pfeiffer Syndrome: The syndrome includes autosomal dominant bone malformation affecting the head, thumbs and toes (acrocephalosyndactyly) (see Fig. P51), the autosomal recessive head-bone (craniostosis) and heart disease. The origin is primarily paternal. The latter type seems to co-segregate with fibroblast growth factor receptor 1 (FGFR1) in human chromosome 8p11.2-p11.1.



Figure P51. Short and broad thumb in Pfeiffer syndrome

Another locus in chromosome 10q26 represents also a fibroblast growth factor receptor, FGFR2. FGFR3 is located in chromosome 4p16.3 and its mutation is concerned with hypo-chondroplasia. Mutations in all three genes involve Pro→Arg replacements at identical sites, 253. This syndrome is allelic to the Crouzon and to the Jackson-Weiss syndromes. Some of the mutations represent gain-of-functions. ▶fibroblast growth factor, ▶Alpert's syndrome, ▶Crouzon syndrome, ▶Jackson-Weiss syndrome, ▶craniosynostosis syndromes, ▶hypo-chondroplasia, ▶achondroplasia, ▶gain-of-function, ▶receptor tyrosine kinase

PfEMP1: A group of *Plasmodium falciparum* protein ligands expressed on the surface of infected red blood cells and mediate cell adhesion (virulence factors) but may incite host immune reaction. PfEMP displays antigenic variation to evade this response. Other pathogenesis proteins of the parasite are rifins. ▶Plasmodium, ▶antigenic variation, ▶rifin; Flick K et al 2001 Science 293:2009.

PFGE (pulsed field gel electrophoresis): PFGE separates very large nucleic acid fragments or even small chromosomes. The megabase size fragments can be used for physical mapping of large chromosomal domains (PFG mapping). ▶pulsed field gel electrophoresis

pfu (p.f.u.): The plaque forming unit. The number of phage particles/mL that can invade a bacterial lawn and then after reaching about 10^7 particle numbers

a clear spot appears on the Petri plate where the bacterial cells had been lysed. ► **plaque**, ► **pu**, ► **CFU**

PG: ► **prostaglandins**

PGA: Phosphoglyceric acid, a 3-carbon product of photosynthesis. ► **photosynthesis**, ► **Calvin cycle**, ► **C3 plants**

PGC (primordial germ cells): Gynogenetic/parthenogenetic cell, the primordial cell of female gonads. ► **gonad**, ► **gynogenesis**, ► **parthenogenesis**

PGC1 (PPAR- γ -coactivator): A regulator of transcription, body heat production, mitochondrial biogenesis and other processes. PGC-1 β is a transcriptional coactivator for the production of cholesterol and triglycerides. PGC1 α regulates both the gluconeogenic and glycolytic pathways during fasting. PGC1 α is also a regulator of the expression of several transcription factors required for the biogenesis of mitochondria and it is down regulated in Huntington disease (McGill JK, Beal MF 2006 Cell 127:465). Sirtuin interacts with and deacetylates PGC in a NAD-dependent manner as part of energy homeostasis, diabetes and lifespan (Rodgers JT et al 2005 Nature [Lond] 434:113). ► **PPAR**, ► **nuclear receptor**, ► **sirtuin**, ► **gluconeogenesis**, ► **glycolysis**, ► **aging**, ► **resveratrol**, ► **Huntington's chorea**; Tsukiyama-Kohara K et al 2001 Nature Med 7:1102.

PGD (preimplantation genetic diagnosis): PGD can be carried out for some human genetic disorders, for e.g., PCR or FISH (for fragile X, aneuploidy, etc.) examining polar bodies or blastomeres at the stage of a few cells in the embryo. The disorders that have been identified by PCR included cystic fibrosis, Tay-Sachs disease, Lesh-Nyhan syndrome, Huntington chorea, Marfan syndrome, ornithine transcarbamylase deficiency, Fanconi anemia, etc. The diagnosis may permit—by using in vitro fertilization—to develop a human offspring of a certain (disease-free) genetic constitution. Misdiagnosis is rare but varies somewhat in different laboratories. It seems likely that all cells in a single eight-cell embryo may not be identical. (See diseases mentioned under separate entries, ► **PCR**, ► **FISH**, ► **ART**; Bickerstaff H et al 2001 Hum Fert 4(1):24; Simpson JL 2001 Mol

Cell Endocrinol 183(Suppl. 1):S69; Findlay I et al 2001 Mol Cell Endocrinol 183(Suppl. 1):S5; PGD tests carried out according to international survey: Sermon K et al 2005 Hum Reprod 20:19).

PGK-neo: A commonly used transformation cassette for gene knockout where the neomycinophosphotransferase gene (*neo*) is fused to the phosphoglycerate kinase (PGK) promoter. ► **knockout**, ► **vector cassette**; Scacheri PC et al 2001 Genesis 30(4):259.

P-Glycoprotein: The 170 kDa product of the human multidrug resistance gene (MDR-1, 7q21.1) that exports different (mainly hydrophobic) toxic substances from the cells in an ATP-dependent manner. ► **multidrug resistance**

PGM: ► **phosphoglucomutase**

PGRS (polymorphic GC-rich repetitive sequences): Mycobacterium tuberculosis proteins (~70) with glycine-glycine doublets that have few charged amino acids and essentially contain no cysteine. These proteins are apparently involved in pathogenesis. ► **Mycobacteria**; Karlin S 2001 Trends Microbiol 9:335.

PgtB: Bacterial kinase that phosphorylates regulator protein PgtA. ► **kinase**, ► **protein kinases**

PH: Pleckstrin homology domain. ► **pleckstrin**

pH: = $-\log(\text{H}_3\text{O}^+)$, negative logarithm of the hydrogen ion concentration; pure water at 25°C contains 10^{-7} mole hydrogen ions; solutions of acids could contain 1 mole and solution of bases 10^{-13} moles per liter.

The pH meters measure the electrical property of solutions which is proportional to pH; pH 7 is neutral and below it is acidic above it is alkaline (basic) (see Fig. P52). The pH of body fluids and tissues is regulated by the function of the ion channels.

The pH of plant tissues is generally below 7 because of the presence of organic acids and the majority of plant tissues can be cultured best in media around pH 6. Most animal tissues display neutral pH (~7). In the human blood, the pH is normally within the narrow range of 7.3 to 7.5. If the blood pH approaches 7, acidosis may result causing coma and at about pH 7.8 alkalosis may cause tetany

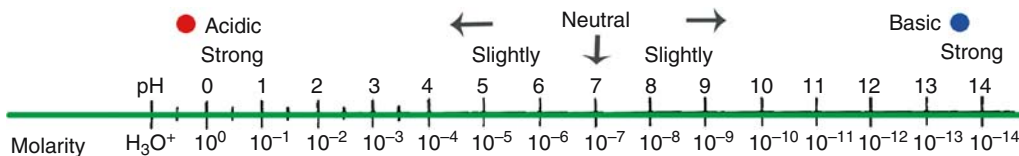


Figure P52. pH scale

(dangerous spasms) but the stomach secretions may be pH 0.9. The pH optima of enzymes vary a great deal but most commonly, it is in the range of 6 to 9. The preferred pH of microbes is also variable; the euryarchaeon bacterium, *Picrophilus torridus* thrives well at pH 0.7 and 60°C. (Fütterer O et al 2004 Proc Natl Acad Sci USA 101:9091). ▶ion channels, ▶buffer

Ph1 Chromosome: ▶Philadelphia chromosome

PhGene (pairing high): An approximately 700 Mb sequence that controls selective pairing in hexaploid wheat. In its presence, homoeologous chromosomes do not pair. It is in chromosome 5B. Plants nullisomic for this chromosome display multivalent associations in meiosis. A similar gene *Ph2* is in chromosome 3D. A *Ph* gene is present also in the A genome. Additional less powerful genes regulate chromosome pairing also. The *Ph* gene is absent from the genome of diploids but it is present in the B and G genomes in tetraploids. This observation indicates that *Ph* originated after polyploidization. ▶Triticum, ▶homoeologous, ▶nullisomic; Sears ER 1969 Annu Rev Genet 3:451; Martinez-Perez E 2001 Nature 411:204; Griffith S et al 2006 Nature [Lond] 439:749; Dvorak J et al 2006 Genetics 174:17.

PHA (phytohemagglutinin): A lectin of bean (*Phaseolus vulgaris*) plants; agglutinates erythrocytes and activates T lymphocytes. ▶lectins, ▶agglutination, ▶erythrocyte, ▶lymphocytes

Phaeochromocytoma (pheochromocytoma): A bladder-kidney carcinoma, over-producing adrenaline and noradrenaline. The disease may be caused by mutation in the von Hippel-Lindau gene or the neurofibromatosis 1 or the RET protooncogenes or by the multiple endocrine neoplasia gene MEN2. Mutations in the subunits of mitochondrial succinate dehydrogenase in the long arm of human chromosome 11 also may be involved. ▶animal hormones, ▶von Hippel-Lindau syndrome, ▶neurofibromatosis, ▶MEN, ▶RET, ▶succinate dehydrogenase; Astuti D et al 2001 Am Hum Genet 69:49; Maher ER, Eng C 2002 Hum Mol Genet 11:2347.

Phaeomelanin: A mammalian pigment. ▶pigmentation of animals

Phage (bacteriophage): A virus of bacteria. ▶bacteriophages, ▶development, ▶phage life cycle

Phage Conversion: The acquisition of new properties by the bacterial cell after infection by a temperate phage. ▶temperate phage

Phage Cross: ▶rounds of matings

Phage Display: Filamentous bacteriophages (M13, fd) have a few copies (3–5) of protein III gene at the end of the particles (see Fig. P53). This protein controls phage assembly and adsorption to the bacterial pilus. When short DNA sequences are inserted into gene III (g3p), the protein encoded may be displayed on the surface of the particles. In case variable region fragments of antibody genes are inserted into the protein III coding sequences, specific antigens may be screened. The peptides can be separated with antibody affinity chromatography (panning). By repeated screening enormous arrays of recombinant libraries become available. The g3p product and the Fvs (fragments of variability) can be separated proteolytically or by inserting a stop codon between g3p and Fv. By the insertion of a large array of nucleotide sequences, a huge combinatorial library of soluble epitopes may be generated. The specificity of the antibodies can be further manipulated by mutation (random or targeted), by error-prone polymerase chain reactions, recombination, by chain shuffling, i.e., trying out various light and heavy chain combinations, synthetic CDR sequences, etc. Similarly, a variety of different antigens may be displayed on the surface of protein III and can be used to screen for cognate antibody. Phage display may be of applied significance for the pharmaceutical industry because extremely large number of variants (up to 10^8 to 10^{10}) of monoclonal antibodies can be selectively isolated and tested. For in vitro testing the two-hybrid method may be employed. The protein-protein interaction may then be studied in mammalian cells and screening techniques can be developed to isolate the cells that can neutralize the cytotoxic virus. The use of phagemid vectors may enhance the efficiency of the procedure. This procedure may facilitate the isolation of novel receptors, ligands, antibodies, anti-cancer reagents, transport proteins, signal transduction molecules, transcription factors, etc. Phage display technique may substitute for the construction of hybridomas (see Fig. P54). It can be used also for typing blood, for various diagnostic procedures, etc. A T7 phage display system permits the selection of RNA-binding regulatory proteins.

By screening large phage libraries for select tissue-specific organ antibodies, luminal endothelial cell

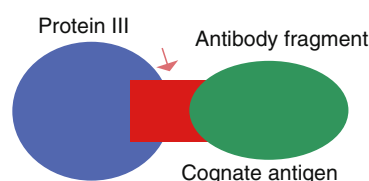


Figure P53. Protein III recognition

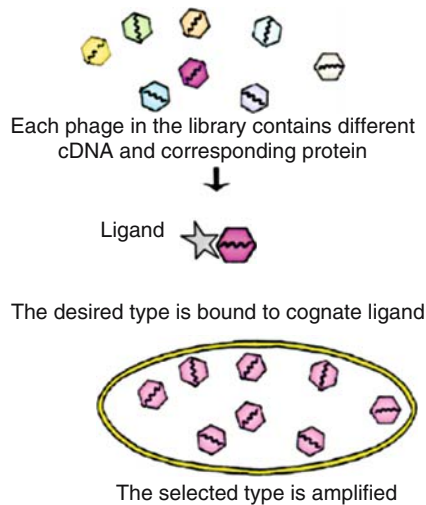


Figure P54. Phage display. (Note that the filamentous phage is represented as 'globular' only for the convenience of drawing).

plasma membranes were enriched from the bloodstream. The phage-displayed antibodies were converted Fv-Fc fusion proteins and monitored target selection by whole-body γ -scintigraphic imaging. Mass spectrometry identified the antigen targets. The procedure permits monitoring the vascular route of specific substances (Valadon P et al 2006 Proc Natl Acad Sci USA 103:407). ▶filamentous phages, ▶affinity chromatography, ▶epitope screening, ▶combinatorial library, ▶pilus, ▶antibody engineering, ▶CDR, ▶monoclonal antibody, ▶mRNA display, ▶two-hybrid method, ▶monoclonal antibody, ▶hybridoma, ▶phagemid, ▶anchored periplasmic expression; Smith GP, Petrenko VA 1997 Chem Rev 97:391; Danner S, Belasco JG 2001 Proc Natl Acad Sci USA 98:12954; Arap W et al 2002 Nature Med 8:121.

Phage Ghost: The empty protein shell of the virus.

Phage Immunity: A lysogenic bacterium carrying a prophage cannot be infected by another phage of the same type. ▶prophage, ▶zygotic induction

Phage Induction: Stimulates the prophage to leave a site in the bacterial chromosome and become vegetative. Physical and chemical agents may be inductive (UV light, mutagens, zygotic induction).

Phage Lifecycle: See Fig. P55, Böhm J et al 2001 Curr Biol 11:1168.

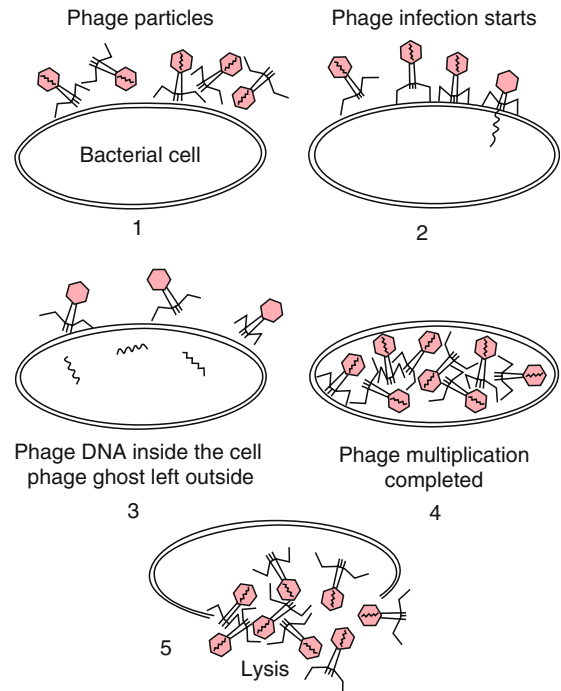


Figure P55. Phage lifecycle. (Redrawn after the illustration provided by Drs. Simon LD, Anderson TF Institute of Cancer Research, Philadelphia, PA, USA)

Phage Morphogenesis: ▶one-step growth, ▶development, ▶phage life cycle

Phage Mosaic: May be generated by phage display, expressing different molecular structures on the surface of a filamentous phage. ▶phage display

Phage Therapy: The bacteriophages are bacteria-eating systems. D'Hérelle, the discoverer of phages, already attempted their therapeutic use in poultry as well as for humans with considerable success. With the discovery of antibiotics, the interest in phage therapy ebbed. Another cause for the decline of interest was the discovery of phage resistance in bacteria.

Also, bacteria encode restriction/modification systems of defense. The human body may also react immunologically against the phages. Recent studies, despite some technical problems indicate feasibility of this type of therapy. (See Summers WC 2001 Annu Rev Microbiol 55:437; Schuch B et al 2002 Nature [Lond] 418:884).

Phagemids: Genetic vectors that generally contain the ColE1 origin of replication and one or more selectable markers from a plasmid and a major intergenic copy of a filamentous phage (M13, fd1). When cells carrying such a combination are superinfected by a filamentous phage, it triggers a rolling

circle type replication of the vector DNA. This single-stranded product is used then for sequencing by the Sanger type DNA sequencing system, for oligonucleotide-directed mutagenesis and as strand-specific probes. The phagemids can carry up to 10 kb passenger DNA. Their replication is fast (in the presence of a helper), and they can produce up to 10^{11} plaque-forming units (pfu)/mL bacterial culture. Their stability is comparable to conventional plasmids. They obviate subcloning the DNA fragments from plasmid to filamentous phage. The most widely used phagemids contain parts of phage M13 and pUC, π VX^c, and pBR322 vectors. ▶**phasmid**, ▶**vectors**, ▶**plasmovirus**, ▶**vectors**, ▶**pfu**, ▶**pUC**, ▶**DNA sequencing**; Sambrook J et al 1989 Molecular Cloning, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; O'Connell D et al 2002 J Mol Biol 321:49.

Phagocytosis: A special cell (phagocyte) engulfs a foreign particle (microorganism, cell debris) and eventually exposes it to lysosomal enzymes for the purpose of destroying it. Dendritic cells and macrophages have important roles. In lower animals, this mechanism substitutes for the immune system. Phagocytosis pathway is controlled by a battery of *Ced* genes (and homologs, e.g., Dock180 in humans) during apoptosis. The CD14 human glycoprotein on the surface of macrophages recognizes and clears apoptotic cells (see Fig. P56). The major phagocyte receptors are CR3 (binds opsonized C3b complement fraction) and the Fc gamma receptor, FcγR (binds immunoglobulin G). Both processes require the reorganization of the cytoskeleton under the control of RAC or RHO G proteins, respectively. ▶**pinocytosis**, ▶**apoptosis**, ▶**macrophage**, ▶**complement**, ▶**antibody**, ▶**opsonins**, ▶**RAC**, ▶**RHO**, ▶**lysosomes**, ▶**cross presentation**, ▶**cell fusion**; Underhill DM, Ozinsky A 2002 Annu Rev Immunol 20:825; Stuart LM, Ezekowitz RAB 2005 Immunity 22:539.



Figure P56. Phagocytosis

Phagosome: A body (vesicle) surrounded by plasma membrane of a phagocyte. They are fused with endosomes and lysosomal compartments to become

degradative organelles (Touret N et al 2005 Cell 123:157). In *Drosophila* phagosomes 617 interactive proteins have been detected that are involved in immune reactions (Stuart LM et al 2007 Nature [Lond] 445:95). ▶**phagocytosis**, ▶**endocytosis**, ▶**endosome**, ▶**lysosomes**, ▶**macrophage**

Phakomatoses (neurocutane syndromes): Hereditary and congenital diseases, which are of ectodermal origin and display spots on the body, such as neurofibromatosis, epiloia/tuberous sclerosis, FAP, von Hippel-Lindau syndrome, nevoid basal cell carcinoma, Cowden disease, Peutz-Jeghers syndrome, polyposis. (See separate entries; Tucker M et al 2000 J Natl Cancer Inst 92:530).

Phalange(s): The three bones in fingers and toes (at left) with the metacarpal bone (at right) (see Fig. P57).



Figure P57. Phalange

Phalloidin: An amanotoxin, similar to, but faster in action than amanitin. When labeled with fluorescent coumarin phenyl isothiocyanate it is suitable to identify filamentous actin in the cells. It is extremely toxic. ▶**amatoxins**, ▶**α-amanitin**; Vetter J 1998 Toxicon 36:13.

Phallus: The penis, a symbol of generative power, also the fetal anlage of the penis and clitoris. ▶**penis**, ▶**clitoris**, ▶**anlage**

Phantom Mutation: Artifacts of the DNA sequencing. They can be filtered out by statistical procedures. (Bandelt, H-J et al 2002 Am J Hum Genet 71:1150).

Pharate: The larva/adult emerging from the puparium.

Pharmaceuticals: The chemical agents used for medical purposes. Data collected on 352 marketed drugs (excluding anti-cancer agents, nucleosides, steroids and peptide-based formulations, which are known to affect DNA); 101 (28.7%) had at least one positive indication for genotoxicity. Four types of tests were used: bacterial mutagenesis, in vitro cytogenetics, in vivo cytogenetics and mouse lymphoma assay. One must keep in mind that carcinogenicity may involve routes that are not testable by these methods. Also, the laboratory assays are not 100% reliable. ▶**genotoxic chemicals**, ▶**combinatorial chemistry**, ▶**bioassays in genetic toxicology**; Snyder RD, Green JW 2001 Mutat Res 488:151.

Pharmacogenetics: The study of the reaction of individuals of different genetic constitution to various drugs and medicines. Most of the differences are monogenic. Polymorphic genes frequently determine drug metabolism, drug transporters and drug responses of the body. Pharmacogenetics studies also study simultaneous drug responses by many genes. Based on these responses drugs with special, selective effect can be developed. Certain drugs have special side effects for individuals of particular genetic constitution ►cytochromes, ►SADR; Roses AD 2001 Hum Mol Genet 10:2261; Kuehl P et al 2001 Nature Genet 27:383; Roses AD 2002 Nature Rev Drug Discov 1:541; Goldstein DB et al 2003 Nature Rev Genet 4:937; Evans WE, Relling MV 2004 Nature [Lond] 429:464; problems and goals in pharmacogenetics/genomics: Need AC et al 2005 Nature Genet 37:671; variation in human genes and drug responses: <http://www.PharmGKB.org>; key therapeutic targets in proteins and nucleic acids: <http://xin.cz3.nus.edu.sg/group/ttd/ttd.asp>; pharmacogenetic substances [proteins, drugs]: <http://bidd.cz3.nus.edu.sg/phg/>.

Pharmacogenomics: The study of drug response of the entire genome of an organism. ►pharmacogenetics, ►SADR

Pharmacokinetics (pharmacodynamics): The study of absorption, tissue distribution, metabolism, and elimination (ADAME) as a function of time of biologically relevant molecules.

Pharmacoproteomics: The study of the proteins in sera or urine as a consequence of disease and/or drug therapy.

Pharmacodynamics: ►pharmacokinetics

Pharming: The production of pharmacologically useful compounds by transgenic organisms. ►transgenic, ►biopharming, ►molecular breeding, ►plantibody

PHAS-1: A heat stable protein ($M_r \approx 12,400$); when it is not phosphorylated it binds to peptide initiation factor eIF-4E and inhibits protein synthesis. Its Ser⁶⁴ site is readily phosphorylated by MAP and then no longer binds to eIF-4E and protein synthesis may be stimulated. ►eIF-4E, ►MAP

Phase Diagram: A graphic representation of the equilibrium between/among components of a system. The phase is an identifiable part of a system. Phase diagrams are used in several scientific fields for the elucidation of the behavior of the phases of the components under dynamic conditions. In biology, phase diagrams can shed light on the mechanisms of interaction within a system, e.g., in a genetic network. Figure P58 represents three hypothetical internal (metabolic) components of the cell and two external

factors (e.g., temperature and light) that determine in an interactive manner the node (red dot). ►networks, ►genetic networks; Park J, Barabási A-L 2007 Proc Natl Acad Sci 104:17916.

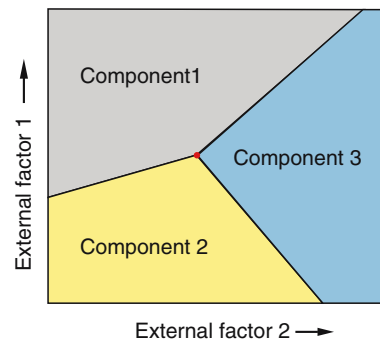


Figure P58. Phase diagram

Phase Variation: A programmed rearrangement in several genetic systems. The flagellin genes of the bacterium *Salmonella* display it at frequencies of 10^{-5} to 10^{-3} . The flagellar protein has two forms, H1 and H2. The *H1* gene is a passive element. When *H2* is expressed no H1 protein is made. When *H2* is switched off the H1 antigen is made. The expression of *H2* is regulated by the expression of the *rhI* repressor (repressing the synthesis of the H1 protein) and the promoter of *H2*. This promoter is about 100 bp upstream from the gene and it is liable to inversion, and then *H2* and *rhI* are turned off. Such an event then switches on the synthesis of H1 protein. Reversing the inversion flip switches back to H2. The *Hin* recombinase that is very similar to the invertases or recombinases of phage Mu or *Cin* from phage P1 catalyze the inversions. They can functionally substitute for each other. *Hin* binds to the *hixL* and *hixR* recombination sites. Additional genes are also involved in the fine-tuning. Defect in type III methyltransferase in restriction modification systems can cause phase variation of different genes in several bacterial species (Srihanta YN et al 2005 Proc Natl Acad Sci USA 102:5547).

Somewhat similar mechanisms control the host-specificity genes of phage Mu and the mating type of budding yeast. ►cassette model, ►regulation of gene activity, ►antigenic variation, ►mating type determination in yeasts, ►Trypanosoma, ►flagellin, ►DNA uptake sequences, ►SSR; Hughes KT et al 1988 Genes Dev 2:937; Snyder LA et al 2001 Microbiology 147:2321.

Phase-Contrast Microscope: It alters the phase of light passing through and around the objects and this permits its visualization without fixation and/or

staining. ►Nomarski, ►fluorescence microscopy, ►microscopy light, ►confocal microscopy, ►electron microscopy

Phaseolin ($C_{20}H_{18}O_4$): An antifungal globulin in bean (*Phaseolus*).

Phasing Codon: Initiates translation (such as AUG) and determines the reading frame. ►genetic code, ►reading frame

Phasmid (phage-plasmid): A plasmid vector equipped with the *att* site of the lambda phage and thus, enables the plasmid to participate in site-specific recombination with the λ genome resulting in incorporation of plasmid sequences into the phage (*lifting*). Because it contains both λ and plasmid origins of replication it may be replicated either as a plasmid or as λ . ►lambda phage, ►phagemid, ►vectors; Briani F et al 2001 Plasmid 45:1.

Phenacetin ($C_{10}H_{13}NO_2$): An analgesic and antipyretic drug and a carcinogen.

Phene: An observable trait that may or may not have direct genetic determination. ►gene

Phenetics: The taxonomic classification based on phenotypes.

Phenocopy: The phenotypic change that mimics the expression of a mutation. ►phenotype, ►epigenetic, ►epimutation, ►morphosis, ►genocopy

Phenodeviate: An individual of unknown genetic constitution displaying a phenotype attributed to various genic combinations within the population.

Phenogenetics: The attempts to correlate the function of genes with phenotypes.

Phenogram: ►character matrix

Phenolics: Compounds containing a phenol ring such as acetosyringone, hydroxyacetosyringone, chalcone derivatives, phenylpropanoids, and some phytoalexins. The mentioned compounds may excite or suppress the *vir* gene cascade of *Agrobacterium* and may affect the response to plant pathogenic agents. Capsaicin, ginger, resveratrol may be anticarcinogens due to their antioxidative properties and may promote apoptosis. Phenylpropenes such as chavicol, *t*-anol, eugenol and isoeugenol repel animals and micro-organism but may attract some pollinators (see Fig. P59). Humans use these compounds as spices, food preservatives and medicine. Coniferyl acetate and NADPH may form as a precursor for enzymatic synthesis of eugenols (Koeduka T et al 2006 Proc Natl Acad Sci USA 103:10128). ►*Agrobacterium*, ►virulence genes of *Agrobacterium*, ►phytoalexins, ►chalcones, ►acetosyringone, ►resveratrol,

►ginger, ►capsaicin, ►apoptosis, ►wound response; Nicholson RL, Hammerschmidt RE 1992 Annu Rev Plant Path 30:369.

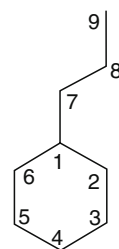


Figure P59. Phenylpropene backbone

Phenology: The study of the effects of the environment on live organisms.

Phenome: The collection of phenotypes; a group of organisms with shared phenotypes. (See Freimer N, Sabatti C 2003 Nature Genet 34:15; ►SNIPs; <http://www.jax.org/phenome>; <http://www.phenomicdb.de>.)

Phenome Analysis: The attempts to determine the expression of genes at the RNA and protein level under different conditions, involving the environment and/or the prevailing genetic system (network). This may be an extremely difficult undertaking because gene expression may vary from complete silence to very variable and great complexity. ►phenotype, ►phenotype MicroArray; Bochner BR 2003 Nature Rev Genet 4:309.

Phenomenology: The description of facts as observed without metaphysical interpretation. The concept that behavior depends on how a person interprets reality rather than what is the objective reality.

Phenoptosis: An apoptosis-like phenomenon in unicellular organisms. ►apoptosis

Phenotype: The appearance of an organism that may or may not represent the genetic constitution. The proteins encoded by the DNA (the genotype) represent the phenotype. The 1014 human (disease) genes displayed 1429 distinguishable phenotypes (~141%). Microarray hybridization data can provide most comprehensive information on phenotype. In budding yeast, similar morphology indicates functional similarity of the coding genes. Triple-stained mutants facilitate the analysis of the morphology as a quantitative trait and can attribute function to many genes with previously unknown function (Ohya Y et al 2005 Proc Natl Acad Sci USA 102:19015). Mutation in the DNA is largely responsible for altered phenotypes. Alterations in transcription and translation also affect the phenotype and generally, as shown, there are more phenotypes than the number of

genes (Bürger R et al 2006 Genetics 172:197). ► [gene ontology](#), ► [microarray hybridization](#), ► [cell comparisons](#), ► [endophenotype](#); Phenomic Data Base facilitates the identification of genes involved in a phenotype or gives the phenotype caused by genes in major organisms: <http://www.phenomicDB.de>; muse phenotypes and relevance to human disease: <http://www.eumorphia.org/>

Phenotype MicroArrays: An automated analysis of phenotypic expression of hundreds of genes on microplates and can be used to monitor the consequences of knockouts or other genetic alterations. ► [microarray hybridization](#), ► [knockout](#); Bochner BR et al 2001 Genome Res 11:1246.

Phenotypic Assortment: ► [macronucleus](#)

Phenotypic Knockout: It means somatic gene therapy that neutralizes intracellular harmful mechanisms. ► [gene therapy](#), ► [knockout](#)

Phenotypic Lag: A period of time may be required for gene expression after transformation or mutagenic treatment. ► [transformation genetic](#), ► [premutation](#); Ryan FJ 1955 Am Nat 89:159.

Phenotypic Mixing: The mixed assembly of viral nucleic acids and proteins upon simultaneous infections by different types of viruses. Therefore, the coat protein properties of the virions do not match the viral genotype by serological or other tests. (See Hayes W 1965 The genetics of bacteria and their viruses. Wiley, New York).

Phenotypic Plasticity: An adaptive property of an organism enabling it to take advantage of local conditions without evolving a particular function and at the expense of another function. ► [homeostasis genetic](#), ► [canalization](#), ► [plasticity](#)

Phenotypic Reversion: An apparent restoration of the normal expression of a mutant gene; it is not, however, inherited. Aminoglycoside antibiotics (paromomycin, geneticin, etc.) may successfully compete with the translation termination factors in eukaryotes in cases when the mRNA carries a stop codon mutation. As a result, some of the polypeptide chains are not terminated/truncated but completed in the presence of the drug. Transposable elements may also alter gene function without causing mutation in the gene. Phenotypic reversion may be exploited for correcting the genetic defects in some diseases. ► [phenocopy](#), ► [amino-glycosides](#), ► [G418](#), ► [paromomycin](#), ► [suppressor tRNA](#), ► [translation termination](#); Gause M et al 1996 Mol Gen Genet 253:370; Franzoni MG, De Castro-Prado MA 2000 Biol Res 33:11; Biedler JL et al 1975 J Natl Cancer Inst 55:671.

Phenotypic Sex: It may not reflect the expectation based on the sex-chromosomal constitution. ► [testicular feminization](#), ► [hermaphrodite](#)

Phenotypic Stability Factor: A measure of developmental homeostasis; it is calculated by the ratios of the quantitative expression of a parameter (gene) under two different environmental conditions. ► [homeostasis](#), ► [logarithmic stability factor](#); Lewis D 1954 Heredity 8:334.

Phenotypic Suppression: An apparently normal but non-hereditary phenotype brought about by translational error due to environmental effects and/or drugs. ► [error in translation](#)

Phenotypic Switch: Alters phenotypes more frequently than expected by point mutation and may be caused by epigenetic methylation or by protein folding. (See Lim HN, van Oudenaarden A 2007 Nature Genet 39:269).

Phenotypic Value: In quantitative genetics, it is defined as the mean value of a population regarding the trait under study and it is generally represented as P value. ► [breeding value](#)

Phenotypic Variance: ► [genetic variance](#)

Phenylalanine (C₉H₁₁NO₂): An essential water-soluble, aromatic amino acid (MW 165.19). Its biosynthetic path (*with enzymes involved in parenthesis*): Chorismate → (*chorismate mutase*) → Prephenate → (*prephenate dihydratase*) → Phenylpyruvate → (*aminotransferase*, glutamate NH₃ donor) → Phenylalanine. ► [chorismate](#), ► [tyrosine](#), ► [phenylketonuria](#)

Phenylalanine Ammonia Lyase (PAL): PAL deaminates phenylalanine into cinnamic acid and it is thus involved in the synthesis of plant phenolics. ► [phenolics](#)

Phenylalanine Hydroxylase (PAH, 12q24.1): The deficiency of PAH leads to phenylketonuria.

Phenylhydrazine (C₆H₉ClN₂): A hemolytic compound but it is also used as a reagent for sugars, aldehydes, ketones and a number of industrial purposes (stabilizing explosives, dyes, etc.). ► [hemolysis](#)

Phenylketonuria (PKU, PAH, Fölling disease): This gene was located to human chromosome 12q24.1. It is a recessive disorder that has a prevalence of about 1×10^{-4} (carrier frequency is about 0.02) in white populations. Thus, an affected person has about 0.01 chance to have an affected child in case of a random mate but the recurrence rate in a family where one of the partners is affected and the other is a carrier it is nearly 0.5 (see Fig. P60).



Figure P60. Mentally retarded heterozygous children of a phenylketonuric mother (indirect epistasis). Courtesy of Dr. C. Charlton Mabry 1963; by permission of the New England Journal of Medicine 269:1404

Its incidence is substantially lower among Asian and black people (one-third of that in whites). PKU is more frequent in European populations of Celtic origin than in the other Europeans. This has been interpreted as the result of natural selection because PKU heterozygosity conveys some tolerance to the mycotoxin, ochratoxin A, produced by *Aspergillus* and *Penicillium* fungi, common in humid northern regions. Before the nature of this disorder and the method of treatment were identified, about 0.5 to 1% of the patients in mental asylums were afflicted by PKU. A deficiency of the enzyme phenylalanine hydroxylase and consequently the accumulation of phenyl pyruvic acid and a deficiency of tyrosine cause the disease:



For the identification of the condition the Guthrie test has been used to cultures of *Bacillus subtilis* containing blood of the patients, β -2-thienylalanine was added. This phenylalanine analog is a competitive inhibitor of tyrosine synthesis. In the presence of excess amounts of phenylalanine, the bacterial growth does not stop. Since in the different families the genetically determined defect in the enzyme varies, so does the severity of the clinical symptoms. The accumulation of phenyl pyruvic acid is apparently responsible for the mental retardation and the musty odor of the urine of the patients.

The reduced amount of tyrosine prevents normal pigmentation (melanin) and thus results in pale color. The good aspect of this condition is that relative normalcy can be established if it is diagnosed early and dietary restrictions for phenylalanine are implemented. The restriction of phenylalanine must

start as early as possible (before birth if feasible), and continue at least until age 10. Restriction should be observed before pregnancy, during pregnancy and during breast-feeding or during the entire life to avoid harm to the nervous system. Phenylketonuria of the mother may damage the nervous system of genetically normal fetus through placental transfer (indirect epistasis). Because of the multiple metabolic pathways involving phenylpyruvic acid, besides the deficiency of phenylalanine hydroxylase, other genes and conditions may cause similar clinical symptoms. Phenylalanine hydroxylase activity requires the availability of the reduced form of the co-factor 5,6,7,8-tetrahydrobiopterin that is made by the enzyme *dihydrobiopterin reductase* from 7,8-dihydrobiopterin. The dihydrobiopterin reductase enzyme is coded in human chromosome 4p15.1-p16.1. Defect in this enzyme also causes phenylketonuria symptoms but lowering the level phenylalanine in the diet does not alleviate the problems. Another form of phenylketonuria is based on a deficiency in dihydrobiopterin synthesis. Using the ϕ BT1 integrating phage vector (containing a site-specific recombinase), equipped with the murine phenylalanine hydroxylase cDNA, PKU could be completely and persistently cured after three injections to the mouse liver (Chen L, Woo SLC et al 2005 Proc Natl Acad Sci USA 102:15581).

Prenatal diagnosis can be carried out by several methods. Mutations at various related metabolic sites in the mouse may serve as a model for studying phenylketonuria. ►epistasis, ►mental retardation, ►one gene-one-enzyme theorem, ►genetic screening, ►Guthrie test, ►tyrosinemia, ►alkaptonuria, ►phenylalanine, ►hyperphenylalaninemia, ►amino acid metabolism, ►prenatal diagnosis, ►enzyme replacement therapy, ►integrase, ►targeting genes; Ledley FD et al 1986 N Engl J Med 314:1276; Gjetting T et al 2001 Am J Hum Genet 68:1353.

Phenylpropanoid: ►phenolics, ►phytoalexins

Phenylthiocarbamide Tasting (PTC): A major incompletely dominant gene appears to be in human chromosome 7q35-q36 (Conneally PM et al 1976 Hum Hered 26(4):276). A major bitter testing locus is assigned to human chromosome 5p15 (Reed DR et al 1999 Am J Hum Genet 64:1478). The TAS2R10 PTC receptor appears to be in the short arm of chromosome 12. A single G protein coupled receptor with allelic variants may account for the taste perception (Bufo B et al 2005 Curr Biol 15:322). In humans and chimpanzees, two alleles at the TAS2R38 locus control bitter tasting but the human and chimpanzee alleles are different (Wooding S et al. 2006 Nature [Lond] 440:930). About 30% of North-American Whites and about 8–10% of Blacks cannot taste the

bitterness of this compound. Persons affected by thyroid-deficiency (athyreotic) cretinism (mental deficiency) are non-tasters. Phenylthiocarbamide (syn. phenylthiourea) has been used for classroom demonstration of human diversity but it should be kept in mind that it is a toxic compound (LD₅₀ oral dose for rats 3 mg/kg and for mice 10 mg/kg). ►taste, ►LD₅₀; Guo SW, Reed DR 2001 Ann Hum Biol 28(2):111; Kim U-K et al 2003 Science 299:1221.

Phenylthiourea: ►phenylthiocarbamide tasting (see Fig. P61).

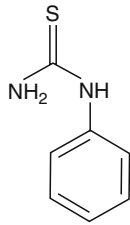


Figure P61. Phenylthiourea

Pheochromocytoma (phaeochromocytoma): An adrenal tumor induced by the SHC oncogene. ►paraganglion, ►SHC, ►adenomatosis endocrine multiple, ►endocrine neoplasian neuroendocrine cancer

Pheresis (apheresis): The medical procedure of withdrawal of blood; after fractionation, some fraction(s) are reintroduced. Such a protocol may use stem cells, transfect them with a vector or apply to them chemotherapy, and eventually place them back in the body of the same individual.

Pheromones: Various chemical substances secreted by animals and cells for the purpose of signaling and generating certain responses by members of the species, such as sex-attractants, stimulants, territorial markers, or other behavioral signals and cues. The male pheromone of Asian elephants, frontalin (exists in two enantiomorphs) is secreted during musth (annual period of increased sexual activity and aggression) by the temporal gland on the face. The proportion of the two forms and the extent of secretion of frontalin are sensed primarily by the ovulating females (Greenwood DR et al 2005 Nature [Lond] 438:1097). About 100 genes control the pheromones and their receptors in rodents and the signals are transmitted through G protein-associated signal transduction pathways. The mouse sex pheromones in the male urine includes several compounds, among them the strongest response is evoked by (methylthio) methanethiol for females. Apparently, only a small number of cells at the olfactory bulb responded to this compound, which for humans had a garlic-like odor (Lin DY et al 2005 Nature [Lond]

434:470). The lacrimal glands of adult male mice secrete a 7 kDa peptide to which the vomeronasal receptors of the sensory neurons of the female animals respond (Kimoto H et al. 2005 Nature [Lond] 437:898). The role of pheromones in humans may not be generally agreed upon. The steroid compounds 4,16-androstadien-3-one (AND) present in the sweat of human males and estra-1,3,5(10)-tetraen-3-ol (EST) present in the female urine appear to have pheromone-like properties. Their smelling causes sex-differentiated activation of the anterior hypothalamus of the brain. Male homosexuals respond to AND but not to EST in contrast to heterosexuals (Savic I et al 2005 Proc Natl Acad Sci USA 102:7356). Heterosexual men were found to respond to AND; lesbian women processed AND (unlike heterosexual women), not by the anterior pituitary but by the olfactory network (Berglund H et al 2006 Proc Natl Acad Sci USA 103:8269).

The pheromone receptor genes in rodents include *V1r* and *V2r*; apparently there are no human homologs. The sexually deceptive orchid plant *Chiloglottis* attracts the *Neozeleboria* insect pollinator males by secreting a volatile compound (2-ethyl-5-propylcyclohexan-1,3-dione), which is chemically identical with the insect female sex pheromone (Schiestl FP et al 2003 Science 302:437). RNA interference technique revealed that in silkworm, for sex pheromone production pheromone activating neuropeptide receptor (*PBANR*), pheromone gland-specific (PG) fatty acyl reductase (*pgFAR*), PGZ11/ Δ 10,12 desaturase (*Bmpgdesat1*), PG acyl CoA-binding protein (*pgACBP*) genes are essential (Ohnishi A et al 2006 Proc Natl Acad Sci USA 103:4398). In *Drosophila*, the male-specific pheromone 1-*cis*-vaccenyl acetate (cVA) acts through olfactory receptor Or67d. The *fruitless* (*fru*) gene controls three classes of olfactory receptors, one of which is Or67d. This single receptor controls both male and female mating behavior. Mutant males display homosexual tendencies whereas mutant females are less receptive to courting indicating that cVA has opposite effects for the two sexes, i.e., inhibiting males' mating behavior but stimulating that in females (Kurtovic A et al 2007 Nature [Lond] 446:542). Male flies show less interest in females, which have mated before, apparently by sensing cVA (Ejima A et al 2007 Curr Biol 17:599). The trichoid sensilla on the antennae has three olfactory receptors; receptor T1 responds primarily to male odor in the cuticular extracts whereas to the odor of virgin females receptors T2 and T3 respond (van der Goes van Naters W, Carlson JR 2007 Curr Biol 17:606). In male *Drosophila*, the synthesis of octopamine (a norepinephrine related substance) mediates aggressive behavior toward other males. In flies defective

for tyramine β -hydroxylase (the enzyme that converts octopamine from its precursor), courtship is observed (Cartel SJ et al 2007 Proc Natl Acad Sci USA 104:4706). Pheromone hydrocarbon chains are longer in females than in males. The transformer gene (*tra*) feminizes males and makes them produce longer (female type) hydrocarbon pheromones (Chertemps T et al 2007 Proc Natl Acad Sci USA 104:4273). ▶mating type determination in yeast, ▶sex determination, ▶*fru*, ▶olfactogenetics, ▶vomeronasal organ, ▶signal transduction, ▶homosexual, ▶RNAi, ▶silkworm, ▶kairomones, ▶mimicry, ▶Bruce effect; Kohl JV et al 2001 Neuroendocrinol Lett 22(5):309; Luo M et al 2003 Science 299:1196; Prestwich GD, Blomquist GJ 1987 Pheromone Biochemistry, Academic Press, Orlando, Florida; Wang Y, Dohlman HG 2004 Science 306:1508; Dulac C, Torello AT 2003 Nature Rev Neurosci 4:531; mini-review: Stowers L, Marton TF 2005 Neuron 46:699; review of vertebrate pheromone communication: Brennanm PA, Zufall F 2006 Nature [Lond] 444:308; pheromone signaling circuits: Dulac C, Wagner S 2006 Annu Rev Genet 40:449; insect pheromones: <http://www.pherobase.com>.

Phialide: Fungal stem cells from which conidia are budded.

Philadelphia Chromosome: In the Philadelphia chromosome, the long arm (q34) of human chromosome 9, carrying the *c-abl* oncogene is translocated to the long arm (q11) of chromosome 22 carrying site *bcr* (breakpoint cluster region). The *bcr-abl* gene fusion is then responsible for 85% of myelogenous (Abelson) and acute leukemia as a consequence of the translocation and fusion. In the acute form, a 7.5 kb mRNA is translated into protein p190, and in the myelogenous form an 8.5 kb mRNA is translated into a chimeric protein p210. The fusion protein is a deregulated tyrosine kinase acting on hematopoietic cells and causes leukemia-like oncogenic transformation in mice. Synthetic antisense phosphorothioate oligonucleotides ([S]ODN) complementary to the 2nd exon of BCR or to the 3rd exon of the ABL of the fused genes block temporarily the proliferation of the chronic leukemic cells, without harming the normal cells, in a mouse model. The outcome of such a therapy could be improved by simultaneously targeting also the *c-Myc* oncogene with an antisense construct. Further effectiveness was observed by exposing the cells to a low concentration of mafosfamide, an antineoplastic drug that promotes apoptosis, or to cyclophosphamide. ▶ABL, ▶BCR, ▶leukemia, ▶hematopoiesis, ▶cancer gene therapy, ▶apoptosis, ▶cyclophosphamide, ▶antisense technologies, ▶transresponder, ▶Knudson's two mutation theory; Saglio G et al

2002 Proc Natl Acad Sci USA 99:9882; Goldman JM et al 2003 N Engl J Med 349:1451.

Phlebotomous: A blood-sucking (insect), or phlebotomy bloodletting surgical procedure.

Phloem: A plant tissue involved in the transport of nutrients; it contains sieve tubes and companion cells, phloem parenchyma, and fibers. ▶sieve tube, ▶parenchyma, ▶xylem, ▶root, ▶proteoglycan; Bonke M et al 2003 Nature [Lond] 426:181.

Phlorizin: A dihalcone in the bark of trees (*Rosaceae*); it blocks the reabsorption of glucose by the tubules of the kidney and causes glucosuria. ▶disaccharide intolerance, ▶chalcones

PHO81: A yeast CDK inhibitor homologous to p16^{INK4}. ▶CDK, ▶p16^{INK4}

PHO85: A cyclin-dependent kinase of *Saccharomyces cerevisiae*. ▶CDK, ▶KIN28, ▶CDC28, ▶PHO81

phoA: A gene for alkaline phosphatase.

Phobias: Phobias exist in different forms, all characterized by unreasonable avoidance of objects, events, or people. A phobia may amount to serious, morbid mental illness. Apparently, duplication in human chromosome 15q24-q26 is associated with one form and also with laxity of the joints. ▶panic disorder, ▶panic obsessive disorder, ▶anxiety; Gratacós M et al 2001 Cell 106:367.

Phocomelia: The absence of some bones of the limbs proximal to the trunk. It may occur as a teratological effect of various recessive and dominant human genetic defects or as a consequence of teratogenic drugs, e.g., thalidomide use during human or primate pregnancy. ▶limb defects in humans, ▶Roberts syndrome, ▶thalidomide

PHOGE (pulsed homogeneous orthogonal field electrophoresis): A type of pulsed field gel electrophoresis, within the range of 50 kb to 1 Mb DNA, permitting straight tracks of large number of samples. ▶pulsed field gel electrophoresis

PhoQ: *Salmonella* kinase, affecting regulator of virulence PhoP. ▶virulence, ▶*Salmonella*

PhoR: Phosphate assimilation regulated by PhoR kinase upon phosphorylation of regulator PhoB.

Phorbol Esters: Facilitators of tumorous growth that work by activating protein kinase C. ▶TPA, ▶protein kinases, ▶procarcinogen, ▶carcinogen, ▶PMA, see formula at ▶PMA

Phorbol 12-Myristate-13-Acetate (PMA): ▶phorbol esters, ▶PMA (see Fig. P62).

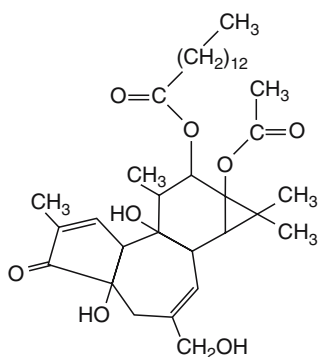


Figure P62. Myristoylphorbol acetate (ester)

Phosphatases: In animals, both acid and alkaline phosphatases are common, in plants acid phosphatases are found. Some of the phosphatases have high specificities and have indispensable role in energy release in the cells. A series of non-specific phosphatases carry out only digestive tasks. In humans, the erythrocyte and fibroblast expressed acid phosphatase (ACP1) isozymes are coded in chromosomes 2 and 4. It has been suggested that these enzymes split flavin mononucleotide phosphates. In megaloblastic anemia, ACP1 level is increased. The tartrate-resistant acid phosphatase type 5 (TR-AP) is an iron-glycoprotein of 34 kDa (human chromosome 15q22-q26), and it is increased in the spleen in case of Gaucher disease. Lysosomal acid phosphatase (ACP2) is located in human chromosome 11p12-p11. Alkaline phosphatase (ALPL) is present in the liver, bone, kidney, and fibroblasts, is often called the non-tissue-specific phosphatase (human chromosome 1p36-p34), and is deficient in hypophosphatasias. The alkaline phosphatase ALPP is located in the placenta (human chromosome 2q37) and several allelic forms have been identified. A similar alkaline phosphatase is present also in the testes and the thymus and the gene occurs at the same chromosomal location, but its expression is highly tissue-specific. Protein phosphatase 2A (PP2A) catalytic subunit, encoded at human chromosome 9q34, is involved in the control of many cellular processes, including the mitotic spindle (Sclaitz A-L et al 2007 Cell 128:115). The structure of the holoenzyme is known (Xu Y et al 2006 Cell 127:1239). ▶serine/threonine and tyrosine protein phosphatases, ▶hypophosphatasia, ▶hypophosphatemia, ▶dual-specificity phosphatase, ▶megaloblastic anemia, ▶Gaucher's disease

Phosphate Response of Plants: The inorganic phosphate level is frequently growth-limiting in plants.

Arabidopsis is an extremely sensitive indicator of P in soils. The photograph illustrates *Arabidopsis* growth on a Missouri soil sample, without and with PO_4 addition (see Fig. P63) (Rédei GP 1966 unpublished).

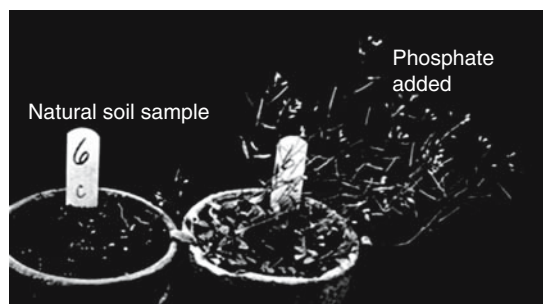


Figure P63. *Arabidopsis* growth with and without PO_4 addition

The physical contact of the *Arabidopsis thaliana* primary root tip with low-phosphate medium arrests root growth. Loss-of-function mutations in *Low Phosphate Root1 (LPR1)* and its close paralog *LPR2* strongly (encoding multicopper oxidases) reduce this inhibition (Svistonoff S et al 2007 Nature Genet 39:792). The non-protein coding gene *IPS1* (Induced by phosphate starvation1) contains a motif with sequence complementarity to the phosphate (Pi) starvation-induced miRNA miR-399. When the pairing is interrupted by a mismatched loop at the expected miRNA cleavage site, IPS1 RNA is not cleaved but instead sequesters miR-399. Thus, IPS1 overexpression results in increased accumulation of the miR-399 target PHO2 mRNA (phosphate-starvation) and, concomitantly, in reduced shoot Pi content (Franco-Zorilla JM et al 2007 Nature Genet 39:1033).

Microarray hybridization of transcript abundance among 22,810 *Arabidopsis* genes indicated that 612 were coordinately induced, whereas 254 genes were suppressed by inorganic phosphate. These genes are involved with metabolic pathways, ion transport, signal transduction, transcriptional regulation and other cellular processes (Misson J et al 2005 Proc Natl Acad Sci USA 102:11).

Phosphatidate: A precursor of diacylglycerol (see Fig. P64). ▶diacylglycerol, formula at right.

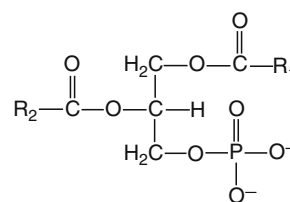


Figure P64. Phosphatidate

Phosphatidylinositol (1,2-diacyl-sn-glycero-3-phospho [1-o-myoinositol]): A cell membrane phospholipid. Phosphatidylinositol-transfer protein is required for vesicle budding from the Golgi complex. Phosphatidylinositol-3,4,5-trisphosphate activates protein kinase B. Phosphatidylinositol-kinase-3 mutations are oncogenic (Kang S et al 2005 Proc Natl Acad Sci USA 102:802). ▶PIK, ▶pleckstrin domain, ▶PKB, ▶Golgi apparatus, ▶PTEN, ▶phosphoinositides, ▶wortmannin; Bourette RP et al 1997 EMBO J 16:5880; Abel K et al 2001 J Cell Sci 114:2207.

3'-Phosphoadenosine-5'-Phosphosulfate: ▶PAPS

Phosphodegron: SCF β -TRCP promotes Chk1-dependent Cdc25A ubiquitination, and this involves serine 76, a known Chk1 phosphorylation site, but other sites of phosphorylated amino acids may make a protein liable to degradation by ubiquitination. ▶SCF, ▶Chk-1, ▶CDC25, ▶ubiquitin

Phosphodiester Bond: A phosphodiester bond attaches the nucleotides into a chain by hooking up the incoming 5'-phosphate ends to the 3'-hydroxy tail of the preceding nucleotide: R¹ and R² represent nucleosides, O: oxygen, H: hydrogen, P: phosphorus (see Fig. P65). ▶Watson-Crick model, formula.

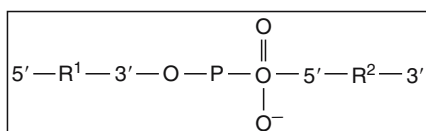


Figure P65. Phosphodiester bond

Phosphodiesterases: Exonucleases. The snake venom phosphodiesterase starts at the 3'-OH ends of a nucleotide chain and splits off the nucleoside-5'-phosphate. The 3'-phosphate terminus does not lend the nucleotide chain for its action. The spleen phosphodiesterase, on the other hand, generates nucleoside-3'-phosphate molecules by splitting on the other side of the nucleotides. Phosphodiesterase converts cyclic AMP into AMP or cGMP into GMP. Phosphodiesterase 5 inhibitors are therapeutics for erectile dysfunction and several other diseases. The sensitivity of RNA phosphodiesterases is affected by the secondary and tertiary structure of the RNA as well by the adjacent nucleotides. ▶phosphodiester bond, ▶nitric oxide, ▶priapism, ▶stroke; structure: Sung BJ et al 2003 Nature [Lond] 425:98; catalytic domains for different inhibitors: Card GL et al 2004 Structure 12:2233.

Phosphoenolpyruvate: Phosphoenolpyruvate is efficient in transferring phosphate group to ADP to form ADP (see Fig. P66).

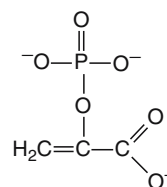


Figure P66. Phosphoenolpyruvate

Phosphofructokinase M (glycogen storage disease VII, 12q13.3): A phospho-fructokinase in the muscles (PFKM). It deficiency may cause muscle cramps and myoglobinuria. Lactate production is reduced and fatigue develops after exertion. ▶glycogen storage diseases, ▶myoglobin, ▶fructose-2,6-bisphosphatase

Phosphofructokinase Platelet Type (PFKP, 10p15.3-p15.2): PFKP is expressed in the platelet but it displays 71% identity of amino acid sequence of the muscle type and 63% identity with the liver enzyme.

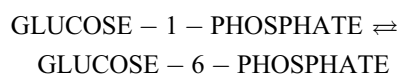
Phosphofructokinase X (PFKX): A chromosome 2-encoded enzyme, which is expressed in the fibroblasts and the brain.

Phosphofructo-2-Kinase/Fructose-2,6-Bisphosphatase (PFKFB, PFRX, Xp11.21): A bifunctional enzyme encoded in the X chromosome of humans and rodents. The PFKFB3 locus is in 10p15-p14. The PFKFB4 enzyme is in 3p22-p21.

Phosphofructose Kinase 1 (PFK-1, PFKL, phosphofructokinase): PFK-1 enzyme catalyzes the formation of fructose-1,6-bisphosphate from fructose-6-phosphate in the presence of ATP and Mg²⁺. PFKL (liver enzyme) is encoded in human chromosome 21q22.3. The tetrameric enzyme may exist in five different forms due to the random association of the products of two different loci.

Phosphofructose Kinase 2 (PFK-2): PFK-2 mediates the formation of fructose-2,6-bisphosphate from fructose-6-phosphate. It enhances the activity of fructosephosphate 1 enzyme by binding to it, and also inhibits fructose-2,6-bisphosphatase and therefore enhances glycolysis. ▶glycolysis

Phosphoglucomutase (PGM): The enzyme that catalyzes the reaction:



Phosphoglucomutase proteins are homologous in structure through the animal kingdom. In humans, there are several PGM enzymes and some with multiple allelic forms with characteristic patterns and are reasonably stable. Therefore, PGM is used in forensic

genetics for personal identification on samples up to 6 months old. Their human chromosomal locations are: PGM1 (1p31), PGM2 (4p14-q12), PGM3 (6q12), and PGM5 (9p12-q12). ►forensic genetics

Phosphogluconate Oxidative Pathway: Same as pentose phosphate pathway.

3-Phosphoglycerate Dehydrogenase Deficiency (PHGDH, 1q12): PHGDH results in recessive serine biosynthetic defect, microcephaly, and neurological defects and seizures. ►serine

Phosphoglyceratemutase Deficiency: ►myopathy, ►glycerophospholipid

Phosphoglyceride: ►glycerophospholipid

Phosphohexose Isomerase (PHI): PHI catalyzes the glucose-6-phosphate⇌fructose-6-phosphate conversions. It is encoded in human chromosome 19cen-q12. Its defects result in dominant hemolytic anemia. ►anemia, ►hemolytic anemia

Phosphoinositide-3-Kinases: ►PIK, ►phosphoinositides

Phosphoinositides: Inositol-containing phospholipids. They play an important role as second messengers, and in phosphorylated/dephosphorylated forms they participate in the regulation of traffic through membranes, growth, differentiation, oncogenesis, neurotransmission, hormone action, cytoskeletal organization, platelet function, and sensory perception. The signals converge on phospholipase C (PLC, 20q12-q13.1). It hydrolyzes phosphatidylinositol-4,5-bisphosphate (PtdInsP₂) into inositol trisphosphate (InsP₃) and diacylglycerol (DAG). PtdInsP₂ segregation is mediated by PTEN, and CDC42 control apical morphogenesis (Martin-Belmonte F et al 2007 Cell 128:383). InsP₃ regulates Ca²⁺ household and DAG activates PLC. InsP₃ levels also regulate pronuclear migration, nuclear envelope breakdown, metaphase-anaphase transitions, and cytokinesis. Cytidine diphosphate-diacylglycerol synthase (CDS) is required for the regeneration of PtdInsP₂ from phosphatidic acid. CDS is a key regulator in the G-protein-coupled photo-transduction pathway. Pleckstrin homology domains selectively bind phosphoinositides. ►inositol, ►phospholipase, ►stoma, ►DAG, ►signal transduction, ►IP₂ [InsP₂ for formula], ►IP₃ [InsP₃ for formula], ►phosphatidylinositol, ►myoinositol, ►PIK, ►pleckstrin, ►PTEN, ►CDC42; Czech MP 2000 Cell 100:603; Vanhaesebroeck B et al 2001 Annu Rev Biochem 70:535; Sato TK et al 2001 Science 294:1881; De Matteis MA et al 2002 Curr Opin Cell Biol 14:434; review: Di Paolo G, Di Camilli P 2006 Nature [Lond] 443:651.

Phosphoinositide-Specific Phospholipase Cδ: Cδ signal transducers and generates the second messengers inositol-1,4,5-triphosphate and diacylglycerol. ►signal transduction, ►second messenger

Phospholamban (phosphorylated pholamban, PLN, 6q22.1): A regulator of sarcoplasmic reticulum Ca²⁺-ATPase (SERCA); it is a kinetic regulator of heart muscle function. Mutation in PLN leads to hereditary cardiomyopathy and premature death (Haghighi K et al 2006 Proc Natl Acad Sci USA 103:1388). ►cardiomyopathy

Phospholipase (PL) A, D, C: Each split specific bond in phospholipids. PLC-β generates diacylglycerol and phosphatidylinositol 2,4,5-triphosphate from phosphatidylinositol 4,5-bis-phosphate. These second messenger molecules play roles in signal transduction. PLC-γ is activated by receptor tyrosine kinases and one of its homologs is the SRC oncoprotein. PLC-γ1 with VEGF—through the FLT-1 receptor—controls the strength of the heartbeat by regulating calcium signaling in the myocytes (Rottbauer W et al 2005 Genes Dev 19:1624). PLA is present in mammalian inflammatory exudates. Form A2 is coded by human chromosome 12, the other PLA2B by chromosome 1. Phospholipase C is coded in human chromosomes at the following locations: PLCB3 (11q11), PLCB4 (20p12), and PLCG2 (16q24.1). ►serine/threonine phosphoprotein phosphatases, ►SRC, ►signal transduction, ►phosphoinositides, ►Ipk1, ►Ipk2, ►VEGF, ►stoma; Rhee SG 2001 Annu Rev Biochem 70:281; Wang X 2001 Annu Rev Plant Physiol Mol Biol 52:211.

Phospholipid: A lipid with phosphate group(s). ►liposome, ►lipids

Phosphomannomutase Deficiency: A rare defect of glycosylation displaying large differences in expressivity. It involves inverted nipples, fat pads, strabismus, hyporeflexia (sluggish responses), mental retardation, hypogonadism, and early death. (See Grünwald S et al 2001 Am J Hum Genet 68:347).

Phosphomannose Isomerase (MPI, 15q22-qter): The defects of MPI affect many glycosylation reactions in the cell. MPI is involved in the conversion of fructose-6-phosphate into mannose-6-phosphate. Clinically, it may cause diarrhea, enlarged liver, hypoglycemia with convulsions, coma, etc. The 5 kb gene includes 8 exons.

Phosphomonoesterase: A phosphatase digesting phosphomonoesters, such as nucleotide chains. ►phosphodiester bond

Phosphonitricin (Basta): ►herbicides

Phosphoramidates: Phosphoramidates are used in antisense technologies by the modification of the sugar-phosphate backbone of oligonucleotides (see Fig. P67). ▶antisense technologies, ▶trinucleotide-directed mutagenesis; Jin Y et al 2001 Bioorg Med Chem Lett 11:2057; Faria M et al 2001 Nature Biotechnol 19:40.

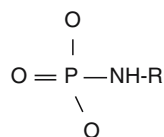


Figure P67. Phosphoramidate

Phosphoramidite/Ink Jotting: A rapid method of DNA analysis. (See Cooley P et al 2001 Methods Mol Biol 170:117).

Phosphorelay: ▶two-component regulatory system

Phosphorescence: ▶fluorescence, ▶luminescence

Phosphoribosylglycinamide Formyltransferase: Phosphoribosylglycinamide formyltransferase is human chromosome 21q22.1 dominant and it controls purine, pyrimidine biosynthesis, and folate metabolism.

Phosphoribosylpyrophosphate Synthetase (PRPS1, Xq22-q24): An enzyme of the purine/pyrimidine salvage pathway. Its deficiency may cause hyperuricemia (excessive amounts of uric acid in the urine), deafness, and neurological disorder.

Phosphorimaging: The detection of radioactive labels in tissues by phosphorescence.

Phosphorolysis: In phosphorolysis, glycosidic linkage holding two sugars together is attacked by inorganic phosphate and the terminal glucose is removed (from glycogen) as α -D-glucose-1-phosphate.

Phosphorothioates: Analogs of oligodeoxynucleotides; they are used in antisense technology. Their attachment to the 3'-end inhibits the activity of nucleases that attacks RNA from that end. They can bind to proteins, but do not stimulate the activity of RNase H (phosphoro-dithioate modified heteroduplexes may stimulate RNase H), inhibit translation, and are relatively easily taken up by cells. Some of the truncated mRNAs can, however, be translated into truncated proteins (Hasselblatt P et al 2005 Nucleic Acids Res 33:114). Some of the effects of these molecules are not based on their anti-sense properties (e.g., binding to CD4, NF- κ B, inhibition of cell adhesion, inhibition of receptors, etc.). Phosphorothioate-modified nucleotides (one of the oxygen attached to P is replaced by S) are used also in vitro mutagenesis to protect

the template strand from nucleases, while the strand to be modified is excised before re-synthesis in a mutant form. ▶antisense technologies, ▶antisense RNA, ▶antisense DNA, ▶OL(1)p53, ▶ribonuclease H, ▶CD4, ▶NF- κ B; Sazani P et al 2001 Nucleic Acids Res 29:3965; ▶quenched autoligation probe

Phosphorylase b Kinase: An enzyme that phosphorylates two specific serine residues in *phosphorylase b*, thus converting it into *phosphorylase a* upon the action of cAMP-dependent protein kinase (synonym protein kinase A). Phosphorylase b kinase mediates glycogen breakdown. This enzyme is a tetramer and for activation the two regulatory subunits (R) must be separated from the two catalytic subunits to be able to function. The dissociation is mediated by cAMP through A-kinase. The δ subunit is calmodulin. ▶epinephrine, ▶cAMP-dependent protein kinase, ▶cAMP, ▶A-kinases, ▶calmodulin; Brushia RJ, Walsh DA 1999 Front Biosci 4:D618.

Phosphorylases (kinases): ▶serine/threonine kinases, ▶tyrosine protein kinase, ▶Jak kinase, ▶phosphorylase B, ▶A-kinases, ▶signal transduction, ▶serine/threonine phosphoprotein phosphatases, ▶phospholipase C, ▶signal transduction, ▶calmodulin, ▶phosphorylase b kinase

Phosphorylation: Adding phosphate to a molecule. It may play an important role in signal transduction, and depending on which of the potentially several sites is phosphorylated, the function of some transcription factors may be altered. In the proteins serine and threonine, residues are frequently phosphorylated. If phosphoserine and phosphothreonine residues are replaced by the lysine analog aminoethylcysteine or β -methylaminoethylcysteine, the lysine-specific proteases cleave at these sites and thus these phosphorylation sites can be revealed (Knight ZA et al 2003 Nature Biotechnol 21:1047). Phosphorylation sites are detectable also by tandem mass spectrometry. The mouse genome contains more than 500 kinases. The nerve synapse system alone operates with 650 phosphorylation events involving 331 sites. Some proteins, like MAP1B, have 33 such sites. The bioinformatics information indicates that a small number of kinases phosphorylate many proteins and some substrates are phosphorylated by many kinases. These phosphorylations form elaborate interacting networks (Collins MO et al 2005 J Biol Chem 280:5972). ▶oxidative phosphorylation, ▶kinase, ▶phosphorylases, ▶tandem mass spectrometry, ▶unstructured proteins; Whitmarsh AJ, Davis RJ 2000 Cell Mol Life Sci 57:1172; protein phosphorylation site prediction (DISPHOS): <http://core.ist.temple.edu/pred/pred.html>; PHOSIDA phosphorylation site database: <http://www.phosida.com/>; protein

three-dimensional phosphorylation sites: <http://cbm.bio.uniroma2.it/phospho3d>.

Phosphorylation Potential (ΔG_p): The change in free energy within the cell after hydrolysis of ATP.

Phosphoserinephosphatase: Phosphoserinephosphatase hydrolyzes O-phosphoserine into serine; it is encoded in human chromosome 7p15.1-p15.1.

Photoactivated Localization Microscopy: Photoactivated localization microscopy can detect activable fluorescent proteins within cells and cellular organelles at nanometer resolution (Betzig E et al 2006 Science 313:1642). ►microscopy

Photoaffinity Tagging: In photoaffinity tagging, the labels may be radioactive or fluorescent and bind to certain compounds by non-covalent bonds upon illumination. (See Knorre DG et al 1998 FEBS Lett 433:9).

Photoaging: In photoaging, skin collagens and elastin are damaged by the ultraviolet light induced metalloproteinases and this results in wrinkling of the skin similar to what occurs during aging. These enzymes are upregulated by AP-1 and NF- κ B transcription factors. ►aging, ►collagen, ►elastin, ►AP-1, ►NF- κ B

Photoallergy: Immunological response to a substance activated by light.

Photoautotroph: An organism that can synthesize in light all its required organic substances and energy from inorganic compounds. The majority of green plants are photoautotrophic. By introducing a glucose transporter gene into obligate photoautotrophic alga, the organism could be converted to light-independent growth on glucose. (See Zaslavskaja LA et al 2001 Science 292:2073).

Photochemical Reaction Center: The site of photon absorption and initiation of electron transfer in the photosynthetic system. ►photosynthesis

Photodynamic Effect: Photosensitivation, photodestruction. A dye or pigment absorbs light and converts the energy to a higher state and exerts specific effects. Photodynamic effects may have various therapeutic applications. Phenothiazines, phthalocyanines, porphyrines, and other molecules with photoactive properties have been successfully tested as photoinactivating agents against Gram-positive and Gram-negative bacteria. After absorption of light, singlet oxygen (1O_2) may be generated and the oxidative damage to proteins and lipids may kill the bacteria even if they are resistant to antibiotics. ►ROS, ►singlet oxygen; Langmack K et al 2001 J Photochem Photobiol B 60:37; Maisch T et al 2007 Proc Natl Acad Sci USA 104:7223.

Photoelectric Effect: The photoelectric effect has very wide applications of modern technology (television, computers and other electronic instruments). Atoms may emit electrons when light hits a suitable target. When X-rays hit a target, very high energy photoelectrons may be generated.

Photogenes: Chloroplast DNA-encoded proteins involved in photosynthesis. One of the most studied is *photogene 32* (*psbA*), which codes for a 32 kDa thylakoid protein involved in electron transport in photosystem II. Also, it binds the herbicide atrazine and by removing or altering this binding site, one can obtain plants resistant to the weed killer through molecular genetic manipulations. ►photosynthesis, ►herbicides; Roderick SR, Bogorad L 1985 J Cell Biol 100:463.

Photography: Photography, in the laboratory, has special requirements depending on the objects. Cell cultures in Petri plates can be best photographed through macrolenses (for extreme close ups, use extension rings or teleconverter) and through using highly sensitive color films, such as Kodak Gold 400. To eliminate reflection, the blue photoflood lamps should be adjusted at an angle of about 45°. Agarose gels can be photographed with a polaroid camera mounted on a copying stand and using high speed (ASA 3000) films. Ultraviolet light sources of the longer wavelength are less likely to damage the DNA. The contrast can be enhanced by the use of orange filters on the camera (such as Kodak Wratten 22A). Note that ultraviolet light is dangerous to the skin and particularly to the eyes. Use gloves, goggles, and wear a long-sleeved shirt. For photomicrography, built-in automatic exposure meters are very advantageous, if frequently used. Otherwise, numerous exposures, at the proper color temperature, are necessary. For photocopying and editing, halftone image computers with (color) scanners can be used. The resolution now provided by digital cameras is satisfactory for most biological applications; they are very convenient and the high pixel (up to 8–10 megapixel [picture elements]) units are very powerful.

Photolabeling: Adding photoactivatable groups to proteins, membranes, or other cellular constituents in order to detect their reaction path. The labels are generally small molecules, stable in the dark and highly susceptible to light. They work without causing photolytic damage to the target and are stable enough to permit analytical manipulations of the sample. Synthetic peptides containing substances, such as 4'-(trifluoromethyl-diaziriny)-phenylalanine or 4'-benzoyl-phenylalanine, etc., have been used to analyze biological structures (membranes, proteins, etc.). ►green fluorescent protein, ►luciferase

Photolithography: A modification of a more-than-a-century-old printing process. A solid plate is coated with a light-sensitive emulsion, overlaid by a photographic film, and then, illuminated. An image is formed after the plate is exposed to light. A similar principle has been adapted now to visualize DNA sequences for the purpose of large scale mapping, fingerprinting, and diagnostics. The process is also used for the synthesis of nucleotide probes. ► [DNA chips](#), ► [microarray hybridization](#); Barone AD et al 2001 *Nucleosides Nucleotides Nucleic Acids* 20 (4–7):525; review of techniques: Truskett VN, Watts MP 2006 *Trends Biotechnol* 24:312.

Photolyase: A flavoprotein repair enzyme (M_r 54,000) that splits cyclobutane pyrimidine dimers (Pyr < > Pyr) into monomers upon absorption of blue light. A photolyase-like 42-nucleotide deoxyribozyme is also capable of repairing thymine dimers optimally at 300 nm light (Chinnapen DJ-F, Sen D 2004 *Proc Natl Acad Sci USA* 101:65). In *E. coli*, two chromophores assist the process of photolyase action; 5,10-methenyltetrahydrofolate absorbs the photo-reactivating light and 8-hydroxy-5-deazariboflavin, and the energy is then transferred to FADH₂, although the latter too absorbs some energy. The excited FADH₂* then transfers the energy to the dimer and while FADH₂ is regenerated, the dimer splits up, the recipient member of the dimer breaks down, and monomeric pyrimidines are formed. A second cofactor, 5,10-methenyl-tetrahydrofolylpolyglutamate (MTHF), may be the light harvester. It is interesting that the blue light photoreceptor cryptochromes of plants bear substantial similarities to the bacterial photolyase and its cofactors are also the same, yet the exact role of photolyases in plant DNA repair is unclear. Cyclobutane photolyase does not split the pyrimidine-pyrimidinone (6-4) photoproducts. The 6-4 photolyases are under the control of two different genes. Topical application of photolyase and light to sunburnt human skin may alleviate the symptoms by repair of the DNA damage. ► [DNA repair](#), ► [direct repair](#), ► [photo-reactivation](#), ► [pyrimidine dimer](#), ► [cyclobutane ring](#), ► [cryptochrome](#), ► [base flipping](#), ► [pyrimidinone](#); Tanaka M et al 2001 *Mutagenesis* 16:1; Komori H et al. 2001 *Proc Natl Acad Sci USA* 98:13560; crystal structure: Mees A et al 2004 *Science* 306:1789; repair process: Kao Y-T et al 2005 *Proc Natl Acad Sci USA* 102:16128.

Photolysis: Degradation of chemicals or cells by light.

Photomixotrophic: An organism that can synthesize some of its organic requirements with the aid of light energy, while for others it depends on supplied organic substances.

Photomorphogenesis: Light-dependent morphogenesis. Light affects the growth and differentiation of plant meristems (photoperiodism), plastid differentiation, and directly or indirectly many processes of plant metabolism. Certain stages in photomorphogenesis can be reached at low intensity (fluence) illumination (or even in darkness), such as the formation of proplastids and etioplasts. Other steps such as the full differentiation of the thylakoid system and photosynthesis-dependent processes require high fluence rate and critical spectral regimes (red and blue). Several genes involved in the control of plastid development have been identified in *Arabidopsis* and other plants. The *lu* mutation is normal green at low light intensity but it is entirely bleached and dies at high light levels. Wild type plants can make etioplasts in the dark but the *deetiololed* (*det1*), *constitutive photomorphogenesis* (*cop1* and *cop9*) mutants develop chloroplasts in darkness. The Cop9 complex includes eight subunits, forming a signalosome in plants and a homolog is found also in animals. The *gun* (*genome uncoupled*) mutants grow normally in the dark but do not allow the development of etioplasts into chloroplasts. Various pale *hy* (*high-hypocotyl*) mutants, deficient in phytochrome, make light green plastids indicating that phytochrome is not a requisite for plastid differentiation to an advanced stage. The *blu* (*blue light uninhibited*) class of mutants is inhibited in hypocotyl elongation by far red light. The *HY4* locus of *Arabidopsis* encodes a protein, homologous to photolyases, and the recessive mutations are insensitive to blue light for hypocotyl elongation. Mutants were identified, some of which showed no response to blue light and others displayed very high blue light requirement for curvature. Most of these light responses appear to be mediated by signal transduction pathways. The chlorophyll-b free, yellow green mutants (*ch*) display chloroplast structure appearing almost normal by electronmicroscopy. Several mutations defective in fatty acid biosynthesis and/or photosynthesis are rather normal in photomorphogenesis. Some mutants are resistant to high CO₂ atmosphere, and normal chloroplast differentiation requires high CO₂. Other mutants can be protected from bleaching only at 2% CO₂ atmosphere. The *Arabidopsis* nuclear mutants of the *im* (*immutans*) type display variegation under average greenhouse illumination, but they are almost normal green under low light intensity and short daily light cycles whereas at high intensity continuous illumination they are almost entirely free of leaf pigments. Under the latter condition, by continuous feeding of an inhibitor or repressor of the de novo pyrimidine pathway, the leaf pigment content may increase twenty-fold. In these variegated plants, the green cells have entirely normal chloroplasts

whereas the white cells lack thylakoid structure. The azauracil-treated plants display fully functional, although morphologically altered thylakoids. An insertional mutation at the *ch-42 locus* (*cs*) identified a thylakoid protein, essential for normal greening of the plants without abolishing cell viability. The *PRF* (*pleiotropic regulatory factor*) locus, tagged by a T-DNA insertion, controls several loci involved in photomorphogenesis. The product of the gene is a subunit of the G-protein family. The *det2*, *cyp90*, *cop*, *fus*, *dim* *axr2*, and the *cbb* dwarf mutations develop their characteristic phenotypes because of defects in the brassinosteroid pathway. The nuclear gene *chm* (*chloroplast mutator*) induces a wide variety of plastid morphological changes, due to extranuclear mutation. ▶[photoperiodism](#), ▶[florigen](#), ▶[phototropism](#), ▶[phytochrome](#), ▶[circadian rhythm](#), ▶[signal transduction](#), ▶[brassinosteroids](#), ▶[COP](#), ▶[proteasome](#), ▶[dominance reversal](#); Wada M, Kadota A 1989 Annu Rev Plant Physiol Plant Mol Biol 40:169; von Arnim A, Deng X-W 1996 Annu Rev Plant Physiol Plant Mol Biol 47:215; Quail PH 2002 Nature Rev Mol Cell Biol 3:85.

Photon: A quantum of electromagnetic radiation, which has zero rest mass and an energy h times the frequency of the radiation. Photons are generated by collisions between atomic nuclei and electrons and other processes when electrically charged particles change momentum. ▶[measurement units](#)

Photoperiodism: The response of some species of plants to the relative length of the daily light and dark periods.

P

Besides the length of these cycles, the spectral properties and the intensity of the light are also important. Responses of plants include, the onset of flowering, vegetative growth, elongation of the internodes, seed germination, leaf abscission, etc. *Short-day*, *long-day* and *day-neutral* plants are commonly distinguished on the basis of the critical daylength or, in the latter category, by the lack of it (see Fig. P68). The geographic distribution of plants is correlated with their photoperiodic response. In the near equatorial regions, short-day species predominate whereas in the regions extending toward the poles long-day plants are common. The onset of flowering of short-day plants is promoted by 15–16 h of dark periods whereas in long-day plants, the flowering is accelerated by continuous illumination or by longer light than dark daily cycles. The critical day-length is not an absolute term; it varies in different species. Usually, there is a minimum number of cycles to evoke the photoperiodic response. Mutants of *Arabidopsis* (*gi*, *co*, *ld*; Rédei GP 1962 Genetics 47:443) and others shed light on some of the basic mechanisms involved (Schultz TF, Kay SA

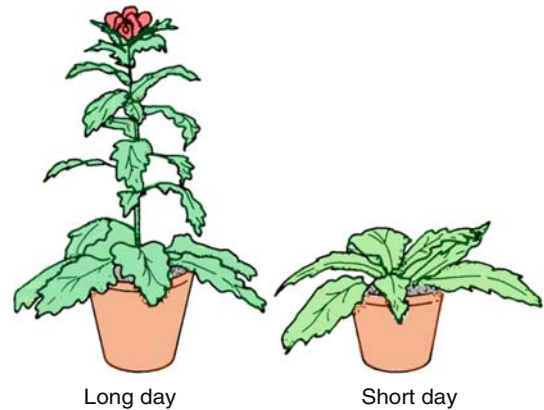


Figure P68. Henbane (*Hyoscyamus niger*) Long-day plants flower only under long daily light periods (after appropriate cold treatment). Courtesy of Professor G. Melchers

2003 Science 301:326). The most important photoreceptor chromoprotein is *phytochrome*. The effect of phytochrome is affected by different plant hormones. Typical long-day plants are henbane (*Hyoscyamus*), spinach, *Arabidopsis* [without a critical daylength], the majority of the grasses and cereal crops (wheat, barley, oats), lettuce, radish, etc. Typical short day plants are Biloxi soybean, cocklebur, aster, chrysanthemum, poinsettia, dahlia, etc. In the majority of species, the photoperiodic response is controlled by one or a few genes. Some processes in animals are also under photoperiodic control. In the Japanese quail, the gene encoding type 2 iodothyronine deiodinase, which catalyzes the conversion of the prohormone into the active 3,5,3'-triiodothyronine is induced by light. The anatomical location of the response center is in the hypothalamus, while the target site is the differentiation of the gonads (Yoshimura T et al 2003 Nature [Lond] 426:178). ▶[phytochrome](#), ▶[florigen](#), ▶[cryptochromes](#), ▶[photomorphogenesis](#), ▶[circadian rhythm](#), ▶[phototropism](#), ▶[vernalization](#), ▶[flower evocation](#), ▶[floral induction](#), ▶[dominance reversal](#); Jackson SD, Prat S 1996 Plant Physiol 98:407; Amador V et al 2001 Cell 106:343; Quail PH 2002 Curr Opin Cell Biol 2002 14:180; Mockler T et al 2003 Proc Natl Acad Sci USA 100:2140S; Yanofsky MJ, Kay SA 2003 Nature Rev Mol Cell Biol 4:265; Chen M et al 2004 Annu Rev Genet 38:87.

Photophosphorylation: ATP formation from ADP in photosynthetic cells.

Photoreactivation: Elimination of the harmful effects of ultraviolet irradiation by subsequent exposure to visible light (that activates enzymes splitting up the pyrimidine dimers in the DNA). With a few exceptions, e.g., *Haemophilus influenzae*, most organisms

possess light-activated repair enzymes. The majority of mammals do not have efficient photoreactivation system, except the marsupials. ►light repair, ►photolyase dark repair, ►excision repair, ►glycosylases, ►error-prone repair, ►DNA repair; Kelner A 1949 J Bacteriol 48:5111; Tuteja N et al 2001 Crit Rev Biochem Mol Biol 36(4):337; Sancar GB 2000 Mutation Res 451:25.

Photoreceptors: Humans have, in the eye, the very sensitive rod cells, mediating black and white vision and the less sensitive cone cells for color vision. ►phytochrome, ►rhodopsin, ►CRX, ►metalloproteinases, ►phototropism, ►sevenless, ►S-cone disease; Calvert PD et al 2006 Trends Cell Biol 16:560.

Photoreduction: In photosynthetic cells, light induced reduction of an electron acceptor.

Photorespiration: Oxygen consumption in illuminated plants used primarily for the oxidation of the photosynthetic product phosphoglycolate; it also protects C3 plants from photooxidation. Step-wise nuclear transformation of *Arabidopsis* with five chloroplast-targeted bacterial genes encoding glycolate dehydrogenase, glyoxylate carboligase, and tartronic semialdehyde reductase converted chloroplast glycolate directly to glycerate. Transgenic plants grew faster, produced more shoot and root biomass, and contained more soluble sugars, reflecting reduced photorespiration and enhanced photosynthesis that correlated with an increased chloroplast CO₂ concentration (Kabeish R et al 2007 Nature Biotechnol 25:593). ►respiration, ►Calvin cycle, ►C3 plants; Wingler A et al 2000 Philos Trans R Soc Lond B Biol Sci 355:1517.

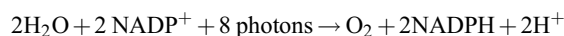
Photorhabdus luminescens: A gram-negative enterobacterium that maintains a mutualistic association with insect-feeding Heterorhabditis species of nematodes. When the nematodes invade the insects, the bacteria are released, kill the host with the help of the toxin, emit light, and make the cadaver luminescent. The toxins (tca and tcd) are potential insecticide, fungicide, and antibacterial agents, somewhat similarly to that of *Bacillus thuringiensis*. *Arabidopsis* plants, transgenic for the *TcdA* gene driven by the constitutive cassava vein mosaic virus promoter and equipped with the 5' and 3' untranslated sequences of the tobacco *osmotin* gene, were especially resistant to feeding insects (Liu D et al 2003 Nature Biotechnol 21:1038). The *osmotin* gene sequences increased the mRNA stability. The activity of the transgene was affected significantly by the position of the insertion site in the plant chromosome. Strain TT01 genome contains 5,688,987 bp and encodes presumably 4839 proteins (Duchaud E et al 2003 Nature Biotechnol 21:1307). ►*Bacillus thuringiensis*; Ehlers RU 2001

Appl Microbiol Biotechnol 56:623; Szállás E et al 1997 Int J Syst Bacteriol 47:402; Bowen D et al 1998 Science 280:2129.

Photosensitizers: Photosensitizers may increase the oxidative damage to DNA. Their action may involve initial electron or hydrogen transfer to the DNA by the excited photosensitizer, followed by the generation of free radicals. Alternatively, they generate singlet oxygen that interacts with the DNA and then produces peroxidic intermediates. Most commonly, guanine suffers lesions. ►oxidative DNA damages

Photosynthesis: Using light energy for the conversion of CO₂ into carbohydrates with the assistance of a reducing agent such as water. The photosynthetic system appears to have evolved from the core of the cyanobacterial genome (Mulikidjanian AY et al 2006 Proc Natl Acad Sci USA 103:13126). ►photosystems, ►Z scheme, ►chlorophyll binding proteins, ►thermotolerance, ►C3 plants, ►C4 plants, ►Calvin cycle; Matsuoka M et al 2001 Annu Rev Plant Physiol Mol Biol 52:297; Xiong J, Bauer CE 2002 Annu Rev Plant Biol 53:503.

Photosystems: In photosynthesis, photosystem I is excited by far red light (~700 nm) while photosystem II requires higher energy red light (~650–680 nm). In the thylakoids of the chloroplast of plants, the immunophilin FKB20-2, an FK-506 binding protein, is required for the assembly of the photosystem II complex (Lima A et al 2006 Proc Natl Acad Sci USA 103:12631). Photosynthesis in bacteria that does not evolve oxygen uses only photosystem I. Upon absorption of photons, photosystem I liberates electrons that are carried through a cascade of carriers to NADP⁺, which is reduced to NADPH. The departure of electrons generates a “void” in the P700 photoreaction center of photosystem I and that is filled then by electrons produced through splitting of water molecules in photosystem II. The overall reaction flow is:



Mutants of *Chlamydomonas* alga lacking photosystem I survive as long as the actinic light (beyond violet) reaches 200 microeinsteins per m²/second. The photosystem II of cyanobacteria (similar to that of plants and algae) is a complex of 20 proteins and 77 cofactors including 14 integrally bound lipids and their crystal structure has been determined at 3.0 Å resolution (Loll B et al 2005 Nature [Lond] 438:1040). Photosystem I has 17 protein subunits and the crystal structure of the supercomplex has been determined at 3.4 Å resolution (Amunts A et al 2007 Nature [Lond] 447:58). ►CAB, ►LHCP, ►antenna, ►chloroplast, ►thylakoid, ►Z scheme, ►immunophilins; Annu Rev

Genet 29:755; Guergova-Kuras M et al 2001 Proc Natl Acad Sci USA 98:4437; Jordan P et al 2001 Nature [Lond] 411:909; Chitnis PR 2001 Annu Rev Plant Physiol Plant Mol Biol 52:593; Szabó I et al 2001 J Biol Chem 276:13784; Rhe K-H 2001 Annu Rev Biophys Biomol Struct 30:307; Saenger W et al 2002 Curr Opin Struct Biol 12:244; Munekage Y et al 2004 Nature [Lond] 429:579; structure of photosystems: Nelson N, Yocum CE 2006 Annu Rev Plant Biol 57:521.

Phototaxis: A movement of organisms (plants, animals and microbes) in response to light.

Phototransduction: The transmission of light signals mediating gene expression. A scaffold protein (InaD in *Drosophila*) assembles the components of the light transduction pathway. ► [signal transduction](#), ► [rhodopsin](#), ► [retinal dystrophy](#)

Phototroph: An organism that uses light to generate energy and uses this energy to synthesize its nutrients from inorganic compounds.

Phototropin: Flavoprotein photoreceptors for plant phototropism. They have two flavin mononucleotide-binding domains (LOV1 and LOV2) and a serine-threonine kinase domain at the carboxyl end. Phototropins 1 and 2 are blue light-activated kinases for low and high intensity light. ► [flavoprotein](#); Harper SM et al 2003 Science 301:1541.

Phototropism: The reaction of an organ or organism to light, involving apparently more than a single photoreceptor (see Fig. P69). In *Arabidopsis*, the phytochromes and two complementary cryptochrome mutations (*CRY1*, *CRY2*) have been identified. Inactivation of both is required to eliminate phototropic response. It was suggested that one of the receptors is a membrane protein with autophosphorylating ability. Additional genes (*NPH1*, *NPH2*, *NPH3*, *RPT*, *NPL1*) are required for processing the responses after perception of the signals. Phototropin (phot1) detects low fluence blue light. Phytochromes

modulate phototropism by phytochrome A signaling components. Phytochrome kinase substrate proteins (Pks1, Pks2 and Pks4), in a complex with phot1 and NPH3 (non-phototropic hypocotyl), are involved in the signaling to phototropism (Lariguet P et al 2006 Proc Natl Acad Sci USA 103:10134). ► [photoreceptors](#), ► [gravitropism](#), ► [phytochromes](#), ► [cryptochromes](#), ► [phototropin](#); Briggs WR, Liscum E 1997 Plant Cell Environ 20:768; Quail PH 2002 Curr Opin Cell Biol 2002 14:180; Chen M et al 2004 Annu Rev Genet 38:87.

Phox: An oxidation subunit of proteins that is activated by phosphorylation. (Hoyal CR et al 2003 Proc Natl Acad Sci USA 100:5130).

Phragmoplast: A hollow-looking ring- or barrel-like structure formed near the end of mitosis in the middle plane of plant cells before the *cell plate* appears, separating the two daughter cells. ► [mitosis](#); Gu X, Verma DP 1996 EMBO J 15:695; Zhang Z et al 2000 J Biol Chem 275:8779.

PHRAP: One of the frequently used DNA sequence alignment programs. A quality score of $10^{X/10} \approx 30$ corresponds to an accuracy of 99.9% regarding the base sequence. ► [PHRED](#), ► [CONSED](#), ► [base-call](#); Harmsen D et al 2002 Nucleic Acids Res 30:416; <http://www.phrap.org>.

PHRED: An automated base-calling computer program. ► [PHRAP](#), ► [PolyPhred](#), ► [base-call](#)

Phycobilins: Highly fluorescent photoreceptor pigments in blue-green, red, and some other algae. They contain a linear tetrapyrrole prosthetic group for light harvesting. They also contain bile pigments and an apoprotein. This family of pigments includes the blue phycocyanins, the red phycoerythrins, and the pale blue allophycocyanins. These pigments may form phycobilisome, attached to the photosynthetic membrane. Phytochromes are also related pigments. ► [light-harvesting protein](#), ► [phytochrome](#); Wu SH et al 1997 J Biol Chem 272:25700.

Phycocyanin: The pigment of blue-green algae. ► [phycobilins](#)

Phycoerythrin: The red pigment of red algae. ► [phycobilins](#), ► [phycocyanin](#)

Phycomycetes: Fungi with some algal characteristics. *Ph. blakesleeana* is easy to grow with four-days-long asexual cycle and about two-months-long sexual cycle. It forms heterokaryons ($n = 14$) and can be subjected to formal genetic analyses, although the tetrads may be irregularly amplified. Transformation is feasible. It is well suited for physiological and developmental studies.

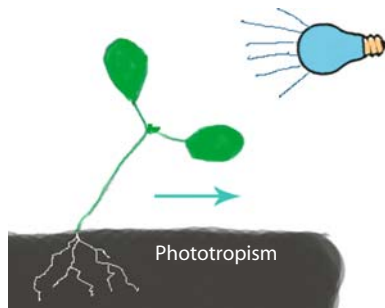


Figure P69. Phototropism

Phyletic Evolution: Gradual emergence of a species in a line of descent. The gaps in the fossil records are supposed to be due to accidents in the preservation of the intermediate forms.

Phyllody: Developmental anomaly of conversion of floral parts into leaves, generally after infection by pathogens.

Phylloquinone: Phylloquinone is composed of a p-naphthokinone and a phytol radical and it catalyzes oxydation-reduction reactions in plants. ▶ [vitamin K](#)

Phyllotaxy (phyllotaxis): In phyllotaxy, the consecutive leaves of plants do not occur above each other. Quite commonly, single leaves are at opposite positions (unless they occur in whorls) (see Fig. P70). This arrangement makes sense for the optimal utilization of light. In many plants, the leaves may not alternate in 180° but they may be arranged in any other determined pattern. This pattern is called phyllotaxy. If the leaves are opposite to each other, the phyllotaxy is 1/2. A common phyllotactic index is 2/5 (144°). This means that if the leaves are positioned by this index, leaf #1 will be followed by #2 at 144°, then #3 will take the place in a spiral at 288°, i.e., it will be above #1 (because $288:144 = 0.5$ and $0.5 \times 360 = 180$), and so on. The arrangement of the fruits on the stem may also be caused by such an obliquity, following either clockwise or counterclockwise directions. The phyllotactic arrangement is determined by the flow of auxin, and it may be negatively regulated by cytokinins in the shoot meristem (Giulini A et al 2004 Nature [Lond] 430:1031). ▶ [embryogenesis in plants](#), ▶ [Fibonacci series](#), ▶ [decussate](#); Hake S, Jackson D 1995 ASGSB Bull 8 (2):29; Kuhlemeier C, Reinhardt D 2001 Trends Plant Sci 6:187; Reinhardt D et al 2003 Nature [Lond] 426:255; Jönsson H et al 2006 Proc Natl Acad Sci USA 103:1633; Smith RS et al 2006 Proc Natl Acad Sci USA 103:1301.



Figure P70. Phyllotaxy

Phylogenetic Analysis: Phylogenetic analysis in forensic science uses pathogen strain DNA comparisons for identifying the source of infection, e.g., the retroviral DNA in case of HIV. ▶ [acquired immunodeficiency](#), ▶ [DNA finger printing](#), ▶ [forensic genetics](#)

Phylogenetic Depth: The total number of genetic changes, which separate an organism from its ancestors.

Phylogenetic Profile Method: The phylogenetic profile method studies the correlations of inheritance of pairs of proteins among various species. These proteins are not necessarily homologous but they appear to be linked functionally. ▶ [rosetta stone sequences](#); <http://dip.doe-mbi.ucla.edu>.

Phylogenetic Tree: The phylogenetic tree graphically represents the phylogeny of organisms. Trees have been constructed in the past on the basis of morphology, the sequences of single genes, or sequences of entire genomes. Similarity between two organisms can also be determined by dividing their total number of genes by the number of genes they have in common. Phylogenetic analysis based on molecular information greatly increases the precision of map construction. Although insights into the various genomes greatly facilitate the elucidation of phylogenetic relationships, none of the molecular methods are completely free of problems because duplications, deletions, horizontal gene transfer, and the evolution of new genes from various sequences may create problems in interpretation. ▶ [evolutionary tree](#), ▶ [BAMBE](#); Madsen O et al 2001 Nature [Lond] 409:610; Murphy WJ et al. 2001 Nature [Lond] 409:614; Kristian H et al 2007 Bioinformatics 23:793; <http://www.treefam.org/>.

Phylogenetic Weighting: As per phylogenetic weighting, DNA sequence information from various taxa is included in the phylogenetic tree in decreasing order of relationship. Thus, alignment from distant relatives should not precede alignment of closer relatives. This procedure prevents confounding similarity and descent. ▶ [evolutionary tree](#), ▶ [maximum parsimony](#), ▶ [homology](#), ▶ [DNA sequence alignment](#), ▶ [homology](#); Robinson M et al 1998 Mol Biol Evol 15:1091.

Phylogenomics: Phylogenomics uses evolutionary information to infer function of genes or the reconstruction of phylogenetic history on the basis of genomes. (See Delsuc F et al 2005 Nature Rev Genet 6:361; metabolic networks from protein structure: Caetano-Anollés G et al 2007 Proc Natl Acad Sci USA 104: 9358; phylogeny of protein domains: <http://www.bioinformatics.nl/tools/treedom/>; Berkeley phylogenomics: <http://phylogenomics.berkeley.edu>; search several gene families

simultaneously: <http://www.cs.nuim.ie/distributed/multiphyl.php>; distributed computing: <http://distributed.cs.nuim.ie/multiphylOnlineManual.php>; prokaryotic phylogenomics: <http://genetrees.vbi.vt.edu>).

Phylogeny: The evolutionary descent of a species or other taxonomic groups. ▶evolution, ▶ontology, ▶speciation, ▶genome conservation; Huelsenbeck JP et al 2001 Science 294:2310; information at the web site: <http://beta.tolweb.org/tree/>; <http://mrbayes.csit.fsu.edu/>.

Phylo type (phylogenetic type): A species representing a branch of a phylogenetic tree on the basis of shared similarity of nucleotide sequences. ▶phylogenetic tree

Phylum: The first main category of the plant and animal, and other kingdoms.

Physarum polycephalum: A single-cell slime mold that displays physiological dioecy. The cell forms a plasmodium, i.e., the nuclei divide without cell division and thus, the cell becomes multinucleate. In the early embryos, only the S and M phases of the cell cycle are detectable.

Physcomitrella patens: A moss with a principal life phase as a haploid gametophyte. It can be used for the production of various mutants, for parasexual research, transformation, study of plant hormones on developmental processes, and various tropisms. Sequencing of the genome is nearly complete by 2005. The estimated genome size ($n = 27$) ~511 Mb (~0.53 pg). The chloroplast genome is 122890 bp encoding 83 proteins. (See Schaefer DG 2002 Annu Rev Plant Biol 53:477; Cove D 2005 Annu Rev Genet 39:339).

Physical Containment: ▶containment

Physical Map: A map where the genome is ordered in DNA fragments or nucleotide sequences rather than in units of recombination. The first physical maps were constructed in bac-terio phages with small genomes. The DNA of phage P4 was cleaved completely by restriction endonuclease EcoRI into four fragments, which could be separated by electrophoresis according to size:

| | | | |
|---|---|---|---|
| v | ζ | ζ | ψ |
| A | C | B | D |

After incomplete digestion for 5 min, larger fragments were also detected that contained fragments A + B + C, C + B, and the combined size of C + D appeared but no fragment appeared with the size B + D. The cause of the absence of B + D must have been that B and D were not adjacent in the circular DNA. Therefore, the sequence of the fragments in the chromosome could only have been: A – B – C – D.

The much larger polyoma genome was mapped by a different procedure. With a single EcoRI cut, the circular DNA was linearized and that cut was designated as the zero coordinate of the map. HindIII cut the circle into two fragments: A = 55% and B = 45% (see Fig. P71). HpaII produced eight fragments: a = 27%, b = 21%, c = 17%, d = 13%, e = 8%, f = 7%, g = 5%, and h = 2% of the total genome. When EcoRI and HpaII cleaved the DNA, fragment b (21%) was not detected by electrophoresis, but instead, two new fragments of 1% and 20% were found. Obviously, the EcoRI cut was 1% from one end and 20% from the other end of fragment b. In the following step, the HindIII is shown to generate a fragment that was digested by HpaII. Fragments c, d, e, g, and h were found again ($17 + 13 + 8 + 5 + 2 = 45$) and two pieces of 3% and 7% were also obtained. When the HindIII fragment of 45% length was exposed to HpaII fragment, f remained intact but two other fragments of 18% and 20% were recovered. Therefore, the fragments could be pieced together as follows:

| | | | | | |
|------------|-----------|---|-----|-----------|-----|
| HindIII A: | 7% | - | 45% | - | 3% |
| | part of a | | | part of b | |
| HindIII B: | 18% | - | 7% | - | 20% |
| | part of b | | f | part of a | |

Figure P71. Fitting the positions of hypothetical double digest fragments

Incomplete digestion of A by HpaII produced fragments: a + c, c + e, e + d, h + g, and g + b, therefore the polyoma DNA appeared as: b – f – a – c – e – d – h – g, with the zero coordinate in b and g near the 100 coordinate.

Larger genomes such as *E coli*, yeast, or those of higher eukaryotes are generally pieced together by a chromosome walking like procedure, using overlapping fragments generated by several restriction endonucleases, e.g.:

Fragments generated by enzyme A :

| | | |
|-------|-----------|-----------|
| 1 | 2 | 3 |
| abcde | fghijklmn | oprstuvwz |

Fragments generated by enzyme B :

| | |
|---------|------------|
| 4 | 5 |
| cdefghi | jklmnoprst |

will be tied into the order 1, 2, 3 on the basis of the hybridization of 4 with 1 and 2, and hybridization of 5 with 2 and 3, but not 5 with 1 or 4 with 3. In the initial steps, generally YAC clones are used because they cover large segments of the genomes. Cosmid clones usually follow this and eventually large

continuities (contigs) are established without gaps. By the employment of anchors, fragments with genetically or functionally known sites, the physical map can be correlated with the genetic map determined by recombination frequencies, and thus *integrated maps* are generated. The individual fragments can then be sequenced and thus maps of ultimate physical resolution can be obtained. ▶RFLP, ▶chromosome walking, ▶FISH, ▶SAGE, ▶integrated map, ▶dynamic molecular combing, ▶anchoring, ▶contigs, ▶cosmids, ▶restriction enzymes, ▶EcoRI, ▶HindIII, ▶HpaII, ▶genomic screening, ▶electronic PCR, ▶PCR; Bhandarkar SM et al 2001 Genetics 157:1021.

Physical Mutagens: The most widely used forms of physical mutagens are *electromagnetic*, ionizing radiations such as X rays and γ rays emitted by radioisotopes. The most commonly used radiation sources for the induction of mutation by γ rays are cobalt⁶⁰ (Co⁶⁰) and cesium¹³⁷ (Cs¹³⁷). *Particulate radiations* such as produced by atomic fission are also ionizing. Ionization is the dislodging of orbital electrons of the atoms. The particulate (corpuscular) radiation source is uranium²³⁵, which releases neutrons, uncharged particles (slightly heavier than that the hydrogen atom) with very high penetrating power and the ability to release about 15 times as much energy along their path as the hard X rays (of short wave length and high energy). The *fast neutrons* have energies between 0.5 and 2.0 MeV (million electron volt). The *thermal neutrons* have much lower level of energy (about 0.025 eV) because they have been “moderated” by carbon and hydrogen atoms. Radioactive isotopes emit also β particles (electrons). Their level of energy and penetrating power depend a great deal on the source; H³ (tritium) has very short path (about 0.5 μ m) and P³² is much more energetic (2600 μ m). Beta emitters are rarely used for mutation induction. They can, however, be incorporated directly into the genetic material by using radioactively labeled precursors or building blocks of nucleic acids, and thus are capable of inducing localized damage, the degree of localization depends on the effective path length. Uranium238 emits α particles (helium nuclei) releasing thousands of times more energy per unit track than X rays. Because of the very low penetrating power, it can be stopped by a couple of sheets of cells in contrast to X rays and gamma rays which require heavy concrete or lead shielding. Alpha radiation, because of its high energy per short path, can very effectively destroy chromosomes. The most common genetic effect of all ionizing radiations is chromosome breakage and particularly deletions.

Another physical mutagen is *ultraviolet (UV)* radiation. The latter causes excitation, rather than

ionization, in the biological material. Excitation may raise the orbital electrons to a higher level of energy, from which they return to the ground state very shortly. UV radiation sources are commonly mercury or cadmium lamps (black light, germicidal, and sun lamps). Natural light also includes UV radiation, especially in the clean air of the higher mountains. Near ultraviolet light, UV-B (290–400 nm) may be present in the emission of fluorescent light tubes and in the presence of sensitizers it may be genetically effective on a few layers of cells. The most common genetic effect of UV light is the production of pyrimidine dimers.

The effect of radiation on cells and organisms may be *direct*, i.e., the radiation actually hits the target molecules or it may be *indirect*, i.e., the radiation produces reactive molecules in the intra- or extra-cellular environment, and these in turn cause the genetic and/or physiological damage. Exposure to high temperature may enhance mutability. If radiation is received during DNA replication, damage is more likely than in the dormant state. Generally, hydrated cells and tissues are more sensitive to ionizing radiation than dry or non-metabolizing cells. ▶X-rays, ▶radioisotopes, ▶radiation effects, ▶ultraviolet light, ▶chemical mutagens, ▶maximal permissive dose, ▶carcinogens, ▶LET, ▶chromosomal mutation, ▶DNA repair, ▶genetic sterilization, ▶cosmic radiation, ▶genomic subtraction, ▶nuclear reactors, ▶atomic radiations, ▶electromagnetic radiation, ▶pyrimidine dimer, ▶cycloputane ring; Hollaender A (ed) 1954–56 Radiation Biology, McGraw-Hill, New York.

Physiology: The discipline dealing with the functions of living cells and organisms.

Phytanic Acid: A 20-carbon, branched chain fatty acid is formed from the phytol alcohol ester of chlorophylls and it degraded by β -oxidation into propionyl-, acetyl-, and isobutyryl-CoA. Deficiency of this oxidation leads to Refsum disease in humans. ▶Refsum diseases, ▶peroxisome

Phytic Acid (inositol hexaphosphoric acid, IP⁶): Phytic acid combined with Ca²⁺ and Mg²⁺ salts are called phytins and are commonly present in plant tissues. Phytate also ties up iron in the plant tissues and limits its availability for human nutrition, unless it is degraded by phytase. ▶myoinositol, ▶phosphoinositides; engineered phytate-free seeds: Stevenson-Paulik J et al 2005 Proc Natl Acad Sci USA 102:12612.

Phytoalexins: Generally relatively low molecular weight, yet diverse, compounds synthesized through the phenylpropanoid pathway. They were attributed to defense systems against various plant pathogens. Currently, they are considered to be mainly consequences of infection rather than active defense

molecules. ►host-pathogen relation, ►phenolics; Hammerschmidt R 1999 Annu Rev Phytopath 37:285.

Phytochromes: Five regulatory proteins with alternating absorbance peaks in red and far-red light (see Fig. P72). Through their absorbance peaks (red [R] 660 nm and far-red [FR] 730), they control various photomorphogenic processes, such as short- and long-day onset of flowering, hypocotyl elongation, apical hooks, pigmentation, etc. These chromoproteins are homodimers of 124 kDa subunits and a tetrapyrrole complex, joined covalently through a cysteinyl residue at about 1/3 distance from the NH₂ end. The molecule exists in two conformations corresponding to the R and FR absorption states. The interconversion between these states is mediated very rapidly by light of R and FR emission peaks. In etiolated plant tissue, the inactive P_r conformation may constitute up to 0.5% of the protein. The transition from the P_r conformation into the active P_{fr} form also entails the degradation of this receptor. The apoprotein, coded by different genes (*PHYA* and *PHYB*) in *Arabidopsis* may have only about 50% homology in amino acid sequences, although they bind the same chromophore. The specificity of PhyA (far-red) and PhyB (red) resides in the N-termini. The C-terminal domain of phytochrome B attenuates the transducing signals (Matsushita T et al 2003 Nature [Lond] 424:571). Phytochromes can induce and silence the expression of genes in a specific selective manner. The transcription of the phytochrome genes is also light regulated; R light reduces the transcription more effectively than FR. Phy-A perceives continuous FR, whereas phy-B responds to continuous red light.

Phytochrome B is also a photoreceptor in the circadian rhythm. Phytochrome A appears to be

serine/threonine kinase. Phytochrome C is a light-stable molecule. SPA1 (suppressor of phy-A), a WD-protein with sequence similarity to protein kinases, mediates, among other factors, the photomorphogenic reactions. The phytochrome responses are under complex genetic regulatory systems involving light response elements, transcription factors, and components of the signal transduction circuits. PIF3 (phytochrome-inducing factor) is a basic helix-loop-helix protein that attaches to the non-photoactive C-terminus of phytochromes A and B and mediates their conversion into active forms. PIF3 also binds to a G-box in the promoter and thus regulates transcription. Nucleoside diphosphate kinase 2 (NDPK2) preferentially binds to the red light activated form of phytochrome and appears to play a role in eliciting light responses. In photomorphogenic responses, phytochromes interact with cryptochromes. Although phytochrome is known as a ubiquitous plant product, the yeast *Pichia* also synthesizes phytochromobilin (PΦB), a precursor of this plant chromophore. PΦB deficient plants can be complemented by the insertion of the algal phycocyanobilin gene (Kami C et al 2004 Proc Natl Acad Sci USA 101:1099). Also, a phytochrome-like protein (Ppr) has been identified in non-photosynthetic prokaryotes (*Deinococcus radiodurans*, *Pseudomonas aeruginosa*). In the *Rhodospirillum rubrum*, a purple photosynthetic bacterium, a photoreactive yellow (PYP) pigment has been identified with a central domain resembling phytochromes.

In cyanobacteria, the circadian input kinase (CikA), a bacteriophytochrome, mediates the circadian oscillations. ►photoperiodism, ►photomorphogenesis, ►signal transduction, ►phycobilins, ►cryptochromes, ►brassinosteroids, ►WD-40, ►G box; Neff MM et al 2000 Genes Dev 14:257; Martinez-Garcia JF et al 2000 Science 288:859; Smith H 2000

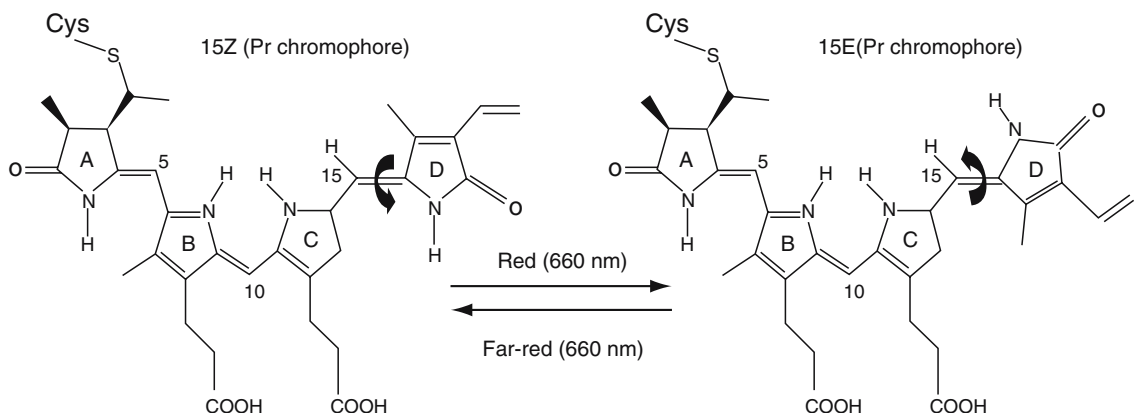


Figure P72. Phytochrome chromophores: The two isomers of phytochromobilin. (See Chen M et al 2004 Annu Rev Genet 38:87; courtesy of Dr. Meng Chen and Dr. Joanne Chory)

Nature [Lond] 407:585; Bhoo S-H. et al 2001 Nature [Lond] 414:776; Nagy F, Schäfer E 2002 Annu Rev Plant Biol 53:329.

Phytoestrogens: Estrogen-like plant products, such as the isoflavones (genistein, daidzein), and they can take advantage of the animal estrogen receptors and regulate gene expression similarly to other estrogens. Isoflavones can thus be used in hormone replacement therapies used to alleviate postmenopausal symptoms and for other purposes of selective modulation of estrogen receptors. ▶[estradiol](#), ▶[estrogen receptor](#), ▶[sterol](#), ▶[genistein](#); An J et al 2001 J Biol Chem 276:17808; Yellayi S et al 2002 Proc Natl Acad Sci USA 99:7616.

Phytoextraction: ▶[bioremediation](#)

Phytohemagglutinin: ▶[PHA](#)

Phytohormones: ▶[plant hormones](#)

Phytophthora: A group of heterothallic plant pathogenic fungi. Each individual can produce both antheridia and oogonia. The fertilized oogonium develops oospores. The A1 mating type secretes $\alpha 1$ hormone (see Fig. P73), which induces oospore formation in A2 mating types, and A2 individuals secrete $\alpha 2$ hormone, which induces oospore formation in A1 types (See Qi J et al 2005 Science 309:1828). A draft of the genomes of *P. soyae* and *P. ramosa* is available, indicating 19,027 and 15,743 genes in the respective species and revealing evolutionary origin of related organisms (Tyler BM et al 2006 Science 313:1261). ▶[hormones](#), ▶[mating type](#), ▶[oöspore](#), ▶[oogonium](#), ▶[antheridium](#); genome: <http://phytophthora.vbi.vt.edu/>; functional genomics: <http://www.pfgd.org/>.

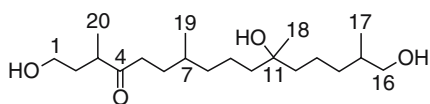


Figure P73. Alpha1 mating hormone

Phytoplankton: Aquatic, free-flowing plants. ▶[bacterioplankton](#)

Phytoplasmas (Mollicutes, 530–1350 kbp circular DNA): Minute, round (200–800 μm or filamentous) bacteria without cell wall, infecting the phloem cells of plants and causing disease. The symptoms vary from yellowing to sterility, stunting, and heavy branching. Phytoplasmas resemble somewhat mycoplasmas of animals but cannot be cultured in cell-free media. They are propagated by sucking insects that cause economic loss in vegetables and trees. Phytoplasma infection may be exploited for gain by floriculture to obtain bushier Poinsettias (Lee I-M

et al 1997 Nature Biotechnol 15:178). Phytoplasmas may be identified by DNA-DNA hybridization and serological means. ▶[mycoplasma](#), ▶[phyllody](#); Lee IM et al 2000 Annu Rev Microbiol 54:221.

Phytoremediation: ▶[bioremediation](#)

Phytosulfokines (PSK): PSK- α , a sulfated pentapeptide, and PSK- β , a tetrapeptide, are cell proliferation promoting compounds of plants.

Phytotron: A plant growth chamber system with maximal physical regulation facilities.

Pi: Inorganic phosphate.

pI (pH_I): Isoelectric point. ▶[isoelectric focusing](#)

PI 3 Kinase: ▶[phosphoinositide 3 kinase](#)

PI Vector: The PI vector contains packaging site (*pac*) and allows about 115 kb to be packaged, and it infects *E. coli* at a pair of *lox P* recombination sites, at which the *Cre* recombinase circularizes DNA inside the host cell. ▶[vectors](#)

Pibids: ▶[trichothiodystrophy](#)

PIC (preinitiation complex): Proteins associated with RNA polymerase before transcription. During pre-initiation, the carboxyterminal domain (CTD) is hypophosphorylated but during initiation, the movement four kinases in a step-wise manner phosphorylate the RNA polymerase. Phosphorylation regulates the attachment of additional proteins. ▶[transcription factors](#), ▶[open promoter complex](#), ▶[TBP](#), ▶[transcript elongation](#), ▶[chromatin remodeling](#), ▶[mediator complex](#); He S, Weintraub SJ 1998 Mol Cell Biol 18:2876; Tsai FT, Sigler PB 2000 EMBO J 19:25; Soutoglou E, Talianidis I 2002 Science 295:1901; Wilcox CB et al 2004 Genetics 167:93; Chen H-T, Hahn S 2004 Cell 119:169.

PIC: ▶[polymorphic information content](#)

PIC (SUMO): A ubiquitin-like protein associated with RanGAP. ▶[ubiquitin](#), ▶[UBL](#), ▶[sentrin](#), ▶[RanGAP](#), ▶[SUMO](#)

Pick Disease (FTDP-17, frontotemporal dementia and parkinsonism): A chromosome 17q21.11 dominant behavioral, cognitive, and motor disease involving variable loss and atrophy of the frontal and temporal part of the brain, caused by defects in the splicing of the Tau microtubule-associated protein. The mutations responsible for the conditions occur in exon 10 of Tau or in its 5'-splicing site, resulting in duplications in Tau mRNA (14q24.3). Frontotemporal dementia (FTD) may be tau-negative in case of mutation/loss of progranulin, a 68.5 kDa regulatory protein encoded at 17q21.31 (Baker M et al 2006 Nature [Lond] 442:916; Cruts M et al 2006 Nature

[Lond] 442:920). ►dementia, ►Parkinsonism, ►tau, ►RNAi

Picornaviruses: The single-stranded RNA genomes of picornaviruses, measuring about 7.2 to 8.4 kb (ca. 2.5 to 2.9×10^6 Da), are transcribed into four major polypeptides. Their RNA transcript lacks the 5' cap in the mRNA, characteristic for other eukaryotic viruses. A functional picornavirus IRES in a dicistronic mRNA may support the activity, not only of the downstream, but also of the upstream reporter gene at high salt concentrations in *cis*. Analysis of different experimental parameters influencing this effect shows that the enhanced availability of the initiation factor eIF4F provided by a functional picornavirus IRES on the same RNA molecule in *cis* causes this translation enhancement effect (Jünemann C et al 2007 J Biol Chem 282:132). They include *enteroviruses* (a group of mostly asymptomatic intestinal viruses. The paralytic *poliovirus* may also belong to this group). *Cardioviruses* (responsible for myocarditis [causing inflammation of the heart muscles] and encephalomyelitis [inflammation of the brain and heart]), *rhinoviruses* (in over 100 variants responsible for the common cold and other respiratory problems in humans and animals), and *aphthoviruses* (causing foot-and-mouth disease in cattle, sheep and pigs and occasionally infecting also people) are other types of picornaviruses. The *hepatitis virus* may also be classified among the picornaviruses. ►papovaviruses, ►animal viruses, ►coxsackie virus, ►polio virus, ►IRES, ►eIF-4F; Knipe DM et al (Eds.) 2001 Fundamentals of Virology, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania.

PIDD: A p53-inducible death domain protein, which promotes apoptosis. ►death domain, ►apoptosis, ►p53

PIE: Polyadenylation inhibition element. ►polyadenylation signal

Piebaldism: Piebaldism in animals is the result of hypomelanosis (low melanin), it is generally restricted to spots on the body; white spots occur on a black background. It may be a mutation of the KIT oncogene (4q12), or may be due to other factors. ►albinism, ►nevus, ►vitilego, ►melanin, ►Himalayan rabbit, ►mouse, ►pigmentation in animals, ►KIT oncogene, ►spotting, ►Hirschsprung disease, see Fig. P74.



Figure P74. Piebald rat

Pierre-Robin Syndrome: An autosomal recessive defect, involving the tongue (glossoptosis), small jaws (micrognathia), and sometimes cleft palate and syndactyly of toes. In an autosomal dominant form, reduced digit number (oligodactyly) is also found. There is also an X-linked form involving clubfoot and heart defect. Another X-linked form shows and increase in the number of the bones in the digits (hyperphalangy). (See terms under separate entries).

Piezoelectric Mechanism: By piezoelectric mechanism, crystalline material, under pressure, may generate electricity. Also, expansion and contraction may take place in matter in response to alternative electric current mechanical stress. This latter property has been exploited for insertion of cell nuclei into eggs after the destruction of its original egg nucleus. This type of nuclear transplantation may help achieve cloning of higher animals. ►nuclear transplantation

PIF: Proteolysis inducing factor.

PIG (*Sus crofa*): $2n = 38$. The domesticated breeds are the descendants of the crosses between the European wild boar and the Chinese pigs and they can still interbreed with the wild forms of similar chromosome number. The wild European pig is $2n = 36$. The Caribbean pig-like peccaries (*Tayassuidae*) are $2n = 30$. There are about 300 breeds of the domesticated pig. The various breeds of minipigs weigh generally less than 50 pounds as adults and are used for biomedical research. Sexual maturity sets in by about five to six months and the gestation period is about 114 days. It is a multiparous species with a litter size of 4–12. By adult somatic cell nuclear transplantation, live clones can be produced. ►animal genetics; Polejaeva IA et al 2000 Nature [Lond] 407:86; dispersal in Southeast Asia: Larson G et al 2007 Proc Natl Acad Sci USA 104: 4834; nuclear transplantation: <http://www.toulouse.inra.fr/lgc/pig/hybrid.htm>; <http://www.animalgenome.org/QTldb/>; <http://www.piggenome.org/>; <http://ascswine.rnet.missouri.edu/Description.html>; <http://www.piggis.org/>; <http://pig.genomics.org.cn/>.

Pigeon: *Columbia livia*, $2n = 80$. Great morphological variations among the various breeds of pigeons had already caught Darwin's attention, who made a few crosses between "pure races" and observed some "mendelian" patterns (see Fig. P75). Homing pigeons follow important landmarks such as railway tracks and highways as guided by their learned memory (Lipp H-P et al 2004 Curr Biol 14:1239). The "homing" ability, i.e., pigeons can return from great distances, is probably based on magnetoreception of the earth magnetic field facilitated by the upper beak

area and may be aided also by olfactory nerves (Mora CV et al 2004 Nature [Lond] 432:508).

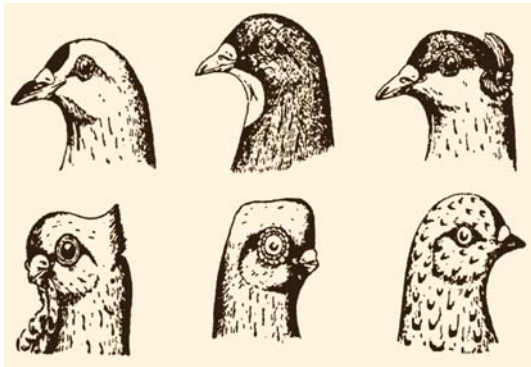


Figure P75. Variations in pigeons

PiggyBac: A cabbage moth (*Trichoplusia ni*) transposon-derived transformation vector of several different insect species. It is 2.5 kb with 13 bp inverted terminal repeats and contains a 2.1 kb open reading frame. Its specific target is TTAA. PiggyBac is particularly useful for large-scale and general disruption of *Drosophila* genes (Thibault S et al 2004 Nature Genet 36:283). PiggyBac efficiently transposes also in human and mouse cells (Ding S et al 2005 Cell 122:473). The high transposition activity of *piggyBac* and the flexibility for molecular modification of its transposase suggest the possibility of using it routinely for mammalian transgenesis (Wu SC-Y et al 2006 Proc Natl Acad Sci USA 103:15008). Frequently green fluorescent protein marker is used for its easy detection. ▶transposon, ▶open reading frame, ▶transposon vector, ▶sleeping beauty, ▶GFP; Handler AM et al 1998 Proc Natl Acad Sci USA 95:7520; Horn C et al 2003 Genetics 163:647; inducible piggyBac: Cadiñanos J, Bradley A 2007 Nucleic Acids Res 35(12):e87.

Pigment Epithelium-Derived Factor (PEDF): A potent inhibitor of angiogenesis of the retina. Its defect leads to opacity of vision and blindness. ▶angiostatin, ▶endostatin, ▶thrombospondin, ▶angiogenesis

Pigmentation Defects: ▶albinism, ▶piebaldism, ▶hypomelanosis, ▶incontinentia pigmenti, ▶pigmentation in animals, ▶LEOPARD syndrome, ▶Fanconi anemia, ▶hematochromatosis, ▶neurofibromatosis, ▶tuberous sclerosis, ▶Waardenburg syndrome, ▶Hermansky-Pudlak syndrome, ▶polyposis hamartomatous, ▶Addison disease, ▶focal dermal hypoplasia, ▶erythralgia, ▶skin diseases

Pigmentation of Animals: In mammals, tyrosine is the primary precursor of the complex black pigment

melanin. The enzyme tyrosinase (located in the melanosomes) hastens the oxidation of dihydroxyphenylalanine (DOPA) into dopaquinone, which is changed by non-enzymatic process into leukodopachrome. Leukodopachrome is an indole-derivative that is oxidized also by tyrosinase into an intermediate of 5,6-dihydroxyindole. After another step of oxidation, indole-5,6-quinone is formed. Coupling the latter to 5,6-dihydroxyindole is the first step in the addition of further dihydroxyindole units in the process of polymerization to melanin. When cysteine is combined with dopaquinone, through a series of steps, reddish pigments are formed in hair and feathers. The different pigments may have also other adducts at one or more positions to yield various colors. In the formation of the eye color of insects, tryptophan is a precursor to the formation of formylkynurenine → kynurenine → hydroxykynurenine → ommin, ommatin. The catabolic pathway of amino acids contributes to the formation of guanine and through the latter to pteridines that contribute to the coloration of insects, amphibians, and fishes, and serves also as a light receptor. The Xanthopterin and leucopterin account for the yellow and white pigmentation of butterflies, sepiapterin, is found in the eyes of *Drosophila* and biopterin is found in the urine and liver of mammals. The degradation of the heme group yields a linear tetrapyrrole from which the bile pigment biliverdin and ultimately bilirubin diglucuronide is synthesized. Bilirubin diglucuronide is secreted into the intestines and may accumulate in the eyes and other organs causing jaundice when the liver does not function normally. Oxidized derivatives of bilirubin, urobilin, and stercobilin color the urine. Mutations were detected already during the early years of genetics that block the biosynthetic paths of these pigments and thus contribute to understanding how genes affect the phenotype. The color of the skin in humans is determined by its melanin content. Pheomelanin is a reddish pigment and eumelanin is black. The former is responsible for the light skin and red hair color and it also potentially generates free radicals and thus may make the individual susceptible to UV damage. Eumelanin provides protection against UV. The melanocyte-stimulating hormone (MSH) and its receptor (MC1R) regulate the relative proportion of these two melanins. A putative cation exchanger (SLC24A5, human chromosome 15q21) has modulatory effect on the formation of melanosomes and due to different single nucleotide polymorphisms has impact on the determination of pigmentation, depending also on the climatic regions and exposure to sunlight (Lamson RL et al 2005 Science 310:1782). In mice, about 100 genes are known that control pigmentation. Differences in the pigmentation of the

human skin in various geographic areas of the world seem to be correlated with the degree of exposure to ultraviolet radiation. ▶chorismate, ▶tryptophan, ▶tyrosine, ▶phenylalanine, ▶albinism, ▶melanin, ▶eye color in humans, ▶Himalayan rabbit, ▶Siamese cat, ▶pigmentation in plants, ▶agouti, ▶melanocyte-stimulating hormone, ▶hair color, ▶tanning, ▶opiocortin; hair and skin color: Rees JL 2003 Annu Rev Genet 37:67; Price T Borntrager A 2001 Curr Biol 11:R405; evolution, genetics, physiology [folate, vitamin D, UV light exposure] and variation in human skin color: Jablonski NG 2004 Annu Rev Anthropol 33:585; Sturm RA 2006 Trends Genet 22:464; Lin JY, Fisher DE 2007 Nature [Lond] 445:843.

plgR (polymeric immunoglobulin receptor): ▶antibody polymers

P_{II}: P_{II} proteins (are involved in bacterial glutamine synthesis) accelerate hydrolysis of NtrC in the presence of NtrB and ATP in limited N supply and low levels of 2-ketoglutarate. P_{II} uridylylation permits the increase of NtrC-phosphate level and increases transcription from the glnAp2 promoter. In excess N supply, P_{II} is not altered resulting in no NtrC build-up and glnA2 activation ceases. ▶NtrB, ▶NtrC, ▶glnAp

PI3K (PI(3)K): ▶PIK

PIK/PI(3)K (phosphatidylinositol kinases): PI(3)K preferentially phosphorylates the 3 and 4 positions on the inositol ring. PIK-catalyzed reaction products (PtdIns) are second messengers. They participate in meiotic recombination, immunoglobulin V(D)J switches, chromosome maintenance and repair, progression of the cell cycle, etc. The mouse Pik3r1 regulatory gene encodes proteins p85 α , p55 α , and p50 α . p55/p50 are essential for viability. Their defect may lead to immunological disorders and cancer. In ovarian cancer, increase of PIK3CA and increased PIK activity were detected. In different types of human cancers, mutations in the catalytic subunit is high (Samuels Y et al 2004 Science 304:554). PIK inactivation of its γ -subunit may lead to invasive colorectal cancer in mice. PI3K γ may signal to phosphokinase B or to MAPK. PI3K is negatively controlled by PTEN. PIK related kinases are TOR, FRAP, TEL, MEI, and DNA-PK. Their inhibitor is wortmannin. ATM, ATR, DNA-P-related protein kinases, ATRIP, and Ku80 share a terminal amino acid sequence motif (734 AKEESLADDLFRYN-PYLKRRR) of the Nijmegen breakage syndrome (Nbs1) protein that recruits these kinases to the site of DNA damage and cell cycle checkpoint control and repair (Falck J et al 2005 Nature [Lond] 434:605). The nuclear GTPase PIKE enhances PIK activity and

is regulated by protein 4.1N. ▶phosphatidylinositol, ▶second messenger, ▶immunoglobulins, ▶DNA repair, ▶ATM, ▶ATR, ▶DNA-PK, ▶Ku, ▶ATRIP, ▶Nijmegen breakage syndrome, ▶cell cycle, ▶wortmannin, ▶MEC1, ▶phosphoinositides, ▶PTEN, ▶protein 4.1N, ▶colorectal cancer, ▶chemotaxis, ▶Langerhans islets; Kuruvilla FG, Schreiber SL 1999 Chem Biol 6:R129; Katso R et al 2001 Annu Rev Cell Dev Biol 17:615.

Pileus: The umbrella-shaped fleshy mushroom fruiting body. Also, it is a membrane that may be present on the head of newborns.

Pilin: The protein material of the pilus. ▶pilus

Pilomatricoma: Usually benign, calcifying skin tumors, densely packed by basophilic cells and developing into hair follicle-like structures. Their origin is attributed to mutation in LEF/ β -catenin. ▶LEF, ▶catenins, ▶basophil, ▶follicle

PILR α : Inhibitory receptor of myeloid cell encoded at human chromosome 7q22. ▶ITIM

Pilus: A bacterial appendage, which may be converted into a conjugation tube through which the entire or part of the replicated chromosome is transferred from a donor to a recipient cell (see Fig. P76). It may also serve as protein conduit. In pathogenic enterobacteria (*Neisseria gonorrhoea*, *Vibrio cholerae*) and in some types of *E. coli*, the so-called pilus type IV may be formed. It facilitates bacterial aggregation (bundle-forming pilus, BFP, encoded by a 14-gene operon), and the expression of the LEE (enterocyte effacement) element enhances the association of the bacteria with the mucous intestinal membranes and triggers diarrhea. The pilin protein may undergo antigenic variation to escape host defenses. The pilus may also form an attachment to the invaded eukaryotic cell. ▶conjugation, ▶conjugation mapping, ▶PapD, ▶pilin, ▶antigenic variation, ▶mating bacterial, ▶shoufflon, ▶pseudopilus [ψ -pilus]; Jin Q, He S-Y 2001 Science 294:2556.

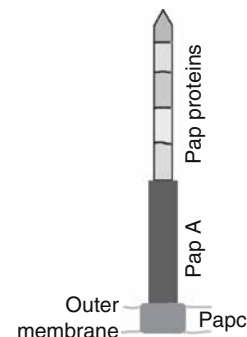


Figure P76. Pilus

PIM Oncogene: The PIM oncogene is located in human chromosome 6p21-p12 and in mouse chromosome 17. The gene is highly expressed in blood-forming (hematopoietic) cells and myeloid cells and over-expressed in myeloid malignancies and some leukemias. The human protein is a serine/threonine kinase. ▶[oncogenes](#), ▶[serine/threonine kinases](#)

Pimento (*Pimento dioica*): Also called allspice. Tropical dioecious spice tree; $2n = 2x = 22$.

PIN1: A peptidyl-prolyl cis/trans isomerase in human cells. It is important for protein folding assembly and/or transport. Its deficiency leads to mitotic arrest, while its overproduction may block the cell cycle in G2 phase. It interacts with NIMA kinase. PIN1 membrane protein of plants regulates auxin transport. ▶[cell cycle](#), ▶[NIMA](#), ▶[parvulin](#)

PIN⁺: The prion form of the yeast protein Rnq1. ▶[prion](#); Bradley ME, Liebman SW 2003 Genetics 165:1675.

pin: The promoter of the transposase gene of a transposon. There are two GATC sites involved in *dam* methylation within pin. ▶[RNA-IN](#), ▶[dam](#)

Pinch: A group of proteins with LIM and additional domain(s). ▶[CRP](#), ▶[LMO](#), ▶[LIM domain](#)

Pineal Gland: The site of melatonin synthesis and photoreception in the brain. ▶[melatonin](#), ▶[opsins](#), ▶[Rabson-Mendenhall syndrome](#), ▶[brain](#)

Pineapple (*Ananas comosus*): A monocotyledonous tropical or subtropical plant ($2n = 50, 75, 100$). The flowers and bracts sit on a central axis and form fleshy fruits. The lack of seeds is caused by self-incompatibility of the commercial varieties but they develop seeds if allowed to cross-pollinate with other varieties. ▶[seedless fruits](#)

Pines (*Pinus* spp): Trees, all 94 species are $2n = 2x = 24$. ▶[spruce](#)

Ping-Pong Kinetics: The property of some dimeric or multimeric enzymes catalyzing two “half reactions.” First, they release the first product and form an enzyme intermediate before binding of the second substrate. After the second reaction and release of the product, the enzyme returns to the initial state. (See Frank RAW et al 2004 Science 306:872).

Pinna: The ear lobe, the lobe of a compound leaf or frond. ▶[hairy ear](#)

Pinning: Pinning uses a floating replication tool with about 100 or more pinheads to test yeast colonies on different culture media. ▶[replica plating](#)

Pinocytosis: The formation of ingestion vesicles for fluids and solutes by the invagination of membranes of eukaryotic cells. ▶[phagocytosis](#), ▶[endocytosis](#)

Pinosome: A small cytoplasmic vesicle originating by invagination of the cell membrane. ▶[endocytosis](#)

PinPoint Assay: The PinPoint assay identifies single nucleotide polymorphism (SNIP). The polymorphic DNA site is extended by a single nucleotide with the aid of a primer annealed immediately upstream to the site. The extension products are analyzed by MALDI-TOF mass spectrophotometry. ▶[SNIP](#), ▶[primer extension](#), ▶[MALDI-TOF](#); Haff LA, Smirnov IP 1997 Genome Res 4:378.

PIN*POINT (protein position identification with a nuclease tail): An in vivo method to ascertain the position of the critical promoter-binding proteins involved in the LCR. Fusion proteins with an unspecific nuclease tail are studied for how the cleavage position affects the expression of the gene (s). ▶[LCR](#); Lee J-S et al. 1998 Proc Natl Acad USA 95:969.

PIP: Phosphatidylinositol phosphate. ▶[phosphoinositides](#), ▶[PIP2\[PIP₂\]](#), ▶[PIP3](#)

PIP2: Phosphatidylinositol (4,5)-bisphosphate is involved (with PIP3) in mediating the inositol phospholipid signaling pathway and in the activation of phospholipase C (PLC). PIP₂ also controls the ATP-regulated potassium ion channel (K_{ATP}) by binding to the intracellular C-domain of the channel protein and interfering with the binding of ATP. Since K_{ATP} channels affect pancreatic β cells and vascular and cardiac muscle tone, they may have relevance for human diseases, e.g., diabetes. Pleckstrin homology domains selectively bind phosphoinositides. ▶[phosphoinositides](#), ▶[PITP](#), ▶[ion channels](#), ▶[diabetes](#), ▶[InsP](#), ▶[pleckstrin](#), ▶[TIRAP](#); Martin TF 2001 Curr Opin Cell Biol 13:493.

PIP3 (phosphoinositol-3,4,5-trisphosphate): An intracellular messenger and stimulator of insulin, epidermal growth factor, etc., that works by adding another phosphate to PIP2 and activating PKB. ▶[PKB](#), ▶[PTEN](#), ▶[chemotaxis](#), ▶[InsP](#); Hinchliffe KA 2001 Curr Biol 11:R371.

Pipecolic Acid (homoproline): An intermediate in lysine catabolism (see Fig. P77). Increase of pipecolic acid (hyperpipecolathemia/hyperpipecolicacidemia) in the blood plasma and urine leads to increase in the size of the liver (hepatomegaly), resulting in growth retardation, vision defects, and demyelination of the nervous system.

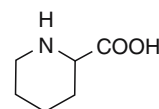


Figure P77. Pipecolic acid

Pipes (piperazine-*N,N'*-bis(2-ethanesulfonic acid): A buffer within the pH range of 6.2–7.3.

PIR (protein information resource): ►MIPS; <http://pir.georgetown.edu/>.

PIR-A, PIR-B: Immunoglobulin-like regulatory molecules (activator/inhibitor) on murine B cells, dendritic cells, and myeloid cells. A single gene encodes Pir-B whereas a multigene family encodes the six Pir-A proteins. ►ITIM; Dennis G Jr et al 1999 J Immunol 163:6371.

Piriformospora indica: Root endophytic fungus that may associate with both dicotyledonous and monocotyledonous plants and convey resistance to fungal disease, salt tolerance, improved nitrogen metabolism, and lead consequently to higher yield. ►symbiont, ►host–pathogen relationship, ►salt-tolerance; Waller F et al 2005 Proc Natl Acad Sci USA 102:13386.

piRNA (Piwi interacting RNA): 26-31-nucleotide-long RNA regulating germ and stem cell development when bound to Argonaute family proteins (Aubergine, Piwi, Ago3). In mouse, the MIWI/Piwi RNA associates with the polysomes and chromatoid body during spermatogenesis (Grivna ST et al 2006 Proc Natl Acad Sci USA 103: 13415). It is involved also in regulating transposons activity (Brennecke J et al 2007 Cell 128:1089). ►RNAi, ►Argonaute, ►chromatoid body, ►Slicer; Aravin A et al 2006 Nature [Lond] 442:203; Girard A et al 2006 Nature [Lond] 442:199; review: O'Donnell KA, Boeke JD 2007 Cell 129:37.

PISA (protein in situ assay): In the PISA assay, PCR-generated DNA fragments are transcribed and translated in a cell-free protein expression system on a coated microtiter plate where the protein was immobilized. Single chain antibody fragments and luciferase have been successfully arrayed. ►PCR; He M, Taussig MJ 2001 Nucleic Acids Res 29(15):E73.

Pistil: A central structure of flowers (gynecium) consisting of the stigma, style, and ovary. ►gametophyte female, ►gametophyte male, ►flower differentiation

Pistillate: Flower or plants that carries the female sexual organs. A female parent in plants.

Pisum sativum (pea): A legume ($2n = 14$). It played an important role in establishing the Mendelian principles of heredity and contributed further information on genetics. Curiously, the famous “wrinkled” gene of Mendel turned out to be an insertional mutation. ►pea

Pit: An indentation. Also, the stony endocarp of some fruits, e.g., plums, apricot, cherry.

Pitalre (cdk9): ►acquired immunodeficiency, ►TEFb; Darbinian N et al 2001 J Neuroimmunol 121:3

Pitch: The length of a complete turn of a spiral (helix) and the translation per residue is the pitch divided by the number of the residues per turn. In a keratin alpha helix, it is $0.54 \text{ nm}/3.6 = 0.15 \text{ nm}$. Also, a dark black residue after distillation. The auditory pitch is the physiological response of the ear to sound depending on the frequency of vibration of the air. Pitch-selective neurons are located in the auditory cortex of the brain in monkeys and humans (Bendor D, Wang X 2005 Nature [Lond] 436:1161). Perfect/absolute pitch is ability for recognizing musical notes by talented artists. ►musical talent, ►prosody

Pith: The parenchyma tissue in the core of plant stems, e.g., in elderberry (*Sambucus*).

Pithecia (saki monkey): ►Cebidae

PITP (phosphatidylinositol transfer proteins, 35 and 36 kDa): PITP is required by for the hydrolysis of PIP₂ (phosphatidyl-inositol bis-phosphate) by PLC (phospholipase C). In a GTP-dependent signal pathway, PITP is required also by epidermal growth factor (EGF) signaling. ►PIP, ►PIP₂, ►EGF, ►GTP, ►phosphoinositides; Cockcroft S 1999 Chem Phys Lipids 98:23.

PI-TR: Phosphatidylinositol transfer protein involved in transfer of lipids among organelles within cells.

PITSRE: Members a cyclin-dependent protein kinase family involved in RNA transcription or processing. They are associated with ELL2, TFIIF, TFIIS, and FACT. ►ELL, ►transcription factors, ►TFIIS, ►protein 14-3-3; Trembley JH et al 2002 J Biol Chem 277:2589.

Pituitary (hypophysis): The hypophysis is located at the base of the brain and is connected also to the hypothalamus (a ventral part of the brain). The anterior part secretes the pituitary hormones and the posterior part stores and releases them. ►brain human, ►gonads, ►septo-optic dysplasia; Fauquier T et al 2001 Proc Natl Acad Sci USA 98:8891; Scully KM, Rosenfeld MG 2002 Science 295:2231.

Pituitary Dwarfism: Pituitary dwarfism is due to recessive mutation, deletion, or unequal crossing over in the gene cluster containing somatotropin and homologs in human chromosome 17q22-q24. Administration of somatotropin may restore growth. The defect may also be in the hormone receptor (human chromosome 5p13.1-p12, mouse chromosome 15) and in these cases, the growth hormone

level may be high (Laron types of dwarfisms). The level of somatomedin (insulin-like growth factors) may also be low. Somatomedin is a peptide facilitating the binding of proteins and in addition shows insulin-like activity. In either case, dwarfism may result. Dominant-negative mutations in IGHD2 (isolated growth hormone deficiency) are also known. ►dwarfism, ►GH, ►insulin-like growth factor, ►hormone receptor, ►binding protein, ►stature in humans, ►pituitary gland, ►growth hormone pituitary; Machinis K et al 2001 Am J Hum Genet 69:961.

Pituitary Hormone Deficiency, Combined Familial: The pituitary hormone deficiency fails to produce normally one or more of these hormones—growth hormone (HGH), prolactin, and thyroid-stimulating hormone (TSH)—because of mutation in the POU1F1 gene (3p11). Mutation in the PROP1 gene (5q), however, cannot produce luteinizing hormone (LH) and follicular stimulating hormone (FSH). Corticotropin deficiency is caused by mutation in the LHX4 gene. LHX3 is a homeobox gene with LIM repeats. ►animal hormones

Pituitary Tumor (GNAS1, 20q13.2): Pituitary tumor is caused by autosomal dominant mutations in the α chain of a G-protein (G_s). This protein is also called gsp (growth hormone secreting protein) oncoprotein. The human securin, mediating sister chromatid cohesion, has substantial sequence homology with the pituitary tumor-transforming gene. Securin may block sister chromatid separation and thereby can be responsible for chromosome loss or gain, common characteristics of tumors. ►G-protein, ►McCune-Albright syndrome, ►sister chromatid cohesion

Piwi: ►piRNA

Pixel: A picture element in the computer that represents a bit on the monitor screen or in the video memory. ►bit, ►byte

pK_a: The negative logarithm of the dissociation constant K_a; stronger acids have higher pK_a whereas weaker acids have lower. The dissociation of weaker acids is higher and that of stronger acids is lower. (See <http://www.jenner.ac.uk/PPD/>).

PKA: Protein kinase A (activated by cAMP). There are two types, PKA-I and PKA-II; they share a common catalytic subunit (C) but distinct regulatory subunits, RI and RII. RI/PKA-I controls positively cell proliferation and neoplastic growth. RII/PKA-II controls growth inhibition, differentiation, and cell maturation. RI is detectable in many types of cancers. Antisense methylphosphonate RNA of the RI_α subunit has been known to arrest proliferation of cancer cells without toxicity to normal cells. ►protein

kinases, ►antisense technologies, ►cocaine, ►export adaptors

PKB (protein kinase B): A serine/threonine kinase, the same as Rac or Akt. It is activated by phosphatidylinositol-3,4,5-trisphosphate by binding to its pleckstrin homology domain. ►CaM-KK, ►protein kinases, ►phosphoinositides, ►pleckstrin domain

PKC: Protein kinase C. ►protein kinases

PKD: ►polycystic kidney disease

PKI (protein kinase I): A small protein, which attaches to the catalytic subunits of the heterotetrameric PKA and, with the aid of its nuclear localization sequence (NES), sends the complex to the nucleus. ►export adaptors, ►PKA, ►nuclear localization sequence

PKR: A double-stranded RNA-dependent serine-threonine protein kinase, involved in NF- κ B signaling. One of the most important targets of PKR is the eIF-2A translation factor and thus, protein synthesis. It may control cell division, apoptosis, and may serve as tumor suppressor. Translation is required for viral infection of mammalian cells. Viral infection may trigger the activation PKR as a defense against infection through shutting off protein synthesis. PKR inhibits protein synthesis by autophosphorylation and phosphorylation of the Ser51 residue of eIF2 α . Mutation at the Thr446 site prevents autophosphorylation at the catalytic domain activation segment and impairs phosphorylation of eIF2 α and viral binding (Dey M et al 2005 Cell 122:901). The PKR active cell may succumb to apoptosis but the animal may survive. Several viruses (adenovirus, vaccinia virus, HIV-1, hepatitis C, poliovirus, SV40, etc.) use various mechanisms to inhibit activation of PKR by interfering either with its dimerization or RNA binding, or regulation of eIF-2A, etc. PKR preferentially binds mutant huntingtin protein in Huntington disease. ►NF κ B, ►oncolytic virus, ►reovirus, ►eIF-2A, ►PERK, ►interferon, ►apoptosis, ►Huntington's chorea; Kaufman RJ 1999 Proc Natl Acad Sci USA 96:11693.

PKS Oncogenes: PKS oncogenes are located in human chromosomes Xp11.4 and 7p11-q11.2. These genes display very high homology to oncogene RAF1 and apparently encode protein serine/threonine kinases. ►raf, ►oncogenes

PKU: ►phenylketonuria

PLAC: Plant artificial chromosome. ►artificial chromosome, ►YAC

Place Cells: Place cells in the brain are the locations for the firing of specific nerve cells.

Placebo: A presumably inactive but similar substance used in parallel to different individuals in order to serve as a concurrent (unnamed) control for testing the effect of a drug. In some instances the placebo has positive effects not by physical or chemical properties but by expectation-caused dopamine release, e.g., in Parkinson disease. ▶concurrent control, ▶double-blind test; de la Fuente-Fernández R et al 2001 Science 293:1164; Ramsay DS, Woods SC 2001 Science 294:785.

Placenta: The maternal tissue that is in most intimate contact with the fetus through the umbilical chord, found within the uterus of animals. Most commonly, the placenta is located on the side of the uterus; the placenta praevia is situated at the lower part of the uterus. The latter situation may be correlated with the age of the mother. Also, placenta refers to the wall of the plant ovary to which the ovules are attached. During pregnancy, the placenta of eutherian mammals includes both maternal and zygotic tissues in close association (feto-maternal interface). The interaction between these two types of tissues is essential for normal embryo development and viability of the conceptus. In normal pregnancy, the uterus is invaded by the cytotrophoblasts (the nutritive cells of the conceptus) but defects in the cell adhesion system may adversely affect the pregnancy and may lead to eclampsia. In embryonic tissues of mouse, after 10.5 day hematopoietic stem cells develop to an extent comparable to the aorta-gonad-mesonephros (AGM) region (Gekkas C et al 2005 Dev Cell 8:365). The mesonephros is part of the embryonic kidney tissue. ▶eclampsia, ▶imprinting, ▶incompatibility; Zhou Y et al 1993 J Clin Invest 91:950; Georgiades P et al 2001 Proc Natl Acad Sci USA 98:4522; placenta of animal species: <http://medicine.ucsd.edu/cpa/>.

Placode: A heavy embryonal plate of the ectoderm from which organs may develop. ▶ecto-derm, ▶AER, ▶ZPA, ▶organizer, ▶neural crest, ▶germ-layer

PLADs (pro-ligand-binding assembly domains): aggregate the (death) receptors before binding the ligands. ▶death receptors

Plagiarist: ▶publication ethics, ▶ethics

Plague: The term plague has been used to loosely define widespread, devastating diseases. Strictly, the term applies today to infection by the *Pasteurella pestis* (*Yersinia pestis*) bacterium. The disease may occur in three main forms: *bubonic* plague (most important diagnostic features of is swelling lymph nodes, particularly in the groin area), *pneumonic* plague (attacking the respiratory system) and *septicemic* plague (causing general blood poisoning). Many of its symptoms overlap with those of other infectious

diseases. A 1°C increase in spring temperature and wetter summers may increase the carrier gerbil (rodent) population and can result in >50% increase of the prevalence of plague in Central Asia (Stenseth NC 13110). It used to be known also as the “black death” on account of the dark spots, appearing in largely symmetrical necrotic tissue with coagulated blood. The bacilli spreads to human populations from rodents by fleas, but infections occur also through cough drops of persons afflicted by pneumonic plague. Various animal diseases are also called plague (*pestis*) but, except those in rodents, are caused by other bacteria or viruses. Pasteurellosis can be effectively treated with antibiotics although some strains become resistant to a particular type of antibiotics (streptomycin, chloramphenicol). Eradication of rodent pests is the best measure of prevention. During the great epidemics in the 14th century, the disease claimed an estimated 25 million victims. Sporadic occurrence is known even today in the underdeveloped areas of the world. ▶zoonosis, ▶*Yersinia*, ▶plant vaccines, ▶biological weapons; Parkhill J et al. 2001 Nature [Lond] 413:523.

Plakin: >200 kDa dimeric, coiled coil, actin-binding proteins forming molecular bridges between the cytoskeleton and other subcellular structures. They also bind microtubules. ▶cytoskeleton, ▶filaments, ▶microtubule; Jefferson JJ et al 2007 J Mol Biol 366:244.

Plakoglobin: 83 kDa protein localized to the cytoplasmic side of the desmosomes. ▶desmosome, ▶adhesion, ▶desmoplakin

Planar Cell Polarity (PCP): PCP is determined by several genes involved in embryonal development, neural tubes, cochlear sensory hair cells of the ear, etc.

Planarians (flatworms): Relatively simple carnivorous organisms inhabiting fresh waters. There are about 15,000 species, all with bilateral symmetry and elaborate digestive tract and nervous system. They are well suited for studies of regeneration. The tapeworms and flukes are serious human parasites. ▶flatworm, ▶regeneration; <http://planaria.neuro.utah.edu/>.

Planck Constant (h): A constant of energy of a quantum of radiation and the frequency of the oscillator that emitted the radiation. $E = h\nu$ where E = energy, ν = its frequency; numerically 6.624×10^{-27} erg^{-s}.

Plankton: The collective name of many minute free-floating water plants, animals, and prokaryotes. ▶phytoplankton, ▶bacterioplankton; microbial oceanography: DeLong EF, Karl DM 2005 Nature [Lond] 437:336; Giovannoni SJ, Stingl U 2005 Nature [Lond] 437:343; Arrigo KR 2005 Nature

[Lond] 437:349; viruses in the sea: Suttle CA 2005 Nature [Lond] 437:356; genetic and metabolic survey of microbial plankton from 10 m to 4000 m oceanic depth: DeLong EF et al 2006 Science 311:496.

Plant Breeding: An applied science involved in the development of high-yielding food, feed, and fiber plants. It is concerned also with the production of lumber, renewable resources of fuel, and many types of industrial raw products (such as latex, drugs, cosmetics, etc.). A major goal of plant breeding is to improve the nutritional value, safety, disease resistance, and palatability of the crops. Plant breeding and technological improvements in agriculture have resulted in a near 10-fold increase in maize production and doubled wheat yields in the twentieth and twenty-first century. Plant breeding is based on population and quantitative genetics, and biotechnology. (Mazur B et al 1999 Science 285:372).

Plant Defense: Plant defense against herbivores is mediated by the signaling peptide *systemin* activating a lipid cascade. Membrane linolenic acid is released by the damage and converted into phytodienoic and jasmonic acids, structural analogs to the prostaglandins of animals. As a consequence, tomato plants produce several systemic *wound response proteins*, similar to those elicited by oligosaccharides upon pathogenic infections. Mutation in the octadecanoic (fatty acid) pathway blocks these defense responses. ▶host-pathogen relations, ▶insect resistance in plants, ▶jasmonic acid, ▶prosta-glandins, ▶fatty acids, ▶systemin, ▶oleuropein

Plant Disease Resistance: ▶host-pathogen relation, ▶plant defense

Plant Genomes: Plant genomes generally differ in size and organization from those in animals and pose new problems and answer unique questions of analysis. (See Peterson AH 2006 Nature Rev Genet 7:174).

Plant Genomics Database: <http://sputnik.btk.fi>; plant molecular markers: <http://markers.btk.fi>; see also crop plants and individual plant species in the alphabetical order.

Plant Hormones: Auxins, gibberellins, cytokinins, abscisic acid, brassinosteroids, jasmonate, and ethylene. Polypeptide hormones play roles in the defense systems of plants (Ryan CA et al 2002 Plant Cell 14:251). The natural *auxin* in plants is indole-3-acetic acid (IAA) but a series of synthetic auxins are also known such as dichlorophenoxy acetic acid (2,4-D), naphthalene acetic acid (NAA), indole-butyric acid (IBA), etc. Auxins are involved in cell elongation, root development, apical dominance, gravi- and phototropism, respiration, maintenance of membrane

potential, cell wall synthesis, regulation of transcription, etc. The bulk (≈95%) of IAA in plants is conjugated through its carboxyl end to amino acids, peptides, and carbohydrates. The conjugate regulates how much IAA is available for metabolic needs, although some conjugates may be directly active as hormones. Enzymes have been identified that hydrolyze the conjugates. Over the developing tissues, auxins show concentration gradients, indicating its role in positional signaling similarly to animal morphogens. The conjugates may transport IAA within the plant. *Gibberellic acid* and gibberellins control stem elongation, germination, and a variety of metabolic processes. *Cytokinins* also occur in a wide variety of forms such as kinetin, benzylamino-purine (BAP), isopentenyl adenine (IPA), zeatin, etc. Their role is primarily in cell division but they regulate the activity of a series of enzymes. Regeneration of plants from dedifferentiated cells requires a balance of auxins and cytokinins. *Abscisic acid* and terpenoids control abscission of leaves and fruits, dormancy and germination of seeds and a series of metabolic pathways. *Ethylene* was recognized as a *bona fide* plant hormone more recently. It is involved in the control of fruit ripening, senescence, elongation, sex determination, etc. The hormone type action of *brassinosteroids* in controlling elongation and light responses has been recognized by genetic evidence only in 1996. *Jasmonic acid* is also a hormone like substance with role in parasite defense. Generally, the various plant hormones signal to each other and their dynamic cooperative effects are essential for plant responses (Schmelz EA et al 2003 Proc Natl Acad Sci USA 100:10552). A survey indicated that hormones affected 4666 genes of *Arabidopsis* but most commonly different hormones regulated distinct members of protein families (Nemhauser JL et al 2006 Cell 126:467). ▶hormones, ▶signal transduction, ▶abscisic acid, ▶ethylene, ▶indole acetic acid, ▶jasmonic acid, ▶gibberellic acid, ▶kinetin, ▶zeatin, ▶brassinosteroids, ▶seed germination; Kende H 2001 Plant Physiol 125:81; Mok DWS, Mok MC 2001 Annu Rev Plant Physiol Mol Biol 52:89; <http://www.ualr.edu/botany/hormimages.html>.

Plant Pathogenesis: Plant pathogens pose risks for agricultural, horticultural, and forest plants and may damage natural habitats of different organisms, plants as well as animals. Several plant pathogens and saprophytes may pose human health hazards, especially for immunologically compromised individuals. (See Vidaver AK, Tolin S 2000 In: Fleming DO, Hunt DL (Eds.) Biological Safety, ASM, Washington DC, pp 27–33; ▶host-pathogen relation; <http://www.pathoplant.de>.

Plant Vaccines: Transgenic plants may express immunogenic proteins, which by consuming the plant tissues by humans or animals, may protect against bacterial or viral diarrhea. Also, plant synthesized immunoglobulins may protect against *Streptomyces mutans*, responsible for dental caries and gum disease. Hepatitis B surface antigen (HBsAg), Norwalk virus capsid protein (NVCP), *E. coli* heat-labile enterotoxin B subunit (LT-B), cholera toxin B subunit (CT-B), and mouse glutamate decarboxylase (GAD67) have been propagated in tobacco and potato tissues, respectively. Hepatitis B vaccine delivered by raw potatoes—when a sufficient quantity was consumed—increased the serum antiHB surface antigen titer in up to 62.5% of the volunteers (Thanavala Y et al 2005 Proc Natl Acad Sci USA 102:3378). So far, these edible vaccines have not shown clinical use. The S1 protein of the SARS corona virus propagated in tomato and tobacco plants displayed good immunogenicity in mice after both parenteral (injection) and oral administration. This result is similar to the early tests of gastroenteritis vaccine in swine and the infectious bronchitis virus vaccination of chickens by plant vaccines (Progrebnyak N et al 2005 Proc Natl Acad Sci USA 102:9062). Apparently, very effective vaccines can be produced by introducing into plants (tobacco) the F1 and V and the F1–V fusion antigens of *Yersinia*, the agent of plague (Santi L et al 2006 Proc Natl Acad Sci USA 103:861). Vaccinia virus antigenic domain B5 propagated in tobacco and collard plants when introduced orally in mice or the minipig (miniature pig) did not generate an anti-B5 immune response, but intranasal administration of soluble pB5 led to a rise of B5-specific immunoglobulins, and parenteral immunization led to a strong anti-B5 immune response in both mice and the minipig. Mice immunized i.m. (intramuscularly) with pB5 generated an antibody response that reduced smallpox virus spread in vitro and conferred protection from challenge with a lethal dose of vaccinia virus (Golovkin M et al 2007 Proc Natl Acad Sci USA 104:6864). ▶vaccines, ▶immunoglobulin, ▶transformation genetic, ▶plantibody, ▶TMV, ▶SARS, ▶plague, ▶*Yersinia*, ▶bronchitis, ▶gastroenteritis; Daniell H et al 2001 J Mol Biol 311:1001; Ruf S et al 2001 Nature Biotechnol 19:870; Sojikul P et al 2003 Proc Natl Acad Sci USA 100:2209.

Plant Viruses: Plant viruses vary a great deal in size, shape, genetic material, and host-specificity. The majority of them have single-stranded positive-strand RNA as genetic material and are either enveloped or not. The Reoviridae may have several double-stranded RNAs, and the Cryptovirus carries two

double-stranded RNAs. The Cauliflower (Caulimo) virus has double-stranded DNA, whereas the Geminiviruses have single-stranded DNA genetic material. The size of their genome usually varies between 4 to 20 kb and their coding capacity is at least four proteins. The 5'-end may form methylguanine cap or it may have a small protein attached to it. The 3'-end may have a polyA tail or may resemble the OH end of the tRNA. Approximately, 600–700 plant viruses have been described. ▶viruses, ▶cap, ▶polyA tail, ▶tRNA, ▶viroid, ▶TMV, ▶CaMV, ▶geminivirus, ▶viroid; Knipe DM et al (Eds.) 2001 Fundamental Virology, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania; Harper G et al 2002 Annu Rev Phytopathol 40:119; Tepfer M 2002 Annu Rev Phytopathol 40:467; general virus database, including plant viruses: <http://www.ncbi.nlm.nih.gov/ICTVdb/ictvdb.htm>.

Plantibody (antibody synthesized by plants): A modified immunoglobulin produced in transgenic plants carrying the genetic sequences required for the recognition of the site of the viral coat or other proteins. The yield of the plantibody molecules is very high, up to 1% of the soluble plant proteins. The modification of the immunoglobulin involves usually the elimination of the constant region of the heavy chain while retaining the variable region. The plant antibodies are usually formed as single chains (ScFv). Other modifications for solubility and tissue-specific expression may be introduced. The plantibodies are modified also by intrinsic plant mechanisms (N-glycosylation) within the endoplasmic reticulum. Unfortunately, plant tissue lack β 1,4-galactosyltransferase, which is required for the synthesis of mammalian-like glycans. By transformation, the gene of this enzyme has been transferred into tobacco plants and it functions normally. Retention and excretion of ScFv immunoglobulin molecules is increased if the KDEL amino acid sequence is present in the polypeptide chain. For some medical applications, the plantibodies may not be suitable because they may carry plant-specific β -1,2-xylose and α -1,3-fucose residues at the galactose-carrying N-glycans and cause allergic reactions in monoclonal antibodies. When, however, a hybrid enzyme called XylGalT that consists of the N-terminal domain of the *Arabidopsis* xylosyltransferase and the catalytic domain of human β -1,4-galactosyltransferases is used in tobacco plants, the core-bound xylose and fucose residues are sharply reduced. This type of monoclonal plantibody thus appears promising (Bakker H et al 2006 Proc Natl Acad Sci USA 103:7577). Single-chain variable fragment (scFv)-Fc (fragment crystalline) antibodies, with N-terminal

signal sequence and C-terminal KDEL tag, can accumulate to very high levels as bivalent IgG-like antibodies in *Arabidopsis thaliana* seeds and illustrate that a plant-produced anti-hepatitis A virus scFv-Fc has similar antigen-binding and in vitro neutralizing activities as the corresponding full-length IgG. As expected, most scFv-Fc produced in seeds contained only oligomannose-type *N*-glycans, but, unexpectedly, 35–40% was never glycosylated. A portion of the scFv-Fc was found in endoplasmic reticulum (ER)-derived compartments delimited by ribosome-associated membranes. Additionally, consistent with the glycosylation data, large amounts of the recombinant protein were deposited in the periplasmic space, implying a direct transport from the ER to the periplasmic space between the plasma membrane and the cell wall. Aberrant localization of the ER chaperones calreticulin and binding protein (BiP) and the endogenous seed storage protein cruciferin in the periplasmic space suggests that overproduction of recombinant scFv-Fc disturbs normal ER retention and protein-sorting mechanisms in the secretory pathway (Van Droogenbroeck B et al 2007 Proc Natl Acad Sci USA 104:1430).

Monoclonal antibody against the non-protein Lewis Y oligosaccharide antigen is over-expressed in breast, lung, ovary, and colon cancers. Monoclonal antibody (mAb BR55-2) specific for LeY was expressed (30 mg/kg fresh weight of leaves) in low-alkaloid content in transgenic tobacco plants and bound specifically to SK-BR3 breast cancer and SW948 colorectal cancer cells. Its binding to the FcγRI receptor was the same as that derived from mammalian cells. The plantibody was effective in cytotoxicity assays as well as in grafting onto nude mice; thus, indicating its potential suitability for immunotherapy (Brodzik R et al 2006 Proc Natl Acad Sci USA 103:8804).

Plant-produced antibodies may find biomedical application in humans and animals. Transgenic plants may produce large quantities of IgA and IgG-IgA at low cost. In *Nicotiana benthamina* leaves, high-level expression of functional full-size monoclonal antibody (mAb) of the IgG class in plants has been ascertained. The process relies on synchronous coinfection and coreplication of two viral vectors, each expressing a separate antibody chain. The two vectors are derived from two different plant viruses that were found to be noncompeting. Unlike vectors derived from the same virus, noncompeting vectors effectively coexpress the heavy and light chains in the same cell throughout the plant body, resulting in yields of up to 0.5 g of assembled mAbs per kg of fresh-leaf biomass (Giritch A et al 2006 Proc Natl Acad Sci USA 103: 4701).

Also, other components of the immunization system may thus be synthesized with single plants after combining the genes through classical crossing procedures. By eating IgA secreting plant tissues, protection is expected through mucosal immunity or may protect against dental caries. If the antibody is expressed in seed tissues, it can be stored at room temperature (perhaps for years) without a loss of the variable region of the antibody and its antigen-binding ability. ▶antibody, ▶host-pathogen relations, ▶ScFv, ▶KDEL, ▶immunization, ▶mucosal immunity, ▶monoclonal antibody, ▶monoclonal antibody therapies, ▶plant vaccine, ▶molecular pharming, ▶Lewis blood group, ▶breast cancer, ▶colorectal cancer, ▶cancer therapy, ▶cancer gene therapy, ▶nude mouse, ▶tobacco, ▶BiP, ▶calreticulin, ▶periplasma; Bakker H et al 2001 Proc Natl Acad Sci USA 98:2899; Mayfield SP et al 2003 Proc Natl Acad Sci USA 100:438; Ma JK-C et al 2003 Nature Rev Genet 4:794.

PLAP Vector: ▶axon guidance

Plaque: The clear area formed on a bacterial culture plate (heavily seeded with cells) as a consequence of lysis of the cells by virus; turbid plaques indicate incomplete lysis (see Fig. P78). ▶lysis

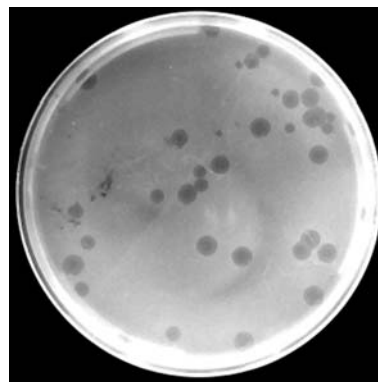


Figure P78. T3 bacteriophage plaques on petri plate heavily seeded by bacteria. (Courtesy of Dr. CS Gowans)

Plaque-Forming Unit: The number of plaques per mL bacterial culture.

Plaque Hybridization: ▶Benton-Davis plaque hybridization

Plaque Lift: Plaque lifts on bacteriophage plates plaques are marked and overlaid by cellulose nitrate films. After denaturation and immobilization of the plaques on the filter, they are hybridized with probes to identify recombinants and return to the saved master

plate for obtaining plugs of interest from the original plate. The procedure generally requires repetition in order to isolate unique single recombinants. ►colony hybridization; Frolich MW 2000 Biotechniques 29:30.

Plasma: The fluid component of the blood in which the particulate material is suspended. The blood plasma is free of blood cells but clotting is not allowed during its isolation, and it contains the platelets, which harbor animal cell growth factors. ►PDGF, ►platelets, ►serum, ►cytoplasm, ►cytosol

Plasma Cell (plasmacyte): B lymphocytes can differentiate into either memory cells or plasma cells and the latter secrete immunoglobulins. ►lymphocytes, ►immunoglobulins, ►immune system

Plasma Membrane: The plasma membrane envelops all cells. ►cell membranes

Plasma Nucleic Acid: During pregnancy, a small number of fetal cells can escape into the plasma and some can also shed their chromosomal DNA (see Fig. P79). Such plasma nucleic acids can be exploited for prenatal diagnosis without many intrusive procedures (Lo YMD et al 2007 Nat Rev Genet 8:71). ►prenatal diagnosis, ►DNA circulating

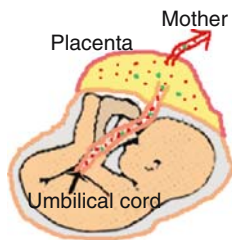


Figure P79. Contact is between fetus and mother through the umbilical cord and both normal (red) and different cells (green) are transferred to the maternal plasma

Plasma Proteins: Proteins in the blood plasma. The major components are serum albumin, globulins, fibrinogen, immunoglobulins, antihemophilic proteins, lipoproteins, α_1 antitrypsin, macroglobulin, haptoglobin, and transfer proteins, such as transferrin (iron), ceruloplasmin (copper), transcortin (steroid hormones), retinol-binding proteins (vitamin A), and cobalamin-binding proteins (vitamin B₁₂). The lipoproteins carry phospholipids, neutral lipids and cholesterol esters. In addition, there are a great variety of additional proteins present in the serum. In a small population of 96 healthy individuals, 76 structural variants were observed in 25 proteins by affinity-based

mass spectrometric assays. This large variation predicts that analysis of plasma proteins may yield important biomarkers for medical purposes (Nedelkov D et al 2005 Proc Natl Acad Sci USA 102:10852)

Plasmablast: A precursor of plasmacyte or precursor cell of the lymphocytes.

Plasmacytoid Cell: Functionally, it is one type of dendritic cells with antigen-presenting properties (see Fig. P80). Plasmacytoid cells may not display dendritic morphology. They produce a large quantity of interferon α/β in response to bacterial or viral infection. They have roles in both innate and acquired immunity. ►dendritic cell, ►interferon, ►acquired immunity; McKenna K et al 2005 J Virology 79:17.

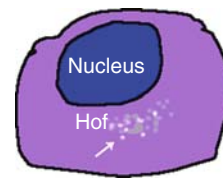


Figure P80. Plasmacytoid cell

Plasmacytoma: The cancer (myeloma) of antibody producing cells. Resistance against it is controlled mainly by different alleles of the complex FRAP. ►Fk506; Bliskovsky V et al 2003 Proc Natl Acad Sci USA 100:14982.

Plasmagene: Non-nuclear genes (mitochondrial, plasmidic or plasmid). ►mitochondrial genetics, ►chloroplast genetics

Plasmalemma: The membrane around the cytoplasm or the envelope of the fertilized egg.

Plasmatocyte: Macrophage-like elements in the insect hemolymph. ►macrophage, ►hemolymph

Plasmid: The dispensable genetic element, which can propagate independently and can be maintained within the (bacterial) cell, and may be present in yeast and mitochondria of a number of organisms. The plasmids may be circular or linear double-stranded DNA. The conjugative plasmids possess mechanisms for transfer by conjugation from one cell to another. The non-conjugative plasmids lack this mechanism and are therefore preferred for genetic engineering because they can be easier confined to the laboratory. During evolution, some of the advantageous plasmid genes are assumed to have been incorporated into the chromosomes and the plasmids, lost. The persistence of the plasmids may be warranted by their ability to disperse genetic information

horizontally. Plasmids occur also in the organelles of higher eukaryotes and lower eukaryotes. ►vectors, ►curing of plasmids, ►pBR322, ►pUC, ►transposon conjugative, ►cryptic plasmids, ►Ty; Summers DK 1996 The biology of plasmids, Blackwell; Thomas CM (Ed.) 2000 The Horizontal Gene Pool: Bacterial Plasmids and Gene Spread, Harwood Press, Durham, UK; <http://plasmid.hms.harvard.edu>.

Plasmid Addiction: The loss of certain plasmids from the bacterial cells may lead to an apoptosis-like cell death, called post-segregational killing or plasmid addiction. ►apoptosis

Plasmid, Chimeric: An engineered plasmid carrying foreign DNA.

Plasmid Incompatibility: Plasmids are compatible if they can coexist and replicate within the same bacterial cell. If the plasmids contain repressors effective for inhibiting the replication of other plasmids, they are incompatible. Generally, closely related plasmids are incompatible, and they thus belong to a different incompatibility group. The plasmids of enterobacteria belong to about two-dozen incompatibility groups. Plasmids may be classified also according to the immunological relatedness of the pili they induce to form (such as F, F-like, I, etc.). The replication system of the plasmids defines both the pili and the incompatibility groups. Cells with F plasmids may form F sex pili; the R1 plasmids belong to FII pili group, etc. ►pilus, ►F⁺, ►F plasmid, ►R plasmids, ►enterobacteria, ►incompatibility plasmids

Plasmid Instability: Plasmid instability indicates difficulties in maintenance caused by defect(s) in transmission, internal rearrangements, and loss (deletion) of the DNA. ►cointegration

Plasmid, 2 μ m: A 6.3 kbp circular DNA plasmid of yeasts, present in 50–100 copies per haploid nucleus. It carries two 599 bp inverted repeats separating 2774 and 2346 bp tracts. Re-combination between the repeats results in A and B type plasmids. Its recombination is controlled by gene *FLP* and its maintenance requires the presence of the *REP* genes. ►yeast; Scott-Drew S, Murray JA 1998 J Cell Sci 111:1779.

Plasmid Maintenance: Plasmid maintenance in prokaryotes is secured either by the high number of copies, or in low copy number plasmids, by a mechanism reminiscent to some extent to that of the centromere in mitosis of eukaryotes. The proteic plasmid maintenance system operates by the coordination of a toxin and an unstable antidote. When the labile antidote decays, the toxin kills the cells that do

not have the plasmid. The antidote may be a labile antisense RNA that keeps in check the toxin gene. A plasmid-encoded restriction-modification may also be involved. When the modification system recedes beyond an effective level in the plasmid-free cells, the genetic material falls victim to the endonuclease. One of such systems in *E. coli* is the *hok* (host killing)-*sok* (suppressor of killing)-*mok* (modulation of killing) system of linked genes. ►partition, ►antisense RNA, ►restriction-modification, ►killer plasmids; Gerdes K et al 1997 Annu Rev Genet 31:1; Møller-Jensen J et al 2001 J Biol Chem 276:35707; Hayes F 2003 Science 301:1496.

Plasmid Mobilization: Plasmid mobilization may take place by bacterial conjugation. Plasmid vectors use the gene *mob* (mobilization) if they do not have their own genes for conjugal transfer. Some plasmids may rely on *ColK* (colicin K, affecting cell membranes) that nicks plasmid pBR322 at the *nic* site, close to *bom* (basis of mobility). Mobilization proceeds from the nicked site (base 2254 in pBR322). Plasmids lacking the *nic/bom* system, e.g., pUC, cannot be mobilized. (See Chan PT et al 1985 J Biol Chem 260:8925).

Plasmid Rescue: The plasmid rescue procedure was designed originally for transformation with linearized plasmids of *Bacillus subtilis* that normally does not transform these bacteria. The linearized plasmid could be rescued for transformation in the presence of the *RecE* gene if recombination could take place.

The linearized monomeric plasmid then could carry also any in vitro ligated passenger DNA into cells. If the host cells carry a larger number of plasmids (multimeric), special selection is necessary to find the needed one. Plasmid rescue has also been used for re-isolation of inserts (plasmids) from the genome of transformed cells of plants.

The re-isolation requires appropriate probes for (the termini) of the inserts to permit recognition, after which, the DNA is re-circularized and cloned in *E. coli* and they have at least one selectable marker and an origin of replication compatible with the bacterium. The cloned DNA insert or its fragments are inserted into the M13 phage for nucleotide sequencing. This permits the identification of any changes that may have taken place in the original transforming DNA and permits an analysis of the flanking sequences of the target sites as well. A number of different variations of the procedure have been adopted in prokaryotes, microbes, animals, and plants. ►T-DNA, ►DNA sequencing, ►Rec; Perucho M et al 1980 Nature [Lond] 285:207, see Fig. P81.

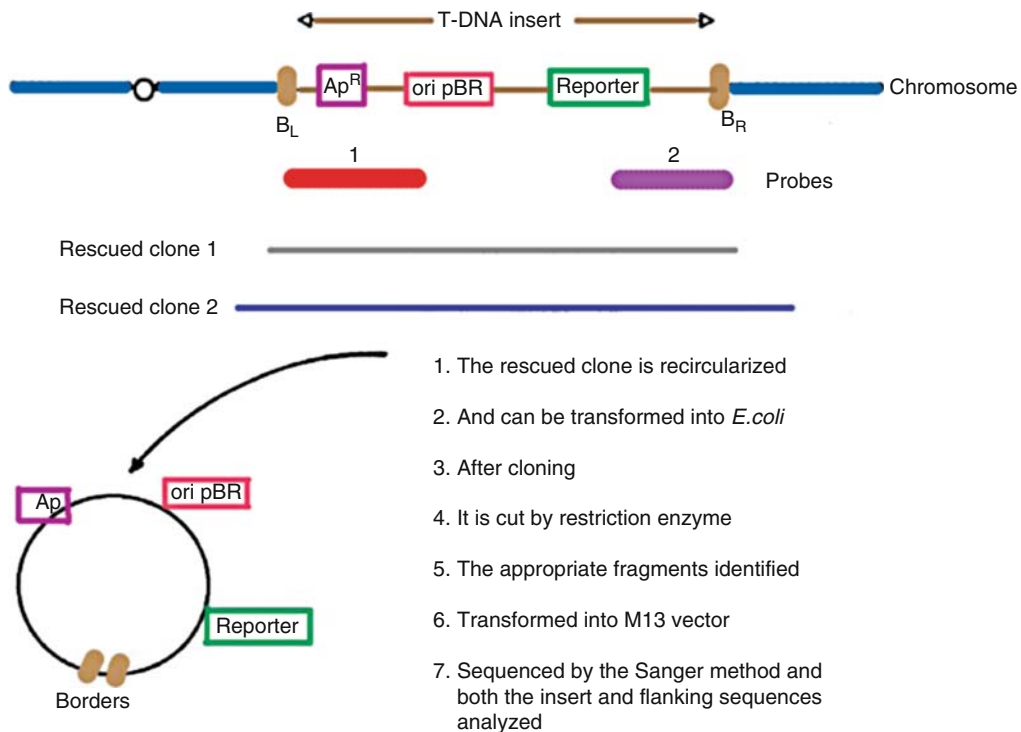


Figure P81. Outline of a plasmid rescue procedure exemplified by isolating T-DNA insert from *Arabidopsis*. Ap = ampicillin-resistance gene (Ap^R) of the pBR322, ori pBR = origin of replication of the PBR322 plasmid present in the plant-transforming vector, reporter is hygromycin resistance, left (B_L) and | right (B_R) border sequence of the T-DNA. (After Koncz C, et al. 1989. Proc. Natl. Acad. Sci. USA 86:8467.)

Plasmid Segregation: In plasmid segregation, before cell division, plasmids are partitioned to ensure transmission to mother and daughter cells. The segregation is mediated by *par* (partitioning) loci of the plasmids. Type I *pars* encode Walker box ATPases and Type II *pars* encode actin-like ATPases. The actin-like filaments act in similarity to the microtubules in higher organisms. The *par* loci involve two proteins and a centromere-like cis-acting site. The presence of Type I *par* locus positions the plasmids in the center of the cell. Integration host factor (IHF) of the bacteria plays a role in plasmid segregation. The mechanisms of plasmid segregation vary among different plasmids. ▶ [actin](#), ▶ [ATPase](#), ▶ [Walker box](#), ▶ [IHF](#); Ebersbach G, Gerdes K 2005 Annu Rev Genet 39:453.

Plasmid Shuffling: The general procedure of plasmid shuffling in yeast first disrupts the particular gene in a diploid strain. After meiosis, the cells can be maintained only if the wild type allele is carried on a replicating plasmid (episome). Mutant copies of that particular gene are then introduced into the cell on a second episome and exchanged (shuffled) for the wild type allele. The phenotype of any of the mutant alleles can be studied in these cells that carry the

disrupted (null) allele. (See Sikorski RS et al 1995 Gene 155:51; Zhao H, Arnold FH 1997 Nucleic Acids Res 25:1307).

Plasmid Telomere: Linear plasmids require exonuclease protection at the open ends. The problem may be resolved by capping with proteins or forming a lollipop type structure by fusing the ends of the single strands as shown in Figure P82. ▶ [telomere](#)



Figure P82. Plasmid telomeres

Plasmid Vehicle: A recombinant plasmid that can mediate the transfer of genes from one cell (organism) to another. ▶ [vectors](#)

Plasmids, Amplifiable: Amplifiable plasmids continue replication in the absence of protein synthesis (in the presence of protein synthesis inhibitor). ▶ [amplification](#)

Plasmids, Conjugative: Conjugative plasmids carry the *tra* gene, promoting bacterial conjugation and can be transferred to other cells by conjugation and can also mobilize the main genetic material of the bacterial cell. ►conjugation, ►F plasmid

Plasmids, Cryptic: Cryptic plasmids have no known phenotype.

Plasmids, Monomeric: Monomeric plasmids are present in a single copy per cell.

Plasmids, Multimeric: Multiple plasmids have multiple copies in a cell.

Plasmids, Non-Conjugative: Non-conjugative plasmids lack the *tra* gene required for conjugative transfer, but have the origin of replication and therefore when complemented by another plasmid for this function, they can be transferred. ►conjugation

Plasmids, Promiscuous: Promiscuous plasmids have conjugative transfer to more than one type of bacteria.

Plasmids, Recombinant: Recombinant plasmids are chimeric; they carry DNA sequences of more than one origin. (See Fig. P83).

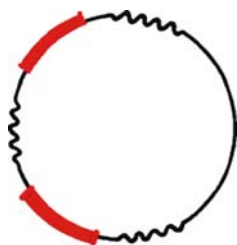


Figure P83. Recombinant plasmid

Plasmids, Relaxed Replication: Relaxed replication plasmids may replicate to 1000 or more copies per cell.

Plasmids, Runaway Replication: In runaway replication plasmids, the replication is conditional, e.g., under permissive temperature regimes they may replicate almost out-of-control whereas under other conditions their number per cell may be quite limited.

Plasmids, Single Copy: Single copy plasmids may have single or very few copies per cell.

Plasmids, Stringent Multicopy: Stringent multicopy plasmids may grow to 10 to 20 copies in a cell.

Plasmin (fibrinolysin): Proteolytic protein (serine endopeptidase) with specificity of dissolving blood clots, fibrin, and other plasma proteins. For its activation, urokinases (tissue plasminogen activator) are required. Plasmin may be used for therapeutic

purposes to remove obstructions in the blood vessels. ►urokinase, ►plasminogen, ►plasminogen activator, ►streptokinase, ►CAM; Lijnen HR 2001 Ann NY Acad Sci 936:226.

Plasmin Inhibitor Deficiency (PLI, AAP): Plasmin inhibitor deficiency is encoded in human chromosome 18p11-q11 as recessive gene, and is involved in the regulation of fibrinolysin. ►plasmin

Plasminogen: A precursor of plasmin. Human plasminogen markedly increases mortality of mice infected with streptococci due to bacterial expression of streptokinase. Streptokinase is highly specific for human plasminogen but not for other mammalian plasminogens (Hun H et al 2004 Science 305:1283). ►plasmin, ►plasminogen activator, ►angiostatin

Plasminogen Activator (PLAT): PLAT cleaves plasminogen into plasmin; it is encoded in human chromosome 8q11-p11. The plasmin activator inhibitor (PLANH1/PAI-1) is encoded in human chromosome 7q21-q22 and PLANH2 at 18q21.1-q22. The plasminogen activator receptor was localized to 19q13.1-q13.2. Tissue-specific plasminogen activator coupled to the surface of red blood cells can dissolve blood clots and prevent thrombosis (Murciano, J-C et al 2003 Nature Biotechnol 21:891). ►plasminogen, ►plasmin, ►urokinase, ►PN-1, ►streptokinase, ►thrombosis, ►MET oncogene

Plasmodesma (plural plasmodesmata): About 2µm or larger channels connecting neighboring plant cells, lined by extension of the endoplasmic reticulum. Functionally, they correspond to the gap junctions of animal cells. Various molecules, signals, including even viruses, may move through these intercellular communication channels. The plasmodesmata are subject to temporal and spatial regulation. ►gap junctions; Zambryski P, Crawford K 2000 Annu Rev Cell Dev Biol 16:393; Hake S 2001 Trends Genet 17:2; Haywood V et al 2002 Plant Cell 14:S303; Kim I et al 2005 Proc Natl Acad Sci USA 102:11945.

Plasmodium: A syncytium of the amoeboid stage of slime molds (such as in *Dictyostelium*).

Plasmodium: One of the several parasitic coccid protozoa causing malaria-like diseases in vertebrates, birds, and reptiles. A single *Plasmodium falciparum* (n = 14, ~23 Mb, ~5268 proteins) parasite transcribes simultaneously multiple *var* genes (at several chromosomal locations), encoding the erythrocyte-membrane protein (PfEMP-1) that binds to the vascular endothelium and red blood cells. Functionally related genes tend to be clustered in the subtelomeric regions of the chromosomes. A protein interaction network of *P. falciparum* expressed at the intra-erythrocyte-stage parasites involving >2000 fragments of 1295 genes

has been constructed on the basis of the two-hybrid system. These networks can reveal potential drug targets (LaCount DJ et al 2005 Nature [Lond] 438:103). These interaction networks are quite different from those known in other organisms (Suthram S et al 2005 Nature [Lond] 438:108). Alignment of these *var* genes in heterologous chromosomes at the nuclear periphery may facilitate gene conversion and promotes diversity of antigenic determinants and adhesive phenotypes. Such a mechanism aids the evasion of the host immune system. The parasite invades the erythrocytes and destroys the host cells through the formation of merozoites (mitotic products) and spreading thus to other cells (see Fig. P84). The merozoites may develop into gametocytes (gamete forming cells) that infect blood-sucking mosquitos where they are transformed into sporozoites (the sexual generation) that are transmitted through insect bites to the higher animal host. The invaders first move to the liver where merozoites are formed and then return to the erythrocytes; thus the cycle continues. *Plasmodium falciparum* causes falciparum malaria. *P. malariae* is responsible for the *quartan*, or fourth day recurring malaria. The protozoan contains two double-stranded extranuclear DNA molecules; that of circular DNA resembles mitochondria whereas the second bears similarities to ctDNA, and contains 68 genes. Mutation in a single gene (*pfmdr1/PfEMP1*) encoding the P-glycoprotein homolog, Pgh1, may result in resistance to several antimalarial drugs of which some may or may not be chemically related. Transformation of the gene encoding the SM1 peptides into the *Anopheles* vector may render the insect resistant to *Plasmodium* infection. The rodent parasite *Plasmodium yoellii yoellii* genome (~23.1 Mb) is similar to that of *P. falciparum*. ▶malaria, ▶sex determination,

▶thalassemia, ▶antigenic variation, ▶mRNAP, ▶mtDNA, ▶chloroplast, ▶PfEMP1, ▶rifins, ▶gene conversion, ▶serpine, ▶antigenic variation, ▶epigenetic memory; Fidock DA et al 2000 Mol Cell 6:861; Ito J et al 2002 Nature [Lond] 417:452; the sequenced *P. falciparum* genome: Nature 419, issue 6906, Oct 30, 2002; *Anopheles* genome: Science 298, 4 Oct 2002; Joy DA et al 2003 Science 3000:318; *P. falciparum* linkage and gene association: Su X et al 2007 Nature Rev Genet 8:497; comparative genome analysis of *P. berghei* and *P. chabaudi*: Hall N et al 2005 Science 307:82; invasion of the blood: Cowman AF, Crabb BS 2006 Cell 124:755; <http://www.plasmodb.org/plasmo/home.jsp>; <http://www.tigr.org/tdb/tgi/>.

Plasmogamy: fusion of the cytoplasm of two cells without fusion the two nuclei and thus resulting in dikaryosis. Plasmogamy is common in fungi but may occur in fused cultured cells of plants and animals.

▶fungal life cycle, ▶cell genetics

Plasmolemma (plasmalemma): Plant cell membrane; the ectoplasm of the fertilized egg of animals.

Plasmolysis: The shrinkage of the plant cytoplasm caused by high concentration of solutes (salt) outside the cell resulting in loss of water. The cytoplasm separates from the cell wall.

Plasmon: The sum of non-nuclear hereditary units such as exists in mitochondrial and plastid DNA.

▶mtDNA, ▶chloroplasts, ▶plastome

Plasmon-Sensitive Gene: ▶nucleo-cytoplasmic interaction

Plasmaphoresis: A procedure to filter blood to allow the plasma proteins of the patient to be removed. At the same time, new donor plasma is replaced into the patient's blood, which is located in the plasmaphoresis machine. Subsequently, the blood is sent back to the patient. ▶hemolysis

Plasmotomy: The fragmentation of multinucleate cells into smaller cells without nuclear division.

Plasmovirus: The plasmovirus bears some similarity to phagemids but in this case a retrovirus is combined with an independent vector cassette containing various elements. The envelope gene of the Moloney provirus is replaced by a transgene to prevent infective retroviral ability and it would not regain it by chance recombination with another retrovirus. Such a construct can express transgene(s), can multiply within the target cells, and provide a tool for cancer therapy.

▶vectors, ▶retrovirus, ▶transgene, ▶cancer therapy, ▶viral vectors, ▶phagemid; Morozov VA et al 1997 Cancer Gene Ther 4(5):286.

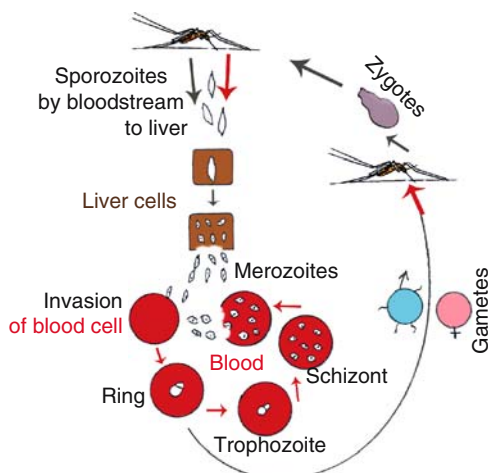


Figure P84. Life cycle of *Plasmodium* in humans and mosquitos

Plasticity: In general, the ability of a cell or organism to display different expressions (phenotype) dependent on the environment. The ability of cells to change from what they normally are enables them to perform tasks not normally found in differentiated cells. ▶stem cells, ▶MAPCs, ▶adaptation, ▶noise, ▶reaction norm

Plastid: The cellular organelle of plants, containing DNA. It may differentiate into chloroplasts, etioplasts, amyloplasts, leucoplasts, or chromoplasts. In *Arabidopsis*, mechanosensitive ion channel proteins (localized in the plastid envelope) seem to control plastid size and shape (Haswell ES, Meyerowitz E M 2006 Curr Biol 16:1). ▶under separate names, ▶plastid number per cell, ▶plastid male transmission, ▶ctDNA, ▶chloroplast, ▶chloroplast genetics, ▶apicoplast

Plastid Male Transmission: Generally, the genetic material in the plastids is transmitted only through the egg cytoplasm but in a few species of higher plants (*Pelargonium*, *Oenothera*, *Solanum*, *Antirrhinum*, *Phaseolus*, *Secale*, etc.) a variable degree of male transmission takes place. Biparental transmission of plastid genes (about 1%) may occur also in the alga *Chlamydomonas reinhardtii*. The male transmission of these nucleoids is controlled by one or two nuclear genes. The nucleoids of the plastid and mitochondria of the male are usually degraded or if they are included in the generative cells of the male, most commonly fail to enter the sperm or are not transmitted to the egg cytoplasm. In contrast to the angiosperms, in conifers (pines, spruces, firs) the plastid DNA is usually transmitted through the males. In some interspecific hybrids, exclusively paternal, exclusively maternal, and biparental transmission were also observed. In other conifer crosses, the mtDNA is transmitted maternally. In redwoods, the transfer is paternal. One scientific claim posits that the destruction of the paternal ctDNA in the females is carried out by a restriction enzyme while the maternal ctDNA is protected by methylation. Others implicate a special nuclease C. ▶chloroplast, ▶genetics, ▶ctDNA, ▶mtDNA, ▶paternal leakage; Diers L 1967 Mol Gen Genet 100:56; Avni A, Edelman N 1991 Mol Gen Genet 225:273; Sears B 1980 Plasmid 4:233.

Plastid Number Per Cell: In the giant cells of *Acetabularia* algae, there may be one million chloroplasts but in the alga *Chlamydomonas* there is only one per cell. In higher plants, the number of plastids vary according to the size of the cells, about 30–40 in the spongy parenchyma to about twice as many in the palisade parenchyma. ▶plastid, ▶ctDNA

Plastochrome: The pattern of organ differentiation in time and space is genetically controlled. (See Miyoshi K et al 2004 Proc Natl Acad Sci USA 101:875).

Plastocyanin: an electron carrier in photosynthesis between cytochromes and photosystem I. ▶Z scheme; Ruffle SV et al 2002 J Biol Chem 277:25692.

Plastome: The sum of hereditary information in the plastids. ▶ctDNA, ▶chloroplast genetics

Plastome Mutation: Mutation in the plastid (chloroplast) DNA. ▶chloroplast genetics, ▶mutation in cellular organelles

Plastoquinone: An isoprenoid electron carrier during photosynthesis. ▶isoprene

Plate: A Petri dish containing a nutrient medium for culturing microbial or plant cells. Cell plate divides the two daughter cells after mitosis.

Plate Incorporation Test: The most commonly used procedure for the Ames test when the *Salmonella* suspension (or other bacterial cultures), the S9 activating enzymes, and the mutagen/carcinogen to be tested are poured over the bacterial nutrient plate in a 2 mL soft agar. After incubation for two days at 37°C, the number of revertant colonies is counted. ▶Ames test, ▶spot test

Platelet Abnormalities: ▶Glanzmann's disease, ▶thrombopathic purpura, ▶thrombopathia, ▶giant platelet syndrome, ▶Hermansky-Pudlak syndrome, ▶May-Hegglin anomaly, ▶platelets

Platelet Activating Factor (PAF): An inflammatory phospholipid. PAF acetylhydrolase may be a factor in atopy. ▶platelets, ▶atopy

Platelet-Derived Growth Factor (PDGF): A mitogen, secreted by the platelets, the 2–3 μm size elements in the mammalian blood, originated from the megakaryocytes of the bone marrow, and concerned with blood coagulation. PDGF controls the growth of fibroblasts, smooth muscle cells, blood vessel formation, nerve cells, cell migration in the oocytes, etc. This protein bears substantial homologies to the oncogenic product of the simian sarcoma virus, the product of the KIT oncogene, and the CSF1R (it activates also other oncogenes, such as c-fos). The PDGF is required for the healing of vascular injuries and in these cases the expression induced Egr-1 (early growth response gene product) may bind to the PDGF β chain promoter after displacing Sp1. PFGF- and insulin-dependent S6 kinase (pp70^{S6k}) is activated by phosphatidylinositol-3-OH kinase. Its receptor (PDGFR) is a tyrosine kinase. The detection of PDGF is facilitated by the construction of aptamers labeled with pyrene monomers at both ends. When an excimer is produced, the fluorescence emission is increased from 400 nm to 485 of PDGF bound excimer. The principle may be applicable to other molecules for facilitating biomedical analyses (Yang CJ et al 2005 Proc Natl Acad Sci USA

102:17278). ▶**oncogenes**, ▶**growth factors**, ▶**signal transduction**, ▶**platelets**, ▶**Sp1**, ▶**S6 kinase**, ▶**phosphatidyl inositol**, ▶**aptamer**, ▶**excimer**, ▶**heart diseases**; Betsholtz C et al 2001 Bioessays 23(6):494; Duchek P et al 2001 Cell 107:17.

Platelets: Platelets originate as cell fragments or “minicells” (without DNA) from the megakaryocytes of the bone marrow. Their function is in blood clotting and in the repair of blood vessels; they also secrete mitogen(s). Platelet abnormalities may cause stroke, myocardial infarction (damage of the heart muscles), and unstable angina (sporadic, spasmic chest pain). A balance between Bcl-x and Bak determines the life span of platelets. Inactive Bcl-x may cause thrombocytopenia (Mason KD et al 2007 Cell 128:1173). ▶**blood**, ▶**megakaryocyte**, ▶**platelet derived growth factor**, ▶**blood serum**, ▶**BAK**, ▶**BCL**, ▶**thrombocytopenia**; Prescott SM et al 2000 Annu Rev Biochem 69:419.

Plating Efficiency: The percentage of cells or protoplasts placed on a Petri plate that grows. The relative plating efficiency compares the fraction of growing cells in a treated series to that of an appropriate control.

Platyfish (*Xiphophorus/Platypoecilus*): Tropical fishes with complex sex determination. WX, WY, and XX are females and the males are XY and YY. The pseudoautosomal region seems to be long. Their melanocytes frequently turn into melanoma. ▶**pseudoautosomal**, ▶**sex determination**, ▶**melanocyte**, ▶**melanoma**

Platykurtic: ▶**kurtosis**

Platypus: ▶**monotreme**

Platysome: The nucleosome core (when it was thought of as a flat structure). ▶**nucleosome**

Playback: The number of non-repetitive sequences in a DNA can be determined by the saturation of single-strand DNA with RNA of unique sequences. The kinetics of saturation, R_{0t} (by analogy to C_{0t}), is then determined. The annealed fraction is generally a small percent of the eukaryotic DNA, which is highly redundant. To be sure that the RNA is hybridized to only the unique DNA sequences, in the DNA-RNA hybrid molecules the RNA is degraded enzymatically and the remaining DNA is subjected to a reassociation test to determine its C_{0t} curve. This “play-back” then reveals whether all the DNA so isolated, includes only genic DNA and is not redundant. Such studies may assist in estimating the number of housekeeping genes plus the genes that were transcribed when the RNA was collected. ▶ **C_{0t}** , ▶**housekeeping genes**, ▶**gene number**

PLC: Phospholipase C. ▶**phospholipase**

Pleated Sheets: Relaxed β -configuration polypeptide chains hydrogen-bonded in a flat layer. ▶**protein structure**

Pleckstrin Domain: The pleckstrein domain is approximately 100-amino acids in length and occurs in many different proteins such as serine/threonine kinases, tyrosine kinases, and the substrates of these kinases, phospholipase C, small GTPase regulators, and cytoskeletal proteins. Pleckstrin domains may participate in various signaling functions; they bind phosphatidylinositol 4,5-bisphosphate. Pleckstrin is a substrate of protein kinase C in activated platelets. separate entries, ▶**PH**, ▶**SHC**, ▶**SH2**, ▶**SH3**, ▶**WW**, ▶**PTB**, ▶**adaptor proteins**, ▶**phosphatidylinositol**, ▶**platelets**, ▶**desensitisation**, ▶**phosphoinositides**; Lemmon MA, Ferguson KM 1998 Curr Top Microbiol Immunol 228:39; Rebecchi MJ Scarlata S 1998 Annu Rev Biophys Biomol Struct 27:503.

Plectin: A 500 kDa keratin of the cytoskeleton encoded in human chromosome 8q24. ▶**epidermolysis** ▶**[bullosa simplex]**, ▶**keratin**

Plectonemic Coils: The DNA double helix represents plectonemic coils (see Fig. P85). Here, the two coils are wound together, therefore they can be separated only by unwinding rather than simple pulling apart, like in paranemic coils. ▶**paranemic coils**



Figure P85. Plectonemic coil

Pleiomorphic: A pleiomorphic organism displays variable expression (without a genetic basis for the special changes).

Pleiomorphic Adenoma: A salivary gland tumor caused by human chromosome breakage points, primarily at 8q12, 3p21, and 12q13-15. The translocation t(3;8) (p21;q12) results in swapping the promoters of PLAG1, a Zn-finger protein encoded in chromosome 8 and β -catenin (CTNNB1), and activation of the oncogene. ▶**Zinc finger**, ▶ **β -catenin**

Pleiotrophin (PTN): A 18 kDa heparin-binding cytokine, inducible by the platelet derived growth factor (PDGF). It is 50% identical with retinoic acid-inducible midkine growth factor, which like PTN is also a growth and differentiation factor. PTN reduces cell colony formation, interacts with receptor protein tyrosine phosphatase, and leads to tumor growth, angiogenesis, and metastasis. PTN regulates phosphorylation of serine 713 and 726 of β -adducin by activating protein kinase C and mediates its translocation to the nucleus. This phosphorylation contributes to uncoupling of the adducin-actin-spectrin

complexes and stabilizes the cytoskeleton (Pariser H et al 2005 Proc Natl Acad Sci USA 102:12407). ►adducin, ►actin, ►protein kinase, ►spectrin, ►cytoskeleton; Meng K et al 2000 Proc Natl Acad Sci USA 97:2603; PTN in breast cancer: Chang Y et al 2007 Proc Natl Acad Sci USA 104:10888.

Pleiotropy: One gene affects more than one trait; mutation in various elements of the signal transduction pathways, in general transcription factors, or in ion channels may have pleiotropic effects. The existence of pleiotropy has been questioned with the emergence of the one gene–one enzyme theory. Earlier, it was inconceivable on the basis that one tract of DNA could code for more than a single function (“Pleiotropism non est... that is the dogma”, p 161. In Genetics, 1959 Sutton EH (ed), Josiah Macey Found, New York). However, it has been since shown that mutation at different sites within single mitochondrial tRNA genes may lead to several different human diseases. Cytokines involved in signaling through different receptors in different pathways are pleiotropic molecules. The complete sequence of the *Drosophila* genome shows that ~13,601 genes encode ~14,113 transcripts indicating that a minimum of nearly 4% of the genes display pleiotropy. An analysis of 150,000 high-abundance human proteins derived from two-dimensional gels indicated an average of 10 isoforms per protein following the (MALDI-TOF) matrix-assisted laser desorption ionization/time of flight mass spectrometry (Humphery-Smith I 2004, p 2 In: Albala JS, Humphery-Smith I (Eds.) Protein Arrays, Biochips, and Proteomics, Marcel Dekker, New York). In yeast, pleiotropy is attributable to multiple consequences of single functions (He X, Zhang J 2006 Genetics 173:1885). *Antagonistic pleiotropy* claims that evolution does not work against variations, which adversely affect the individuals after the completion of the reproductive stage of life, and the alternative genotypes display opposite phenotypes. Actually, the genes displaying antagonistic pleiotropy can be silent in early life but are harmful later and contribute to aging; yet, they may have some selective advantage early and this assures their maintenance in populations.

The F1F0-ATP synthase is a ubiquitous mitochondrial enzyme that works as a rotary motor, harnessing the electrochemical proton gradients to carry out ATP synthesis from ADP and inorganic phosphate. It is composed of a membrane-embedded proton-translocating sector (F0), coupled to a soluble sector (F1) that contains catalytic sites for ATP synthesis/hydrolysis. Several of the most deleterious human mitochondrial diseases, such as the maternally inherited Leigh syndrome, neurogenic ataxia, retinitis pigmentosa, and some cases of Leber hereditary optic neuropathy are caused by point mutations in the mitochondrial

ATP6 gene that encodes subunit 6 of the ATP synthase F0 sector. The same single point mutation can produce either Leigh syndrome or retinitis pigmentosa, depending on the mtDNA mutation load. The mtDNA mutations most frequently associated with retinitis pigmentosa or Leigh syndrome are T8993G, T8993C, T9176G, and T9176C, which replace the conserved leucine residues at positions 156 or 217 of subunit 6 by arginine or proline, respectively. The primary molecular pathogenic mechanism of these deleterious human mitochondrial mutations is functional inhibition in a correctly assembled ATP synthase (Cortés-Hernández P et al 2007 J Biol Chem 282:1051). ►signal transduction, ►transcription factors, ►epistasis, ►two-hybrid method, ►mitochondrial diseases in humans, ►MALDI-TOF, see Fig. P86.

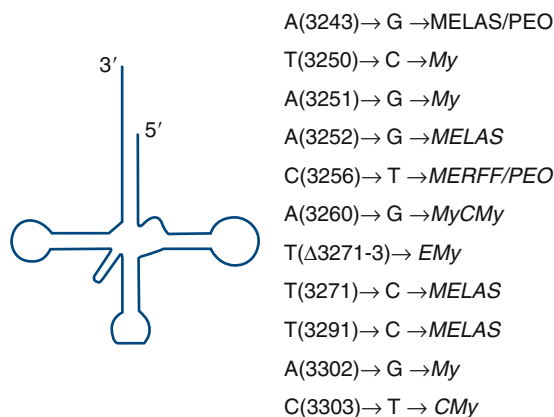


Figure P86. Pleiotropic mutations in the mtDNA Leu tRNA^{UUR} gene. The diagram displays the mutations in the human mitochondrial Leu tRNA^{UUR}. The first letter indicates the base that is changed, in parenthesis is the nucleotide number at the physical map, after the → the substituted base is given and after → the diseases described under mitochondrial diseases in humans are identified with abbreviations. Redrawn after Moraes CT 1998, p 167 In: Singh KK (Ed.) Mitochondrial DNA Mutations in Aging, Disease and Cancer, Springer, New York

P

Pleomorphism: Carl Wilhelm Nägeli’s nineteenth century suggestion claiming lack of hard heredity in bacteria and that they simply exist in a variety of pliable forms. This idea held back the development of bacterial genetics, although physicians like Robert Koch and the taxonomist W. Migula sharply criticized it and stated that it ignored facts known by the 1880s. ►*Hieracium*

Plesiomorphic: A trait in its more primitive state among several evolutionarily related species. ►apomorphic, ►symplesiomorphic, ►synapomorphic

Pleura: Serous (moist) membrane lining the lung or insects' thoracic cavity.

Plexins: Receptors for semaphorins. Plexin-B1 is activates GTPase for RAS (Oinuma I et al 2004 Science 305:862). ►semaphorins, ►RAS, ►GTPase

PLGA: See Fig. P87, ►angiogenesis

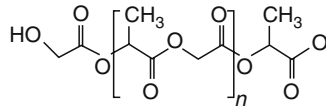


Figure P87. PLGA

Plk (polo-like kinase): Plk regulates the maturation of the centrosome, spindle assembly, the PICH checkpoint helicase, and the removal of cohesins, inactivates the anaphase promoting complex inhibitors, and controls mitotic exit and cytokinesis. ►polo, terms in alphabetical order; Baumann C et al 2007 Cell 118:101.

Ploidy: Ploidy represents the number of basic chromosome sets in a nucleus. The haploids have one set (x), the diploids two (xx), autotetraploids (xxxx), and so on. ►polyploidy

P-Loop: The ATP- and GTP-binding proteins have a phosphate-binding loop, the primary structure of which typically consists of a glycine-rich sequence followed by a conserved lysine and a serine or threonine. (See Saraste M et al 1990 Trends Biochem Sci 15:430).

P

PLTP (phospholipid transfer protein): The PLTP mediates the exchange of HDL cholesteryl esters with very low-density triglycerides and vice versa. ►HDL, ►cholesterol, ►CETP

Plug-In: A small circuit in a developmental function that can be present in several developmental networks.

Plum (*Prunus*): Basic chromosome number $x = 7$ but a variety of polyploid forms exist. (Bliss FA et al 2002 Genome 45:520).

Plumule: The embryonic plant shoot-initial.

Pluralism in Evolutionary Biology: Pluralism indicates sympatric speciation. ►sympatric

Pluripotency: A cell with pluripotency has the ability to develop into various, but not necessarily all types of tissues. Embryonic stem cells (from the inner mass of blastocysts), embryonic germ cells (primordial cells of the gonadal ridge), and the mesenchymal stem cells of the bone marrow possess pluripotency. Transcription factor Zfx controls the self-renewal of embryonic and hematopoietic stem cells (Galan-Caridad JM et al 2007 Cell 129:345). The

good cultures may grow for more than 70 doublings ($2^{70} \geq 10^{20}$) and may be free of chromosomal defects. The ability of the embryonic stem cells to differentiate into many types of cells is regulated by MYC and Nanog proteins that regulate transcription factors, signal molecules, and suppress lineage specific cells. These two factors target a core set of 345 genes. The mouse and human MYC and Nanog target sites overlap in ~9 to 13% (Loh Y-H et al 2006 Nat Genet 38:431). Nanog proteins enable the reprogramming of somatic cells into pluripotent stem cells after fusion with embryonic stem cells of mouse (Silva J et al 2006 Nature [Lond] 441:997). Histone3 arginine26 methylation appears to be a crucial event in the formation of the pluripotent inner cell mass of the four-cell stage mouse embryos. CARM1 methyltransferase activity also upregulates Nanog and Sox2 proteins (Torres-Padilla A-E et al 2007 Nature [Lond] 445:214). ►totipotency, ►CARM1, ►MYC, ►Nanog, ►Sox, ►stem cells, ►ZFX; Donovan PJ, Gearhart J 2001 Nature [Lond] 414:92.

Plus and Minus Method (Sanger F et al 1975 J Mol Biol 94:441): The plus and minus method was an early version of DNA sequencing using dideoxy analogs of nucleosides (+ batch) during replication. After the analog was incorporated to a site, T4 exonuclease failed to continue degradation. In the minus (–) batch the synthesis stopped depending upon which single nucleotide was omitted (the precursor mixture containing only 3 deoxyribonucleotides). Thus nucleotide sequences of specific ends and length were generated and the fragments of different lengths were analyzed by electrophoresis. The Sanger et al (1977 Proc Natl Acad Sci USA 74:5463) method and its improvements replaced it. ►DNA sequencing

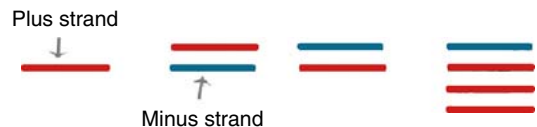


Figure P88. Plus and minus strands

Plus End: The preferential growing end of microtubules and actin filaments. ►minus end

Plus Strand: The plus strand of the single stranded DNA or RNA of a virus is represented in the mature virion whereas the minus strand serves as a template for the transcription (replication) of the plus strand and the mRNA (see Fig. P88). In most cases, the plus strands are synthesized far in excess to the minus strands. (►replicative form, ►RNA replication). The plus strand viral genomic RNA serves directly as mRNA.

Plutonium (Pu): A metallic fissile element (atomic number 94, atomic weight 242) produced by neutron bombardment of uranium (U^{238}) during the production of nuclear fuel and used for making nuclear weapons. Radioactive Pu powers some heart pacemakers. Thus, the wearers, as well as his/her family members and surgeons, will be exposed to some radiation, generally below 1.28 Sv per person per year, a little more than the average natural background (the doses are additive, however). If the highly toxic particles of Pu are inhaled (the most common type of ingestion), the element may affect the lung and may eventually be preferentially deposited in the skeletal system, causing bone cancer by the emission of X and γ rays. Pu^{238} has a half-life of 86.4 years. It propels some space vehicles. Pu^{239} has a half-life of 24.3×10^3 years and targets primarily the bone marrow. Other Pu isotopes have an even longer half-life. The level of Pu may be detected by radioactivity in the urine and by instruments placed on the body. Appropriate instruments can detect as low as 4 nCi (nanoCurie) values. ▶atomic radiation, ▶isotopes, ▶radiation hazard assessment, ▶Curie

Plx1: A kinase that phosphorylates the amino-terminal domain of Cdc25. ▶Cdc25

Plymouth Rock: A recessive white-feathered breed of chickens with the genetic constitution of *iicc*. The dominant *I* gene is a color inhibitor and *C* symbolizes color. ▶White Wyandotte, ▶Leghorn White

PLZF: The zinc-finger protein encoded in human chromosome 11q23. It normally represses the promoter of cyclin A but a transposition of RAR α (retinoic acid receptor) results in transactivation of the cyclin A gene, and may be involved in the initiation of cancer. ▶cyclin A, ▶RAR, ▶transcriptional activator, ▶transactivator, ▶leukemia [acute promyelotic leukemia].

PMA: See ▶phorbol 12-myristate-13-acetate (Fig. P89)

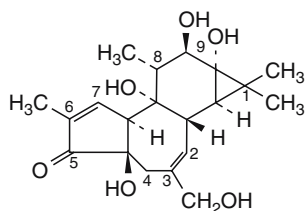


Figure P89. Phorbol

PMAGE (polony multiplex analysis of gene expression): PMAGE can detect single mRNA molecules in three cells (Kim JB et al 2007 Science 316:1481). ▶polony

pMB1: ▶ColE1

PMCA (protein misfolding cyclic amplification): ▶prion

PMDS (persistence of Müllerian duct syndrome): ▶Müllerian ducts

PME: Point mutation element where in the 3'-UTR regulatory proteins may bind and cause developmental switching.

PMF (peptide-mass fingerprinting): A method of rapid identification of proteins without sequencing but using mass spectrometry information. ▶MALDI; Jonsson AP 2001 Cell Mol Life Sci 58:868.

PML (promyelotic leukemia): A putative Zinc finger protein, encoded in human chromosome 15q21. Formerly, this gene was called MYL. There are about 10–20 PML bodies of ~ 0.3 – $1 \mu\text{m}$ per mammalian nuclear matrix. In acute promyelotic leukemia, these bodies become disorganized as the PML-RAR α oncogenic complex is formed. PML bodies are associated with caspase- and FAD-induced apoptosis. Casein kinase 2 (CK2) promotes PML ubiquitin-mediated degradation by phosphorylation at serine 517. In case of resistance to CK2, tumor-suppressor activity of PML is enhanced (Scaglioni PP et al 2006 Cell 126:269). Overexpressed PML also promotes apoptosis but without an enhanced caspase-3 activity. In the absence of PML (PML $^{-/-}$), the cells become resistant to ionizing radiation. ▶leukemia, ▶PLZF, ▶nuclear matrix, ▶RAR, ▶apoptosis, ▶POD, ▶AKT; Lallemand-Breitenbach V et al 2001 J Exp Med 193:1361.

PML39: A yeast upstream effector regulating Mlp1/Mlp2 nucleopore-associated proteins suppressing nuclear export of un-spliced mRNA (Palancade B et al 2005 Mol Biol Cell 16:5258). ▶nuclear pores

PMS1 (2q31-q33), **PMS2** (7q22) yeast homologs and colorectal cancer: Increased post-meiotic segregation in yeast and increased colorectal cancer (or Turcot syndrome) in humans due to mismatch repair deficiency. ▶mismatch repair, ▶colorectal cancer, ▶Turcot syndrome

PN-1 (protease nexin): A 43 kDa inhibitor of serine proteases (thrombin, plasminogen activator). It is involved in the development of embryonic organs (cartilage, lung, skin, urogenital system, and nervous system). PN-1 is abundant in the seminal vesicle and its dysfunction leads to male infertility. ▶thrombin, ▶plasminogen activator, ▶urokinase, ▶nexin, ▶infertility, ▶claudin-11; Murer V et al 2001 Proc Natl Acad Sci USA 98:3029.

pN: ▶Newton

PNA: ▶peptide nucleic acid

Pneumococcus: ▶*Diplococcus pneumoniae*

Pneumocystis carinii: A group of pathogenic ascomycetes with special susceptibility to immune-compromised individuals (e.g., AIDS patients) and rodents. It carries about 3740 genes in the about 8 Mb genome. It reproduces both asexually and sexually. ▶acquired immunodeficiency, ▶ascomycete; Kolls JK et al 1999 J Immunol 162:2890.

PNPase: ▶polynucleotide phosphorylase

Pocket: The motif of the retinoblastoma (RB) tumor-suppressor protein family that binds to viral-DNA coded oncoproteins. Binding of RB to the E2F family of transcription factors blocks transcription, needed for the progression of the cell cycle. The pocket proteins share this retinoblastoma (RB) motif. ▶E2F1, ▶tumor suppressor, ▶cell cycle, ▶transcription factors, ▶retinoblastoma, ▶p107, ▶p130; Botazzi ME et al 2001 Mol Cell Biol 21:7607.

POD (PML-oncogenic domain): ▶PML

Podophyllotoxin (epipodophyllotoxin): Antimitotic plant product.

Podosomes (invadopodia): Actin-containing electron-dense adhesion structures on human primary macrophages, Src-transformed fibroblasts, and in some cancer cells, controlling cell motion migration and immune reactions. N-WASP WH2 nucleation promoting protein domains capture the barbed end (the protrusive attachment structure of actin) to the podosome (Co C et al 2007 Cell 128:901). ▶Src, ▶macrophage, ▶actin, ▶WASP, ▶immune reaction; Linder S, Aeppelbacher M 2003 Trends Cell Biol 13:376.

Podospora anserina: $n = 7$, is a genetically well-studied ascomycete fungus.

Pof (Painting of fourth): *Drosophila* protein that binds only to the small 4th chromosome.

pogo: ▶hybrid dysgenesis

Poikilocytosis: A hemolytic anemia with variable-shape red blood cells. The defect is due to the reduction of ankyrin binding sites or mutation in spectrin. ▶ankyrin, ▶spectrin, ▶anemia

Poikiloderma Atrophicans (poikiloderma telangiectasia): ▶Rothmund-Thompson syndrome

Poikiloploidy: In poikiloploidy, different cells of the body have different numbers of chromosomes.

Poikilothermy: In poikilothermy, the body temperature or the organism depends on the surrounding environmental conditions.

Point Mutation: Point mutations do not involve detectable structural alteration (loss or rearrangement of the chromosome), and are expected to involve base

substitutions. The point mutation rate per locus in eukaryotes is about 10^{-5} and may vary from locus to locus and among various organisms. The rate per nucleotides of a locus is in the range of 10^{-8} . ▶substitution mutation; Krawczak M et al 2000 Hum Mut 15:45.

Point-of-Care Technologies: Point-of-care technologies use small bench top analyzers (for example, saliva, blood gas, and electrolyte systems) and hand held, single use devices (such as urine albumin, blood glucose, and coagulation tests). Hand held devices have been developed using microfabrication techniques. They are outwardly simple but internally complex devices that perform several tasks for example, separate cells from plasma, add reagents, and read color or other end points (Price CP 2001 BMJ 322:1285). These are also called bedside technologies, because the samples do not have to be transferred for analysis to laboratories and therefore are much faster, especially when the newest microfluidic devices are used. ▶microfluidics; Herr AE et al 2007 Proc Natl Acad Sci USA 104:5268.

Poise: ▶viscosity, ▶stoke

Poison Sequence: A poison sequence may be present in the genomes of some RNA viruses and thus even their cDNA cannot be cloned in full length in bacterial hosts. The problem may be overcome by propagating it in segments. (Brookes S et al 1986 Nucleic Acids Res 14:8231).

Poisson Distribution: Basically, an extreme form of the normal distribution, found when in large populations rare events occur at random, such as e.g., mutation. The general formula is $e^{-m} (m^i/i!)$, and expanded $e^{-m}(m^0/0!, m^1/1!, m^2/2! \dots m^i/i!)$, where e = base of natural logarithm ($\cong 2.718$), m = mean number of events, i = the number by which a particular m is represented at a given frequency, $!$ = factorial (e.g., $3! = 3 \times 2 \times 1$, but $0! = 1$). (See Fig. P90, ▶negative binomial).

Pokemon: A repressor of the tumor suppressor ARF; thus, it represents a protooncogene. ▶ARF, ▶oncogenes; Maeda T et al 2005 Nature [Lond] 433:278.

poky (synonym: *mi-1*): A slow-growing and cyanide-sensitive respiration defective mitochondrial mutation in *Neurospora*. The basic defect appears to be a four-base deficiency of the 15 bp consensus at the 5'-end of the 19S rRNA of the mitochondria. Because of this defect, a further upstream promoter is used, making the transcript longer but during processing, shorter RNAs are made. It is analogous to the petite colony mutations of budding yeast. ▶petite colony mutation, ▶stoppers, ▶mtDNA; Akins RA, Lambowitz AM 1984 Proc Natl Acad Sci USA 81:3791.

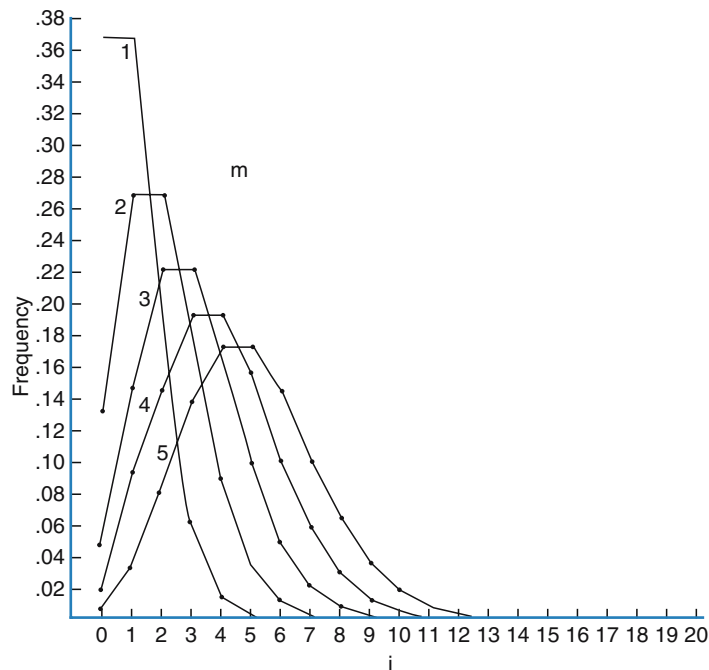


Figure P90. The Poisson distribution. Each curve corresponds to a numbered m value. The i classes represent the distribution of each mean value (m) with the ordinate indicating the frequencies

pol (bacterial RNA polymerase): pol synthesizes all the bacterial and viral RNAs in the bacterial cells. Its subunits are $\alpha\alpha\beta\beta'$ and σ . The σ subunit identifies the promoter sequences and is required for the initiation of transcription within the cell. After about a half dozen nucleotides are hooked up, it dissociates from the other subunits and further polymerization continues with the assistance of elongation protein factors. ▶transcription, ▶pol I, ▶pol II, ▶pol III eukaryotic RNA polymerases

pol I: Prokaryotic DNA polymerase, where the polymerase (Klenow fragment) and exonuclease functions are located about 30 Å distance apart in a subunit, and editing (removal of wrong bases) follows the melt and slide model. It plays a major role in prokaryotic repair and in the extension of the Okazaki fragments for joining them into a contiguous strand by ligase. It adds 10–20 nucleotides/second to the chain and so it is much slower than pol III. ▶melt and slide model, ▶DNA replication, ▶replication fork, ▶Klenow fragment, ▶pol III, ▶DNA ligase

pol I: RNA polymerase involved in the synthesis of ribosomal RNA (except 5S rRNA) in eukaryotes. By endonucleolytic cleavage, it generates the 3' end of rRNA from longer transcripts. The upstream control regions for transcription initiation (binding proteins) vary from species to species. The human RNA pol I requires an activator UBF (upstream binding factor)

and promoter selectivity factor SL1, including the TBF (TATA box binding protein) and associated subunits, TAF_I 110, TAF_I 63, and TAF_I 48. The former two keep contact with the promoter, whereas TAF_I 48 interacts with UBF and prevents RNA pol II from using this promoter site. ▶ribosome; Reeder RH 1999 Progr Nucleic Acid Res Mol Biol 62:293; Grummt I 1999 Progr Nucleic Acid Res Mol Biol 62:109.

pol II: Prokaryotic DNA polymerase, the functions of which are not completely defined so far; it has known role in repair. ▶DNA repair

pol II: The RNA polymerase transcribes messenger RNA and most of the snRNAs of eukaryotes with the assistance of different transcription factors. Nine or ten of its subunits are very similar to other polymerases; pol II has four to five smaller unique subunits. The two largest subunits are very similar in the three eukaryotic RNA polymerases and are similar also to prokaryotic subunits. It is most sensitive to α -amanitin inhibition (0.01 µg/mL). The site of sensitivity is in the largest 220 kDa polypeptide. This large subunit is activated by phosphorylation. At the carboxy terminal, there are 26 (yeast), 40 (*Drosophila*), or 52 (mouse) heptapeptide (Tyr-Ser-Pro-Thr-Ser-Pro-Ser) repeats. These repeats are essential for function. The Ser and Thr residues may be phosphorylated. Phosphorylation of the carboxy-terminal domain may affect the promoter-specificity of

the enzyme. The C-terminus of (CTD) of the large subunit is instrumental also in the processing of the 3'-end of the transcript and the termination of transcription downstream of the polyA signal. CTD does not seem to affect initiation of transcription but it also mediates the response to enhancers. This enzyme is different from RNA pol I and RNA pol III inasmuch that it requires a hydrolyzable source of ATP for the initiation of transcription. RNA pol II is different from the other polymerases in its requirement for a large array of special transcription factors that modulate the transcription of the thousands of proteins. ►transcription factors, ►regulation of gene activity, ► α -amanitin, ►transcription factories, ►RNA polymerase; Cramer P et al 2001 Science 292:1863.

pol III: Prokaryotic DNA polymerase, where the α subunit carries out the replication function and the ϵ -subunit is involved in editing (exonuclease) activity. It plays a major role in the replication of the leading and lagging strands. The replication has a speed of ≈ 1 kb/sec. There are only about 10–20 copies of the 10-subunit holoenzyme/cell. ►DNA replication, ►replication fork, ►core polymerase, ►replisome

pol III: RNA polymerase involved in the synthesis of transfer RNA, 5S rRNA, 7S rRNA and U6 snRNA in eukaryotes. Transcription of pol III is higher during S and G2 phases of the cell cycle than during G1. Many neoplastic cells display high pol III activity indicating that protein synthesis is demanded for tumorous growth. The RET protein appears to be a suppressor of increased pol III activity. ►tRNA, ►ribosomal RNA, ►ribosomes, ►La; Geiduschek EP, Tocchini-Valentini GP 1988 Annu Rev Biochem 57:873; Huang Y, Maraia RJ 2001 Nucleic Acids Res 29:2675.

pol IV: A low-fidelity lesion bypass DNA polymerase belonging to the Y family. ►Y-family DNAs polymerases, ►RNA polymerase

pol α : DNA polymerase (encoded in fission yeast by gene *pol1/swi7*), replicating the nuclear DNA (lagging strand) in cooperation with the primase of eukaryotes. Its mutation may result in mutator activity (Gutiérrez PJA, Wang TS-F 2003 Genetics 165:65). ►lagging strand, ►replication fork, ►DNA polymerases, ►primase

pol β : A eukaryotic DNA repair polymerase. ►DNA polymerases

pol δ : A eukaryotic DNA polymerase (replicating the leading strand) of the nuclear chromosomes. ►replication fork, ►DNA polymerases

pol δ_2 : Synonymous with pol ϵ . ►DNA polymerases

pol ϵ : A eukaryotic DNA polymerase (*cdc20*) with repair role. ►DNA polymerases

pol γ : A DNA polymerase replicating eukaryotic organelle DNA. ► θ type replication, ►DNA polymerases

pol ζ : A eukaryotic DNA polymerase without exonuclease activity. It is a repair enzyme inasmuch that it can bypass pyrimidine dimers more efficiently than pol α . It is insensitive to 200 μ M aphidicolin (and in this respect it is similar to pol β and pol γ) and also insensitive to dideoxynucleotide triphosphates (which inhibit pol β and pol γ). It is moderately sensitive to 10 μ M butylphenyl-guanosine triphosphates. It is relatively inactive with salmon sperm DNA or primed homo-polymers. ►DNA polymerases

Poland Syndrome: An autosomal dominant defect with low penetrance. the teratogenic effects of diverse exogenous factors complicate the inheritance pattern. It is characterized by fusion of fingers (syndactily), short fingers, and anomalies of chest and, sometimes, other muscles. ►limb defects, ►syndactily, ►penetrance, ►teratogenesis

Polar: Hydrophilic, i.e., soluble in water; molecules with polarized bonds.

Polar Body: ►gametogenesis in animals

Polar Body Diagnosis: In polar body diagnosis, the genetic constitution of the polar body is tested by molecular techniques prenatally. ►prenatal diagnosis

Polar Bond: A polar bond is covalent, yet the electrons are more firmly tied to one of the two molecules and therefore the electric charge is polarized.

Polar Coordinate Model: The polar coordinate model of regeneration states that when cells are in non-adjacent positions, the process of growth restores all intermediate positions by the shortest numerical routes. The shortest intercalation mandates that small fragments may undergo duplication and large fragments may require regeneration. The position of each cell on a collapsed cone (the idealized primordium) is specified by the radial distance from a central point at the tip of the cone and the circumferential position on the circle defined by the radius of the base. ►distalization; Held LI 1995 Bioessays 17:721.

Polar Cytoplasm: Polar cytoplasm is situated in the posterior (hind) portion of the fertilized egg cell. ►pole cells

Polar Ejection Force (PEF): Microtubule

Polar Granules: The polar granules are present in the posterior pole region of insect eggs and have maternal effect and germ cell specification roles during

embryogenesis. These granules are the mitochondrially coded 16S ribosomal RNA large subunits (mtRNA), exported from that organelle. ►[animal pole](#), ►[morphogenesis in *Drosophila*](#), ►[RNA localization](#); Strom S, Lehmann R 2007 Science 316:392.

Polar Molecule: A polar molecule is generally soluble in water; the distribution of the positive and negative charges are not even, thus resulting in a polarized effect.

Polar Mutation: A polar mutation may be a base substitution (nonsense mutation), insertion, frame shift, or any chromosomal alteration that affects the expression of genes down-stream in the transcription–translation system. ►[frame shift mutation](#); Jacob F, Monod J 1961 Cold Spring Harbor Symp Quant Biol 26:193.

Polar Nuclei: The polar nuclei occur in the embryosac of plants, and are formed at the third division of the megaspore. After they have fused ($n + n$) and have been fertilized by one sperm (n) they give rise to the triploid ($3n$) endosperm nucleus. ►[megagametophyte](#), ►[embryosac](#)

Polar Overdominance: An unusual type of inheritance, i.e., mutants heterozygous for the dominant *calypige* gene of sheep (chromosome 18) display the (*CLPG*) allele only when inherited from the males but not from the females. The phenotype is a muscular hypertrophy resulting from the cis-regulation of four imprinted genes. ►[imprinting](#), ►[overdominance](#); Charlier C et al 2001 Nature Genet 27:367; Smit M et al 2003 Genetics 163:453.

Polar Transport: Certain metabolites move only in one direction in the plant body, e.g., the auxins under natural conditions are synthesized in the tissues over the ground and then move toward the roots.

Polarimeter: The polarimeter measures the rotation of the plane of polarized light.

Polarisome: A polarisome defines polarity within a cell with the aid of several proteins. (See Weiner OD 2002 Curr Opin Cell Biol 14:196).

Polarity, Embryonic: Embryonic polarity is required for differentiation and requires asymmetric cell divisions. In *Caenorhabditis*, the PAR proteins (serine/threonine kinase) control embryonic polarity and a non-muscle type myosin II heavy chain protein (NMY-2) is a cofactor of this polarity. Upon fertilization the Rho guanosine triphosphatase-activating protein CYK-4—enriched in the sperm—and the RhoA guanine exchange factor ECT-2—modulate myosin light chain activity and create an actomyosin gradient, which determines the anterior domain in the one-cell embryo in *Caenorhabditis*

(Jenkins N et al 2006 Science 313:1298). In *Drosophila*, the major body axes, primarily the anterior-posterior polarity are controlled by the gurken-torpedo gene products, but other genes are also involved. Polarity may be achieved either by the asymmetric distribution of proteins or mRNA. ►[morphogenesis in *Drosophila*](#), ►[differentiation](#), ►[polar cytoplasm](#), ►[RNA localization](#), ►[BUD](#), ►[RHO](#), ►[myosin](#), ►[actomyosin](#); Drees BL et al 2001 J Cell Biol 154:549; Wodarz A 2002 Nature Cell Biol 4:E39; Frizzled pathway: Seifert JRK, Mlodzik M 2007 Nature Rev Genet 8:126.

Polarity of Hyphal Growth: See Fig. P91, Nelson WJ 2003 Nature [Lond] 422:766.

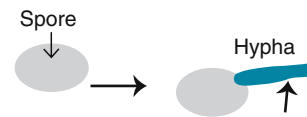


Figure P91. Polarity of hyphal growth

Polarity Mapping: ►[mapping mitochondrial genes](#)

Polarization: The distortion of the electron distribution in one molecule caused by another. ►[bouquet of chromosomes](#)

Polarized Differentiation: the basis of morphogenesis, chemotactic response, response to pheromones, etc. Polarized differentiation and growth is typical for neural and microtubule growth, for the pollen tubes, and for the roots of plants. Neuronal polarization requires the activity of SAD kinases in mammals (Kishi M et al 2005 Science 307:929). ►[asymmetric cell division](#); Hepler PK et al 2001 Annu Rev Cell Dev Biol 17:159; Science [2002] 298:1941–1964.

Polarized Light: Polarized light exhibits different properties in different directions at right angles to the line of propagation. Specific rotation is the power of liquids to rotate the plane of polarization.

Polarized Recombination: ►[polarized segregation](#)

Polarized Segregation: Polarized segregation may be brought about by meiotic anomalies, e.g., in maize plants heterozygous for some knobbed chromosomes (and syntenic markers) are preferentially included into the basal megaspore. Polarized segregation has been observed as a result of gene conversion, e.g., in *Ascobolus immersus* alleles of the *pale* locus in the cross $\frac{188w^+}{188^+w}$ segregated in both cases, it is 6:2, but in the first case the results were $(4[188] + 2[w^+]) : 2(w)$ whereas in the cross $\frac{w^{137+}}{w^{+137}}$ the conversion asci were $(4[w] + 2[137]) : 2(w^+)$. The genetic order of these alleles were *188 w 137*. Thus in the first cross *white*

was in the minority class whereas in the second cross it was part of the majority class. ►[gene conversion](#), ►[meiotic drive](#), ►[map expansion](#); Whitehouse HLK, Hastings PJ 1965 Genet Res 6:27.

Polarizing Microscope: The polarizing microscope uses a *polarizer* (a polaroid screen) in front of the light beam and an *analyzer* (permitting rotation) over the eyepiece. The anisotropic specimens (having difference in transmission or reflection depending on the angle of light) will display optical contrast. ►[microscopy](#)

Polarography: Electrochemical measurement of reducible elements.

Polaroid Camera: The Polaroid camera was developed during the 1940s and has found many uses in biological laboratories because it can provide almost immediate negative or positive images for recording observations such as those of electrophoretic gels. The combined developing and fixing solution is contained in between the exposed negative film and the receiving film or paper and when the storage “pod” bursts under pressure of pulling, the processing is carried out within the camera. For the majority of tasks, the digital cameras are even better suited for fast imaging.

Polaron: The part of a locus within which gene conversion (or recombination) is polarized. ►[gene conversion](#), ►[polarized segregation](#); Whitehouse HLK, Hastings PJ 1965 Genet Res 6:27.

Pole Cells: Pole cells localized in the posterior-most part of the cellularized embryo and give rise eventually to the germline. ►[germline](#)

Polintons: Typically, 15–20 kb long transposable elements in a wide range of lower and higher eukaryotes. They require a unique set of proteins for transposition such as protein-primed DNA polymerase B, retroviral integrase, cysteine protease, and ATPase. They show a 6 bp target site duplication and long inverted terminal repeats with 5'-AG and 3'-TC termini (Kapitonov VV, Jurka J 2006 Proc Natl Acad Sci USA 103:4540). ►[transposable elements](#)

Polioviruses: Icosahedral single-stranded RNA viruses with about 6.1 kb RNA in a total particle mass of about 6.8×10^6 Da; Type 1 was responsible for about 85% of the poliomyelitis (infantile paralysis) cases before successful vaccination (live oral, Sabin or inactivated, Salk) began to be widely used in the developed countries (see Fig. P92). These small RNA viruses are highly mutable because their genetic material lacks repair systems. The three serotypes produce a cell-surface receptor (PVR) by alternative



Figure P92. Apparent polio-stricken leg on a more than 3000 year old Egyptian hieroglyph

splicing of its transcript. Infectious poliovirus has been synthesized *de novo* without a natural template (Cello J et al 2002 Science 297:1016). Susceptibility to poliovirus was located to human chromosome 19q12-q13. Mice are very resistant to this virus because they lack the membrane receptor for the infection. ►[picornaviruses](#), ►[IRES](#), ►[synthetic genes](#)

Polled: A dominant/recessive gene (PIS) in goats and cattle, responsible for lack of horns/inter-sexuality. The forkhead transcription factor (FOXL2)—responsible also for blepharophimosis—may be involved. In goats, an 11.7 kb deletion at 1q43 (homologous to human band 3q23) normally encodes two mRNAs. The FOXL2 transcript is homologous with the human blepharophimosis syndrome gene. ►[blepharophimosis](#); Crisponi L et al 2001 Nature Genet 27:159; Pailhoux E et al 2001 Nature Genet 29:453.

Pollen: The male gametophyte of plants developing from the microspores by two postmeiotic divisions (see Fig. P93). The first division results in the formation of a vegetative and a generative cell. The round vegetative cell directs the elongation of the pollen tube growing through the pistil toward the ovule. Pollen tube growth is guided by sporophytic secretions (GABA, arabinogalactans and

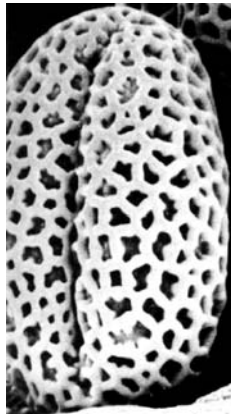


Figure P93. The sculptured surface of the mature pollen of *Arabidopsis*. (From Craig S, Chaudhury A 1994 In: Bowman JL (Ed.) *Arabidopsis: An Atlas of Morphology and Development*. Courtesy of Bowman JL By permission of Springer-Verlag, New York)

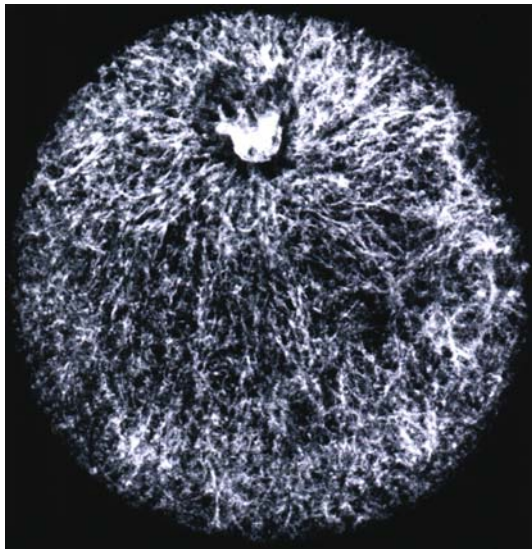


Figure P94. Fluorescent-phalloidin staining of the F-actin cytoskeleton in maize pollen. The bright spot on top is the pollen tube initial. (Courtesy of Dr. Chris Staiger. See Gibbon BC et al 1999 *Plant Cell* 11:2349)

proteins) (see Fig. P94). Synergids provide attraction by the 94-amino acid ZmEA1 protein in maize (Márton M et al 2005 *Science* 307:573).

The crescent-shaped generative cells may divide before or after the shedding of the pollen grains. One of them fertilizes the egg and thus, gives rise to the diploid embryo, the other fuses with the diploid polar cell in the embryosac and thus contributes to the formation of the endosperm. The pollen tube

elongates quite rapidly; it may grow 15 cm in just 5 to 15 h. A protein that is glycosylated in that tissue regulates the pollen tube elongation. In allogamous species, a single individual may shed over 50,000,000 pollen grains whereas in autogamous species the number of pollen grains per anther may not exceed a couple of hundreds. Since the pollen grain is haploid and may be autonomous (gametophytic control), it may express its genetic constitution independently from the genotype of the anther tissues (e.g., waxy pollen, various color or sterility alleles), in some instances, however, the morphology of the pollen grain is under sporophytic control. Since the pollen is a more independent product than the megaspore, it is more likely to suffer from genetic defects for which the surrounding tissues cannot compensate, therefore pollen sterility is more common in plants than female sterility. However, pollen sterility may not necessarily affect the fertility of the individuals because of the abundance of functional pollen grains in case of heterozygosity for the defects. Under normal atmospheric conditions (high humidity) and high temperature, the viability of the pollen is maintained (depending on the species) for a few minutes or for several hours. In a refrigerator, at low humidity the viability of the pollen can be extended substantially. Freeze-dried and properly stored pollen of several species retains its ability to fertilize for years. Insects may carry viable pollen for long distances. According to a study, in rye populations cross-pollination (mediated by wind) may occur to 50% at 100 m distance and to 20% at about 400 m distance, but only to 3% at 600 to 700 m. Other studies reported in rye only 7% cross-pollination within a distance of 20 m. Creeping bentgrass (*Agrostis stolonifera*) pollen, transgenic for a resistance marker (5-enolpyruvylshikimate-3-phosphate synthase), was spread by the wind primarily within a distance of 2 km but some dispersal occurred up to 21 km (Watrud LS et al 2004 *Proc Natl Acad Sci USA* 101:14533). The prevailing environmental conditions (humidity, temperature, wind, etc.) and the quantity of the pollen influences the spread and viability. These problems gained new interest with the use of genetically engineered crops that are opposed by some environmentalists. The extracellular matrix of the pollen contains proteins, which recognize species-specificity and efficient pollination (Myfield JA et al 2001 *Science* 292:2482). These proteins are lipid-binding oleosins and lipases. ▶microsporogenesis, ▶gametogenesis, ▶pollen tetrad, ▶gametophyte, ▶self-incompatibility, ▶cross-pollination, ▶GMO, ▶autogamy, ▶allogamy

Pollen Competition: ▶certation

Pollen-Killer: Pollen-killer or spore-killer genes in wheat, tomato, and tobacco render the pollen incapable of functioning effectively in fertilization and may cause segregation distortion. ▶segregation distorter, ▶pollen tube competition, ▶killer strains, ▶killer plasmids, ▶killer genes

Pollen Mother Cell: Microspore mother cell, microsporeocyte. ▶gametogenesis

Pollen Sterility: The inability of the pollen to function during fertilization. It can frequently be detected by the poor staining of the pollen grains with simple nuclear stains (acetocarmine, acetoorcein, etc.). Deletions, translocations, and inversion heterozygosity generally result in pollen sterility. Mitochondrial plasmids may also be responsible for some types of male sterility. ▶pollen, ▶certation, ▶gametophyte, ▶cytoplasmic male sterility, ▶fertility restorer genes

Pollen Tetrad: The four products of a single male meiosis (see Fig. P95). The components of the pollen tetrad may not stick together and may shed in a scrambled state. In some instances (*Salpiglossis*, *Elodea*, some orchids), the tetrads remain together, however, in a way similar to the unordered tetrads of fungi. In *Arabidopsis*, induced mutations (*qrt1*, *qrt2*, *quartet*) cause the four pollen grains to stay together because of the alteration of the outer membrane of the pollen mother cell. Each tetrad may then fertilize four ovules. ▶tetrad analysis



Figure P95. Pollen tetrad

Pollen Tube: In the majority of plants, the time between pollination and fertilization takes 24 to 48 h or less. In the alder tree (*Alnus*) the pollen tube travels slowly in the pistil (for about one month) because the ovary matures late and it arrives at fertilization in five successive steps. Also in some species, the ovaries may have multiple megaspore tetrads although, generally only one is fertilized (Sogo A, Tobe H 2005 Proc Natl Acad Sci USA 102:8770). ▶pollen, elongating pollen tube in Figure P96, ▶synergid,

▶GABA, ▶gametophyte, ▶double fertilization; Palavinelu R, Preuss D 2000 Trends Cell Biol 10:517.

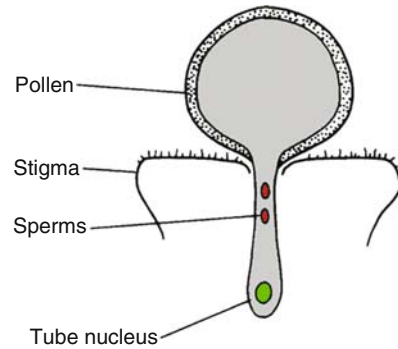


Figure P96. Pollen tube germination

Pollen-Tube Competition: ▶certation

Pollination: The transfer of the male gametophyte to the stigmatic surface of the style (ovary). Obligate allogamous plant populations may suffer if the pollinator insect populations are reduced by adverse environmental conditions (Vamosi J C et al 2006 Proc Natl Acad Sci USA 103:956). ▶gametophyte, ▶autogamy, ▶alogamy, ▶fertilization, ▶self-sterility

Pollinium: A mass of pollen sticking together and may be transported as such by the pollinator insects or birds.

Pollitt Syndrome: ▶trichothiodystrophy

Pollution: Spoiling the environment by the release of unnatural, impure, toxic, mutagenic, carcinogenic, or any other undesirable and unaesthetic material, or to disturb nature by sound, odor, heat, and light. Pollution may cause mutation, cancer, and various other diseases. ▶DNA-zyme; <http://www.scorecard.org>.

Polo: A 577-amino acid serine/threonine protein kinase of *Drosophila*, required for mitosis. It regulates centromeric cohesion protein MEI-S332 (Clarke AS et al 2005 Dev Cell 8:53). During interphase, it is predominantly cytoplasmic but at the end of prophase it associates with the chromosomes until telophase. Loss of polo kinase 4 allele(s) increases the probability of mitotic errors and cancer. In about 60% of the cells of mice, loss of heterozygosity takes place (Ko MA et al 2005 Nat Genet 37:883). ▶CDC5, ▶FEAR, ▶cohesin; Llamazares S et al 1991 Genes Dev 5:2153; Alexandru G et al 2001 Cell 105:459.

Polony (polymerase colony): A small batch of DNA synthesized by PCR with the assistance of a primer to

be used for sequencing. The PCR colonies on the glass microscope slide are the “colonies.” On a single slide in the polyacrylamide film, as many as 5 million clones can be amplified. The amplified products stay at the vicinity of the linear DNA. If acrydite modification is used, the DNA is covalently attached to the polyacrylamide matrix and thus further enzymatic modifications are possible on all clones. The technology is well suited for genotyping and localizing of SNPs. ▶PCR, ▶SNPs; Mitra RD, Church GM 1999 Nucleic Acids Res 27(24):e34; Mitra RD et al 2003 Proc Natl Acad Sci USA 100:5926.

Poly I-G: A DNA strand containing more cytosine is called heavy chain of a DNA double helix because it binds more of the polyI-G (inosine-guanosine) sequences. Ultracentrifugation in CsCl separates these DNA heavy strands. ▶ultracentrifuge, ▶density gradient centrifugation, ▶DNA heavy chain, ▶inosine

PolyA⁺ Element: Transposons without long terminal repeats but poly-A sequences at the 3'-OH end. The RNA elements are usually mobilized via a DNA transcript with the aid of their encoded reverse transcriptase. Such elements are L1 (LINE) in mammals, the TART of *Drosophila*, the TRAS1 of silkworm, or the yeast Ty5 telomere-specific elements. Other polyA⁺ elements (L1, I, and fungal and plant elements) can target a variety of other sites. ▶TART, ▶hybrid dysgenesis, ▶transposable elements

polyA mRNA: Eukaryotic mRNAs post-transcriptionally polyadenylated at the 3' tail before leaving the nucleus. Subsequently, in the cytoplasm, the tail may be reduced to 50–70 residues or further extended to hundreds. Polyadenylation improves the stability and efficiency of translation in cooperation with mRNA cap. The polyA tail and the mRNA cap seem to cooperate in the initiation of translation. PolyA tail is frequently added also to bacterial RNA. The addition of polyA tail accelerates the decay of RNA I of *E. coli*. All the data are consistent with polyadenylation being part of a quality control process targeting folded bacterial RNA fragments and non-functional RNA molecules to degradation. In *Escherichia coli*, polyadenylation may directly control the level of expression of a gene by modulating the stability of a functional transcript. Inactivation of poly(A) polymerase I causes overexpression of glucosamine-6-phosphate synthase (GlmS) and both the accumulation and stabilization of the *glmS* transcript (Joanny G et al 2007 Nucleic Acids Res 35:2494).

The majority of eukaryotic viruses (except arenaviruses and reoviruses) also produce a poly A tail. In *Drosophila*, the length of the poly(A) tail may be

correlated with the function in the differentiation of the mRNA. The regulatory mechanism of polyadenylation is interchangeable between mouse and *Xenopus*. Some genes use alternative polyadenylation sites (Edwards-Gilbert G et al 1997 Nucleic Acids Res 25:2547). ▶polyadenylation signal, ▶mRNA tail, ▶RNA I, ▶PABP, ▶mRNA degradation, ▶capping enzymes, ▶eIF; de Moor CH, Richter JD 2001 Int Rev Cytol 203:567; <http://polya.umdj.edu/>.

polyA Polymerase (PAP): adds the polyA tail post-transcriptionally to the eukaryotic mRNA and antisense RNA transcripts (see Fig. P97). In yeast, at least two other genes *RNA14* and *RNA15* are involved in the processing of the 3'-end of the pre-mRNA.

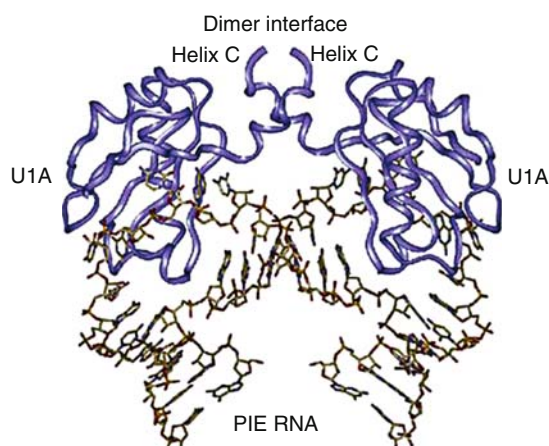


Figure P97. Poly(A) polymerase is regulated by inhibition (or stimulation) by the polyadenylation inhibition RNA element (PIE). PIE forms a trimolecular complex including the two U1A protein molecules. The U1A consists of a four-stranded β -sheet and two α -helices. The two C helices of the protein interface. The PIE RNA, which contains two asymmetric internal loops is separated by four Watson-Crick-paired nucleotides. (From Puglisi JD 2000 Nature Struct Biol 7:263)

E. coli also encodes at least two PAP enzymes. PolyA polymerase also facilitates the degradation of mRNA because it provides single-strand tails for polynucleotide phosphorylase. Bacterial PAP and tRNA nucleotidyl transferase are highly similar in structure but different in function inasmuch the latter catalyzes the addition of CCA to the 3'-end of tRNA. The C-terminal domain of nucleotidyl transferase restricts polymerization to these three nucleotides whereas a 27-aminoacid sequence determines whether the protein becomes a transferase or PAP. Both proteins have identical nucleotide recognition and incorporation domains (Betat H et al 2004 Mol Cell 15:389). ▶mRNA tail, ▶polyadenylation signal, ▶polynucleotide phosphorylase; Dickson KS et al

2001 J Biol Chem 276:41810; Steinmetz EJ et al 2001 Nature [Lond] 413:327.

polyA Tail: ►polyadenylation signal, ►polyA mRNA

Polyacrylamide: See Fig. P98, ►electrophoresis, ►gel electrophoresis

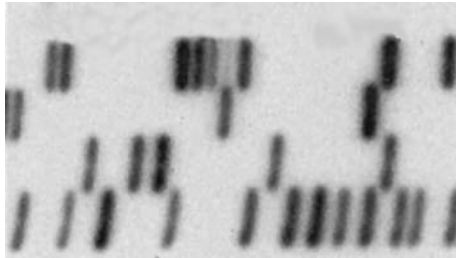


Figure P98. Polyacrylamide gel

Polyadenylation Signal: The endonucleolytic processing of the primary transcript of the majority of eukaryotic genes is followed by post-transcriptional addition of adenylic residues downstream of the structural gene. The consensus signal for the process is 5'-AAUAAA-3' in animals and fungi, about half of the plants use the same signal, the rest rely on diverse signals. In humans, ~54%, and in mouse, ~32% of the genes have alternative polyadenylation sites and different cleavage sites resulting in heterogeneity of the transcripts, which may represent a type of regulation of gene expression (Tian B et al 2005 Nucleic Acids Res 33:201). In eukaryotes, the number of added A residues might vary from 50 to 250. The crystal structure of the 73 kDa subunit of the human polyadenylation-specificity endonuclease has been determined (Mandel CR et al 2006 Nature [Lond] 444:953).

Polyadenylation is under the control of several genes (see Fig. P99). The RNA transcript of eukaryotes besides the poly(A) signal contains a CA element (PyA in yeast) and a GU-rich downstream element.



Figure P99. Some of the mechanisms in polyadenylation

To the AAUA AA *positioning element*, binds the *polyadenylation specificity factor* (CPSF) that is a tetrameric protein consisting of 160, 73, 100, and 33 kDa subunits. The *cleavage stimulating factor* (CstF), a trimeric protein of 64, 77, and 50 kDa subunits, binds to GU-rich element of the RNA. The *polyadenylation polymerase* protein (PAP) binds

downstream of the CPSF binding sites. The *cleavage factors* (CFI) and (CFII) are positioned upstream of the GU-rich element and they terminate the mRNA. The polyadenylation complex of yeast is somewhat different. The PABP (poly-A-binding protein, 70 kDa) regulates mRNA stability, translation, and degradation. CPEB (cytoplasmic element binding protein), maskin, and cyclin B1 are regulators of polyadenylation and the transcription of some mRNAs. Poly(A)-specific ribonuclease (PARN) is a cap-interacting 3' exonuclease. In cooperation with the cap, it mediates de-adenylation from cis position, or at low concentration it may be inhibitory to de-adenylation. From trans position, it inhibits de-adenylation if its concentration is high. The poly(A) tail, in synergy with the mRNA cap, stimulates the initiation of translation. The poly(A) binding protein (PABP) interacts with eIF4G of the eIF4F complex and eIF4E interacts with the cap and stabilizes mRNA. PABPs are located both in the nucleus and in the cytoplasm. In the human testes, a specific poly(A) binding protein occurs that is absent from other tissues (Féral C et al 2001 Nucleic Acids Res 29:1872). De-adenylation of the tail initiates mRNA decay and when less than ten A residue is left, an exonuclease attacks the RNA in 5'→3' direction (Martínez J et al 2001 J Biol Chem 276:27923). In prokaryotes, rarely a few (14–60) adenine residues are also found at the mRNA 3'-terminus in 1 to 40% of the cases. In bacteria, *host factor q* (Hfq) plays a role similar to PABP. It stimulates the elongation of the polyA tail by poly(A) polymerase I (PAP) and protects against exoribonuclease attack. Some adenine sites are found in about 30% of both the early transcripts (transcribed by host polymerase) and late transcripts (transcribed by viral polymerase). Sometimes the poly-A sequence has interspersed other bases and may be located also within coding sequences. An interspersed long poly(A) sequence was detected also in chloroplast RNA transcripts. In mitochondria, the poly-A tract (35–55 A residues) directly attaches to the termination codon without an untranslated sequence, after the endonucleolytic cleavage of the polycistronic transcript. In liver cancer, mitochondria tails of hundreds of As have been observed. In prokaryotes, two similar (36 and 35 kDa) poly-A polymerases with overlapping functions have been identified. With the exception of histone transcripts, all eukaryotic mRNAs appear polyadenylated, although some can be processed to become non-polyadenylated and the two types may coexist (bimorphic transcript). Polyadenylation of RNA in bacteria regulates plasmid replication and the degradation of RNAI. In yeast, the Trf4 complex recruits exosomes and the incorrectly folded polyadenylated RNA is degraded (Vaňáčová S et al 2005 PLoS Biol 3(6):e189). (In *Archaea* short poly-A tracts

exist). Cordycepin (3'-deoxyadenosine) is an inhibitor of polyadenylation.

In the *Drosophila melanogaster* genome, 17 polyadenylated sequences were detected without protein coding transcripts, yet many of these sequences were conserved in related species indicating some roles because of their conservation (Tupy JL et al 2005 Proc Natl Acad Sci USA 102:5495). Let-7 miRNPs, containing, Argonaute and GW182, dampen the synergistic enhancement of translation by the 5'-cap and 3'-poly(A) tail, resulting in translational repression (Wakayama M et al 2007 Genes Dev 21:1857). ▶mRNA tail, ▶U1 RNA, ▶polyA polymerase, ▶RNA I, ▶cleavage stimulation factor, ▶PABp, ▶mRNA circularization, ▶eIF4, ▶TRAP, ▶symplekin, ▶microRNA, ▶Argonaute, ▶GW body; Hirose Y, Manley JL 1998 Nature [Lond] 395:93; Sarkar N 1997 Annu Rev Biochem 66:173; Beaulieu E et al 2000 Genome Res 10:1001; Mendez R Richter JD 2001 Nature Rev Mol Cell Biol 2:521; Wang L et al 2002 Nature [Lond] 419:312; <http://polya.umdj.edu/>; http://polya.umdj.edu/PolyA_DB2.

Poly(ADP-Ribose) Polymerase: A DNA-binding enzyme but it appears to have no indispensable function.

Polyamides: Polyamides containing *N*-methylimidazole and *N*-methylpyrrole amino acids have high affinity for specific DNA sequences and may regulate the transcription similarly to DNA binding proteins. ▶binding proteins, ▶inhibition of transcription, ▶netropsin, ▶lexitropsin; Maeshima K et al 2001 EMBO J 20:3218.

Polyamidoamine Dendrimers (PAMAM): Highly branched, soluble, non-toxic molecules with amino groups on their surface. They are suitable for attaching to this surface antibodies, various pharmaceuticals, and DNA. They are effective vehicles for transfection. (See Gebhart CL, Kabanov AV 2001 J Control Release 73:401).

Polyamines: Polyamines are various protein molecules derived in part from arginine and present in cells in millimolar concentrations, yet have important roles in RNA and DNA transactions, replication, supercoiling, bridging between strands, binding phosphate groups, biosynthesis, degradation, etc. Typical polyamines are spermine, spermidine, putrescine, etc. ▶antizyme, ▶lexitropsins; Coffino P 2001 Nat Rev Mol Cell Biol 2:188; van Dam L et al 2002 Nucleic Acids Res 30:419.

Polyandry: A form of polygamy involving multiple males for one female. It may have the advantage of reducing the relatedness within colonies of social insects and thereby increasing fitness. In the

live-bearing pseudoscorpions (*Cordylochernes scorpioides*), outbred embryos have beneficial effects on inbred half-siblings in mixed-paternity broods developing in the external, translucent brood sac and fed by nutrients of the maternal reproductive tract by an unclear mechanism (Zeh JA, Zeh DW 2006 Nature [Lond] 439:201). Honeybee queen matings with several drones enhances productivity and fitness of the colony (Mattila HR, Seeley TD 2007 Science 317:362). ▶fitness; Tregenza T, Wedell N 2002 Nature [Lond] 415:71.

Polyaromatic Compounds: Polyaromatic compounds include various procarcinogens and promutagens, such as benzo(a)pyrene, dibenzanthracene, methylcholanthrene, etc. ▶polycyclic hydrocarbons.

Polybrene (hexadimethrine bromide): A polycation used for introduction of plasmid DNA into animal cells; it is also an anti-heparin agent and an immobilizing agent in Edman degradation. Polybrene may have different toxicity to various cells. ▶transformation genetic animal cells, ▶heparin, ▶Edman degradation

Polycentric Chromosome: ▶neocentromeres

Polychlorinated Biphenyl (PCB): A highly carcinogenic compound and an inducer of the P-450 cytochrome group of monooxygenases. It had been used in electrical capacitors, transformers, fire retardants, hydraulic fluids, plasticizers, adhesives, pesticides, inks, copying papers, etc. *Pseudomonas* sp. KKS102 is capable of degrading PCB into tricarboxylic acid cycle intermediates and benzoic acid. ▶microsomes, ▶S-9, ▶P-450, ▶carcinogen; Ohtsubo Y et al 2001 J Biol Chem 276:36146.

Polychromatic: A polychromatic substance is stainable by different dyes or displays different shades when stained.

Polycistronic mRNA: A contiguous transcript of adjacent genes, such as exist in an operon but may also be formed in the short genes of eukaryotes, e.g., oxytocin. The *Trypanosomas* produce multicistronic transcripts. A gene (*mlpt*) of *Tribolium* involved in body segmentation also produces polycistronic mRNA. ▶operon, ▶oxytocin, ▶*Trypanosoma*, ▶*Caenorhabditis*, ▶*Tribolium*

Polyclonal Antibodies: Polyclonal antibodies are produced by a population of lymphocytes in response to antigens. These are not homogeneous as are the monoclonal antibodies. ▶monoclonal

Polycomb (*Pc*, chromosome 3-47.1): The *Drosophila* gene is a negative regulator of the *Bithorax* (*BXC*) and *Antennapedia* (*ANTC*) complexes (see Fig. P100). The homozygous mutants are lethal and the locus

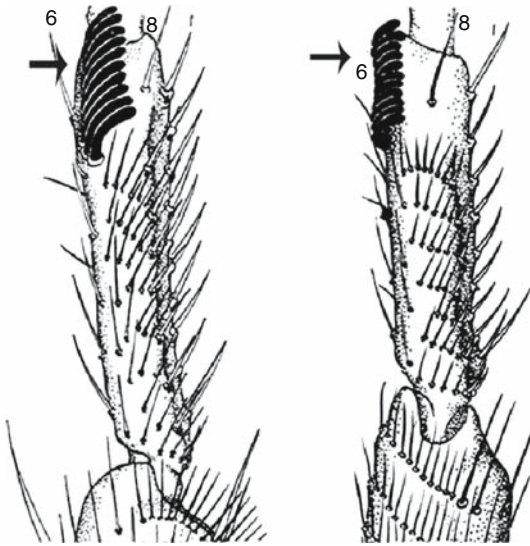


Figure P100. Sex combs on the second legs of male *Drosophila* in the *Sex comb extra* (*Scx*, 3.47, at left) and *Scx-Pc* (at right) homeotic mutants. Similar extra sex combs appear also on the third leg whereas sex combs in the wild type are limited to the first pair of legs. (After Hannah-Alava A 1958 *Genetics* 43:878)

(and its homologs in vertebrates [*M33* in mice]) is involved in the repression of homeotic genes, which control body segmentation. *Pc* is a member of a group (*Pc-G*) of repressors of homeotic genes (Cao R et al 2002 *Science* 298:1039). Although *Pc* is located in the euchromatin, it is involved in the silencing of genes by heterochromatin (Francis N et al 2004 *Science* 306:1574). Genes have been identified that are targeted for transcriptional repression in human embryonic stem (ES) cells by the *Pc-G* proteins suppressor of zeste 12 (*SUZ12*) and embryonic ectoderm development (*EED*), which form the Polycomb repressive complex 2 (*PRC2*) and which are associated with nucleosomes that are trimethylated at Lys27 of histone H3 (H3K27). Stem cell occupancy by *SUZ12* and *EED* and the trimethylation status of H3K27 for 77/177 genes showed evidence of cancer-associated DNA methylation when compared with matched normal colorectal mucosa. The observations suggest that the first predisposing steps towards malignancy may occur very early and are consistent with reports of field changes in histologically normal tissues adjacent to malignant tumors. These results provide a mechanistic basis for the predisposition of certain promoter CpG islands to cancer-associated DNA hypermethylation as an early epigenetic cancer marker (Widschwendter M et al 2007 *Nat Genet* 39:157).

Pc is involved in Histone2A ubiquitylation and the inactivation of mammalian X chromosome

(de Napoles M et al 2004 *Dev Cell* 7:663). Insertion into the 5th exon of *M33* caused male→female sex-reversal. *Pc* is required for the activation of other silencing elements and its mutation may lead to derepression of these elements. The suppressive effect of *Pc* may be associated with chromatin remodeling and histone deacetylation. The Polycomb group of proteins forms a large complex and the TATA-box-binding proteins, Zeste and others, are associated with the general transcription machinery (Czermin B et al 2002 *Cell* 111:185). The *SUZ12* subunit of the Polycomb Repressive Complex 2 (*PRC2*) extends over 200 genes encoding developmental regulators of human embryonic stem cells (such as Nanog, Oct4, Sox2, RNAP2 and *SUZ12*) (see Fig. P101). These genes are transcriptionally repressed because in the nucleosomes histone H3K27 is trimethylated. The *PRC2* target genes are repressed in order to maintain pluripotency of these cells but they are activated during differentiation (Lee TI et al 2006 *Cell* 125:301). The *PRC1* and *PRC2* polycomb complexes co-occupy 512 genes and bind hundreds of others (►Venn diagram) coding for transcription factors during mouse embryonic development until differentiation (Boyer LA et al 2006 *Nature [Lond]* 441:349).

►morphogenesis in *Drosophila*, ►transdetermination, ►*SWI*, ►homeobox, ►homeotic genes, ►chromodomain, ►sex-reversal, ►*w* locus, ►*zeste*, ►*Antennapedia*, ►*Bithorax*, ►*trithorax*, ►chromatin remodeling, ►nucleosomes, ►histone deacetylase, ►histones, ►TBP, ►transcription factors, ►Lyonization, ►ubiquitin, ►epigenesis, ►stem cells, ►genetic networks, ►pairing-sensitive repression; Breilling A et al 2001 *Nature [Lond]* 412:651; Simon JA, Tamkun JW 2002 *Curr Opin Genet Dev* 12:210; Polycomb repressor complex in epigenesis: Kuzmichev A et al 2005 *Proc Natl Acad Sci USA* 102:1859; review: Schwartz YB, Pirrotta V 2007 *Nat Rev Genet* 8:9; review: Schüttengruber B et al 2007 *Cell* 128:735.

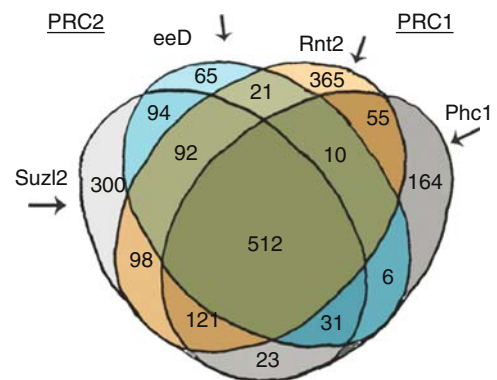


Figure P101. Polycomb group proteins overlap and repress many developmental regulators of mouse

Polycross: An intercross among several selected lines to produce a “synthetic variety” of a crop (See Tysdal HM et al 1942 Alfalfa Breeding, Nebr Agric Exp Sta Res Bull 124, Lincoln, Nebraska).

Polycyclic Aromatic Hydrocarbons (PAH): Generally, carcinogenic and mutagenic compounds. They become more active during the process of attempted detoxification by the microsomal enzyme complex. PAHs are the products of burning organic material (coal, charbroiling, smoking, etc.). Mice oocytes exposed to PAHs suffer apoptosis by activation of BAX. ▶carcinogens, ▶procarcinogens, ▶mutagens, ▶promutagens, ▶benzo(a)pyrene, ▶environmental mutagens, ▶PAH, ▶BAX, ▶apoptosis; Matikainen T et al 2001 Nature Genet 28:355.

Polycystic Lipomembraneous Osteodysplasia with Sclerosing Leukoencephaly (PLOS), Nasu-Hakola disease, 19q13.1): A recessive psychosis turning into presenile dementia and bone cysts limited to the wrists and ankles. Prevalence in Finland is 2×10^{-6} . The basic problem is a loss of function of the TYROBP/DAP12 tyrosine kinase binding transmembrane protein, an activator of killer lymphocytes. ▶killer cells

Polycystic Kidney Disease (PKD): PKD occurs in two main forms, and within each several form variations exist (see Fig. P102). The short arm of human chromosome 16p13.31-p13.12 apparently controls the adult type dominant (ADPKD), which involves fragility of the blood vessel walls. In the autosomal recessive ARPKD, the basic defect is in the

Ca^{2+} -permeable non-selective cation channel. About 15% of the APKD cases are due to mutation in the gene (PKD2) encoding polycystin. Another gene (PKD1) is involved in the proliferation of the epithelial cells lining the cyst cavity, the thickening of the basement membrane, fluid secretion, and protein sorting (Bukanov NO et al 2002 Hum Mol Genet 11:923). ARPKD generally has an early onset. Both forms occur at frequencies of 0.0025 to 0.001. Even the late onset type may be detectable early by tomography. The symptoms vary and involve kidney disease, cerebral vein aneurism (sac like dilatation), underdeveloped lungs, liver fibrosis, and growth retardation, etc. The dominant type can be identified with high accuracy using chromosome 16p13 DNA probes but less than 10% of the cases are due to genes not in chromosome 16. The autosomal recessive form is at an unknown location and it can be identified after the third trimester by ultrasonic methods because the kidneys are enlarged. The genetic transmission of the dominant and recessive diseases is very efficient. One polycystic kidney (PKD1, 4300-amino acid integral membrane glycoprotein) locus was assigned to 6q21-p12, and sequences were also found in 2p25-p23 and 7q22-q31; these are homologous to polycystic kidney disease of the mouse. There is a PKD2 locus in 4q21-q23 and this is similar in function to PKD1. PKD2 interacts with PKD1 and PKD2 interacts also with the Hax-1 protein binding F-actin, suggesting that the system affects the cytoskeleton. Thus defect in PKD2 may be one of the causes of cyst formation in the kidney, liver, and pancreas. The

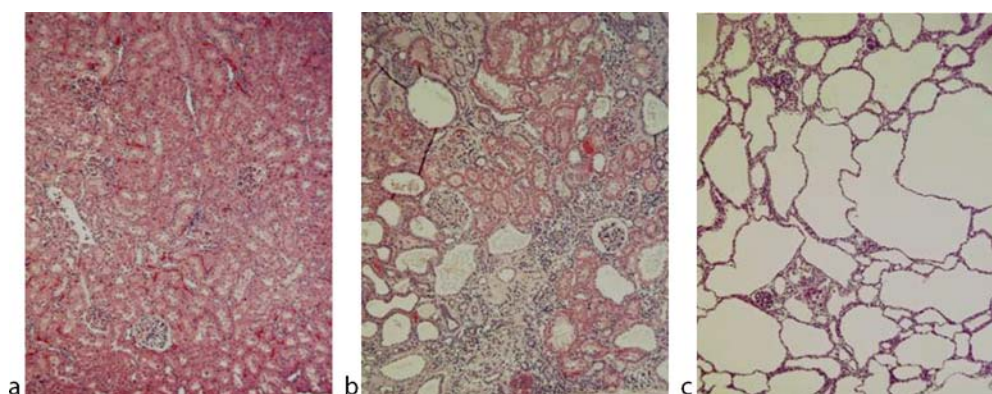


Figure P102. Polycystic kidney disease in RRRCHa:SPRD rat. a: wild type, b: heterozygote, and c: homozygous *Pkdr1* mutant. The homozygous mutant rats die at age 3–4 weeks. Heterozygous males develop renal failures by about 6 months whereas the heterozygous females rarely progress to renal failure and death. Heterozygous males can be identified by blood urea nitrogen (BUN) level of the serum or plasma at age 9–10 weeks. PCR analysis and sequencing detected A for G substitution in exon 12 of the mutant gene. (The histological images are the courtesy of Professors Beth A. Bauer and Craig L. Franklin, Rat Resource and Research Center University of Missouri, Columbia, Missouri 6211; <http://www.nrrrc.missouri.edu/Straininfo.asp?apn=46>)

infantile type recessive PKD is also called Caroli disease. The ARPKD locus encodes a 968-amino acid protein, which forms six transmembrane spans with intracellular amino and carboxyl ends. It appears to be a voltage-activated Ca^{2+} (Na^+) channel protein. In a mouse model and in humans, TOR antagonist rapamycin protein may alleviate the dominant ADPKD disease (Schillingford JM et al 2006 Proc Natl Acad Sci USA 103:5466). The CDK inhibitor roscovitine ($\text{C}_{19}\text{H}_{26}\text{N}_6\text{O}$) appears to be an effective inhibitor of PKD in mouse (Bukanov NO et al 2006 Nature [Lond] 444:949). PKD1 may involve haplo-insufficiency. The PKD1 homolog in *Caenorhabditis* (*LOV-1*) controls sensory neurons required for male mating behavioral steps. The traditional Chinese drug, a diterpene triptolide (Lei Gong Teng), induces PC2-dependent calcium release and attenuates cyst formation (see Fig. P103) (Leuenroth SJ et al 2007 Proc Natl Acad Sci USA 104:4389). ▶cardiovascular disease, ▶Caroli disease, ▶hypertension, ▶genetic screening, ▶ion channels, ▶haplo-insufficient, ▶rapamycin, ▶CDK; Pei Y et al 2001 Am J Hum Genet 68:355; Lin F et al 2003 Proc Natl Acad Sci USA 100:5286; autosomal dominant polycystic kidney disease: <http://pkdb.mayo.edu/>.

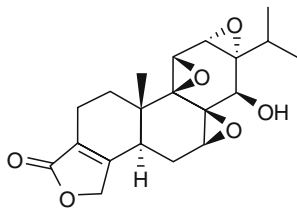


Figure P103. Triptolide

Polycystic Liver Disease; (PCLD, 19p13.2-p13.1): A dominant, often accompanying polycystic kidney disease. It involves fluid-filled cysts on the liver. The protein involved is hepatocystin. (See Drenth JPH et al 2003 Nat Genet 33:345).

Polycystic Ovarian Disease (Stein-Leventhal syndrome): Polycystic ovarian disease generally involves enlarged ovaries, hirsuteness, obesity, lack of or irregular menstruation, increased levels of testosterone high ratios of luteinizing hormone: follicle-stimulating hormone, and infertility. It appears to be due an autosomal factor, yet 96% and 82% of the daughters of affected mothers and carrier fathers, respectively, developed the symptoms indicating a meiotic drive-like phenomenon. Deficiency of 1- α -ketosteroid reductase/dehydrogenase (9q22) may cause polycystic ovarian disease as well as pseudohermaphroditism with gynecomastia in males. ▶infertility, ▶luteinization, ▶Graafian follicle, ▶meiotic drive, ▶pseudohermaphroditism, ▶gynecomastia

Polycystin: Polycystin proteins are supposed to regulate different functions, such as mating behavior, fertilization by the sperm, asymmetric gene expression, and mechanosensory transduction (Delmas P 2004 Cell 118:145).

Polycythemia (PFCP): An autosomal dominant proliferative disorder of the erythroid progenitor cells, resulting in an increase in the number of red blood cells and in vitro hypersensitivity to erythropoietin. Mutations in the von Hippel-Lindau protein are responsible for about half of the cases. Mutations of valine→phenylalanine at amino acid site 617 in Janus kinase 2 occurs in more than 80% of acquired polycythemic mice and leads to constitutive tyrosine phosphorylation and increased sensitivity to cytokinins (James C et al 2005 Nature [Lond] 434:1144) ▶erythropoietin, ▶Janus kinases, ▶von Hippel-Lindau syndrome; Pastore Y et al 2003 Am J Hum Genet 73:412.

Polydactyly: The presence of extra fingers or toes. In *postaxial* polydactyly (the most common type), the extra finger is in the area of the “little finger” (see Fig. P104) and in *preaxial* cases, this malformation is on the opposite side of the axis (thumb) of the palm or foot. The various types of polydactyly may be determined by autosomal recessive or dominant gene(s) and their expression is usually part of other syndromes. Crossed polydactyly indicates coexistence of postaxial and preaxial types with discrepancy between hands and feet. Synpolydactyly is caused by an expansion of the normal 15 GCG trinucleotides to 22–29.



Figure P104. Polydactyly (From Bergsma D (ed) 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

►Ellis-van Creveld syndrome, ►Opitz syndrome, ►Meckel syndrome, ►Majewski syndrome, ►orofacial-digital syndromes, ►Patau's syndrome, ►diastrophic dysplasia, ►syndactyly, ►polysyndactyly, ►Greig's cephalopolysyndactyly syndrome, ►Rubinstein-Taybi syndrome, ►Pallister-Hall syndrome, ►focal dermal hypoplasia, ►ectrodactyly, ►adactyly, ►*hedgehog*

Polyelectrolytes: Polymers with attached anions and cations, respectively. Proteins and nucleic acids can be polyelectrolytes by carrying negatively and positively charged groups.

Polyembryony: In polyembryony, more than one cell of the embryo sac develops into an embryo in plants or in insects a single egg by clonal reproduction of hundreds of embryos. ►adventive embryos, ►embryo sac; Zhurov V et al 2004 Nature [Lond] 432:764.

Polydna Virus: ►parasitoid

Polyethylene Glycol (PEG): A viscous liquid or solid compound of low-toxicity, promoting fusion of all types of cells. PEG is widely used in textile, cosmetics, paint, and ceramics industry. ►PEG

Polyethyleneimine (PEI): A water-soluble polymer, which binds and precipitates DNA. It assists in the uptake of molecules including transforming DNA, especially in RGD-coated particles. Polyethyleneimine (25 kDa) contains N-acyl groups, which handicap its use for genetic transfection (see Fig. P105). Removal of these groups enhances its utility as an artificial vector. New linear PEIs synthesized by acid-catalyzed hydrolysis of poly(2-ethyl-2-oxazoline) yielded products, which increased transfection efficiency up to 115-fold compared to deacetylated commercial PEI. In addition, its efficiency for targeting lung cells increased 200-fold. Using this vector for RNAi delivery against the nucleocapsid protein gene of influenza virus dropped the virus titer in the lung of mice. A further advantage was the lower toxicity. Note: ethyleneimines are poisonous and mutagenic. ►RGD, ►vectors, ►gene therapy

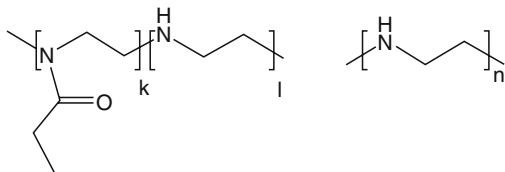


Figure P105. Left: PEI25 commercially available before hydrolysis. Right: Newly synthesized PEI after hydrolysis. After Thomas M et al. 2005 Proc. Natl. Acad. Sci. USA 102:5679

Polygalacturons: Complex carbohydrates in the plant cell wall.

Polygamy: Polygamy implies having more than one mating partner. In western human societies, it is illegal but in others, it is still acceptable for men to have more than one wife at the same time. Polyandry or polygyny is a common practice in animal breeding but it may be objectionable to humans on moral grounds. In the USA, polygamy laws are applied to all citizens, irrespective of religious affiliation or cultural tradition.

Polygenes: A number of genes involved in the control of quantitative traits. ►gene number in quantitative traits, ►QTL

Polygenic Inheritance: Polygenic inheritance is determined by a number of non-allelic genes, all involved in the expression of a single particular trait (such as height, weight, intelligence, etc.). Polygenic inheritance is characterized by counting and measurements and the segregating classes are not discrete but display continuous variation. ►quantitative genetics, ►QTL, ►complex inheritance, ►chaos, ►digenic diseases, ►selection long term, ►gain; Tanksley SD 1993 Annu Rev Genet 27:205; Klose J et al 2002 Nature Genet 30:385.

Polygenic Plasmids: are obtained when two plasmids carrying identical genes cointegrate. Such plasmids may have merit in genetic engineering if the genes show positive dosage effect for anthropocentrically useful traits. ►cointegration

Polygyny: In polygyny, one male has more than a single female mate. In *sororal polygyny*, the females are sisters. ►polygamy, ►effective population size

Polyglutamylase: The polyglutamylase enzyme adds several glutamic acids to the γ -carboxyl of a glutamate residue of proteins, such as tubulin and nucleosome assembly proteins (Janke C et al 2005 Science 308:1758).

Polyglutamine Diseases: ►trinucleotide repeats, ►res-veratrol

Polygyne: Polygyne describes social insect colonies with more than a single queen. ►monogyne

Polyhaploid: A polyhaploid has half the number of chromosomes of a polyploid. The gametes of polyploids are polyhaploid. ►polyploidy

Polyhedrosis Virus, Nuclear (BmNPV): An about 130 kbp DNA baculovirus of the silkworm (and other insects). It has been used (after size reduction) as a 30 kb cloning vector and it may propagate in a single silkworm larva about 50 μ g DNA. ►baculoviruses,

►viral vectors, ►silkworm; Xia Q et al 2003 J Biol Chem 278:1094.

Polyhybrid: A polyhybrid is heterozygous for many gene loci.

Polyhydroxybutyrate (PHB): A bacterial polymer that can be manufactured by transgenic plants and is biodegradable.

Polyisoprenyl Phosphates: Intermediates in cholesterol biosynthesis; they play a role in signaling to the immune system. ►immune system, ►cholesterols

Polyketenes: Polymers of $\text{CH}_2 = \text{C} = \text{O}$ (ketene). Their biosynthesis is related to fatty acids. Several antibiotics (tetracycline, griseofulvin, etc.) contain ketenes. ►antibiotics

Polyketides: Various naturally occurring compounds, built from residues, which each usually contribute two carbon atoms to the assembly of a linear chain of which the β -carbon carries a keto group. These keto groups are frequently reduced to hydroxyls. The remaining keto groups at many of the alternate carbon atoms form the chains, which are called polyketides. Polyketide synthesis pathway resembles the fatty acid path. Flavonoids, mycotoxins, antibiotics, etc., occurring in plants from angiosperms to bacteria qualify for the polyketide collective name. Polyketide synthetases generate the precursors of erythromycin, rapamycin, and rifamycin antibiotics. ►lovastatin, ►epothilone; Khosla C et al 1999 Annu Rev Biochem 68:219; Walsh CT 2004 Science 303:1805.

P

Polykinetic Chromosome: A polykinetic chromosome has centromeric activity at multiple sites. ►neocentromeres

Polylinker: A DNA sequence with several restriction enzyme recognition sites (multiple cloning sites, MCS) used in construction of different cloning or transformation vehicles (plasmids). e.g., TTCTA-GAATTCT sequence has an overlapping XbaI (TCTAGA) and an EcoRI recognition sites (GAATTC) and thus linking it to the DNA may

generate both types of cloning sites. ►vectors, ►restriction enzymes, ►cloning sites, ►pUC

Poly(L-Lysine): A polycation that can form complex(es) with negatively charged DNA and mediate gene transfer using retroviral vector. In case the polycation has bound specific ligand(s), it can be targeted to special cell types. Without such a complex, the viral vector would have no target specificity. Some of the polycationic delivery systems are cytotoxic and/or may be subject to lysosomal degradation. ►transformation genetic; Putnam D et al 2001 Proc Natl Acad Sci USA 98:1200.

Poly-Marker Test: ►DNA fingerprinting

Polymer: A large molecule composed of a series of covalently linked subunits such as amino acids, nucleotides, fatty acids, carbohydrates, etc. ►DNA, ►protein; biopolymer motifs: <http://bayesweb.wadsworth.org/gibbs/gibbs.html>.

Polymerase: An enzyme that builds up large molecules from small units, such as the DNA and RNA polymerases generated from nucleotides DNA and RNA, respectively. ►pol

Polymerase Accessory Protein (RF-C): An essential part of the DNA replication unit in SV40. ►SV40

Polymerase Chain Reaction (PCR): A method of the rapid amplification of DNA fragments, employed when short flanking sequences of the fragments to be copied are known (see Fig. P106). The reaction begins by the denaturation of the target DNA, then primers are annealed to the complementary single strands. After adding a heat-stable DNA polymerase, such as Taq or Vent/Tli (originally the less thermostable Klenow fragment of polymerase I was used), chain elongation proceeds starting at the primers. The cycles are repeated 20–30 times, resulting in over a million fold ($2^{20} = 1,048,576$) replication of the target. The actual rate of replication may be less (80%) than that theoretically expected.

The DNA amplified can be subjected to molecular analysis such as preimplantation analysis, genetic

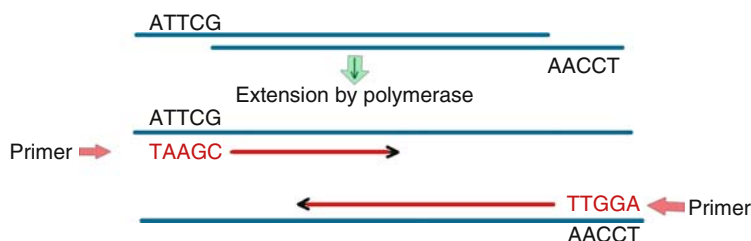


Figure P106. Polymerase chain reaction

screening, prenatal analysis, sperm typing, gene identification, etc. The error frequency for the Klenow fragment is about 8×10^{-5} , for Taq 10^{-5} to 10^{-4} , for Tli 2 to 3×10^{-5} . PCR amplification can be performed with a variety of mechanical devices, including chemical amplification on a microchip where the 20 cycles may be completed as fast as in 90 seconds. All types of technical information and references are available at <http://apollo.co.uk/a/pcr>. ▶RAPDS, ▶DNA fingerprinting, ▶vectorette, ▶sperm typing, ▶genetic screening, ▶prenatal analysis, ▶preimplantation genetics, ▶tissue typing, ▶primer extension, ▶ancient DNA, ▶molecular evolution, ▶RT-PCR, ▶in situ PCR, ▶recursive PCR, ▶inverse PCR, ▶capture PCR, ▶PCR overlapping, ▶tail-PCR, ▶electronic PCR, ▶PCR broad-base, ▶PTPCR, ▶methylation-specific PCR, ▶AP-PCR, ▶PCR asymmetric, ▶PCR allele-specific, ▶immuno-PCR, ▶RNA-PCR, ▶PCR-based mutagenesis, ▶small-pool PCR, ▶INTER-SS PCR, ▶PRINS, ▶reverse ligase-mediated polymerase chain reaction, ▶thermal cycler, ▶hot-start PCR, ▶touch-down PCR, ▶double PCR and digestion, ▶PCR-LSA; Mullis KB, Faloona FA 1989, p 189 In: Wu R et al (Eds.) Recombinant DNA Methodology, Academic Press, San Diego, California; Innis M et al (Eds.) 1990 PCR Protocols: A Guide to Methods and Applications, Academic Press, San Diego, California; quantitative PCR primers: <http://www.ncicrf.gov/rtp/gel/primerdb/>; <http://medgen.ugent.be/rtp/primerdb/>; PCR primer design for mutation screening: <http://bioinfo.bsd.uchicago.edu/MutScreener.html>.

Polymerase Switching: In polymerase switching, DNA replication is initiated by the polymerase α /primase complex, but subsequently the chain elongation is continued by the eukaryotic polymerase δ . Polymerase ϵ may also have some role in the initiation and elongation. ▶replication fork, ▶DNA polymerases, ▶primase, ▶processivity

Polymery: In polymery, several genes cooperate in the expression of a trait. ▶polygenes

Polymorphic: A trait that occurs in several forms within a population. The polymorphism may be balanced and genetically determined. ▶polymorphism, ▶balanced polymorphism, ▶RFLP, ▶SNP

Polymorphic Information Content (PIC): PIC is used to identify and locate a hard-to define marker locus. If the alleles of the marker locus are codominant, then PIC is the fraction of the progeny (the informative offspring) that cosegregates by phenotype with an index locus. The index locus (which is used for the detection of linkage with marker alleles) has two alternative alleles, a wild type and a dominant (mutant)

allele. The marker locus is polymorphic for dominant (genetic or physical [nucleotide sequences]) alleles. Only those progenies are informative, where the index locus is homozygous in one of the parents and the other parent is heterozygous for the marker. The converse constitutions are not informative. In case both parents are heterozygous at the marker locus, only half of the offspring is informative.

$$\text{PIC} = 1 - \sum_{i=1}^n p_i^2 - \left(\sum_{i=1}^n p_i^2 \right)^2 + \sum_{i=1}^n p_i^4$$

where p_i = frequency of the index allele and i and n are the number of different alleles. The PIC values may vary theoretically from 0 to 1. A hypothetical example: four A alleles occur in a population with frequencies A^1 : 0.2, A^2 : 0.1, A^3 : 0.15, and A^4 : 0.55. After substitution, $\text{PIC} = 1 - (0.2^2 + 0.1^2 + 0.15^2 + 0.55^2) - (0.2^2 + 0.1^2 + 0.15^2 + 0.55^2)^2 + (0.2^4 + 0.1^4 + 0.15^4 + 0.55^4)$, thus $\text{PIC} = 1 - 0.375 - 0.140625 + 0.0937125 \approx 0.578$, and in this case almost 58% of the progeny is informative. Usually, PIC values of 0.7 or larger are required for showing good linkage. The larger the number of the marker alleles, the more informative is the PIC. ▶microsatellite typing; Da Y et al 1999 Anim Biotechnol 10:25.

Polymorphism: In polymorphism, morphologically different chromosomes, or different alleles at a gene occur, or variable length restriction fragments are found within a population. Polymorphism can now be also detected through automated molecular techniques. During PCR amplification of a gene, one or more fluorescent reporter probes are attached to the 5' end, and a quencher substance(s) added slightly downstream or at the 3'-end. During amplification, the quencher may be cleaved by the Taq polymerase if it hybridizes to an amplified segment. The cleavage of the quencher enhances the fluorescence of the reporter fluorochrome. The samples placed in a 96-well plate can be scanned at three wavelengths in about 5 min. The procedure may be sensitive enough to detect a single base difference. In the human DNA sequences, there is ca. one variation/500 bp. About 15% of the polymorphism involves insertions or deletions. At least 100 chromosomes are usually examined for base substitution before the alteration is considered as a polymorphism. The average estimated nucleotide polymorphism in human populations is $\sim 8 \times 10^{-4}$. The diversity is variable at different loci and affected by several factors. Among normal human individuals, on the average, 11 deletions and duplications of the average length of 465 kb have been observed (Sebat J et al 2004 Science 305:525). ▶balanced polymorphism, ▶mutation, ▶diversity, ▶mutation detection, ▶fluorochromes, ▶PCR, ▶clone validation, ▶RLP, ▶SNP,

►microsatellite, ►blood groups, ►linkage disequilibrium, ►haplomap; Reich DE et al 2002 *Nature Genet* 32:135; polymorphism detection tool for large datasets: <http://pda.uab.es/pda/>; <http://pda.uab.es/pda2/>; mammalian: <http://mampol.uab.es/>.

Polymorphonuclear Leukocyte (PMN): ►granulocytes, ►leukocyte

Polyomyositis: The inflammation of muscle tissues, which may lead to rheumatoid arthritis, lupus erythematosus, scleroderma, Sjögren syndrome, and neoplasia. Polyomyositis is caused by two autoantigens PMSCL1 and PMSCL2. Dermatomyositis is a form affecting the connective tissues. Polyomyositis as such are not under direct genetic control. conditions under separate entries, ►IVIG; Wang HB, Zhang Y 2001 *Nucleic Acids Res* 29:2517.

Polyneme: The linear structure includes more than one strands, e.g., polytenic chromosomes (salivary gland chromosomes) may have $1024 (2^{10})$ parallel strands.

Polynucleotide: A nucleotide polymer hooked up through phosphodiester bonds.

Polynucleotide Kinase (PK): PK phosphorylates 5' positions of nucleotides in the presence of ATP, such as $\text{ATP} + \text{XpYp} \xrightarrow{\text{PK}} \text{p} - 5'\text{XpYp} + \text{ADP}$ (where X and Y are nucleotides), and can heal nucleic acid termini with ligase assistance. It functions in base excision repair and in non-homologous end-joining. ►ligase, ►DNA repair, ►non-homologous end-joining; crystal structure: Bernstein NK et al 2005 *Mol Cell* 17:657; Wang LK, Shuman S 2001 *J Biol Chem* 276:26868.

Polynucleotide Phosphorylase (PNPase): PNPase generates random RNA polymers $[(\text{NMP})_n]$ —without a template—from ribonucleoside diphosphates (NDP) and releases inorganic phosphate (P_i): $(\text{NMP})_n + \text{NDP} \rightarrow (\text{NMP})_{n+1} + \text{P}_i$. It degrades mRNA from the 3'-end.

Polynucleotide Phosphotransferase: Polynucleotide phosphotransferase transfers nucleotides to the ends of DNA or RNA sequences, such as in the polyadenylation of mRNA or nucleotidyl transferase of DNA. ►polyA polymerase, ►terminal deoxynucleotidyl transferase

Polynucleotide Vaccination: Inoculation by subcutaneous, intravenous, or particle bombardment-mediated transfer of specific viral or other nucleotides/nucleoproteins to develop an immune response. The immune reaction is generally low. ►immunization genetic

Polyoma: Neoplasia induced by one of the polyomaviruses. The globoid (icosahedral) mouse polyoma

viruses (a papova virus of 23.6×10^6 Da) contain double-stranded, circular DNA (4.5 kb). The BK and the JC viruses infect humans. ►Papova viruses; Cole CN, Conzen SD 2001, p 985 In: Knipe DM, Howley PM (Eds.) *Fundamental Virology*, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania.

Polyp: An outgrowth on mucous membranes such as may occur in the intestines, stomach, or nose. They may be benign, precancerous, or cancerous. Nasal polyps may occur in aspirin sensitivity and can be treated surgically or with nasal steroid drugs. ►PAP, ►polyposis adenomatous, ►Gardner syndrome

Polypeptide: A chain of amino acids hooked together by peptide bonds. ►protein synthesis, ►amino acids, ►peptide bond

Polyphenols: Polyphenols are catechol-related plant products causing the formation of melanin-like brown color. The polyphenols in tea (theaflavin, catechins) have apparently antimutagenic and anticarcinogenic effects. ►thea

Polypheny: In polyphony, the same gene(s) can determine alternative phenotypes in response to internal or external cues, e.g., the queens and workers in social insects. Polyphenism in insect coloration may be the result of mutation of juvenile hormone-regulatory pathway and temperature effects may reveal hidden genetic variations. The mechanism that regulates developmental hormones can mask genetic variations and can act as an evolutionary capacitor for facilitating novel adaptive changes by genetic accommodation (Suzuki Y, Nijhout HF 2006 *Science* 311:650). Some older dictionaries and glossaries equate it with pleiotropy but this does not conform to current usage. ►genetic accommodation

Polyphosphates: Linear polymers of orthophosphates (n up to 100 or more) present in all types of cells with roles similar to ATP in metal chelation, bacterial competence for transformation, mRNA processing, growth regulation, etc. (see Fig. P107). Polyphosphates can buffer cellular phosphate levels in case of limited external supply and affect phosphate uptake (Thomas MR, O'Shea EK 2005 *Proc Natl Acad Sci USA* 102:9565). ►competence of bacteria, ►chelation; Kulaev I, Kulakovskaya T 2000 *Annu Rev Microbiol* 54:709.

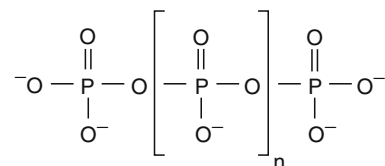


Figure P107. Polyphosphate

PolyPhred: A computer program that automatically detects heterozygotes for single nucleotide substitutions by fluorescence-based sequencing of PCR products at high efficiency. It is integrated by the Phred, Phrap, and Consed programs. ▶SNIP, ▶PCR, ▶Phred, ▶Phrap, ▶Consed; Nickerson DA et al 1997 Nucleic Acid Res 25:2745.

Polyphyletic: An organism (cell) that originated during evolution from more than one line of descent. A polyphyletic group may contain species that are classified into this group because of convergent evolution. ▶convergence, ▶divergence

Polypeplexes: Polypeplexes are employed for delivery of DNA to cells. They include DNA-binding and condensing molecules, cell-specific ligands, and other molecules necessary for protection and uptake.

Polyploid Crop Plants: The most important polyploid crop plants include alfalfa (4x), apple (3x), banana (3x), birdsfoot trefoil (4x), white clover (4x), coffee (4x, 6x, 8x), upland cotton (4x), red fescue (6x, 8x, 10x), johnsongrass (8x), cultivated oats (6x), peanut (4x), Euro-pean plum (6x), cultivated potatoes (4x), sugarcane (*x), common tobacco (4x), bread wheat (6x), and macaroni wheat (4x). Most of these are apparently allopolyploids. ▶allopolyploid

Polyploidy: Having more than two genomes per cell. Definitive identification of polyploidy requires cytological analysis (chromosome counts), although many of the polyploid plants display broader leaves, larger stomata, larger flowers, etc. Polyploidy regulates the expression of individual genes in + or – manner. A yeast study (using microarray hybridization) found that the level of expression of some genes remained the same in haploid and tetraploid cells, whereas the expression of some cyclin genes decreased with tetraploidy. Additionally, a gene associated with cell adhesion was greatly over-expressed with tetraploidy (see Fig. P108).



Figure P108. Autotetraploid (top) and diploid (bottom) flowers of *Cardaminopsis petraea* (G.P. Rédei, unpublished)

Polyploidy may permit separate evolutionary paths for the additional gene copies. ▶autopolyploid, ▶endopolyploidy, ▶inbreeding autopolyploids, ▶chromosome segregation, ▶duplication, ▶maximal equational segregation, ▶alpha parameter, ▶allopolyploid, ▶tetrasomic, ▶trisomy, ▶microarray hybridization; Otto SP, Whitton J 2000 Annu Rev Genet 34:401.

Polyploidy in Animals: Polyploidy in animals is rare and limited mainly to parthenogenetically reproducing species (e.g., lizards). It occurs also in bees, silkworm, and other species. Some cells in special tissues of the diploid body may have increased chromosome number as a normal characteristic. Among mammals, tetraploidy was found in the red visacha rat, *Tympanoctomys barrarae* (2n = 112). The rarity of polyploidy in animals is attributed to its incompatibility with sex determination and dosage compensation of the X chromosome. ▶parthenogenesis, ▶honey bee, ▶silkworm; Zimmet J, Ravid K 2000 Exp Hematol 28:3; Wolfe KH 2001 Nature Rev Genet 2:333.

Polyploidy in Evolution: Polyploidy in evolution is common in the plant kingdom but the majority of polyploid species are allopolyploid. Some of the single copy genes of invertebrates are, however, detectable up to four copies in vertebrates. A survey of plants indicated only 38% of polyploid species in the Sahara region, 51% in Europe, 82% in the Peary Islands, and thus show an increasing trend towards the North. In yeast, after polyploidization, different genes were lost leading to speciation (Scannell DR et al 2006 Nature [Lond] 440:341). In parasites, haploidy is advantageous because selection favors organisms that express a narrow array of antigens and elicitors. In contrast, in the host mounting a defense response, selection favors a broader array of recognition molecules and thus diploids or polyploids (Nuismer SL, Otto SP 2004 Proc Natl Acad Sci USA 101: 11036). Polyploids are also less vulnerable to mutation despite the fact that the mutational target numbers are larger. ▶allopolyploid, ▶duplications; Otto SP, Whitton J 2000 Annu Rev Genet 34:401; Wu R et al 2001 Genetics 159:869; function of the duplicated genes: Kellog EA 2003 Proc Natl Acad Sci USA 100:4369; Adams KL et al 2003 Proc Natl Acad Sci USA 100:4649.

Polyposis Adenomatous, Intestinal (APC): APC is controlled by autosomal dominant genes responsible for intestinal, stomach (Gardner syndrome), or other types (kidney, thyroid, liver, nerve tissue, etc.) of benign or vicious cancerous tumors. The various forms are apparently controlled by mutations or deletions in the 5q21-q22 region of the human chromosome and represent allelic variations. Retinal lesions (CHRPE)

are associated with truncations between codons 463–1387; truncations between codons 1403–1528 involve extra-codonic effects, etc. In addition, it is conceivable that this is a *contiguous gene* region where adjacent mutations affect the expression of the polyposis. By the use of single strand conformation polymorphism technique, DNA analysis may permit the identification of aberrant alleles prenatally or during the presymptomatic phase of the condition. The situation is further complicated, however, by the possibilities of somatic mutations. The *Min* gene of mouse appears to be homologous to the human APC, thus, lending an animal model for molecular, physiological, and clinical studies. The expression of *Min* is regulated also by the phospholipase-encoding gene *Mom1*, indicating the involvement of lipids in the diet. Polyposis may affect a very large portion of the aging human populations, especially high is the risk for females. Certain forms of polyposis may affect the young (juvenile polyposis). Regular monitoring by colorectal examination is necessary for those at risk. Bloody diarrhea and general weakness are symptoms usually too late for successful medical intervention. Molecular genetic information suggests that vertebrates use the same pathway of signal transduction as identified by *Drosophila* genes: *porcupine* (*porc*, 1.59)→*wingless* (*wg*, 2-30.0)→*dishevelled* (*dsh*, 1-34.5)→*zeste white3* (*z^{w3}*, 1.1.0)→*armadillo* (*arm*, 1-1.2)→cell nucleus. The normal human APC gene appears to be either a negative regulator (tumor suppressor) or an effector, acting between *z^w* and the nucleus. When it mutates, it can either no longer carry out suppression or it may become an effector. The product of *dsh* also appears to be a negative regulator of *z^w*. When the *zeste* product, glycogen synthase kinase (GSK3β) is inactive, the *arm* product (catenin) is associated with the APC product and a signal for tumorigenesis is generated. Alternatively, when no signal is received, GSK phosphorylates and activates a second binding site on APC for catenin but that causes the degradation of catenin and thus no tumor signal is generated. The APC protein may act as a tumor gene also by docking at its COOH end with a human homolog of the *dlg1* (*disc large*, 1-34.82) of *Drosophila*). The *Dlg* product belongs to the *membrane associated guanylate kinase* protein family that is analogous to proteins in vertebrates sealing adjacent cell membranes (tight junction). *Dlg* is also considered to be a tumor gene. Although, the molecular information reveals a number of mechanisms of action, it is not clear which one is being used or if multiple pathways are involved in polyposis. APC/FAP has a prevalence of about 1×10^{-4} . The EB1 protein binds the APC protein, is situated on the microtubules of the mitotic spindle, and serves as a checkpoint for cell division. ▶Gardner syndrome, ▶Turcot syndrome, ▶cancer, ▶single-strand conformation, ▶GSK3β,

▶polymorphism, ▶hereditary non-polyposis colorectal cancer, ▶contiguous gene syndrome, ▶animal models, ▶tight junction, ▶catenin, ▶effector, ▶polyposis hamartomatous, ▶polyposis juvenile, ▶spindle, ▶cyclooxygenase, ▶microtubule, ▶PTEN

Polyposis Hamartomatous (Peutz-Jeghers syndrome, PJS): A chromosome-19p13.3 rare dominant overgrowth of mucous membranes (polyp), especially in the small intestine (jejunum), but also in the esophagus (the canal from mouth to stomach), bladder, kidney, nose, etc. Melanin spots may develop on lips, inside the mouth, and fingers. Ovarian and testicular cancers were also observed. The susceptibility to this cancer is due to deletion in a serine/threonine protein kinase gene (LKB). LKB1 mediates glucose homeostasis in the liver (Alessi DR et al 2006 Annu Rev Biochem 75:137). This gene signals to VEGF and it is a player in the anterior-posterior axis formation as well as in epithelial polarity. ▶pigmentation of the skin, ▶cancer, ▶Gardner syndrome, ▶colorectal cancer Muir-Torre syndrome, ▶polyposis adenomatous intestinal, ▶multiple hamartomas, ▶VEGF; Hemminki A et al 1998 Nature [Lond] 391:184; Sapkota GP et al 2001 J Biol Chem 276:19469; Ilikorkala A et al 2001 Science 293:1323; Bardeesy N et al 2002 Nature [Lond] 419:162.

Polyposis, Juvenile: An early onset polyposis frequently turning malignant, caused by a defect at the carboxyl terminal of the SMAD4/DPC4 (552 amino acids) protein, encoded in human chromosome 18q21.1. SMAD4 in a trimeric association is involved in TGF-β signaling pathway. Although some of the symptoms are similar to other hamartomas, the Cowden disease gene (PTEN, phosphatase and tensin homolog) is encoded in chromosome 10 and the Peutz-Jeghers syndrome is coded for in chromosome 19. ▶multiple hamartomas, ▶TGF, ▶polyposis hamartomatous, ▶SMAD, ▶DCC, ▶PTEN; Howe JR et al 2002 Am J Hum Genet 70:1357.

Polypeptide: A contiguously translated long chain polypeptide that is processed subsequently into more than one protein.

Polypurine: A stretch of purine residues in nucleic acids.

Polypyrimidine: A sequence of multiple pyrimidines (mainly Us) in nucleic acids adjacent to the 3' splicing site. Py-tract-binding proteins (PTB) recognize these such as the essential splicing factor U2AF⁶⁵, the splicing regulator sex-lethal (*Sxl*), etc. ▶splicing, ▶introns, ▶sex determination; Le Guinier C et al 2001 J Biol Chem 276:43677.

Polyribosome: Same as polysome (see Fig. P109).
 ▶protein synthesis

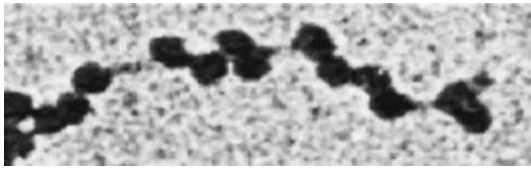


Figure P109. Polyribosome

Polysaccharide: Monosaccharides joined by glycosidic bonds (e.g., starch, glycogen, glycoprotein).

Polysome: In a polysome, the mRNA holds multiple ribosomes together. The ovalbumin polysomes comprise an average of 12 ribosomes and one peptide initiation takes place in every 6–7 s if all the required factors are functioning normally. The average polysome size for globin is ~5 ribosomes (1 ribosome/~90 nucleotides). Pactamycin may be an inhibitor of translation initiation and cycloheximide may interfere with peptide chain elongation. ▶ribosome, ▶mRNA, ▶transcription, ▶translation, ▶pactamycin, ▶cycloheximide

Polysome Display: In a polysome display, polysomes are isolated and screened by the affinity of the nascent peptides on an immobilized specific monoclonal antibody. The mRNA of the enriched pool of polysomes is reverse-transcribed into cDNA and amplified by PCR. The amplified template may be cloned and translated in vitro. The procedure is highly efficient for the screening of large, specific peptide pools. ▶reverse transcription, ▶cDNA, ▶PCR, ▶translation in vitro; Mattheakis LC et al 1994 Proc Natl Acad Sci USA 91:9022.

Polysomic Cell: In a polysomic cell, some chromosomes are present in more than the regular number of copies. The polyploids are polysomic for entire genomes. ▶aneuploidy, ▶polyploidy

Polysomy: In polysomy, some of the chromosomes in a cell are present in more than the normal numbers, examples of these cases in humans are 48,XXXX, 48,XXXY, 49,XXXXX or 49,XXXXY ▶nondisjunction, ▶polyploid, ▶trisomy

Polyspeirism: In polyspeirism, one cell makes several types of related molecules, e.g., different chemokines. (See Montovani A 2000 Immunol Today 2(4):199).

Polyspermic Fertilization: In polyspermic fertilization, more than a single sperm enters the egg and, because each may provide a centriole, multipolar mitoses may take place resulting in aneuploidy and abnormal embryogenesis. ▶fertilization

Polysyndactyly: Polysyndactyly is encoded by the HOXD13 gene at human chromosome 2q31-q32 (see Fig. P110). The amplification of the alanine codons (CCG, GCA, GCT, GGC) leads to an expanded (25 to 35) alanine residues in the protein. Some polysyndactyly is due to mutation in GLI3 gene at 7p13. ▶trinucleotide repeats, ▶syndactyly, ▶Pallister-Hall syndrome



Figure P110. Polysyndactylic toes

Polytenic Chromosomes: Polytenic chromosomes are composed of many chromatids (e.g., in salivary-gland cell nuclei) because in such cases DNA replication is not followed by chromatid separation (see Fig. P111). The polytenic chromosomes in the salivary glands nuclei of diptera may have undergone ten cycles of replication ($2^{10} = 1024$) without division and may have over 1000 strands. Also, the polytenic chromosomes in the salivary glands are extremely long. A regular feature is the very close somatic pairing. Additionally, they all are attached at one point, at the chromocenter.

Polytenic chromosomes have been extensively exploited for analysis of deletions, duplications,

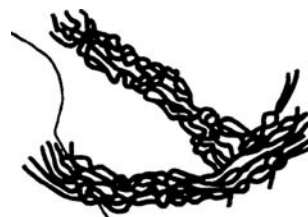


Figure P111. Polytenic chromosomes of *Allium ursinum*. Courtesy of G. Hasischka-Jenschke

inversions, and translocations. The characteristic banding pattern was used also as a cytological landmark for identification of the physical location of genes. Rarely, polyteny occurs in some specialized plant tissues (antipodals) too. ►salivary gland chromosomes, ►giant chromosomes, ►somatic pairing

Polytocous Species: Polytocous species produce multiple offspring by each gestation. ►monotocous

Polytomy: Multifurcating rather than bifurcating analysis of phylogenetic relations. ►evolutionary tree; Walsh HE et al 1999 Evolution 53:932.

Polytopic Protein (multispanning): A polytopic protein traverses the plasma membrane several times.

Polytopic Retrovirus: ►amphotropic retrovirus

Polytypic: A species that includes more than one variety or subtype.

POMC (pre-pro-opiomelanocortin): ►melanocortin, ►opiocortin, ►ACTH

Pomegranate (*Punica granatum*): A Mediterranean fruit tree, $2n = 2x = 16$ or 18 .

Pompe's Disease: ►glycogen storage diseases

Pongidae (anthropoid primates [hominoidea]): *Gorilla gorilla gorilla* $2n = 48$ (see Fig. P112); *Hylobates concolor s* [gibbon] $2n = 52$; *Hylobates lar* [gibbon] $2n = 44$; *Pan paniscus* [pygmy chimpanzee] $2n = 48$; *Pan troglodytes* [chimpanzee] $2n = 48$; *Pongo pygmaeus* [orangoutan] $2n = 48$; *Symphalangus brachytanites* $2n = 50$. ►primates, ►chimpanzee



Figure P112. Gorilla

Pontin: ►chromatin remodeling

PO-PS Copolymers: Phosphorothioate-phosphodiester copolymers are used for antisense technologies. ►antisense RNA

POP': POP' symbolizes the ends of the temperate transducing phage genome integrating into the bacterial host chromosome. The corresponding bacterial integration sites are BOB' and after integration (recombination) the sequence becomes: BOP' and POB', respectively ►attachment sites

Pop1p: A protein component of ribonuclease P and MRP. ►ribonuclease P, ►MRP

Poplar (*Populus* spp): $2n = 2x$, $2n = 38$ (see Fig. P113). Poplar includes cottonwood trees also. The genome of the black cottonwood (*Populus trichocarpa*, 485 ± 10 Mb) has been sequenced and 45,000 putative protein-coding genes detected. Substantial portions of the nuclear and organellar (chloroplasts and mitochondria) genes the genome have been annotated in different tissues. About 8000 duplications were found (Tuskan GA et al 2006 Science 313:1596). (See Cervera M-T et al 2001 Genetics 158:787).

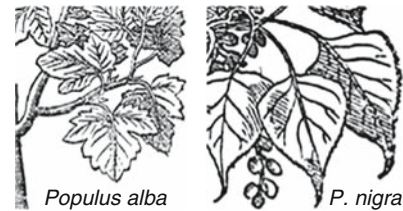


Figure P113. Poplars

Popliteal Pterygium Syndrome (PPS, 1q32-q41): PPS is allelic to the Van der Woude syndrome and it involves a defect in the interferon regulatory factor 6 (Irf6). Clinical symptoms include cleft palate, harelip, and webbing of the skin. Pterygium is membrane or skin folding; popliteal indicates THE ligament behind the knee. ►Van der Woude syndrome, ►epithelial cell, ►Pterygium

Pop-Out, Chromosomal: Chromosomal pop-out originates due to the intrachromatid reciprocal exchange between direct repeats. It excises one of the repeats (the popout) but may retain the other member of the duplication. ►intrachromosomal recombination, ►sister chromatid exchange

Poppy (*Papaver somniferum*): The latex of poppy is a source of opium, codein, morphine, heroin, and other alkaloids. Their biosynthetic pathway, including a mutant blocked in the biosynthesis of the illicit drug (morphine and codeine) pathways (See Millgate AG et al 2004 Nature [Lond] 431:413). The plant is grown for its oil-rich seed as a food and also for pharmaceutical purposes (see Fig. P114). Basic chromosome number $x = 11$, diploid and tetraploid forms are known.



Figure P114. Poppy seed capsule

Population: A collection of individuals that may either interbreed and freely trade genes (Mendelian population, deme) or may be a closed population that is sexually isolated from other groups that share the same habitat. ▶ **Hardy-Weinberg theorem**, ▶ **population equilibrium**

Population Critical Size: ▶ **critical population size**

Population Density: The number of cells or individuals per unit volume or area.

Population Effective Size (N_e): The number of individuals in a group or within a defined area that actually transmit genes to the following reproductive cycles (offspring). Each breeding individual has 0.5 chance to contribute an allele to the next generation, and $0.5 \times 0.5 = 0.25$ is the probability to contribute two particular alleles. The probability that the same male contributes two alleles is $(1/N_m) 0.25$ and for the same female it is $(1/N_f) 0.25$ where N_m and N_f are the number of breeding males and females, respectively. The probability that any two alleles are derived from the same individual is $0.25N_m + 0.25N_f = 1/N_e$ and N_e is computed as $4N_mN_f / (N_m + N_f)$. ▶ **founder principle**, ▶ **genetic drift**, ▶ **inbreeding and population size**; Wright S 1931 *Genetics* 16:97.

Population Equilibrium: ▶ **Hardy-Weinberg theorem**

Population Genetics: Population genetics studies the factors involved in the fate of alleles in potentially interbreeding groups (see Fig. P115). The individuals within these groups (demes) may actually reproduce by random mating or selfing or by the combination of the two within this range. Population genetics can be entirely theoretical and developing mathematical formulas for predicting the allelic frequencies and the effect of various factors that affect these frequencies and the historical paths of the genes and factors as they emerge, become established or disappear, form equilibria or remain unstable during microevolutionary periods. Experimental population

genetics conducts biological studies in the sense of the theoretical framework. Population genetics thus deals with the consequences of mutation, genetic drift, migration, selection and breeding systems and is also one of the most important approaches to experimental (micro) evolution. It provides also the theory for many human genetics, animal and plant breeding research efforts. The availability of molecular information greatly advanced the resolving power of population genetics. The availability of mitochondrial (maternally transmitted) and Y chromosomal (paternally transmitted) markers provide effective tools to study the dynamics and history of human populations. ▶ **terms mentioned**, and ▶ **SNIPS**, ▶ **DNA chips**, ▶ **microsatellites**, ▶ **minisatellites**, ▶ **mtDNA**, ▶ **Y chromosome**; population modeling software: <http://www.trinitysoftware.com>; population genetics tools and Internet resources: Excoffier L, Heckel G 2006 *Nature Rev Genet* 7:745; Arlequin, analysis of molecular genetic variations: Marjoram P, Tavaré S 2006 *Nature Rev Genet* 7:759.



Figure P115. Population genetics is concerned with the fate of genes in large collection of organism rather than in the descendants of single individuals

P

Population Growth, Human: $P_t = P_0(1 + r)^t$ where P_0 = the population at time 0, r = rate of growth and t = time. It can be calculated also by $P_t = P_0e^{rt}$ where e = the base of the natural logarithm. ▶ **age-specific birth and death rates**, ▶ **human population growth**, ▶ **Malthusian parameter**

Population Size, Ancestral: Ancestral population size can be estimated by different methods. The ancestral modern human population might have been about 10,000, whereas the common ancestral human and chimpanzee populations were of the order of 100,000. Newer estimate of the latter is only about 20,000 (Rannala B, Yang Z 2003 *Genetics* 164:1645).

Population Structure: Population structure is endemic by subpopulation groups. The dispersal of the subdivisions reflect adaptive genetic differences, gene

flow and natural selection pressure, inbreeding, overlapping generations, effective population size, and sometimes genetic drift. Sometimes there are too few differences in some population and therefore it is difficult to trace the origin of possible demographic changes. Parasites, e.g., viruses may evolve much faster and from their dispersal one may get good information on the demography/distribution of the host in a region (Bick R et al 2006 Science 311:538). ▶population genetics, ▶endemic, ▶natural selection, ▶genetic drift, ▶population effective size, ▶stratification; Marth G et al 2003 Proc Natl Acad Sci USA 100:376.

Population Subdivisions: Smaller relatively separated breeding groups with restricted gene flow among them. ▶gene flow, ▶migration

Population Tree: The population tree is constructed on the basis of genes frequencies among populations indicating their evolutionary relationship. ▶evolutionary tree, ▶gene tree

Population Wave: Periodic changes in the effective population size. ▶population size effective, ▶random drift, ▶founder principle, ▶gene flow

Porcupine Man (ichthyosis hystrix): Ichthyosis is a dominant form of hyperkeratosis. ▶keratosis, ▶ichthyosis

Porencephaly: Porencephaly is a generally rare dominant (13qter region) brain disease with cerebrospinal fluid-filled cavities or cysts, affecting primarily infants and young children. Few survivors are plagued by many other debilitating symptoms. In a mouse mutant, single-nucleotide alteration in collagen Col4a1 was the primary cause of the disease. ▶collagen; Gould DB et al 2005 Science 308:1167.

Porin: Porin is a voltage-dependent anion channel. It is opened by Bax and Bak pro-apoptotic proteins and closed by the anti-apoptotic Bcl-x_L. Bax and Bak permit the exit of cytochrome c from the mitochondria and thus facilitate apoptosis by the activation of caspases. In case of IL-7 deficiency and increase in pH over 7.8 the conformation of Bax is altered and the protein moves from the cytoplasm to the mitochondria and facilitates apoptosis. The anti-apoptotic, 24 amino acid-peptide prevents the translocation of Bax to the mitochondria (Guo B et al 2003 Nature [Lond] 423:456). The Bcl-2 protein, localized to the mitochondrial membrane, normally suppresses the release of cytochrome c. Bax deficiency extends the ovarian life span into advanced age of mice. Normally the ovarian follicles fade by menopause in women and at similar developmental stages also in mice. Degradation of Bax by the proteasomes may protect against the apoptosis over-protective effect of Bcl-2 and reduce

cancer cell survival. For drug therapy of epithelial cancer the state of BAX vs. Bcl-2 may be significant. ▶Bak, ▶ion channels, ▶cytochrome c, ▶apoptosis, ▶hypersensitive reaction; Suzuki M et al 2000 Cell 103:645; Gogvadze V et al 2001 J Biol Chem 276:19066; Scorrano L et al 2003 Science 300:135.

Porphyria: Porphyria is a collective name for a variety of genetic defects involved in heme biosynthesis resulting in under- and/or over-production of metabolites in the porphyrin-heme biosynthetic pathway. These diseases may be controlled by recessive or dominant mutations. The affected individuals may be suffering from abdominal pain, psychological problems and photosensitivity. The autosomal dominant acute *intermittent porphyria* (human chromosome 11q23-ter) is caused by a periodic 40–60% reduction in porphobilinogen deaminase enzyme resulting in insufficient supplies of the tetrapyrrole hydroxymethyl bilane that is normally further processed by non-enzymatic way into uroporphyrinogen I. It was speculated that the famous Dutch painter van Gogh was a victim of this rare disease. Prevalence is in the range of 10^{-4} to 10^{-5} . Exogenous effects such as barbiturate, sulfonamide, alkylating and many other drugs, alcohol consumption, poor diet, various infections and hormonal changes, generally elicit the periodic attacks. An *adult type* of (hepatocutaneous) porphyria, controlled by another human gene locus (1p34), involves light-sensitivity and liver damage by the accumulation of, porphyrins caused by uroporphyrinogen decarboxylase deficiency. The general effect may be less severe than in the intermittent porphyria. The rare congenital *erythropoietic porphyria* (CEP) is the result of a defect in the enzyme uroporphyrinogen III co-synthetase controlled by a recessive mutation in human chromosome 10q25.2-q26.3. The laboratory identification is generally based on urine analysis for intermediates in the heme pathway. Porphyrias affect also various mammals. Defects in the porphyrin pathways are involved in several types of pigment deficiency mutations of plants. The *variegate porphyria* is caused by a defect of protoporphyrinogen oxidase (PPOX) with symptoms basically similar to that of intermittent porphyria. This dominant disease has low penetrance. Its prevalence is very high (about 3×10^{-3}) in South-African populations of Dutch descent; it apparently represents founder effect. The mental problems of King George III of England (reigned during the US War of Independence) were also attributed to variegate porphyria.

ALAD porphyria also known as “Doss porphyria,” is a very rare porphyric disorder linked to a profound lack of porphobilinogen synthase PBGS, also known as δ -aminolevulinatase (ALAD), is encoded by the *ALAD* gene (9q34). Human (PBGS) exists as an

equilibrium of functionally distinct quaternary structure assemblies, known as morphoeins, in which one functional homo-oligomer can dissociate, change conformation, and reassociate into a different oligomer. In the case of human PBGS, the two assemblies are a high-activity octamer and a low-activity hexamer (Jaffe EK, Stith L 2007 Am J Hum Genet 80:329). ►porphyrin, ►heme, ►skin diseases, ►light-sensitivity diseases, ►founder effect, ►coproporphyrin, ►aminolevulinic acid conformation

Porphyrin: Four special pyrroles joined into a ring; generally with a central metal, like iron in hemoglobin or in chlorophylls with magnesium (see Fig. P116). ►porphyria, ►coproporphyrin, ►heme

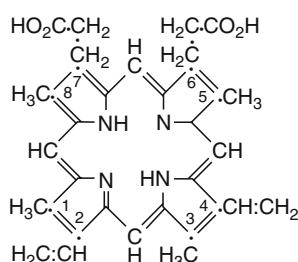


Figure P116. Protoporphyrin

Porphyria: ►porphyria

Porpoise: *Lagenorhynchus obliquidens*, 2n = 44. ►dolphins

Portable Dictionary of the Mouse Genome: Data on ~12,000 genes and anonymous DNA loci of the mouse, homologs in other mammals, recombinant inbred strains, phenotypes, alleles, PCR primers, references, etc. The dictionary can be used on Macintosh, PC in FileMaker, Pro, Excel, and text formats, and is accessible through the Internet (WWW, Gopher, FTP), CD-ROM, or on floppy disk. Information: R.W. Williams, Center for Neuroscience, University of Tennessee, 875 Monroe Ave., Memphis, Tennessee 36163. Phone: 901-448-7018. Fax: 901-448-7266. e-mail: rwilliam@nb.utmem.edu.

Portable Promoter: An isolated DNA fragment, including a sufficient promoter that can be carried by transformation to other cells, and may function in promoting transcription. ►promoter, ►transformation, ►gene fusion

Portable Region of Homology: Insertion and transposon elements may represent homologous DNA sequences and can recombine. The recombination may then generate deletions, cointegrates or insertion, or inversions. These events can take place even in RecA⁻ hosts.

►Tn10, ►cointegrate, ►deletion, ►inversion, ►targeting genes

Position Effect: change in gene expression by a change in the vicinity of the gene.

The new expression may be *stable* or *variable* (*variegation type position effect*) (see Fig. P117). Stable position effect is observed when promoterless structural genes are introduced by transformation and the transgene is expressed with the assistance of a “trapped” promoter that is regulated differently than the gene’s natural (original) promoter. Variegated position effect (PEV) is more difficult to interpret by molecular models. When, however, centromeric heterochromatin was inserted at the *brown* locus of *Drosophila* during larval development the transposed heterochromatin stochastically associated with the centromeric region and caused PEV (Dernburg AF et al 1996 Cell 85:745). The telomere-linked *ADE2* locus of yeast displayed alternative *ADE* and *ade* phenotypes (Gottschling DE et al 1990 Cell 63:751). It has been assumed that heterochromatin affects the intensity of somatic pairing and variations in somatic association and variations in cross-linking between the homologs by binding proteins bring about the silencing. The *trithorax-like* gene of *Drosophila* encodes a GAGA-homology transcription factor that enhances variegation type position effect (PEV) by decondensation of the chromatin. The mosaicism may also be the result of the spontaneous and random derepression of the promoter in the presence of an activator. The telomeric isochores have been also implicated in position effect (TPE). Position effect may be observed by altering the site or distance of the locus control region. In *Drosophila* over 100 genes were found that affect variegation type position effect (PEV). In *Drosophila* HP1, HP2 proteins of the heterochromatin and histone H3 lysine⁹ methyltransferase play important role in gene silencing. It seems that RNAi also affects the heterochromatin and several genes encode the RNAi system and their mutations results in loss of silencing (Pal-Bhadra M et al 2004 Science 303:669). It has been hypothesized that these genes control the packaging of the DNA. Many of the cancers develop after translocations or transpositions, indicating the significance of position effect on the regulation of growth. Proteins affecting AT-rich heterochromatin can modify PEV. Transposable elements may also cause position effect (Kashkush K et al 2003 Nature Genet 33:102). Position effects may be exerted even from long distances (2 Mb) and may make difficult to distinguish the position effect causing gene from mutation within the target gene. Such cases may complicate positional cloning. Position effect occurs also in yeasts and other organisms. Some human genetic disorders are due to

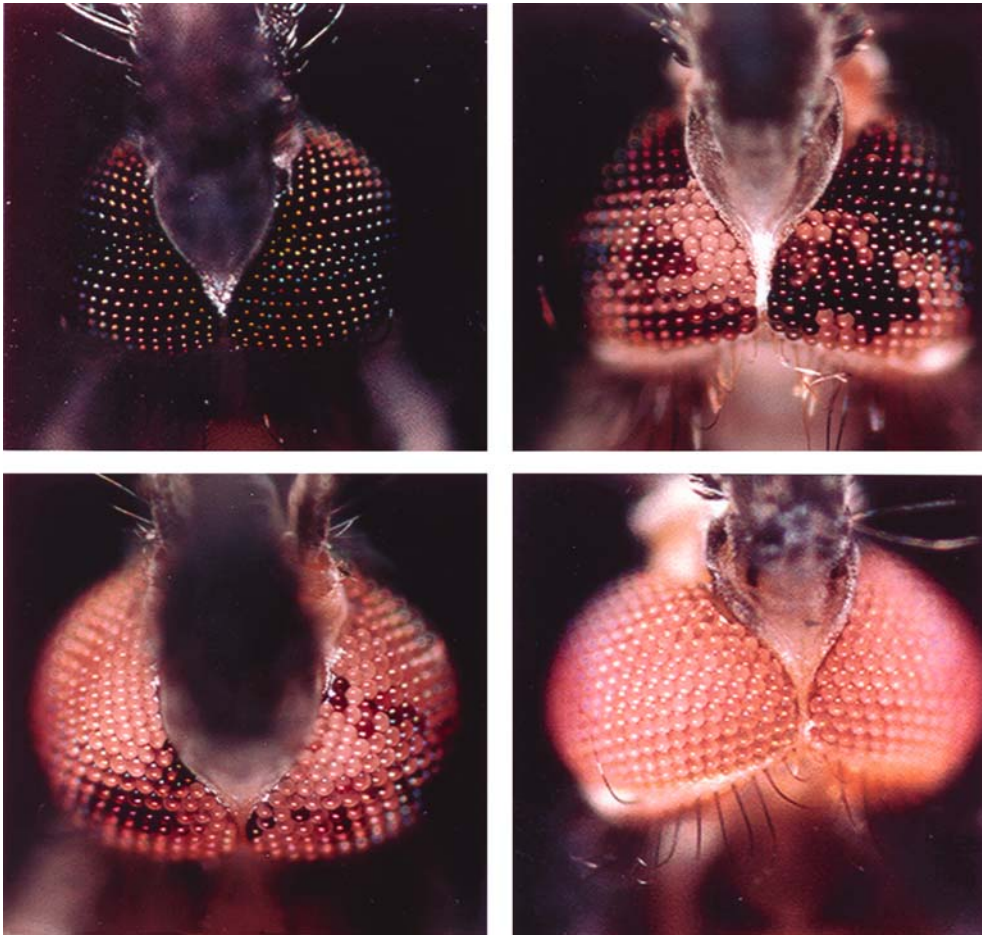


Figure P117. Duplication of the wildtype (p^+) allele into heterochromatic DNA results in the (p) eyes variegated expression of p^+ in the malaria mosquito *Anopheles gambiae*. (Courtesy of Dr. Mark Benedict, original photograph by James Gathany, CDC)

P

position effect. ▶heterochromatin, ▶histone methyltransferases, ▶RdMD, ▶LCR, ▶Offermann hypothesis, ▶regulation of gene activity, ▶mating type determination in yeast, ▶silencer, ▶cancer, ▶chromosomal rearrangements, ▶chromosome breakage, ▶locus control region, ▶isochores, ▶transposable elements, ▶epigenesis, ▶paramutation, ▶positional cloning, ▶RPD3, ▶developmental-regulator effect variegation, ▶RIGS, ▶Dubinin effect; Kleinjahn DJ Heyningen V 1998 Hum Mol Genet 7:1611; Baur JA et al 2001 Science 292:2075; Ahmad K, Henikoff S 2001 Cell 104:839; Csink AK et al 2002 Genetics 160:257; suppressors: Ner SS et al 2002 Genetics 162:1763; Monod C et al 2002 EMBO Rep 3:747; Ebert A et al 2006 Chromosome Res 14:377; heterochromatin proteins: Greil F et al 2007 EMBO J 26:741.

Position-Specific Scoring Matrix (PSSM): PSSM represents amino acids at specific positions in a

sequence alignment. It can be used for scanning proteins with matches to this tract. ▶PWM; Gribskov M et al 1987 Proc Natl Acad Sci USA 84:4355.

Position Weight Matrix: ▶PWM

Positional Cloning: ▶chromosome walking, ▶chromosome landing, ▶map-based cloning

Positional Information: Positional information is provided to some cells by signal transducers in a multicellular organism and has an important influence on differentiation and development. ▶morphogenesis, ▶differentiation

Positional Sensing: Positional sensing provides information for specific differentiation functions. ▶morphogenesis

Positive Control: In positive control, gene expression is enhanced by the presence of a regulatory protein (in contrast to negative control, where its action is

reduced). The arabinose operon of *E. coli* is a classic example. The regulator gene *araC* produces a repressor (P_1) in the absence of the substrate arabinose. If arabinose is available, P_1 is converted to P_2 (by a conformational change), which is an activator of transcription in the presence of cyclic adenosine monophosphate (cAMP). While the negative control (P_1) is correlated with a low demand for expression, the activator (P_2) appears in response to the demand for high level of expression. In general cases, the addition of an activator protein to the DNA makes possible normal transcription but adding a special ligand to the system removes the activator and the gene is turned off. ▶ *arabinose operon*, ▶ *negative control*, ▶ *lac operon*, ▶ *autoregulation*, ▶ *catabolite activator protein*, ▶ *regulation of gene activity*

Positive Cooperativity: Binding of a ligand to one of the subunits of a protein facilitates the binding of the same to other subunits.

Positive Interference: ▶ *interference*, ▶ *coincidence*

Positive/Negative Selection: Selection may be used to isolate cloned constructs containing the desired integrated sequence (positive selection). Negative selection is expected to eliminate integration sites containing the entire vector inserted at non-targeted sites and vector components that have no relevance to cloning. Negative selection is usually less efficient—if it takes place at all—than positive selection. For positive selection in case of hypoxanthine/guanine phosphoribosyl transferase marker, one may use hypoxanthine, aminopterin, and thymidine (HAT) chemicals, whereas in the same experiment for negative selection 6-thioguanine or 5-bromodeoxyuridine may be used.

Positive Selection: In general, it indicates the selection of a desirable type in a population rather than the elimination of the undesirable phenotype/genotypes. ▶ *selection entries*

Positive Selection of Lymphocytes: A process of maturation of lymphocytes into functional members of the immune system. In contrast, negative selection eliminates, by apoptosis, early lymphocytes with autoreactive receptors. ▶ *immune system*, ▶ *lymphocytes*

Positive Selection of Nucleic Acids: Positive selection of nucleic acids isolates and enriches desired types of nucleic acid sequences. The desired (tracer) sequences are digested by restriction endonucleases that generate cohesive ends. The rest of the nucleic acids (driver) are exposed to sonication (or the ends may be even dephosphorylated) and so much sticky ends are not expected. Thus, mainly the tracer-tracer sequences are annealed when the mixture is treated with a ligase enzyme. ▶ *subtractive cloning*, ▶ *genomic*

subtraction, ▶ *RFLP subtraction*, ▶ *ligase DNA*, ▶ *cohesive ends*, ▶ *sonicator*

Positive-Strand Virus: The genome of a positive-strand virus is also a mRNA. Upon transcription, the virus may directly produce an infectious nucleic acid. This is a very large class of RNA viruses including the Brome Mosaic Virus, the Hepatitis C Virus, West Nile Virus, Corona Viruses, etc. Their replication is affected by at least 100 genes (Kushner DB et al 2003 Proc Natl Acad Sci USA 100:15764). ▶ *replicase*, ▶ *plus strand*, ▶ *mRNA*, ▶ *negative strand virus*

Positive Supercoiling: The overwinding follows the direction of the original coiling, i.e., it takes place rightward. ▶ *supercoiling*, ▶ *negative supercoil*

Positron Emission Tomography (PET): ▶ *tomography*

Post-Adaptive Mutation: Post-adaptive mutation is supposed to arise de novo in response to the conditions of selection. Actually, post-adaptive mutation may not be found if the data are well scrutinized. ▶ *directed mutation*, ▶ *pre-adaptive mutation*

Post Coitum (p.c.): During embryonal development, the days that follow mating.

Posterior: Pertaining to the hind part of the body or behind a structure toward the tail end.

Posterior Distribution: A summary of random variables collected after new empirical data became available. It is the product of likelihood and prior distribution. ▶ *prior distribution*

Posterior Probability: ▶ *Bayes theorem*

Post-Genome Analysis: The post-genome analysis studies the experimental results and the informatics of the sequential function (metabolic pathways) and interactions of genes and their products. ▶ *annotation of the genome*, ▶ *genetic networks*; Lin J et al 2002 Nucleic Acids Res 30:4574, <http://www.genome.ad.jp>; <http://www.genome.ad.jp/kegg/comp/GFIT.html>.

Postmeiotic Segregation: Postmeiotic segregation takes place when the DNA was a heteroduplex at the end of meiosis. Among the octad spores of ascomycetes, this may result in 5:3 and 3:5 or other types of aberrant ratios instead of the normal 1:1. Postmeiotic segregation may be an indication of failures in mismatch or excision repair. ▶ *DNA repair*, ▶ *tetrad analysis*, ▶ *gene conversion*

Postnatal: Postnatal refers to that which occurs after birth; generally one to 12 months after birth.

Postprandial: After consuming a meal, a process, e.g., protein anabolism modifies protein synthesis due the change in the amino acid pool or change in insulin supply after eating (postprandially).

Postreduction: As per postreduction, the segregation of the alleles takes place at the second meiotic division.
 ▶tetrad analysis, ▶meiosis, ▶prereduction

Postreplicational Repair: ▶unscheduled DNA synthesis, ▶DNA repair

PostScript: A computer application to handle text and graphics the same time. The PostScript code determines what the graphics look like when printed, although may not be visible on the screen of the monitor.

Post-Segregational Killing: ▶plasmid addiction

Post-Transcriptional Gene Silencing (PTGS): As per PTSG, the transcript of a transgene is degraded before translation takes place and thus, its expression is prevented. Also, it may be a defense mechanism against viruses in plants. The viral gene may be integrated into the chromosome and duly transcribed, yet it is not expressed. In addition, since the replication of the virus is mediated through a double-stranded RNA that has been found to be a potent inhibitor, it is conceivable that both the plant defense and the transgene silencing rely on similar mechanism(s). In some plant species, the potyviruses, tobacco etch virus, and cucumber mosaic virus may produce a *helper component protease* (HC-Pro) and may inactivate this plant defense by degradation. The HC-Pro may have another role. When a plant is infected simultaneously by two different viruses, one of them promotes the vigorous replication of the other, and the latter by its production of HC-Pro eventually facilitates the spread of the first type of the virus and thus enhances the symptoms of the viral disease. In some of the silenced plant cells, a 25-nucleotide long antisense RNA has been detected that seems to inactivate the normal transcript or infectious viral RNA. According to other studies, the ~25-nt RNA sequence apparently conveys specificity for a nuclease by homology to the substrate mRNA. Several types of hairpin structures of RNAs involving sense and antisense sequences and introns appeared to silence very effectively viral genes in plants. A calmodulin-related plant protein (rgs-CAM) may also suppress silencing. ▶silencing, ▶plant viruses, ▶RNAi, ▶RNA interference, ▶co-suppression, ▶homology-dependent gene silencing, ▶methylation of DNA, ▶host-pathogen relations; Bass BL 2000 Cell 101:235; Jones L et al 1999 Plant Cell 11:2291; Waterhouse PM et al 2001 Nature [Lond] 411:834; Mitsuhashi I et al 2002 Genetics 160:343.

Post-Transcriptional Processing: The primary RNA transcript of a gene is cut and spliced before translation or before assembling into ribosomal subunits or functional tRNA; it includes removal of introns, modifying (methylating, etc.) bases, adding

CCA to tRNA amino arm, polyadenylation of the 3' tail, etc. ▶opiotropin; McCarthy JEG 1998 Microbiol Mol Biol Revs 62:1492; Bentley D 1999 Curr Opin Cell Biol 11:347.

Post-Transcriptional Operons: A hypothesis according to which, functionally related genes may be regulated post-transcriptionally as groups by mRNA-binding proteins that recognize common sequence elements in the untranslated 5' and 3' subsets of the transcripts. This conclusion is based on findings that mRNA-binding proteins recognize unique subpopulations of mRNAs, the composition of these subsets may vary depending on conditions of growth and the same mRNA occurs in multiple complexes. These conserved *cis* elements were named USER (untranslated sequence elements for regulation) codes. These systems may permit plasticity during developmental processes or responses to drug treatment. ▶operon, ▶genetic networks; Keene JD, Tenenbaum SA 2002 Mol Cell 9:1161.

Posttranslational Modification: Enzymatic processing of the newly synthesized polypeptide chain, the product of translation. The modification may include proteolytic cleavage, glycosylation, phosphorylation, farnesylation, conformational changes, assembly into quaternary structure, etc. These modifications may alter function. Mass spectrophotometry is generally used for the identification the alterations. ▶protein synthesis, ▶protein structure, ▶conformation, ▶proteomics; Németh-Cawley JF et al 2001 J Mass Spectrom 36:1301; Mann M, Jensen ON 2003 Nature Biotechnol 21:255; <http://dbptm.mbc.nctu.edu.tw/>; tandem mass spectra interpretation server: <http://modi.uos.ac.kr/modi/>.

Post-Transplantational Lymphoproliferative Disease (PTDL): In PTDL, after engraftment, the Epstein-Barr virus-infected B cells may continue to proliferate because the immuno-suppressive therapy required to maintain the graft inhibits cytotoxic T lymphocytes. Bone marrow transplantation may alleviate the problems. ▶Epstein-Barr virus, ▶immuno-suppression, ▶CTL

Postzygotic: ▶prezygotic

Postzygotic Isolation: Postzygotic isolation arises when in allopatric evolution the taxa diverge from the common ancestor by accumulation of different non-deleterious mutations. Although the divergent forms are well adapted, their hybrids may be inviable or sterile because the negative effects of the alleles in a shared background. ▶allopatric speciation; Orr HA, Turelli M 2001 Evolution 55:1085.

Potassium-Argon Dating: Potassium-Argon dating is based on the conversion of K^{40} into Ar^{40} , a stable gas.

It is used for dating rocks over 100,000 years old.
 ►argon dating, ►radiocarbon dating

Potassium Ion Channel: ►ion channel

Potato (*Solanum tuberosum*): The genus has 170 to 300 related species with basic chromosome number $x = 12$. In nature, species with diploid, tetraploid, and hexaploid chromosome numbers are found. The cultivated potatoes originated from the *S. brevicaulis* group in the Andes Mountains (Spooner DM et al 2005 Proc Natl Acad Sci USA 102:14694), and secondarily from *Solanum andigena* in Central America where they produce tubers under short-day conditions. The majority of the modern varieties is day-neutral and develops tubers under long-day conditions. The cultivated potatoes are usually cross-pollinating species but many set seeds also by selfing. Generally, the seed progeny is very heterogeneous genetically. Potatoes are rarely propagated by seed, as is a crop. The diploid relatives are usually self-incompatible whereas the polyploids may set seeds by themselves. Among the cultivated groups, the tuber color may vary from white to yellow to deep purple. Also the chemical composition of the tubers shows a wide range, depending on the purpose of the market. Potato, besides being a popular vegetable, is an important source of industrial starch. The related species carry genes of agronomic importance (disease, insect resistance, etc.) that have not yet been fully exploited for breeding improved varieties. The application of the molecular techniques of plant breeding seems promising. ►patatin; Isidore E et al 2003 Genetics 165:2107; <http://www.tigr.org/tdb/tgi>; <https://gabi.rzpd.de/projects/Pomamo/>; <http://www.sgn.cornell.edu>.

Potato Beetle: (*Leptinotarsa decemlineata*, $n = 18$): One of the most devastating pests of the agricultural production of potatoes (see Fig. P118). Plants transgenic for the δ endotoxin of *Bacillus thuringiensis* are commercially available ►potato, ►*Bacillus thuringiensis*



Figure P118. Potato beetle

Potato Leaf Roll Virus: The potato leaf roll virus has double-stranded DNA genetic material.

POTE: A family of genes encoding proteins with an amino-terminal cysteine-rich domain, a central domain

with ankyrin repeats, and a carboxyl-terminal domain containing spectrin-like helices. In humans, the POTE gene family is composed of 13 closely related paralogs dispersed among eight chromosomes. These genes are found only in primates, and many paralogs have been identified in various primate genomes. The expression of POTE family is generally restricted to a few normal tissues (prostate, testis, ovary, and placenta but several family members are expressed in breast cancer and many other cancers (Lee Y et al 2006 Proc Natl Acad Sci USA 103:17885).

Potocki-Shaffer Syndrome: ►exostosis

Potocytosis: Moving ions and other molecules into cells by caveola vehicles. ►caveolae

POU: A region with several transcriptional activators of 150–160 amino acids (including a homeo-domain), involved with a large number of proteins controlling development. The acronym stands for a prolactin transcription factor (PIT), an ubiquitous and lymphoid-specific octamer binding protein (OTF), and the *Caenorhabditis* neuronal development factor (Unc-86). A POU domain may directly facilitate the recruitment of TBP and transcriptional activators and may stimulate transcription even when the enhancer is at a distance from the core promoter. POU domain proteins are involved in shuttling between nucleus and cytoplasm (Baranek C et al 2005 Nucleic Acids Res 33:6277). ►homeodomain, ►transcription factor, ►TBP, ►transcriptional activator, ►enhancer, ►core promoter, ►octa, ►unc, ►*Caenorhabditis*, ►deafness; Ryan AK, Rosenfeld MG 1997 Genes Dev 11:1207; Bertolino E, Singh H 2002 Mol Cell 10:397.

pOUT: A strong promoter opposing pIN and directing transcription to the outside end of an insertion element. ►RNA-OUT, ►pIN

Power of a Test: Algebraically, the power of a test is $1 - \beta$, where β = type II error. This test reveals the probability of rejecting a false null hypothesis and accepting a correct alternative. The experimenter needs as large a value of $1 - \beta$ as possible, by reducing β to a minimum. To improve the power, the size of the experiment (population) can be increased. In case the size cannot be increased, a more powerful test (statistics) should be chosen. ►error types, ►significance level

Pox Virus: A group of oblong double-stranded DNA viruses of 130–280 kbp (see Fig. P119). Some of these are parasites on insects, others in the family are the chicken pox, cowpox (vaccinia), and smallpox viruses (see Fig. P120).

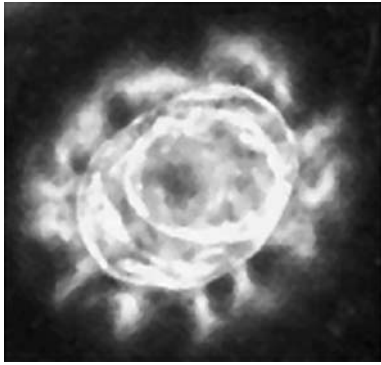


Figure P119. Pox virus



Figure P120. Pox virus lesion

Their transmission takes place through insect vectors or by dust or other particles. Engineered pox virus vectors that are not able to multiply in mammalian cells may have the ability to express passenger genes without the risk of disease. Due to the success of vaccination, smallpox as a disease has now been eradicated and vaccination against is no longer necessary except in case of terrorist attacks (Halloran ME et al 2002 Science 298:1428). The smallpox virus (VARV) linear DNA genome is about 186 kbp with inverted terminal repeats containing 196 to 207 open reading frames. Apparently, there is small variation among the various isolates. The genes of the smallpox virus overlap and its mRNA is not spliced (Esposito JJ et al 2006 Science 313:807).

Poxvirus based vectors are being used orally to protect wild life (red fox) from rabies, for the protection of chickens against the Newcastle virus. Recombinant canarypox virus is employed for the protection of dogs and cats against the distemper, feline leukemia, equine influenza, etc. Highly attenuated derivatives, expressing rabies virus glycoprotein, Japanese encephalitis virus polyprotein, or seven antigens of *Plasmodium falciparum* are used for safe and effective vaccination. Smallpox virus disease has been eradicated and at this time only the Center of Disease Control and Prevention in Atlanta, GA in the USA and the Russian State Research Center of Virology and Biotechnology in Kolsovo, Novosibirsk, Russia, maintain active samples. Limited-scale

vaccinations have been performed as protection against terrorism. Large-scale use of the current vaccine may involve side effects such as heart disease in some individuals. A new vaccine developed and used in Japan does not pose serious side effects even at very high doses. It may revert to the wild type progenitor due to mutation of gene *B5R*. Fortunately, this gene can be eliminated without effect on protective immunity (Kidokoro M et al 2005 Proc Natl Acad Sci USA 102:4252). ▶*malaria*, ▶*Plasmodium falciparum*, ▶*variation*; Moss B, Shisler JL 2001 Semin Immunol 13:59; Takemura M 2001 J Mol Evol 52(5):419; Enserink M 2002 Science 296:1592; L1 protein: Su HP et al 2005 Proc Natl Acad Sci USA 102:4240; <http://www.poxvirus.org>.

POZ: Protein–protein interaction domain of Zinc finger-containing transcriptional regulatory proteins. ▶*Zinc finger*, ▶*αβ T cells*

PP-1, PP-2: Protein serine/threonine phosphatases that are inhibited by okadaic acid. PP-1 may be associated with chromatin through the nuclear inhibitor of PP-1 (NIPP-1). PP enzymes play key roles in many cellular processes. ▶*okadaic acid*, ▶*DARPP*

pp15: A protein factor required for nuclear import. ▶*membrane transport*, ▶*RNA export*

pp125^{FAK}: ▶*CAM*

PP2A: The proline-directed heterotrimeric protein serine-threonine phosphatase dephosphorylates proteins in the MAP pathway of signal transduction and thus balances the effect of kinases. Its deregulation seems to be associated with several types of cancers, Alzheimer disease, and susceptibility to infections by pathogens. The crystal structure of the holoenzyme has been determined (Cho US, Xu W 2007 Nature [Lond] 445:53). PP2A subunit B56 regulates β-catenin signaling and several metabolic processes. PP2A is very sensitive to okadaic acid, a tumor-inducing agent. The non-catalytic α4 subunit of PP2A is a regulator of apoptosis by dephosphorylating c-Jun and p53 transcription factors, which upon phosphorylation promote apoptosis (Kong M et al 2004 Science 306:695). ▶*Sit*, ▶*MAP*, ▶*signal transduction*, ▶*MAP kinase phosphatase*, ▶*okadaic acid*, ▶*catenins*, ▶*cyclin G*, ▶*apoptosis*, ▶*calcineurin*, ▶*TGF*

PPAR (peroxisome proliferator-activated receptor, 17q12): A transcription factor in the adipogenic (fat synthetic) pathways. The three types α, γ, and δ show different distribution in human tissues and associate with different ligands. PPARα is the target for the drugs and fibrates (amphipathic carboxylic acids) that reduce triglycerides. Type α also acts as a transcription

factor for several genes affecting lipoprotein and fatty acid metabolism. PPAR γ is a (3p25) regulator of glucose, lipid, and cholesterol metabolism, may be sensitized by thiazolidinediones (TZD), and offers some hope to be used for the treatment of diabetes mellitus type2 (IDDM). PPAR γ 2 deficiency dramatically reduces adipogenesis in mouse fibroblasts whereas PPAR γ 1 affects obesity and diabetes (Zhang J et al 2004 Proc Natl Acad Sci USA 101:10703). The PPAR γ 12Ala allele is associated with a small yet significant reduction in the risk for diabetes type II. PPAR γ agonists have a controversial—promoting and suppressing—effect on polyposis of the colon and other cancers. In human thyroid carcinoma, PAX8–PPAR γ 1 has been observed. PPAR- α agonists are also successful for the treatment of some autoimmune diseases. PPAR γ deficiency can also lead to hypertension. ▶[peroxisome](#), ▶[ROS](#), ▶[diabetes mellitus](#), ▶[polyposis](#), ▶[famesoid X receptor](#), ▶[leukotrienes](#), ▶[leptin](#), ▶[obesity](#), ▶[Krox20](#), ▶[hypertension](#), ▶[PAX](#), ▶[thiazolidinedione](#), ▶[dizygotic twins](#), ▶[sirtuin](#), ▶[mesenchyma](#), ▶[retinoic acid](#); Lowell BB 1999 Cell 99:239; Kersten S et al 2000 Nature 405:421; Willson TM et al 2001 Annu Rev Biochem 70:341; Michalik L et al 2004 Nature Rev Cancer 4:61; review: Lehrke M, Lazar MA 2005 Cell 123:993.

pPCV: Plasmid plant cloning vector, designation (with additional identification numbers and/or letters) of agrobacterial transformation vectors constructed by Csaba Koncz.

ppGpp: ▶[discriminator region](#)

PPI (peptidyl prolyl isomerase): An endoplasmic reticulum-bound protein assisting chaperone function. There are 3 PPI families: cyclophilins, FK506, and parvulins. ▶[chaperone](#), ▶[PDI](#); Dolinski K, Heitman J 1997, p 359 In: Gething MJ (Ed.) Guidebook to Molecular Chaperones and Protein Folding Catalysis, Oxford University Press, Oxford, UK.

ppm: Parts per million.

PP2R1B: PP2R1B at human chromosome 11q22-q24 encodes the β isoform of the PP2A serine/threonine protein phosphatase. The gene displays alterations (LOH) in a variable fraction of lung, colon, breast, cervix, head and neck, ovarian cancers and melanoma, and it is thus a suspected tumor suppressor gene. ▶[tumor suppressor gene](#), ▶[LOH](#); Mumby MC, Walter G 1993 Physiol Rev 73:673.

PPTs (palmitoyl-protein thioesterases): PPTs hydrolyze long chain fatty acyl CoA and PPT1 may cleave cysteine residues in the lysosomes. Its deficiency may lead to Batten disease. ▶[Batten disease](#)

Prader-Willi Syndrome (Prader-Labhart-Willi syndrome):

A very rare (prevalence 1/25,000) dominant defect involving poor muscle tension, hypogonadism, (hyperphagia [over-eating]) obesity, short stature, small hands and feet, mental retardation, compulsive behavior that sets in by the teens, caused by methylation of the paternal chromosome and by disomy for maternal chromosome 15 (see Fig. P121). The recurrence risk in affected families is about 1/1000. This and cytological evidence indicate that the condition is caused in about 60% of the cases by a chromosomal breakage in the so-called imprinting center (IC) in the long arm of human chromosome 15q11.2-q12. The same deletion (4–5 Mbp or sometimes shorter), when transmitted through the mother, results in the Angelman syndrome. At the breakpoints, the HERC2 gene (encoding a very large protein) may be repeated. The repeats may then recombine and generate the deletions. See two chromosomes shown in Figure P122, with different number of repeats, as detected by FISH. In some cases, there is no deletion but a mutation in an ubiquitin protein ligase gene (UBE3A). Mutations in the proximal part of IC lead to the Angelman syndrome and in the distal part to the Prader-Willi syndrome. Molecular studies indicated in many cases the missing (uniparental disomy) or silencing (imprinting) of a paternal DNA sequences in the patients.

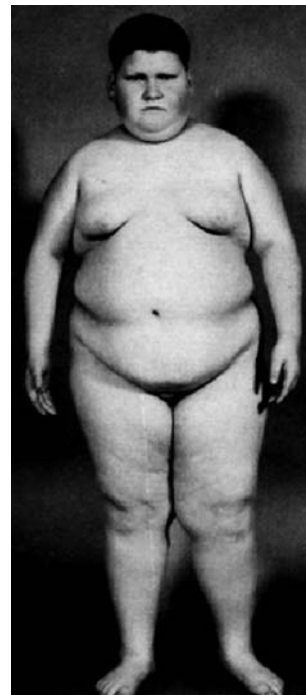


Figure P121. Prader-Willi syndrome at age 15. (From Bergsma, D., ed. 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)



Figure P122. Duplications in the Prader-Willi syndrome. (Redrawn from Amos-Landgraf JM et al 1999 Am J Hum Genet 65:370)

The deletions of this syndrome usually involve the promoter of an snRPN gene, resulting in the silencing (imprinting) of flanking genes (ZNF127 encoding a Zn-finger protein, NDN [necdin], IPW and PAR) on either side. Necdin and Magel2 also interact with Fez (fasciculation) protein and BBS4 (Bardet-Biedl protein) and they affect centrosome function (Lee S et al 2005 Hum Mol Genet 14:627). Lack of expression of snRNP is the most reliable clinical criterion for the syndrome, although snRPN alone does not appear to be the major pathogenic factor in the syndrome. The snoRNA appears to control alternative processing of the serotonin receptor 2C (Kishore S, Stamm S 2006 Science 311:230). Also, exon 1 (1920 bp) includes more than 100 5'-CG-3' and 5'-GC-3' dinucleotides liable to methylation. Among the 19 methyl-sensitive restriction enzyme sites within the telomeric region were completely methylated in this syndrome but none of these were methylated in case of the Angelman syndrome. A 2.2 kb spliced and polyadenylated RNA is transcribed 150 kb telomerically to snRPN in human chromosome 15q11.2-q12 and the homologous mouse chromosome 7 region. The transcript is not translated, however. This gene (IPW) is not expressed in individuals with the Prader-Willi syndrome and is therefore said to be imprinted in Prader-Willi syndrome. In the mouse gene *Ipw*, multiple copies of 147 bp repeats are found with retroviral transposons (IAP) insertions. ►obesity, ►imprinting, ►imprinting box, ►epigenesis, ►disomic, ►serotonin, ►alternative splicing, ►Angelman syndrome, ►head/face/brain defects, ►snPRN, ►IAP, ►Bardet-Biedl syndrome; Fulmer-Smentek SB, Francke U 2001 Hum Mol Genet 10:645.

Prairie Dog (ground squirrel, *Sciuridae*): Burrowing mammals with five different species. They are rodents, and not canidae, inhabiting arid areas (see Fig. P123).



Figure P123. *Cynomys ludovicianus* Prairie dog

pRB: Retinoblastoma protein. ►retinoblastoma

PRC1: A spindle midzone-associated kinase. ►midzone

PRD1: An icosahedral, double-stranded-DNA phage (*Tectiviridae*) of Gram-negative bacteria. It lacks the common phage tail and it acquires an injection device from the host membrane during phage assembly. The mature virion is 66 Mda, containing 20 protein species. It is evolutionarily related to adenovirus. ►phage, ►adenovirus; Abrescia NGA et al 2004 Nature [Lond] 432:68.

Pre-Adaptive: A pre-adaptive trait or mutation is that which occurs before selection would favor it but it becomes important when the conditions become favorable for this genotype. ►adaptation, ►post-adaptive mutation, ►fluctuation test

Prebiotic: Prebiotic refers to the period before life originated. ►evolution prebiotic

Precambrian: ►Proterozoic, ►Cambrian, ►geological time periods

Precise Excision: In precise excision, the genetic vector or transposon leaves the target site without structural alterations; the initially disrupted gene or sequence can return to the original (wild type) form.

Precursor Ion Scanning: A powerful technique in proteomics in connection with MS/MS and TOF. ►MS/MS, ►TOFMS; Steen H et al 2001 J Mass Spectrom 36:782; Hager JW 2002 Rapid Commun Mass Spectrom 16:512.

Predetermination: In predetermination, the phenotype of the embryo is influenced by the maternal genotypic constitution but the embryo itself does not carry the gene(s) that would be expressed in it at that particular stage. ►delayed inheritance, ►maternal effect genes

Predictive Value: The true estimate of the number of individuals afflicted by a condition on the basis of the tests performed in the population.

Predictivity: The predictivity of an assay system is, e.g., the percentage of carcinogens correctly identified

among carcinogens and non-carcinogens, by indirect carcinogenicity tests, based mainly on mutagenicity. ►accuracy, ►specificity, ►sensitivity, ►bioassays for environmental mutagens

Predictome: A database of protein links and networks. ►genetic networks

Predictor Gene: The expression of a predictor gene signals difference(s) among phenotypically similar but functionally different forms of malignancies. ►cancer classification

Predisposition: Susceptibility to disease. It may be based on a large number of alleles and environmental factors may also have a major role. A predispositional testing, based on the genetic constitution, may or may not indicate the probability of a disease.

Preeclampsia: ►ecclampsia

Preferential Repair: Transcriptionally active DNA is repaired preferentially. ►DNA repair

Preferential Segregation: Non-random distribution of homologous chromosomes toward the pole during anaphase I of meiosis. There are four loci in the Abnormal 10 chromosome (carrying a terminal large knob) in maize that affect neocentromere activity, increased recombination, and preferential segregation (Hiatt EN, Dawe RK 2003 Genetics 164:699). If harmful combination of genes (gene blocks) is preferentially included in the gametes, this may constitute a genetic load. ►meiotic drive, ►neocentromere, ►polarized segregation; Rhoades MM, Dempsey E 1966 Genetics 53:989; Buckler ES et al 1999 Genetics 153:415.

Prefoldins (PFDN): Molecular chaperones built as hexamers from the α and β subunits and four β -related subunits in eukaryotes. Prefoldin 1 was assigned to human chromosome 5, and prefoldin 4 to chromosome 7. Prefoldins may be required for gene amplification in tumors. ►chaperone; Siegert R et al 2000 Cell 103:621; prefoldin-like Skp structure: Walton TA, Sousa MC 2004 Mol Cell 15:367.

Preformation: An absurd historical idea supposing that an embryo preexists in the sperm (spermists) or in the egg (ovists) of animals and plants, rather than developing by epigenesis from the fertilized egg. ►epigenesis; Richmond ML 2001 Endeavour 25(2):55.

Pre-Genome RNA: The replication intermediate in retroid viruses. ►retroid virus

Pregnancy, Male: In seahorses (*Hippocampus*, Syngnathidae), the female lays unfertilized eggs in the ventral pouch of the male where he fertilizes them and the fetus develops.

Pregnancy Test: Pregnancy is the formation of a fetus in the womb; there are about 40 known pregnancy tests, based on chemical study of blood and urine or other criteria. The currently used tests rely on estrogen level. ►Aschheim-Zondek test

Pregnancy, Unwanted: The estimated frequency of unwanted pregnancy in the human population of the whole world was estimated between 35 to 53 million per year. ►pregnancy test, ►abortion medical

Pregnenolone: A precursor in the biosynthesis of several steroid hormones: CHOLESTEROL PREGNENOLONE→PROGESTERONE→ANDROSTENEDIONE→TESTOSTERONE→ESTRADIOL. These steps are under the control mainly of several cytochrome P450 (CYP) enzymes and their deficiency or misregulation lead to pseudohermaphroditism, hermaphroditism, and various other anomalies of the reproductive system. ►steroid hormones

Preimmunity: ►host-pathogen relation

Preimplantation Genetics: Preimplantation genetics detects genetic anomalies either in the oocyte or in the zygote before implantation takes place. This can be done by molecular and biochemical analyses, and cytogenetic techniques. The status of the egg—in some cases of heterozygosity for a recessive gene—may be determined prior to fertilization by examining the polar bodies. Since the first polar bodies are haploid products of meiosis, if they show the defect, then presumably the egg is free of it. The purpose of this test is to prevent transmission of identifiable familial disorders. The technology permits selection for sex of the embryo but this is ethically controversial. ►gametogenesis, ►in vitro fertilization, ►ART, ►micromanipulation of the oocyte, ►polymerase chain reaction, ►sperm typing, ►PGD; Delhanty JD 2001 Am J Hum Genet 65:331; Wells D, Delhanty JD 2001 Trends Mol Med 7:23; Bickerstaff H et al 2001 Hum Fertil 4:24; Braude P et al 2002 Nature Rev Genet 3:941; ethical and legal considerations: Knoppers BM et al 2006 Annu Rev Genomics Hum Genet 7:201.

Preinitiation Complex: ►PIC, ►open promoter complex

Pre-mRNA (pre-messenger RNA): The primary transcript of the genomic DNA, containing exons and introns and other sequences. ►mRNA, ►RNA processing, ►introns, ►hnRNA, ►post-transcriptional processing, ►RNA editing, ►splicing enhancer exonic

Pre-Mutation: A genetic lesion, which potentially leads to mutation unless the DNA repair system remedies the defect before it is visually manifested. Pre-mutational lesions lead to delayed mutations. UV irradiation or chemical mutagens with indirect effects (that is the mutagen requires either activation or it induces the

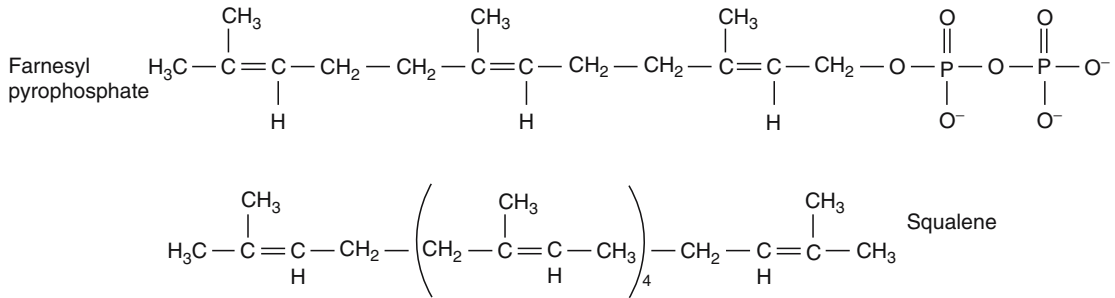


Figure P124. Two molecules of farnesyl pyrophosphate are converted into 30-C squalene in the presence of NADPH

formation of mutagenic radicals, peroxides) frequently cause pre-mutations. Incomplete expansion of trinucleotide repeats may also be considered pre-mutational, e.g., in the fragile X chromosome. ▶chromosomal mutation, ▶chromosome breakage, ▶point-mutation, ▶telomutation, ▶trinucleotide repeats, ▶fragile X, ▶Sherman paradox under mental retardation; Auerbach C 1976 Mutation research. Chapman and Hall, London, UK.

Prenatal Diagnosis: Prenatal diagnosis determines the health status or distinguishes among the possible nature of causes of a problem with a fetus before birth. The results of cytological or biochemical analysis permit the parents to prepare psychologically and medically to the expectations. Although chromosomal abnormalities cannot be remedied, for metabolic disorders (e.g., galactosemia) advance preparations can be made. Similarly, fetal erythroblastosis may be prevented. In case of very severe hereditary diseases, abortion may be an option if it is morally acceptable to the parents and does not conflict with the existing laws. Prenatal diagnosis is now available for more than hundred anomalies. Until recently, prenatal diagnosis required mainly amniocentesis or sampling of chorionic villi, now in some instances the maternal blood can be scanned for fetal blood cells and by the use of the polymerase chain reaction, the DNA of the fetus can be examined. ▶genetic testing, ▶genetic screening, ▶genetic counseling, ▶amniocentesis, ▶polymerase chain reaction, ▶RFLP, ▶DNA fingerprinting, ▶DNA circulating, ▶plasma nucleic acid, ▶PUBS, ▶MSAFP, ▶sonography, ▶fetoscopy, ▶echocardiography, ▶hydrocephalus, ▶galactosemias, ▶chorionic villi, ▶pre-implantation genetics, ▶ART; Weaver DD, Brandt IK 1999 Catalog of prenatally diagnosed conditions, Johns Hopkins University Press, Baltimore, Maryland; Fetal Evaluation: <http://www.cpdx.com/>.

Prenylation: The attachment of a farnesyl alcohol, in thioether linkage, with a cystein residue located near the carboxyl terminus of the polypeptide chain. The donor is frequently farnesyl pyrophosphate.

Cytosolic proteins are frequently associated with the lipid bilayer of the membrane by prenyl lipid chains or through other fatty acid chains. Prenyl biogenesis begins by enzymatic isomerization of isopentenyl pyrophosphate ($\text{CH}_2=\text{C}[\text{CH}_3]\text{CH}_2\text{CH}_2\text{OPP}$) into dimethylallyl pyrophosphate ($[\text{CH}_3]_2\text{C}=\text{CHCH}_2\text{OPP}$). These then react to form geranyl pyrophosphate ($[\text{CH}_3]_2\text{C}=\text{CHCH}_2\text{CH}_2\text{C}[\text{CH}_3]=\text{CHCH}_2\text{OPP}$). Geranyl pyrophosphate is then converted into farnesyl pyrophosphate as shown in Figure P124.

Members of the RAS family proteins, involved in signal transduction, cellular regulation, and differentiation are prenylated at cysteine residues of the COOH-terminus. Prenylation determines the cellular localization of these molecules. Cellular fusions are mediated by prenylated pheromones. The cytoskeletal lamins attaching to the cellular membranes are farnesylated. Prenylation of the C-termini of proteins is generally mediated by farnesyltransferase, a heterodimer of 48 kDa α and 46 kDa β subunit. Protein farnesylation is essential for early embryogenesis and for the maintenance of tumorigenesis (Mijimolle N et al 2005 Cancer Cell 7:313). Squalene is a precursor of cholesterol and other steroids (see Fig. P125). ▶lipids, ▶abscisic acid, ▶lamin, ▶RAS, ▶cytoskeleton, ▶pheromone

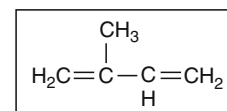


Figure P125. Isoprene units

Prepatent: The period before an effect (e.g., infection) becomes evident.

Prepattern Formation: The distribution of morphogens precedes the appearance of the visible pattern of particular structures. ▶morphogen; Chiang C et al 2001 Dev Biol 236:421.

Prepriming Complex: A number of proteins at the replication fork of DNA involved in the initiation of DNA synthesis. ▶DNA replication, ▶replication fork

Preprotein: A preprotein is a protein molecule that has not completed yet its differentiation (trimming and processing).

Prereduction: In prereduction, the alleles of a locus separate during the first meiotic anaphase because there was no crossing over between the gene and the centromere. ▶tetrad analysis, ▶meiosis, ▶post-reduction

Pre-rRNA: The unprocessed transcripts of ribosomal RNA genes; they are associated at this stage with ribosomal proteins and are methylated at specific sites. The cleavage of the cluster begins at the 5' terminus of the 5.8S unit and proceeds to the 18S and 28S units. ▶rRNA, ▶rm, ▶ribosomal RNA, ▶ribosome

Presence-Absence Hypothesis: The presence-absence hypothesis was advocated by William Bateson during the first few decades of the 20th century as an explanation for mutation. The recessive alleles were thought to be losses whereas the dominant alleles were supposed to indicate the presence of genetic determinants. Similar views, in a modified form, were maintained for decades later and were debated in connection with the nature of induced mutations. ▶null mutation, ▶genomic subtraction; Bateson W et al 1908 Rep Evol Comm R Soc IV, London, UK.

Presenilins (PS): Proteins associated with precocious senility, such the presenilin 1 (S182/AD3) encoded at human chromosome 14q24.3 (442 amino acids) and presenilin 2 (STM2/AD4, 467 amino acids encoded at 1q31-q34.2) proteins of the Alzheimer's disease. Mutations in presenilins account for about 40% of familial cases of the Alzheimer's disease. Presenilins are integral membrane proteases. Presenilin 1 and presenilin 2 increase the production of β -amyloid either directly or most likely by their effect on secretases. They may also promote apoptosis. Presenilins control calcium ion channels of the endoplasmic reticulum and the disruption of these channels can lead to Alzheimer's disease (Tu H et al 2006 Cell 126:981). Mutant PS1 strongly affects both the amplitude of evoked excitatory currents as well as the frequency of spontaneous excitatory synaptic currents by decreasing the number of functional synapses (Priller C et al 2007 J Biol Chem 282:1119). p53 and p21^{WAF-1} promote inhibition of presenilin 1, and that may encourage apoptosis and tumor suppression as well. Presenilin 1 is associated with β -catenin and in the complex β -catenin is stabilized. Mutations in Presenilin 1 may destabilize β -catenin and the latter is usually degraded in

Alzheimer's disease. Thus, mutation in Presenilin 1 may predispose to early onset Alzheimer's disease. Presenilin also controls pigmentation of the retinal epithelium and epidermal melanocytes, and mutation may lead to aberrant accumulation of tyrosinase (Wang R et al 2006 Proc Natl Acad Sci USA 103:353). Presenilin 2 contains a domain that is similar to that of ALG3 (apoptosis linked gene) and inhibits apoptosis. Presenilin 1 may also affect various (non-neurodegenerative) cancer-related pathways. The presenilins are involved in the processing of the transmembrane domain of amyloid precursor proteins (APP), and they are essential for normal embryonal development. Protein TMP21 is a component of presenilin complexes and modulates selectively γ -secretase but not ϵ -secretase (Chen F et al 2006 Nature [Lond] 440:1208). Presenilins also control the transduction of Notch signals. A presenilin locus exists in the third chromosome also (77A-D) of *Drosophila melanogaster*. ▶Alzheimer disease, ▶prion, ▶apoptosis, ▶p53, ▶p21, ▶calsenilin, ▶catenins, ▶ubiquitin, ▶Notch, ▶secretase, ▶nicastrin; Sisodia SS et al 1999 Am J Hum Genet 65:7; Baki L et al 2001 Proc Natl Acad Sci USA 98:2381; Wolfe MS, Haass C 2001 J Biol Chem 276:5413; Marjaux E et al 2004 Neuron 42:189.

Present: The expressed open reading frames during particular times or conditions when analyzed by microarrays. ▶open reading frame, ▶microarray hybridization

Presenting: Behavioral signs shown by the female indicating receptivity to mating.

Presequence: A generic name for signal peptides and transit peptides.

Presetting: The penchant of a transposable element to undergo reversible alteration in a new genetic milieu. It may be caused by the methylation of the transposase gene. ▶Spm, ▶Ac-Ds

Presymptomatic Diagnosis: The identification of the genetic constitution before the onset of the symptoms. ▶prenatal diagnosis, ▶genetic screening

Pre-tRNA: ▶tRNA

Prevalence (K, λ): The proportion of a genetic or non-genetic anomaly or disease in a particular human population at a particular time. The percentage of hereditary diseases caused by presumably single nuclear genes in human populations: autosomal dominant 0.75, autosomal recessive 0.20, X-linked 0.05. Besides these, multifactorial abnormalities account for about 6% of the genetic anomalies. In case the general prevalence of the diseases in a population is x, the expected expression among sibs for autosomal

dominant is $1/2x$, for autosomal recessives it is $1/4x$, and for multifactorial control $1/\sqrt{x}$. ▶incidence, ▶mitochondrial diseases in humans

Prevention of Circularization of Plasmids: ▶circularization

Preventive Medicine: Preventive medicine studies the genetic and physiological conditions of individuals and societies in order to take measures to avoid the onset of diseases. ▶diseases in humans, ▶genetic counseling, ▶counseling genetic, ▶genetic risk, ▶recurrence risk, ▶empirical risk, ▶heritability

Prey: ▶two-hybrid system

Prezygotic: The DNA molecule in the prokaryotic cell before recombination (transduction or transformation); after integration it becomes postzygotic.

Pri: ▶cis-acting elements

PriA: Replication priming protein. ▶replication fork, ▶DNA replication, ▶primase

Priapism: An uncommon prolonged engorgement of the penis or erection of the penis or the clitoris. Phosphodiesterase-5A dysregulation is one cause (Champion HC et al 2005 Proc Natl Acad Sci USA 102:1661). It is generally called idiopathic but in some families it occurs repeatedly. It may be evoked by alcoholism or by certain drugs. Chronic hemoglobinopathies and genital cancer may also cause it. ▶idiopathic, ▶hemoglobinopathies, ▶nitric oxide, ▶phosphodiesterase

Pribnow Box (TATA box): 5'-TATAATG-3' (or similar) consensus preceding the prokaryotic transcription initiation sites by 5–7 nucleotides in the promoter region at about –10 position from the translation initiation site. Separated by 17 bp there is another conserved element (called extended promoter) in prokaryotes at –35 (TTGACA). The eukaryotic homolog of the Pribnow box is the Hogness box. ▶Hogness box, ▶open promoter complex, ▶σ; Gold L et al 1981 Annu Rev Microbiol 35:365.

Pride: A living and mating community of animals under the domination of a particular male(s).

Primary Cells: Primary cells are taken directly from an organism rather than from a cell culture.

Primary Constriction: The centromeric region of the eukaryotic chromosome (see Fig. P126).

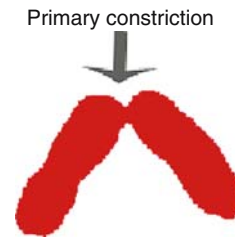


Figure P126. Primary constriction

Primary Nondisjunction: ▶nondisjunction

Primary Response Genes: The induction of primary response genes occurs without the synthesis of new protein but requires only pre-existing transcriptional modifiers such as hormones. ▶sign transduction, ▶secondary response genes

Primary Sex Ratio: Ratio of males to females at conception. ▶sex ratio

Primary Sexual Characters: The female and male gonad, respectively. ▶secondary sexual characters

Primary Structure: The sequence of amino acid or nucleotide residues in a polymer.

Primary Transcript: The RNA transcript of the DNA before processing has been completed. ▶processing, ▶pre-mRNA, ▶pre-rRNA

Primase: Polymerase-α/primase synthesizes an about 30-nucleotide RNA primer for the initiation of replication of the lagging strand of the DNA. In prokaryotes, the primosome protein complex fulfills the function. In bacteriophage M13, an imperfect hairpin is formed at the origin of replication, which is recognized by *E. coli* RNA polymerase σ^{70} holoenzyme and it synthesizes a 18–20 nucleotide primer suitable for synthesis by DNA polymerase III. The RNA polymerase leaves a protruding 3'-end of the RNA but maintains an RNA-DNA hybrid molecule of 8–9 bp. This 3-end of the RNA can then interact with DNA polymerase III. Filamentous phages and bacterial plasmids probably use the priming mechanisms (Zenkin N et al 2006 Nature [Lond] 439:617). The function of the primase is much slower than the processing of the DNA polymerase. Since the Okazaki fragments need priming several times while the leading strand is synthesized by the DNA polymerase, there must be a molecular brake there to assure that the two (leading and lagging) strands are synthesized in concert (Lee J-B et al 2006 Nature [Lond] 439:621). In *E. coli*, gene *DnaG* (66 min) encodes it and it is associated with the replicative helicase. In eukaryotes, the ~60 and ~50 kDa subunits of DNA polymerase α represent the primase.

The latter complex is associated with proteins and forms a mass of ~300 kDa. The primases prime any single-stranded DNA but they are far more effective at specific sequences. DnaG recognizes the 5'-CTG-3' trinucleotide and synthesizes a 26–29 nucleotide RNA. The mouse primase works at ~17 sites that share either 5'-CCA-3' or 5'-CCC-3' at about 10 nucleotides downstream from the priming initiation site at the 3'-end. The active template is usually rich in pyrimidines. In eukaryotes, the primer is directly transferred to the DNA pol α without dissociating from the template. Primase inhibitors (cytosine or adenosine arabinoside, 2'-deoxy-2'-azidocytidine, etc.) have therapeutic potentials. Several binding proteins assist priming. ►replication fork, ►DNA replication, ►PriA, ►DNA polymerases, ►polymerase switching, ►Okazaki fragment, ►primosome, ►replication restart; Keck JL et al 2000 Science 287:2482; Arezi B, Kuchta RD 2000 Trends Biochem 25:572; Frick DN, Richardson CC 2001 Annu Rev Biochem 70:39; Augustin MA et al 2001 Nature Struct Biol 8:57.

Primates: The taxonomic group that includes humans, apes, monkeys, and lemur. To the higher primates, also called anthropoidea or simians, belong the old world monkeys (Cercopithecidae) such as the *Macaca*, *Cercopithecus*, etc., hominoidea (chimpanzee [*Pan*], gorilla [*Gorilla*], orangutan [*Pongo*], and humans, and also the now extinct early evolutionary forms. The anthropoidea includes also the new world monkeys (*Cebioidea*). The lower primates or prosimians mean the genera of the lemur, galago, etc. According to data of D.E. Kohne et al (1972 J Hum Evol. 1:627), on the basis of thermal denaturation of hybridized DNA the numbers in million years of divergence (and the % of nucleotide difference) of various primates from man was estimated to be: chimpanzee 15 (2.4), gibbon, 30 (5.3), green monkey 46 (9.5), capuchin 65 (15.8), galago 80 (42.0). Some of the DNA differences now need revisions (►chimpanzee). Humans have substantially lower variations in the DNA than the great apes, chimpanzees, and orangutan (see Table P2) (Kaessmann H et al 2001 Nature Genet 27:155).

Table P2. The expressed genes indicate relations among three primate species as follows

| | Chimpanzee | Orangutan | Rhesus macaque |
|------------|------------|-----------|----------------|
| Humans | 110 | 128 | 176 |
| Chimpanzee | - | 150 | 141 |
| Orangutan | - | - | 129 |

(Data from Gilad, Y. et al. 2006 Nature [Lond] 440:242)

The taxonomic tree of primates can be outlined as:

PRIMATES: *I. Catarrhini*. IA1 Cercopithecidae (Old World Monkeys). IA1a Cercopithecinae, IA1b Colobinae. IA1c Cercopithecidae. IB. Hominidae (Gorilla, Homo, Pan, Pongo). IC. Hylobatidae (Gibbons). *II. Platyrrhini* (New World Monkeys): IIA. Callitrichidae (Marmoset and Tamarins). IIA1. Callimico. IIA2. Callithrix. IIA3. Cebuella. IIA4. Callicebinae. IIA5. Cebinae. IIA6. Pitheciinae. *III. Strepsirhini* (Prosimians) IIIA Cheirogalidae. IIIA1 Cheirogaleus. IIIA2. Microcebus. IIIB. Daubentonidae (Ayeayes). IIIB1. Daubentonia. IIIC Galagonidae (Galagos). IIIC1. Galago. IIIC2. Otolemur. IIID. Indridae. IIID1 Indri. IIID2. Propithecus (Sifakas). IIIE. Lemuridae (Lemurs). IIIE1. Eulemur. IIIE2. Hapalemur. IIIE3. Lemur. IIIE4. Varecia. IIIF. Loridae (Lorises). IIIF1. Loris. IIIF2. Nycticebus. IIIF3. Perodicticus. IIIG Megalapididae. IIIG1. Lepilemur. *IV. Tarsii* (Tarsiers). IVA Tarsiidae (Tarsiers). IVA1. Tarsius. ►human races, ►apes, ►prosimii, ►Cebidae, ►Callithricidae, ►Cercopithecidae, ►Colobidae, ►Pongidae, ►Homo sapiens, ►Hominidae, ►evolutionary tree; DeRousseau CJ (ed) 1990 Primate Life History and Evolution, Wiley-Liss, New York; Enard W et al 2002 Science 296:340; <http://www.primat.wisc.edu/pin>; phylogeny database: <http://www.hvrbase.org/>.

Primatized Antibody: A chimeric antibody constructed using the variable region of monkey antibody linked to the human constant region. ►antibody chimeric

Primer: A short sequence of nucleotides (RNA or DNA) that assists in extending the complementary strand by providing 3'-OH ends for the DNA polymerase to start transcription. In some viruses (hepadna viruses, adenoviruses), the replication of viral DNA, and in some cases viral RNA is primed by proteins. The 3' OH group of a specific serine is linked to a dCMP and a viral enzyme drives the reaction. Replication may proceed from both ends of the linear molecules without being in the same replication fork. ►nested primers, ►primase, ►PCR, ►Vpg; <http://www.genome.wi.mit.edu>; primer identification: <http://ihg.gsf.de/ihg/ExonPrimer.html>; <http://web.ncicrf.gov/rtp/gel/primerdb/>; primer design for promoters and exons: <http://genepipe.ngc.sinica.edu.tw/primerz/>; may better opens by: http://www.citeulike.org/user/sebastien_vigneau/article/1357047; Primer3 primer selection: <http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi>.

Primer Extension: RNA (or single-strand DNA) is hybridized with a single strand DNA primer (30–40 bases), which is 5'-end-labeled. Generally, the primers are complementary to base sequences within 100 nucleotides from the 5'-end of mRNA to avoid

heterogeneous products of the reverse transcriptase which is prone to stop when it encounters tracts of secondary structure. After extension of the primer by reverse transcriptase, the length of the resulting cDNA (measured in denaturing polyacrylamide gel electrophoresis) indicates the length of the RNA from the label to its 5'-end. When DNA (rather than RNA) is used as template DNA-DNA hybridization must be prevented. The purpose of the primer extension analysis is to estimate the length of 5' ends of RNA transcripts and identify precursors of mRNA and processing intermediates. The cDNA so obtained can be directly sequenced by the Maxam-Gilbert method or also by the chain termination methods of Sanger if dideoxynucleoside triphosphates are included in the reaction vessels. Primer extension preamplification (PEP) facilitates the preparation of multiple copies of the genome of a single sperm (Zhang L et al 1992 Proc Natl Acad Sci USA 89:5847). ▶DNA sequencing, ▶primary transcript, ▶post-transcriptional processing, ▶chimeric proteins, ▶PCR-based mutagenesis, ▶amplification; Reddy VB et al 1979 J Virol 30:279; Sambrook J et al 1989 Molecular cloning, Cold Spring Harbor Laboratory Press.

Primer Shift: The primer shift is used for confirmation that a PCR procedure indeed amplified the intended DNA sequence. For this purpose, a primer different from the one initially employed is chosen and attached to the template a couple of hundred bases away from the position of the first. After the completion of the PCR process, the amplified product is supposed to be as much longer as the difference between the position of the first and the second primer if the amplification involved the intended sequence. Such a procedure may be used when a DNA sequence corresponding to a deletion is amplified. ▶PCR, ▶primer

Primer Walking: A method in DNA sequencing whereby a single piece of DNA is inserted into a large-capacity vector. After a shorter stretch had been sequenced, a new primer is generated from the end of what has been already sequenced and the process is continued until the sequencing of the entire insert is completed. ▶DNA sequencing; Zevin-Sonkin D et al 2000 DNA Seq 10(4-5):245; Kaczorowski T, Szybalski W 1998 Gene 223:83.

Primitive Streak: The earliest visible sign of axial development of the vertebrate embryo when a pale line appears caudally at the embryonic disc as a result of migration of mesodermal cells. ▶organizer, ▶differentiation, ▶morphogenesis, ▶Hensen's node, ▶embryo node; Ciruna B, Rossant J 2001 Dev Cell 1:37.

Primordium: The embryonic cell group that gives rise to a determined structure.

Primosome: The complex of prepriming and priming proteins involved in replication of the Okazaki fragments (see Fig. P127). It moves along with the replication fork in the opposite direction to DNA synthesis. The primosome (containing helicase and primase) unwinds the double-stranded DNA and synthesizes RNA primers. ▶DNA replication, ▶replication fork, ▶Okazaki fragment, ▶primase; Marsin S et al 2001 J Biol Chem 276:45818; replication restart primosome PriB component structure: Lopper M et al 2004 Structure 12:1967; Zhang Z et al 2005 Proc Natl Acad Sci USA 102:3254; electron microscopic structure: Norcum MT et al 2005 Proc Natl Acad Sci USA 102:3623.

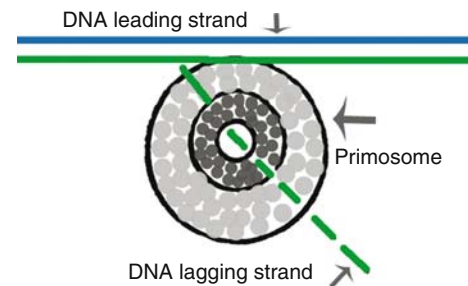


Figure P127. Primosome

Primula (Primrose): An ornamental plant. *P. kewensis* ($2n = 36$) is an amphidiploid of *P. floribunda* ($2n = 18$) and *P. verticillata* ($2n = 18$).

Principal Component Analysis: The aim of the principal component analysis is to reduce the apparent complexity of the original variables and summarize the information in a simpler manner. The principal components are construed as linear functions of the original variables. ▶factorial analysis, ▶stratification; Jolliffe IT 1986 Principal Component Analysis, Springer, New York.

PRINS (primed in situ synthesis): An in situ hybridization technique bearing some similarities to other methods of probing (e.g., FISH). The PRINS procedure uses small oligonucleotide (18–22 nucleotides) primers from the sequence of concern. After the primer is annealed to denatured DNA (chromosomal or other polynucleotides), a thermostable DNA polymerase is employed to incorporate biotin-dUTP or digoxigenin-dUTP. The procedure is very sensitive to mismatches (because the primer is short) and a mismatch at the 3'-end may prevent chain extension. The concentration of the primer (C) = $Ab_{260}/\epsilon_{max} \times L$

where Ab_{260} = absorbance at 260 nm, ϵ_{\max} = molar extinction coefficient (M^{-1}) and L = the path length of the cuvette of the spectrophotometer. The molar extinction coefficients are determined $\epsilon_{\max} = (\text{number of A} \times 15,200) + (\text{number of T} \times 8400) + (\text{number of G} \times 12,010) + (\text{number of C} \times 7050) M^{-1}$. (A = adenine, T = thymine, G = guanine, C = cytosine). PRINS are useful for many purposes, including determination of aneuploidy, DNA synthesis, viral infection, etc. ►PCR, ►FISH, ►in situ hybridization, ►LISA, ►biotinylation, ►extinction, ►non-radioactive label; Hindkjaer J et al 2001 Methods Cell Biol 64:55.

PrintAlign: A computer program for graphical interpretation of fragment alignments in physical mapping of DNA. ►physical map

PrintMap: A computer program that produces a restriction map in PostScript code. ►PostScript

PRINTS: A database for the analysis of the hierarchy of protein families on the basis of fingerprints. ►protein families; <http://www.bioinf.man.ac.uk/dbbrowser/PRINTS/>.

Prion (PrP^C , PrP^{Sc} , PrP^* , PrP^{Pres}): Infective, protease-resistant glycoprotein particles, responsible for the degenerative brain diseases such as scrapie in sheep, chronic wasting disease in deer and elk, BSE in cattle, kuru, Creutzfeldt-Jakob disease, Gerstmann-Sträussler syndrome, fatal familial insomnia of man and, possibly, also Alzheimer's disease. Protease-sensitive prions ($sPrP^{Sc}$) also exist. Prions are transmitted among various animal species although the expression may require a longer lag. Decreased transmission of the prion state between divergent proteins is termed "species barrier" and was thought to occur because of the inability of divergent prion proteins to co-aggregate. Species barrier can be overcome in cross-species infections, e.g., from "mad cows" to humans. The counterparts of yeast prion protein Sup35, originated from three different species of the *Saccharomyces sensu stricto* group exhibit the range of prion domain divergence that overlaps with the range of divergence observed among distant mammalian species. All three proteins were capable of forming a prion in *Saccharomyces cerevisiae*, although prions formed by heterologous proteins were usually less stable than the endogenous *S. cerevisiae* prion. Heterologous Sup35 proteins co-aggregated in the *S. cerevisiae* cells. However, in vivo cross-species prion conversion was decreased and in vitro polymerization was cross-inhibited in at least some heterologous combinations, thus demonstrating the existence of prion species barrier (Chen B et al 2007 Proc Natl Acad Sci USA 104:2791).

Mutations in the gene may result in prion potentiation. The non-familial Creutzfeldt-Jakob disease may be traced to infections by gonadotropins, human growth hormones extracted from cadavers, grafts, improperly-sterilized medical equipment contaminated by prions, or to eating the meat (primarily brain, lymphatic and nerve tissues) of infected animals. In case of chronic inflammation of the kidneys, scrapie-infected mice excrete prions by the urine (Seeger H et al 2005 Science 310:324). Normal prion protein, PrP^{Sen} (PrP^C protease sensitive), is expressed as a membrane-bound glycoprophosphatidylinositol (GPI)-anchored protein (see Fig. P128). The GPI anchor may be the requisite for infectious transmission of this protein and the expression of typical scrapie (Chesebro B et al 2006 Science 308:1435). Other amyloidogenic proteins, which are involved in brain degeneration but lack GPI anchor, are not infectious. GPI-anchorless proteins can be secreted from the blood and can form deposits in the amyloid or non-amyloid forms in the brain and heart endothelia. In infected non-transgenic mice, it appears mainly in the non-amyloid form but in transgenic animals, mainly in the amyloid form. The protease-resistant prion causes heart disease (Trifilo MJ et al 2006 Science 313:94).

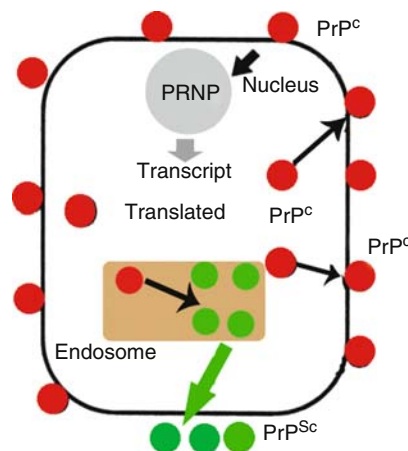


Figure P128. The normal PrP^C protein is encoded in the nucleus by the PRNP gene and after transcription the RNA transcript is translated in the cytoplasm. Some of the PrP^C molecules decorate the surface of the nerve cells and others may be sequestered into the endosomes or lysosomes. Within these compartments, a conformational alteration may take place and the infectious PrP^* or PrP^{Sc} protein molecules are released. These altered molecules may then infect other, normal cells and initiate a process of degenerative protein accumulation. The conformational changes may be caused by mutations in PRNP and other genes located in several human chromosomes. (Modified after Weissmann C 1999 J Biol Chem 274:3)

On the basis of the degree and extent of glycosylation, about 400 prions have been distinguished. The N terminus of PrP contains a glycosaminoglycan (GAG)-binding motif. Binding of GAG is important in prion disease. Accordingly, all human mutant recombinant rPrPs bind more GAG, and GAG promotes the aggregation of rPrP more efficiently than wild-type recombinant normal cellular PrP (rPrP^C). Furthermore, point mutations in *PRNP* gene also cause conformational changes in the region between residues 109 and 136, resulting in the exposure of a second, normally buried, GAG-binding motif. Importantly, brain-derived PrP from transgenic mice, which express a pathogenic mutant with nine extra octapeptide repeats also binds more strongly to GAG than wild-type PrP^C (Yin S et al 2007 Proc Natl Acad Sci USA 104:7546).

Prions appear like virus particles but are free of nucleic acid. The 25 nm virus-like arrays in two cell lines with transmissible spongiform encephalitis (TSE) virions are structurally independent of pathological PrP in the intact cell (Manuelidis L et al 2007 Proc Natl Acad Sci USA 104:1965). It appears that a normal protein is structurally modified; the α helical structure is largely converted into β sheets, leading to the formation of these autonomous disease-causing proteins. Transmission of the disease in the absence of the protease-resistant prion is exceptional (Lasmézas CI 1997 Science 275:402). Although prions are infectious diseases of protein folding, some RNAs of mammals appear adjuvants of the pathogenic alterations in vitro whereas invertebrate RNA has no such effect (Deleault NR et al. 2003 Nature [Lond] 425:717). Experimental protein misfolding cyclic amplification (PMCA) reaction can yield in vitro generated prions that are indistinguishable from prions isolated from scrapie hamster brain in terms of proteinase K resistance, autocatalytic conversion activity, and, most notably, specific biological infectivity (Weber P et al 2006 Proc Natl Acad Sci USA 103:15818).

In order to develop prion disease in mice, the organism must have PrP^C, and if it is absent the animals become resistant to scrapie and show normal neuronal functions (Büeler H et al 1993 Cell 73:1339). PrP^C-deficient cattle produced by a sequential gene-targeting system over 20 months of age are clinically, physiologically, histopathologically, immunologically and reproductively normal. Brain tissue homogenates are resistant to prion propagation in vitro (Richt JA et al 2007 Nature Biotechnol 25:132). Also, microglia (cells that surround the nerves and phagocytize the waste material of the nervous tissue) must be present to develop prion disease. Depletion of the endogenous neuronal PrP^C from mice by the Cre recombinase prevents the

progression of the disease. The non-neural accumulation of PrP^{Sc} is not pathogenic but leads to an arrest of PrP^C→PrP^{Sc} conversion within neurons and prevents neurotoxicity (Mallucci G et al 2003 Science 302:871). Depletion of endogenous neuronal prion protein (PrP^C) in mice with early prion infection reversed spongiform change and prevented clinical symptoms and neuronal loss. Thus, early functional impairments precede neuronal loss in prion disease and can be rescued. Further, they occur before extensive PrP^{Sc} deposits accumulate and recover rapidly after PrP^C depletion, supporting the concept that they are caused by a transient neurotoxic species, distinct from aggregated PrP^{Sc} (Malucci GR et al 2007 Neuron 53:325).

If microglia are destroyed by L-leucine-methylester, the neurotoxic PrP fragment, containing amino acids 106–126, does not harm the neurons. The transition from the normal PrP^C→PrP^{Sc} (the insoluble scrapie prion) conformation involves changes in amino acid residues 121–231, involved two antiparallel β -sheets and in three α -helices (see Fig. P129).

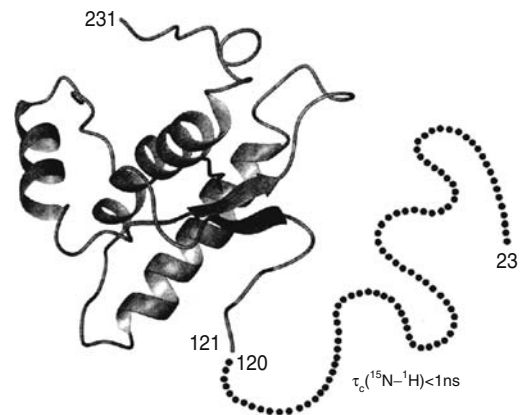


Figure P129. The nuclear magnetic resonance-revealed structure of the PrP^C protein. The amino end displays an about 100 residue flexible sequence that is modified when PrP^{Sc} is formed. (Modified after Riek R et al 1997 FEBS Lett 413:282. By Permission of Elsevier Science and Authors)

Monoclonal antibody 15B3 (Peretz D et al 2001 Nature [Lond] 412:739) and the anti-DNA antibody OCD4 as well the gene 5 protein (Zou W-Q et al 2004 Proc Natl Acad Sci USA 101:1380), both DNA-binding proteins, discriminate between the PrP^C and PrP^{Sc} and may help in the diagnosis of prion diseases or perhaps cure. Early diagnosis of prions (CJD) is possible because two peptides of PrP^C bind 3800 fold more effectively to PrP^{Sc} than to PrP^C (Lau AL et al 2007 Proc Natl Acad Sci USA 104:1151). The Tyr-Tyr-Arg monoclonal antibodies discriminate between PrP^C and PrP^{Sc} and hold promise that immunoprophylaxis and/or immunotherapy may eventually

become available (Paramithiotis E et al 2003 Nat Med 9:893). Conformation-dependent immunoassay (CDI) can discriminate among different prion strains. This assay quantifies PrP isoforms by simultaneously following antibody binding to the denatured and native prion protein. When the denatured/native PrP is graphed as the function of PrP^{Sc} concentration, each strain occupies a different position indicating a unique conformation (Safar J et al 1998 Nature Med 4:1157). The CDI test is extremely reliable (Safar JG et al 2005 Proc Natl Acad Sci USA 102:3501).

It has been hypothesized—on the basis of experimental observations—that the toxicity of this protein is based on increased oxidative stress. The inactivation of the *PrP* gene in mice does not lead to an immediate deleterious condition, but by the age of 70 weeks, an extensive loss of the Purkinje cells (large neurons in the cerebellar cortex) takes place and the animals have problems with movement coordination (ataxia). In case the normal PrP protein accumulates in the cytosol, a self-perpetuating PrP^{Sc}-like transformation takes place and neurodegeneration results (Ma J et al 2002 Science 298:1781). The disrupted *PrP* genes make them resistant to prions. Susceptibility in mice is affected also by QTLs in chromosomes 4, 6, 8, and 17 (Moreno CR et al 2003 Genetics 165:2085). On the basis of some genetic tests, it was concluded that the period of incubation of the mouse scrapie is controlled by allelic forms of a separate gene (*Sinc/Prni*). Molecular evidence indicates, however, that codons 108 and/or 109 of the *Prp* gene control incubation. In the mouse, there is a second *PrP* locus 16 kb down-stream. This *Prnd* (d for Doppelgänger [alterego in German], downstream prion protein-like) is truncated at the amino end domain and encodes only 179 amino acids.

Although its amino acid sequence shows only 25% homology with PrP, the structure of Prnd is quite similar. Prnd originated probably as an ancient duplication. Mice homozygous knockouts for Prnd and PrC are sterile. Its expression is normally limited to the testes, but if it is expressed in the brain, it causes neurodegeneration.

In case the *PrP* (*Prnp*) exons are deleted, Doppelgänger exons can be spliced into the PrP mRNAs. In ataxic animals, this intergenic splicing is highly expressed. Apparently, the manifestation of ataxia, the loss of Purkinje cells, and the degeneration of cerebellar granule cells is correlated with the alteration of a ligand-binding site.

A mutant form of PrP, ^{C_{tm}}PrP, a trans-membrane protein, can also cause prion disease in the absence or presence of PrP^{Sc}. The latter may also modulate the synthesis of the transmembrane form. Actually “the ability of polypeptide chains to form amyloid structures is not restricted to the relatively small

number of proteins associated with recognized clinical disorders, and it now seems to be a generic feature of polypeptide chains” (Dobson CM 2003 Nature [Lond] 426:884). PrP^{Sc} molecules could be formed *de novo* from defined components in the absence of preexisting prions. PrP^{Sc} can be formed from a minimal set of components including native PrP^C molecules, co-purified lipid molecules, and a synthetic polyanion. Inoculation of samples containing either prion-seeded or spontaneously generated PrP^{Sc} molecules into hamsters caused scrapie, which was transmissible on second passage (Deleault NR et al 2007 Proc Natl Acad Sci USA 104:9741).

PrP^C may be involved in signal transduction in nerve function. PrP^{Sc} apparently binds plasminogen that selectively imparts neurotoxicity to the prion protein.

In budding yeast, two non-nuclear elements [*URE3*] and [*PSI*] appear (among others) to be the infectious prion forms of the Ure2p protein that is also a regulator of nitrogen catabolism. When Urep was overexpressed in wild type strains, the frequency of occurrence of the [*URE3*] increased 20–200 fold. If the overexpression of Urep was limited only to the amino ends of this protein, the frequency of occurrence of [*URE3*] increased 6000 times. The carboxyl domain of Urep seemed to carry out nitrogen catabolism whereas the amino end induced the prion formation. Both [*URE3*] and [*PSI*] are the prion causing forms of nuclear genes *URE2* and *SUP35*, respectively. The *URE2* gene is involved in the control of utilization of ureidosuccinate as a nitrogen source, while the *SUP35* nuclear gene encodes a subunit (eRF3, eukaryotic release factor) of the yeast translation termination complex. Mutations in both the nuclear genes involve derepression of nitrogen catabolism that is normally repressed by nitrogen. The propagation of [*URE3*] and [*PSI*] depends on *URE2* and *SUP35* nuclear genes, respectively. Guanidine-HCl blocks the propagation of *PSI*⁺. Gdn-HCl-induced loss of the [*PSI*⁺] prion is due to a failure to segregate propagons from daughter cells and not because of degradation of the preexisting propagons (Byrne LJ et al 2007 Proc Natl Acad Sci USA 104:11688). In vitro, the Sup35 protein may show prion-like properties. Normally, translation terminates at a stop codon by an interaction between Sup35 and other proteins such as Sup45. If the Sup35 proteins aggregate, they may assume prion conformation and the translation continues beyond the stop codon and an additional protein sequence is formed (►eRF). The conformation of the SUP35 prion motif varies among different fungal species and is important for its transmissibility. The amyloid fiber morphology and size may vary in different yeast prion strains (Diaz-Avalos R et al 2005 Proc Natl Acad Sci USA 102:10165). A certain conformation of SUP35 of *Saccharomyces cerevisiae* permits transmission to

Candida albicans and such *Candida* can then infect *Saccharomyces*. Thus strain conformation is critical for cross-species transmission (Tanaka M et al 2005 Cell 121:49; Tanaka M et al 2006 Nature [Lond] 442:585). A similar conclusion has been reached in mammals where a single or two residues determine critical requirement for amyloid transmission, yet preformed fibrils may overcome sequence-based structural preferences. For transmission, the amyloid protein conformation is the critical factor (Jones EM, Surewicz WK 2005 Cell 121:63). The cross- β spine structure explains the critical features of stability and self-perpetuation of the amyloid fibers (►cross- β spine). Heat shock protein Hsp104 catalyzes the formation and also the destruction of this yeast prion (Shorter J, Lindquist SW 2004 Science 304:1793). Deletion of Hsp104 eliminates Sup35 and Ure2 prions, whereas overexpression of Hsp104 purges cells of Sup35 prions, but not Ure2 prions. For both Sup35 and Ure2, Hsp104 catalyzes de novo prion nucleation from soluble, native proteins. Hsp104 fragments both prions to generate new prion-assembly surfaces. For Sup35, however, the fragmentation endpoint is an ensemble of noninfectious, amyloid-like aggregates and soluble proteins that cannot replicate conformation (Shorter J, Lindquist S 2006 Mol Cell 23:425). Five glutamine/asparagine-rich oligopeptide repeats at the N-terminus of Sup35 stabilize the aggregated form, and for replication, a chaperone-dependent element is also required (Osherovich LZ et al 2004 PLoS Biol 2(4): E86). In a somewhat different amyloid disease associated with transthyretin, only the highly destabilized molecules are degraded in the endoplasmic reticulum and only in certain tissues, indicating that endoplasmic reticulum-assisted folding depends on energetics, chaperone distribution, and metabolites (Sekijima Y et al 2005 Cell 121:78).

The human PrP repeat (PHGGGWGQ) can substitute for the yeast peptides (Parham SN et al 2001 EMBO J 20:111). This feature of prions allows the development of diversity and may have evolutionary significance. Structurally, neither [URE3] nor [PSI] are similar to the mammalian PrP protein, indicating that there is more than one way for prions to arise. In the fungus *Podospora anserina*, the heterokaryosis incompatibility locus (*Het*) also makes prion-like proteins. The infectious forms of the normal Prp are also called PrP*, and the PrP^{Sc} is designated also PrP^{res} (protease-resistant prion). PrP^C and PrP^{Sc} appear to be conformational isomers. PrP* is the misfolded pathological core form. The yeast prion [PSI⁺] can be reversibly removed, “cured” to [psi⁻] 100% in seven to eight generations when exposed to guanine hydrochloride or methanol. Guanidin inactivates Hsp104 and Sup35 depolymerizes without a need for cell division (Wu Y-X et al 2005 Proc Natl

Acad Sci USA 102:12789). The denaturants induce the expression of chaperones, giving further support to the notion that the prion functions are based on conformational changes. Recent evidence indicates that the PrP^C→PrP^{Sc} transition may involve the chemical thiol/disulphide exchange between the terminal thiolate of PrP^{Sc} and the disulfide bond of a PrP^C monomer and not only a conformational change (Welker E et al 2001 Proc Natl Acad Sci USA 98:4434). The protein chaperones HSP104, and to a lesser extent, HSP70, can affect the expression and transmission of [PSI⁺] and its conversion to [psi⁻]. In silico screening for compounds that fitted into a “pocket” created by residues undergoing the conformational rearrangements between the native and the sparsely populated high-energy states (PrP*) and that directly bind to those residues identified 2-pyrrolidin-1-yl-N-[4-[4-(2-pyrrolidin-1-yl-acetylamino)-benzyl]-phenyl]-acetamide (GN8), which efficiently reduced PrP^{Sc} and improved the survival of affected mice (Kuwata K et al 2007 Proc Natl Acad Sci USA 104:11921).

When the *URE2* and *SUP35* genes or the N-terminal domain of their products are deleted, the [URE3] and [PSI⁺] elements permanently disappear. These yeast proteins are different from each other and from the prion proteins of higher eukaryotes, except the N-terminal region where homology exists. The NH₂ domain of SUP35, when fused to the rat glucocorticoid receptor protein, can interact with the endogenous Sup35 protein and it undergoes a prion-like change of state. Self-replication requires a conformational conversion of initially unstructured Sup35 protein. Thus, the prion-like behavior is transmissible to another protein (Derkatch IL et al 2001 Cell 106:171). More recently, additional yeast proteins (RNQ1, NEW1) with prion-like properties have been identified (Tuite MF 2000 Cell 100:289; Derkatch IL 2000 EMBO J 19:1942). The *het-s* gene product of *Podospora anserina*, responsible for spore killer properties, also meets the criteria of being a prion (Perkins DD 2003 Proc Natl Acad Sci USA 100:6292). The so-called C hereditary units in *Podospora* have a nature similar to prions; they contain the MAPK cascade and trigger cell degeneration (Kicka S et al 2006 Proc Natl Acad Sci USA 103:13445).

The vCJD (variant of Creutzfeldt-Jakob disease) prions appear to have either single amino acid differences or differences in glycosylation which may also be the cause or consequence of conformational differences. The differences in electrophoretic mobility of the protease-digested prions are expected to shed light upon the problems of tracing the transmission of prions from cattle to man or among different animal species. The PrP gene in humans is in chromosome 20p12, and encodes 253 amino acids by a single exon.

The corresponding mouse gene is in chromosome 2. Other mammalian genes display very substantial homologies, although they may be transcribed by up to three exons. The NH²-end of the protein displays an 8 amino acid repeat consensus (PHGGGW) in five to six copies, depending on the species. Deletions in these repeats do not involve disease symptoms. Short conserved amino acids downstream of the last repeats are important for PrP^C→PrP^{Sc} conversion. Another unique feature of PrP is an alanine-rich tract (AGAAAAGA). The transmission of prions among different species prolongs the incubation period. Mice lacking the gene for PrP^C cannot develop the disease even when inoculated (Büeler H et al 1993 Cell 73:1339). The PrP^C deficient mouse appears normal. Knocking out PrP^C from larger mammals would be an approach to avoid prion formation but because of technical difficulties, the use of shRNA is a viable alternative to block PrP expression and prevent encephalitis. Transgenic goats and cows produced by nuclear transplantation of the cognate shRNA gene resulted in more than 90% reduction in PrP expression (Golding MC et al 2006 Proc Natl Acad Sci USA 103:5285). The most infectious property was attributed to 300–600 kDa particles (14–28 PrP molecules) and less than five molecules, as well as very large aggregates, were much less effective in evoking neurodegenerative disease (Silveira JR et al 2005 Nature [Lond] 437:257). Also, immunodeficient mice, despite the fact that they may accumulate plaques upon scrapie infection, fail to develop the disease. It appears that human individuals who might have been exposed to the same BSE source may not all respond with the development of the disease.

PrP^C→PrP^{Sc} conversion by infection with a prion from another species (heterotypic conversion), especially when the inoculum is small or the inoculation occurs rarely, is less likely. The amino acid sequence in the 125–231 sequence displays differences among cow, sheep, dog, cat, pig, mouse, Syrian hamster, and human PrP^Cs and the structure varies as well (Lysek DA et al 2005 Proc Natl Acad Sci USA 102:640). Similarly, structural differences exist in elk compared to cow PrP^C (Gross AD et al 2005 Proc Natl Acad Sci USA 102:646). The chicken, turtle, and *Xenopus* PrP^Cs display only about 30% identity with the mammalian protein amino acid sequence, yet the molecular architectures are similar (Calzolari L et al 2005 Proc Natl Acad Sci USA 102:651).

Wild type mice brain infected with hamster prions did not develop scrapie, although a low level of maintenance of the hamster protein was detectable and reintroduced into hamsters; encephalitis followed. When the human prion is transferred to an animal, the PrP sequences in the new host are determined by the recipient and not by the donor, except when the animal

is transgenic for the human PrP. Thus, the prion inoculum acts as a catalyst or as a chaperone. It is known that in Prp-deficient mice the immune system eliminates the PrP^C. It is also conceivable that in mice the hamster PrP^{Sc} is immunologically tolerated. The presence of the PrP gene is a requisite for the development of the PrP^{Sc} protein. PrP^{Sc} exists in multimeric rather than monomeric forms but PrP may become part of the interacting PrP^{Sc} molecular network. There are indications that prion and DNA interaction may modulate the harmful aggregation of the protein (Cordeiro Y et al 2001 J Biol Chem 276:49400). Hamster-adapted prion protein heated up to 600°C for 5 to 15 min (actually ashed) still retained some infectivity and points to the role of an inorganic template in the replication of scrapie. Heating to 1000°C abolished all activity. In case of relatedness between these two proteins, PrP^{Sc} may easily facilitate the conversion to prion. The expression of the PrP^{Sc} may require chaperones. One such protein was named X but its role is unclear. In vitro assay is available for fast and relatively inexpensive assaying of prions using mouse neuroblastoma cell line N2a (Klöhn P-C et al 2003 Proc Natl Acad Sci USA 100:11666).

According to some views, the “protein only” mechanism requires further proof, although all current evidence indicates a “protein only” basis. There is definite proof that the prions of yeast can be caused by the amino-terminal fragment of the Sup-35 protein without the help of any other substance (King C-Y, Diaz-Avalos R 2004 Nature [Lond] 428:319; Tanaka M et al 2004 *ibid.* 323). Additional recent evidence further supports this protein-only principle. A synthetic peptide (free of nucleic acids), containing mutation at site 102 leucine (see Fig. P130) folded into a β -conformation-rich form, was introduced into mice; and animals developed disease homologous to the Gerstmann-Sträussler syndrome in humans (Tremblay et al 2004 J Virol 78:2088). Furthermore, the peptide-induced disease was serially passed into healthy mice, which developed symptoms indistinguishable from those appearing spontaneously in PrP^{Sc} leucine mutants. Similarly, recombinant protein consisting of the mouse prion sequence 89–231, rich in β -sheets, was cloned in *Escherichia coli* and then introduced into the brain of animals that over-expressed the normal PrP^C. Mice developed neuropathological symptoms characteristic of specific encephalopathy, and their protease-resistant extract evoked disease symptoms in other animals. There were two essential differences from the normal infection. The responding recipients produced excessive amounts of PrP^C before inoculation, and the period of incubation was substantially extended compared with the normal course of disease development (Legname et al 2004 Science 305:673).

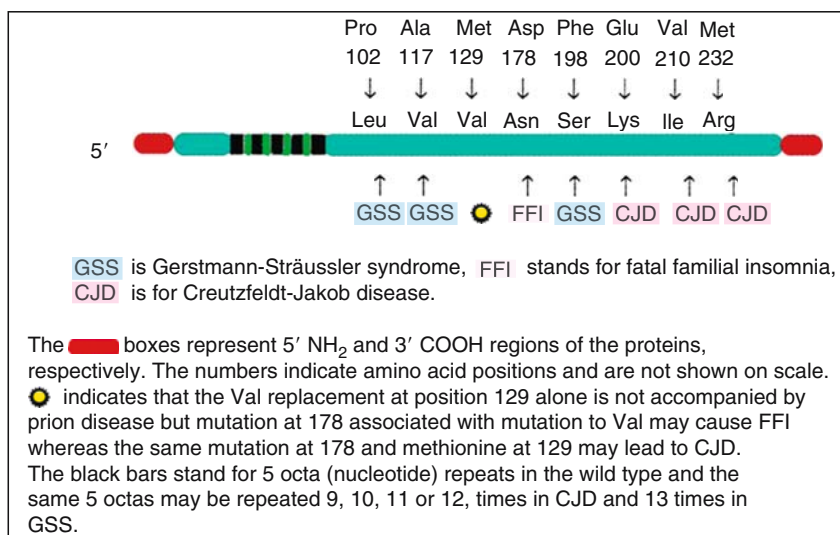


Figure P130. Prion mutations (Redrawn after Weissmann, C. 1999. J. Biol. Chem. 274:3.)

Cyclic amplification of protein misfolding (PMCA) in vitro produced protein identical to the protease resistant form in the brain of sick animals. Furthermore, this in vitro produced prion when introduced into healthy hamster caused the same type of disease as infection by PrP^{Sc} (Castilla J et al 2005 Cell 121:195). PMCA amplification technology can be automated and in 140 cycles leads to a 6600-fold increase in sensitivity compared to older techniques. Two successive rounds of PMCA increase the sensitivity of detection 10-million fold and can detect as few as 8000 molecules of PrP^{Sc} at 100% specificity (Castilla J et al 2005 Nature Med 11:982) and permit the detection of prions in the blood before the disease symptoms manifest (Saá P et al 2006 Science 313:92).

The existence of prions seems to be an exception to the “nucleic doctrine.” Some evidence seemingly contradicts the infectious nature of the prions and points to accumulation of protein waste. The prion diseases may be familial, with an onset at about 50 years of age in humans. The sporadic forms are attributed to dominant somatic mutations. From cultured scrapie-infected mouse (but not of hamster) neuroblastoma cells, the branched polyamines (polyamidoamide dendrimers, polypropyleneimine, polyethyleneimine) purged PrP^{Sc} prions at non-toxic concentrations. Bis-acridines and a few other compounds appear inhibitory to prion replication in cell cultures (May BCH et al 2003 Proc Natl Acad Sci USA 100:3416). Kastellopaolitrine, phenanthridines, 6-aminophenanthridine, quinacrine, and chlorpromazine appear effective in yeast against mammalian prions (see Fig. P131) (Bach S et al 2003 Nat

Biotechnol 21:1075). By 2003, no real cure or preventive measures had emerged for prion diseases. There are some positive cues that proline-rich oligopeptides may restore the conformation of PrP^{Sc} to normal PrP. Preliminary results indicate that the lymphotoxin-β receptor may delay the onset of the symptoms temporarily in mice.

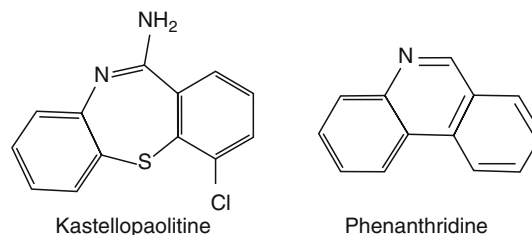


Figure P131. Kastellopaolitrine 1 (left) is one of the other similar compounds, which have different substitutions at other positions at the right ring. Phenanthridine (right) basic structure

It seems that the complement component C3 is important for the prions to attach to the follicular dendritic cells, which mediate infection. Antibodies generated against the μ chain of PrP are a promising approach for the prevention of pathogenesis. ▶Creutzfeldt-Jakob disease, ▶Gerstmann-Sträussler disease, ▶presenilin, ▶kuru, ▶encephalopathies, ▶fatal familial insomnia, ▶protein structure, ▶Protein X, ▶tau, ▶curing plasmids, ▶plasmin, ▶chaperones, ▶PSI⁺, ▶PIN⁺, ▶quinacrine mustard, ▶Cre/loxP, ▶virino hypothesis, ▶conformation-dependent immunoassay, ▶transthyretin, ▶PMCA,

►MAPK, ►polyelectrolyte; Prusiner SB, Scott MR 1997 Annu Rev Genet 31:139; Cohen FE, Prusiner SB 1998 Annu Rev Biochem 67:793; Prusiner SB (ed) 2004 Prion Biology and Diseases, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Umland T C 2001 Proc Natl Acad Sci USA 98:1459; Heppner FL et al 2001 Science 294:178; Baskakov IV et al 2002 J Biol Chem 277:21140; Kanu N et al 2002 Curr Biol 12:523; Uptain SM, Lindquist S 2002 Annu Rev Microbiol 56:703; Chien P 2004 Annu Rev Biochem 73:617; Curr Mol Med 2004 June issue; valine at site 129 prevents CJD: Wadsworth JDF et al 2004 Science 306:1793; potential therapy: Cashman NR, Caughey B 2004 Nature Rev Drug Discovery 3:874; characterization review: Caughey B, Baron GS 2006 Nature [Lond] 443:803; characterization: Prusiner SB, McCarty M 2006 Annu Rev Genet 40:25.

Prior Distribution: A probability distribution of variables or parameters before empirical information was obtained. Generally, it is part of Bayesian inference. ►Bayes' theorem, ►posterior distribution

Prior Probability: The suspected incidence of a disease before a diagnostic test or change of environmental effects or other extrinsic factors before the onset of a condition are identified.

Prisoner's Dilemma: A game theory, applicable to the interpretation of pairwise competition between two types of organisms using conflicting strategies. The two may cooperate, or either may "defect" for selfish reasons(s) and exploit the other and consequently the fitness may decrease to $1 - s_1$. In case both of them defect (are uncooperative), the population has to pay a cost (c), and the fitness becomes $1 - c$. In case the defector gains a fitness advantage ($1 + s_2$), it may invade the cooperators territory. If c is high ($[1 - c] < [1 - s_1]$), a stable polymorphism may result. This theory is applicable also to studies on economic activities and to other fields. ►snowdrift game, ►cooperation, ►tragedy of the common; Page KM, Nowak MA 2001 J Theor Biol 209:173; Neill 2001 J Theor Biol 211(2):159; Doebeli M et al 2004 Science 306:859; Imhof LA et al 2005 Proc Natl Acad Sci USA 102:10797.

Pristionchus pacificus: The *Pristionchus pacificus* nematode is somewhat similar to *Caenorhabditis elegans* <http://www.pristionchus.org>. ►Caenorhabditis

Privacy Rule: An individual's privacy is legally protected against unwanted disclosures, yet medical research has a legitimate need to use, access, and disclose protected health information with certain limitations. ►GWA; <http://privacyrulesandresearch.nih.gov>; http://privacyruleandresearch.nih.gov/pr_02.

asp; European guidelines for human data: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2007/wp136_en.pdf; recommended confidentiality certificate of the US National Institutes of Health: <http://grants.nih.gov/grants/policy/coc>; human molecular genetic data: Lowrance WW, Collins FS 2007 Science 317:600.

Private Blood Groups: A collective name of various blood groups with low frequencies compared to *public blood* group systems that occur frequently.

Private Mutation: Private mutation occurs very rarely in a very limited number of families.

Privilege: ►immune privilege

PRL: ►prolactin

PRL-3 (PTP4A3, 8q24.3): A 22 kDa tyrosine protein phosphatase situated at the cytoplasmic membrane; its elevated expression is associated with metastasis of colorectal cancer. ►colorectal cancer, ►metastasis; Saha S et al 2001 Science 294:1343.

PRM (pattern recognition proteins): PRMs are involved in the regulation of transcription.

PRMT: Protein-arginine methyltransferase. (See Boisvert FM et al 2003 Mol Cell Proteomics 2:1319).

P_{RNP}: The human gene encoding the normal isoform of the prion protein; the same in mouse is P_{rnp}.

Proaccelerin: A labile blood factor (V); its deficiency may lead to parahemophilia and excessive bleeding during menstruation or after surgery or bruising. ►antihemophilic factors

Probabilistic Graphical Models of Cellular Networks: In biological modeling we may be interested in different attributes, e.g., in the random expression of the genes observed and the hidden attributes of the model, such as the cluster assignment of a gene. The model includes the joint probability distribution of all relevant random attributes. The probabilistic graphical model represents multivariate joint probability distributions by a product of terms, each involving only a few variables. In Bayesian Networks, the joint distribution is represented as a product of conditional probabilities of the genotype of each individual, given the genotypes of its two parents. In pedigree analysis, the joint distribution of genotypes is the product of conditional probabilities. In phylogenetic models, the probability, over all evolutionary sequences, is the product of the conditional probability of each sequence, given its latest ancestral sequence in the phylogeny. Another classes of models are Markov Networks representing joint distribution as product of potentials. Cellular networks are based upon gene expression data observed on thousands of genes over a large number of microarrays. Then *GeneCluster_g* denotes the cluster assignment of gene g and

ArrayCluster_a denotes the cluster assignment of array *a*. Co-expression of genes is assumed to be due to co-regulation. The regulation is mediated by the transcription factors attached to specific sequences of the promoter during transcription, and to interaction of protein products of the gene clusters. The interaction of the proteins may be dependent on modifications. The regulatory networks can be partitioned to expression modules rather than to the study of individual genes. Because of the large number of factors involved, appropriate statistics are necessary to evaluate the reality of the observations and the evaluations. Validation of the models against all biochemical information available is highly desirable. New experimental procedures, high-throughput systems, and bioinformatics are under continuous development. This field is impossible to summarize adequately in the frame of this work. A good overview of the status of the field in 2004 is provided by Nir Friedman in Science 303:799. ▶joint probability, ▶multivariate analysis, ▶Bayes' theorem, ▶Markov chain statistics, ▶microarray hybridization, ▶networks, ▶genetic networks, ▶model, ▶small-world networks

Probability: The statistical measure of chance on a scale between 0 to 1, inclusive. 0 means the lack of chance for an event to occur, 1 indicates a certainty that it will occur, and any value expressed as a decimal or fraction indicate the intermediate chances. The probability function indicates the value of a frequency predicted from the observations related to the parameter. The *simple probability* reveals the chance of a single event; the *compound probability* is the chance of multiple events. When two events are independent, their *joint probability* is the product of their independent probabilities. *Alternate probability* exists in case of sex in dioecious species, when an individual is either female or male; no intermediates are considered. One must keep in mind that probability does not absolutely prove or disprove a point; it simply indicates the chance of its occurrence. ▶binomial probability, ▶conditional probability, ▶likelihood, ▶maximum likelihood

Proband: Person(s) through which a family study of the inheritance of a human trait is initiated (also called propositus if male, or proposita if female). Determining the pattern of inheritance on the basis of families chosen by probands may display an excess of affected individuals relative to Mendelian expectations because of the bias in sampling of the population. ▶ascertainment test, ▶pedigree analysis

Probasin: A secreted and nuclear protein abundant in the prostate epithelium. Its expression is regulated by androgens (two receptors at 5' of the 17.5 kb gene) and zinc. Its promoter is extensively used with

various modifications for the study of prostate function/cancer. ▶androgen, ▶prostate cancer; Logg CR et al 2002 J Virol 76:12783.

Probe: A labeled nucleic acid fragment used for identifying or locating another segment by hybridization. Similarly, immunoprobes using primarily monoclonal antibodies or enzyme probes or enzymes linked to antibodies can also be employed (see Fig. P132). The probe binds a reporter protein and another binding protein (binding p). For enzymatic detection of a probe, most commonly alkaline phosphatase or horseradish peroxidase are used. The tissue is incubated with the appropriate substrate of the enzyme and the colored precipitate formed through its action identifies its location. ▶synthetic DNA probes, ▶heterologous probe, ▶recombinational probe, ▶immunoprobe, ▶labeling, ▶nick translation, ▶padlock probe, ▶histochemistry

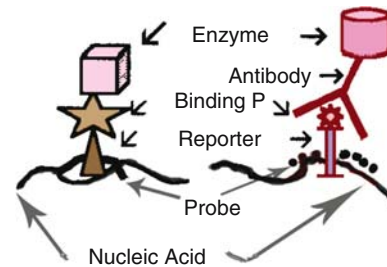


Figure P132. Protein-mediated detection of probe

Probe (primer oligo base extension, PO-BE): A diagnostic procedure for the identification of localized variation in DNA. It is a primer extension procedure using a polymerase, three different deoxyribonucleotide triphosphates, and a dideoxynucleotide triphosphate (ddNTP). The primer is extended until the variable SNP site is reached where the ddNTP is incorporated. The synthetic product is then analyzed by matrix-assisted laser desorption time of flight mass spectrometry. ▶primer extension, ▶MALDI-TOF, ▶SNIP, ▶dideoxyribonucleotide; Braun A et al 1997 Clin Chem 43:1151.

Probe Arrays: Oligonucleotides immobilized on silicon wafers in order to study simultaneously the functions of many genes. ▶DNA chips, ▶microarray

ProbeMaker: A computer program that converts DNA sequence files in FASTA format to digital restriction maps used for MapSearch Probes.

Probiotics: Beneficial bacteria in the body.

Probit: A cumulative normal frequency distribution is represented by an S curve. A cumulative curve can become a straight line by *probit transformation*. We

may represent the probability scale in units of standard deviations. Thus the 50% point is the 0 standard deviation, the 84.13 unit becomes +1, and the 2.27 point the -2 standard deviations. The cumulative percentages are also called *normal equivalent deviates* (NED). If the ordinates are in NED units and we plot the cumulative normal curve, a straight line results. Probits are thus the NEDs with 5.0 added and thus we do not get negative values for the majority of deviates. The probit value of 5.0 indicates a cumulative frequency of 50% and a probit value of 6.0 means a cumulative frequency of 84.13% whereas probit 3.0 indicates a cumulative frequency of 2.27%. Probit value tables are available (Fisher RA, Yates F 1963 Statistical Tables. Hafner, New York). Probit transformations are frequently used for dosage mortality responses to chemicals indicating the regression of cumulative mortalities on dosage. The graphs can be plotted on probit papers with abscissa on logarithmic scale. ▶normal distribution, ▶logit

Proboscis: Tubular snout (nose-like emergence) on the head such as the feeding apparatus of *Drosophila*, elephant trunk, snout of tapirs, shrews, etc. ▶morphogenesis in *Drosophila*

Procaine Anesthetics: Benzoic acid derivatives with local numbing of nerves or nerve receptors.

Procambium: The primary meristem that gives rise to the cambium and the primary vascular tissue of plants. ▶cambium, ▶meristem, ▶root

Procapsid: The empty capsid precursor of phage into which the DNA can be packaged. ▶development, ▶phage

Procarcinogen: A procarcinogen requires chemical modification to become carcinogenic. ▶carcinogen, ▶phorbol esters, ▶activation of mutagens

Procaryote: ▶prokaryote

Procentriole: An immature centriole that upon maturing becomes the anchoring site of the spindle fibers, cilia, and flagella. ▶centriole, ▶centromere, ▶spindle fibers

Process, Genetic: Gene product(s) mediated changes to reach a certain goal in the cell.

Processed Genes: Processed genes are obtained by reverse transcriptase from mRNA and therefore are free of all elements (e.g., introns) removed during processing of the primary transcript. They are widely expressed, highly conserved, and short and low in GC. ▶cDNA, ▶intron, ▶primary transcript

Processed Pseudogene (retropseudogene): A processed pseudogene is similar to mRNA, lacks introns, and

may have a polyA tail, yet it is non-functional. The faulty reverse transcription of mRNA may have produced processed pseudogenes. Pseudogenes are widely expressed, generally short, highly conserved, and low in GCs. Many of the processed pseudogenes lack promoters and cannot be transcribed. About half of the human pseudogenes are the processed type. Some of processed pseudogenes are actually retro-elements. Processed pseudogenes can be mapped in the genome and provide information on ancestral transcripts (Shemesh R et al 2006 Proc Natl Acad Sci USA 103:1364). ▶reverse transcriptases, ▶cDNA, ▶processed genes, ▶pseudogene, ▶LINE; Gonçalves I et al 2000 Genome Res 10:672; <http://pbil.univ-lyon1.fr/>.

Processing: The trimming and modifying of the primary transcripts of the DNA into functional RNAs or cutting and modifying polypeptide chains prior to becoming enzymes or structural proteins. ▶primary transcripts, ▶protein synthesis, ▶postranslational modification

Processing Body: ▶P body

Processivity: Processivity defines the number of nucleotides added to the nascent DNA chain before the polymerase is dissociated from the template. The processivity for *E. coli* DNA polymerase I, II, and III is 3–200, >10,000, >500,000, respectively. ▶error in aminoacylation, ▶clamp-loader, ▶DNA polymerases, ▶polymerase switching, ▶replication fork

Processor: Data-processing hardware or a computer program (software) that compiles, assembles, and translates information in a specific programming language.

Prochiral Molecule: An enzyme substrate that after attaching to the active site undergoes a structural modification and becomes chiral. ▶chirality, ▶active site

Prochloron: ▶evolution of organelles

Pro-Chromatin: A state of the chromatin that is conducive to transcription.

Prochromosome: Heterochromatic blocks detected during interphase. In this interphase nucleus of *Arabidopsis*, the centromeric heterochromatin was stained by fluorescent isothiocyanate and displayed yellow-green color (see Fig. P133). Courtesy of Drs. Maluszinszka J, Heslop-Harrison JH. ▶heterochromatin, ▶Barr body, ▶mitosis

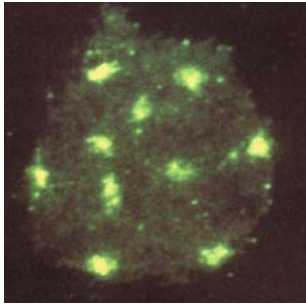


Figure P133. Prochromosomes

Procollagen: Precursor of collagen. ▶collagen

Proconsul: A fossil ape that lived about 23–17 million years ago.

Proconvertin: Antihemophilic factor VII, and the deficiency of which may lead to excessive bleeding and hypoproconvertinemia. ▶hypoproconvertinemia, ▶antihemophilic factors

Proctodeum: An invagination of the embryonal ectoderm where the anus is formed later.

Procyclic: The stage at which *Trypanosoma* is in the gut of the intermediate host (tse-tse fly) and at is not infectious to higher animals. ▶metacyclic *Trypanosoma*, ▶*Trypanosoma*

Prodroma (prodrome): Ominous sign(s) of a looming disease before the actual onset.

P

Prodrug: A prodrug is processable to a biologically active compound. ▶suicide vector, ▶activation of mutagens, ▶ADEPT

Producer Cell: An infected cell continuously produces recombinant retrovirus.

Product-Limit Estimator: The product-limit estimator is based on a number of conditional probabilities, e.g., the probability of survival after surviving for one day, then for the next day, and so on. Where $\hat{S}(t)$ the survival function at subsequent times, r_j = the number of individuals at risk at time $t_{(j)}$, d_j = the number of individuals involved in the event at risk time $t_{(j)}$.

$$\hat{S}(t) = \prod_{j|t_{(j)} \leq t} \left(1 - \frac{d_j}{r_j}\right)$$

Product-Moment Correlation (Pearson's product-moment correlation coefficient): The correlation coefficient of a sample that is used as an estimator for the correlation coefficient of the population:

$$r_{XY} = \frac{\sum_i (X_i - M_X)(Y_i - M_Y)}{N s_X s_Y}, \quad s_X = \sqrt{\frac{\sum_i (X_i - M_X)^2}{N}},$$

$$s_Y = \sqrt{\frac{\sum_i (Y_i - M_Y)^2}{N}}$$

Where the N pairs of values (X_i , Y_i) represent the size of the sample and s_X and s_Y are the standard deviation of the respective variables as shown above.

▶correlation

Product Ratio Method: ▶F₂ linkage estimation

Product Rule: ▶joint probability

Productive Infection: In productive infection, the virus is not inserted into the eukaryotic chromosome and can propagate independently from the host DNA and can destroy the cell while releasing progeny particles.

▶lysis

Proembryo: The minimally differentiated fertilized egg.

Profile: A nucleotide or amino acid sequence probability motif. ▶motif

Profilin: Profilin mediates actin polymerization. ▶actin, ▶Bni1, ▶cytoskeleton, ▶formin; Carlsson L et al 1977 J Mol Biol 115:465.

Proflavin: An acridine dye, capable of inducing frameshift mutations. ▶acridine dye, ▶frameshift mutation; Brenner S et al 1958 Nature [Lond] 182:933.

Progenitor: An ancestor or an ancestral cell of a lineage. Progenitor cells—unlike stem cells—may lose their ability of self-renewal yet they retain their mitotic ability and may generate one or different types of differentiated cells. ▶stem cells, ▶cancer stem cell; Reya T et al 2001 Nature [Lond] 414:105; Weissman IL et al 2001 Annu Rev Cell Dev Biol 17:387.

Progenote: The evolutionarily common, primitive ancestor of the eukaryotic cytoplasm and the bacterial cell (Woese CR, Fox GE 1977 J Mol Evol 10:1).

Progeny Test: A procedure for determining the pattern of inheritance. ▶Mendelian segregation, ▶Mendelian laws

Progeria (premature aging): ▶aging, ▶Hutchinson–Gilford syndrome

Progeroid Syndromes: ▶aging

Progesterone: ▶animal hormones, ▶steroid hormones, ▶testosterone, ▶estradiol, ▶progesterin (see Fig. P134), formula

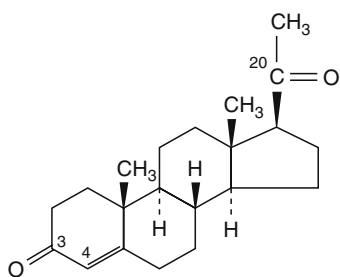


Figure P134. Progesterone (progestin)

Progesterone Receptors (PR): PRs are assembled with the cooperation of at least eight chaperones, including Hsp40, Hsp70, Hsp90, Hip, p60, p23, FKBP, and cyclophilins. PRs are transcriptional regulators of progesterone-responsive genes. named proteins under separate entries; Hernández P et al 2002 J Biol Chem 277:11873.

Progestin: A steroid hormone, used as medication for the prevention of repeated spontaneous abortion. When added to estrogen, it reduces the risk of endometrial cancer. ►[progesterone](#)

Prognosis: The prediction of the course or outcome of a process, e.g., disease, cancer, etc.

Program: A set(s) of instructions in computer language (software) that permits the user to carry out specified tasks. In biology, program refers to the development proceeds according to a genetically determined pattern, realized by environmental effects.

Programmed Cell Death: ►[apoptosis](#)

Programming, Dyanamic: In dynamic programming, large groups of data are broken down to subsets to facilitate programming of the complex. ►[genetic networks](#)

Progression: A process involved in oncogenic transformation; after the initial mutation of a proto-oncogene progression changes it into an active oncogene. ►[cancer](#), ►[phorbol esters](#)

Prohibitin: A 30 kDa tumor-suppressor protein localized mainly in the mitochondria, although it is encoded at human chromosome 17q21. The well-conserved protein is present in other mammals, *Drosophila*, the plant *Arabidopsis*, and several microbes (*Pneumocystis carinii*, the cyanobacterium *Synechocystis*).

Projectin: A myosin-activated protein kinase. ►[myosin](#)

Projection Formula: Modeling configurations of groups around chiral centers of molecules. ►[chirality](#)

Prokaryon: Same as prokaryote.

Prokaryote: An organism without membrane-enveloped (cell nucleus) genetic material (such as the case in bacteria). The majority of prokaryotic bacteria have circular double-stranded DNA chromosomes. However, *Borrelia*, *Streptomyces*, and *Agrobacterium tumefaciens* have a linear chromosome. The GC content varies between ~72% to ~27%. The genome size of prokaryotes varies 20-fold. The majority of bacteria carry their genes in the leading strand of the DNA. The pathogenic strain may have reduced genome size and/or increased number of pseudogenes. (<http://www.cbs.dtu.dk/databases/DOGS/>). ►[cell comparisons](#), ►[GC skew](#), ►*Borrelia*, ►*Streptomyces*, ►*Agrobacterium tumefaciens*; Bentley SD, Parkhill J 2004 Annu Rev Genet 38:771; regulation: <http://regtransbase.lbl.gov>.

Prolactin (PRL): A 23 kDa mitogen, stimulating lactation and the development of the mammary glands. Prolactin receptors are present on human lymphocytes and prolactin may form complexes with IgG subclasses. A prolactin releasing peptide was identified in the hypothalamus. ►[lymphocytes](#), ►[immunoglobulins](#), ►[mitogen](#), ►[brain](#), ►[cathepsins](#); Mann PE, Bridges RS 2001 Progr Brain Res 133:251.

Prolamellar Body: The crystalline-like, lipid-rich structure in the immature plastids that upon illumination develops into the internal lamellae of the proplastids and into the thylakoids of the chloroplasts (see Fig. P135). ►[chloroplast](#)



Figure P135. Prolamellar body

Prolamine: ►[zein](#), ►[high lysine corn](#)

Proliferating Cell Nuclear Antigen: ►[PCNA](#)

Proliferation: The multiplication of cells or organisms. In cells, cytotoxic agents that may induce first cell death may cause proliferation and then regenerative growth, or it may be the result of the action of mitogens. ►[mitogen](#), ►[cancer](#)

Proline Biosynthesis: Proline biosynthesis proceeds from glutamate through enzymatic steps involving glutamate kinase, glutamate dehydrogenase, and finally Δ^1 -pyrroline-5-carboxylate, which is converted to proline by pyrroline carboxylate reductase (see

Fig. P136). In some proteins, e.g., collagen, prolyl-4-hydroxylase generates 4-hydroxyproline from proline. The latter enzyme is coded in human chromosomes 10q21.3-q23.1 (α -subunit) and 17q15 (β -subunit).
 ▶amino acid metabolism, ▶hyperprolinemia

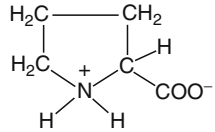


Figure P136. Proline

Prolog: A database management and query system in physical mapping of DNA. (See <http://portal.acm.org/citation.cfm?id=711875&dl=ACM&coll=&CFID=15151515&CFTOKEN=6184618>).

Prolyl Isomerase: ▶PPI, ▶immunophilin

Promastigote: ▶*Trypanosoma*

Prometaphase: Early metaphase. ▶mitosis

Prominin: ▶CD133

Promiscuous DNA: Homologous nucleotide sequences occurring in the various cell organelles (nucleus, mitochondrion, plastid). They are assumed to owe their origin to ancestral insertions during evolution.
 ▶insertion elements; Ayliffe MA et al 1998 Mol Biol Evol 15:738; Lin Y, Waldman AS 2001 Nucleic Acids Res 29:3975.

Promiscuous Plasmids: ▶plasmids promiscuous

P

Promiscuous Protein: A promiscuous protein has affinity to more than one substrate. ▶conformational diversity; Copley SD 2003, Curr Opin Chem Biol 7:265.

Promitochondria: Organelles in anaerobically grown (yeast) cells that can differentiate into mitochondria in the presence of oxygen. ▶mitochondria

Promoter: The site of binding of the transcriptase enzyme (RNA polymerase), transcription factor complexes, and regulatory elements, including also the ribosome-binding untranslated sequences (see Fig. P137). Usually, the basal promoter is situated in front of the genes although pol III may rely on both upstream and downstream promoters.

The promoters of the 5S and tRNA genes are internal. Also, some *E. coli* genes have some weak promoters within open reading frames (Kawano M et al 2005 Nucleic Acids Res 33:6268). The arrangement of the promoter used by pol II is outlined.

The promoters used by RNA polymerase II may encompass several hundred nucleotides in yeast but in higher eukaryotes it may extend to several thousand bases. In yeast, UAS (upstream activating sequences) and URS (upstream repressing sequences) are regular binding sites. The transcription start site is usually within a stretch of 30 to 120 nucleotides downstream of the TATA box (see Fig. P138). The pol II enzyme frequently uses in mammals multiple promoters, within which there are multiple start sites, and alternative promoter usage generates diversity and complexity in the mammalian transcriptome and proteome (Sandelin A et al 2007 Nature Rev Genet 8:424). Some of the mammalian promoters are localized more than 100 kb upstream or located downstream, may be multiple, may overlap several genes, and are shared by other genes (Denoed F et al 2007 Genome Res 17:746).

At the ends of the genes, insulators (boundary elements) separate the genes or the used promoters from the others. The DNase hypersensitive site(s) (also called locus control region) may permit the attachment of sequence-specific transcriptional activators, making the gene competent for transcription. The competence may involve histone acetylation.

Among 1031 human protein-coding genes, the Pol II-like enzymes commonly (~32%) use a TATA box both in prokaryotes and eukaryotes. The TATA box ca. 25 bp upstream from the initiation point of transcription is usually surrounded by GC-rich tracts (97%). Near the transcription initiation site (−3 to +5), there may be an initiator (Inr, 85%) with an ~average type of sequence: (Pyrimidine)₂CA(Pyrimidine)₅. Many eukaryotic genes do not have Inr but the TATA box directs the initiation. CAAT box is also a frequent (64%) element in the promoter. Some large eukaryotic genes utilize more than one promoter and the transcripts may vary. Some housekeeping and RAS genes do not use the TATA box. DNA-dependent RNA polymerase I synthesizes ribosomal RNAs; it has a core sequence adjacent to the transcription initiation site and upstream regulator binding sites (UCE). Pol III promoters facilitating the transcription of tRNA usually have split

enhancer - PROMOTER - leader - exons - introns - termination signal - polyadenylation signal - downstream regulators

Transcription factor-binding sites, DNase hypersensitive site, TATA box, transcription start

Figure P137. Organization of the promoter and other genic elements

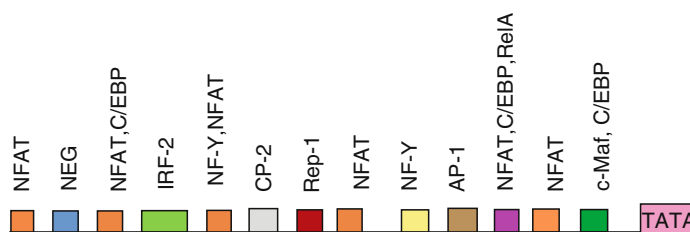


Figure P138. The promoter usually includes several regulatory boxes to which protein factors are recruited. (Modified after Guo, J. *et al.* 2001 J. Biol. Chem. 276:48871)

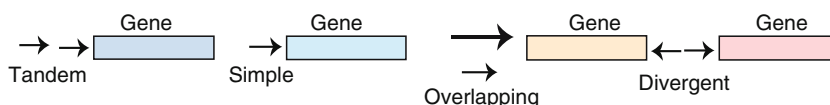


Figure P139. Arrows symbolize promoters; boxes represent structural genes

promoters with an A-box and a B-box about 40 bases apart, situated inside the transcription unit 20 and 60-bases downstream from the transcription initiation site. The pol III promoter of some U RNAs has, however, a TATA box 30–60 bases upstream from the transcription initiation site and further upstream a proximal sequence element (PSE) near the TATA box. Synthetic promoters can be constructed with increased activity. The Promoter Scan II program identifies pol II promoters in genomic sequences and is available through Internet: <http://www.cbs.umn.edu/software/software.html>.

Promoters (→) may be of different types and some genes may rely on multiple promoters (see Fig. P139): TFD, TRANSFAC, or IMD databases can use the Signal Scan to find transcription factor binding sites. A high-resolution analysis revealed 10,567 promoters corresponding to 6763 genes in the human genome. Almost half of all mammalian genes have evolutionarily conserved alternative promoters (Baek D *et al* 2007 Genome Res 17:145). About 11% of the human promoters are bidirectional/divergent, are more active in transcription than other promoters, and are involved with RNA polymerase II and the modified histones H3K4me2, H3K4me3, and H3ac (Lin JM *et al* 2007 Genome Res 17:818). This information resulted by mapping the preinitiation complexes labeled by the attached TATA box associated protein and analysis by microarray hybridization of immunoprecipitated complexes (Kim TH *et al* 2005 Nature [Lond] 436:876). Libraries of engineered promoters can provide a fruitful approach for quantitative study of gene expression (Alper H *et al* 2005 Proc Natl Acad Sci USA 102:12678). The promoter of the *lac* operon of *E. coli* is controlled by cis elements that integrate signals coming from the cAMP receptor and the Lac repressor (Mayo AE *et al* 2006 PLoS Biol 4:e45).

Active promoters are marked by trimethylation of Lys4 of histone H3 (H3K4), whereas enhancers are

marked by monomethylation, but not trimethylation, of H3K4. Computational algorithms, using these distinct chromatin signatures to identify new regulatory elements, predicted over 200 promoters and 400 enhancers within the 30 Mb region of the vertebrate genome (Heintzman N *et al* 2007 Nature Genet 39:311).

In vivo spatiotemporal analysis for approximately 900 predicted *C. elegans* promoters (~5% of the predicted protein-coding genes), each driving the expression of green fluorescent protein (GFP) using a flow-cytometer adapted for nematode profiling, generated “chronograms,” two-dimensional representations of fluorescence intensity along the body axis and throughout development from early larvae to adults. Automated comparison and clustering of the obtained in vivo expression patterns show that genes coexpressed in space and time tend to belong to common functional categories (Dupuy D *et al* 2007 Nature Biotechnol 25:663).

► basal promoter, ► core promoter, ► DPE, ► minimal promoter, ► complex promoter, ► UAS, ► URS, ► portable promoter, ► cryptic promoter, ► divergent dual promoter, ► divergent transcription, ► transcription complex, ► transcription factors, ► open promoter complex, ► closed promoter complex *Lac* operon, ► *Tryptophan* operon, ► *Arabinose* operon, ► pol I, ► pol II, ► pol III, ► regulation of gene activity, ► promoter clearance, ► promoter trapping, ► TATA box, ► TBP, ► TAF, ► insulator, ► enhancer, ► LCR, ► chromatin remodeling, ► histone acetyl-transferase, ► promoter inducible, ► promoter tissue-specific, ► antisense DNA, ► microarray hybridization, ► preinitiation complex; analysis of ~900 putative human promoters: Cooper SJ *et al* 2006 Genome Res 16:1; Chalkley GE, Verrijzer CP 1999 EMBO J 18:4835; Suzuki Y *et al* 2001 Genome Res 11:677; Pilpel Y *et al* 2001 Nature Genet 29:153; Schuetten-gruber B *et al* 2003 J Biol Chem 278:1784; Ohler U *et al* 2002 Genome Biol 3:research0087.1; eukaryotic

promoters: <http://www.epd.isb-sib.ch>; eukaryotic promoters: <http://cmgm.stanford.edu/help/manual/databases/epd.html>; eukaryotic promoters: <http://doop.abc.hu/>; transcriptional start sites: <http://dbtss.hgc.jp/>; human promoter binding sites: <http://genome.imim.es/datasets/abs2005/index.html>; transcription factor binding sites: <http://www.isrec.isb-sib.ch/httpselex/>; mammalian promoters/transcription factors/regulation: <http://bioinformatics.med.ohio-state.edu/MPromDb/>; mammalian regulatory promoters:

<http://bioinformatics.wustl.edu/webTools/portalModule/PromoterSearch.do>; tissue specific promoters: <http://tiprod.cbi.pku.edu.cn:8080/index.html>; knowledge-based promoter search: <http://bips.u-strasbg.fr/PromAn/>; promoter motif search: <http://melina2.hgc.jp/public/index.html>.

Promoter Bubble: ►promoter clearance

Promoter Clearance (promoter escape): In promoter clearance, the RNA polymerase complex (promoter bubble) starts moving forward from the promoter as the first ribonucleotides are transcribed. The RNA polymerase can synthesize a few bases without leaving the promoter site, but after that tension develops, which discontinues the contact between the DNA and the RNA polymerase. Clearance is regulated by both positive and negative elongation factors. Negative elongation requires four polypeptides and two polypeptides sensitivity inducing factor (DSIF). Inhibition takes place when about 18 nucleotides were added to the growing transcript. The transcript length is regulated also by the inhibition of the transcript cleavage factor TFIIS; the latter can be active along the entire length of the transcript (Palangat M et al 2005 Proc Natl Acad Sci USA 102:15036).

The movement may be represented by an inch-worm model or a moving domain model (the translocation involves the entire transcription box with minimal stretching) or the tilting model without a flexible polymerase, which is tilted along the axis of the DNA. ►bubble, ►replication bubble, ►inch-worm model; Pal M et al 2001 Mol Cell Biol 21:5815; Liu C, Martin CT 2002 J Biol Chem 277:2725.

Promoter Conversion (Pro-Con): Promoter conversion changes the promoter to a heterologous one.

Promoter Escape: ►promoter clearance

Promoter, Extended: ►Pribnow box

Promoter, Inducible: Inducible promoters turn on genes in response to biological, chemical, or physical signals. ►metallothionein, ►Lac

Promoter Interference: Promoter interference may occur when within a single viral vector two genes

are placed under separate controls, e.g., the strong promoter within the long terminal repeat (LTR) may suppress the function of an internal promoter irrespective of its orientation. This problem may be overcome by utilizing an IRES for the second gene in the common transcript:

LTR — 1st Gene — IRES — 2nd Gene —. ►IRES

Promoter Melting: In promoter melting, the double-stranded DNA unwinds (forms a promoter bubble) to allow access to the template strand for the RNA polymerase enzyme. In *E. coli*, the N-terminal 1–314 amino acids of the β' subunit and the 94–507 amino acids of the σ subunit cooperate in the melting. ►RNA polymerase, ►promoter; Young BA et al 2004 Science 303:1382.

Promoter Occlusion: Promoter occlusion occurs when, in retroviral elements with direct LTR repeats, the promoters at the 3'-end are inactivated and prevented from binding enhancers or transcription factors because they cannot facilitate transcription due to their wrong orientation. ►LTR, ►enhancer, ►transcription factors

Promoter Swapping: An exchange of promoter by, e.g., reciprocal chromosome translocation. ►translocation, ►pleiomorphic adenoma

Promoter, Tissue-Specific: A tissue-specific promoter permits the transcription of genes only or mainly in specific tissue(s) (see Fig. P140). ►promoter, ►tissue specificity



Figure P140. Tobacco seedlings segregating for kanamycin resistance on a root-tissue-specific promoter. Transformation was made by a promoter-less vector construct. The non-transgenic plants cannot grow roots on kanamycin medium. (From Y. Yao & G.P. Rédei)

Promoter Trapping: ▶trapping promoters, ▶transcriptional gene fusion vectors, ▶translational gene fusion vectors, ▶gene fusion, ▶promoter; Medico E et al 2001 Nature Biotechnol 19:579.

Promoters of Tumorigenesis: Environmental substances or gene products that guide a group of precancerous cells toward malignant growth. The promoters themselves do not initiate cancer. ▶carcinogenesis, ▶phorbol esters, ▶cancer, ▶conversion

Promutagen: A promutagen requires chemical modification (activation) to become a mutagen. ▶mutagen, ▶activation of mutagens

Promyelocytic Body (PML): A nuclear product of the promyelocytic leukemia gene; it mediates the degradation of ubiquitinated proteins and is regulated by the nucleolus. PMLs contain also TRF1 and TRF2 telomeric proteins required for the maintenance of telomeres. PMLs may be targeted by viruses, may act as suppressors of growth and tumors, and mediate apoptosis. PML body may also occur in the cytoplasm and modulates TGF- β signaling. The PML protein also regulates centrosome duplication by the suppression of the Aurora protein. ▶leukemia, ▶ubiquitin, ▶telomerase, ▶apoptosis, ▶transforming growth factor β , ▶centrosome

Pronase: A powerful general (non-specific) proteolytic enzyme isolated from *Streptomyces*.

Pronucleus: The male and female gametic nucleus to be involved in the sexual union.

Proof-of-Concept (proof of principle): Experimental evidence that an idea works in practical application. ▶validation

Proofreading: Bacterial DNA polymerase I (and analogous eukaryotic enzymes) can recognize replicational errors and remove the inappropriate bases by its editing 3' - 5' exo-nuclease function. In case the editing function is diminished by mutation, mutator activity is gained. In case of gain in editing, function antimutator attributes are observed. In bacteria, proofreading is performed also by the *dnaQ* gene encoding the ϵ subunit (an exonuclease) of the DNA polymerase III holoenzyme. The product of gene

dnaE carries out the base selection. The enzymes MutH, MutL, and MutS and the corresponding homologs in higher organisms repair mismatches. The fidelity of replication due to the combined action of the sequentially acting bacterial genes was estimated to be in the range of 10^{-10} per base per replication. During the process of translation, the EF-Tu•GTP \rightarrow EF-Tu•GDP change releases a molecule of inorganic phosphate (P_i) and allows a time window to dissociate the wrong tRNA from the ribosome. A similar correction is made also by the aminoacyl synthetase enzyme, by virtue of its active site specialized for this function. DNA polymerase η lacks exonuclease function required for proofreading, but correction is still accomplished by recruiting an extrinsic exonuclease to the error site. ▶DNA polymerase I, ▶DNA polymerase III, ▶DNA polymerases, ▶exonuclease, ▶proofreading paradox, ▶DNA repair, ▶error in replication, ▶error in aminoacylation, ▶ambiguity in translation, ▶protein synthesis, ▶DNA repair; Friedberg EC et al 2000 Proc Natl Acad Sci USA 97:5681; Livneh Z 2001 J Biol Chem 276:25639; Shevelev IV, Hübscher U 2002 Nat Rev Mol Cell Biol 3:364.

Propagule: A part of an organism that can be used for propagation of an individual by asexual means.

Propeller Twist in DNA: The surface angle formed between individual base-planes viewed along the C⁶-C⁸ line of a base pair.

Properdin (Factor P): A serum protein of three to four subunits (each ca. 56 kDa, encoded in human chromosome 6p21.3). It is an activator of the complement of the natural immunity system that works by stabilizing the convertase. ▶convertase, ▶complement, ▶complement, ▶immune system; Perdikoulis MV et al 2001 Biochim Biophys Acta 1548:265.

Prophage: The proviral phage is in an integrated state in the host cellular DNA and it is replicated in synchrony with the host chromosomal DNA until it is induced and thus, becomes a vegetative virus (see Fig. P141). ▶prophage induction, ▶temperate phage, ▶lysogeny, ▶lambda phage

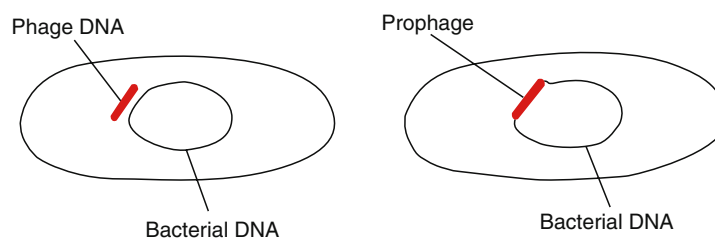


Figure P141. Phage DNA incorporated into bacterial DNA becomes prophage

Prophage Induction: Treating the bacterial cells by physical or chemical agents that cause the moving of the phage into a vegetative lifestyle resulting in asynchronous, independent replication from the host and eventually the lysis and liberation of the phage. ▶prophage, ▶lysogeny, ▶zygotic induction

Prophage-Mediated Conversion: In prophage-mediated conversion, the integrated prophage causes genetic changes in the host bacterium, and it is expressed as an altered antigenic property, etc.

Prophase: ▶meiosis, ▶mitosis

Prophylaxis: Disease prevention.

Propionicacidemia: ▶glycinemia ketotic, ▶methylmalonicaciduria, ▶isoleucine-valine biosynthetic pathway, ▶tiglicacidemia; Chloupkova M et al 2002 Hum Mut 19:629.

Propionyl-CoA-Carboxylase Deficiency: ▶glycinemia ketotic

Proplastid: The young colorless plastid without fully differentiated internal membrane structures; it may differentiate into a chloroplast (see Fig. P142). ▶etioplast, ▶chloroplasts

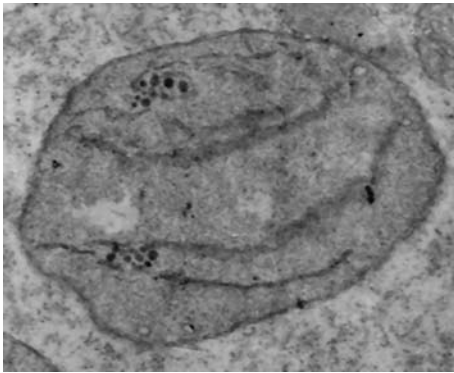


Figure P142. Proplastid

Proportional Counters: Proportional counters are used for measuring radiation-induced ionizations within a chamber. The voltage changes within are proportional to the energy released. It may be used for measuring neutron and α radiations with an efficiency of 35–50%. The equipment must be calibrated to the radiation source. ▶radiation measurement, ▶radiation hazard assessment

Propositus (Proposita): ▶proband, ▶pedigree analysis

Propyne ($\text{CH}_3\text{-C}\equiv\text{CH}$): An alkyne used as a modifier at the C-5 position of pyrimidines in antisense oligonucleotides, frequently in combination with other

modifications such as phosphorothioate. ▶antisense technologies

Prosimii (prosimians): A suborder of lower primates, including Galago, Lemur, Tarsius, and Tupaia. Lorisidae. ▶primates, ▶Lemur, ▶Tupaia, ▶Lorisidae

Prosite: A protein sequence database, searchable by PROSCAN (Bairoch A et al 1977 Nucleic Acid Res 25:217); <http://pbil.univ-lyon1.fr/pbil.html>; PROSITE for uncharacterized proteins: <http://www.expasy.org/prosite/>; improved PROSITE: <http://www.expasy.org/tools/scanprosite/>.

Prosody: The inability of sensing or expressing variations of the normal rhythm of speech. It seems to be independent of processing musical pitch. ▶amusia, ▶musical talent, ▶pitch

Prosome: Small ribonucleoprotein body. It is identical with the $\sim 20\text{S}$ multifunctional protease complex of the proteasome of eukaryotes and prokaryotes. ▶proteasome

Prospective Study: Prospective study involves the epidemiological surveillance of a population after the occurrence of a disease or other harmful exposure. The exposed or involved individuals are compared with a concurrent control cohort. Prospective cohort studies improve on case control information. ▶case control, ▶concurrent control, ▶cohort

PROST (pronuclear state embryo transfer): Basically, very similar to intrafallopian transfer of zygotes but the zygote here is at a very early stage. ▶intrafallopian transfer, ▶ART

Prostacyclins: Prostacyclins may be derived from arachidonic acid or prostaglandins, regulate blood platelets, cause vasodilation, and are antithrombotic. ▶thrombosis, ▶prostaglandins, ▶COX

Prostaglandins: Long-chain fatty acids in different mammalian tissues with hormone-like muscle-regulating, inflammation-regulating, and reproductive functions; they exist in several forms. They occur in the majority of the cells and act as autocrine and paracrine mediators. Fever development is controlled by prostaglandin E_2 and EP_3 receptors. Prostaglandin synthesis is regulated by cyclooxygenases. Prostaglandin E (cyclopentenone prostaglandins) appears to be an inhibitor of I κ B kinase. ▶animal hormones, ▶autocrine, ▶paracrine, ▶cyclooxygenases, ▶I κ B, ▶leukotrienes, ▶eicosanoids, ▶pain-sensitivity, ▶implantation, ▶misoprostol, ▶colorectal cancer; Rudnick DA et al 2001 Proc Natl Acad Sci USA 98:8885.

Prostanoids: Bioactive lipids such as the prostaglandins, prostacyclin, and thromboxane. Aspirin-like

drugs may inhibit prostanoid biosynthesis, reduce fever and inflammation, and interfere with female fertility. ►prostaglandins, ►prostacyclins

Prostate Cancer (HPC): About 9–10% of USA males eventually develop prostate cancer. The autosomal dominant gene has a high penetrance: about 88% of the carriers become afflicted by the age of 85. Several other genes involved in prostate function may mutate and cause cancer. Recurrent fusion of the androgen-responsive promoter element of TMPRSS2 (a transmembrane protease serine 2, 21q22.3) with members of the ETS oncogene family ETV1 at 7p21.2 leads to prostate cancer (Tomlins SA et al 2005 *Science* 310:6744). Relative to low-grade prostate cancer (Gleason pattern 3) and high-grade cancer (Gleason pattern 4) shows an attenuated androgen signaling signature, similar to metastatic prostate cancer, which may reflect dedifferentiation and explain the clinical association of grade with prognosis (Tomlins SA et al 2007 *Nature Genet* 39:41). Androgen receptor and PTEN–AKT signaling may initiate and maintain prostate cancer. For therapeutic intervention, androgen receptor and AKT and/or growth factor receptor tyrosine kinases that activate AKT can be targeted (Xin L et al 2006 *Proc Natl Acad Sci USA* 103:7789). The high level of testosterone may increase the chances for this cancer. Reduced level of testosterone may not slow down advanced prostate cancer growth and metastasis. There is a possible therapeutic approach to prostate cancer in overexpressing an androgen receptor by ligand-independent activation of the N-terminal domain peptide to create decoy molecules that competitively bind the interacting proteins required for activation of the endogenous full-length receptor.

A genetic variant in the 8q24 region, identified by GWA, in conjunction with another variant, accounts for about 11–13% of prostate cancer cases in individuals of European descent and 31% of cases in African Americans (Gudmundsson J et al 2007 *Nature Genet* 39:631). Seven risk variants, five of them previously unreported, spanning 430 kb and each independently predicting risk for prostate cancer ($P = 7.9 \times 10^{-19}$ for the strongest association, and $P < 1.5 \times 10^{-4}$ for five of the variants, after controlling for each of the others). The variants define common genotypes that span a more than fivefold range of susceptibility to cancer in some populations. None of the prostate cancer risk variants aligns to a known gene or alters the coding sequence of an encoded protein (Haiman CA et al 2007 *Nature Genet* 39:638).

There is evidence that in vivo expression of the receptor decoys decreased tumor incidence and inhibited the growth of prostate cancer tumors (Quayle SN et al 2007 *Proc Natl Acad Sci USA*

104:1331). Growth hormone-releasing hormone (GHRH) antagonists increased the intracellular Ca^{2+} and activated tumoral GHRH receptors and induced apoptosis (Rékási Z et al. 2005 *Proc Natl Acad Sci USA* 102:3435). Metastatic prostate cancer cells may show high levels of caveolin-1 and reduced amount of testosterone. Caveolin-1 antisense RNA promoted apoptosis and increased testosterone. A metastasis suppressor gene, KAI1, in human chromosome 11p11.2, has been identified. The KAI1 protein appears to contain 267 amino acids with four transmembrane hydrophobic and one large hydrophilic domains. This glycoprotein is expressed in several human tissues and also in rats. A negative regulator of the MYC oncogene, MXI1 (encoded in human chromosome 10q24-q25), is frequently lost in prostate cancer. KAI1 is involved in chromatin remodeling by suppressing Tip60, β -catenin, and reelin, and in metastasis of prostate cancer cells (Kim JH et al 2005 *Nature [Lond]* 434:921). Cytokine-activated IKK α controls metastasis by repressing Maspin (Luo J-L et al 2007 *Nature [Lond]* 446:690). In the chromosome 10pter-q11 region, a prostate cancer suppressor gene, causing apoptosis of carcinoma, has been detected from loss of heterozygosity mutations (LOH). A major susceptibility locus was identified in human chromosome 1q24-q25 and at Xq27-q28. Candidate genes are expected in human chromosomes 3p, 4q, 5q, 7q32, 8p22-p23 and 8q, 9q, 10p15 (KLF6), 13q, 16q, 17p11, 18q, 19q12, 20q13, and 22q12.3. At 16q22 the transcription factor ATBF1 is transcribed, which negatively regulates AFP and MYB but transactivates CDKN1A and it may be reduced in about a third of the prostate cancer cells (Sun X et al 2005 *Nature Genet* 37:407). Insulin-like growth factor (IGF-1) levels may be predictors of prostate cancer risks before cancerous growth is observed but some other data are at variance with the claim. In prostate tumors, the prostate-specific cell-surface antigen (STEAP), in human chromosome 7p22.3, is highly expressed in different organs and tissues, except the bladder. A predisposing gene in 17p has been cloned. The various types of prostate cancers can be classified on the basis of DNA microarray and the result may assist treatment and prognostication (Lapointe J et al 2004 *Proc Natl Acad Sci USA* 101:811). In Northern Europe, about 42% of the cases were found to be hereditary and 58% were sporadic (Lichtenstein P et al 2000 *N Engl J Med* 343:78). The first-degree relative risk is 1.7–3.7 or more. American blacks have higher and Asians lower risks than Caucasians (Stanford JL, Ostrander EA 2001 *Epidemiol Rev* 23:19).

Prostate stem cell antigen (PSCA) may be the target for immunological therapy. About 11–12% of all prostate cancer patients harbored mitochondrial mutations in cytochrome oxidase I subunit; mutations

inhibiting oxidative phosphorylation can increase ROS and tumorigenicity (Petros JA et al 2005 Proc Natl Acad Sci USA 102: 719). Prostate cancer is the second most frequent cause of cancer mortality in the US but it is very rare in other animals, except dogs. ▶PSA, ▶cancer, ▶tumor suppressor gene, ▶IKK, ▶Maspin, ▶MYC, ▶MYB, ▶fetoprotein- α , ▶CDKN1A, ▶insulin-like growth factor, ▶caveolin, ▶antisense technology, ▶automaton, ▶testosterone, ▶apoptosis, ▶microarray hybridization, ▶gene fusion, ▶probasin, ▶ROS, ▶mitochondrial genetics, ▶mitochondrial diseases in humans, ▶Gleason score, ▶automaton, ▶chromatin remodeling, ▶*erbB*, ▶androgen, ▶PTEN, ▶AKT; Ostrander EA, Stanford JL 2000 Am J Hum Genet 67:1367; Xu J et al 2001 Am J Hum Genet 69:341; Stephan DA et al 2002 Genomics 79:41; Ostrander EA et al 2004 Annu Rev Genomics Hum Genet 5:151; susceptibility markers: <http://cgems.cancer.gov/>.

Prostates (prostata): Gland in the animal (human) male surrounding the base of the bladder and the urethra; upon ejaculation injects its content (acid phosphatase, citric acid, proteolytic enzymes, etc.) into the seminal fluid. ▶PSA, ▶prostate cancer; <http://www.pedb.org>.

Prosthesis: Any type of mechanical replacement of a body part, such as artificial limbs, false teeth, etc.

Prosthetic Group: A non-peptide group (iron or other inorganic or organic group) covalently bound (conjugated) to a protein to assure activity.

Prot: Na^+/Cl^- -dependent proline transporter that also transports glycine, GABA, betaine, taurine, creatine, norepinephrine, dopamine, and serotonin in the brain. ▶transporters

Protamine: The basic (arginine-rich) protein occurring in the sperm substituting for histones.

The protamine gene cluster is in human chromosome 16p13.2 and it includes genes PRM1, PRM2, and TNP2 (transition protein 2). They are transcribed at the postmeiotic round spermatid stage of spermatogenesis and translated in elongating spermatids (see Fig. P143). These messages are bound as cytoplasmic messenger ribonuclear protein particles until histone replacement is initiated with the transition proteins in late elongating spermatids. At this time the mRNAs are activated and then translated

into the peptides that will repackage and compact the male genome in terminally differentiated spermatozoa. In humans and mice, the genes first acquire a DNase I-sensitive conformation in pachytene spermatocytes that is even maintained in human spermatozoa and transcription is facilitated (Martins RP, Krawetz SA 2007 Proc Natl Acad Sci USA 104:8340). Protamine 4 is a minor protein and it is different from PRM2 and PRM3 only by a short extension. The genes are potentiated at late pachytene before the haploid (n, 1C) spermatids are formed. In the mature spermatozoon, the histones are replaced by protamines. Protamine controls both condensation and decondensation of the DNA by anchoring to it at about each 11 bp. After fertilization it is removed. In *Drosophila*, the *Hira* gene is involved in the decondensation. The HIRA gene of mammals is essential for chromatin assembly in the male pronucleus and it uses histone variant H3.3 (Lappin B et al 2005 Nature [Lond] 437:1386). In the somatic cells, protamines constitute less than 5% of the nucleus. The majority of mammals have only a single protamine but mice and men have four. If protamines are deleted missing functional sperm is not produced because of haplo-insufficiency. ▶histones, ▶transition protein, ▶haploinsufficiency, ▶spermiogenesis, ▶gametogenesis, ▶C amount of DNA; Cho C et al 2001 Nature Genet 28:82.

Protandry: in monoecious plants the pollen is shed before the stigma is receptive. ▶monoecious, ▶stigma, ▶protogyny, ▶self-sterility

Protanope: ▶color blindness

Protease (proteinase): Enzyme, which hydrolyzes proteins at specific peptide bonds; for *protease 3* see antimicrobial peptides. The human genome codes for at least 553 proteases. Proteases may either facilitate or reduce the expression of enzymes. ▶proteasome, ▶peptidase; Ehrmann M, Clausen T 2004 Annu Rev Genet 38:709; <http://cutdb.burnham.org>.

Protease Inhibitors: Protease inhibitors, such as leupeptin, antipain, and soybean trypsin inhibitors are credited with anticarcinogenic effects and potential cures for asthma, schistosomiasis. Proteases process the primary proteins into their functional role in viral/microbial or other systems. If this processing

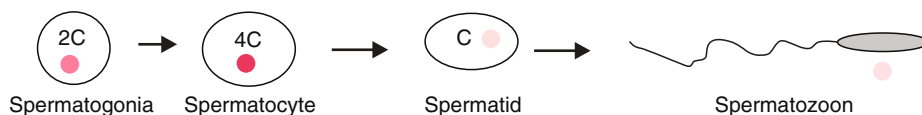


Figure P143. Development of the nuclear DNA in spermatozoa

is prevented, infectious or other agents may not or may have reduced adverse effect to the cells. ►carcinogen, ►cancer, ►AIDS, ►schistosomiasis, ►asthma

Proteasomes: Tools of degradation of intracellular proteins (see Fig. P144). Proteasomes have non-degradatory functions too, such as in transcription, DNA repair, and chromatin remodeling. ATP-dependent ubiquitinated proteins process intracellular antigens into short peptides that are then transported to the endoplasmic reticulum with the aid of TAP, and are responsible for MHC class I-restricted antigen presentation. Proteasomal polymorphism is determined, among others, by LMP2 and LMP7 genes encoded within the MHC class II region in the vicinity of TAPs that are upregulated by interferon γ . The 26S (~2500 kDa) proteasomes (~31 subunits) are hollow cylinders engulfing ubiquitinated proteins and degrade them with proteases. The lid and the base each are 19S (890 kDa). The ATP-dependent dissociation of the 19S subunits from the 26S complex leads to the protein degradation (Babbitt SE et al 2005 Cell 121:553). The ~20S (720 kDa) middle section barrel of the proteasomes contain multiple peptidases. Their active site is at the hydroxyl group of the N-terminal threonine in the β subunit. The PA proteins are proteasome activators. The 26S proteasome is associated with at least 18 ancillary and essential proteins (PSM proteins, including ATPase) and many of these are now genetically mapped to different human chromosomes. Chymostatin, calpain, and leupeptin, etc., are inhibitors. The proteases of the 20S proteasome are activated by the heptameric 11S regulators, which also control the opening of the barrel-shaped structure. The assembly of the 28 subunits of the 20S mammalian proteasomes is mediated by the heteromeric chaperones PAC1 and PAC2 (Hirano Y et al 2005 Nature [Lond] 437:13481). Proteasomes have also ubiquitin-independent function, such as the degradation of the excess amounts of ornithine decarboxylase, a key enzyme in polyamine biosynthesis. The proteasomes have important—although not fully understood—roles in differentiation and development by mediating protein turnover. Proteasomes control also apoptosis and carcinogenesis (Adams J 2004 Nat Rev Cancer 4:349). According to

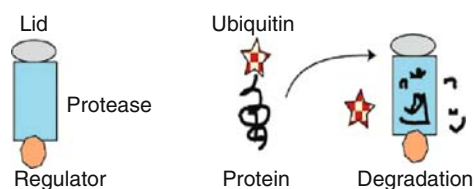


Figure P144. Proteasome and its function

Princiotta MF et al 2003 (Immunity 18:343) each cell of the immune system contains 800,000 proteasomes (immunoproteasomes). The product peptides of the immunoproteasome are different from the regular proteasomes. They degrade 2.5 viral translation product substrates per minute and thus generate one MHC class I peptide complex for each 300 to 5000 viral translation product degraded. The misfolded proteins are removed from the endoplasmic reticulum and in the cytoplasm, after ubiquitination and de-glycosylation, they are degraded by the proteasome. On the average cellular proteins are degraded in about two days and about a third of the new proteins of mammals have less than 10 min half-life. The majority of these have a synthetic defect. In active mammalian cells, about 10 million polypeptides are formed per minute and within seconds these are degraded to amino acids by peptidases (Yewdell JW 2005 Proc Natl Acad Sci USA 102:9089). Membrane proteins US11 and Derlin-1 mediate MHC molecule dislocation from the endoplasmic reticulum (Lilley BN Ploegh HL 2004 Nature [Lond] 429:834; Ye Y et al 2004 *Ibid.* 841). In case the proteasome function is inhibited or lost, inhibitor resistant cells may grow out of the cultures that have a compensating mechanism for proteasome function. The Cop9 signalosome of *Arabidopsis* is functionally homologous to the lid element of the proteasome. It appears that the various elements of the proteasome complex are co-regulated by the RPM4 putative transcription factor. The yeast activators Gcn4, Gal4, and Ino2/4 are actually activated by exposure to the ubiquitin–proteasome system. It appears that after the transcription has started, the removal of the promoter-bound activators is beneficial for the continuation of transcription (Lipford JR et al 2005 Nature [Lond] 438:113). ►ubiquitin, ►LID, ►TAP, ►N-end rule, ►antigen presenting cell, ►MHC, ►antigen processing, ►JAMM, ►DRiP, ►immune system, ►polyamine, ►Skp1, ►tripeptidyl peptidase, ►Clp, ►photomorphogenesis, ►signalosome, ►lysosomes, ►unfolded protein response, ►immunoproteasomes, ►Gcn4, ►Gal4, ►exosome; Voges D et al 1999 Annu Rev Biochem 68:1015; Bochtler M et al 1999 Annu Rev Biophys Biomol Struct 28:295; Klotzel P-M 2001 Nature Rev Mol Cell Biol 2:179; Ottosen S et al 2002 Science 296:479; Liu C-W et al 2003 Science 299:408; Puente XS et al 2003 Nature Rev Genet 4:544; Goldberg AL 2003 Nature [Lond] 426:895; lid structure: Sharon M et al 2006 PLoS Biol 4(8):e267; minireview: DeMartino GN, Gillette TG 2007 Cell 129:659.

Protectin (CD59): A protein component of the complement encoded at 11p13. ►complement, ►paroxysmal nocturnal hemoglobinuria; Kawano M 2000 Arch Immunol Ther Exp 48(5):367.

Protein: A large molecule (polymer) composed of one or more identical or different peptide chains. The distinction between protein and polypeptide is somewhat uncertain; generally a protein has more amino acid residues (50–60) and therefore can fold. In animal cells, there are about 1×10^5 protein species. ►protein synthesis, ►protein structure, ►amino acid sequencing, ►subcellular localization; protein data Bank [PDB]: Westbrook J et al 2002 Nucleic Acids Res 30:245; <http://www.rcsb.org/pdb/>; <http://pir.georgetown.edu/>; <http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi>.

Protein 14-3-3: A family of 28–33 kDa acidic chaperone proteins named after their electrophoretic mobility. The proteins occur in many forms in different organisms and have roles in signal transduction (RAS-MAP), apoptosis, exocytosis, the regulation of the cell cycle (checkpoint), DNA repair, and oncogenes. They generally bind to phosphoserine/threonine domains. Protein 14-3-3 σ isoform binds tumor suppressor p53, regulates translation through eukaryotic translation initiation factor 4B, and reduces the mitotic endogenous ribosomal entry site (IRES)-dependent cyclin Cdk1 (PITSLRE), among performing other functions. In the absence of this isoform, mitotic exit is impaired and causes aneuploidy and tumorigenesis (Wilker EW et al 2007 Nature [Lond] 446:329). ►Chk1, ►cell cycle, ►Cdc25, ►p53, ►CaM-KK, ►checkpoint, ►chaperone, ►longevity, ►PITSLRE, ►IRES, ►cdk, ►eIF-4B; Muslin AJ, Xing H 2000 Cell Signal 12(11–12):703; Masters SC, Fu H 2001 J Biol Chem 276:45193; Tzivion G, Avruch J 2002 J Biol Chem 277:3061; Sehnke PC et al 2002 Plant Cell 14:S339.

Protein A: Protein A is isolated from *Staphylococcus aureus*; it binds the Fc domain of immunoglobulins without interacting with the antigen-binding site. It is used both in soluble and insoluble forms for the purification of antibodies, antigens, and immune complexes. ►antibody, ►immunoglobulins

Protein Abundance: ►genome-wide location analysis

Protein Alignment: <http://mozart.bio.neu.edu/topofit/index.php>.

Protein Arrays: Protein arrays are used in a manner analogous to microarrays of DNA. On specially treated microscope slide or microtiter plates, samples of a protein or proteins are lined up and exposed to other proteins or to drug molecules or molecular fragments in order to assess their interaction. This new procedure is expected to be useful for analytical purposes and particularly for the development of new drugs. ►microarray hybridization, ►protein chips,

►reverse array; Avseenko NV et al 2001 Anal Chem 73:6047; Brody EN, Gold L 2000 J Biotechnol 74:5.

Protein Assays: ►Bradford method, ►Lowry test, ►Kjeldhal method; for analysis with single cell resolution: Zhang HT et al 2001 Proc Natl Acad Sci USA 98:5497; detection on magnetic nanoparticle-bio-barcode and antibody at 30 attomolar concentration: Nam J-M et al 2003 Science 301:1884.

Protein C (2q13-q14): A vitamin K-dependent serine protease, which selectively degrades antihemophilic factors Va and VIIIa, and it is thus, an anticoagulant. ►protein C deficiency, ►antihemophilic factors, ►thrombin, ►anticoagulation, ►thrombophilia

Protein C Deficiency (thrombotic disease): Protein C deficiency is human chromosome 2q13-q14 dominant and may be a life-threatening cause of thrombosis. ►thrombosis, ►protein C

Protein Chips: A protein mixture (e.g., serum) applied to an about 1 mm² surface containing a “bait” that is an antibody, a specific receptor, or other kind of specific molecule, which selectively binds a particular protein (tagged by fluorescent dye) and thus facilitates its isolation even when present only in minute amounts. Alternatively, recombinant proteins are immobilized on the chips and then putative interacting proteins (cell lysates) are applied to it. The unbound material is removed by washing and the bound one(s) are analyzed by mass spectrometry, or phage display or two-hybrid method may be used. These procedures can handle speedily huge number of samples and bear similarity to DNA chips. ►microarray hybridization, ►ELISA, ►DNA chips, ►mass spectrum, ►MALDI, ►electrospray, ►phage display, ►two-hybrid method, ►gene product interaction, ►proteomics, ►protein microarray; Zhu H et al. 2001 Science 293:2101.

Protein Classification for Machine Learning: ►machine learning; <http://hydra.icgeb.trieste.it/benchmark>.

Protein Clock: ►evolutionary clock

Protein Complexes: Protein complexes usually play an important role in protein and cellular function. Their study requires enrichment of the complex either by chromatography, co-immunoprecipitation, co-precipitation by affinity-tagged proteins, and SDS-PAGE separation of the components before additional analytical techniques are employed. One study involving 1739 yeast genes, including 1143 human homologous, revealed 589 protein assemblies. Among these, 51% included up to five proteins, 6% more than 40 proteins, 4% 31–40, 6% 21–30, 15% of the complexes 11–20 proteins, and 18% displayed interactions among 6–10 proteins. The technology did not reveal interactions of very short durations.

Obviously, within the cells even more proteins interact. The modules of the interacting systems are better conserved during evolution than are random samples of other proteins. This indicates their importance in specific functions (Wuchty S et al 2003 *Nature Genet* 35:176). ▶immunoprecipitation, ▶immunolabeling, ▶SDS-PAGE, ▶LC-MS, ▶mass spectrometry, ▶TAP, ▶two-hybrid method, ▶genetic networks, ▶SAGE, ▶TAP; Gavin A-C et al 2002 *Nature [Lond]* 415:141; Ho Y et al 2002 *Nature [Lond]* 415:180; global surveys of budding yeast cell machineries: Gavin A-C et al *Nature [Lond]* 440:631; Krogan NJ et al 2006 *Nature [Lond]* 440:637; <http://www.biond.org/>; protein-DNA complexes: <http://gibk26.bse.kyutech.ac.jp/jouhou/readout/>.

Protein Conducting Channel: Membrane passageways for proteins that interact with the membrane protein and lipid components. ▶protein targeting, ▶SRP, ▶translocon, ▶translocase, ▶TRAM, ▶ABC transporters, ▶Sec61 complex; Spahn CM et al 2001 *Cell* 107:373.

Protein Conformation: ▶conformation

Protein Data Bank (PDB): An archive of macromolecular structures. ▶protein structure; <http://www.pdb.org/>; <http://www.wwpdb.org/>.

Protein Degradation: ▶proteasome, ▶ubiquitin, ▶anti-zyne, ▶lysosomes, ▶endoplasmic reticulum, ▶endocytosis, ▶major histocompatibility complex, ▶TAP, ▶F-box, ▶microRNA, ▶RNAi, ▶half-life

Protein Degradation within Cells: In protein degradation, endogenous proteins are digested primarily by the proteasomes and exogenous proteins are cleaved mainly by the lysosomal system, although the compartmentalization is not rigid. ▶proteasome, ▶lysosome, ▶N-end rule

Protein Design: Computer programs exist now to design new proteins for physico-chemical potential function and stereochemical arrangements using combinatorial libraries of amino acids. The *designability of a protein* is determined by the amino acids that permit alterations without loss of structure or function. (See Dahiat BI, Mayo SL 1997 *Science* 278:82).

Protein, Disordered: A disordered protein contains at least one experimentally determined disordered region and lacks fixed structure. Such proteins and regions can carry out important biological functions and may be involved in regulation, signaling, and control. (See <http://www.disprot.org/>).

Protein Domains: Protein domains are generally formed by the folding of 50–350 amino acid sequences for carrying out particular function(s). Small proteins may have only a single domain but larger complexes may have multiple modular units. The

alternations of α helices and β sheets constitute a characteristic *motif*. The two β -sheet motifs are shown in Figure P145 in black and red, respectively. The compact motifs are generally covered by polypeptide loops. Domain similarities among proteins from different organisms indicate possible functional relationship (homology) of those proteins. ▶protein structure- β sheets, ▶ α helices, ▶helix-turn-helix, ▶helix-loop-helix, ▶zinc finger, ▶binding proteins, ▶motif; Ponting CP, Russell RR 2002 *Annu Rev Biophys Biomol Struct* 31:45; Pearl FM et al 2003 *Nucleic Acids Res* 31:452; http://smart.embl-heidelberg.de/help/smart_about.shtml; <http://www.ebi.ac.uk/interpro>; <http://smart.embl.de/>; domain homology: <http://genespeed.uchsc.edu/>; conserved domains: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=cdd>; conserved domains in new sequences: <http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi>; three-dimensional structures: <http://www.toulouse.inra.fr/prodom.html>; domain search on the basis of sequence: <http://www.icgeb.trieste.it/sbase>; Superfamily domains: <http://supfam.org>; protein domain prediction: <http://www.bioinfotool.org/domac.html>.



Figure P145. Protein domains

Protein Engineering: Constructing proteins with amino acid replacements at particular domains and positions (e.g., substrate-binding cleft, catalytic and ligand-binding sites, etc.) or adding a label or another molecule, etc., to explore their effect on function. Incorporation of unnatural amino acids into particular proteins is a common way to accomplish it (Nowak MW et al 1998 *Methods Enzymol* 293:504). ▶directed mutation, ▶semisynthesis of proteins, ▶DNA shuffling, ▶iterative truncation, ▶nonsense suppression, ▶suppressor tRNA, ▶expressed protein ligation, ▶proteomics, ▶enzyme design; Tao H, Cornish VW 2002 *Curr Opin Chem Biol* 6:858; Brennigan JA, Wilkinson AJ 2002 *Nature Rev Mol Cell Biol* 3:964; Wang L et al 2003 *Proc Natl Acad Sci USA* 100:56.

Protein, Essential: Essential for the viability of the organism in an environment.

Protein Families: Protein families share structural and functional similarities; generally share more than 30% sequence identity. The number of different families in vertebrates is about 750, in invertebrates and plants ~670, in yeast and larger bacteria ~550, and in small parasitic bacteria ~220 (Chotia C et al

2003 Science 300:1701). The average family size in higher organisms is about 20 whereas in lower forms it is 8 to 2. *Superfamilies*: (i) catalyze the same chemical reaction or (ii) different overall reactions that share common mechanistic properties (partial reaction, intermediate or transition state) and share 20 to 50% sequence identity. *Suprafamilies*: homologous enzymes but catalyze different reactions. Mutations affecting amino acid sequences in three different evolutionary groups (mammals, chickens, bacteria) are strikingly similar. For categories with the same divergence, common accepted mutations have similar frequencies and rank orders in the three groups. With increasing divergence, mutations increase at different rates in the buried, intermediate, and exposed regions of protein structures in a manner that explains the exponential relationship between the divergence of structure and sequence. This work implies that commonly allowed mutations are selected by a set of general constraints that are well defined and whose nature varies with divergence (Sasidharan R, Chothia C 2007 Proc Natl Acad Sci USA 104:10080). ►*gene family*, ►*PRINTS*; Enright AJ et al 2002 Nucleic Acids Res 30:1575; Aravind L et al 2002 Curr Opin Struct Biol 12:392; <http://pfam.wustl.edu/>; <http://www.ebi.ac.uk/interpro>; <http://www.biochem.ucl.ac.uk/bsm/cath>; <http://mia.sdsc.edu/mia/html/bioDBs.html>; <http://systems.molgen.mpg.de>; shifts in subfamilies: <http://funshift.cgb.ki.se/>; families in evolution: <http://www.pantherdb.org/>.

Protein Folding: The majority of proteins fold to acquire functionality, although some (mainly) surface proteins do not require folding. The pattern of hydrophobic and polar residues of a relatively small number may be required for folding. The native conformation is reached through intermediate stage(s) (see Fig. P146) (Sadqi M et al 2006 Nature [Lond] 442:317). Even at high (88%) amino acid identity, two proteins may have different structures and functions (Alexander PA et al 2007 Proc Natl Acad Sci USA 104:11963).

The native structure is stabilized primarily by hydrogen bonding between amide and carbonyl groups

of the main chain. Glycosylation in the endoplasmic reticulum may affect the conformation of proteins.

The folding is determined by the amino acid sequence, however other factors (chaperones) may be needed to facilitate the process. the energetics of backbone hydrogen bonds dominate the folding process, with preorganization in

Besides the primary structure of amino acids, the energetics of backbone hydrogen bonds can dominate the folding process, with pre-organization in the unfolded state. Then, under folding conditions, the resultant fold is selected from a limited repertoire of structural possibilities, each corresponding to a distinct hydrogen-bonded arrangement of α -helices and/or strands of β -sheets (Rose GD et al 2006 Proc Natl Acad Sci USA 103:16623).

The classical diffusion–collision and nucleation–condensation models may represent two extreme manifestations of an underlying common mechanism for the folding of small globular proteins. Characterization of the folding process of the PDZ domain, a protein that recapitulates three canonical steps, is involved in a unifying mechanism, namely: (1) the early formation of a weak nucleus that determines the native-like topology of a large portion of the structure, (2) a global collapse of the entire polypeptide chain, and (3) the consolidation of the remaining partially structured regions to achieve the native state conformation. Classical kinetic analysis identified two activation barriers along the reaction coordinate, corresponding to a more unfolded transition state *TS1* and a more native-like transition state *TS2*. The PDZ2 (PDZ repeat from Protein Tyrosine Phosphatase-Bas Like folding process; Bas for basophil) provides evidence that its folding mechanism is distinct from the pure diffusion–collision as well as from the nucleation–condensation mechanism, but displays characteristic features of both models (Gianni S et al 2007 Proc Natl Acad Sci USA 104:128).

Prokaryotic proteins (which are generally smaller, two to three hundred amino acid residues) fold correctly only after the completion of the entire length of the amino acid chain. Eukaryotic proteins (usually on the average over four to five hundred residues) may

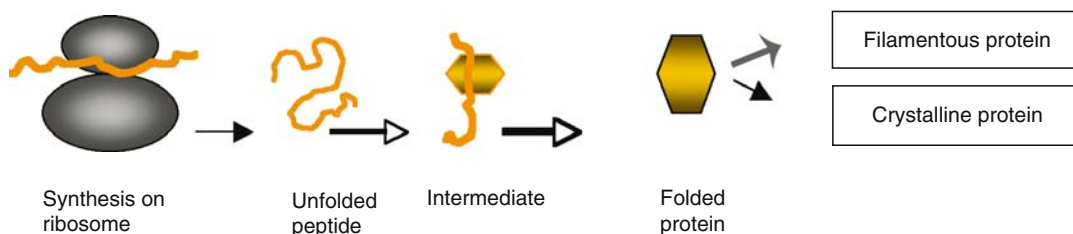


Figure P146. Protein folding

fold the separate domains in a sequential manner during their translation. Both prokaryotic and eukaryotic proteins may start folding before their translation is completed, i.e., co-translationally. Because of this, fusion proteins can also fold and this might have been of an evolutionary advantage. There is evidence that α helices fold faster than β sheets. Local interactions may facilitate speedier folding.

The global pattern of co-evolutionary interactions of amino acids is relatively sparse and a small set of positions in the proteins mutually co-evolves. The co-evolving residues are spatially organized into physically connected networks linking distant functional sites through packing interactions. By the method of statistical coupling analysis (SCA), it was revealed that the amino acid interactions specifying the atomic structure are conserved among the members of protein families. The conservation is not site independent and it occurs due to energetic interactions. The statistical energy functions can be appropriately estimated by the SCA method (Socolich M et al 2005 Nature [Lond] 437:512; Russ WP et al 2005 Nature [Lond] 437:579). Certainly many factors may affect the rate of folding and the rate among different proteins may be nine orders of magnitude. Besides folding, intrinsic plasticity of the enzyme proteins is a characteristic feature of catalysis. The motion is not limited to the active site but a more dynamic network is also involved (Eisenmesser EZ et al 2005 Nature [Lond] 438:117). Diseases may occur due to the misfolding of protein(s) such as in cystic fibrosis, Parkinsonism, prion, Alzheimer's disease, sickle cell anemia, etc. Some of the misfolding problems can be alleviated by inhibitors of the enzyme or by aiding its degradation by small molecules or by stabilizing the conformation (Cohen FE, Kelly JW 2003 Nature [Lond] 426:905). ▶chaperones, ▶chaperonins, ▶conformation, ▶calnexin, ▶calreticulin, ▶protein structure, ▶amyloidosis, ▶prion, ▶encephalopathies, ▶GroEL, ▶trigger factor, ▶endoplasmic reticulum, ▶Sec61 complex, ▶protein synthesis, ▶folding, ▶SCA; Bukau B et al 2000 Cell 101:119; Baker D 2000 Nature [Lond] 405:39; Parodi AJ 2000 Annu Rev Biochem 69:69; Klein-Seetharaman J et al 2002 Science 295:1719; Hartl FU, Hayer-Hartl M 2002 Science 295:1852; Myers JK, Oas TG 2002 Annu Rev Biochem 71:783; Gianni S et al 2003 Proc Natl Acad Sci USA 100:13286; Dobson CM 2003 Nature [Lond] 426:884; Selkoe DJ 2003 Nature [Lond] 426:900; evolutionary implications: DePristo MA et al 2005 Nat Rev Genet 6:678; protein misfolding and amyloid disease: Chiti F, Dobson CM 2006 Annu Rev Biochem 75:333; protein misfolding-human disease: Gregersen N et al 2006 Annu Rev Genomics Hum Genet 7:103; <http://bioresearch.ac.uk/browse/mesh/D017510.html>; protein refolding: [http://refold.med.](http://refold.med.monash.edu.au/)

monash.edu.au/; protein folding potential software: <http://flexweb.asu.edu/software/>; predicting protein folding on the basis of amino acid sequence: <http://psfs.cbrc.jp/fold-rate/>; folding database: http://www.foldeomics.org/pfd/public_html/index.php.

Protein Function: Protein function is generally determined by biochemical and genetic analyses such as enzyme assays, two-hybrid system, etc. Many proteins are involved in complex functions and interact with several other proteins. These complex functions can be inferred from the known role of proteins in evolutionarily different organisms, from amino acid sequence information, by the rosetta stone sequences, the correlation of mRNA expression, and gene fusion information from sequence data. During evolution, some structural and functional properties of the diverging proteins are retained in the protein families but some groups have acquired new function such as substrate-specificity. These shifts can be analyzed by: <http://FunShift.cgb.ki.se>. ▶rosetta stone sequences, ▶microarray hybridization, ▶two-hybrid system; <http://biozon.org>; functional sites, ligands: <http://firedb.bioinfo.cnio.es>.

Protein G: An immunoglobulin-binding (IgG) streptococcal extracellular cell surface protein.

Protein Grafting: The transfer of a binding epitope in biologically active conformation unto the surface of another protein. Such a procedure may produce an effective antiviral protein or may be used for other biological purposes. ▶epitope; Sia SK, Kim PS 2003 Proc Natl Acad Sci USA 100:9756.

Protein H: Streptococcal IgG-binding protein. ▶immunoglobulins

Protein Index: Guides to the main databases on proteomes such as Swiss-Prot, RefSeq, Ensembl, etc. ▶protein classification; <http://kinemage.biochem.duke.edu/~jsr/html/anatax.3a4.html>.

Protein Information Resource: ▶PIR; <http://pir.georgetown.edu>; the largest and most comprehensive source is the Swiss-Prot: <http://www.expasy.ch/>; ▶databases

Protein Interactions: Interaction density (PID) is calculated as observed protein interaction/total number of possible pair-wise combinations. Conformational switches detectable by nuclear magnetic resonance relaxation experiments at the microsecond to millisecond time scale may modulate protein interactions (Koglin A et al 2006 Science 312:273). The various proteins may interact in many different ways and the ~6000 proteins of yeast may display about 100,000 relations. In a preliminary attempt to develop a human genome-wide interaction network,

~8100 Gateway-cloned ORFs allowed the detection of 2800 interactions (Rual J-F et al 2005 Nature [Lond] 437:1173). A new method permits prediction of interactions on the basis of protein sequence (Shen J et al 2007 Proc Natl Acad Sci USA 104:4337). Bioinformatic technology is required to separate the genuine from the spurious interactions (Jansen R et al 2003 Science 302:449). In *Drosophila* a draft of 7048 proteins and 20,405 interactions were detected and at a high confidence level 4679 proteins and 4780 interactions were verified by the two-hybrid method and mapped (Giot L et al 2003 Science 302:1727).

Photo-cross-linking permits detection of protein–protein interactions in living cells. Photoreactivable amino acids (e.g., photomethionine, as shown in Figure P147, the critical change is circled by dashed line) are very similar to natural counterparts and can be incorporated into the protein by the translation machinery. Activation by ultraviolet light results in cross-linking of the interacting proteins and it can be detected by western blotting (Suchanek M et al 2005 Nature Methods 2:261).

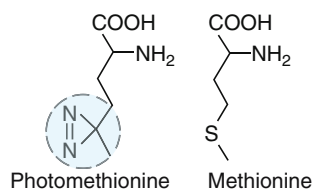


Figure P147. Photomethionine (left); methionine (right). (After Suchanek, M. et al. 2005 Nature Methods 2:261)

The bimolecular fluorescence complementation (BiFC) method permits the visualization of interaction *in situ* within living cells using yellow fluorescent protein variants (Hu C-D, Kerppola TK 2003 Nature Biotechnol 21:539). Protein interaction networks are largely preserved during evolution from prokaryotes to eukaryotes, although some specialization is also evident (Kelley BP et al 2003 Proc Natl Acad Sci USA 100:11394). A recent analysis of more than 70,000 binary interactions in humans, yeast, *Caenorhabditis*, and *Drosophila* showed only 42 were common to human, worm, and fly and only 16 were common to all. An additional 36 were common between fly and worm but not to humans, although by co-immunoprecipitation 9 were present in humans. Proteins known to be involved in similar disorders in humans showed interaction (Gandhi TKB et al 2006 Nat Genet 38:285). ►gene product interaction, ►two-hybrid method, ►protein-DNA interaction, ►affinity tagging, ►protein chips, ►networks, ►genetic networks, ►GRID, ►BIND,

►DIP, ►ORF, ►Gateway cloning, ►interactome; Bock JR, Gough DA 2001 Bioinformatics 17:455; Fernández A, Scheraga HA 2003 Proc Natl Acad Sci USA 100:113; MIPS database: Mewes HW et al 2002 Nucleic Acids Res 30:31; Jansen R et al 2002 Genome Res 12:37; <http://bind.ca>; <http://string.embl.de>; human protein reference/interaction database: <http://www.hprd.org/>; domain–domain interactions: <http://3did.embl.de>; <http://mimi.ncibi.org>; interactions from PubMed abstracts: <http://cbioc.eas.asu.edu>; protein interfaces: <http://scoppi.org/>; <http://pre-s.protein.osaka-u.ac.jp/~prebi>; protein domain interaction database: <http://mint.bio.uniroma2.it/domino/>; <http://mint.bio.uniroma2.it/mint/Welcome.do>; <http://www.hsls.pitt.edu/guides/genetics/tools/protein/interaction/URL1138211431/info>; Apid interaction analyzer: <http://bioinfow.dep.usal.es/apid/index.htm>; protein docking server: <http://vakser.bioinformatics.ku.edu/resources/gramm/grammx>; interaction software: <http://www.ebi.ac.uk/intact/site/index.jsf>; molecular ancestry network MANET: <http://www.manet.uiuc.edu/>.

Protein Intron: ►intein

Protein Isoforms: Closely related polypeptide chain family, encoded by a set of exons, which share structurally identical or almost identical subset of exons. ►family of genes

Protein Kinase: A protein kinase phosphorylates one or more amino acids (frequently threonine, serine, tyrosine) at certain positions in a protein, and thus two negative charges are conveyed to these sites, altering the conformation of the protein. This alteration then involves a change in the ligand-binding properties. The catalytic domain of this large family of enzymes is usually 250 amino acids. The amino acids outside the catalytic domains may vary substantially and specify the recognition abilities of the different kinases and serve in responding to regulatory signals. During the last three to four decades, hundreds of protein kinases have been discovered that can be classified into serine/threonine (TGF- β [transforming growth factor]), tyrosine (EGF [epidermal growth factor receptor], PDGF [platelet-derived growth factor receptor] protein kinases, SRC [Rous sarcoma oncogene product], Raf [product of the Moloney and MYC oncogenes]), MAP kinase, cell cyclin-dependent kinase (Cdk), cell division cycle (Cdc), cyclic-AMP- and cyclic-GMP-dependent kinases, myosin light chain kinase, Ca^{2+} /calmodulin dependent kinases, etc. Protein kinase R (PKR, dsRNA-dependent protein kinase) down-regulates protein synthesis in virus-infected cells. In the N-terminal region, two double-stranded RNA binding domains activate PKR by binding to dsRNA

and recruit it to the ribosome where it phosphorylates the eukaryotic elongation factor eIF2 α . The consensus sequences for a few protein kinases are shown below:

Protein kinase A
(?)-Arg-(Arg/Lys)-(?)-(Ser/Thr)-(?)
Protein kinase G
(?)-{[Arg/Lys] 2x or 3x}-(?)-(Ser/Thr)-(?)
Protein kinase C
(?)-([Arg/Lys] 1-3x)-([?] 0-2x)-(Ser/Thr)-([?]0-2x)-(Ser/[Thr]1-3x)-(?)
Ca⁺⁺/calmodulin kinase II
(?)-arg-(?)-(?)-(?)-(Ser/Thr)-(?)
Insulin receptor kinase
Thr-Arg-Asp-Ile-Tyr-Glu-Thr-Asp-Tyr-Tyr-Arg-Thr
EGF receptor kinase
Thr-Ala-Glu-Asn-Ala-Glu-Tyr-Leu-Arg-Val-Arg-Pro

(?) indicates any amino acid, the numbers after the amino acid with an "x" indicate how many times it may occur.

The majority of protein kinases require phosphorylation in their activation loop to perform their function. The human genome apparently includes 518 protein kinase genes. Protein kinases play an important role in signal transduction as well in the development of diseases (cancer), behavior and memory. Protein kinase inhibitors have therapeutic potentials. The inhibitors must pass the gatekeeper function of selectivity filters at the site of one or more amino acids (Cohen MS et al 2005 Science 308:1318).
►cAMP-dependent protein kinase, ►epinephrine, ►phosphorylase b kinase, ►signal transduction, ►obesity, ►PKB, ►kinase, ►TGF, ►EGF, ►PDGF, ►RAF, ►MYC, ►MAP, ►tyrosine kinase, ►selectivity filter; Plowman GD et al 1999 Proc Natl Acad Sci USA 96:13603; Ung TL et al 2001 EMBO J 20: 3728; Cohen P 2002 Nature Cell Biol 4:E127; Huse M, Kuryan J 2002 Cell 109:275; Manning G et al 2002 Science 298:1912; Noble MEM et al 2004 Science 303:1800; regulation: Nolen B et al 2004 Mol Cell 15:661; drug targets: Sebolt-Leopolt JS, English JM 2006 Nature [Lond] 441:457; protein kinase locking server: http://abcis.cbs.cnrs.fr/LIGBASE_SERV_WEB/PHP/kindock.php.

Protein Binding: Protein binding involves binding protein to protein, to RNA, and to DNA. Induced fit, van der Waals interactions, electrostatic interactions, hydrogen bonds, and aromatic stacking (involving mainly tyrosine and phenylalanine) have been implied. Organic chemistry also uses pi-pi (π - π) stacking. terms mentioned; Mignon P et al 2005 Nucleic Acids Res 33:1779; Hunter CA 2004

Angew Chem Int Ed Engl 43:5310; protein ligands: <http://www.bindingdb.org>.

Protein Knots: Structural sites for ligand binding and enzyme activity.

Protein L: *Peptostreptococcus* bacterial protein binding to the framework of immunoglobulin κ chains.
►immunoglobulins, ►framework amino acids

Protein Length: Protein length shows great differences among individual molecules by the number of amino acids. There is a statistically significant increase along the advancement in the evolutionary rank, e.g., in Archaeobacteria 270 ± 9 , in bacteria 330 ± 5 , and in eukaryotes (budding yeast and *Caenorhabditis*) 449 ± 25 . Some of the mammalian proteins are huge, e.g., dystrophin.

Protein Likelihood Method: The protein likelihood method is used to determine evolutionary distance when the organisms are not closely related and when the non-synonymous base substitutions are higher than the synonymous ones. In such cases, the protein method may provide more reliable information.
►evolutionary distance, ►evolutionary tree, ►least square methods, ►four-cluster analysis, ►un-rooted evolutionary trees, ►transformed distance, ►Fitch-Margoliash test, ►DNA likelihood method; Whelan S Goldman N 2001 Mol Biol Evol 18:691.

Protein Machines: Multimolecular interacting systems such as metabolic circuits, intracellular signal transduction, or cell-to-cell communication. These systems are operated under process control strategies involving integrated feedback control. The input and output of the circuits or modules are coordinated to assure the normal or adaptive function of the cell or organism. ►feedback control, ►microarray hybridization; Baines AJ et al 2001 Cell Mol Biol Lett 6:691; Tobaben S et al 2001 Neuron 31:987.

Protein Mapping: Protein mapping localizes the pattern of expression of genes by identifying the sites of proteins within cells. An automated, multidimensional fluorescence microscopy technology permits mapping and interaction of hundreds of different proteins in a single cell (Schubert W et al 2006 Nat Biotechnol 24:1270). ►gene expression map; Huh W-K et al 2003 Nature [Lond] 425:686; Ghaemmaghami S et al 2003 Nature [Lond] 425:737.

Protein Microarray: Microspots of proteins immobilized on solid support and exposed to samples of binding molecules. In such a system, enzyme-substrate and protein-ligand relations can be visualized by the use of fluorescence, chemiluminescence, mass spectrometry, radioactivity, or electrochemistry.
►protein chips, ►protein profiling, ►antibody microarray, ►chemiluminescence, ►fluorescence,

►mass spectrum; Templin MF et al 2002 Trends Biotechnol 20:160.

Protein Network: The protein network detects functional organization of genomes. Two proteins may be related to other in the cell in case the presence of one seems to affect the presence or absence of another. Such a relation exists if both are required to form a structural complex or if they carry out sequential steps in an unbranched pathway. Under natural, biological conditions the presence or absence of multiple proteins exists. Another simple situation is where three proteins are followed. These may display eight different relations, such as C being present only if both A and B are present or A being present if only either B or A are present and so on. The various probabilities or uncertainties of the clusters can then be calculated in a single genome and in phylogenetic relatives to obtain information of the protein network organization (Bowers PM et al 2004 Science 306:2246). ►genetic networks; <http://www.cellcircuits.org>.

Protein 4.1N: 4.1 N binds to the nuclear mitotic apparatus protein NuMA, a non-histone protein that is associated with the mitotic spindle. It regulates the antimitotic function of the nerve growth factor NGF. ►NGF, ►PIK; Kontragianni-Konstatonopoulos A et al 2001 J Biol Chem 276:20679; Scott C et al 2001 Eur J Biochem 268:1084.

Protein-Nucleic Acid Interaction: ►transcription factors, ►two-hybrid method; thermodynamics of interactions: <http://gibk26.bse.kyutech.ac.jp/jouhou/pronit/pronit.html>.

P

Proteins, Number of in a human cell: may exceed that of the number of genes by a factor 5 or more but at this stage it is not known.

Protein Phosphatases: Protein phosphatases remove phosphates from proteins. They include enzymes that reverse the action of protein kinases and have an important role, together with the kinases, in signal transduction. ►protein kinases, ►membrane fusion, ►FK506; Barford D et al 1998 Annu Rev Biophys Biomol Struct 27:133; Terrak M et al 2004 Nature [Lond] 429:780.

Protein pI: isoelectric point of proteins varies between <3 to >12. ►isoelectric point

Protein Profiling: The characterization or identification of proteins on the basis of sequence, structure, mass spectrum, MALDI, MS/MS, high-performance liquid chromatography, protein microarrays, two-dimensional gel electrophoresis, etc. ►proteomics, ►protein chips, ►antibody microarray

Protein Purification: To purify proteins, disrupt cells→separate subcellular organelles by differential centrifugation→wash by buffer the separated bodies→

treat the fraction(s) needed by denaturing agents→dialyze to remove the denaturing agent→use reducing agents for protection→concentrate→remove the unneeded or improperly folded protein fractions by ion-exchange chromatography, gel filtration, immunoaffinity, isoelectric focusing, high performance liquid chromatography or other steps→the wanted pure protein. Quantitate the amount or yield of the protein obtained by UV absorption or by the Lowry or Bradford methods. Each of these steps may need detailed operations. ►UV spectrophotometry of proteins, ►Lowry test, ►Bradford method

Protein Quality Control: ►unfolded protein response, ►endoplasmic reticulum-associated degradation

Protein Repair: Protein repair can be managed with assistance of chaperones. If the refolding is not feasible, proteolytic enzymes destroy proteins either directly or by the mediation of ubiquitins. Nascent polypeptides, transcribed from truncated mRNAs without a stop codon, acquire a C-terminal oligopeptide (Ala, Ala, Asn, Asp, Glu, Asn, Tyr, Ala, Leu, Ala, Ala or a variant), encoded by an *ssrA* transcript. The *ssrA* is a 362-nucleotide tRNA-like molecule that can be charged with alanine. The addition of the peptide tag takes place on the ribosome by cotranslational switching from the truncated mRNA to the *ssrA* RNA. The polypeptide chain so tagged is degraded in the *E. coli* cytoplasm or periplasm by carboxyl-terminal-specific proteases. The Clp chaperone recognizes the peptides by the *ssrA* tag of AANDENYALAA and targets the proteins to the ClpX and ClpA ATPases. ►amino acids, ►chaperone, ►ubiquitin, ►periplasm, ►protease, ►DNA repair, ►tmRNA, ►Clp, ►ssrA; Wawrzynow A et al 1996 Mol Microbiol 21:895.

Protein S (PROS): The human chromosome 3p11 vitamin K-dependent plasma proteins preventing blood coagulation and a cofactor for Protein C. Their deficiency and dysfibrinogenemia are genetically determined causes of thrombosis. ►protein C, ►anti-thrombin, ►dysfibrinogenemia, ►thrombosis, ►APC, ►anticoagulation, ►thrombophilia, ►tissue factor

Protein Sequencing: ►amino acid sequencing

Protein Shuttling: The flow of protein within cells or cellular organelles. (See Ando R et al 2004 Science 306:1370).

Protein Similarity Matrix: <http://mips.gsf.de/simap/>.

Protein Sorting (protein traffic): The mechanism by which the polypeptides synthesized on the ribosomes in the endoplasmic reticulum reach their destination in the cell through secretory pathways by transport, with the aid of endocytotic vesicles. ►endocytosis, ►clathrin, ►Golgi apparatus, ►COP transport vesicle, ►RAFT, ►Sec, ►Fts; Tormakangas K et al 2001 Plant Cell

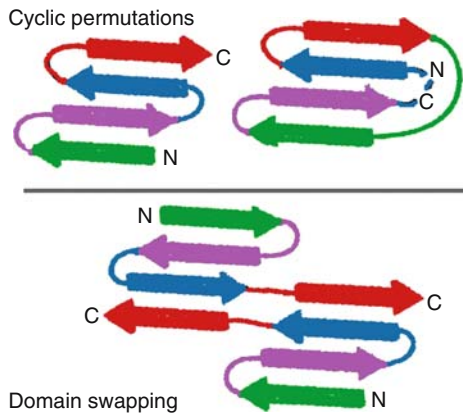


Figure P149. Cyclic permutations of the secondary structure or domain swapping of the α and β strands is tolerated in many proteins. The essential feature of a protein fold is the complementary packing of the secondary structural elements and not the precise manner of connection of the elements. Some of these changes retain stability of the protein and binding ability and can be used in protein engineering. (Diagram is modified after Tabtiang RK et al 2005 Proc Natl Acad Sci USA 102:2305)

fcgi?db=Structure; <http://astral.stanford.edu/>; <http://www.imb-jena.de/IMAGE.html>; <http://scop.mrc-lmb.cam.ac.uk/scop/>; ►protein synthesis, ►protein domains, ►molecular modeling, ►conformation, ►databases, ►CATH, ►SCOP, ►FEMME, ►electron density map of proteins, ►x-ray diffraction analysis, ►MANET, ►MOLSCRIPT, ►block; Goodsell DS, Olsen AJ 2000 Annu Rev Biophys Biomol Struct 29:105; Marti-Renom MA et al 2000 Annu Rev Biophys Biomol Struct 29:291; Koonin EV et al 2002 Nature [Lond] 420:218; Ouzounis CA et al 2003 Nature Rev Genet 4:508; review on structure predictions and biological significance: Petrey D, Honig B 2005 Mol Cell 20:811; tertiary structure matching of proteins: <http://proteindb.mst.missouri.edu/index.php>; molecular structure database tool: <http://bip.weizmann.ac.il/oca-bin/ocamain>; structural neighbors: http://fatcat.burnham.org/fatcat-cgi/cgi/struct_neibor/fatcatStructNeibor.pl; structural and functional annotation of protein families: <http://cathwww.biochem.ucl.ac.uk:8080/Gene3D/>; functional site prediction: <http://sage.csb.yale.edu/sitefinder3d/>; functional sites from sequence alignment: <http://zeus.cs.vu.nl/programs/seqharmwww/>; interacting protein motifs: <http://caps.ncbs.res.in/imotdb/>; comparative structure models: <http://modbase.compbio.ucsf.edu/modbase-cgi-new/index.cgi>; protein modeling: <http://a.caspar.it/PMDB/>; 3D structures: <http://molprobiy.biochem.duke.edu/>; 3D conserved residues: <http://3dlogo.uniroma2.it/>; annotated three-dimensional structures: <http://swissmodel.expasy.org/repository/>; automated

prediction: <http://pcons.net/>; tertiary structure: <http://prokware.mbc.nctu.edu.tw/>; protein short sequence motif search:

<http://past.in.tum.de/>; computing physicochemical properties on the basis of amino acid sequence: <http://jing.cz3.nus.edu.sg/cgi-bin/prof/prof.cgi>; stability of mutant proteins: <http://cupsat.uni-koeln.de/>; <http://www.ces.clemson.edu/compbio/protcom>; interactive structures: <http://www.compbio.dundee.ac.uk/SNAP/PI/downloads.jsp>; solvability and interfacing: <http://pipe.scs.fsu.edu/>; protein structure modeling: <http://manaslu.aecom.yu.edu/M4T/>; unstable (disorder) regions: <http://prdos.hgc.jp/cgi-bin/top.cgi>; <http://bio.miner.cse.yzu.edu.tw/ipda/>; structure animation (movie): <http://bioserv.rpbs.jussieu.fr/~autin/help/PMGtuto.html>.

Protein Synthesis: Has many basic requisites and a large number of essential regulatory elements. It intertwines with all cellular functions. The blueprint for protein synthesis in the vast majority of organisms (DNA viruses, prokaryotes and eukaryotes) is in the nucleotide sequences of the DNA code. In RNA viruses the genetic code is in RNA. However, the viruses do not have their own machinery for the actual synthesis of protein, rather they exploit the host cell for this task. The genetic code specifies individual amino acids by nucleotide triplets, using one or several synonyms for each of the 20 natural amino acids. The triplet codons are in a linear sequence of the nucleic acid genes. In the organisms with DNA as the genetic material, the process of transcription produces a complementary RNA sequence from one or both strands of the anti-parallel strands of the DNA. The double-strands unwind and the RNA polymerase(s) synthesize(s) a complementary RNA copy of the sequence in the DNA. In the single stranded DNA and RNA viruses, the DNA or RNA may serve both purposes of being the genetic material and the transcript for protein synthesis. In cellular organisms three main classes of RNAs are made, messenger RNA (mRNA), transfer RNA (tRNA) and ribosomal RNA (rRNA), and all three are indispensable for protein synthesis. In addition to these RNAs, a large number of proteins are required for the transcription process (transcription factors), for the organization of the ribosomes (50–80 ribosomal proteins), for the termination of transcription, for the activation of the tRNAs, etc. A broad overview (without details) is shown in Figure P150. Some of the details of the transcriptional process are different in prokaryotes from that in eukaryotes. In the latter group, one DNA-dependent RNA polymerase is responsible for the synthesis of all RNAs. In eukaryotes, pol I synthesizes rRNAs with the exception of the 5S and 7S rRNA, pol II transcribes mRNA and the small nuclear RNAs (snRNA) and pol III synthesizes tRNAs and 5S and 7S rRNA.

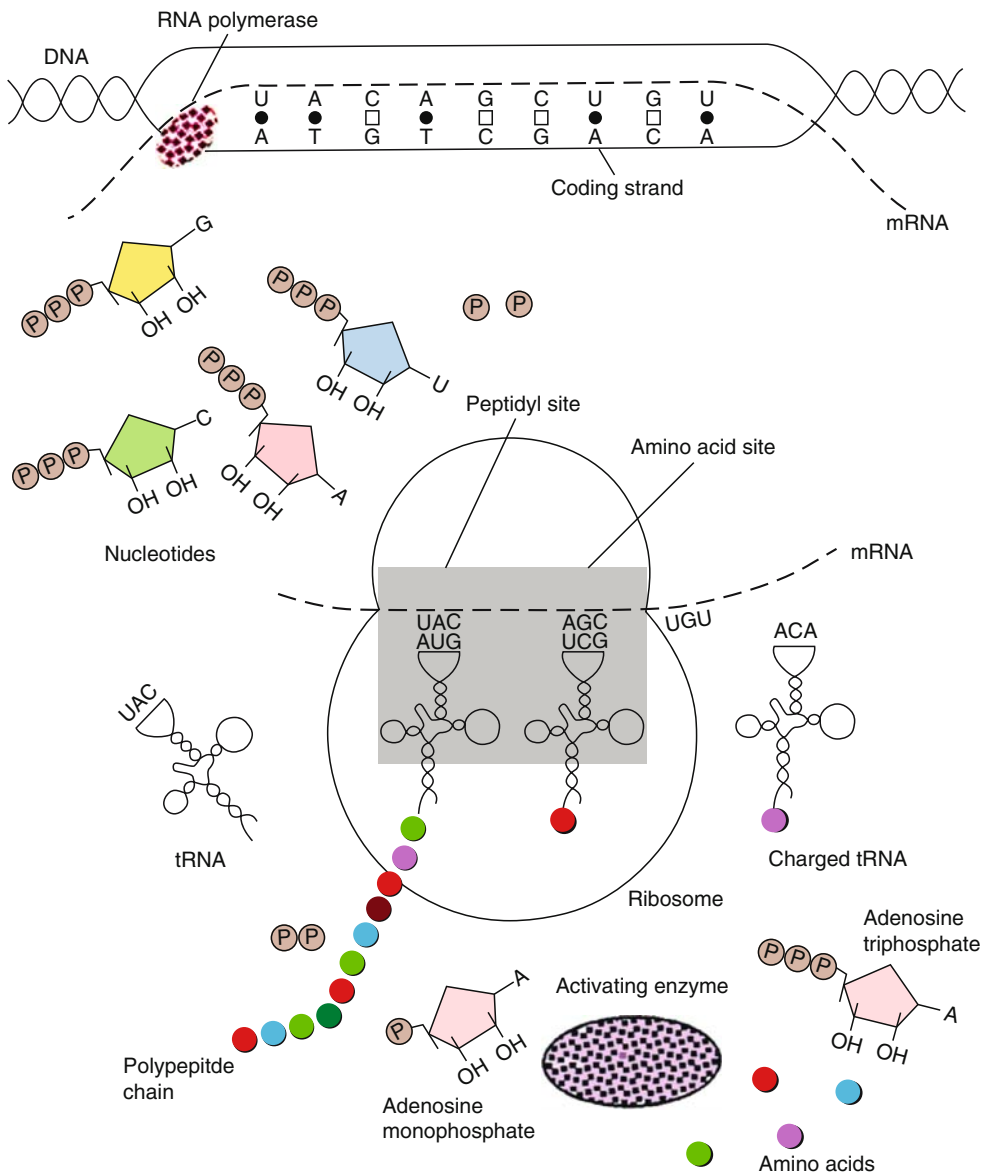


Figure P150. An over-simplified view of the protein synthesizing machinery

In prokaryotes, the process of transcription and translation are *coupled*, i.e., as soon as the chain of mRNA unwinds from the DNA it is associated with the ribosomes and protein synthesis begins. The primary RNA transcripts must be processed to functional size molecules in all categories that may require splicing and other post-transcriptional modifications (capping, formylation, etc.).

In eukaryotes when the mRNA is released from its DNA template it moves into the cytosol where protein synthesis takes place. A small fraction of polypeptides may be synthesized also in the nucleus of eukaryotes (Iborra FJ et al 2001 Science 293:1058). There is evidence for the association of ribosomal

components into ribonucleoprotein complexes at the transcription sites of salivary gland chromosomes (Brognia S et al 2002 Mol Cell 10:93). The fate of the mRNA can be monitored by electronmicroscopy in both groups and these pictures show the elongation of RNA and protein strands (see Fig. P151). The first products of both display long strands and the short ones indicate the stage and place where they were started. The ribosomes are captured by the mRNA and form an association of multiple units in the form called *polysomes* (see Fig. P152).

The prokaryotic mRNA is directed to the proper position in the 30S ribosomal subunit by the Shine-Dalgarno nucleotide sequence within 8 to 13-base

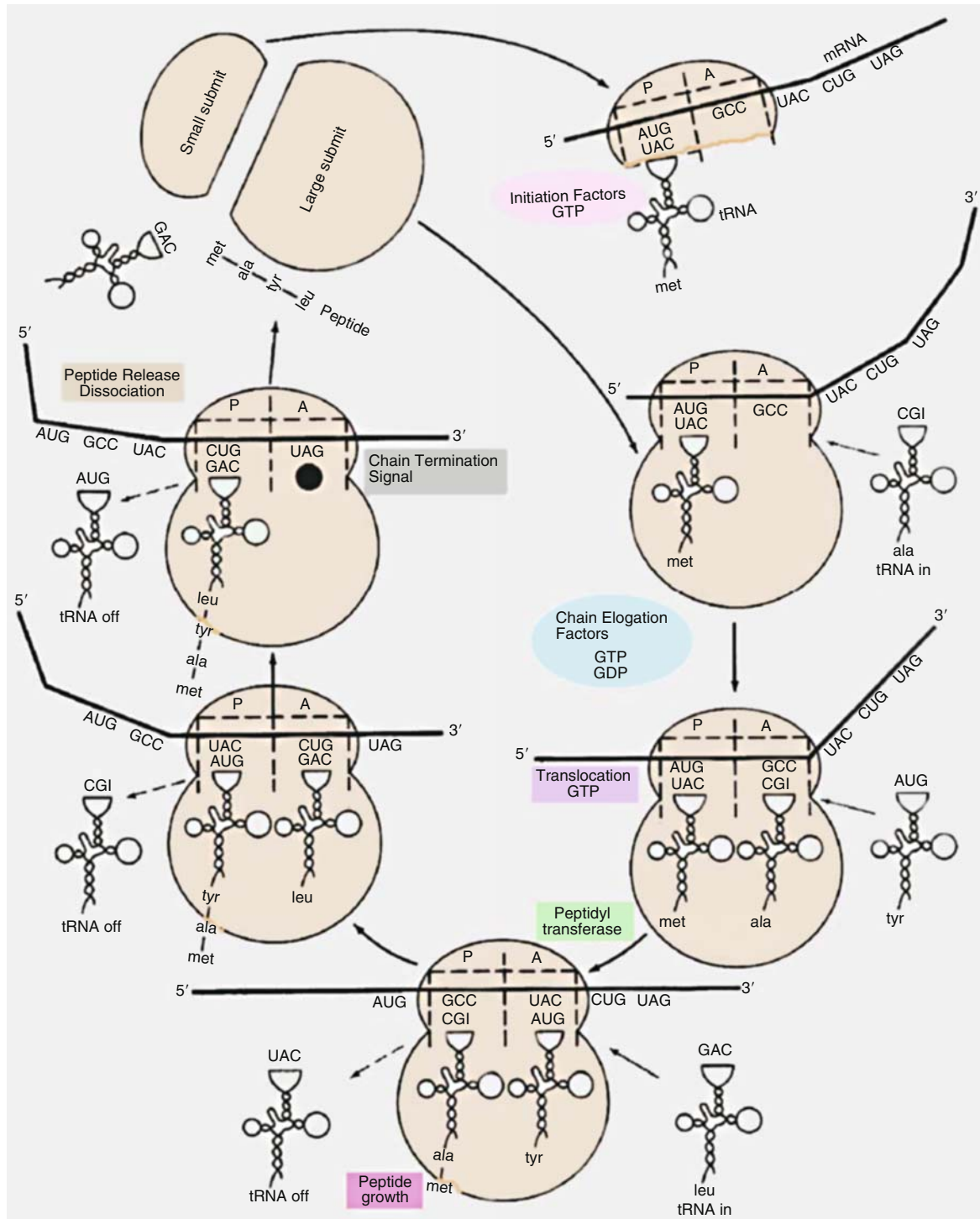


Figure P151. Classical model of translation on ribosomes

area upstream from the initiation codon. In eukaryotes, such a sequence does not exist and the mRNA is simply scanned by the ribosome until the first methionine codon is found.

The ribosomal units then slide from the 5'-end of the mRNA toward the 3'-end and thus, the amino end of the polypeptide chain corresponds to the 5'-end of the mRNA. The ribosomes in both prokaryotes and

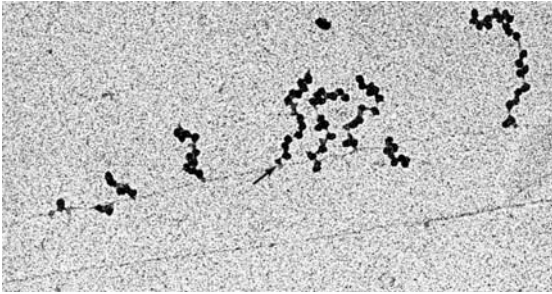


Figure P152. Transcription and translation coupled in *E. coli*. The thin thread is the DNA, the dark round structures are polysomes. The transcriptase attachment → is indicated. (From Hamkalo BA et al 1974 Stadler Symp 6:91)

eukaryotes are composed of a small and a large subunit. The size of these units is somewhat different in the two major taxonomic categories. The small and large subunits of the ribosomes jointly form two compartments, the so-called P (peptidyl-tRNA binding site) and the A (aminoacyl-tRNA binding site). A newer *hybrid-states model* of the translational process is described under the entry “ribosomes.” The ribosomes actually do not look like as shown in these diagrams, because they are three-dimensional and have a more elaborate structure. Before protein synthesis (translation) begins and the primary structure of the mRNA is translated from the nucleotide triplet codon words into the singular amino acid word language of the protein, the tRNA molecules must be charged with amino acids. This process is also called activation of tRNA. (► [aminoacyl-tRNA synthetase](#)).

The amino-acid-charged methionine-tRNA (tRNA^{Met}) in eukaryotes and the formylated $\text{tRNA}^{\text{fMet}}$ in prokaryotes seek out the cognate codon in the mRNA at the P site of the ribosome through the complementary anticodon. This event requires the presence of protein initiation factor(s) and GTP as energy source. The GTP is cleaved to GDP + inorganic phosphate (Pi) and thus liberates some of the needed energy. The elongation factor proteins and GTP and GDP complexes also police the system to prevent the wrong charged tRNA to go to an A site (proofreading function). Actually a similar correction mechanism is carried out earlier in the process by one of the active sites of the aminoacyl synthetase (activating) enzyme that usually dissociates the amino acid—tRNA link in case of a misalliance. With the double checks available, misincorporation of amino acids is approximately in the 10^{-4} range. Protein synthesis in the mitochondria and chloroplasts is essentially patterned after the prokaryotic systems.

The 5'-base of the anticodon triplet may not be the exact and conventional base, yet it may function

normally (► [wobble](#)). The two subunits of the ribosomes are combined and the second charged tRNA can now land at the A ribosomal site. The carboxyl end of the methionine forms a peptide bond with the amino terminus of the next incoming amino acid at the A site. This process is mediated by the enzyme peptidyl transferase. For this transferase function a 23S rRNA in the large subunit (a ribozyme) is responsible and not a protein. Again energy donors and elongation protein factors are cooperating in the process of peptide chain growth (► [initiation and elongation factors IF](#), ► [eIF](#), ► [EF](#), ► [EF-T](#), ► [EF-Tu](#)). When each peptide bond is completed the tRNA is released and recycled for another tour of duty. The *open reading frame* of the gene is terminated by a nonsense or chain-termination codon. When the ribosome slides to this point the mRNA is released from the ribosomes with the assistance of release factors (► [transcription termination in eukaryotes](#), ► [transcription termination in prokaryotes](#)). Protein synthesis proceeds at a rather rapid rate; it has been estimated that in *E. coli* 50–200 amino acids may be incorporated into peptides in 5–10 s. The process is slower in eukaryotes (3–8 s) (see Fig. [P153](#)). According to Princiotta MF et al 2003 (Immunity 18:343), the cells of the immune system produce 40 million proteins/min on the 6 million ribosomes.

The ribosomes have an important role in the regulation of protein synthesis. It appears that the availability of active ribosomes is controlled at the level of the transcription of the rRNA genes. In most of the cases, the number of ribosomes is not a limiting factor of translation. Some of the bacterial ribosome proteins have dual roles and participate in transcription and translation (Squires CL, Zaporjets D 2000 Annu Rev Microbiol 54:775). When the supply of ATP and GTP is adequate, rRNA genes are activated for transcription. In case the level of these nucleotide triphosphates is low, rRNA transcription is reduced or halted. Abundance of free ribosomal proteins may feedback-inhibit ribosomal production. The ribosome-associated Rel-A protein may mediate the formation of ppGpp from GTP (and possibly from other nucleotides). Then ppGpp may shut off rRNA and tRNA synthesis by binding to the promoter of RNA polymerase or to its antitermination signal.

Some of the nascent peptides are segregated into the endoplasmic reticulum through the Sec61 conductance opening of the large subunit of the ribosomes. Within the endoplasmic reticulum, the translation continues and the protein is folded by the appropriate chaperones. In prokaryotes, only the completed polypeptide chains are folded whereas in eukaryotes, the separate domains of the large polypeptides are folded as the chain grows.

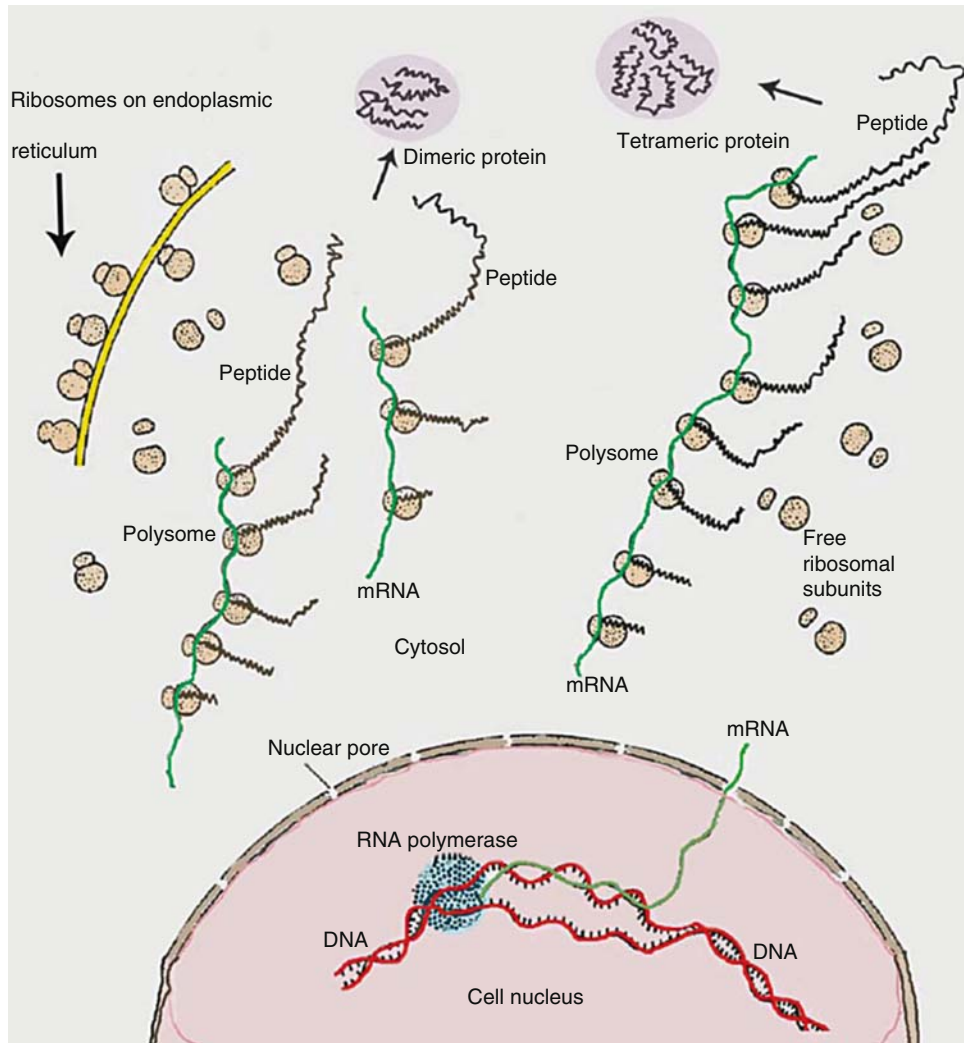


Figure P153. An overview of eukaryotic translation

The dimeric NAC (nascent-polypeptide associated complex) interacts with the emerging polypeptide chains before 30 or fewer residue long chain is formed, and protects the nascent chain from becoming associated with other cytosolic proteins until the signal peptide fully emerges and then the signal recognition particle (SRP) crosslinks to the polypeptide. The purpose of the NAC is to assure that the polypeptide would be oriented to the proper SRP and the endoplasmic reticulum. Alternatively, if the protein does not carry a signal peptide, the nascent chain may be folded by chaperones such as heatshock proteins Hsp40 Hsp70 and TRiC. The completed amino acid sequences, the polypeptides, must be then converted to biologically active forms. This post-translational process may involve trimming (removal of some amino acids), proteolytic cleavage, folding to a tertiary structure, aggregation of different

polypeptide chains to form the quaternary structure, addition of prosthetic groups (such as heme, lipids, metals), and other non-amino-acid residues such as acyl, phosphate, methyl, isoprenyl and sugar groups.

Some proteins are expressed at very low level and by the classical methods of biochemistry or molecular biology the synthesis may not be detectable. A microfluidic device can, however, detect protein expression at the level of a single molecule (Cai L et al 2006 Nature [Lond] 440:358).

►code genetic, ►mRNA, ►tRNA, ►rRNA, ►ribosomes, ►aminoacyl-tRNA synthetase, ►wobble, ►cap, ►Shine-Dalgarno sequence, ►ribosome recycling, ►RNA polymerases, ►transcription factor, ►transcription initiation, ►elongation initiation factors, ►eIF, ►transcription termination, ►rho factor, ►transcription complex, ►signal sequences, ►transit peptide, ►signal peptides, ►regulation of

gene activity, ►antibiotics, ►toxins, ►ambiguity in translation, ►chaperone, ►SRP, ►signaling to translation, ►translation initiation, ►initiation complex, ►polysome, ►introns, ►prenylation, ►TRiC, ►heatshock, ►E site, ►EF-TU•GTP, ►discriminator region, ►protein folding, ►Sec61 complex, ►non-ribosomal peptides, ►tmRNA, ►translation in vitro, ►translation nuclear, ►subcellular localization, ►microfluidics; Sonenberg N et al (Eds.) 2000 *Translational Control of Gene Expression*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Fredrick K, Noller HK 2002 *Mol Cell* 9:1125.

Protein Synthesis, Chemical: Building proteins from peptide domains by non-biological means. The peptides may be synthesized by the methods of organic chemistry and then ligated, spliced and folded in order to assure some specific function. Changing individual amino acids in the sequence may lead to new proteins. This procedure may become cumbersome because aggregation may create problems for proper folding. In contrast, solid phase synthesis is practical and any type of non-natural protein can now be produced using synthetic amino acids and peptides. Chemical synthesis of peptides requires stepwise addition of amino acids on solid support. Unfortunately, with the current technology (2005), routinely the synthetic proteins can be made only of about 40 residues although, e.g., 238-residue precursor of the green fluorescent protein has been made years ago (Nishiuchi Y et al 1998 *Proc Natl Acad Sci USA* 95:13549. [Bradley L et al. 2005 reviewed the principles of the various available peptide ligation techniques in *Annu Rev Biophys Biomol Struct* 34:91]. See Dawson PE, Kent SBH 2000 *Annu Rev Biochem* 69:923; Wei Y et al 2003 *Proc Natl Acad Sci USA* 100:13270).

Protein Synthesis Inhibitors: ►antibiotics, ►toxins, ►interferons

Protein Targeting: Can be co-translational, i.e., newly synthesized proteins are delivered to specific sites (endoplasmic reticulum) in the cell before the chain is completed or post-translational when the transport takes place after the polypeptide is completed. ►signal hypothesis, ►signal sequence recognition particle, ►translocon, ►TRAM, ►protein conducting channel, ►mitosome; Bachert C et al 2001 *Mol Biol Cell* 12:3152; Zaidi SK et al 2001 *J Cell Sci* 114:3093; Takayama S, Reed JC 2001 *Nature Cell Biol* 3:E237.

Protein Trafficking: ►protein sorting

Protein Transduction: The introduction of protein into the blood stream or organs for experimental or

therapeutic purposes. This procedure is usually limited to small size (<600 Da) molecules. When, however, the 120 kDa β -galactosidase was fused to an 11-amino acid NH₂ domain of the Tat protein of HIV and introduced into the intraperitoneal cavity of the mouse, the protein was detected in a biologically active form in several organs including the brain. ►AIDS, ►BBB, ►galactosidase, ►protein targeting; Embury J et al 2001 *Diabetes* 50:1706.

Protein Transport: ►protein sorting

Protein Truncation Test: The test may be used to detect the effects of several mutations that do not permit the completion of a polypeptide chain. The gene is transcribed by using polymerase chain reaction and the RNA is translated in vitro and the polypeptide is analyzed in SDS minigels. ►PCR, ►SDS-polyacrylamide gel, ►rabbit reticulocyte in vitro translation; Lutz S et al 2001 *Nucleic Acids Res* 29:E16.

Protein Tyrosine Kinases (PTK): The phosphorylate tyrosine residues in some proteins. This function is frequently coded for by v-oncogenes of retroviruses but cellular oncogenes and other proteins may be involved and are controlling signal transduction and other cellular processes such as cell proliferation and differentiation. Cytosolic tyrosine kinases preferentially phosphorylate their own SH2 domains or related SH2 domains with hydrophobic amino acids at key positions, e.g., Ile or Val at -1 and Glu, Gly or Ala at the +1 position. Receptor tyrosine kinases prefer Glu at -1 position. These preferences specify their signaling role. The RET oncogene's receptor tyrosine kinase product can shift substrate specificity and thereby cause multiple endocrine neoplasia. Quercetin, genistein, lavendustin A, erbstatin and herbimycin are all natural plant products and inhibitors of these enzymes. ►tyrosine kinase, ►receptor tyrosine kinase, ►protein kinases, ►SH2, ►endocrine neoplasia multiple, ►signal transduction; Hubbard SR, Till JH 2000 *Annu Rev Biochem* 69:373; Blume-Jensen P, Hunter T 2001 *Nature [Lond]* 411:355.

Protein Tyrosine Phosphatase: ►tyrosine phosphatases

Protein X: A hypothetical chaperone facilitator of the PrP^C → PrP^{Sc} conversion in prion diseases. ►prion

Protein Zero: A major part of the nerve cell myelin sheath of vertebrates. Its defect may lead to neurological anomalies.

Proteinase A: An endopeptidase involved in protein folding. ►endopeptidase, ►protein folding

Proteinase K: A proteolytic enzyme, frequently used to remove nucleases during the extraction of DNA and

RNA. With appropriate heat treatment any DNase associated with it can be safely removed. ►protease

Proteinoid: A polymerized mixture of amino acids formed during prebiotic stage of evolution (or simulated conditions in the laboratory). They may resemble primitive cells and display fission like phenomena (see Fig. P154). ►prebiotic



Figure P154. Proteinoid (From S. W. Fox., 1964 BioScience 14(12):13, © Am Inst Biol Sci)

Proteinosis: Anomalous accumulation of protein at particular structures of the body.

Protein-DNA Interaction: Takes place between transcription factors and the DNA template of the RNA. These interactions have been mapped in vivo over the entire mammalian genome (Johnson DS et al 2007 Science 316:1497). ►transcription factors, ►regulation of gene activity

Protein-Protein Interaction: Mediates structural and functional organization of the cells. The knowledge of these processes reveals the essential nature of the biology of organisms. The two-hybrid method may reveal the pair-wise interactions, and by sequential and systematic analysis the interacting systems, the metabolic modules can be identified. ►two-hybrid method, ►microarray hybridization, ►networks, ►gene product interaction, ►networks

Protein-RNA Recognition: Almost all RNA functions involve RNA-protein interactions such as regulation of transcription, translation, processing, turnover, viral transactivation and gene regulatory proteins in general, tRNA aminoacylation, ribosomal proteins, transcription complexes, etc.

Proteobacteria: Gram-negative purple bacteria, putative ancestors of mitochondria. ►NUMTs

Proteoglycan: Heteropolysaccharides with a peptide chain attached through O-glycosidic linkage to a serine or threonine residue. Such molecules are enzymes, animal hormones, structural proteins, basement membranes, cellular lubricants (such as mucin), extracellular matrix proteins and the “antifreeze proteins” of Antarctic fishes. They control plant and animal growth, differentiation, development and signal transduction. The proteoglycan-like xylogen accumulates in the meristem of plants and directs continuous vascular

development (Motoso H et al 2004 Nature [Lond] 429:873). ►antifreeze proteins, ►amyloids, ►glypican, ►syndecan, ►glycosaminoglycan, ►glycoprotein, ►phloeme, ►xyleme; Selleck SB 2000 Trends Genet 16:206.

Proteolipid Protein: A major part of myelin in the brain. ►myelin

Proteolysis: The hydrolyzing peptide bonds of proteins. The tobacco etch virus (TEV) NIa protease recognizes a seven-residue consensus (Glu-X-X-Tyr-X-Gln/Ser) sequence and does not affect proteins not containing it. The protease attached to the ribosomal exit site is most efficient and permits selective cleavage special target proteins (Heinrichs T et al 2005 Proc Natl Acad Sci USA 102:4246). ►proteasome, ►ubiquitin; Ciechanover A 2005 Nature Rev Mol Cell Biol 6:79.

Proteolytic: Enzymes hydrolyze peptide bonds in proteins. ►proteolysis, ►peptide bond, ►peptidase

Proteome: All the cellular proteins encoded by the cellular DNA; it is the protein complement of the genome. In bacteria 10% of the genes encode 50% of the bulk of the protein in eukaryotes ~90% of the proteome is contributed by 10% of the cellular proteins (Humphery-Smith I 2004, p 5 In: Albala JS, Humphery-Smith I (Eds.) Protein Arrays, Biochips, and Proteomics, Marcel Dekker, New York). The genome is very stable (except rare mutations) and it is the same in practically all cells of an organism. The proteome displays variations according to the developmental stage, organs, metabolic rate and health of the organism, etc. Since the proteins are organized and expressed in interacting systems, their study may be very complicated. While the genome does not reveal the detail of the function of a cell(s), proteomics has exactly this goal. The immediate products of the genome, the RNA is frequently processed in more than one way (alternative splicing and combinatorial assembly) to be translated into more than a single type of polypeptide. The translated product can be further modified by trimming, docking, forming multimeric associations, recruitment of ligand, phosphorylation and/or dephosphorylation, acetylation, glycosylation and various other epigenetic mechanisms. Because of alternatives in transcription (using different promoters and processing of the transcripts) there are in general substantially more proteins than genes in the cells. The proteins have also various regulatory roles at the levels of replication, transcription, translation, etc. The amount and kind of RNAs are correlated with the amount of polypeptides yet this correlation is variable. Proteins may undergo substantial post-translational modifications. Although the genome is essentially constant,

the encoded proteins may display great variations during differentiation and development. There are no well-established procedures “fit for all” proteins such as DNA sequencing after cloning, PCR or microarray hybridization. Two-dimensional gel electrophoresis is powerful for the separation of thousands of proteins and monoclonal antibody techniques can be used for the localization of proteins. Although definitive information on the proteome may not come easily it should permit an insight into the function of cells, organisms, evolution and disease that cannot be matched by other means. The size of the human proteome much exceeds that of the number of genes determined by sequencing the genome. The size of the human proteome has been estimated by the formula $N_{\text{CDS}} = f_1 \cdot f_2 \cdot N_{\text{genes}}$ where f_1 is the proportion of non-pseudogenic genes and f_2 is the ratio of the total number of protein-coding transcripts to the total number of genes, including those that are spliced alternatively. The estimates so obtained also vary within a wide range (see Harrison PM et al 2002 Nucleic Acids Res 30:1083). ►genome, ►genomics, ►metabolic pathway, ►transcriptome, ►monoclonal antibody, ►two-dimensional gel electrophoresis, ►two-hybrid method, ►protein chips, ►MALDI/TOF/MS, ►electrospray, ►ICAT, ►ACESIMS, ►MS/MS, ►microarray hybridization, ►networks, ►genetic network, ►TOGA, ►core proteome; protein–protein interaction: HUPO: <http://www.hupo.org>; ►Uniporter; <http://www.expasy.ch>; <https://www.proteome.com/proteome/>; <http://us.expasy.org>; human proteome: <http://www.hprd.org/>; mass spectrometric characterization of peptide fragments: <http://nwsr.bms.umist.ac.uk/cgi-bin/pepseeker/pepseek.pl?Peptide=1>; mass spectrum of body proteome: <http://www.mapuproteome.com>; ►protein, ►genomic sequences, ►exon structure, ►polarity, ►hydrophobicity; Ito T et al 2001 Proc Natl Acad Sci USA 98:4569; Walhaut AJM, Vidal M 2001 Nature Rev Mol Cell Biol 2:55; Harrison PM et al 2002 Nucleic Acids Res 30:1083; Auerbach D et al 2002 Proteomics 2:611; Burley SK, Bonnano JB 2002 Annu Rev Genomics Hum Genet 3:243; Rost B 2002 Curr Opin Struct Biol 12:409.

Proteomic Profiling: Uses chemical labels for the identification of active groups of enzymes in complex mixtures and attempts the identification of the functional role of these groups of proteins. The procedure may reveal the role of protein arrays in the development of disease and may suggest targets for intervention. (See Adam GC et al 2002 Nature Biotechnol 20:805).

Proteomics: The study of the system of the proteome, the modules of metabolism as they carry out cellular functions of the organisms. The new technologies

detect the composition/structure of proteins, isoforms, conformational changes, modulatory alterations during development, post-transcriptional and post-translational modifications (phosphorylation, glycosylation), interactions with other proteins or drugs, etc. With low mass tolerance, e.g., 10 ppm single proteins can be identified in a mixture among thousands of molecules. Proteomics has modified the basic approach to investigating biological function. Earlier the experimental design was based on hypotheses. With the aid of the proteomics technologies more direct approaches are possible based on the simultaneous expression patterns of interacting genetic networks. *Expression Proteomics* analyses proteins of the cells by two-dimensional gel electrophoresis (Wagner K et al 2002 Anal Chem 74:809). *Cell-Map Proteomics* is interested in the interaction between/among proteins at various phases of the cell function (Blackstock WP, Weir MP 1999 Trends Biotechnol 17(3):121). *Functional Proteomics* targets specific functions rather than the entire proteome (Graves PR, Haystead TA 2002 Microbiol Mol Biol Rev 66:39). *Structural Proteomics* seeks understanding of protein function on the basis of three-dimensional analysis and modeling (Norin M, Sundstrom M 2002 Trends Biotechnol 20:79; Sali A et al 2003 Nature [Lond] 422:216). *Reverse Proteomics* starts with the genes and proceeds to proteins. Liquid chromatography, two-dimensional polyacrylamide gel electrophoresis and tandem mass spectrometry are important tools of proteomics at large scale. Proteomics is concerned not only with the variability and interactions of proteins but may assist in modifying proteins for new types of interactions. The α -carboxyl group and preceding residues at the C-end of polypeptides may offer a useful target for modifications. The PDZ and TPR domains are well qualified for interactions with the C-termini and may facilitate temporal and spatial interactions, degradation, neuronal signaling and other functions (Chung JJ et al 2002 Trends Cell Biol 12:146). The proteome data are expected to be much more complex than that of the genome sequences. The number of proteins and their isoforms far exceeds that of the number of genes. There is a need to develop computer programs that can properly assist in interpreting the “mountain” of information. One of the most complete sources of information on the *E. coli* metabolic system is at: <http://ecocyc.org/>. The increasing amount of information is fast becoming impossible to integrate for a single human mind and advanced computer models are indispensable. Now proteomic information has important impact of applied biology such as medicine, drug development and agriculture. In painted artwork protein (egg white) has been used since the fourteenth century and before then as

binding material. These old paintings now need restoration and for doing the best work, it is necessary to determine in a minimally invasive way the material the artists used. Modern proteomics technology can reveal the nature of the binder used in Renaissance paintings in ~10 µg samples (Tokarski C et al 2006 Anal Chem 78:1494). ▶proteome, ▶PFAM, ▶Atlas human cDNA, ▶genomics, ▶annotation, ▶MALDI, ▶HMS-PCI, ▶TAP, ▶PDZ domain, ▶TPR, ▶peptide mass fingerprints, ▶NMR, ▶post-translational modification, ▶quadrupole, ▶LC-MS, ▶FTMS, ▶MS/MS, ▶ion trap mass analyzer, ▶linear ion trap analyzer, ▶two-dimensional gel electrophoresis, ▶two-hybrid system, ▶protein chips, ▶protein microarray, ▶X-ray crystallography, ▶genetic networks, ▶networks, ▶gene product interaction, ▶nucleolomics, ▶laser-capture microdissection, ▶MCA, ▶mass-coded abundance tagging, ▶display technologies, ▶MudPIT, ▶PEDRO, ▶protein engineering, ▶semisynthesis of proteins, ▶bioinformatics, ▶International Protein Index; Washburn MP et al 2001 Nature Biotechnol 19:242; Mann M et al 2001 Annu Rev Biochem 70:437; MOWSE 2001 Trends Biotechnol 19(10):Suppl; Fraunfelder H 2002 Proc Natl Acad Sci USA 99(Suppl 1):2479; Altman RB, Klein TE 2002 Annu Rev Pharmacol Toxicol 42:113; Regnier FE et al 2002 J Mass Spectrom 37:133; Laurell T, Mako-Varga G 2002 Proteomics 2:345; Auerbach D et al 2002 Proteomics 2:611; Petricoin EF et al 2002 Nature Rev Drug Discov 1:683; Huber LA 2003 Nature Rev Mol Cell Biol 4:74; Patterson SD, Aebersold RH 2003 Nature Genet 33 (Suppl):311; analytical methods: Phizicky E et al 2003 Nature [Lond] 422:208; Zhu H et al 2003 Annu Rev Biochem 72:783; de Hoog CL, Mann M 2004 Annu Rev Genomics Hum Genet 5:267; mass spectrometry methods: Domon B, Aebersold R 2006 Science 312:212; <http://www.ebi.ac.uk/interpro>; <http://dip.doe-mbi.ucla.edu/>; Proteomics Identification Database: www.ebi.ac.uk/pride/.

Proterozoic (precambrian): The geological period five billion to 570 million years ago. Aquatic forms of living systems appeared during this era. ▶geological time periods

ProtEST: A bioinformatics program tool for protein alignments. ▶UniGene; Wasmuth JD, Blaxter ML 2004 BMC Bioinformatics 5:187.

Proteus Syndrome: Involves gigantism of parts of the body probably caused by lipomatosis (abnormally large local fat accumulation). The genetic control is unclear. ▶PTEN; Cohen MM Jr 1993 Am J Med Genet 47:645.

Prothallium: The haploid gametophyte generation of ferns.

Prothrombin Deficiency: Caused by autosomal recessive, semidominant defects in the formation of anticoagulation factor VII, Stuart factor, Christmas factor and prothrombin. The human gene for prothrombin was assigned to chromosome sites 11p11-q12. Prothrombin is normally generated in sequential reactions by prothrombinase (Bianchini EP et al 2005 Proc Natl Acad Sci USA 102:10099). These proteins have similar proteolytic properties and the synthesis of all four depends on the presence of vitamin K. The patients have a tendency of bleeding similarly to hemophiliacs. Hereditary deficiency of factor VII itself is rare but it may be fatal if bleeding affects the central nervous system. Stuart factor deficiency has symptoms similar to those in deficiency of factor VII. All of these conditions can be treated by transfusion with blood plasma. ▶antihemophilia factors, ▶hemophilia, ▶vitamin K dependence, ▶coumarin-like drug resistance

Protist: A general term for single-cell eukaryotic organisms. The *Monera* including bacteria, blue green algae, viruses are also sometimes called protists although these are prokaryotes.

Protocell: Abiotic ancestor of living cells under prebiotic conditions. ▶origin of life

Protochlorophyll: The precursor of chlorophyll ($C_{55}H_{70}O_5N_4Mg$); if the magnesium is removed protophaeophytin results. The NADPH:protochlorophyllide oxidoreductases in the prolamellar body of the etioplast are required for the establishment of the photosynthetic apparatus (deetiolation) and for photoprotection in plants. ▶chloroplast, ▶etioplast, ▶NADP, ▶photomorphogenesis, ▶photosynthesis; Reinbothe S et al 2003 J Biol Chem 278:800.

Protogyny: In monoecious plants, the stigma is receptive before the pollen is shed. ▶protandry, ▶monoecious, ▶stigma, ▶self-incompatibility

Protomer: A polypeptide subunit of an oligomeric protein encoded by a cistron of a gene. ▶cistron, ▶oligomer

Proton: The positive nucleus of the hydrogen atom. The proton carries a positive charge equal to the negative charge of an electron but its mass is 1837 times larger.

Proton Acceptor: An anion capable of accepting protons. ▶anion, ▶proton

Proton Donor: An acid

Proton Pump: Mediates transport or exchange of protons across cellular membranes; energy is supplied usually by ATP or light. ▶proton, ▶ion pumps; Ferreira T et al 2001 J Biol Chem 276:29613.

Protonema: A filamentous stage in the formation of the gametophyte of mosses.

Protonoma: A red-color insensitive color blindness; an X-chromosomal anomaly. ▶color blindness

Proto-Oncogenes: These are cellular c-oncogenes, which after genetic alteration(s) may initiate or predispose to cancerous transformation. They generally have their counterparts in oncogenic viruses (v-oncogenes). Also, they may be involved in processes of signal transduction in a variety of organisms in fungi, plants and animals. ▶oncogenes, ▶signal transduction, ▶carcinogenesis, ▶tumor suppressors, ▶cell cycle

Protoperithecium: ▶ascogonia, ▶perithecium

Protoplasia: Formation of a new tissue.

Protoplasm: The viscous “live” content of the eukaryotic cell. ▶cytoplasm

Protoplast: A cell surrounded by the cell membrane but stripped of the cell wall, generally by a combination of pectin and cellulose digesting enzymes. Protoplasts under appropriate conditions may be regenerated into normal cells and intact plants (see Fig. P155). The bacterial protoplasts are generally called spheroplasts and may have some parts of the cell wall still attached. ▶cellulase, ▶macerozyme, ▶pectinase

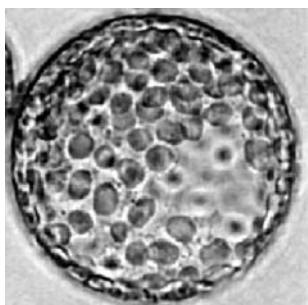


Figure P155. Plant protoplast (Durand J et al 1973 Z. Pflanzenphys. 69:26)

Protoplast Fusion: Protoplasts may fuse in the presence of polyethylene glycol (and some other agents). The fusion may take place within sister cells or with the cells (protoplasts) of any taxonomically distant organisms such as mammalian and plant cells (see Fig. P156). These somatic hybrids, unlike the zygotes derived from the fusion of eggs and sperm, contain all the contents of the two cells, nuclei and cytoplasm, although some cytoplasmic organelles may be lost eventually.

In certain rodent-human cell hybrids even the human chromosomes may be eliminated; similar observations are available for carrot and parsley cell hybrids. When the genetic differences between the

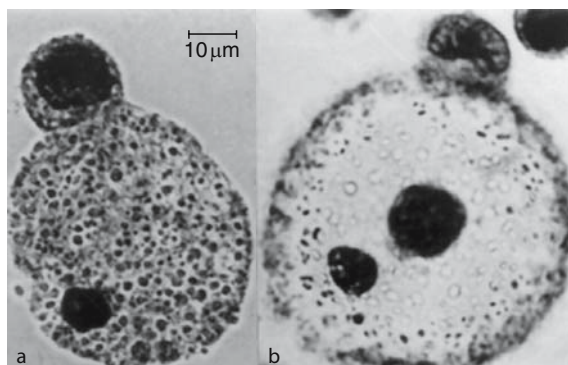


Figure P156. Human HeLa cells attached to tobacco protoplast (a), the HeLa nucleus (larger) inside the tobacco cell (b). (From Jones CW et al Science 193:401)

fused protoplasts is large, the fused cells may not divide or may not divide continuously. Somatic hybrids between related species may, however, behave like allopolyploids and form fertile or sterile hybrids after regeneration. Fusion of animal cells with bacterial spheroplasts is shown in Figure P157. ▶cell fusion, ▶polyethylene glycol

Protoporphyria, Erythropoietic: An autosomal (human chromosome 18q21.3) dominant (or recessive) disease involving light-sensitive itching, inflammation of the skin. The porphyrin level of the blood may increase by over 16-fold, to 1 g/100 mL. The excess protoporphyrin is deposited in the liver, causing potentially serious damage. The basic defect probably involves a deficiency (10 to 25%) of the mitochondrially located ferrochelatase (FECH). ▶light-sensitivity defects, ▶mitochondrial disease in humans, ▶porphyria; Todd DJ 1994 Brit J Derm 131:751.

Protoporphyrin: The organic part of heme consisting of four pyrroles joined by methylene bridges. ▶heme

Protosilencer: On its own, it is incapable of silencing gene(s) or its silencing effect is minimal but it can reinforce and maintain the function of silencers. ▶silencers

Protosplice Site: Evolutionarily, the original splice site which is frequently AAG/CAG|GT where | is the insertion site. ▶splicing

Protostome: Organisms that develop the mouth from the blastopore such as annelids, molluscs, arthropods. ▶blastopore

Prototroph: A genotype that has wild type nutritional requirement. ▶autotroph, ▶auxotroph

Protozoa: Unicellular animals, mainly free-living (such as the *Paramecia*) some are, however, parasitic

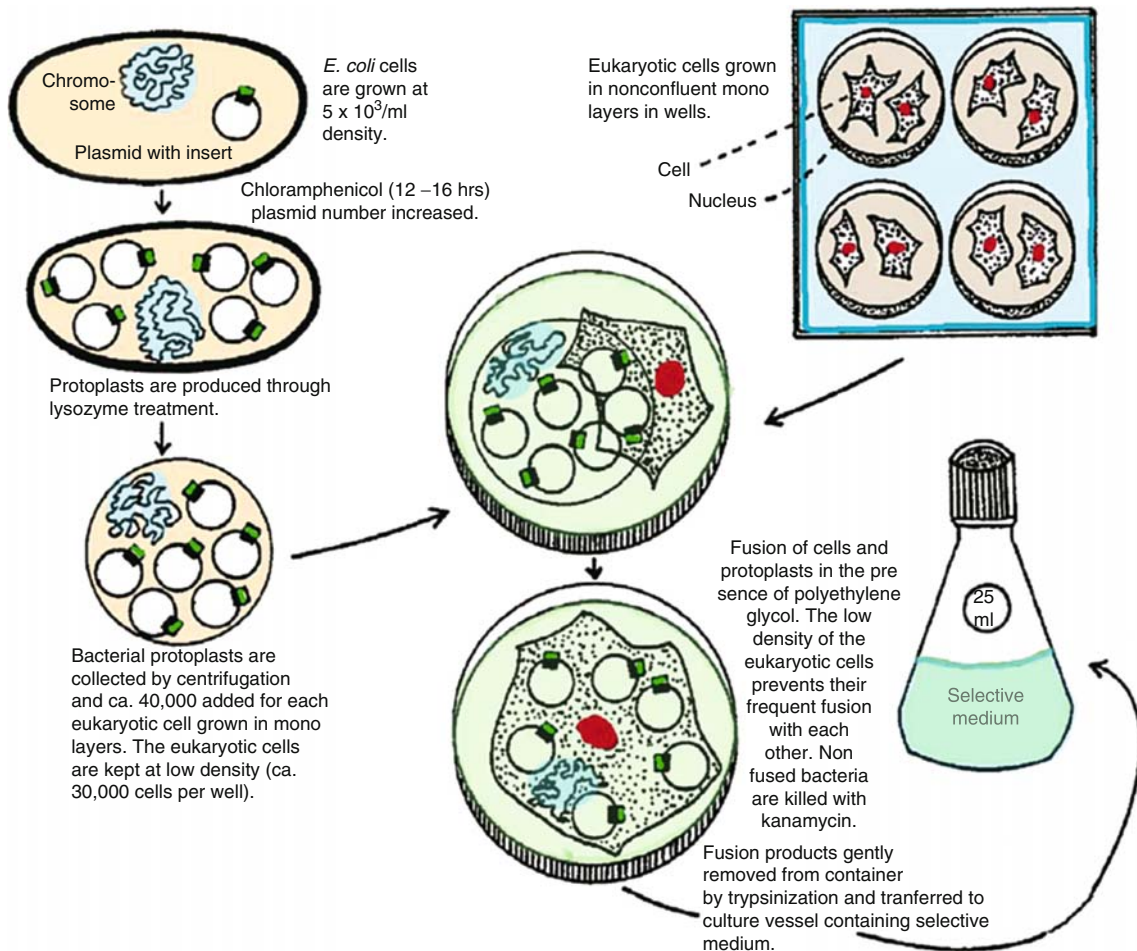


Figure P157. Transformation of mammalian cells by fusion to bacterial spheroplasts. (Modified after Sandri-Goldin, RM et al 1983 *Methods Enzymol* 101:402)

(such as the *Giardias* which frequently contaminate drinking water sources), the *Trypanosomas* and *Leishmanias* which cause potentially lethal infections in animals and humans. ▶*Trypanosoma*, ▶*Leishmania*; for the genetic nomenclature of *Tetrahymena* and *Paramecia* see *Genetics* 149:459; micro- and macronuclear genes: <http://oxytricha.princeton.edu/dimorphism/database.htm>.

Provenance/Provenience: The origin of a genetic stock.
▶*accession*

Provirus: A DNA sequence in the eukaryotic chromosomal DNA that is a reverse transcriptase product of a retroviral RNA. ▶*retroviruses*, ▶*reverse transcription*, ▶*prophage*

Proximal: Situated in the vicinity of a reference point; e.g., a gene near the centromere is proximal, versus another that is in the direction of the telomere, and thus called distal. In conjugational transfer of bacteria

the marker that is transferred before another is the proximal. ▶*centromere*, ▶*telomere*, ▶*conjugation mapping*

Proximal Mutagen: A chemical that has been activated into a mutagenic substance; it may not have reached yet its most reactive state. ▶*promutagen*, ▶*activation of mutagens*, ▶*ultimate mutagen*, ▶*chemical mutagens*, ▶*activation of mutagens*

Proximity Ligation: A protein analysis technique using specific DNA sequences, which bind specific proteins. Sensitivity is much enhanced when polyclonal or monoclonal antibodies are used in connection with oligonucleotide extensions brought in the proximity of the target. ▶*antibody*; Gullberg M et al 2004 *Proc Natl Acad Sci USA* 101:8420.

PRP: An RNA-splicing factor component of the U snRNP complex. ▶*splicing*

PrP (protease resistant protein): ▶*prion*

Prp73: A mammalian chaperon binding to the first 20 residues (S peptide) of ribonuclease A and stimulates the uptake of polypeptides by lysosomes. ▶[ribonuclease A](#), ▶[Hsp70](#), ▶[lysosome](#)

Prp20p: The yeast homolog of RCC1. ▶[RCC](#)

PrPres (PrP^{*}): A partially protease resistant aggregate of PrP^C and PrP^{SC}. ▶[prion](#)

PrP-SEN: The general name of the protease-sensitive prion protein. ▶[prion](#)

PRR: Post-replication repair. ▶[DNA repair](#)

PRR: Positive regulatory region. ▶[negative regulation](#), ▶[Arabinose operon](#)

PRR: Pathogen recognition receptor.

PRTF: Pheromone receptor transcription factors, co-operating with GRM (general regulator mating factor) in the determination of mating type. ▶[pheromone](#), ▶[mating type determination in yeast](#), ▶*Schizosaccharomyces pombe*; Tan S, Richmond TJ 1990 Cell 62:367.

Przewalsky Horse: The Mongolian wild horse but can be found (~1200) only in captivity, although its reintroduction into the wild in Mongolia and China is underway. All existing individuals have descended from the 13 animals captured about a century ago. Its chromosome number is $2n = 66$ yet it makes viable hybrids with the domesticated species. ▶[horse](#)

PSA (prostate-specific antigen): A M_r 33,000 kallikrein type protease glycoprotein (APS) encoded at human chromosome 19q13. High levels of this protein in the serum may be an indication of prostatic carcinoma. The level of PSA varies a great deal and it is high after ejaculation and may provide false positive indication of cancer. It may serve as a target for cancer gene therapy. The six-transmembrane epithelial antigen of the prostate (STEAP, 7p22.3) is also elevated in prostate cancer. Hepsin (transmembrane serine protease) and pim-1 (serine/threonine kinase) levels are strongly correlated with prostate cancer as detected by tissue microarray analysis. The prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer cells and in other solid tumors. It is a glutamate carboxypeptidase and cuts methotrexate and the neuropeptide *N*-acetyl-L-aspartyl-L-glutamate; its crystal structure may facilitate drug development (Davis MI et al 2005 Proc Natl Acad Sci USA 102:5981). ▶[prostate cancer](#), ▶[cancer gene therapy](#), ▶[tissue microarray](#); Berry MJ 2001 N Engl J Med 344:1373; Dhanasekara S et al 2001 Nature [Lond] 412:822.

PSD-95: A family of membrane associated guanyl kinases; they also anchor K⁺ channels by their PDZ domains. ▶[ion channels](#), ▶[GTP](#)

PSE: Proximal sequence element. ▶[Hogness box](#)

PSE: Pale soft exudative meat is controlled in pigs by the *Halothane* gene.

Pseudoachondroplasia: A dominant human-chromosome 19p12-p13.1 gene mutation controlling the cartilage oligomeric matrix protein (COMP), and it is responsible for short stature (see Fig. P158). ▶[achondroplasia](#), ▶[multiple epiphyseal dysplasia](#), ▶[COMP](#); Hecht JT et al 1995 Nature Genet 10:325; Briggs MD, Chapman KL 2002 Hum Mut 19:465.

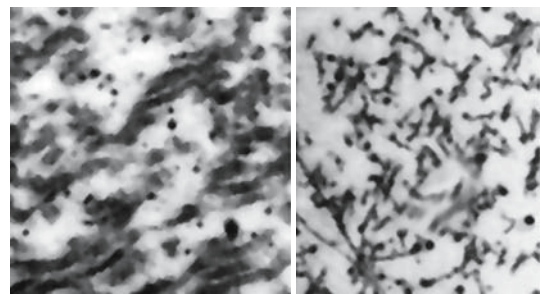


Figure P158. Left: Pseudoachondroplasia, Right: Normal extracellular cartilage matrix

Pseudoaldosteronism (Liddle syndrome): A human chromosome 4 hypertension associated with hypoaldosteronism, hypokalemia, reduced renin and angiotensin. ▶[aldosteronism](#), ▶[hypokalemia](#), ▶[renin](#), ▶[angiotensin](#)

Pseudoalleles: A cluster of not fully complementing genes, separable by recombination. Pseudoalleles, e.g., a^1 and a^2 when heterozygous in trans position $a^1 a^+ // a^+ a^2$ show mutant phenotype whereas in cis position $a^1 a^2 // a^+ a^+$ are complementary (wild type), except when dominant alleles are involved. Since these alleles are closely linked, in order to be able to prove that recombination takes place (rather than mutation), the pseudoalleles must be genetically marked by flanking genes within preferably less than 10 m.u. apart of the locus. ▶[complex locus](#), ▶[step allelomorphism](#), ▶[morphogenesis in Drosophila](#), ▶[cis-trans test](#), ▶[SSNC](#); Carlson EA 1959 Quart Rev Biol 34:33.

Pseudoaneuploid: The chromosome number appears aneuploid but it is not truly the case only, centromere fusion or misdivision of the centromeres have caused the changes in numbers. ▶[Robertsonian translocation](#), ▶[misdivision](#), ▶[B chromosomes](#)

Pseudoautosomal (PAR): Genes located in both telomeric regions of the X and Y chromosomes (~2.6 Mbp at the short arm [PAR1] and a similar PAR2 site in the long arm in the human genome) where recombination can take place and consequently, despite the sex-chromosomal location, sex-linkage is not obvious. A gene for schizophrenia was suggested to be pseudoautosomal. *SYBL1*, encoding a synaptobrevin-like protein is present in both X and Y chromosomal PAR regions and it displays lyonization in the X-chromosome and inactivation in the Y. The pseudoautosomal boundary is apparently spanned by one or another (depending on the species) 5'- or 3'-truncated gene. The short stature gene (*SHOX1/SHOXY*), the Leri-Weill dyschondrosteosis and a Hodgkin disease gene are all located in the PAR at Xpter-p22.32. The *SHOX2* gene is at 3q25-q26.

All human and chicken homologues of the snake Z-linked genes were located on autosomes, suggesting that the sex chromosomes of snakes, mammals, and birds were all derived from different autosomal pairs of the common ancestor (Matsubara K et al 2006 Proc Natl Acad Sci USA 103:18190). ▶ [auto-some](#), ▶ [sex determinations](#), ▶ [differential segment](#), ▶ [holandric genes](#), ▶ [syntagmin](#), ▶ [lyonization](#), ▶ [IL-9](#), ▶ [Hodgkin disease](#), ▶ [short syndrome](#); Ciccodicola A et al 2000 Hum Mol Genet 9:395; Cormier-Daire V et al 1999 Acta Paediatr 88 (Suppl):55.

Pseudobivalent: The chromosomes associated are not homologous. ▶ [synapsis](#), ▶ [illegitimate pairing](#)

P

Pseudoborder: DNA sequences in certain agrobacterial vectors or within the cloned foreign DNA and may cause deletions and rearrangements within the T-DNA inserts in the transgenic plants. ▶ [T-DNA](#), ▶ [transformation genetic](#)

Pseudocentromeric: ▶ [supernumerary marker chromosome](#)

Pseudocholinesterase Deficiency (CH1, BCHE): A dominant (human chromosome 3q26.1-q26.2) breathing difficulty (apnea) after treated with the muscle relaxant succinylmethonium (succinylcholine chloride), a drug used for intubation, endoscopy, cesarean section, etc., as an adjuvant to anesthesia. Several allelic forms respond differently to drugs. Individuals with a defective enzyme may be particularly sensitive to cholinesterase inhibitor insecticides (parathion). The frequency of the gene varies a great deal in different populations. In Eskimos, the frequency of the gene controlling the deficiency may be higher than 0.1; in other populations it may be less than 0.0002. The BCHE2 form was assigned to 2q33-35 and the same enzyme was suggested to 16p11-q23.

Pseudodiploidy: Retroviral particles because after infection only a single provirus is detected in the host. Normally retroviruses carry two RNA genomes associated by base pairing at several sites, particularly at the 5' end. It is assumed that the two copies are maintained for the purpose of assured survival and possible repair by recombination. They also contain tRNAs that prime replication. Other RNAs (5S, 7S and cellular mRNA fragments) may also be included.

▶ [retroviruses](#)

Pseudodominance: When a heterozygote loses the dominant allele, the recessive allele is uncovered (expressed) because of the lack of the dominant allele. Treating heterozygotes with mutagens (e.g., ionizing radiation) that cause deletions can readily induce pseudodominance. Before such experiments are conducted, it is advisable to place flanking genetic markers to the chromosome carrying the recessive markers to be able to rule out recombination and reversions. Segregation after somatic recombination may be a common cause of pseudo-dominance. Loss of heterozygosity is a frequent cause of oncogenic transformation. Pseudodominance-like phenomenon occurs in a population when the mating is between some cryptic heterozygotes. ▶ [deletion](#), ▶ [LOH](#), ▶ [segregation](#), ▶ [oncogenic transformation](#), ▶ [mitotic crossing over](#)

Pseudoextinction: The disappearance of a species by evolution into another form.

Pseudogamy: Apomictic or parthenogenetic reproduction. ▶ [apomixis](#), ▶ [parthenogenesis](#)

Pseudogene: Has substantial homology with (clustered) functional genes of eukaryotes but it is inactive because of numerous mutations that prevent its full expression and may no longer be available for transcription. Some pseudogenes are transcribed but the transcript is degraded by nonsense-mediated mRNA decay (Mitrovich QM, Anderson P 2005 Current Biol 15:963). Of the 201 pseudogenes identified by the 2007 ENCODE project, 20% were found to be transcribed (Zheng D et al 2007 Genome Res 17:839). Although pseudogenes may not have a protein product they may regulate the expression of their normal homolog either by stabilizing the normal transcript by blocking an RNase or by competitively inhibiting a transcriptional repressor (Hirotune S et al 2003 Nature [Lond] 423:91). The number of pseudogenes is variable in different species. The human genome may contain 20,000 pseudogenes. Organisms with small genomes (e.g., *Drosophila*) have very few and it appears that some organisms eliminated from their genome the DNA sequences that are no longer functional. Pseudogenes may make difficult the estimation of the number of

genes on the basis of incomplete sequences and lack of functional information. Pseudogenes originated either from duplication or in case of processed pseudogenes (without intron) by reverse transcription. Their nucleotide sequence is rather well conserved indicating functional significance. Paired-end diTAG (PET) analysis may permit their detection (Ruan Y et al 2007 Genome Res 17:828). ►C-value paradox, ►gene relic, ►processed pseudogene, ►duplications, ►mRNA surveillance, ►paired-end diTAG; Harrison PM et al 2001 Nucleic Acids Res 29:818; Avise JC 2001 Science 294:86; Echols N et al 2002 Nucleic Acids Res 30:2515; Balakirev ES, Ayala FJ 2003 Annu Rev Genet 37:123; human pseudogenes-gene conversion targets: <http://genome.uiowa.edu/pseudogenes/>.

Pseudohairpin: The overall structure is folded back yet there is not full complementarity along the strands (see Fig. P159).

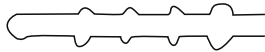


Figure P159. Pseudohairpin

Pseudohemophilia: A bleeding disease, distinct from hemophilia; it is caused by some abnormalities of the platelets. ►hemophilia, ►platelet anomalies, ►hemostasis

Pseudohermaphroditism: ►hermaphrodite

Pseudohermaphroditism, Male: It is determined by a gene in human chromosome 17q12-q21. It is responsible for the deficiency of 17-ketosteroid reductase/17-β-hydroxysteroid dehydrogenase and consequently for feminization in prepubertal males and gynecomastia and virilization after puberty when usually the enzyme is expressed. The affected individuals may be surgically assisted to develop into sterile female phenotype (by removal of the hidden testes) or into male phenotype by reconfiguration of the external male genitalia. Infertility, however, cannot be corrected. Recessive mutations in the luteinizing hormone receptor gene (LHB, 19q13.32) may also be responsible. The condition may be due to deficiency of steroid 5-α-reductase (SRD5A2, 2p23). The SRDA1 isozyme encoded at 5p15 does not appear to be involved in this disorder. The afflicted XY individuals may have blind vagina and a rudimentary hypospadiac penis but no gynecomastia. They may produce viable sperm although they may sire offspring only by intrauterine insemination because of underdeveloped prostate and seminal vesicles. Several defects in steroid biosynthesis may cause male pseudohermaphroditism. The 17,20 desmolase deficiency is most likely X-chromosome linked. Lipoid adrenal hyperplasia

(8p11.2) responsible for complex defects in cortisol or aldosterone may cause even life-threatening conditions. Luteinizing hormone/choriogonadotropin receptor (LHCCGR, 2p21) may cause abnormalities of the Leydig cell differentiation in XY and possibly in XX individuals. Methemoglobinemia and deficiency of cytochrome b5 (18q23) may also cause pseudohermaphroditism. ►gynecomastia, ►polycystic ovarian cancer, ►hermaphroditism, ►infertility, ►testicular feminization, ►luteinization, ►Müllerian ducts, ►anti-Müllerian hormone, ►Reifenstein syndrome, ►hypospadias, ►Wilms tumor, ►adrenal hyperplasia, ►adrenal hypoplasia, ►androgen-insensitivity, ►methemoglobin, ►cytochromes

Pseudohitchhiking: Adaptive mutations near neutral loci may simulate genetic drift. ►hitchhiking

Pseudohomothallism: In the fungus (e.g., *Podospira anserina*) binucleate ascospores are formed and each spore contains both mating types and is thus self-fertile. ►homothallism, ►heterothallism

Pseudo-Hurler Syndrome: ►mucopolipidosis

Pseudohypha (in *Saccharomyces cerevisiae*): The formation occurs by deficiency of nutrient (N) and may cause polarized growth on the surface of the agar medium favoring delay in mitosis and precocious entry into meiosis. The pseudohyphal growth is symmetric and synchronous in comparison to the regular budding that is asymmetric and asynchronous. Cyclins 1 and 2 promote pseudohyphal growth whereas cyclin 3 is inhibitory in yeast. Alternative controls exist. Protein Ste12, the MAP kinase signal transduction pathways also regulate hyphal growth. Filamentous growth is a requisite for pathogenicity of *Ustilago maydis* and *Candida albicans*. ►cyclin, ►CDK, ►*Ustilago maydis*, ►candidiasis, ►MAP, ►Ste

Pseudohypoadosteronism (PHA; 1q31-q42, 17p11-q21, 12p13, 16p13-p12): hyperkalemic, hyperchloremic acidosis and hypertension. The genes at chromosomes 17 and 1 encode a threonine/serine kinase, WNK4, localized in the tight junctions. The disease in this protein is due to missense mutations. Mutations in WNK4 in mice cause higher blood pressure, hyperkalemia, hypercalciuria and marked hyperplasia of the distal convoluted tubule (DCT). WNT4 (chromosome 17) regulates the balance between NaCl reabsorption and K⁺ secretion (Laloti MD et al 2006 Nature Genet 38:1124) by altering the mass and function of the DCT through its effect on NCC (Na/Cl co-transporter). In chromosome 12 the cytoplasmic WNK1 is encoded and the defect is due to large intronic deletions that boost the expression of the protein. Both of these proteins are in the distal

nephron (a basic morphological and functional unit of the kidney) that is responsible for potassium and pH homeostasis. These two anomalies are dominant. The recessive PHA in chromosome 16 encodes subunits of an epithelial Na^+ ion channel. ▶aldosteronism, ▶Gordon syndrome, ▶hypoadosteronism, ▶hyperkalemic, ▶hypertension, ▶intron, ▶ion channels; Wilson FH et al 2001 Science 293:1107.

Pseudohypoparathyroidism: ▶Albright hereditary osteodystrophy

Pseudoknot: Formed when a stem-and-loop RNA structure is bound at the base of the loop by hydrogen bonds or by a ligand resulting in a two-stem two-loop stacking (see Fig. P160). The actual configurations of the pseudoknots may vary. Pseudo-half-knots form only a single loop. Such structures may modulate RNA functions and can be exploited also in designing highly selective drugs. Some insect RNA viruses, which use CAA (glutamine) rather than AUG (methionine) for translation initiation do not require an initiator tRNA but apparently rely on a pseudoknot formed between a 15–43 nucleotide upstream loop and the sequence immediately preceding the CAA codon. Pseudoknot structure is highly conserved in telomerases. Mutations that disrupt the pseudoknot helix abolished telomerase activity whereas intraloop hairpin base-pairing did not reduce telomerase activity (Chen J-L, Greider CW 2005 Proc Natl Acad Sci USA 102:8080). Pseudoknots initiate translational frame-shifting in overlapping genes. The Pseudoknot Local Motif Model and Dynamic Partner Sequence Stacking (PLMM_DPSS) algorithm, which predicts all PLM model pseudoknots within an RNA sequence in a neighboring-region-interference-free fashion. The PLM model is derived from the existing Pseudobase (collection of pseudoknots) entries and it is most sensitive. The innovative DPSS approach calculates the optimally lowest stacking energy between two partner sequences (Huang X, Ali H 2007 Nucleic Acids Res 35:656). ▶repeat inverted, ▶antisense RNA, ▶overlapping genes, ▶TFO, ▶telomerase, ▶frame-shifting ribosomal; Kim Y-G et al 1999 Proc Natl Acad Sci USA 96:14234; Xayaphoummine A et al 2003 Proc

Natl Acad Sci USA 100:15310; pseudoknot folding: <http://bibiserv.techfak.uni-bielefeld.de/pknotsrg/>.

Pseudolinkage: The linkage due to translocation between non-homologous chromosomes. ▶affinity

Pseudolysogen: Lyses the bacterial cells so slowly as if it would be lysogenic. ▶lysogeny

Pseudomonas: *Pseudomonas* bacteria include several species that degrade oil spills, polycyclic hydrocarbons, benzene and other pollutants. ▶oil spills, ▶biodegradation; Coates JD et al 2001 Nature [Lond] 411:1039.

***Pseudomonas aeruginosa*:** A 6.3 million-bp bacterium and an opportunistic human parasite. It is the most common cause of death in cystic fibrosis but it is involved in some pneumonias and other infections (urinary tract, burn victims, etc.). It grows also on soil and plant and animal tissues. This Gram-negative bacterium is highly resistant to antibiotics and disinfectants. Close to 10% of its genes is regulatory and the large number of its putative pump proteins explains its resistance to drugs. ▶cystic fibrosis; Stover CK 2000 Nature [Lond] 407:959; genome, annotations: <http://www.pseudomonas.com/>; <http://www.systomonas.de>.

***Pseudomonas* Exotoxin:** Kills by irreversible ribosylation of ADP and subsequent inactivation of translation elongation factor, EF-2. Its applied significance is the potential for cancer therapy. ▶toxins

***Pseudomonas syringae*:** A plant pathogenic relative of *P. aeruginosa*. The 6.5 megabase sequenced genome includes a circular chromosome plus two plasmids including 5763 open reading frames of which 298 are putative virulence genes. This bacterium may promote secondary infection by the same pathogen rather than display a hypersensitive response in the host by a jasmonic acid structural mimic (coronatine). It can increase susceptibility also to herbivorous insects without relying on coronatine (Cui J et al 2005 Proc Natl Acad Sci USA 102:1791). Related *Pseudomonas* subspecies, distinguished by host-specificity, display differences in genes of antibiotic resistance, DNA repair and ectoin ([4S]-2-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylacid), a natural protective agent against external harmful effects (Feil H et al 2005 Proc Natl Acad Sci USA 102: 11064). ▶ORF, ▶host–pathogen relation; Buell CR et al 2003 Proc Nat Acad Sci USA 100:10181.

***Pseudomonas tabaci*:** A bacteria causing “wildfire” disease (necrotic spots) on tobacco leaves (see Fig. P161). The symptoms may be mimicked by methionine sulfoximine, a methionine analog.

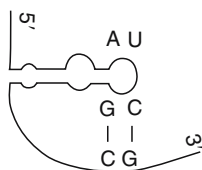


Figure P160. Pseudoknot



Figure P161. Wildfire disease spots (Courtesy of Dr. Peter. Carlson)

Pseudomosaic: May occur in a sample of amniocentesis caused by the conditions of culture rather than the genetic/chromosomal condition of the fetus.

Pseudo-Overdominance: Certain phenotype(s) may appear in excess of expectation in a population because of the close linkage of the responsible gene to advantageous alleles. Also QTL loci may appear overdominant if they are relatively closely linked and display heterosis because the QTL mapping techniques cannot determine the map positions with great accuracy, and the molecular function of the genes involved is not known. ▶overdominance, ▶fitness, ▶QTL, ▶interval mapping, ▶hitchhiking

Pseudopilus (Ψ -pilus): A bacterial appendage (~55 nm) that may extend beyond the cell surface into the periplasm and may be a conduit for macromolecular transport in bacteria. ▶pilus, ▶DNA uptake

Pseudoplasmodium: A migrating slug of cellular slime molds. ▶*Dictyostelium*

Pseudopodium: ▶amoeba

Pseudopregnant: Female (mice) mated with vasectomized males and then implanted with blastocyst stage embryos derived from other matings. ▶vasectomy, ▶allopheny

Pseudoqueen: In social insects (bees, ants, termites) one worker (XX) may become fertile pseudoqueen after the loss of the queen of the colony. This type of development is promoted by special feeding (royal treatment) of the originally worker caste insects. ▶honey bee

Pseudorecombinant: Reassortment of two viral genome components from different viruses, transmitted by the same insect vector.

Pseudoreplication: The samples are not independent replicates and the conclusion based on them may not be statistically reliable.

Pseudoreversion: An apparent back mutation caused by an extra-site suppressor mutation. ▶reversion

Pseudorheumatoid Dysplasia: A rare recessive cartilage defect due to mutation in the cysteine-rich secreted protein gene family (see Fig. P162). ▶arthritis, ▶rheumatic fever

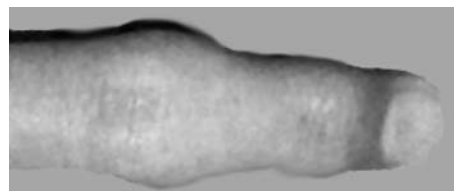


Figure P162. Swollen joints of a finger in pseudorheumatoid dysplasia

Pseudosubstrate: A molecule with similarity to an enzyme substrate but it is actually an inhibitor, and special regulators are required for its removal so the enzyme is permitted to access its true substrate. ▶substrate, ▶intrasteric regulation

Pseudotemperate Phage: It has a lysogenic cycle yet does not have a stable prophage state, e.g., the PBS1 transducing phage of *Bacillus subtilis*. ▶lysogeny, ▶prophage

Pseudotransduction: The virus is not integrated into the chromosome and the passenger DNA can be expressed only from the cytoplasm when the appropriate promoter is present in the vector.

Pseudo-Trisomic: It is actually disomic but one of the chromosomes is represented by two telocentric chromosomes, each represent one and the other arm of the same chromosome, thus two telocentrics + one normal chromosome occurs. ▶trisomy, ▶telocentric chromosome

Pseudotype: The virus carrying foreign protein on his envelope and may expand the normal host range.

Pseudotyping: If two types of viruses invade the same cell, genetic material of one may slip into the capsid of the other and this type of packaging permits the introduction of the viral genome into a host, which otherwise would be incompatible with the virion. This phenomenon may be taken advantage of also during the construction of viral vectors and helper viruses. The ability of a virus to infect a certain type of cell depends on the interaction between the viral glycoprotein and the nature of the cell surface receptors. The vesicular stomatitis virus viral envelope glycoprotein (VSV-G) is highly fusogenic for a wide range of cell types and organisms. Thus, it can be employed for pseudotyped viral vectors to expand their effective host range. The hemagglutinating

paromyxovirus of Japan (HVJ) and other viruses can also be used similarly. ►[pseudovirus](#) [pseudovirion], ►[amphotropic](#), ►[ecotropic](#), ►[packaging cell lines](#), ►[retroviral vectors](#); Mazarakis ND et al 2001 Hum Mol Genet 10:2109; Peng KV et al 2001 Gene Ther 8:1456.

Pseudouridine (ψ): A pyrimidine nucleoside (5- β -ribofuranosyluracil) occurs in the T arm of tRNA by post-transcriptional modification of a uracil residue. Pseudouridine has been also found in ribosomal RNAs and snRNAs. The modification is mediated by the nucleolar ψ synthase with the assistance of other proteins. A requisite for the process is that a small nucleolar RNA (snoRNA) carrying a single stranded H box (ANANNA) and a ACA-3' Box would pair with the target RNA at about 12 or less region of complementarity. After the enzyme gained access to the U site, the N1—C1' bond in a uracil is severed and after a 180° rotation the C5 position becomes available for the formation of a new bond. Thus the N1 and N3 sites may become readily available for hydrogen pairing and pseudouridine can bind easier in inter- or intramolecular reactions. Pseudouridine deficiency is not lethal in yeast yet it adversely affects growth. The crystal structure and function of the H/ACA ribonucleoprotein, a member of pseudouridine synthases, has been determined (Li L, Ye K 2006 Nature [Lond] 443:302). ► ψ for formula, ►[tRNA](#), ►[snoRNA](#); Bortolin M-L et al 1999 EMBO J 18:457; Hoang C, Ferré-D'Amaré AR 2001 Cell 107:929.

Pseudovirion (pseudovirus): Contains non-viral DNA within the viral capsid and can thus be used to unload foreign DNA into a cell if a helper virus is provided. ►[virion](#), ►[capsid](#); Liu Y et al 2001 Appl Microbiol Biotechnol 56:150; Ou WC et al 2001 J Med Virol 64:366.

Pseudowild Type: Displays wild phenotype because a mutation at a site different from the mutant locus that it masks, but most commonly a duplicated segment, compensates for the original and still present recessive mutation. In *Neurospora* it occurs at much higher frequency than expected by back mutation. It may also be due to a suppressor mutation. (See Mitchell MB et al 1952 Proc Natl Acad Sci USA 38:569).

Pseudoxanthoma Elasticum (PXE, 16p13.1): Autosomal recessive or dominant disorders of an ABCG6 (multiple drug resistance) transporter causing by degenerative changes in the skin (peau d'orange = orange rind), veins, eyes, intestines, etc., resulting in heart disease and hypertension. The defect involves dysplasia of elastin fibers and it affects the skin, retina, arteries, teeth, etc. ►[coronary heart disease](#), ►[hypertension](#), ►[skin diseases](#), ►[ABC transporters](#);

Le Saux O et al 2001 Am J Hum Genet 69:749; problems of translation and advocacy of research models: Terry SF et al 2007 Nature Rev Genet 8:157.

Pseudo-Zellweger Syndrome: ►[peroxisomal 3-oxoacyl-coenzyme A thiolase deficiency](#), ►[Zellweger syndrome](#)

PSI (ψ): Pseudouridine, and also the packaging signal in retrovirions. ►[tRNA pseudouridine loop](#), ►[retrovirus](#), ►[retroviral vectors](#), pseudouridine formula on page at ► ψ

PSI⁺: A yeast prion, an extrachromosomal protein suppressing nonsense codons. It functions in collaboration with the nuclear genes *SUP35*. Overexpression of this gene induces the formation of PSI⁺ probably by a conformational change in the protein. Cells deleted in the amino-terminal region of Sup35 are resistant to PSI⁺. Expansion of imperfect oligopeptide repeats in Sup35 (PQGGYQQYN) and in PrP (PHGGWGQ) seems to be responsible for the abnormality. Overexpression of Hsp104 heat shock protein cures the cells from PSI⁺. ►[prion](#), ►[Hsp](#); Masison DC et al 2000 Curr Issues Mol Biol 2:51; Jensen MA et al 2001 Genetics 159:527.

Psi Vector: ►[E vector](#)

PSI-Blast: ►[Blast](#)

PsnDNA: 150–300 bp pachytene DNA sequences flanking 800–3000 bp internal chromosomal segments in eukaryotes, and the two short and the central DNA sequences are called PDNA (pachytene DNA). The PsnDNAs are supposed to be nicked by an endonuclease after homologous small nuclear RNA (snRNA) and a non-histone protein (PsnProtein) have opened the sequences to the action of the enzyme. These molecules appear only during late leptotene to pachytene and are assumed to be mediating recombination. ►[crossing over](#), ►[meiosis](#), ►[snRNA](#), ►[ZygDNA](#); Stern H, Hotta Y 1984 Symp Soc Exp Biol 38:161.

Psoralen Dye: Can combine with the DNA connecting nucleosomal core particles. After irradiation with near-ultraviolet light, cross-link between the two DNA strands occurs. Psoralen-conjugated triple helix forming oligonucleotides have been used to induce site-specific mutations in COS cells at very high frequency (see Fig. P163). Targeting psoralen cross-links with triple helix forming oligonucleotides can induce in base substitution and deletion mutations in mammalian cells. Deficiencies in non-homologous

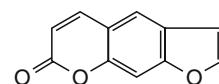


Figure P163. Psoralen

end-joining and mismatch repair did not influence the mutation pattern. In contrast, the frequency of base substitutions depended on ERCC1 and DNA polymerase ζ but it was independent of nucleotide excision repair and transcription-coupled repair genes (Richards S et al 2005 *Nucleic Acids Res* 33:5382). Some celery stocks may contain higher than normal amounts of psoralen. ▶triple helix formation, ▶site-specific mutation, ▶COS cell, ▶DNMA repair, ▶DNA polymerases; Cimino GD et al 1985 *Annu Rev Biochem* 54:1151; Luo Z et al 1997 *Proc Natl Acad Sci USA* 97:9003; Oh DH et al 2001 *Proc Natl Acad Sci USA* 98:11271.

Psoriasis (PSOR): A scaly proliferation of keratinocytes, a type of autoimmune skin defect determined either by dominant gene(s) of reduced penetrance or polygenic inheritance involving relatively few genes. Its incidence is common in Caucasian populations (1–3%) but it is much less frequent in Orientals (Eskimos, American Indians and Japanese) and it was almost absent in Africa. Recurrence rate may vary (8–23% among first-degree relatives), depending on the type involved. If both parents are affected the recurrence among children may reach up to 75%. Concordance among monozygotic twins is 35% to 72% and only 12% to 23% in fraternal twins (Duffy DL et al 1993 *J Am Acad Dermatol* 29:428). The psoriasis haplotype appears to include HLA-BW 17, HLA-C and HLA-A 13 genes. Some observations indicate that bacterial superantigens may trigger psoriasis. Psoriasis-like skin disease and arthritis may be caused by epidermal deletion of Jun proteins in mice (Zenz R et al 2005 *Nature [Lond]* 437:369). Psoriasis susceptibility genes have been assigned to 16q, 10q, 19p13.3, 3q21, 1q21, 17q25, 4qter, 14q31-q32, 6p21 and 20p. Runx transcription factors may stimulate it. AP1/4/08 and AIRE may cause loss of self-tolerance (*Nature Genet* 17:399 [1997]). Linkage with other chromosomes is less certain. Psoriasis increases the risk of basal cell carcinoma. Microarray analysis revealed upregulation of transcription of at least 161 genes in psoriasis. Some the transcripts are modulated also in other skin diseases. ▶HLA, ▶keratosis, ▶ichthyosis, ▶skin diseases, ▶nevroid basal cell carcinoma, ▶Hirschsprung disease, ▶dermatitis atopic, ▶IL-20, ▶APEBEC, ▶AIRE, ▶Runx, ▶autoimmune disease, ▶Jun; Bhalerao J, Bowcock AM 1998 *Hum Mol Genet* 7:1537; Bowcock AM et al 2001 *Hum Mol Genet* 10:1793; Int Psoriasis Genet Consortium 2003 *Am J Hum Genet* 73:430; review: Schön MP et al 2005 *N Engl J Med* 352:1899; Bowcock AM 2005 *Annu Rev Hum Genet* 6:93; review: Lowes MA et al 2007 *Nature [Lond]* 445:866.

P{Switch}: ▶Gene-Switch, ▶hybrid dysgenesis

Psychiatric Disorder: ▶psychoses

Psychomimetic: Drugs affect the state of mind in a manner similar to psychoses. ▶psychoses, ▶psychotropic drugs, ▶ergot

Psychoses: A group of mental-nervous disorders with variable genetic and environmental components. ▶autism, ▶manic depression, ▶schizophrenia, ▶paranoia, ▶affective disorders, ▶attention deficit hyperactivity, ▶Tourette's syndrome, ▶IQ, ▶dyslexia, ▶panic disorder, ▶bipolar mood disorder

Psychopathology: The manifestation of a neuronal disease involved in mental and behavioral illness.

Psychotherapy: The treatment/support provided for transient or lasting emotional and behavioral disorders. It may involve verbal support or chemical medication. Genetic counselors need familiarity with the verbal support option. ▶counseling genetic

Psychotropic Drugs: These affect the state of mind. They are used as medicine in various types of psychoses and may be very beneficial (e.g., lithium, valium, etc.) if applied under medical monitoring. Possible adverse side effects vary by the chemical nature of the drug and may include heart disease, birth defects, addiction, etc. ▶psychoses, ▶psychomimetic

Psychrophiles: Organisms that grow under low temperatures. ▶antifreeze proteins

PTA Deficiency Disease: Controlled by incompletely dominant (4q35) genes. Plasma thromboplastic antecedent protein deficiency is involved that results in unexpected bleeding after tooth extraction or various surgeries. Nose bleeding (epistaxis) is common but uterine bleeding (menorrhagia) or blood in the urine (hematuria) is rare. The carrier frequency in Ashkenazy Jewish populations is about 8.1%. ▶antihemophilia factors, ▶pseudohemophilia

PTB (phosphotyrosine-binding domain): PTB is present in proteins involved in signaling. ▶SH2, ▶SH3, ▶WW, ▶SCK, ▶pleckstrin, ▶signal transduction

PTB (polypyrimidine tract binding protein, 58 kDa): Involved in regulation of eukaryotic mRNA metabolism, regulation of splicing, IRES-mediated translation initiation and mRNA stability. ▶splicing, ▶IRES, ▶translation; Oberstrass FC et al 2005 *Science* 309:2054.

PTC: ▶phenylthiocarbamide; also papillary thyroid carcinoma; a variant of the RET oncogene caused neoplasia. ▶RET

PtdInsP₂: ▶phosphoinositides

PTEN (phosphatase and tensin homolog; deleted in chromosome 10 [10ter-q11, 10q24-q26, 10q22-q23],

syn. MMAC1 [mutated in multiple advanced cancer]): A tumor suppressor involved in brain, prostate, breast, multiple hamartomas (Lhermitte-Duclos disease/Cowden syndrome), Bannayan-Zonona syndrome and other cancers. It inhibits cell migration and cell adhesion and dephosphorylates FAK, serine, threonine and tyrosine residues in proteins. The primary target of PTEN appears to be phosphatidylinositol-3,4,5 trisphosphate (PIP3) and acts as tumor suppressor by promoting apoptosis. PTEN and p53 mutually promote each other in tumor suppression (Chen Z et al 2005 Nature [Lond] 436:725). In vivo, PTEN may act as a lipid phosphatase and this function may be essential for tumor suppression. PTEN appears to guard centromere-kinetochore integrity and chromosomal stability (Shen WH et al 2007 Cell 128:157). The protein (tyrosine, serine/threonine) phosphatase activity may not be important for tumor suppression. Some cancer cells (glioma, prostate, breast cancer) may be reverted to normalcy by the addition of PTEN. The PTEN-Akt pathway probably governs stem cell activation by helping control nuclear localization of the Wnt pathway effector β -catenin. Akt phosphorylates β -catenin at Ser552, resulting in a nuclear-localized form in intestinal stem cells (ISC). Our observations show that intestinal polyposis is initiated by PTEN-deficient ISCs that undergo excessive proliferation driven by Akt activation and nuclear localization of β -catenin (He XC et al 2007 Nature Genet 39:189).

The catalytic domain identity motif is HCXXGXXRS/T. The two α -helix domains flanking the catalytic domain are encoded in its exon 5, and must be intact for proper function. The tensin-homology domain enables the recognition of the cell adhesion system (actin, integrin, FAK, Src). In mouse the *Pten*^{+/-} heterozygotes are subject to autoimmune disease and FAS-mediated apoptosis. The normal FAS function can be restored by the administration of phosphatidyl inositol 3 kinase. PTEN has an influence on cyclin D1 and signal transduction. Mutations in PTEN may be found in Proteus syndrome or Proteus-like syndrome. Experimental deletion of *Pten* (by using seven doses of polyinosine-polycytidine in *Mx-1 Cre* mice) initiated leukemia cancer stem cell as well as hematopoietic stem cell proliferation. Without *Pten*, the hematopoietic stem cells were depleted by time in a cell autonomous manner. In contrast, the leukemia stem cells became transplantable and progressed to leukemia within 4–6 weeks. Rapamycin, which targets TOR, however, depletes leukemia stem cells and rescues *Pten*-deficient hematopoietic stem cells. Thus the two types of stem cells can be distinguished (Yilmaz ÖH et al 2006 Nature [Lond] 441:475; Zhang J et al 2006 Nature [Lond] 441:518). ▶tumor suppressor, ▶tensin, ▶FAK, ▶multiple hamartomas syndrome, ▶Bannayan-Zonona syndrome,

▶polyposis juvenile, ▶AKT, ▶catenins, ▶Wingless, ▶phosphatidylinositol, ▶prostate cancer, ▶PIP2, ▶PIP3, ▶PIK, ▶TOR, ▶rapamycin, ▶hematopoiesis, ▶stem cell, ▶chemotaxis, ▶apoptosis, ▶wound healing, ▶Parkinson disease, ▶Proteus syndrome, ▶NEDD; Di Cristofano A, Pandolfi PP 2000 Cell 100:387; Wen S et al 2001 Proc Natl Acad Sci USA 98:4622; Maehama T et al 2001 Annu Rev Biochem 70:247; Waite KA, Eng C 2002 Am J Hum Genet 70:829; Zhou X-P et al 2003 Am J Hum Genet 73:404.

Pteridines: Purine derivatives, involved in coloring of insect eyes, wings, amphibian skin, etc. Pteridines may be light receptors. Reduction in tetrahydrobiopterin and related amines may be responsible for nervous disorders (see Fig. P164). ▶photoreceptors, ▶rhodopsin, ▶ommochromes, ▶GTP cyclohydrolase deficiency; Blau N et al 1998 J Inherit Metab Dis 21:433.

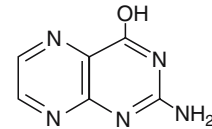


Figure P164. Pterine

Pterygium, Multiple, Syndrome (Escobar syndrome, 2q33-q34): The webbing of the neck and depressed areas (fossae) under the elbow, and other joints and hypogonadism in males, small labia and clitoris in females and other anomalies. ▶hypogonadism, ▶clitoris, ▶Popliteal pterygium

PTG (protein targeting glycogen): Forms complexes of phosphatases, kinases and glycogen synthase with glycogen. ▶glycogen, ▶kinase

PTGS: Post-transcriptional gene silencing presumably by degradation of the mRNA or inactivation of infectious (viral) RNA. Recent evidence indicates the presence of a 25-nucleotide long antisense RNA in the silenced cells. ▶RNAi, ▶RIGS, ▶methylation of DNA, ▶epigenesis, ▶post-transcriptional gene silencing, ▶RNA surveillance

Ptilinum: An inflatable head of the larva emerging from the puparium that cyclically is inflated/deflated to pry open the puparium by a wedging type of operation.

PTIP (PAX transactivation interacting domain protein): Contains tandem BRCA1 carboxy terminal domains (BRCT) and it is responsible for phosphorylation-dependent protein binding a condition required for DNA repair. The Met¹⁷⁷⁵ → Arg mutation in the BRCA1 (breast cancer) gene product fails to bind phosphopeptides and increases the susceptibility to

cancer. ►PAX, ►breast cancer; Manke IA et al 2003 Science 3002:636.

PTK: Protein-tyrosine kinase involved in regulation of signal transduction and in growth and differentiation of cells. ►protein kinases

Ptois: Drooping eyelid(s). ►epicanthus, ►blepharophimosis

PTP: ►tyrosine phosphatase, ►protein-tyrosine phosphatase non-receptor

PTPCR (PicoTiterPlate PCR): A DNA amplification procedure on an extremely small platform in pL quantities. Subsequently the products can be transferred to solid support and transcription, translation or sequencing can be carried out (Leamon JH et al 2004 Electrophoresis 25:1176). ►amplification, ►polymerase chain reaction, ►measurement units

PTPN (protein tyrosine phosphatase non-receptor type, PTPN22, 1p13): Associated with autoimmune diseases (diabetes I, rheumatoid arthritis, lupus, Graves thyroiditis, Addison disease, etc.). In case of a gain-of-function mutation the T cell produce lower amounts of interleukin-2 when stimulated the T cell receptors (TCR) and the phosphatase negatively regulates activation of T lymphocytes. (See Vang T et al 2005 Nature Genet 37:1317).

PTPRC: Protein tyrosine phosphatase receptor type C.

pu (particle units): Used for quantifying the number of potentially infectious virus particles per volume. It is a newer alternative for the *pfu* units but it is supposed to be employed for highly purified preparations. The particle count is determined from the absorbance at 260 nm according to the formula that 1 unit at $A_{260} = 1.25 \times 10^{12}$ particles/mL. Generally, it corresponds to 10–100 times of the *pfu* titer. ►*pfu*

PU.1 (PU1): A transcription factor in blood-forming cells regulating the differentiation of macrophages, B lymphocytes and monocytes; it belongs to the ETS family of oncogenes. Deletion of an upstream regulatory element (URE) leads to acute myeloid leukemia (Rosenbauer F et al 2006 Nat Genet 38:27). ►ETS, ►monocytes, ►macrophages, ►lymphocytes, ►leukemia, ►transcriptional priming; Dekoter RP, Singh H 2000 Science 288:1439; Lewis RT et al 2001 J Biol Chem 276:9550.

PubChem: Biological activities of small molecules database: <http://pubchem.ncbi.nlm.nih.gov/>.

Puberty: The time of sexual maturation, accompanied by the appearance of secondary sexual characteristics such as facial hair in males, enlargement of the breast in females, etc. Puberty is initiated by the secretion of gonadotropin releasing hormone by

the brain that activates the release of the pituitary hormones required for gonadal functions. It is facilitated by the KiSS-1 peptide and its receptor, GPR54 (Kaiser UB, Kuohung W 2005 Endocrine 26:277). ►gonadotropin, ►pituitary, ►gonads

Puberty Precocious: Autosomal dominant disorders occur in two forms: isosexual, when sexual maturation in both males and females takes place before age 10 and 8.5, respectively but may be even much earlier, especially in females. Another form is male-limited. Testosterone production seems to be independent from gonadotropin releasing hormone production. The disorder is associated with a defect in the luteinizing hormone receptor. ►luteinizing hormone-releasing factor, ►animal hormones, ►hormonal effects on sex expression, ►G-proteins

PubGene: A human gene-to-gene co-citation index involving 13,712 named human genes. (See Jenssen T-K et al 2001 Nature Genet 28:21).

Public Blood Systems: ►private blood groups

Public Opinion: In the underdeveloped world with inadequate educational systems, superstitions greatly affect people's view on all aspects of life and society. In the culturally and technically advanced nations the newspapers, television and Internet resources may influence public opinion to a great degree. Application of scientific principles is commonly decided by plebiscites or by legislative action. In a democratic society the citizens' view must necessarily be considered. The dilemma of how well informed is the general public or the legislative/governmental system regarding the implications of scientific principles is an important problem. In a survey in England the public indicated that automobiles are safer than trains. The actual statistics indicated, however, that the safety of trains is about 100 times better. People generally believe that atomic power plants expose the public to unnecessary health and genetic risks. The hazards burning fossil fuels or using wood fireplaces are much less frequently considered although they generate carcinogenic and mutagenic emissions. Very often even the scientists are unable to predict the future consequences of the scientific achievements they brought about as it was apparent by the consensus reached on recombinant DNA by the historical Asilomar Conference. The problems of using genetically modified organisms, cloning, stem cell applications cannot be resolved by political approaches. The problems created by technology and science can be resolved only by better scientific research. ►gene therapy, ►stem cells, ►GMO, ►recombinant DNA and biohazards, ►atomic radiations, ►informed consent, ►criticism on genetics

Publication Ethics: Subject to the same common sense rules as any other principle of ethics. The detailed guidelines in Human Reproduction 2001, vol 16:1783–1788 contain specific, valid points. Fabricated data in publications have serious effect on scientific research conducted in other laboratories unaware of the misconduct but faked reports are even more critical and dangerous when they influence clinical practice and may endanger life of patients (Unger K, Couzin J 2006 Science 312:38). ►ethics, ►misconduct scientific

PubMed Central: A digital archive of peer-reviewed journals containing >300,000 full text articles. Can be entered through Entrez. ►Entrez

PUBS: Percutaneous (through the skin) umbilical blood sampling, a method of prenatal biopsy for the identification of hereditary blood, cytological and other anomalies. ►amniocentesis, ►prenatal diagnosis

pUC Vectors: Small (*pUC12/13* 1680 bp, *pUC18/19* 2686 bp) plasmids containing the replicational origin (*ori*) and the *Amp^r* gene of pBR322, and they carry the *LacZ'* fragment of the bacterial β -galactosidase (see Fig. P165). The *Z'* indicates that within this region there is multiple cloning site (MCS) for recognition by 13 restriction enzymes. The orientation of the MCS is in reverse in pUC18 relative to pUC19. Genes inserted into *Lac* may be expressed under the control of the *Lac* promoter as a fusion protein. Most commonly, the insertion inactivates the *Lac* gene and white colonies are formed in Xgal medium rather than blue when the gene is active. The pUC vectors can be used with JM105 and NM522

E. coli strains. ►vectors, ►Xgal, ►Lac, ►filamentous phages; Messing J 1996 Mol Biotechnol 5:39.

Puccinia graminis: ►stem rust

PUF Proteins: They control mRNA stability by binding to the 3'-untranslated end. (Wickens M et al 2002 Trends Genet 18:150).

Puff: The swollen area of polytenic chromosomes active in transcription. Puffing is induced by expression of transcription factor genes regulated by steroid hormones (ecdysone).

Ecdysone formation comes in sequential pulses and thereby sequential activation of genes involved in metamorphosis of insects can be visualized at the level of the giant chromosomes. The puffs represent active transcription at particular genes, and the pattern of puffing shifts along the salivary gland chromosomes during development (see Fig. P166) and/or activation and the RNA extracted from the puffs reflect the differences in the base sequences of the genic DNA. Puffing has been described also in the rare polytenic chromosomes of some plant species, e.g., *Allium ursinum* or *Aconitum ranunculifolium*. These have been observed in specialized tissues of the chalaza or in the antipodal cells. ►giant chromosomes, ►ecdysone, ►PARP; Beermann W 1961 Verh Dtsch Zool Ges 1961:44; Mok EH et al 2001 Chromosoma 110:186.

Pufferfish, Japanese (*Fugu rubripes*, Tetraodontidae): A small vertebrate with about 365 Mbp DNA, i.e., only somewhat more than 1/10 of that of most mammals, and therefore it is suitable for structural and functional studies at the molecular level (see

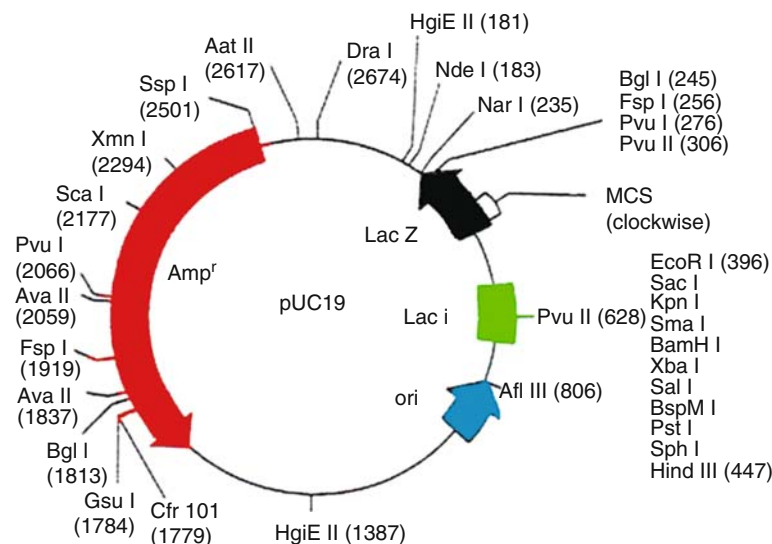


Figure P165. pUC₁₉ (The diagram is the courtesy of CLONTECH Laboratories Inc., Palo Alto, CA.)

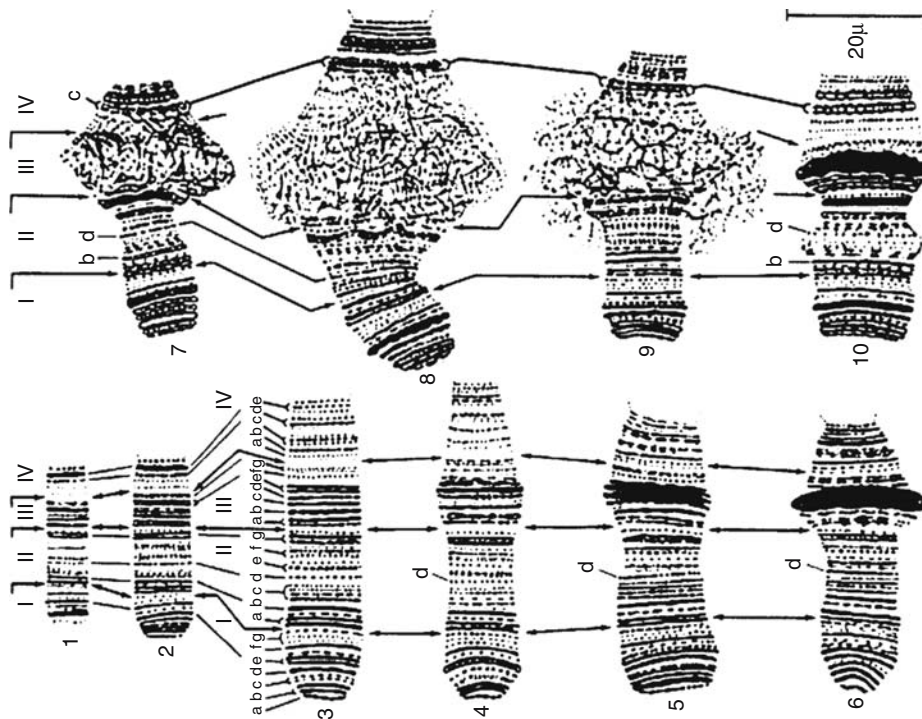


Figure P166. Selective activity of genes during development of the Dipteran fly *Rhynchosciara angela* is reflected in the puffing pattern of the salivary gland chromosomes. Lower case letters designate bands. Roman numerals indicate regions of the chromosomes. (After Breuer M E, Pavan C 1954. By permission from Kühn A 1971 Lectures on Developmental Physiology, Springer-Verlag, New York)



Figure P167. *Takifugu rubripes* (courtesy of Wikipedia; author Chris 73)









Fig. P167). More than 95% of the genome has been sequenced by 2002. About one-third of the genome is genic and repetitive sequences occupy less than one-sixth. The species, *Spheroides nephelus* is also used for studies of control of gene expression. *Tetraodon nigroviridis* ($n = 21$) DNA (27,918 genes) sequences have been used for the determination of human gene number. About 14,500 human ecores are conserved also in this pufferfish species ►[ecores](#); Crolius HR et al 2000 Genome Res 10:939; Aparicio S et al 2002 Science 297:1301; Jaillon O et al 2004 Nature [Lond] 431:946.

Pull-Down Assay: Expected to reveal interacting proteins. One of the proteins is attached to agarose beads and so immobilized. Then the test protein is added and the mixture is incubated to allow time for forming some links. Subsequently the mix is centrifuged. If there is a binding between them both proteins are found in the pellet and interaction is assumed. ►[immunoprecipitation](#), ►[genetic networks](#); Brymora A et al 2001 Anal Biochem 295:119.

Pullulanase: A secreted *Klebsiella* enzyme (~117 kDa) which cleaves starch into dextrin. It occurs also in the endosperm of cereals and other plant tissues and it is regulated by thioredoxin. ►[thioredoxin](#); Schindler I et al 2001 Biochim Biophys Acta 1548:175.

Pulmonary Adenoma: Lung cancer controlled by QTL. Dense SNP map of mouse identified the pulmonary susceptibility locus (*Pas1*) including within a 0.5 Mb region *Kras2* (Kirsten rat sarcoma oncogene 2) and *Casc1/Las1* susceptibility genes in chromosome 6. The *Glu102* allele of *Casc1* preferentially promotes susceptibility to tumorigenesis by chemicals (Liu P et al 2006 Nat Genet 38:888). Change from in the balance of expression of *Kras2* and *Pas1* entails susceptibility to resistance (To MD et al 2006 Nature

Table P3. Pulse-chase method. Autoradiographic analysis of the replication of the DNA in chromosomes by the pulse-chase procedure. (Drawn after Taylor JH et al 1957 Proc Natl Acad USA 43:122)

| Grown without label | Replication in ³ H | Labeled chromosomes replicated in ³ H-free medium | | |
|---|---|---|---|--|
| | | no exchange | sister chromatids exchanged | |
|  |  |  |  | Cytological observation |
|  |  |  |  | Interpretative drawing of the distribution of the radioactive label ■ |
| | | | | Interpretation of the replication of the DNA helices in the two chromatids ³ H. . . . |

Genet 38:926). LKB1 hemizygosity or homozygous loss substantially accelerated pulmonary adenoma (Hongbin J et al 2007 Nature [Lond] 448:807). ▶QTL, ▶RAS, ▶small cell lung carcinoma, ▶non-small-cell lung carcinoma, ▶LKB

Pulmonary Emphysema: The increase in size of the air space of the lung by dilation of the alveoli (small sac-like structures) or by destruction of their walls. Smoking may be a cause.

Pulmonary Hypertension (PPH, FPPH): Characterized by shortness of breath, hypoxemia and arterial hypertension caused by the proliferation of endothelial smooth muscles and vascular remodeling. It is a 2q33 dominant disorder with reduced penetrance. Various drugs (such as the banned anti-obesity drug fen-phen) may trigger it. The basic defect is in gene BMPR2 (bone morphogenetic protein receptor II). Haplo-insufficiency may cause it. The consequence is inappropriate regulation by the serine/threonine kinases of the phosphorylated Smad proteins leading to inadequate maintenance of blood vessel integrity. ▶bone morphogenetic protein, ▶Smad, ▶hypertension, ▶haplo-insufficient, ▶bone morphogenetic protein, ▶Smad; Machado RD et al 2001 Am J Hum Genet 68:92.

Pulmonary Surfactant Proteins: ▶respiratory distress

Pulmonary Stenosis: ▶stenosis

Pulse-Chase Analysis: Expose cells, for a period of time, to a radioactive compound such as ³H-thymidine (pulse) and examine the labeling of chromosomes in some cells. The culture is then transferred to non-radioactive thymidine and allowed to complete a

division (chased to another stage) and study again the distribution of the label and determine its fate in the cells. The experiment permitted the first time the valid conclusion that DNA replication is semi-conservative. ▶radioactive tracer, ▶radioactive label, see Table P3.

Pulsed Field Gel Electrophoresis (PFGE): A procedure combining static electricity and alternating electric fields with gel electrophoresis for the separation of DNA of entire chromosomes of lower eukaryotes, such as of yeast and *Tetrahymena* or large DNA fragments cloned in YAC vectors of any genome cut by rare-cutting restriction enzymes. ▶CHEF, ▶FIGE, ▶OFAGE, ▶YAC, ▶PHOGE, ▶TAFE, ▶RGE; Mulvey MR et al 2001 J Clin Microbiol 39:3481.

Puma Cat (*Felis concolor*, *Puma concolor*): 2n = 38. (see Fig. P168).



Figure P168. Puma

PUMA (p53 upregulated modulator of apoptosis): ►p53, ►apoptosis, ►BAX, ►SLUG

PUMA2: The evolutionary analysis of metabolism, <http://compbio.mcs.anl.gov/puma2/>.

Pump: The various transmembrane proteins mediating active transport of ions and molecules through biological membranes. ►sodium pump

Punctuated Equilibrium: ►punctuated evolution

Punctuated Evolution: A theory that evolution would follow alternating periods of rapid changes and relatively stable intervals (punctuations). Natural selection of beneficial mutations appears after some intervals and spread over the population. At the DNA level about 22% of the substitutional changes represent punctuated evolution. Punctuational changes are more common in plants and fungi than in animals (Pagel M et al 2006 Science 314:119). ►speciation, ►beneficial mutation, ►neutral mutation, ►hopeful monster, ►shifting balance theory, ►gradualism; Gould SJ, Eldredge N 1993 Nature [Lond] 366:223; Elena SF et al 1996 Science 272:1797; Voigt C et al 2000 Adv Protein Chem 55:79.

Punctuation Codons (UAA, UGA, UAG): Terminate translation of the mRNA.

Punnett Square: Permits simple prediction of the expected pheno- and genotypic proportions. It is a checkerboard where on top and at the left column the male and female gametic output is represented and in the body of the table the genotypes are found (see Figure P169). If, e.g., the heterozygote has the genetic constitution of *Aa*, *Bb*, the gametes and genotypes will be AB, Ab aB and ab. In case of linkage and recombination the actual frequency of each type of gamete must be used to obtain the correct genotypic proportions in the body of the checkerboard. ►modified Mendelian ratios, ►Mendelian segregation

| Male gametes | | AB | Ab | aB | ab |
|----------------|----|----------|----------|----------|----------|
| Female gametes | AB | AB AB | AB Ab | AB aB | AB ab |
| | Ab | Ab AB | Ab Ab | Ab aB | Ab ab |
| | aB | aB AB | aB Ab | aB aB | aB ab |
| | ab | ab AB | ab Ab | ab aB | ab ab |

Figure P169. Punnett square

Pupa: A stage in insect development between the larval stage and the emergence of the adult (imago) (see Fig. P170). ►*Drosophila*, ►juvenile hormone

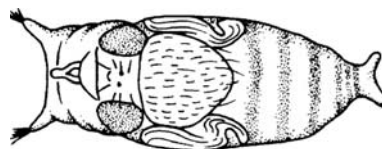


Figure P170. *Drosophila* pupa

Puparium: The case in which the *Drosophila* (and other insect) pupa develops for about four days after hatching of the egg, and in another four days the imago emerges. ►*Drosophila*

Pure Culture: Involves only a single organism. ►axenic culture

Pure Line: Genetically homogeneous (homozygous), and its progeny is expected to be identical with the parental line unless mutation occurs. (See Johannsen W 1909 Elemente der exakten Erblchkeitslehre, Fischer, Jena, Germany).

Pure-Breeding: Homozygous for the genes considered.

Purine: A nitrogenous base composed of a fused pyrimidine and imidazole ring; the principal purines in the cells are adenine, guanine, xanthine, hypoxanthine (but theobromine, caffeine and uric acid are also purines).

5',8-Purine Cyclodeoxynucleosides: Formed in two diastereoisomers by exposure of DNA to reactive oxygen species. The cyclopurines may cross-link the C-8 adenine or guanine and the 5' position of 2-deoxyribose (see Fig. P171). These diastereoisomers may block DNA replication and are cytotoxic.

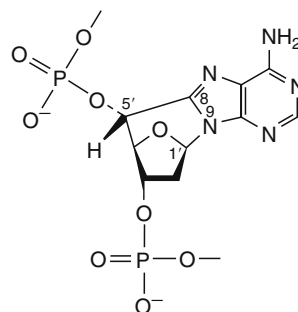


Figure P171. 5',8-cyclo-2'-deoxyadenosine phosphate

Commonly excision repair may not correct the damage although the xeroderma pigmentosum A protein may cut at both flanks and excises them. These types of damaged nucleosides may accumulate by time and result in progressive neurodegeneration in xeroderma pigmentosum patients. ▶[cyclobutane](#), ▶[excision repair](#), ▶[xeroderma pigmentosum](#); Kuraoka I et al 2000 Proc Natl Acad USA 97:3837.

Purine Repressor (PurR): A member of the *Lac* repressor family of proteins regulating 10 operons involved in the biosynthesis of purine and affecting to some extent 4 genes controlling de novo pyrimidine synthesis and salvage. Its ca. 60 amino acids, the NH₂ domain binds to DNA and its ca. 280 residue COOH domain binds effectors and it functions in oligomerization. ▶[Lac repressor](#), ▶[salvage pathway](#); Moraitis MI et al 2001 Biochemistry 40:8109.

Purity of the Gametes: One of the most important discoveries of Mendel. At anaphase I of meiosis of diploids the bivalent chromosomes segregate and at anaphase II, the chromatids separate. Therefore, in the gametes of diploids only a single allelic form of the parents is present with rare exceptions, e.g., nondisjunction and polyploids. ▶[meiosis](#), ▶[nondisjunction](#), ▶[gene conversion](#), ▶[Mendelian laws](#)

Purkinje Cells: Large pear-shaped cells in the cerebellum, these are connected to multi-branched nerve cells traversing the cerebellar cortex. In the heart they are tightly appositioned cells transmitting impulses. ▶[cerebellum](#), ▶[motor proteins](#)

P

Puromycin: An antibiotic, it inhibits protein synthesis by binding to the large subunit of ribosomes; its structure resembles the 3'-end of a charged tRNA. Therefore it can attach to the A site of the ribosome and forms a peptide bond but it cannot move to the P site and thus causes premature peptide chain termination. ▶[antibiotics](#), ▶[signaling to translation](#), (see Fig. P172) formula

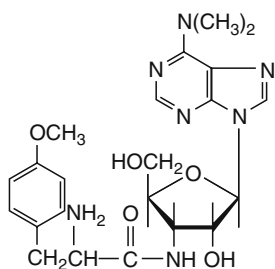


Figure P172. Puromycin

PUS: ▶[pyogenic](#)

Pushme-Pullyou (pushmi-pullyu) Selection: A positive-negative selection system to isolate engineered chromosomes in somatic cell hybrids, which have retained the segment positively selected for, and lost the regions selected against. (See Higgins AW et al 1999 Chromosoma 108:256; Trimarchi JM, Lees JA 2002 Nature Rev Mol Cell Biol 3:11).

PV16/18E6: A human papilloma virus oncoprotein. (▶[oncoprotein](#)) Burkitt lymphoma and murine lymphocytomas and may have activating role for MYC that is in the same chromosome. ▶[MYC](#), ▶[oncogenes](#), ▶[Burkitt lymphoma](#)

πVX: A microplasmid (902 bp) containing a polylinker and an amber suppressor for tyrosine tRNA. It can be used for cloning eukaryotic genes. ▶[recombinational probe](#)

PWM (position weight matrix): Used for identification of and search for functional nucleotide sequences, which are highly degenerate, e.g., the TATA boxes in the promoters. The PWM reflects the frequency of the four nucleotides (A, T, G, C) in an aligned set of different sequences sharing common function. After it had been determined in well-characterized core promoter regions, the PWM can be used to scan for TATA boxes in anonymous nucleotide sequences. The similarities between PWM and specific sequences and the matching value (within an accepted range) is determined and called a signal. Bucher (J Mol Biol 212:563) used a PWM for TATA box: GTATAAAGGCGGGG, and when the best fit was designated as 0, the majority of "unknown" TATA boxes scored within 0 to -8.16. Some of these might be, however, false positives. ▶[TATA box](#), ▶[core promoter](#), ▶[anonymous DNA segment](#), ▶[position-specific scoring matrix](#); Audic S, Claverie J-M 1998 Trends Genet 14:10.

PX (phox): A 125-amino acid module present in a variety of proteins involved in binding phosphoinositides.

P2X₁: A receptor for ATP in the in ligand-gated membrane cation channels. P2X is a component of the contractile mechanism of the vas deferens muscles, which propel the sperm into the ejaculate during copulation. Its defect entails ~90% sterility although without apparent harm to the male or the female mice. It has also several other signaling functions. ▶[vas deferens](#), ▶[ion channels](#), ▶[congenital aplasia of the vas deferens](#); Khakh BS, North RA 2006 Nature [Lond] 442:527.

PX DNA: A four-stranded molecule where the parallel helices are held together by reciprocal recombination at every site of juxtaposition. Its topoisomer is JX₂ and it also contains adjacent helices but there is no reciprocal exchange at the contact points. (See Yan H et al 2002 Nature [Lond] 415:62).

Pxr: ►SXR

Pycnidium: A hollow spherical or pear-shaped fruiting structure of fungi producing the pycnidiospores, which are released through the top opening, the ostiole. ►stem rust

Pycnodysostosis: A rare autosomal recessive (1q21) human malady characterized by defects in ossification (bone development) resulting in short stature, deformed skull with large fontanelles (soft, incompletely ossified spots of the skull common in fetuses and infants) and general fragility of the bones. The primary defects appears to be in cathepsin K, a major bone protease although interleukin-6 receptor has also been implicated. (see Fig. P173) ►Toulouse-Lautrec, ►cleidocranial dysostosis, ►cathepsins



Figure P173. The famous French artist Henri Toulouse-Lautrec (1864–1901) might have suffered from this malady and his self-portrait reveals some of the characteristics of the malformations. The exact nature of his condition cannot be diagnosed but it is known that his parents were close relatives. (By permission of the St. Martin Press, New York)

Pycnosis (pyknosis): A physiological effect of ionizing radiation on chromosomes expressed as clumping or stickiness. It is dose-dependent and the late prophase stage irradiation is most effective in causing it. Anaphase proceeds but the chromosomes have difficulties in separation, display chromatin bridges and may break up into fragments. ►bridge, ►karyorrhexis, ►heteropycnosis, ►acinus

Pygmy: The Central African human tribe of about 100,000 has an average height of 142 cm. In comparison, the average height of Swiss and Californian is 167–169 and 170–172 cm, respectively. The Pygmies do not respond to exogenous somatotropin but the concentration of serum somatomedins in the adolescent Pygmies is about a third below that in non-Pygmies of comparable

age. Although the shortness of Pygmies appears recessive, intermarriages indicate polygenic determination of height. ►dwarfism, ►stature in humans, ►nanism, ►somatomedin, ►somatotropin

PYK2: Protein tyrosine kinase links Src with G_i and G_q-coupled receptors with Grb2 and Sos proteins in the MAP kinase pathway of signal transduction. Lyso-phosphatidic acid (LPA) and bradykinin stimulate its phosphorylation by Src. Over-expressing mutants of Pyk or the protein tyrosine kinase Csk reduces the stimulation by LPA, bradykinin or over-expressed Grb2 and Sos. ►CAM, ►MAP, ►Src, ►G_i, ►G_q, ►lysophosphatidic acid, ►kininogen, ►Csk, ►Grb2, ►Sos, ►signal transduction; Felsch JS et al 1998 Proc Natl Acad Sci USA 95:5051; Sorokin A et al 2001 J Biol Chem 276:21521.

Pyknons: Short RNA motifs shared by genic and non-genic transcript regions of the human genome and are presumably mediating post-transcriptional gene silencing and RNA interference. Pyknons are most frequent in the 3'-nontranslated areas of genes (Rigoutsos I et al 2006 Proc Natl Acad Sci USA 103:6605).

Pyknosis: ►pycnosis

Pyloric Stenosis: A smaller than normal opening of the pylorus, the lower gate of the stomach that separates it from the small intestine (duodenum). It does not appear to have independent genetic control but it is part of some syndromes. It affects males five times as frequently as females; the overall incidence for both sexes is about 3/1000 birth. About 20% of the sons of affected females display this anomaly but only about 4% of the sons if the father has the malady. It may be caused by a deficiency of neuronal nitric acid synthase. ►sex-influenced, ►nitric oxide, ►imprinting

PYO: Personal years of observations; a term used in medical and clinical genetics

Pyocin: A bacteriotoxic protein produced by some strains *Pseudomonas aeruginosa* bacteria. ►bacteriocins

Pyogenic: Producing pus (DNA and protein-rich) excretum upon inflammation containing leukocytes in a yellowish fluid. It is produced abundantly by the body also after *Streptococcus* and *Staphylococcus* and other bacterial infections. ►IRAK, ►leukocyte, ►Streptococcus, ►Staphylococcus

Pyramidal Cells: Excitatory neurons in cerebral cortex. ►brain, ►neuron

Pyramiding: To build up on a larger base; to accumulate in plant protection introduction of more than one gene

and different transgenes into a plant variety conveying resistance to the same agent, in order to slow down or prevent development of resistance in the pathogen or pest.

Pyrene: A fluorochrome, frequently used as a bimolecular excimer (see Fig. P174). Pyrene incorporation into the sugar position of DNA by one carbon linker results in very weak monomer fluorescing because of quenching. Similar was the observation with RNA or RNA–DNA hybridization. Pyrene-modified RNA displayed drastically increased fluorescence however when paired with complementary RNA and is a useful tool for monitoring RNA hybridization (Nakamura M et al 2005 Nucleic Acids Res 33:5887). ▶FRET, ▶excimer

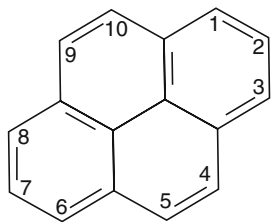


Figure P174. Pyrene

Pyrenoid: A dense, refringent protein structure in the chloroplast of algae and liverworts associated with starch deposition. ▶chloroplast

Pyrethrin (pyrethroids, permethrin): Insecticides are natural products of *Pyrethrum* (*Chrysanthemum cinerariaefolium*) plants (Compositae). They affect the voltage-gated Na⁺ ion channels and humans may have severe allergic reactions to pyrethrins. ▶ion channels, ▶insecticide resistance

Pyrethrum (*Chrysanthemum* spp): A plant source of the natural insecticide, pyrethrin, with basic chromosome number $x = 9$ (see Fig. P175). Some species are diploid or tetraploids or hexaploids. ▶pyrethrin



Figure P175. Pyrethrum

Pyridine Nucleotide: A coenzyme containing a nicotinamide derivative, NAD, NADP.

Pyridoxine (pyridoxal): Vitamin B₆ is part of the pyridoxal phosphate coenzyme, instrumental in transamination reactions (see Fig. P176). In *E. coli* bacteria vitamin B₆ is synthesized through deoxyxylulose 5-phosphate and phosphohydroxy-L-threonine. In plants (*Arabidopsis*) the synthetic pathway differs in as much as it is biosynthesized from ribose 5-phosphate or ribulose 5-phosphate and from dihydroxyacetone phosphate or glyceraldehyde 3-phosphate in the cytosol rather than in the chloroplasts (Tambasco-Studart M et al 2005 Proc Natl Acad Sci USA 102:13687).

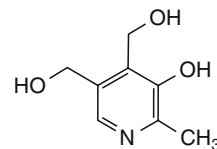


Figure P176. Pyridoxine

An apparently autosomal recessive disorder in humans involving seizures is caused by pyridoxin deficiency because of a deficit in glutamic acid decarboxylase (GAD) activity and consequently insufficiency of GABA, required for normal function of neurotransmitters. Administration of pyridoxin caused cessation of the seizures. The GAD gene was located in the long arm of human chromosome 2. An autosomal dominant regulatory pyridoxine kinase function has also been identified in humans. ▶epilepsy

Pyridoxine Dependency: It may manifest as autosomal recessive seizures with perinatal onset (around birth).

Pyrimidine: A heterocyclic nitrogenous base such as cytosine, thymine, uracil in nucleic acids but also the sedative and hypnotic analogs of uracil, barbiturate and derivatives (see Fig. P177). Pyrimidine biosynthesis may follow either a de novo or a salvage pathway. Some of the pyrimidine moieties, e.g., of thiamin are biosynthesized through a route different from that of nucleic acid pyrimidines. ▶J base, ▶thiouracil, ▶pseudouracil, ▶de novo synthesis, ▶salvage pathway, ▶formulas; Fox BA, Bzik DJ 2002 Nature [Lond] 415:926.

Pyrimidine Dimer: Cross-linked adjacent pyrimidines (thymidine or cytidine) in DNA causing a distortion in the strand involved and thus interfering with proper functions (see Fig. P178). It is induced by short-wavelength UV irradiation. The thymidine dimers may be split by visible light-inducible enzymatic repair (light repair) or by excision repair (dark repair). ▶cyclobutane ring, ▶physical mutagens, ▶genetic repair, ▶DNA repair, ▶photolyase, ▶CPD, ▶glycosylases, ▶pyrimidine-pyrimidinone photoproduct,

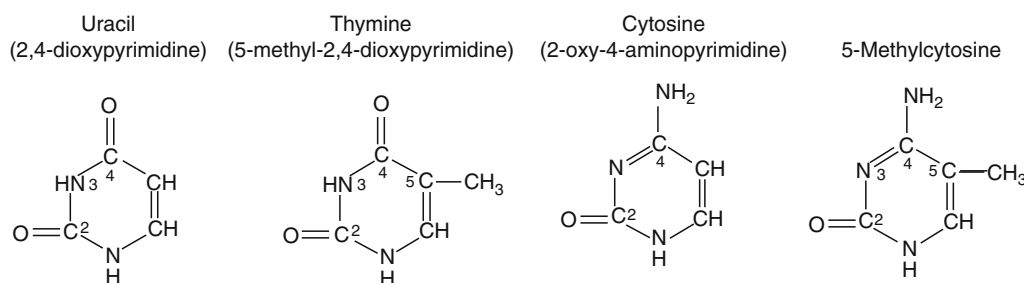


Figure P177. The major cellular pyrimidines

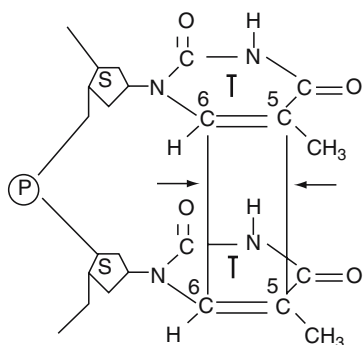


Figure P178. Cross-linked neighboring thymines in the DNA

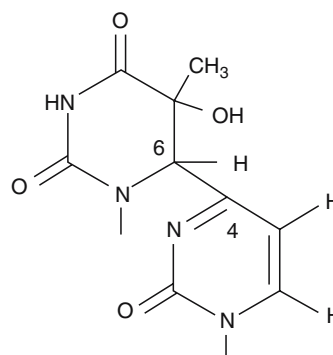


Figure P179. Thymine–Cytosine photoproduct

► [photoreactivation](#); Otoshi E et al 2000 *Cancer Res* 60:1729.

Pyrimidine Dimer N-Glycosylase: A DNA repair enzyme that creates an apyrimidinic site. Then the phosphodiester bond is severed and a 3'-OH group is formed on the terminal deoxyribose. Exonuclease 3'→5' activity of the DNA polymerase splits off the new 3'-OH end of the apyrimidinic site. After this, the replacement-replication—ligation process repairs the former thymine dimer defect. ► [glycosylase](#), ► [DNA repair](#), ► [pyrimidine dimer](#); Piersen CE et al 1995 *J Biol Chem* 270:23475.

Pyrimidine 5'-Nucleotidase Deficiency (P5N): May cause hereditary hemolytic anemia as the pyrimidines inhibit the hexose monophosphate shunt in young erythrocytes. There are two isozymes of which P5N1 is most commonly the cause of the anemia. ► [pentose phosphate pathway](#), ► [anemia](#); Marinaki AM et al 2001 *Blood* 97:3327.

Pyrimidine-Pyrimidinone Photoproduct: A pyrimidine dimer involving a 6—4 linkage between thymine and cytosine (see Fig. P179). ► [cyclobutane](#), ► [Dewar product](#), ► [cis-syn dimer](#), ► [translesion pathway](#), ► [photolyase](#); Vreeswijk MP et al 1994 *J Biol Chem* 269:31858.

Pyrimidone: Hydroxypyrimidine (see Fig. P180).

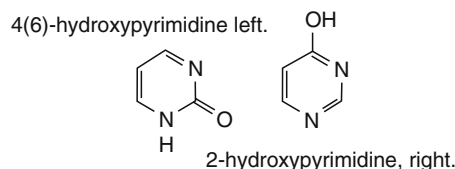


Figure P180. 4(6)-hydroxypyrimidine (left); 2-hydroxypyrimidine (right)

Pyrimidopurines: A malondialdehyde-DNA adduct derived from deoxyguanosine. ► [adduct](#)

Pyronin: A histochemical red stain used for the identification of RNA.

Pyrosequencing: Used for the analysis of the nucleotide sequence of less than 200 base long DNA strands for the detection of mutational alteration(s). Pyrosequencing has been applied to the analysis of the genome of Neanderthals. It uses the enzymes DNA polymerase, sulfurylase, firefly luciferase and apyrase. The incorporation of the nucleotides (which are not labeled) in the growing end is monitored by light flashes in a single tube. Electrophoresis is not used. Nucleotide triphosphates added to the reaction in sequence. Visible light is generated and detected when pyrophosphate is released during incorporation

from the nucleotide triphosphates with the cooperative effects of the sulfurylase and the luciferase. This is a very fast procedure and may be automated.

Another fast and convenient method of sequencing by synthesis involves four chemically cleavable fluorescent nucleotide analogues as reversible terminators. Each of the nucleotide analogues contains a 3'-*O*-allyl group and a unique fluorophore with a distinct fluorescence emission at the base through a cleavable allyl linker. These nucleotide analogues are good substrates for DNA polymerase in a solution-phase DNA extension reaction and that the fluorophore and the 3'-*O*-allyl group can be removed with high efficiency in aqueous solution. By this procedure 20 continuous bases of a homopolymeric DNA template immobilized on a chip were accurately sequenced. Such a method can be extended eventually to longer sequences (Ju J et al 2006 Proc Natl Acad Sci USA 103:19635).

►DNA sequencing, ►sulfurylase, ►luciferase, ►apyrase, ►Neanderthal; Ronaghi M 2001 Genome Res 11:3; Marziali A, Akeson M 2001 Annu Rev Biomed Engr 3:195; Fakhrai-Rad H et al 2002 Hum Mut 19:479; Goldberg SMD et al 2006 Proc Natl Acad Sci USA 103:11240; Margulies M et al 2005 Nature [Lond] 437:376; note corrigendum Nature [Lond] 441:120.

Pyrrole: A saturated five-membered heterocyclic ring such as found in protoporphyrin. Pyrrole-imidazole polyamides may bind to specific DNA of the transcription factor TFIIIA and regulate the transcription of the 5S RNA. *N*-methylimidazole (Im)—*N*-methylpyrrole (Py) may target G=C and Py—Im the C=G base pairs, respectively. The Py—Py combination is specific for T=A and A=T. ►porphyrin, ►porphyria, ►heme

Pyrrolizidine Alkaloids (petasitenine, senkirkine): Occur in several plant species (*Tussilago*, *Heliotropium*, etc.) and some of which are used as food or medicinal plants but they are mutagenic/carcinogenic. They occur also in some moths and convey protection against predators. ►Echinacea; Ober D, Hartmann T 1999 Proc Natl Acad Sci USA 96:14777.

PZD: ►micromanipulation of the oocyte
Historical vignette

“...alle essentiellen Merkmale...epigenetisch sind, und da die Determinierung ihrer Spezifität durch den Kern erhalten.”

“... all characters are epigenetic and their specificity depends on the cell nucleus.”

Pyrrolysine: The 22nd amino acid encoded in Archaea and Eubacteria by the stop codon UAG. Pyrrolysine is charged to tRNA^{CUA} (encoded by *pylT*) by PylS aminoacyl-tRNA synthetase and thus can be incorporated into *E. coli* proteins (Blight SK et al 2004 Nature [Lond] 431:333). ►amino acids, ►genetic code, ►aminoacyl tRNA synthetase, ►unnatural amino acids, ►selenocysteine; Hao B et al 2002 Science 296:1462; Srinivasan G et al 2002 Science 296:1459; pyrrolysyl-tRNA synthetase crystal structure: Kavran JM et al 2007 Proc Natl Acad Sci USA 104:11268.

Pyruvate Dehydrogenase Complex: Contains three enzymes, pyruvate dehydrogenase, dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase and the function of the complex requires the coenzymes: thiamin pyrophosphate (TPP), flavin adenine dinucleotide (FAD), coenzyme A (CoA), nicotinamide adenine dinucleotide (NAD), and lipoate. The result of the reactions is oxidative decarboxylation whereby CO₂ and acetyl CoA are formed. ►oxidative decarboxylation; Zhou ZH et al 2001 J Biol Chem 276:21704.

Pyruvate Kinase Deficiency: A recessive (human chromosome 1q21-q22, PK1) hemolytic anemia actually caused by two enzymes that are the products either of differential processing of the same transcript or chromosomal rearrangement. In the presence of some tumor promoters hepatic pyruvate kinase activity decreases. ►anemia, ►hemolytic anemia, ►glycolysis

Pyruvic Acid: A ketoacid (CH₃COCOOH) formed from glycogen, starch and glucose under aerobic conditions (under anaerobiosis is reduced to lactate and NAD⁺ is formed). Hyperpolarization technology permits imaging of pyruvate metabolic path in real time without invasive procedures (Golman K et al 2006 Proc Natl Acad Sci USA 103:11270). ►Emden-Meyerhof pathway, ►pentose phosphate shunt

PyV: Polyoma virus.

PYY₃₋₃₆: A neuropeptide Y (NPY)-like, but it is a gastrointestinal hormone that inhibits food uptake. ►obesity, ►leptin, ►neuropeptide Y; Batterham RL et al 2002 Nature [Lond] 418:650.

Q

q: Long arm of chromosomes. ►p

Q Banding: Chromosome staining with quinacrine that reveals cross bands. Due to the availability of newer microtechniques, this procedure is no longer generally used. ►chromosome banding, ►quinacrine mustard; Caspersson TG et al 1971 *Hereditas* 67:89.

Q2 Domain: ►CREB

Q-β: An RNA bacteriophage of a molecular weight of about 1.5×10^6 Da. The Qβ replicase is an RNA-dependent RNA polymerase that synthesizes the single-stranded RNA genome of the phage without an endogenous primer. The replicase can use both the + and the - strand as a template and therefore it amplifies the genome rapidly. It is a heterotetramer consisting of one viral encoded and three host polypeptides. ►replicase, ►plus strand; Munishkin AV et al 1991 *J Mol Biol* 221:463.

Q-Q-TOF: Has uses to quadrupoles and time of flight analysis for proteins and proteome.

qORF: An open reading frame with questionable information on its transcription. ►ORF, ►transcription

QSTAR Pulsar: A quadrupole time-of-flight mass spectrometer. ►quadrupole, ►MALDI, ►proteomics; Steen H et al 2001 *J Mass Spectrom* 36:782.

QTDt: Quantitative transmission disequilibrium test (Abecasis GR et al 2000 *Eur J Hum Genet* 8:545).

QTL (quantitative trait loci): Control the expression of complex traits such as weight, height, cognitive ability, and many diseases, etc. Their expression is usually not strict and even in the absence of the critical genes a quantitative trait may appear under the influence of extrinsic factors yet their expression is more likely when the appropriate alleles are present. Their physical presence may be traced in restriction fragments separated by electrophoresis because the DNA is independent of extrinsic factors. Their cosegregation is identified, and can be used for improving quantitative traits for plant breeding purposes, and for genetically defining behavioral traits and other polygenic characters. QTLs can be genetically mapped by several procedures, and most commonly using the principles of maximum likelihood for statistical analysis. In a backcross generation the phenotype (ϕ_i) and genotype (g_i) relations are

expressed as: $\phi_i = \mu + bg_i + \epsilon_i$ where g_i corresponds to the homozygous and heterozygous dominants of the QTL and its value may vary between 1 and 0. The mean of ϵ_i (a random variable) = 0 and its variance is σ^2 . The values of μ , b and σ^2 are unknown. The genotypic value of Qq and other contributors to the quantitative trait is μ and b is the effect of a substitution of another allele at the quantitative trait loci. The statistical procedures shown below were adapted from Arús P, Moreno-González J 1993, p 314 In: Hayward MD et al (Eds.) *Plant Breeding*, Chapman & Hall, London, New York.

The likelihood function $Lg_i(\mu, b, \sigma^2)$

$$= \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(\phi_i - \mu - bg_i)^2}{2\sigma^2}}$$

and the likelihood that all individuals will be in the flanking parental marker classes (k) $M_1M_1M_2M_2$, $M_1M_1M_2m_2$, $M_1m_1M_2M_2$, and $M_1m_1M_2m_2$ will be $L_k(\mu, b, \sigma^2) = \prod_i [P_i(1)L_i(1) + P_i(0)L_i(0)]$ where $P_i(1)$, and $P_i(0)$ are the probabilities that QQ and Qq quantitative genes will be in the recombinant classes, respective the flanking markers concerned. The maximum likelihood estimates for incomplete data can also be determined (Dempster AP et al 1977 *J R Stat Soc* 39:1). The likelihood for all observations is: $L(\mu, b, \sigma^2) = \prod_k L_k(\mu, b, \sigma^2)$. For the determination of the LOD score, to ascertain that the information obtained is real rather than a false, spurious conclusion would be drawn the following equation has to be resolved:

$$LOD = \frac{\log L(\mu, b, \sigma^2)}{L(\mu_0, b_0, \sigma_0^2)}$$

One must keep in mind that the estimates are as good as the data collected. Large populations and genes with greater quantitative effects improve the chances to find linkage. For estimating linkage information from multiple marker data, computer assistance is required; various programs are available. For mapping QTL in humans generally sib pairs are used. Statistical analysis indicates that choosing extreme discordant pairs makes the analysis more efficient. Just because of this selection, QTL estimates may be loaded with errors of under and overestimation. Expectation-maximization-likelihood-ratio test may permit assessing the effects of missing data (Niu T et al 2005 *Genetics* 169:1021). Least squares, Bayesian and non-parametric methods are also available. Allison DB et al (2002 *Am J Hum Genet* 70:575) are discussing methods useful for eliminating errors. Although most commonly single quantitative traits are analyzed at a time, the simultaneous study of multiple traits may be desirable. Quantitative traits

generally are not expressed in isolation and we may have to face epistasis of multi-traits. The abundance of mRNA transcripts can be considered as expression QTL (eQTL). The differences in eQTL may represent different sets of genes and can be mapped (Schadt EE et al 2003 Nature [Lond] 422:297). Microarray analysis can reveal large number of genes that influence phenotypic variation (Morley M et al 2004 Nature [Lond] 430:743). It is highly desirable that QTL would be amenable to isolation and cloning. (see Frary A et al 2000 Science 289:85) to better understand their function. A transition mutation (A→G) in intron 3 of an IGF2 (insulin-like growth factor) locus, despite the fact that it is not translated, may increase muscle growth by about three-fold. It is expressed only in the paternal gene copy and it indicates that regulatory genes may have major phenotypic effect (Van Laere A-S et al 2003 Nature [Lond] 425:832). In yeast, sporulation efficiency was resolved to single-nucleotide changes at the non-coding regulatory region (*RME1*) and to two nonsense mutations (*TAO3* and *MKT1*). The control of sporulation may be heterogeneous in the different strains (Deutschbauer AM, Davis RW 2005 Nature Genet 37:1333).

In introgression lines of tomato a *Solanum penellii* chromosome segment, containing the flower- and fruit-specific invertase locus, *LIN5* increased sugar yield of the common tomato (*Solanum lycopersicon*). A single amino acid substitution near the catalytic site of the enzyme exerted a critical effect, depending in extent on the genetic milieu of the recombinants (Fridman E et al 2004 Science 305:1786). In yeast crosses, the median variance of heritable QTL appeared 27% and no QTLs were detected for 40% of highly heritable transcripts. Modeling of QTLs indicated that only 3% of the highly heritable traits could be attributed to a single locus, 17 to 18% were apparently determined by one or two loci and half seemed to be under the control of more than five loci. Interaction among the gene products was indicated in 16% of the highly heritable traits (Brem RB, Kruglyak L 2005 Proc Natl Acad Sci USA 102:1572). In most complex traits several gene loci interact to a variable extent. In *two-locus mapping* two-stage procedure was proposed. For each transcript and marker a Wilcoxon test was used for the segregants at a locus. On the basis of the Wilcoxon test the quantitative trait with the most significant rank was named as the primary QTL. Besides the primary locus secondary loci were identified. Then non-parametric empirical Bayes' estimate determined the posterior probability that the primary QTL was a true positive and then the posterior probability of the true positive nature of the secondary QTL was

determined. The product of these two probabilities is the joint probabilities for the two estimates. An interaction test for each locus pair used the model

$$t = ax + by + cxy + d$$

where $t = \ln$ of the ratio of expression between the strain of interest and the reference sample; a , b , c and d are parameters specific for a given sample of a transcript, x is the inheritance at the first locus and y is inheritance at the second locus. An F-test determined that $c + 0$ and compared the goodness-of-fit of this model with a pure additive model. The P value of the interaction was evaluated by the Q-VALUE program available free through the Internet <http://faculty.washington.edu/~jstorey/qvalue/> (Brem RB et al 2005 Nature [Lond] 436:701). This two-stage test detected many interactions missed by single-locus tests. A robust bootstrap procedure identified 843 QTLs in mouse with an average 95% confidence interval of 2.8 Mb (Valdar W et al 2006 Nature Genet 38:879; <http://gscan.well.ox.ac.uk>). Multivariate version of the Bayes methodology for joint mapping of QTLs, using the Markov chain–Monte Carlo (MCMC) algorithm is also useful (Liu J et al 2007 Am J Hum Genet 81:304). ►LOD score, ►mapping genetic, ►linkage, ►gene block, ►RFLP, ►liability, ►ASP analysis, ►interval mapping, ►complex inheritance, ►infinitesimal model, ►BLUP, ►bootstrap, ►co-suppression, ►introgression, ►least squares, ►Bayes' theorem, ►non-parametric tests, ►Wilcoxon rank correlation test, ►goodness of fit, ►F-distribution, ►SNIPs, ►Hase-man-Elston regression, ►genetic genomics, ►rice; see also Darvasi A 1998 Nature Genet 18:19; Kao C-H 2000 Genetics 156:855; Mackay TFC 2001 Nature Rev Genet 2:11; Flint J, Mott R 2001 Nature Rev Genet 2:437; Mackay TFC 2001 Annu Rev Genet 35:303; Dekkers JCM, Hospital F 2002 Nature Rev Genet 3:22; Korstanje R, Paigen B 2002 Nature Genet 31:235; Feingold E 2002 Am J Hum Genet 71:217; Hoh J, Ott J 2003 Nature Rev Genet 4:701, review on sibling pairs: Cuenko KT et al 2003 Am J Hum Genet 73:863; functional QTL map for developmental traits: Wu R, Lin M 2006 Nature Rev Genet 7:229; QTL mapping, molecular bases in animals: Georges M 2007 Annu Rev Genomics Hum Genet 8 131; QTL comparisons: <http://pmrc.med.mssm.edu:9090/QTL/jsp/qtlhome.jsp>; miRNA QTL target sites: <http://compbio.utmem.edu/miRSNP/>; domesticated (agricultural) animal QTL: <http://www.animalgenome.org/QTLdb/>.

QTN: The nucleotide sequences for quantitative traits.

Quadrant: Consists of four parts, e.g., a tetrad.

Quadratic Check: Used for testing two genes presumed to be required for phytopathogenic infection in the manner shown in Fig. Q1. Resistance in the plants is usually a dominant trait. ►Flor's model

| Plant \ Pathogen | Pathogen | |
|---------------------|-------------------|--------------------|
| | Low pathogenicity | High pathogenicity |
| Plant reaction low | No infection | Infection |
| Plant reaction high | Infection | Infection |

Figure Q1. Quadratic check

Quadriplegia: ►tetraplegia

Quadriradial Chromosome: May be produced by cross-linking mutagens (see Fig. Q2).



Figure Q2. Quadriradial

Quadrivalent: Partially or completely identical four chromosomes in a polyploid that display pairing although of the four, at any particular position, only two can be synapsed. During meiosis they show quadrivalent association of four chromosomes. ►synapsis, ►meiosis, ►bivalent

Quadroma (hybrid hybridoma): The fusion product of two hybridomas. ►hybridoma; Lindhofer H et al 1995 J Immunol 155:219.

Quadruplets: Fourfold twins, and in the absence of the use of fertility increasing treatment, their expected frequency is about 1 in $(89)^3$ whereas the expectation for triplets and quintuplets is about $(89)^2$ and $(89)^4$, respectively. ►twinning

Quadruplex: A tetraploid or tetrasomic with four doses of the dominant alleles at a locus. ►autopolyploid, ►G quartet

Quadruplex DNA: Has four parallel and antiparallel strands in vitro, and blocks replication. In some instances G-quadruplex DNA may boost c-Myc gene proliferating activity (Siddiqui-Jain A et al 2002 Proc Natl Acad Sci USA 99:11593). ►Myc, ►tetraplex;

Schaffitzel C et al 2001 Proc Natl Acad Sci USA 98:8572; G-quadruplex search tool: <http://bioinformatics.ramapo.edu/QGRS/index.php>; <http://miracle.igib.res.in/quadfinder/>.

Quadruplicate Genes: Four genes conveying identical or similar phenotype but segregating independently in F_2 and displaying a dominant recessive proportion of 255:1.

Quadrupole: Used in specific mass spectrometers for the tracking of ion density in proteomic analysis. The quadrupole is made up of four rods, which permit the filtering of the mass that traverses them with the mediation of an oscillating electric field to obtain the mass spectrum. The amplitude of the electric field is scanned and recorded. Triple quadrupole devices usually analyze peptides. The unit mass resolution is excellent with an accuracy of 0.1 to 1 Da. ►mass spectrum, ►proteomics, ►MALDI, ►Q-Q-TOF; Hager JW 2002 Rapid Commun Mass Spectrom 16:512.

Quality of Life: A subjective judgment of the functional ability of a patient.

Quality Protein Maize: ►high-lysine corn

Quantitative Gene Numbers: They are difficult to determine because environmental effects obscure the impact of genes with minor effects. Several statistical procedures have been worked out for approximation. The simplest one is as follows:

$$N = \frac{R^2}{8(s_1^2 - s_2^2)}$$

where N = gene number, R is the difference between the parental means, s_1^2 = variance of the F_1 , s_2^2 = variance of the F_2 generations. The most common view is that quantitative traits are determined by large number of genes and each of them contributes only little to the observed phenotype. The association between bristle numbers (a quantitative trait) and the *scabrous* locus of *Drosophila* indicated, however that approximately 32% of the genetic variation in abdominal and 21% of the sternopleural bristle number was associated with DNA sequence polymorphism at this single locus. ►gene number, ►quantitative trait, ►QTL; Mather K, Jinks JL 1977 Introduction to Biometrical Genetics, Cornell University Press, Ithaca, New York; Jones CD 2001 J Hered 92[3]:274.

Quantitative Genetics: Studies genetic mechanisms involved with the expression of quantitative traits and its techniques involve those of population genetics and biometry. ►quantitative trait, ►QTL,

►population genetics, ►biometry, ►selection, ►heritability, ►statistics

Quantitative Trait: Shows continuous variation of expression and can be characterized by measurement or by counting in contrast to qualitative traits, which can be identified satisfactorily by simple description such as black or white. ►gene titration, ►dichotomous trait

Quantitative Trait Loci: ►QTL

Quantized: Using synchronous cultures and time-lapse video tape microscopy showed that the generation time in mammalian cells occurs with intervals of 3–4 h between bursts in division. The length of the cycles is dependent on the prevailing temperature, shorter at higher and longer at lower. This indicates that the cells have an oscillatory clock. ►oscillator; Klevecz RR 1976 Proc Natl Acad Sci USA 73:4012.

Quantum: The unit to quantify energy. ►photon

Quantum Computer: Fundamentally different from the standard binary computers where the information *bits* are either 0 or 1, in the quantum computer the *qubit* can be 0 and 1 and simultaneously both. This concept is different from the existing computers based on physics and it obeys the laws of quantum mechanics. At present there are difficulties in actually building the machines. A new approach to the problem is one-way four-qubit quantum state tomography (Walther P et al 2005 Nature [Lond] 434:169). The quantum computer may not be of general usefulness but may be especially useful to study electronic state of atoms or ions, their structures and reactivity. Quantum computers have the property of *entanglement*, i.e., the qubits can be interdependent. The entangled state may become, unfortunately, quickly unstable (*decoherence*) and one qubit can affect others too. The quantum computers are also much more error prone than the classical ones. There are still both theoretical and engineering problems to solve yet some progress is underway. (See Steane A 1998 Rep Progr Physics; Kim J et al 2004 J Magn Res 166:35; Stix G 2005 Sci Am 292(1):78; Keyes RW 2005 Computer 38(1):65; Ball P 2006 Nature [Lond] 440:398).

Quantum Dot (qdot): Built of semiconductor, luminescent nanometer-size crystals (e.g., of zinc sulfide-capped cadmium selenide). They may bind fluorochromes, organic and macromolecules and thus permit their tracing as stable, very bright, narrow-band emissions can be tuned from ultraviolet to infrared, water-soluble and non-invasive labels. This technology may increase the contrast in MRI, PET, computed tomography, etc. The fluorescence lifetime of the qdots is long and permits the separation from autofluorescence found in cells. The surface

molecules can be protected from oxidation or other chemical reactions and this shell conveys to qdots photostability of several orders larger compared to other dyes. The dots are available in a wide range of well-separable colors all of which can be excited by a single wavelength. Confocal microscopy and other devices can track single qdots up to a few hours. The qdots can be tagged by various ligands such as DNA oligonucleotides, aptamers or antibodies. Besides animal and whole cell labeling, special cytoplasmic and nuclear targets, cell lineages, signal transduction pathways, membrane proteins, microtubules, actin, nuclear antigens, chromosomes and pathogens can be monitored. The qdots can be equipped with membrane-crossing and cell internalization or enzymatic functions. Generally qdots are innocuous yet they may adversely effect embryo development at higher concentrations. Quantum dot technology permits relatively fast identification of 10 bacteria/mL samples if amplification is allowed. This procedure facilitates biodefense and identification of other infections. Specific phages are biotinylated in vivo and attached to streptavidin-coated qdots. After infection in 20–45 min 10–1000 phages are released and can be readily detected (Edgar R et al 2006 Proc Natl Acad Sci USA 103:4841). ►nanocrystal semiconductor, ►nanotechnology, ►non-isotopic labeling, ►aptamer, ►semiconductor, ►luminescence, ►confocal microscopy, ►MRI, ►tomography, ►bio-tin, ►streptavidin, ►pathogen identification, ►bio-terrorism; Han M et al 2001 Nature Biotechnol 19:631; Jaiswal JK et al 2003 Nature Biotechnol 21:47; Michalet X et al 2005 Science 307:538.

Quantum Speciation: A rapid formation of a new species by selection and genetic drift. ►selection, ►genetic drift

Quarantine: A state of isolation and observation without any external contact, especially from infection for a period of time in case of a contagious disease.

Quarter-Power Scaling: Biological scaling can be expressed by the formula $Y = Y_0 M^b$ where Y is a variable (e.g., life span or metabolic rate), Y_0 is a normalization constant and b = scaling exponent, M = body mass. Y_0 varies with the trait and type of an organism, b is practically constant 1/4 or multiples of it. E.g. blood circulation time and life span are $M^{1/4}$, whole organism metabolic rate is $M^{3/4}$, diameter of tree trunks and aortas $M^{3/8}$, etc. ►synaptic scaling; West GB et al 1999 Science 284:1677.

Quartet: A structure consisting of four elements. ►G quartet

Quartile: One-fourth or 25% of the data or population.

Quasi: In various combinations it indicates almost, resembling or about of the notion that the following word specifies, e.g., quasi-species means that its difference from other form(s) may not qualify it for the status of a separate species with certainty.

Quasidominant: Recessive inheritance is misclassified as dominant because the mating took place between a heterozygote and a homozygous recessive individual.

Quasi Linkage: ► [affinity](#)

Quasi-Monoclonal Antibody: Produced by mice heterozygous for the V(D)J IM-immunoglobulin heavy chain (Ig) and the other allele being non-functional. Functional κ chain is also missing. When the heavy chain, specific for the hapten 4-hydroxy-3-nitrophenyl acetyl could join any λ chain, the antibody was monospecific but somatic mutation and secondary rearrangements changed the specificity of 20% of the B cell antigen receptors. Such a system can thus be used to study antibody diversity. ► [antibody](#)

Quasi-Species: A small degree of genetic (nucleic acid) variation does not qualify it clearly for separate

species status. In RNA viruses due to high mutation rate (low repair) this state seem to exist and play role in their pathogenesis (Vignuzzi M et al 2006 Nature [Lond] 439:344).

Quaternary Structure: The aggregate of multiple polypeptide subunits into a protein or by cross-linking DNA strands into a joint structure. ► [cross-linking](#), ► [protein structure](#); <http://www.mercity.com/>; <http://pqs.ebi.ac.uk>.

Queen: The reproductive female in cast insect colonies such as exist in bees, ants. ► [pseudoqueen](#)

Queen Victoria: ► [hemophilias](#), ► [Romanovs](#), see Fig. Q3.

Quelling: A gene or chromatin repeat-associated post transcriptional silencing of genes without methylation, but involving RNAi (siRNA). It occurs when into plants or fungi foreign DNA is introduced by transformation. ► [co-suppression](#), ► [MSUD](#), ► [transvection](#), ► [sense suppression](#), ► [silencer](#), ► [RNAi](#); Maine EM 2000 Genome Biol 1(3): Reviews 1018.

Quenched Autoligation Probe (QUAL): QUAL probes use a pair of modified oligonucleotides. An electrophilic probe with internal fluorophore and



Figure Q3. Queen Victoria's family was the most famous to be affected by hemophilia, shown here, at a reunion on April 23, 1894. (1) Kaiser Wilhelm II, grandson, (2) Queen Victoria, (3) daughter Victoria, (4) granddaughter Tsarina Alexandra, (5) granddaughter Irene, (6) granddaughter Alice, (7) son and future king of England Edward VII, (8) daughter Beatrice, (9) son Arthur, (10) granddaughter Marie, (11) granddaughter Elizabeth. For most likely genetic constitutions regarding hemophilia see under hemophilia. (Courtesy of the Humanities Research Center, Gernsheim Collection, University of Texas, Austin, Texas)

a DABOSYL quencher is attached to the 5' terminus by a sulfonate ester linkage, and a nucleophilic probe containing a 3'-phosphorothioate group is employed. In the presence of a target, the two probes bind side-by-side and nucleophilic displacement of the quencher by the phosphorothioate leads to probe ligation and unquenching of the fluorophore. The reaction can be monitored by the gradual increase of fluorescence over minutes or hours. The probe can tell apart 16S RNAs even in very closely related bacteria. ►DABOCYL acid, ►phosphorothioate, ►fluorophore, ►bacteria, ►pathogen identification; Silverman AP, Kool ET 2005 Nucleic Acids Res 33:4978.

Quenching: The suppression of fluorescence, transfer of electrons or suppression of an activator by blocking the binding site of the activator or binding it to another protein which prevents its binding to the activator binding site in the DNA.

Quetelet Index: Essentially the same as body mass index, $(\text{weight})/(\text{height})^2$. L.A.J. Quételet, an astronomer, a pioneer of biometry has already shown in 1835 that human stature follows the normal distribution. Old textbooks of genetics referred to the principle of normal distribution of quantitative traits as Quetelet's Law. According to the Quetelet-Galton Law when a quantitative trait did not follow the normal distribution the role of heredity in the expression of the trait was questioned and the variation was attributed to environmental causes. ►body mass index

Q

Queunine: A rare modified purine. It is a derivative of guanine and it occurs in tRNA. Mammals cannot synthesize it and they obtain it from the intestinal microflora. Cancer cells have less of queunine in the tRNA. ►colicines, ►deazanucleotides

Quick-Stop: The temperature-sensitive DNA replication mutant *dna* of *E. coli* stops DNA replication immediately when the temperature rises to 42°C from the permissive 37°C. ►temperature-sensitive mutation; Rangarajan S et al 1999 Proc Natl Acad Sci USA 96:9224.

Quiescent Zone: A small region at the root tip where no cell division takes place in contrast to the neighboring cells, which are meristematically active (see Fig. Q4). In Arabidopsis roots, a *Retino-Blastoma-Related* gene is the main regulator of the meristematic (stem cell) state (Wildwater M et al 2005 Cell 123:1337). ►root, ►meristem, ►retinoblastoma

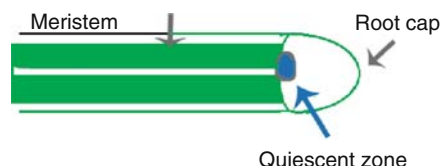


Figure Q4. Quiescent zone

Quinacrine Mustard (ICR 100): A light-sensitive, fluorescent compound used for chromosome staining (see Fig. Q5). Quinacrine (atabrine) staining permitted the first time the visualization of banding in the human chromosomes. It caused particularly bright fluorescence of the long arm of the human Y chromosome and facilitated the recognition of the XYY karyotype (see Fig. Q6). ICR 100 is strongly mutagenic; it is also a highly toxic antihelminthic drug. ►Q banding, ►acridine dyes



Figure Q5. ICR-stained Y chromosome

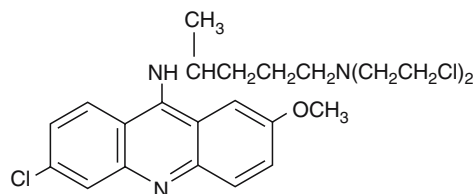


Figure Q6. Quinacrine mustard

Quintuplex: ►quadruplex

Quormone: Quorum-sensing signaling molecules, acylated homoserine lactones.

Quorum Factors: Signaling molecules in autoinduction. ►autoinduction

Quorum Quenching: *N*-acyl-L-homoserine lactone hydrolase disrupts signals to quorum-sensing (Liu D et al 2005 Proc Natl Acad Sci USA 102:11882).

Quorum-Sensing: A system of cell density-dependent expression of specific gene sets. In the luminescent bacteria *Vibrio fischeri* and *V. harveyi* the quorum-sensing signal is acylated homoserine lactone (AHL). AHL triggers biofilm production in the infectious *Pseudomonas aeruginosa* and that protects the bacteria from antibiotics. AHL production is quite

widespread among bacteria, including bacteria living on plant hosts. *P. aeruginosa*—in response to AHL—can produce, e.g., phenazine (mutagen involved also in electron transport), an antibiotic that keeps away other (Gram positive) bacteria and thus may protect its host, e.g., wheat. Besides AHL, other quorum-sensing signals have been detected in various bacteria and also in fungi. The toxic *Enterococcus faecalis* when it detects target cells, releases high level of cytolysin (Coburn PS et al 2004 Science 306:2270). In several species of bacteria quorum-sensing is dependent of an autoinducer (AI-2) product of the LuxS enzyme (4,5-dihydroxy-2,3-pentanedione, Xavier KB, Bassler BL 2005 Nature [Lond] 437:750). AI-2 signal transduction requires the integral membrane receptor LuxPQ, which has a periplasmic component LuxP and a histidine sensor kinase

subunit, LuxQ. Light-induced conformation change in LuxPQ seems to regulate quorum sensing (see Fig. Q7) (Neiditch MB et al 2006 Cell 126:1095). ►autoinduction, ►biofilm, ►multicellular, ►cytolysin, ►quorum quenching, ►luciferase; Miller MB Bassler BL 2001 Annu Rev Microbiol 55:165; Fuqua C et al 2001 Annu Rev Genet 35:439; Mok KC et al 2003 EMBO J 22:870; Miller ST et al 2004 Mol Cell 15:677; Neiditch MB et al 2005 Mol Cell 18:507.

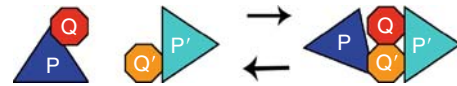
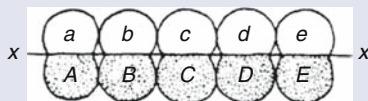


Figure Q7. Cartoon of conformational changes in the four lux subunits leading to quorum sensing

q.v. (quod vide): see it.

Historical vignettes

The majority of geneticists know that Carl Correns was one of the three rediscoverers of the Mendelian principles in 1900. Actually he named them as Mendel's Rules. In the same year in a footnote he also noted that the allelic frequencies comply with the $p^2 + 2pq + q^2$ binomial (nine years before Hardy and Weinberg), and reported linkage in *Matthiola*.. He was also one of the discoverers of cytoplasmic inheritance. In 1902 (Botanische Zeitung 60:64–82) he suggested a mechanism for crossing over nine years before Morgan's paper appeared in J. Exp. Zool. (11:365). “We assume that in the same chromosome the two Anlagen of each pair of traits lie next to each other (A next to a and B next to b, etc.) and that the pairs of Anlagen themselves are behind each other. The picture is shown in Fig. 1.



A, B, C, D, E, etc. are the Anlagen of parent I; a, b, c, d, e, etc. are those of parent II.

Through the usual cell- and nuclear divisions the same type of products are obtained as the chromosomes split longitudinally...”

When one pair contains antagonistic Anlagen, while the rest of the pairs are formed of two identical types of Anlagen, or the Anlagen are ‘conjugated’ as they are in *Matthiola* hybrids, which I have described, then further assumptions are necessary... Then AbCdE/aBcDe and aBcDe/AbCdE yield both AbCdE and aBcDe; ABcdE/abCDe and abCDe/ABcdE both ABcdE and abCDe, etc.”

Peter Starlinger (discoverer of insertion mutations in bacteria with Heinz Saedler in 1972 [Biochimie 54:177] made the remark below in 2005 in Annu. Rev. Plant Biol. 56:1.

“It was only then that we realized the relation of these element to McClintock’s transposable elements, in spite of the fact that I had known McClintock’s work since my student days, and in spite of a series of seminars that we had held on this topic in the institute in Cologne. Sometimes we are blind!”

R

R (r, Röntgen, Roentgen): This is a unit of ionizing radiation (1 electrostatic unit of charge in 1 cm³ dry air at 0 °C and 760 mm pressure; about 93 ergs/living cells). ▶Rad, ▶Rem, ▶rep, ▶Gy, ▶Sv, ▶cR, ▶measurement units

R: This is a free software environment for statistical computing and graphics. (See <http://www.r-project.org/>).

ρ (population recombination parameter): This is inversely proportional to linkage disequilibrium in a population (Hudson RR 2001 Genetics 150:1805). The size of ρ under conditions of selection is generally lower than expected under condition of neutral equilibrium; conversely linkage disequilibrium increases under domestication (Wright SI et al 2005 Science 308:1310). ▶linkage disequilibrium

ρ (rho): ▶buoyant density, ▶petite colony mutants, ▶transcription termination in prokaryotes

R1: Refer to methylation sites in the cytoplasmic region of *E. coli* chemotaxis transducer proteins.

R1, R2: These are ubiquitous retroposons in arthropod ribosomal RNA. ▶retroposon; Pérez-González CE, Eickbush TH 2002 Genetics 162:799.

R2: ▶hybrid dysgenesis I–R

rl: ▶rapid lysis mutants of bacteriophages

R Bands: These are heat-denaturation resistant chromosomal bands and half of them have telomeric sites. The bright field R bands usually show the reverse Giemsa pattern of the bands (see Fig. R1). ▶isochores, ▶C banding, ▶G banding, ▶chromosome banding; Dutrillaux B, Lejeune J 1974 Adv Hum Genet 5:119.

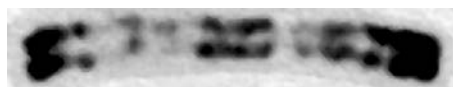


Figure R1. R-banded human chromosome

R Bodies: These refractive bodies are temperate bacteriophages within the κ particles of paramecia. ▶symbionts hereditary, ▶*Paramecium*

R End: ▶packaging of λ DNA

R Factors: Denote resistance factors in bacterial plasmids that may make the host bacteria insensitive

to antibiotics and to normally bacteriotoxic drugs. They are common among gram negative bacteria and are readily transmitted to other strains because the plasmids are generally endowed with transfer factors. These plasmids usually do not integrate into the bacterial host genome but can recombine with each other and generate new plasmids with multiple resistance factors. Because of the presence of multiple resistance factors, only simultaneous administration of multiple antibiotics may stop the multiplication of the bacteria. ▶plasmid, ▶plasmid mobilization, ▶plasmid conjugative, ▶antibiotics; Watanabe T 1963 Bacteriol Rev 27:87; Falkow S 1975 Infectious multiple drug resistance, London; Patterson JE 2000 Semin Respir Infect 15[4]:299.

R Group (a radix): Abbreviation of an alkyl group or any other chemical substitutions.

R Locus of Maize: Along with the B locus this is involved in the activation of several genes of the anthocyanin biosynthetic pathway. These genes are separable by recombination and give rise to the phenotypes represented in Figure R2. P stands for plant color and S for seed color. In this figure the embryo represents the plant. The R locus includes a large number of different alleles. A detailed structure of the locus is described by May & Dellaporta (1998 Plant J 13:247), and Walker (1998 Genetics 148:1973). Additional references are also provided. ▶tissue specificity, ▶paramutation

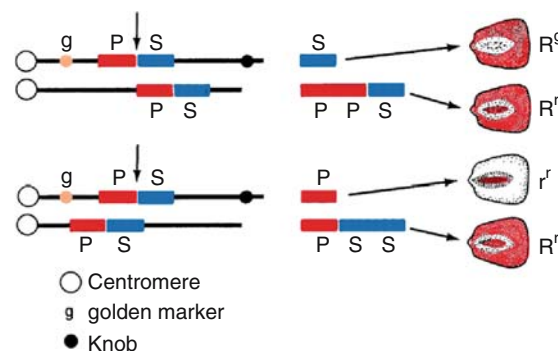


Figure R2. Resolution of the R locus of maize

R Loop: Refers to the DNA strand displaced by RNA in a double-stranded DNA-RNA heteroduplex; also the genomic DNA intron forms a R loop when the gene is hybridized with cDNA or mRNA. At the beginning of the replication of the mtDNA a R loop is formed which is synthesized on the light strand of the mtDNA. This R loop is processed into primers for the heavy chain replication. ▶DNA replication mitochondrial, ▶primer; White RL, Hogness DS 1977 Cell 10:177.

R Plasmids: These carry resistance factors (genes for antibiotic resistance and other agents).

R Point (restriction point): Before the S phase, cells in the G1 phase pause and may or may not continue the cell cycle. Cancer cells bypass the restriction point and continue uncontrolled divisions. Cultured cells may require serum or amino acids to pass from G1 to S. ► [cell cycle](#); Ekholm SV et al 2001 *Mol Cell Biol* 21:3256.

R Unit: ► [r \(Röntgen\)](#)

RA (rheumatoid arthritis): ► [autoimmune disease](#), ► [rheumatoid fever](#)

rAAV: Refers to recombinant adeno-associated virus. ► [adeno-associated virus](#)

RAB: RAS oncogene homologs (20–29 kDa guanosine triphosphatase) that regulate transport between intracellular vesicles (Golgi apparatus), and control endosome fusion. It has been traced to human chromosome 19p13.2. In the human genome there are more than 60 Rabs. Rab3A functions in neural synaptic vessels. Rabs have an ever-increasing number of effectors, which control specific functions. ► [RAS oncogene](#), ► [Sec](#), ► [Ypt](#), ► [Mss](#), ► [synaptic vessel](#), ► [GTPase](#), ► [endosome](#), ► [SNARE](#), ► [NSF](#), ► [Golgi apparatus](#), ► [RNA export](#), ► [EEA1](#), ► [SNARE](#), ► [Griscelli syndrome](#), ► [Warburg micro syndrome](#), ► [Charcot-Marie-Tooth syndrome](#); Zerial M, McBride H 2001 *Nature Rev Mol Cell Biol* 2:107; Rak A et al 2003 *Science* 302:646; homolog specificities: Eathiraj S et al 2005 *Nature [Lond]* 436:415; RAB structure: Pan X et al 2006 *Nature [Lond]* 442:303; review of Rab effectors and functions: Grosshans BL et al 2006 *Proc Natl Acad Sci USA* 103:11821; Rab family of proteins: <http://www.ncbi.nlm.nih.gov/Structure/cdd/cddsrv.cgi?uid=cd00154>.

Rabbit: *Oryctolagus cuniculus*, 2n = 44; *Sylvilagus floridanus*, 2n = 42. ► [hare](#); See <http://locus.jouy.inra.fr/cgi-bin/lgbc/mapping/common/intro2.pl?BASE=rabbit>.

Rabbit Reticulocyte In Vitro Translation: Mammalian mRNA (extracted from cells or transcribed in vitro) can be translated into protein under cell-free conditions using lysates of immature red blood cells of anemic rabbits. Anemia is induced in animals by subcutaneous injections of neutralized 1.2% acetylphenylhydrazine solutions (HEPES buffer) for five days. After the larger white blood cells are removed by centrifugation, the red blood cells are lysed at 0 °C by sterile double-distilled water. Then the endogenous mRNA is destroyed by micrococcal nuclease in the presence of Ca²⁺. Without calcium the nuclease does not work. The reaction is stopped by EGTA

(ethylene glycol tetraacetic acid, which chelates calcium). Hemin [C₃₄ H₃₂ ClFeN₄O₄], dissolved in KOH, is needed for suppressing an inhibitor of eukaryotic translation-initiation factor eIF-2. The translation mixture must contain spermidine or RNasin ribonuclease inhibitors, creatine phosphate (an energy donor), dithiothreitol (a reducing agent to prevent the formation of sulfoxides from the S-labeled amino acids), all normal amino acids (except the one which will carry the radioactive label), buffer, radioactive amino acid (e.g., [³⁵S]methionine), reticulocyte lysate, tRNAs, KCl and magnesium acetate (to enhance translation) and polyadenylate-tailed mRNA (to be translated into protein). It should be ensured that all solutions are made of RNase-free material and the vessels are free of RNase. Incubation is at 30 °C for 30 to 60 min. Before precipitating (by 10% trichloroacetic acid) the synthesized protein, the ³⁵S-methionine-tRNA is destroyed either by 0.3 N NaOH or, in case SDS-polyacrylamide gels are used for subsequent analysis, by pancreatic ribonuclease. Immunoprecipitation may also be used for the analysis of the translation product. The amount of protein synthesized can be measured by scintillation counting. Rabbit reticulocyte lysates are also available commercially. Numerous variations of the procedure are available in laboratory manuals. Alternatively, wheat germ extract may be used for in vitro translation. ► [wheat germ translation system](#), ► [eIF-2](#), ► [translation repressor proteins](#), ► [polyA mRNA](#), ► [SDS polyacrylamide gels](#), ► [immunoprecipitation](#), ► [scintillation counters](#); Olliver L, Boyd CD 1998 *Methods Mol Biol* 86:221; Lorsch JR, Herschlag 1999 *EMBO J* 18:6705.

Rabies: Encephalomyelitis caused by infection of a non-segmented negative-strand RNA virus. The (–) strand genome is condensed as a nucleoprotein into a nucleocapsid and serves as a template for the RNA-dependent RNA polymerase. Replication produces a full length (+) viral RNA copy, which serves as template for the (–) RNAS genomic copy and is then encapsidated in the virion. Switching from transcription to replication is regulated by the amount of nucleoprotein in the cytoplasm. The 11 oligomers are built from 99-nucleotide RNA segments (see Fig. R3). In some insects the nucleoprotein rings may have 9, 10, 11, 12 or 13 copies (Albertini AAV et al 2006 *Science* 313:360). The onset of the disease is characterized by inflammation and hyperactivity eventually leading to death. A wide range of wild (raccoons, foxes, mice) and domestic animals (dogs, cats) are susceptible to infection through saliva in their bites. Humans have relatively greater resistance, there is about 15% lethality without treatment. For prevention attenuated virus or genetic immunization (immunoglobulin G) may be used. ► [replicase](#),

►vaccination, ►genetic immunization, ►encephalomyelitis, ►positive strand, ►RNA viruses, ►segmented genomes; new immunotherapy: de Kruif J et al Annu Rev Med 58:359.



Figure R3. Ribbon diagram of the 11-nucleotide oligomer nucleoprotein-RNA ring viewed from bottom. Nucleoprotein protomers are colored differently; the RNA is represented by thin black coil. (Courtesy of Winfried Weissenhorn and Aurélie A.V. Albertini)

Rabl Orientation: In the late 1800s K. Rabl provided evidence for the continuity of the chromosomes inasmuch as in the very early prophase the chromosomes emerge from the premeiotic interphase in the same configuration as they entered the anaphase and telophase, i.e., the centromeres target the nuclear envelope at special locations and face the centrioles in close proximity. ►co-orientation; Marshall WF et al 1996 Mol Biol Cell 7:825.

Rabson-Mendenhall Syndrome (19p13.2): This is a dominant insulin-receptor defect (degradation) resulting in insulin-resistant diabetes. The condition is characterized by hypertrophy of the pineal gland, dental and skin anomalies (acanthosis nigricans) and early lethality. ►pineal gland, ►brain, ►diabetes, ►insulin-receptor protein

RAC (same as Akt or PKB): A serine/threonine kinase member of the RAS protein family and transmits signals from the cell surface membrane to the cytoskeleton. Human RAC1 (homolog of CED10) mediates the removal of dead cells destroyed by apoptosis. When activated it inhibits transferrin-receptor mediated endocytosis and along with RHO regulates the formation of clathrin-coated vesicles and actin polymerization. It has an important role in RAS-mediated oncogenic transformation. RAC

activates NADPH oxidase and thus free radical production as a defense against infections. Rac2 guanosine triphosphatase is selectively expressed in T_H1 lymphocytes (mediating cellular immunity) and in cooperation with NF-κB it induces IFN-γ promoter. Rac mediates the progression of the cell cycle. The prokaryotic RacA protein fastens the chromosomes to the opposite poles for cell division (Ben Yehuda S et al 2005 Mol Cell 17:773). ►serine/threonine kinase, ►RAS, ►RHO, ►PAK, ►Pac, ►p35, ►clathrin, ►signal transduction, ►cell membrane, ►cytoskeleton, ►PKB, ►endocytosis, ►apoptosis, ►transferrin, ►ROS, ►oxidative burst, ►IFN-γ, ►NF-κB, ►T cell, ►dendritic cell; Mettouchi A et al 2001 Mol Cell 8:115; Hakeda-Suzuki S et al 2002 Nature [Lond] 416:438.

RAC: Recombinant DNA Advisory Committee of the National Institute of Health (USA) oversees the application of recombinant DNA technology. (See <http://www4.od.nih.gov/oba/rac/aboutrdagt.htm>).

Raccoon (*Procyon lotor*): 2n = 38. This is primarily a North American, omnivorous, furry mammal with an average weight of about 10 kg (see Fig. R4).



Figure R4. Raccoon

R

Race: A group within a species, distinguished by several characteristics, such as allelic frequencies and morphology. For instance, it has been suggested that a combination of isosorbide dinitrate and hydralazine (BiDiI) is particularly effective for the treatment of heart failure among American blacks (Taylor A et al 2004 New Engl J Med 351:2049). For many people, talking about race is discriminatory and, therefore, they deny the racial basis of diseases. Certainly many social, environmental and economic factors contribute to the development of a particular disease but if ethnicity also plays a role, it must not be ignored because of “political correctness” as long as genetic factors common in a particular lineage can help in identifying and curing the disease. ►evolutionary distance, ►human races, ►racism, ►ethnicity

RACE: Refers to rapid amplification of cDNA ends by PCR. ►[polymerase chain reaction](#); Schafer BC 1995 Anal Biochem 227:255.

RACEfrags: Denotes rapid amplification of cDNA fragments.

Racemate: This is a Mixture of D and L optical stereoisomers (enantiomorphs) which subsequently becomes optically inactive. All naturally synthesized amino acids are in the L form but degradation generates the D enantiomorph. The degree of racemization of aspartic acid is faster than that of other amino acids. It has been recently used to determine the authenticity of ancient samples of DNA because the degradation of DNA and the racemization of amino acids, particularly Asp, indicate whether the spurious DNA is really ancient or just a contaminant in the archeological sample. In case the D/L Asp ratio exceeds 0.08 the ancient DNA cannot be retrieved. Degradation also depends on a number of factors, most notably the temperature to which the specimen had been historically exposed. The best preservation has been observed in insects enclosed in amber (although there is some controversy about these samples). In specimens where the D/L Asp ratio is about 0.05, up to 340 bp long DNA sequences can be detected using PCR technology. ►[enantiomorph](#), ►[radiocarbon dating](#), ►[evolutionary clock](#)

Raceme: Refers to inflorescence with an elongated main stem and flowers on near equal-size pedicels (see Fig. R5).



Figure R5. Raceme

Rachis: Refers to the axis of a spike (grass ear) and fern leaf (frond).

Racial Distance: ►[evolutionary distance](#)

Racism: The assumption of superiority of any particular ethnic group or groups and the consequent inferiority of some others. It advocates hatred and social discrimination on the basis of differences. The origin of racism can be traced back to prehistoric times where it served the purpose of exploitation of conquered or minority groups. Some forms of racism may be found in nearly all societies; even the Bible, arguably, is not exempt from racist ideas, and it has been frequently used as a justification by bigots. In the nineteenth century the rise of the eugenics

movement gave false scientific encouragement to racism, providing biological and ideological support for colonialism and social exploitation. Racist ideas were used to justify slavery. Racism culminated in the Third Reich of Hitler's Germany resulting not just in discrimination and suppression, but also in mass physical elimination of "Non-Aryan" people in an attempt to establish Rassenhygiene (race hygiene). Racism cannot be justified on the basis of any scientific evidence and it is morally unacceptable to enlightened societies. Human racial differences are based on a limited number of genes and all racial groups share the vast majority of genes. Actually, the world's most successful societies excelled because of their multiracial and multicultural composition. There is ample biological evidence supporting the superiority of hybrids of mammalian and plant species. ►[human races](#), ►[evolutionary distance](#), ►[hybrid vigor](#), ►[eugenics](#), ►[miscegenation](#), ►[human intelligence](#), ►[admixture in populations](#)

RACK: Denotes the receptor for activated C kinase. ►[C kinase](#)

RAD: A unit of ionizing radiation absorbed dose (100 ergs/wet tissue). ►[r](#), ►[rem](#), ►[Gray](#), ►[Sievert](#)

RAD: The genes of yeast are involved in DNA repair and recombination. ►[ABC excinucleases](#)

RAD1: Refers to a yeast gene involved in cutting damaged DNA in association with *RAD10* (ERCC1); its human homolog is XPF/ERCC4. ►[mismatch repair](#), ►[RAD51](#), ►[xeroderma pigmentosum](#), ►[aging](#)

RAD2: A yeast gene involved in cutting DNA; its human homolog is XPG. ►[DNA repair](#)

RAD3: A yeast DNA helicase and a component of transcription factor TFIIF; its human equivalent is XPD. In yeast *RAD3* regulates telomere integrity. A defect in a Rad3 like protein may be responsible for ataxia telangiectasia. ►[DNA repair](#), ►[ataxia telangiectasia](#), ►[telomeres](#)

Rad4: ►[RAD23](#)

Rad5: This is a member of the SWI/SNF family of ATPases and it also has the characteristic of ubiquitin ligases. ►[SWI/SNF](#), ►[ubiquitin](#)

Rad6: A protein with Ubc2 functions involved in both proteolysis and genetic repair in yeast. ►[ubiquitin](#), ►[Ubc2](#), ►[DNA repair](#)

RAD10: A yeast homolog of human gene ERCC1, which is involved in nucleotide excision repair. ►[nucleotide excision repair](#), ►[mismatch repair](#)

RAD14: This is a yeast gene, its protein product binds to damaged DNA. The human homolog is XPA. ►DNA repair

Rad18: A yeast protein involved in genetic repair in association with Rad6. ►Rad6

RAD21: This controls double-strand break repair caused by ionizing radiation.

RAD23: This is involved in nucleotide exchange repair. It interacts with the 26S proteasome by binding to the RAD4 repair protein. ►DNA repair, ►proteasome, ►xeroderma pigmentosum

Rad24: This is a 14-3-3 protein regulating nuclear export-import. ►Chk1, ►protein 14-3-3

RAD25 (ERCC): A helicase subunit of the general transcription factor TFIIH which is credited with promoter clearance for the onset of transcription following ATP hydrolysis and after the open promoter complex is formed. It is also a DNA repair enzyme encoded by the xeroderma pigmentosum gene F. ►transcription factors, ►open promoter complex, ►regulation of gene activity, ►helicase, ►DNA repair, ►promoter clearance, ►xeroderma pigmentosum, ►progeria

RAD27/FEN1 (Rthp/Fen-1): This 45 kDa 5'→3' exonuclease/endonuclease removes the RNA primer from Okazaki fragments with the cooperation of other proteins such RNA-DNA junction endonuclease, PCNA and DNA helicase. The FEN-1/DNase IV protein of eukaryotes performs the same functions as carried out by prokaryotic DNA polymerases beyond polymerization. The eukaryotic cells rely for this function on the PCNA-associated FEN-1. FEN-1 can cut also branched DNA molecules. ►Okazaki fragment, ►DNA replication in eukaryotes, ►flap nuclease, ►PCNA; Lieber MR 1997 Bioassays 19:233; Debrauwère H et al 2001 Proc Natl Acad Sci USA 98:8263.

RAD28: This is the yeast homolog of the gene of the Cockayne syndrome. ►Cockayne syndrome

RAD30: This encodes DNA polymerase η and it homologous to *E. coli*'s DinB, UmuC and *S. cerevisiae* Rev1.

RAD50, RAD51, RAD52, RAD53, RAD54, RAD55, Rad56, RAD57: These yeast genes are involved in radiation sensitivity, DNA double-strand break, repair and recombination. Rad51 and Rad52 proteins are vital for eukaryotic recombination. Overexpression of

RAD51 and RAD52 reduces double-strand break-induced homologous recombination in mammalian cells (Kim PM et al 2001 Nucleic Acids Res 29:4352). Replication protein A interacts with Rad proteins. The human breast cancer gene forms a complex with hRad50-p95-hMre11 proteins. Rad 53 along with chromatin assembly factor Asf1 mediates the deposition of acetylated histones H3 and H4 on to the newly replicated DNA. ►DNA repair, ►replication, ►replication fork, ►replication protein A, ►radiation-sensitivity, ►recombination mechanisms eukaryotes, ►non-homologous end-joining, ►chromatin assembly; Masson J-Y et al 2001 Proc Natl Acad Sci USA 98:8440; Davis AP, Symington LS 2001 Genetics 159:515.

RAD51: A gene of budding yeast regulates double-strand breaks and genetic recombination depending on ATP. RAD51 protein bears resemblance to the human protein (15q151) with similar functions. The human Rad51 protein (hRAD51) forms a helical filament on single-stranded DNA and regulates homologous recombination by controlling ATP activity through its ATPase function stimulated by Ca^{2+} . Ca^{2+} preserves the hRad51-ATP-ssDNA complex by slowing down ATP hydrolysis. Mg^{2+} promotes ATP hydrolysis and converts the complex into a recombination inactive form ((Bugreev DV, Mazin AV 2004 Proc Nature Acad Sci USA 101:9988). Disruption of *RAD51* in mice has embryonic lethal effects. *RAD51* is homologous with the bacterial gene *RecA* and bacteriophage T4 gene *Uvsx* mediating strand exchange in genetic recombination. In the recombination function RAD52 and its various yeast homologs (RAD55, RAD57 and other proteins) assist RAD1. The RPA (replication protein A, its homologs are the SSB [single strand binding protein] in bacteria and the p32 protein in phage) prepares the broken ends of the DNA to find the proper sequences in the homologous chromosomes that may be suitable for joining. In the plant *Arabidopsis* the homologous locus has almost the same role in recombination as in other eukaryotes but it has no adverse effect on vegetative growth. The *rad51-1* mutation, however, causes male and female sterility (Li W et al 2004 Proc Natl Acad Sci USA 101: 10596). ►DNA repair, ►SRS2, ►RecA1, ►Dmc1, ►recombination mechanisms in eukaryotes, ►RAD54; Fasullo M et al 2001 Genetics 158:959; Yu X et al 2001 Proc Natl Acad Sci USA 98:8419.

RAD53: A yeast kinase gene encoding pRAD53 signal transducer and S phase checkpoint controller; it is also known as SAD1, MEC2 and SPK1. Rad53 is activated by a conserved protein, Mrc1 (mediator of replication checkpoint) in response to DNA damage.

►MEC1, ►DNA replication; Alcasabas AA et al 2001 Nature Cell Biol 3:958.

RAD54: It has been proposed that this has a helicase function but it appears that this protein is DNA-dependent ATPase. It interacts with RAD1 scaffold and promotes homologous DNA pairing at the expense of ATP hydrolysis. Rdh54/Tid1 of yeast—similar to Rad54—also mediates the DNA exchange. ►helicase, ►ATPase, ►RAD1; Solinger JA, Heyer W-D 2001 Proc Natl Acad Sci USA 98: 8447; Ristic D et al 2001 Proc Natl Acad Sci USA 98:8454; Kim PM et al 2002 Nucleic Acids Res 30:2727.

Radiation, Acute: The irradiation is delivered in a single dose at a high rate, in contrast to *chronic radiation* in which the same dose is administered over a prolonged period of time. ►radiation effects, ►physical mutagens

Radiation, Adaptive: ►radiation evolutionary

Radiation, Background: It includes all radioactive (ionizing) radiation in the environment arising from inadequately shielded X-ray machines, cosmic radiation, fallout, laboratory isotope pollution, and radioactive rocks or radon gas that increases the dose delivered by medical treatment or other intended sources.

Radiation, Brain Damage: Actively dividing cells are most likely to suffer from ionizing radiation. The epidemiological data collected from the population of Hiroshima and Nagasaki indicated that the greatest susceptibility was during the first 8–15 weeks of the human fetus.

R

Radiation Cancer: Many of the different cancers are associated with chromosomal rearrangement(s), and ionizing radiation causes chromosomal breakage and rearrangements. Proximity of the X-ray-induced breakage sites favors rearrangements. Ultraviolet radiation may be responsible for the induction of skin cancer, especially if the body's genetic repair mechanism is weakened. According to estimates, 10 mSv may be responsible for 1 cancer death per 10,000 people. In the USA the permissible legal dose limit for the public is 0.25 mSv/year but it should be reduced to 0.20 mSv/year. Ionizing radiation is used to treat cancer. ►Sievert, ►DNA repair, ►ultraviolet radiation, ►xeroderma pigmentosum, ►excision repair, ►physical mutagens, ►radiation hazard assessment, ►radiation safety hazards

Radiation Chimera: An antigenically different bone marrow transplant is harbored in the body after

extensive radiation treatment destroys or substantially reduces the immune reaction of the recipient. Also, mutant sector(s) caused by radiation-induced mutations or deletions (see Fig. R6).



Figure R6. Chimeric Dahlia flower, the consequence of radiation exposure. (Photograph of Dr. Arnold Sparrow. Courtesy of the Brookhaven National Laboratory, Upton, New York)

Radiation Chronic: ►radiation acute

Radiation Density: This is generally measured by LET (linear energy transfer) values, i.e., the average amount of energy released per unit length of the tract. In case the density is low the genetic damage is expected to be discrete. High LET radiation causes extensive damage along a very short path (see Fig. R7). ►physical mutagens, ►radiation effects

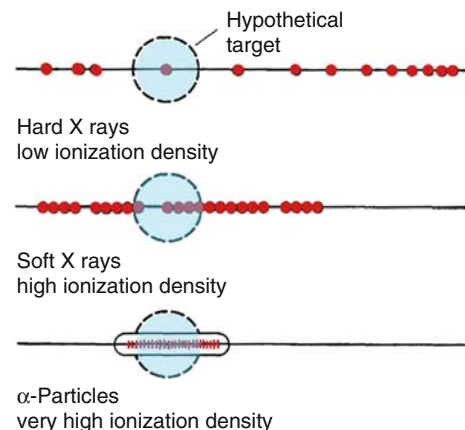


Figure R7. Radiation density. The pattern of ionization density along the track of hard and soft X-rays and α -particles. (After Gray LH from Wagner RP, Mitchell HK 1964 Genetics and Metabolism. Wiley, New York)

Radiation Doubling Dose: ▶doubling dose

Radiation Effects: Ionizing radiation may cause gross chromosome breakage (deletions, duplications, inversions, reciprocal translocations, isochromatid breaks, transpositions, change in chromosome numbers if applied to the spindle apparatus) or minute changes including destruction of a single base in the nucleic acids or very short deletions involving only a few base pairs or oxidation of bases. The damage is often clustered. These effects depend on the quality of the ionizing radiation and the status of the biological material involved. The physical effect of radiation is frequently characterized by LET (linear energy transfer in keV/nm path), indicating the amount of energy released per unit tract as ionization and excitation in the biological target (▶radiation density). Also, if the dose is delivered at a low rate, most of the damage may be repaired by the metabolic system of the cells. In prophase the chromatid breaks may remain open only for a few minutes but at the interphase they may remain open substantially longer. The frequency of chromosome breakage is considerably increased in the presence of abundant oxygen, whereas anoxia has the opposite effect. Actively metabolizing cells are more susceptible to radiation damage than dormant ones (germinating seeds versus dry ones). Chromosomal aberrations requiring two breaks (e.g., inversions, translocations) occur by second order kinetics whereas the induction rate of point mutations shows first order kinetics. Ultraviolet radiation causes excitation rather than ionization in the genetic molecules. The most prevalent damage is the formation of pyrimidine dimers although chromosome or chromatid breaks may also occur. Radiation-induced malignant growth appears to be mediated by protein tyrosine phosphorylation followed by activation of the RAF oncogene. Suppressing cell proliferation due to interferon regulatory factor (IRF) that arrests the cell cycle may prevent the accumulation of radiation-induced mutations. Independently from IRF, p53 may have a similar effect. Also, ionizing radiation may induce the transcription of p21, a cell cycle inhibitor, by a p53 and IRF dependent mechanism. The adverse effect of radiation therapy may be circumvented by the application of pifithrin (small molecule inhibitor of p53). The potential pathway of events after exposure to radiation is as follows: (i) initial hit, (ii) excitation/ionization, (iii) radical formation and other chemical reactions, (iv) DNA/chromosome damage, (v) DNA repair or mutation, (vi) cell death, (vii) modifying physiological events, and (viii) teratogenesis/carcinogenesis/mutation fixation. For years radiation damage was attributed to damage within the cell exposed, but recent evidence (Azzam EI et al 2001

Proc Natl Acad Sci USA 98:473) has indicated that the damage is also communicated to the neighboring cells through gap junctions with the mediation of connexin 43. As a consequence in the neighboring cells the stress-inducible protein p21^{Waf1} and genetic changes become detectable. The effect of radiation on a wide array of genes (Goss Tusher V et al 2001 Proc Natl Acad Sci USA 98:5116) can be assessed by microarray hybridization. ▶ionizing radiation hazards, ▶doubling dose, ▶hormesis, ▶radiation measurement, ▶UV, ▶ultraviolet light, ▶DNA repair, ▶RAF, ▶signal transduction, ▶p21, ▶p53, ▶interferon, ▶radiation hazard assessment, ▶X-ray caused chromosome breakage, ▶kinetics, ▶target theory, ▶mental retardation, ▶Kudson's two-mutation theory, ▶Armitage-Doll model; Hollaender A (Ed.) 1954–55 Radiation Biology, McGraw-Hill, New York, see also General References.

Radiation, Evolutionary: The spread of taxonomic categories as a consequence of adaptation and speciation mediated by forces of selection, mutation, migration and random drift.

Radiation Hazard Assessment: For the exposure of the whole human body to X or γ radiation, the minimal biologically detectable dose in mSv (milliSievert) is: no symptoms 0.01–0.05, chromosomal defects detectable by cytological analysis 50–250, physiological symptoms at acute exposure 500–700, vomiting in 10% of cases 750–1250, disability and hematological changes 1,500–2,000, median human lethal dose 3,000 but at doses above 4,500 the mortality is expected to be over 50%. Prolonged exposure below 1,000 Sv may cause leukemia and death. Single exposure of the spermatogonia to 0.5 Sv may block sperm formation. In mice, the LD₅₀/cGy for primary spermatocytes was 200, meiosis (leptotene-diplotene) 500, diplotene 800, diakinesis 900, secondary spermatocytes 1,000, spermatids 1,500 and spermatozoa 50,000 (mouse data from Alpen, 1998). In mice, 1 Gy may kill the fertilized zygote but the same dose may have no such effect 5–8 days after conception, indicating the potentials of cell replacement. In humans, the most common response of the fetus is mental retardation following intrauterine exposure to 1–5 Gy. Carcinogenesis is well demonstrated by radiation exposure but the course of the initial effect may be greatly influenced by a variety of innate and environmental factors. The risk of very low doses of radiation is very difficult to quantify. Generally, extrapolation is used from higher doses and therefore the risk may be under- or overestimated (Brenner DJ et al 2003 Proc Natl Acad Sci USA 100:13761).

A single exposure of women to 3–4 Sv and 10–20 Sv over a longer time (2 weeks) may result in permanent sterility. A fetus in a pregnant woman should not be exposed to any radiation but in the case of an emergency it should not exceed a total of 0.005 Sv and any person under 18 years of age should not receive an accumulated dose over 0.05 Sv/year. A single 0.1 Sv dose may cause cancer in 0.01 fraction of the exposed individuals. For *occupational exposure*, the maximal limit in mSv for the whole body is 50, for lens of the eye 150, and for other specific organs or tissues 500. In the case of cumulative exposure the maximal limit should be below 10 mSv \times age in years. For public, educational and training exposure, the recommended maximal limit in mSv/year is 1 for the whole body, and 5.0 for the eye, skin and extremities. In the spring of 1996 the European Union (EU) lowered the permissible dose limits following which members of the public can be exposed to a maximum of 1 mSv every year (the earlier limit was 5 mSv). However, recent analysis has revealed no harmless dose even at low exposure. The limit of exposure for the personnel of radiation industry is now 100 mSv over five consecutive years and an average limit of 20 mSv/year (previous limit was 50 mSv). These guidelines must be implemented within four years by EU member states.

The exposure by routine *medical* X-ray examination is not supposed to be higher than 0.04 to 10 mSv, by fluoroscopy or X-ray movie not more than 25 mSv, and by dental examination involving the entire jaws not above 30 mSv. Nuclear medicine using radioactive tracers or positron emission tomography also involves some exposure (~ 0.012 Sv). The replacement of ^{131}I by ^{123}I is desirable for thyroid analyses. Smoking tobacco may increase the degree of exposure to ^{210}Pb and ^{210}Po . By comparison, in a normally operated nuclear power plant the exposure may range from 3 to 30 mSv/year. Those living in a granite building may be exposed to 5 mSv/year and a transcontinental flight may involve an exposure of 0.03 mSv. The terrestrial radiation (^{40}K , ^{87}Rb , U, Th series, Rn) may also be a source to reckon with. Radiation from a color television/video display set may be 0.001 mSv/year to the viewer if he/she remains very close to the set, however modern units are safer (2–3 μSv /year). Inspection of luggage at the airports may add 0.002 mrem, and smoke detectors 0.008 mrem to personal exposure. A plutonium-powered cardiac pacemaker may increase the radiation exposure of the wearer by 100 mrem. It should be borne in mind that there may be no threshold below which ionizing radiation would have no effect. It has been assumed until recently that radiation damage is caused by direct hits. There is, however, a significant

bystander effect to the cells in the vicinity of the hit cells. Within 1 mm distance α radiation increases the number of micronuclei (broken chromosomes) by a factor of 1.7 and apoptosis increases 2.8-fold. The bystander effect is apparently mediated through gap-junction signals (Belyakov OV et al 2005 Proc Natl Acad Sci USA 102:14203).

The worldwide average exposure from natural sources amounts to ~ 2.4 mSv, mostly from α particles of radon gas and cosmic rays (muons) and terrestrial γ rays. Moreover, 100 h of air travel adds ~ 0.5 mSv and medical X-rays contribute ~ 0.4 mSv annually. The 1945 atmospheric explosion and the following weapon tests constitute a fallout of 0.005 mSv.

The current approximate incidence of mutation in live-born human offspring and the estimated increase per rem per generation in parenthesis are as follows: autosomal dominant 0.0025 – 0.0075 (0.000005 – 0.00002), recessive 0.0025, X-linked 0.0004 (0.000001), translocations 0.0006 (0.0025) and trisomy 0.0008 (0.000001). Approximately 5 Gy (500 rem) is considered the human lethal dose, the bacterium *Deinococcus radiodurans* can recover from doses as high as 30,000 Gy.

The very efficient recombinational repair in this prokaryote can explain this high radiation resistance. The chromosomes are just as well broken into pieces as other DNAs but its genetic material exists in pairs and within 12 to 24 h repair by recombination at the Holliday junctures restores their integrity. Even small doses, such as delivered by therapeutic X-radiation, may increase by about one-third the number of broken chromosomes and radiation by isotope treatment has a similar effect, depending on the dose and the duration of the exposure. Eventually, the broken chromosomes, or at least some of them, may be eliminated from the body. Radiation sensitivity is generally positively correlated with the size of the genetic material although in polyploids the damage may not be readily detectable because of the redundancy of the genes. There is no universal consensus on the hazards involved in exposure to very low levels of ionizing radiation. ►atomic radiation, ►isotopes, ►radiation effects, ►radiation measurement, ►radiation sensitivity, ►radiation protection, ►doubling dose, ►hormesis, ►radiation threshold, ►mental retardation, ►DNA repair, ►Holliday model of recombination, ►X-ray chromosome breakage, ►Sv, ►Gy, ►BERT, ►hemical, ►rem, ►BERT, ►bystander effect; personal exposure: www.umich.edu/~radinfo; Dowd SB, Tilson ER 1999 Practical Radiation Protection and Applied Radiobiology, Saunders, Philadelphia; the book includes more than 100 Internet information addresses; Sankaranarayanan K 1999 Mutation Res

429:45; Mrázek J 2002 Proc Natl Acad Sci USA 99:10943; Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase2 National Academic Press, Washington DC, 2005; ▶ [measurement units](#)

Radiation Hybrid (RH): Human chromosomes are broken into several fragments with 8000 rad dose of X-rays. The irradiated cells are quickly fused (with the aid of polyethylene glycol) to somatic cell hybrids with Chinese hamster cells and thus translocations and insertions into the hamster chromosomes are generated. The greater the distance between two human DNA markers, the higher the chances of a breakage. To estimate the frequency of breakage, information is obtained about “recombination” in a manner analogous to classical genetic recombinational mapping. The recombination frequency in radiation hybrids varies between 0 and 1 (no recombination or the markers are always independent, respectively). In meiotic recombination the maximal value is 0.5 for independent segregation. The formula given here and the recombination frequencies (expressed in centiRays [cR]) give an estimate of the frequency of breakage. At 65 Gy the estimated 1 cR \approx 30 kb, at 90 Gy 1 cR \approx 55 kb. $\theta = [(A^+B^-) + (A^-B^+)]/[T(R_A + R_B - 2R_AR_B)]$ where (A^+B^-) are the hybrid clones retaining A but not B and (A^-B^+) retain B but not A, T = the total number of hybrids and R_A, R_B denote the recombinant fractions. The linkage analysis can be extended to more than two points. The fragments retained can be analyzed by PCR procedures and they are expected to carry with them neighboring sequences and thus provide information on the physical linkage for sequences of about 10 megabase. The recombination process is dose-dependent. In one study 50 Gy permitted the retention of an intact chromosome arm in 10% of the cases whereas 40% had fragments of 3–30 Mb and 50% 2–3 Mb. Using 250 Gy less than 6% of the hybrids involved larger than 3 Mb pieces. If the fragments generated are intended for positional cloning, usually higher doses are used. The retention of fragments varies; centromeric pieces are more likely to be retained. The fragmented DNA can be further analyzed by probing with Southern blots, polymerase chain reaction, using sequence tagged sites (STS), FISH, etc. The fragments are unstable unless they are fused with rodent chromosomes. The radiation hybrids may retain up to a dozen or more fragments. An added special advantage is that genes without allelic variation can also be mapped. The radiation hybrid mapping method has been applied to plants as well. Single maize chromosome additions to oat lines permitted the resolution of 0.5 to 1.0

megabase sequences using 30 to 50 krad γ -rays. The hexaploid oat background assured the survival of the (diploid) maize chromosome fragments. Radiation hybrid transcript maps are available for mouse, rat, human, dog, cat and zebrafish and are useful tools for evolutionary analyses. ▶ [somatic cell hybrid](#), ▶ [mapping genetic](#), ▶ [physical mapping](#), ▶ [framework map](#), ▶ [Rhalloc](#), ▶ [Rhdb](#), ▶ [recombination](#), ▶ [Gy](#), ▶ [centiRay](#), ▶ [STS](#), ▶ [FISH](#), ▶ [Southern blot](#), ▶ [probe](#), ▶ [positional cloning](#), ▶ θ [theta], ▶ [WGRH](#), ▶ [PRINS](#), ▶ [IRS-PCR](#), ▶ [RHKO](#), ▶ [Rhalloc](#), ▶ [addition lines](#); a radiation hybrid map of the mouse genome: <http://www.ncbi.nlm.nih.gov/genemap>; <http://www.ebi.ac.uk/RHdb>; Van Etten WJ et al 1999 Nature Genet 22:384; Riera-Lizarazu O et al 2000 Genetics 156:327; Olivier M et al 2001 Science 291:1298; Hudson TJ et al 2001 Nature Genet 29:201; Avner P et al 2001 Nature Genet 29:194.

Radiation Hybrid Panel: A set of DNA samples containing radiation hybrid clones derived by the fusion of human and rodent cells. ▶ [radiation hybrid](#), ▶ [TNG](#)

Radiation Indirect Effects: Radiation generates reactive radicals (e.g., peroxides) in the environment that in turn inflict biological damage. ▶ [radiation effects](#), ▶ [target theory](#)

Radiation, Ionizing: ▶ [ionizing radiation](#), ▶ [electromagnetic radiation](#)

Radiation Mapping: ▶ [radiation hybrid](#); mouse radiation mapping: <http://www.jax.org/resources/documents/cmdata/>.

Radiation Measurement: ▶ [Geiger counter](#), ▶ [scintillation counter](#), ▶ [proportional counter](#), ▶ [ionization chambers](#), ▶ [dosimeter pocket](#), ▶ [dosimeter film](#), ▶ [thermoluminescent detectors](#), ▶ [neutron flux detection](#), ▶ [radiation hazard assessment](#), ▶ [autoradiography](#)

Radiation, Natural: ▶ [isotopes](#), ▶ [cosmic radiation](#)

Radiation vs Nuclear Size: The harmful biological and genetic effects of ionizing radiation depend on the size of the cell nuclei, at the same dose. Larger nuclei present a larger target and suffer more damage than smaller ones. Haploid nuclei are more sensitive because the genes are normally present in a single dose. Polyploids are relatively less sensitive because of the multiple copies of the chromosomes. ▶ [radiation effects](#), ▶ [ionizing radiation](#), ▶ [physical mutagens](#), see Fig. R8.

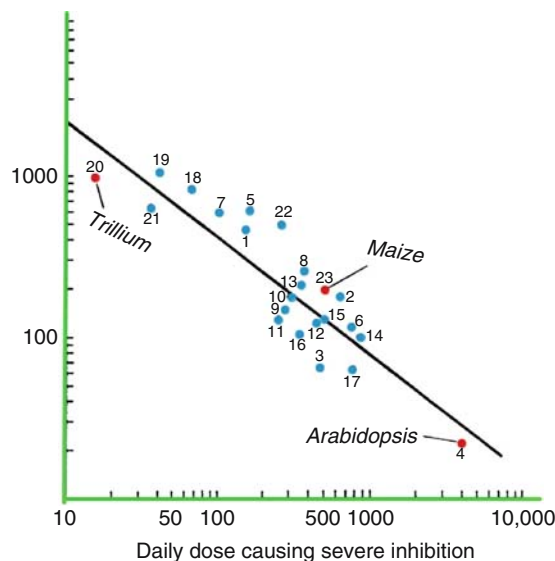


Figure R8. Radiation-sensitivity in plants depending on nuclear volume. 1. *Allium cepa*, 2. *Anethum graveolens*, 3. *Antirrhinum majus*, 4. *Arabidopsis thaliana*, 5. *Brodiaea bridgesi*, 6. *Graptopetalum bartramii*, 7. *Haworthia attenuata*, 8. *Helianthus annuus*, 9. *Impatiens sultanii*, 10. *Luzula purpurea*, 11. *Nicotiana glauca*, 12. *Oxalis stricta*, 13. *Pisum sativum*, 14. *Raphanus sativus*, 15. *Ricinus communis*, 16. *Saintpaulia ionantha*, 17. *Sedum oryzifolium*, 18. *Tradescantia ohiensis*, 19. *Tradescantia paludosum*, 20. *Trillium grandiflorum*, 21. *Tulbaghia violacea*, 22. *Vicia faba*, 23. *Zea mays*. (From Sparrow AH et al Radiation Bot 1: 10)

Radiation Particulate: ►physical mutagens

Radiation Physiological Factors: The effect of radiation may be influenced by the species, age, developmental conditions, type of tissue and cells, metabolic state, genetic back-ground, repair mechanisms, temperature and the chemical environment (presence of oxygen and other enhancing or protective compounds). Actively dividing cells, imbibed seeds are far more sensitive to radiation damage than quiescent tissue or dry material. During pregnancy radiation exposure should be avoided especially during the early stages of gestation when cell division is most rapid. Also, developing children are at a higher radiation risk than adults. Any condition with the possibility of diminished genetic repair increases the chances of chromosomal aberration and gene mutation. ►physical mutagens, ►target theory, ►radiation hazard assessment, ►radiation brain damage, ►radiation vs nuclear size, ►radiation-sensitivity

Radiation Protection: This can be achieved by using isotopes, ventilation should be provided by exhaustion via seamless ducts through the buildings

and the particulate material should be trapped in appropriate filters or washed (scrubbed) before environmental discharge.

The source of radiation should be shielded. The transmission of the shielding material depends on the peak voltage of the X-ray or on the energy of the emitting isotope and the thickness of the shield (attenuating material is characterized by half-value [HVL] or tenth-value layers [TVL]) (see Table R1).

Table R1. Data on shielding effectiveness of commonly used radiation insulating material

| kV X-ray | Lead in millimeters | | Concrete in centimeters | |
|----------------------|---------------------|------|-------------------------|-------|
| | HVL | TVL | HVL | TVL |
| 50 | 0.05 | 0.16 | 0.43 | 0.15 |
| 100 | 0.24 | 0.8 | 1.5 | 5.0 |
| 200 | 0.48 | 1.6 | 2.5 | 8.25 |
| 500 | 3.6 | 11.9 | 3.5 | 11.5 |
| 1,000 | 7.9 | 26.0 | 4.38 | 14.5 |
| 4,000 | 16.5 | 54.8 | 9.00 | 30.00 |
| 10,000 | 16.5 | 55.0 | 11.5 | 38.25 |
| ⁶⁰ Cobalt | 6.5 | 21.6 | 4.75 | 15.50 |

Cracks, seams, conduits, filters, ducts, etc. should be regularly checked for possible leaks. Protective clothing (aprons, gloves, etc.) affords very limited protection. Radioactive waste should be disposed of in accordance with the government and local standards, whichever is higher. Caution signs should be used to identify radiation areas. “Radiation Area” is defined by the Occupational Safety and Health Standards of the USA as an area where a major portion of the body could receive in any hour a dose in excess of 5 millirem, or in any 5 consecutive days a dose in excess of 100 millirem. “High Radiation Area” means any area, accessible to personnel, in which radiation is present at such levels that a major portion of the body could receive in any one hour a dose in excess of 100 millirem. For non-ionizing electromagnetic radiation within the range of 10 MHz (megahertz, 10⁷ cycles/sec) to 100 Ghz (gigahertz, 10¹¹ cycles/sec) the energy density should not exceed 1 mW (milliwatt)/cm²/0.1 h. [Such radiations are within the realm of radio, microwave and radar range.] Emergency plans must be prepared for spillage, cleanup and fire. Before working with any hazardous material all personnel should be given proper training for safe storage, handling and

emergencies involved. ▶ isotopes, ▶ atomic radiation, ▶ ionizing radiation, ▶ radiation effects, ▶ radiation hazard assessment, ▶ radiation measurement, ▶ electromagnetic radiation, ▶ sulfhydryl

Radiation Resistant DNA Synthesis: Normally, the ataxia telangiectasia gene/protein (ATM) is a target of the damaging effects of ionizing radiation. ATM activated by radiation results in the activation of the cell cycle (G1→S) checkpoint kinase Chk2. The activation of Chk2 results in the phosphorylation of phosphatase Cdc25A at residue Ser¹²⁵. Cdc25A prevents dephosphorylation of Cdk2 and this leads to a transient stoppage of DNA synthesis at the S phase. If Chk2 cannot bind or phosphorylate Cdc25A, radiation resistant DNA synthesis proceeds. Thus, Chk2 acts as a tumor suppressor in ataxia telangiectasia. ▶ Chk2, ▶ Cdc25, ▶ cell cycle, ▶ ataxia telangiectasia; Falck J et al 2001 Nature [Lond] 410:842.

Radiation Response: Deletions (single chromosomal breaks) and mutations occur with 1st order kinetics, whereas the majority of chromosomal rearrangements (inversions, translocations) are proportional to the square of the dose and thus follow 2nd or 3rd order kinetics. The irradiated cell may communicate with the neighboring cells via IL-8 and these neighbors may also suffer oxidative stress as a bystander effect. ▶ IL8, ▶ physical mutagens, ▶ radiation effects, ▶ kinetics, ▶ chromosomal aberrations, ▶ radiation vs nuclear size, ▶ oxygen effect, ▶ radiation-sensitivity; Rothkamm K, Löbrich M 2003 Proc Natl Acad Sci USA 100:5057.

Radiation Safety: ▶ radiation protection, ▶ radiation hazard assessment, ▶ atomic radiation, ▶ cosmic radiation

Radiation Safety Standards: ▶ radiation hazard assessment, ▶ radiation protection

Radiation-Sensitivity: This characteristic of the DNA depends on many diverse factors such as the degree of coiling, the status of the nuclear matrix, hydration, copper ions, OH scavengers and thiols. The microbial flora seems to be protective against intestinal radiation effects (Crawford PA, Gordon JI 2005 Proc Natl Acad Sci USA 102:13254). In budding yeast a genome-wide screen of 3670 non-essential genes revealed 107 new loci that influence sensitivity to γ -rays. Further, 50% of these yeast genes display homology to human genes. ▶ DNA repair, ▶ chromosome breakage, ▶ aging, ▶ microcephaly [Nijmegen breakage syndrome], ▶ nevoid basal cell carcinoma, ▶ ataxia telangiectasia, ▶ xeroderma pigmentosum, ▶ radiation hazard assessment, ▶ radiation protection, ▶ radiation response, ▶ radiation vs

nuclear size, ▶ *Deinococcus radiodurans*, ▶ radiation physiological factors; Bennett CB et al 2001 Nature Genet 29:426.

Radiation Sickness: This occurs when the whole human body or parts of it is exposed to ionizing radiation. The symptoms and hazards are dependent on the dose. ▶ radiation hazard assessment

Radiation Therapy: Ionizing, electromagnetic radiation has anti-mitotic and destructive effects on live tissues and it is used to suppress cancerous growth. The therapeutic effects of radiation in cancer therapy may not have a direct impact on the genetic material of the cancer cells. The effective target may be the surrounding (endothelial) cells that provide angiogenesis to satisfy the cancer cells' increased requirement for blood (Paris F et al 2001 Science 293:293). Radiotherapy has been used to treat lymph nodes to suppress Hodgkin's disease, radioactive isotopes can be injected for localized radiation. Similar effects are expected by the use of magic bullets. Blood withdrawn from the body has been irradiated by UV light and returned to the system. The level of radio-curability varies for tumors of different tissues from 2000–3000 rad for reproductive and nerve tissues, to 5000–6000 rad for lymphatic node and breast cancers, to 8000 rad for melanomas and thyroid cancer. The proper function of the radiation source must be regularly monitored to ensure the safety of patients and operators. It has been assumed that very high doses of radiation may not be as dangerous because they destroy the irradiated cells whereas a lower level of radiation involves higher cancer risks. However, recent observations have indicated that in radiotherapy after the initial killing specific areas in breast and lung cancer are repopulated by new cells, which have a high chance to develop second-cancer growth (Sachs RK, Brenner DJ 2005 Proc Natl Acad Sci USA 102:13040). ▶ radiation effects, ▶ magic bullet, ▶ Hodgkin's disease, ▶ lymph node, ▶ radiation hazard assessment; Bharat B et al (Eds.) 1998 Advances in Radiation Therapy, Kluwer, Boston, Massachusetts.

Radiation Threshold: The minimal harmful radiation dose is very difficult to determine because the visible physiological signs may not truly reflect the long-range mutagenic and carcinogenic effects. The maximal permissible doses for medical, diagnostic or occupational radiation exposures reflect only conventional limits that have been revised many times as the sensitivity of physical and biological detection methods as well as the instrumentation of delivery have improved. It is conceivable that no low threshold exists. ▶ radiation response, ▶ cosmic

radiation, ►mutation frequency-undetected mutations, ►radiation safety standards, ►radiation hazard assessment

Radical: Refers to an atom or a group with an unpaired electron, a free radical.

Radical Amino Acid Substitution: This occurs when nucleotide substitution alters the physicochemical property (e.g., charge, polarity, volume) of the mutant protein. By conservative substitution the physical/chemical characteristics are not altered. The proportions of radical/conservative ratios are positively correlated with the non-synonymous/synonymous replacements. Also, transversions are more likely to cause radical changes. ►synonymous codons; Zhang J 2000 *J Mol Evol* 50:56; Dagan T et al 2000 *Mol Biol Evol* 19:1022.

Radical Scavenger: This may combine with free radicals and reduce the potential harm caused by the highly reactive molecules.

Radicle: The seed or primary root of a plant embryo. It also refers to the smallest branches of blood vessels and nerve cells.

Radin Blood Group (Rd): This is encoded in the short arm of human chromosome 1; its frequency is low.

Radioactive Decay: ►isotopes

Radioactive Isotope: ►isotopes, ►radioactive tracer, ►radioactive label

Radioactive Label: Compounds (nucleotides, amino acids) containing radioactive isotopes are incorporated into molecules to detect their synthesis, fate or location (radioactive tracers) in the cells. For detection purposes, scintillation counters or autoradiography is used most frequently. Geiger counters may also qualitatively detect their presence. For cytological analysis, isotopes that have a short path of radiation and display distinct, sharp marks on the film are used, e.g., tritium (^3H). For molecular biology, most commonly ^{32}P (in DNA, RNA) or ^{14}C and ^{35}S (in proteins) or ^{125}I in immunoglobulins are used. Radioactive labeling for genetic vectors or transgenes is not practical because at each subsequent division the label is diluted to about half. Labeling with integrated genetic markers is more useful because these are replicated along with the genetic material. ►Southern blotting, ►Northern blotting, ►Western blotting, ►nick translation, ►non-radioactive labels, ►isotopes, ►radioactive tracer

Radioactive Tracer: A radioactively labeled compound that permits tracing the biosynthetic transformations of the supplied chemical by determining when the

radioactivity appears in certain metabolites after the supply. It also reveals what part of a later metabolite has acquired the label from the supplied substance. The availability of $^{14}\text{CO}_2$ permits tracing the path of photosynthesis, and through the use of various isotopes, the metabolism of pharmaceuticals and the role of hormones, etc., can be determined. ►radioactive label, ►radioimmunoassay

Radioactivity: Refers to the emission of radiation (electromagnetic or particulate) by the disintegration of atomic nuclei.

Radioactivity Dating: ►evolutionary clock

Radioactivity Measurement: ►radiation measurements

Radioautography: Same as autoradiography.

Radiocarbon Dating: The age of ancient samples of less than 50,000 years (late Pleistocene to Holocene) is generally estimated by this method in archeology and evolution. Natural radiocarbon is the product of the interaction of cosmic radiation with nitrogen 14 (N^{14}) in the earth's atmosphere. This unstable nitrogen is converted to carbon 14 (C^{14}), which is oxidized to $^{14}\text{CO}_2$ and enters plants through photosynthesis and from them to animals. C^{14} is very rare, only $\sim 1 \times 10^{-10}$ fraction of all naturally occurring carbon. Plants absorb this unstable C in proportion to the total C in the environment. When the plant dies, metabolism ceases and in its tissues the proportion of C^{14} decays according to the age of the relic. After every 5568 years the amount of C^{14} isotope is reduced by half. The reduction is measured in terms of the emission of 160 keV β -rays (electrons) by the sample. The wood found in the tomb of the pharaoh in the pyramid Djoser in 1949 contained 50% C^{14} indicating that its age was about 5568 years. The validity of this estimate required that the atmosphere contained the same amounts of C^{14} during that period as it did at the time of the analysis. The half-life figure of 5568 was later corrected to 5730 ± 40 (Cambridge half-life). Today improved methods are available such as the accelerator mass spectrometry or liquid scintillation, which provide greater accuracy yet even the most advanced methods struggle with some uncertainties. Nevertheless, the radiocarbon dating principle developed by Willard F. Libby in 1949 earned a much-deserved Nobel Prize in 1960.

Carbon dating is also used for determining human age. The carbon dating method may yield erroneous results if the samples are contaminated by more recent carbon. For example, 1% of such contamination in a 40,000 year old specimen may falsely reduce the age by 7,000 years. Another source of bias is that the C^{14} to C^{12} proportions varied in the earth's atmosphere because the magnetic field varied during

the ages and also sunspots affected the amount of cosmic radiation reaching the upper atmosphere. Newer techniques using higher molecular weight of animal and human bone gelatins substantially improved the accuracy level by eliminating contamination by C^{12} . The other source of error was considerably reduced by more accurate determination of C^{14} in deep sea strata during the last 50,000 years. The new calibrations indicate that human dispersal in Europe was thousands of years faster than originally estimated. Also, in Southern France humans appeared around 36,000 BP rather than 31,000 to 32,000 BP. As the methods of calibration improve, changes even in the newer estimates are likely (Mellers P 2006 Nature [Lond] 439:931).

After 1955 (the beginning of the atmospheric nuclear weapons tests) the C^{14} level in the air increased and it was fixed from carbon dioxide by photosynthetic plants and ingested by herbivores through the diet. C^{14} has accumulated in the teeth during the formation of new enamel up to the age of 12. Tooth enamel contains $\sim 0.4\%$ C. In spite of the fact that after the test ban treaties in 1963 the atmospheric C^{14} is decreasing yet the level is sufficient for the determination of its presence in the teeth in proportion to that in the atmosphere at the age of tooth development. Although individual variations in the age of tooth formation and diet affect the incorporated amounts, it is a very sensitive indicator of age (Spalding KL 2005 Nature [Lond] 437:333). [▶isotopes](#), [▶half-life](#), [▶evolutionary clock](#), [▶argon dating](#), [▶out-of-Africa hypothesis](#), [▶Eve foremother](#), [▶Lascaux cave](#); Libby WF 1955 Radiocarbon dating, University Chicago Press; Guilderson TP et al 2005 Science 307:362.

Radioimmunoassay (RIA): The most commonly used isotope for radioimmunoassays, $^{125}\text{I}^+$ is generated by oxidation of Na^{135}I by chloramine-T (*N*-chlorobenzene sulfonamide). This labels tyrosine and histidine residues of the immunoglobulin without affecting the binding of the epitope and provides an extremely sensitive method for identifying minute quantities (1 pg) of antigen in an experiment. ^{35}S -methionine or ^{14}C can radiolabel target proteins. In the *Competition*

RIA an unlabeled target protein competes with a labeled antigen for binding sites on the antibody. The amounts of bound and unbound radioactivity are then quantified. In the *Immobilized Antigen RIA* an unlabeled antigen is attached to a solid support and exposed to a radiolabeled antibody (see Fig. R9). The amount of radioactivity bound then measures the amount of specific antigen present in the sample. In the *Immobilized Antibody RIA* a single antibody is bound to a solid support and exposed to a labeled antigen. Again, the amount of bound radioactivity indicates the amount of antigen present. In the *Double-Antibody RIA* one antibody is bound to a solid support and exposed to an unlabeled antigen. After washing, the target antibody is quantitated by a second radiolabeled antibody (instead of the radiolabel, biotinylation can also be used). This assay is very specific because it involves a step of purification. [▶antibody](#), [▶immune reaction](#), [▶immunoglobulins](#), [▶isotopes](#), [▶Protein A](#), [▶IRMA](#); Eleftherios P et al (Eds.) 1996 Immunoassay. Academic Press, San Diego, California.

Radioisotope: [▶isotopes](#)

Radioisotope Dating: [▶fossil records](#)

Radiomimetic: These agents, primarily alkylating mutagens, may break single or both chromatids (isochromatids). Although it cannot be ruled out that the two chromatids break at the same place simultaneously, it is believed that isochromatid breaks are due to replicational events involving initially single chromatid breaks. They mimic the effects of ionizing radiation. [▶alkylating agents](#), [▶nitrogen mustards](#), [▶sulfur mustards](#), [▶epoxides](#), [▶ionizing radiation](#); Dustin AP 1947 Nature [Lond] 159:794.

Radiomorphoses: Morphological alterations in plants caused by ionizing irradiation during the life of the irradiated individuals. These effects may not be genetic.

Radionuclide: A nuclide that may disintegrate upon irradiation by corpuscular or electromagnetic radiation. [▶nuclides](#)

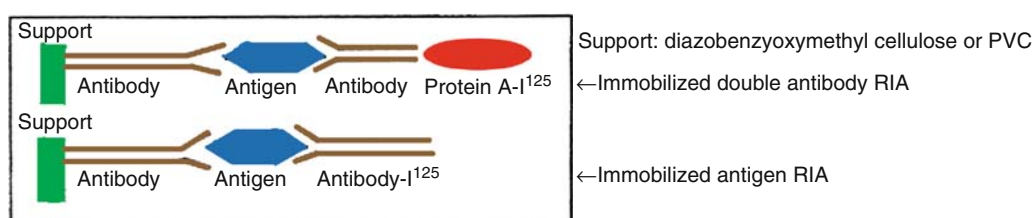


Figure R9. Radioimmuno assay

Radioprotectors: These protect against the harmful effect of ionizing radiation, e.g., sulfhydryl compounds, antioxidants, cysteine, cysteamine, amifostin and melatonin. (See separate entries; Maisin JR 1989 Adv Space Res 9[10]:205).

Radiotherapy: ►radiation therapy

Radioulnar Synostosis with Amegakaryocytic

Thrombocytopenia: Refers to dominant (7p15) bone fusion due to mutation in HOXA11 gene associated with abnormal easy bleeding. ►thrombocytopenia; Thompson AA, Nguyen LT 2000 Nature Genet 26:397.

Radish (*Raphanus sativus*): A cruciferous vegetable crop; $2n = 2x = 18$. The hybrid of *R. sativus* and *R. raphanistrum* appears to have an unusually superior fitness to both parental species and over a few generations drive to extinction the parental forms within a territory (Hegde SG et al 2006 Evolution 60:1187). ►Raphanobrassica, ►Brassica oleracea, ►mustards, ►fitness

Radix (root): A multiplier of successive integral powers of a sequence of digits, e.g., if the radix is 4, then 213.5 means 2 times 4 to the second power plus, 1 times 4 to the first power plus 3 times 4 to the zero power plus 5 times 4 to the minus 1 power.

Radon (Rn): ^{219}Rn (An) is a member of the actinium series, ^{220}Rn (Tn) is a member of the thorium emanation group and ^{222}Rn is derivative of uranium, a heavy (generally accumulates in basements), colorless radioactive noble gas which is formed by uranium (radium emanation) contaminated rocks. It may pose health hazards in buildings at some locations and with poor ventilation. In the USA, an estimated 200 mrem of radon is the average annual exposure/person. ►radiation hazards, ►cosmic radiation, ►rem, ►WL; Field RW, Becker K 2001 Radiat Prot Dosimetry 95:75.

RAF1: ►raf

raf: v-oncogene (cytoplasmic product is protein-serine/threonine kinase). The cellular homolog RAF1 is closely related to ARAF oncogenes. The v-raf is homologous to the Moloney murine leukemia virus oncogene. The avian MYC oncogene is the equivalent of the murine RAF. RAF1 has been assigned to human chromosome 3 and a pseudogene RAF2 is in chromosome 4. Human renal, stomach and laryngeal carcinoma cells reveal RAF1 sequences. Raf may be recruited to the cytoplasmic membrane by a carboxy-terminal anchor (RafCAAX) and its activation then

becomes independent from Raf which is associated with the plasma membrane cytoskeletal elements and not with the lipid bilayer. RAF-1 phosphorylates MEK-1 kinase involved in the signal transduction process of extracellular signal regulated kinases. RAF induces NF- κ B through MEKK1. Raf-1 is regulated by RKIP (Raf kinase inhibiting protein). Phosphorylation at the appropriate sites activates/inactivates RAF. The activation of Raf by basic fibroblast growth factor results in phosphorylation of serine 338 and 339 and activation by VGF phosphorylates tyrosine 340 and 341. Both pathways protect against apoptosis (Alavi A et al 2003 Science 301:94). ►ARA, ►MYC, ►Moloney, ►signal transduction, ►RAS, ►BRAF, ►v-oncogene, ►PAK, ►MAP kinase NF- κ B, ►MEKK, ►FGF, ►VGF, ►apoptosis; Chong H et al 2001 EMBO J 20:3716.

RAFT: The association of sphingolipids and cholesterol (~50 nm in diameter) and it mediates membrane traffic and cell signaling in mammals. Lipid rafts incorporate glycosylphosphatidyl inositol-anchored proteins, doubly acylated peripheral membrane proteins, cholesterol-linked proteins and transmembrane proteins. Host membrane-derived lipids surround enveloped viruses (e.g., HIV) that are acquired during budding in the replication process. The composition of these lipids is different from that of the host membrane. These lipid-enclosed structures indicate the existence of rafts within living cells (Brügger B et al 2006 Proc Natl Acad Sci USA 103:2641). Each raft does not carry more than 10 to 30 proteins. ►caveolae, ►endocytosis, ►sphingolipids, ►cholesterols, ►TOR, ►protein transport, ►liposome, ►SFK, ►HIV; Langlet C et al 2000 Curr Opin Immunol 12:250; Brown DA, London E 2000 J Biol Chem 275:17221; Simons K, Toomre D 2001 Nature Rev Mol Cell Biol 2:216.

RAFTK: ►CAM

RAG1, RAG2 (recombination activating gene): These are closely linked (11p13) and encode the proteins of lymphocyte-specific recombination of the V(D)J sequences of immunoglobulin genes. The functional part of RAG1 is the core sequence whereas other tracts can be deleted without affecting recombination. Mutation in RAG results in the inability to form functional antigen receptors on B and T cells and antibodies. The recombinational cleavage takes place between the *coding sequence* of the immunoglobulin genes and the so-called *recombinational signal sequence* (RSS) nucleotides. Recombination usually occurs between the original coding sequences or it may take place by the rejoining of one coding end, the signal sequence, which originally belonged to the other coding end (hybrid joint) or the same coding

and signal sequence end can be reunited (open-and-shut joint). Besides RAGs, the joining reaction requires the double-strand repair protein XRCC4, a DNA-dependent protein kinase and the Ku protein(s). For recombination, an accessory protein HMG1 or HMG2 is also required. Nucleotides may be added or deleted in each type of joining. RAG1 and RAG2 are actually transposons but after the joining of the V(D)J ends, normally following the formation of the antibody genes, RAGs are inactivated. RAG proteins seem homologous to the *Tc1* transposon of *Caenorhabditis*. The V(D)J recombinase shows a sequence similarity to retroviral integrase superfamily (Zhu L et al 2004 Nature [Lond] 432:995). RAG1 and RAG2 genes are coordinately regulated by cell-type specific elements upstream of RAG2. The 5' promoter upstream sequences in RAG2 regulate B and T cells differently. For T cells there are four T cell receptors (TCR) and for the B cell to recombine there are three immunoglobulin loci. ▶antibody, ▶immunoglobulins, ▶junctional diversification, ▶NHEJ, ▶combinatorial diversification, ▶RSS, ▶V(J)D recombinase, ▶XRCC4, ▶Ku, ▶DNA-PK, ▶TCR, ▶hybrid dysgenesis, ▶reticulosis familial histiocytic, ▶integrase; Schultz HY et al 2001 Molecular Cell 7:65; Qiu J-X et al 2001 Molecular Cell 7:77; Raghavan SC et al 2001 J Biol Chem 276:29126; Jones JM, Gellert M 2001 Proc Natl Acad Sci USA 98:12926.

RAGE (receptor for advanced glycation endproduct): A member of the immunoglobulin protein family on the cell surface. It interacts with multiple ligands and mediates homeostasis, development, inflammation, tumor proliferation, development and manifestation of some diseases (diabetes, Alzheimer's disease). RAGE is also a receptor for amphoterin. In cooperation with p21^{Ras}, MAP, NF-κB, CDC42, SAP/JNK, p44/p42 may alter cellular programming. By blocking the major factor complex of RAGE—amphoterin may prevent invasiveness of cancer and metastasis. (See individual entries of mentioned terms).

RAGE: Refers to random activation of gene expression.

Ragweed: A largely annual species of the genus *Ambrosia elatior* (Compositae) which is widespread in North America and Central Europe and causes pollen allergy (hay fever) of the nose and eye, skin irritations and even asthma without hay fever. The susceptibility is genetically controlled by a locus, *I_r*, within the HLA complex. The antigen E contained in the ragweed pollen elicits the IgE antibody. ▶HLA, ▶allergy, ▶atopy (See Fig. R10).

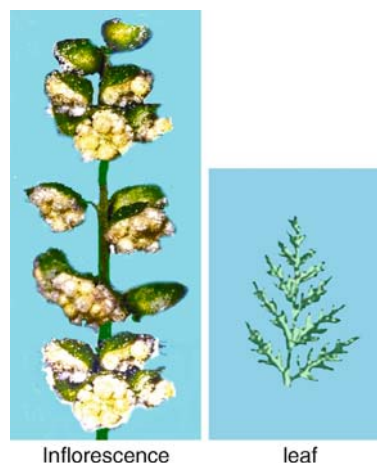


Figure R10. Ragweed (*A. artemisiifolia*)

RAIDD: An adaptor protein that joins the ICE/CED-3 apoptosis effector molecules. ▶apoptosis, ▶ICE

RALA: A RAS-like protein encoded in human chromosome 7. ▶RAS oncogene

RALB: A RAS-like protein encoded in human chromosome 13. ▶RAS oncogene

Raloxifene: A lipid-like molecule that enters the cell nucleus and can bind to the special raloxifene-response element in the DNA and activate the tumor growth factor-β3 gene (see Fig. R11). 17-epiestriol, an intermediate in the secretion of estrogen, activates Raloxifene. Raloxifene, an anti-estrogenic compound, is used in chemotherapy of breast cancer. Its advantage over the related compound tamoxifen is that it does not pose an appreciable risk for uterine cancer. ▶hormone-response elements, ▶estrogen receptor, ▶tamoxifen, ▶breast cancer, ▶estradiol; Greenberger LM et al 2001 Clin Cancer Res 7:3166.

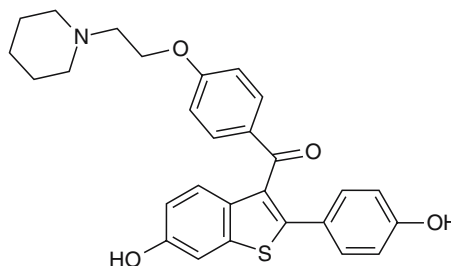


Figure R11. Raloxifene

RAM: ▶random-access memory in the computer, also rabbit-antimouse immunoglobulin

ram: Refers to ribosomal ambiguity mutation causing high rate of translational error. ►ambiguity in translation

Raman Spectroscopy: Similar to infrared spectroscopy, it uses 10,000 to 1,000 nm spectral regimes to detect different rotational and vibrational states of molecules. If two atoms are far apart, their interaction is negligible. If they are very close they may show repulsion. It is useful to obtain information on the physical state of nucleic acids. The technique can be applied for the detection of a variety of breast cancers. Although the signals are weaker than in other optical methods, they are very specific (Haka AS et al 2005 Proc Natl Acad Sci USA 102:12371). ►FT-IR; Thomas GJ Jr 1999 Annu Rev Biophys Biomol Struct 28:1.

Ramet: This is a clonal descendant of a plant capable of independent reproduction. ►genet

Ramie (*Boehmeria nivea*): A subtropical-tropical, monoecious fiber plant; $2n = 2x = 14$.

Rammer: Refers to the annotation of ribosomal genes (Lagesen K et al 2007 Nucleic Acids Res 35:3100).

RAMP (ribosomally encoded antimicrobial peptide): Refers to the natural defense molecules of animals, plants and fungi. ►antimicrobial peptides, ►defensin

Ramus (plural rami, Latin word): Denotes a branch; it is used in various word combinations.

RAN (RAS-like nuclear G protein, TC4): A guanosine triphosphatase (GTPase) which is required for import and export through nuclear pores and activation of the mitotic spindle. It acts as a switch of GTP→GDP in DNA synthesis and cell cycle progression. The proper balance between RanGTP and RanGDP determines the nucleo-cytoplasmic traffic. Cytoplasmic RanGTP may inhibit transport to the nucleus. The binding protein RanBP enhances the activity of RanGTP-activating protein RanGAP. RanBP1 is a nucleus-localized transporter binding well to RanGTP and weakly to RanGDP. RanBP2 is localized primarily in the cytoplasmic fibers of the nuclear pore complex. RAN also monitors the integrity of tRNAs before they are exported to the cytoplasm. RAN processes the 7S RNA into 5.8 ribosomal RNA of eukaryotes. ►GTPase, ►RAS, ►importin, ►export adaptor, ►signal transduction, ►cell cycle, ►RNA transport, ►RCC, ►GAP, ►nuclear pore, ►nuclear localization signal, ►Pat1, ►meiosis, ►TPX, ►SUMO; Nachury MV et al 2001 Cell 104:95; Carazo-Salas RE et al. 2001 Nature Cell Biol 3:228; Seewald M J et al 2002 Nature [Lond] 415:662.

Rana (genus of frogs): Both the American leopard frog (*Rana pipiens*) and the European frog *R. temporaria* have $2n = 26$ chromosomes. Frogs are generally more aquatic than toads. ►frog, ►Bufo, ►Xenopus, ►toad

Random Access Memory (RAM): This storage of information can be referred to at any order as long the computer is switched on.

Random Amplified Polymorphic DNA: ►RAPD

Random Chromosome Segregation: The gene under study is (absolutely) or very closely linked to the centromere in polyploids. ►maximal equational segregation

Random Fixation: ►random genetic drift, ►founder principle

Random Genetic Drift: A change in gene frequency by chance. Such random changes are most likely to occur when the effective size of the population is reduced to relatively few individuals. Since random drift may occur repeatedly, large changes may eventually result in the genetic constitution of the population. Such changes are likely when a few individuals migrate to a new (isolated) habitat. ►effective population size, ►founder principle; Whitlock MC 2000 Evolution Int J Org Evolution 54:1855.

Random Mating: Each individual in the population has an equal chance to mate with any other of the opposite sex (panmixis). Random mating is assumed in the majority of principles of theoretical population genetics. The rules are based on the Hardy-Weinberg theorem and on that basis the genetic structure of the population can be predicted as long as the allelic frequencies do not change or the change is negligible. Allelic frequencies may be altered primarily by selection, migration and, if the size of the population is very small, by random genetic drift. In the short run mutation does not affect allelic frequencies because of its rarity and the chances of survival of the majority of new mutations are low.

In a population involving two different allelic pairs the frequency of the mating genotypes and the genotypic proportion of their progenies derived from the binomial distribution by expanding $(p + q)^4$ (see Table R2). ►Hardy-Weinberg theorem, ►mating systems, ►Pascal triangle

Random Oligonucleotide Primers Used For Synthesis of Radioactive Probes: Heterogeneous oligonucleotides can anneal to different and many positions along a nucleic acid chain. They can also serve as primers for the initiation of DNA synthesis. If the precursors are one type of radioactive [α - 32 P]-deoxyribonucleotide (dNTP), and cold dNTPs, highly radioactive

Table R2. Random mating. $MATES \rightarrow (A1A1) \times (A1A1), (A1A1) \times (A1A2), (A1A2) \times (A1A2), (A1A2) \times (A2A2), (A2A2) \times (A2A2), (A1A1) \times (A2A2)$

| Frequency $\rightarrow p^4$ | $4p^3q$ | $6p^2q^2$ | $4pq^3$ | q^4 |
|-----------------------------|----------|-----------|--------------------------|-------|
| Progeny | A1A1 | A1A2 | A2A2 | |
| | p^4 | $2p^3q$ | p^2q^2 | |
| | $2p^3q$ | $4p^2q^2$ | $2pq$ | |
| | p^2q^2 | $2p^3$ | q^4 | |
| | 4 | 8 | 4 \rightarrow Sum = 16 | |

probes can be obtained. Single-stranded DNA templates can be copied with the aid of Klenow fragment of DNA polymerase I or in the case of RNA template reverse transcriptase can be used. The primers are usually short (6 to 12 base) and can be generated either by DNase digestion of commercially available DNA (from calf thymus or salmon sperm) or by an automatic DNA synthesizer. ►[probe](#), ►[nick translation](#)

Random Sample: This type of sample is withdrawn from a collection without any selection.

Random Variables: These may occur unpredictably in a sample because of unknown factors but their breadth can be described by statistical probability. ►[significance level](#), ►[inference statistical](#)

Random Walk: This is a physical theory of material distribution within media such as cell migration within connective tissues, Markov processes in DNA, diffusion in gases, liquids and solids, population changes as a result of birth and death, and evolutionary changes such as the emergence and extinction of species. (Berg HC 1993 Random walks in biology, Princeton University Press, Princeton, New Jersey; Cornette JL, Lieberman BS 2004 Proc Natl Acad Sci USA 101:187).

Range Constraints: The number of repetitive units of a microsatellite has limitations because of viability or adaptability. ►[microsatellite](#)

RANK (receptor activator of NF- κ B): ►[TRANCE](#)

RANTES (regulated on activation normally T-cell expressed and secreted): This is a chemoattractant of cytokines for monocytes and T cells. The chemokine receptors appear to be seven membrane proteins, coupled to G proteins. RANTES is also involved in a transient increase of cytosolic Ca^{2+} as well as Ca^{2+} release. The opening of the calcium channel increases the expression of interleukin-2 receptor, cytokine release and T cell proliferation. In

addition to inducing chemotaxis, RANTES can act as an antigen-independent activator of T cells in vitro. RANTES and MIP-1 chemokines along with the receptor CC CKR5 and fusin are believed to suppress replication of HIV. ►[MIP-1a](#), ►[fusin](#), ►[chemotaxis](#), ►[cytokine](#), ►[CC CKR5](#), ►[HIV](#), ►[acquired immunodeficiency](#), ►[T cell](#); Alam R et al 1993 J Immunol 150:3442; Casola A et al 2001 J Biol Chem 276:19715; structure of glycosaminoglycan interaction domain: Shaw JP et al 2004 Structure 12:2081.

RAP: ►[RNAIII/rnaii](#)

RAP: RAP30 and RAP74 are subunits of the general transcription factor TFIIF, which binds RNA polymerase II and recruits TFIID and TFIIB transcription factors to pol II (Conaway JW et al 2000 Trends Biochem Sci 25:375).

RAP1A (1p13.3), **RAP1B** (12q14), **RAP2** (13q34): These are RAS related eukaryotic proteins but unlike RAS they are localized on intracellular membranes. The guanine exchange factor of RAP1, Epac (exchange protein activated by cAMP) is activated by cAMP and it bears homologies to the regulatory subunit of PKA. Rap1A is a suppressor protein of Ras-induced transformation. It has identical amino acid sequences with the effector region of Ras p21. Along with SIR3, RAP1 is a transcriptional repressor of telomeric heterochromatin. RAP74 is a subunit of transcription factor TFIID and RAP74 is involved in binding to the serum response element. RAP1 (repressor/activator protein) of yeast binds to upstream activator sequences (UAS) alone as well as in association with other proteins; it also activates many genes besides silencing the mating type and the telomerase functions. Rap1 activates about 37% of RNA polymerase II initiations in yeast. Rap1 is also a negative regulator of TCR-mediated transcription of interleukin-2 (IL-2) gene. RAP1 may enhance meiotic recombination and opening up of the nucleosomal chromatin. RAP1 may stimulate the formation of boundary elements. The nerve growth factor (NGF) may signal to ERK (environmental regulated kinases) either through RAS or RAP. ►[RAS oncogene](#), ►[silencer](#), ►[serum response element](#), ►[transcription factors](#), ►[mating type determination](#), ►[telomerase](#), ►[TRF1](#), ►[TCR](#), ►[IL-2](#), ►[nucleosome](#), ►[PKA](#), ►[cAMP](#), ►[ORC](#), ►[HML and HMR](#), ►[boundary element](#), ►[adherens junction](#), ►[nucleoporin](#); Rousseau-Merck MF et al 1990 53:2; Morse RH 2000 Trends Genet 16:51; IdrissiF-Z et al 2001 J Biol Chem 276:26090.

Rapamycin (sirolimus): This immunosuppressor may block the cell cycle through the G1 phase by controlling mitogen-activated signal transduction. It regulates the prokaryotic ribosomal protein S6

and the elongation initiation protein eIF-4E (see Fig. R12). ▶FK506, ▶TOR, ▶cell cycle, ▶signal transduction, ▶S6 kinase, ▶eIF-4E, ▶immunosuppressant, ▶immunophilins, ▶non-ribosomal peptide; Cardenas ME et al 1998 Trends Biotechnol 16:427; Rohde, J. et al. 2001 J Biol Chem 276:9583.

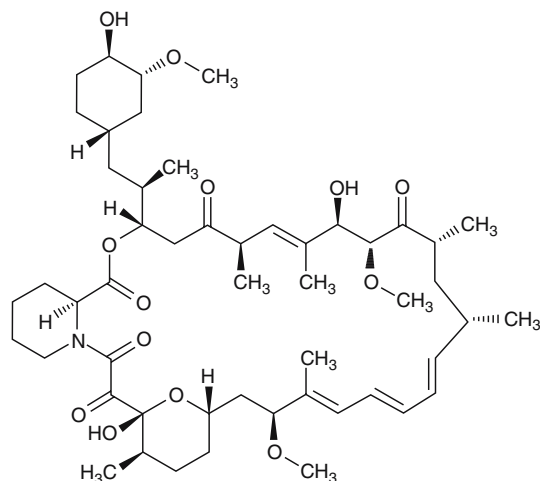


Figure R12. Rapamycin

RAPD (pronounce rapid): These markers are generated by random amplified polymorphic DNA sequences using (on average) 10 base pair primers and the PCR technique for the physical mapping of chromosomes on the basis of DNA polymorphism in the absence of “visible” genes. The map so generated may be integrated into RFLP and classical genetic maps. ▶polymerase chain reaction, ▶physical mapping, ▶sequence-tagged site, ▶integrated map; Reiter RS et al 1992 Proc Natl Acad Sci USA 89:1477.

R

Rape (*Brassica napus*): This is an oil seed crop ($2n = 38$, AC genomes). The new varieties are low in the toxic erucic acid and glucosinolates. ▶canola, ▶erucic acid

Raphanobrassica: This is a man-made amphidiploid ($2n = 36$) of radish (*Raphanus sativus*, $n = 9$, R genome) and cabbage (*Brassica oleracea*, $n = 9$, C genome). ▶*Brassica oleracea*, ▶radish, ▶amphidiploid

Raphe: Refers to a ridge on the seeds where the stalk of the ovule was attached; it also refers to the seam of animal tissues.

Raphids: These are needle-like crystals within plant cells (often of oxaloacetic acid).

Raphilin: This is a peripheral membrane protein. It may bind RAB proteins in a GTP-dependent manner and may be phosphorylated by various kinases and may bind Ca^{2+} and phospholipids. ▶RAB

Rapid Lysis Mutants: *r* mutants of bacteriophage rapidly lyse the infected bacteria and, therefore, the size of the plaques is much larger than the ones made by wild type phage (see Fig. R13). ▶lysis, ▶plaque lift, ▶lysis inhibition

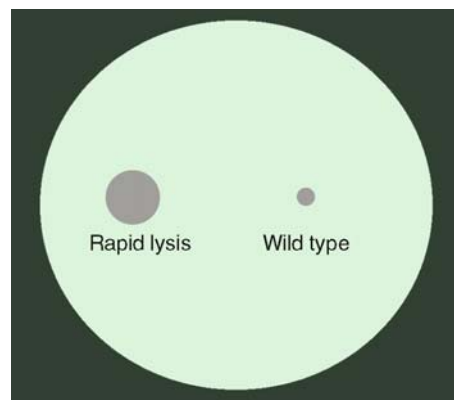


Figure R13 Rapid lysis mutants

Rapp-Hodgkin Syndrome: An anhidrotic ectodermal dysplasia with cleft lip and cleft palate. The latter symptoms do not always co-occur (mixed clefting). ▶ectodermal dysplasia, ▶anhidrosis, ▶cleft palate; Neilson DE et al 2002 Am J Med Genet 108:281.

Rapsyn (43 kDa): A peripheral membrane protein co-localized with the acetylcholine receptors at the neuromuscular synapsis. Mutations in rapsyn may lead to myasthenia. ▶acetylcholine, ▶myasthenia; Ohno K et al 2002 Am J Hum Genet 70:875.

RAR: Refers to repair and recombination.

RAR, RARE (retinoic acid receptor [element]): RAR and RXR- α , - β , - γ retinoid-X receptors are transducers of ligand-activated morphogenetic and homeostasis signals. RAR and RXR can form homodimers but are usually found as heterodimers. These then bind to the cognate hormone response elements and increase the efficiency of transcription. Docosahexaenoic acid ($\text{CH}_3[\text{CH}_2\text{CH}=\text{CH}]_6[\text{CH}_2]_2\text{CO}_2\text{H}$) is an activator of RXR. RAR- α ligands can accomplish the binding of the RXR-RAR- α dimers to DNA causing RXR activation and initiating the transcriptional activity of RAR- α . The RXR-RAR complex may also repress transcription. It is encoded in human chromosome 17q12. RAR may play a role in the development of promyelocytic leukemia (PML) when it associates with histone-deacetylase and other co-factors (see Fig. R14). In PML-RAR α patients pharmacological doses of retinoic acid lead to cancer remission because of the near normal differentiation of the hematopoietic (red blood-forming) cells but in

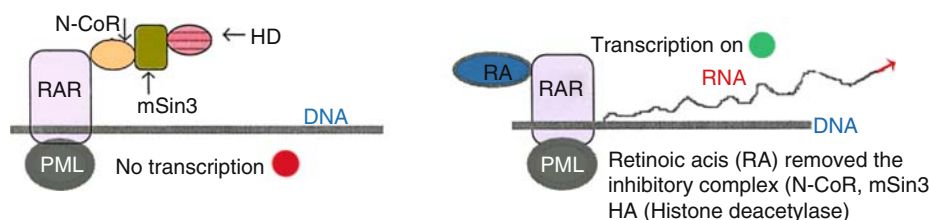


Figure R14. The action of RAR in promyelocytic anemia (Redrawn after Grignani, F. *et al.* 1998 Nature (Lond) 39:815)

promyelotic leukemia Zinc finger (PLZF) patients this treatment is quite ineffective. Retinoic acid may downregulate telomerase activity. The retinoid system also plays a role in differentiation, motor innervation of the limbs, skeletal development and in the development of the spinal cord. *RAR1* genes in plants play a defense role. ▶hormone response elements, ▶retinoic acid, ▶leukemia, ▶PPAR, ▶histone deacetylase, ▶Zinc finger, ▶innervation, ▶Sin3; Zhong S *et al* 1999 Nature Genet 23:287; Pendino F *et al* 2001 Proc Natl Acad Sci USA 98:6662.

RARE (RecA-assisted restriction endonuclease): At the site of a restriction enzyme recognition in or near a locus a triplex structure, with an oligonucleotide, is generated with the assistance of enzyme RecA. The genome is enzymatically methylated and RecA is removed. Only the site now unprotected will be cut by the restriction endonuclease. This procedure reduces the actual cleavage sites in the DNA. ▶recA, ▶restriction enzyme, ▶DNA methylation Ferrin LJ 2001 Mol Biotechnol 18[3]:233.

Rare-Cutter: This is a restriction enzyme with a longer DNA sequence (>8 nucleotides) recognition site. Therefore it cleaves DNA much less frequently (because of the greater specificity for sites) than enzymes which recognize only 4 bases in a sequence. ▶restriction enzyme

Rare-Mating: Cells of non-mating yeast strains are mixed with cells that are expected to mate under favorable conditions. Low frequency of mating may take place and the progeny may be isolated by efficient selection. Rare-mating is presumed to be the result of mitotic recombination or non-disjunction of chromosome III in the non-mating strain. When normal mating fails, protoplast fusion may generate hybrids. The latter procedure, however, produces complex progeny. ▶mating type determination, ▶protoplast fusion; Spencer JF, Spencer DM 1996 Methods Mol Biol 53:39.

RAS (p21^{ras}, 11p15.5): This is a protooncogene originally found in rat sarcoma virus; it codes for a monomeric GTP-binding protein in which point mutation mainly in codons 12, 13, 59 or 61 may lead

to oncogenic transformation. Alterations in site 12 in humans and in site 61 in rodents are common in tumors. RAS proteins have an important role in transmembrane signaling. Ras may have an alternate location at the Golgi membrane, depending on de/reacylation (Rocks O *et al* 2005 Science 307:1746). Protein Spred is an inhibitor of the RAS-MAP signaling pathway. The role of RAS may vary according to the cell type, from stimulation of adenylate cyclase to mating factor signal transduction and from proliferation to differentiation. The RAS protein becomes active only after prenylation by the 15-carbon farnesyl pyrophosphate. The prenylation is a thioether formation with an amino acid, resulting in the association of the protein with a membrane. RAS is not only one of the most important turnstile in signal transduction, but also one of the most common activated oncogenes. The activation involves changing of the bound GDP into GTP. GAPs (GTPase activating proteins) inactivate RAS by hydrolysis of GTP. In contrast GNRPs (guanine nucleotide releasing proteins) mediate the replacement of bound GDP by GTP and the activation of RAS. Receptor tyrosine kinases activate RAS either by inactivating GAP or activating GNP. The guanine-nucleotide exchange reaction is mediated by the SOS (son of sevenless) protein which has a GEF (guanidine exchange factor) domain. RAS is localized to the cell membrane. After ligand binding, SOS attaches to the adaptor protein Grb2 containing an SH3 domain and through the SH2 domain of Grb2 the complex binds to the phosphotyrosine residues of the signal receptor. The complex moving close to RAS makes possible that with the assistance of Cdc25, Sdc25 and GEF/GRF, respectively, the guanidine nucleotide is released. The RAS family is represented in various human chromosomes: NRAS in 1p21, HRAS in 11p15, KRAS in 6p12-p11 and RRAS in 19. Kras2 in mice has a tumor-inhibitory feature (Zhang Z *et al* 2001 Nature Genet 29:25). On the basis of homology three groups may be classified in mammals: (i) RAS, RAL, RRAS, (ii) RHO, and (iii) RAB. In *Drosophila* there are *Ras1* in 3–49, *Ras2* in 3–15 and *Ras3* in 3–1.4 (the latter has a higher homology to *Rap1* and it is now known as *Rap1*). In yeast, RAS homologs (*RAS1* and *RAS2*) are very closely related to the human protooncogenes

and can be replaced by them. RAS protein is also necessary for the completion of mitosis, in association with other factors. Probably, all eukaryotes carry RAS homologs. The p21 protein is also a mobile RAS protein. The RAS oncogene is generally active in tumorigenesis in the presence of the MYC or the E1A “immortalizing” oncogene products. MYC in cooperation with RAS mediates the progression of the cell cycle from G1 to the S phase through induction of the accumulation of active cyclin-dependent kinase and transcription factor E2F. The presence of RAS is necessary for tumor maintenance. The RAS promoter is high in GC and lacks a TATA box. The various RAS genes (human, mouse) may have more than 50% difference at the nucleotide level but the amino acid composition is highly conserved. RAS mutations have been detected in 90% of pancreatic adenocarcinomas, ~40–50% of colon adenocarcinomas and in other cancers. According to a genome-wide survey, RAS affects the expression of more than 250 genes. ▶G-proteins, ▶RAB, ▶raf, ▶BRAF, ▶RALA, ▶RALB, ▶RHO, ▶RAP, ▶RASA, ▶oncogenes, ▶signal transduction, ▶adenylate cyclase, ▶farnesyl, ▶prenylation, ▶p21, ▶GTPase, ▶MYC, ▶cell cycle, ▶retinoblastoma, ▶GEF, ▶Cdc25, ▶Sdc25, ▶GD, ▶SOS, ▶SH2, ▶SH3, ▶Grb2, ▶EF-Tu, ▶animal models, ▶Costello syndrome, ▶Seladin-1; Zuber J et al 2000 Nature Genet 24:144; Johnson L et al 2001 Nature [Lond] 410:1111; Stacey D, Kazlauskas A 2002 Current Opin Genet Dev 12:44; Quilliam LA et al 2002 Progr Nucleic Acid Res Mol Biol 71:391; Downward J 2003 Nature Rev Cancer 3:11; Asha H et al 2003 Genetics 163:203.

RASA: This is a guanosine triphosphate activating RAS protein (21 kDa [p21]) encoded by human chromosome 5q13.3 and in mouse chromosome 13. ▶RAS oncogene

rasiRNA (repeat-associated siRNA): This silences endogenous (selfish) retroelements and repetitive sequences in the *Drosophila* germ line. rasiRNA (24–29 nucleotides) is produced primarily from the antisense strand of the double-strand precursor unlike siRNA, which is made of both strands. rasiRNA does not require Dicer-1 or Dicer-2 and it functions through the Piwi system rather than through the Argonaute. ▶siRNA, ▶microRNA piRNA, ▶retroelements; Vagin VV et al 2006 Science 313:320; Lalith S et al 2007 Science 315:1587.

Raspberry (*Rubus* spp.): The majority of raspberries are diploid ($2n = 14$), loganberry is $2n = 42$, and blackberries have $2n = 28$, 42 and 56 chromosomes. It is likely that some wild blackberries are allopolyploids with $2n = 35$ and $2n = 84$; the latter is dioecious.

Rasmussen's Encephalitis: ▶epilepsy

Rassenhygiene: This is the German term for negative eugenics [often so used]. The purpose was to protect the “purity” of the Aryan (German) race and it was enforced by the laws of the Nazi state. Between 1933 and 1945, it led to 350,000 forced sterilizations, mass murder of millions and ban on marriages between genetically fit and “unfit”, and persons whose ancestry included more than 1/4 Jews, Gypsies or other racial groups. ▶eugenics, ▶racism; Hubbard R 1986 Int J Health Serv 16:227.

Rat (*Rattus norvegicus*, $2n = 42$): A genetic linkage map was published by Jacob and others (1995 Nature Genetics 9:63). A radiation hybrid map of 5,255 markers was prepared by Watanabe and associates. (1999 Nature Genet. 22:27). A high quality nucleotide sequence map covers more than 90% of the 2.75 gigabase genome (Nature [Lond] 428:493 [2004]). The chromosome number of other rat species may be different. A strain of albino rats developed by the Sprague-Dawley Animal Company is widely used in experimental work because of the calmness and ease of handling. (For EST map see Scheetz TE et al 2001 Genome Res 11:497). (See knockdowns: Tenenhouse DC et al 2006 Proc Natl Acad Sci USA 103:11246; EST map: <http://ratEST.uiowa.edu>; <http://ratmap.gen.gu.se>; <http://www.tigr.org/tdb/tgi/>; <http://rgd.mcw.edu/>; genome: <http://www.hgsc.bcm.tmc.edu/projects/rat/>; physiological studies: <http://pga.mcw.edu/>; rat resource and research center: <http://www.nrrtc.missouri.edu/>; rat genome database, strains: <http://rgd.mcw.edu/7778/strains/>; <http://www.nrrtc.missouri.edu/Straininfo.asp?appn=46>).

Rate-Limiting Step: This requires the highest amount of energy in a reaction chain or in a metabolic path, the slowest step.

Rate Matrix: Refers to base pair changes between two genomes. It is used by different algorithms to reveal the most likely evolutionary path of genomes. ▶genomics

Ratio Labeling: Using the FISH cytological technology different chromosomes may be labeled by varying proportions of the same fluorochromes to distinguish individual chromosomes in the genome by color. ▶FISH, ▶combinatorial labeling

Rationale: This is the logical basis of an act, a process or an argument.

Rationalize: Refers to an attempt to make something conform to reason. Sometimes apparent rationalization is used in an effort to explain facts or ideas for which there is no adequate justification.

Raynaud Disease (hereditary cold fingers): This condition is characterized by familial periodic numb and white finger attacks. ► [vasculopathy](#)

Raynaud Syndrome: This condition is characterized by scleroderma, cyanosis, cold intolerance, chromosomal aberrations, telangiectasia without a clear pattern of inheritance. ► [scleroderma](#), ► [telangiectasia](#), ► [cyanosis](#)

RB: Refers to the right border of T-DNA. ► [T-DNA](#)

Rb: ► [retinoblastoma](#)

RbAp: These are proteins of the WD family of wide regulators of chromatin, transcription and cell division. ► [WD-40](#); Rossi V et al 2001 Mol Genet Genomics 265:576.

rBAT/4F2hc: These are four membrane-spanning proteins involved in membrane transport or regulation of transport of neutral and positively charged amino acids. ► [cystinuria](#), ► [transporters](#); Malandro MS, Kilberg MS 1996 Annu Rev Biochem 65:305.

rbc: Denotes ribulose biphosphate carboxylase/oxidase genes. ► [chloroplast genetics](#)

RBE (relative biological effectiveness of radiation): This depends on a number of physical (type of radiation, wavelength, dose rate, temperature, presence of oxygen, hydration, etc.), physiological (developmental stage) and biological factors (species, nuclear size and DNA content, level of ploidy, repair system, etc.). The comparison usually relates to ^{60}Co gamma radiation. ► [rem](#), ► [radiation effects](#)

RBF (recoverable block of function): This system permits exogenous (conditional) regulation of fertility of plants. For example, when the barnase gene is linked to any gene it inactivates its pollen and therefore cannot be transmitted by sexual means. The expression of barnase in tobacco is under the control of sulfhydryl endopeptidase. Recovery from the barnase effect is managed by barnstar under the control of a heatshock promoter. Such a system may be used to reduce the risk of escape of transgenes from GMO plants into related organisms in the environment. ► [barnase](#), ► [barnstar](#), ► [heat-shock proteins](#), ► [terminator technology](#), ► [GMO T-GURT](#); Kuvshinov VV et al 2001 Plant Sci 160:517.

RBM (RNA-binding-motif, also called RBMY, YRRM): This gene family is found only in the Y chromosome of mammals involved in male fertility. The HNRPG (hnRPG) gene located in human autosome 6p12 shows ~60% homology to RBM. It is assumed that this autosomal locus was retrotransposed in an early ancestor to the Y chromosome. Similarly, in Xq26 sequences virtually identical to

exon 12 of hnRPG have been found. It appears that the chromosome 6p12 sequence is a processed pseudogene of the Xq26 sequence and there are similar sequences in chromosomes 1, 4, 9 and 11, all retrotransposed from Xq26. BFLS actually manifests hypogonadism and it is assigned to the same location as RBM. ► [DAZ](#), ► [boule](#), ► [PABp](#), ► [chromosome](#), ► [Borjeson-Forssman-Lehmann syndrome \[BFLS\]](#), ► [NRY](#), ► [azoospermia](#)

R2Bm: This is a silkworm retroelement without long terminal repeats. ► [retrovirus](#), ► [silkworm](#); Luan DD et al 1993 Cell 72:595.

RBMY: ► [RBM](#)

RBTN (rhombotin): A cystine-rich oncoprotein family (encoded in human chromosome 11) containing a LIM domain. ► [LIM domain](#); Chan SW, Hong W 2001 J Biol Chem 276:28402.

Rbx1: A ring finger protein homolog of APC (anaphase-promoting complex) which is required for SCF and VCB-mediated ubiquitination of Sic1 and probably other proteins. ► [ubiquitin](#), ► [APC](#), ► [ring finger](#), ► [SCF](#), ► [Sic1](#); Carrano AC, Pagano M 2001 J Cell Biol 153:1381.

RCA (regulators of complement activation): ► [MCP](#), ► [complement](#)

RCA (replication competent adenovirus): This should be kept as low as possible (<1 RCA/dose) for adenoviral vectors to avoid damage. RCA reduction can be accomplished by deleting the E1 region of the vector and shortening the potentially complementing tract of the host. ► [adenovirus](#)

RCAF (replication-coupling assembly factor): Mediates chromatin organization into nucleosomes during replication. It consists of Asf1 protein, H3 and H4 histones. ► [nucleosomes](#), ► [CAF](#), ► [ASF1](#); Tyler JK et al 1999 Nature [Lond] 402:555.

RCC1: This is a chromatin-bound guanine nucleotide release factor that forms complexes with RAN (a G protein). Its deficiency interferes with the cell cycle progression, chromosome decondensation, mating, RNA export and protein import. It is a part of the nuclear pore complex. Its yeast homolog is Prp20p. ► [RAN](#), ► [cell cycle](#), ► [nuclear pores](#), ► [RNA transport](#), ► [TPX](#); Hood J 2001 Trends Cell Biol 11:321; Renault L et al 2001 Cell 105:245.

RCC (renal cell carcinoma, human chromosome 3p14.2): RCC gene product frequently interacts with that of the von Hippel-Lindau (VHL) gene. ► [renal cell carcinoma](#), ► [von Hippel-Lindau disease](#)

RCR: Denotes recombination competent retrovirus. ► [retrovirus](#), ► [retroviral vectors](#), ► [gene therapy](#)

RcsC: Refers to *E. coli* kinase affecting capsule synthesis regulator RcsB. (See Davalos-Garcia M et al 2001 J Bacteriol 183:5870).

RcsG: A 30.6 kDa protein with a C-terminal motif and a N-terminal sequence similar to that of DnaJ. In concert with RcsC/B and DnaK and GrpE, it induces the *cps* capsule polysaccharide operon of *E. coli*.
 ▶DnaJ, ▶RcsC

RDA (representational difference analysis): This is a genome scanning procedure for the detection and identification of genetic markers representing disease, other genes and chromosomal aberrations. The cellular DNA is cut by restriction endonuclease(s) and the smaller fragments are amplified by PCR. DNA samples from affected and disease-free samples are denatured and the mixtures of the two samples are allowed to anneal. The sequences which do not match fail to hybridize and are believed to cause the disease. In principle, the process is similar to cascade hybridization. The relatively rapid mass screenings were expected to identify individuals predisposed to particular hereditary differences (diseases). The same procedure may be applicable to non-disease genes of eukaryotes. RDA and GDRDA procedures can be used to generate genetic maps in organisms with a paucity of chromosomal markers. ▶cascade hybridization, ▶PCR, ▶GMS, ▶GDRDA, ▶genetic screening, ▶positional cloning, ▶RNA fingerprinting, ▶genomic subtraction, ▶comparative genomic hybridization; Lisitsyn N et al 1993 Science 259:946; Tyson KL et al 2002 Physiol Genomics 9:121; copy number variations between normal and tumor specimens of mice: Lakshmi B et al 2006 Proc Natl Acad Sci USA 103:11234.

RdDM (RNA-dependent DNA methylation): DNA sequences identical to silenced RNA are methylated at cytosine residues in plants (Cao X et al 2003 Curr Biol 13:2212) but not necessarily in mammalian cells (Park CW et al 2004 Biochem Biophys Res Commun 323:275). ▶RNAi, ▶methylation of DNA

rDNA: Refers to DNA complementary to ribosomal RNA. The ribosomal RNA genes are in the nucleolar organizer region of the eukaryotic chromosomes and there are multiple tandem repeats of transcriptional units consisting of 18S, 5.8S, 5S and 26S RNAs. The mature rRNAs are cleaved from the large transcripts. In yeast the *FOB1* gene enhances recombination in rDNA. ▶ribosome, ▶rRNA; Long EO, Dawid IB 1980 Annu Rev Biochem 49:742.

RdRP (RNA directed RNA polymerase, RDR): This may be involved in gene silencing by synthesizing antisense transcripts from aberrant RNA and thereby causing PTGS. RdRP may generate double-stranded

RNA of single-strand transcripts and play a role in RNAi production. RdRP may convey virus resistance to plants and various types of post-transcriptional gene silencing (Sugiyama T et al 2005 Proc Natl Acad Sci USA 102:152). ▶PTGS, ▶epigenesis, ▶antisense RNA, ▶RNAi, ▶host-pathogen relation, ▶RNAi; Cheng J et al 2001 Virus Res 80:41.

Reaction, Chemical: Denotes a change in the atoms in or between molecules.

Reaction Intermediate: Refers to a short life chemical in a reaction path.

Reaction Norm: This denotes the range of phenotypic potentials of expression of a gene or genotype. Usually, the genes do not absolutely determine the phenotype but they permit a range of expressions, depending on the genetic background, developmental and tissue-specificity conditions and the environment. ▶genotype, ▶phenotype, ▶regulation of gene activity, ▶epigenesis, ▶plasticity, ▶homeostasis, ▶fitness, ▶adaptation, see Fig. R15; Wolterreck R 1909 Verhandl Dtsch Zool Ges p 110.

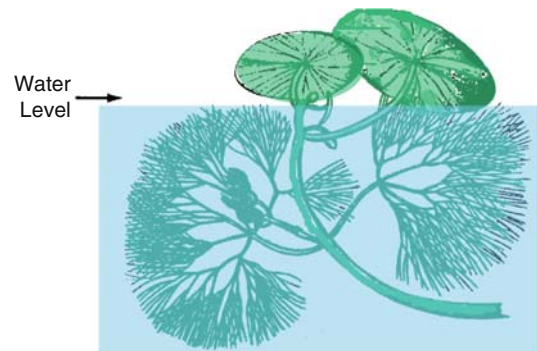


Figure R15. Reaction norm of water lily (farnwort): above water the leaves are different from below water (Goebel, K. 1893 Pflanzenphysiologische Schilderungen Elvert, Marburg, Germany)

Reactivation: ▶multiplicity reactivation, ▶Weigle reactivation, ▶marker rescue

Reactivity in Hybrid Dysgenesis: ▶VAMOS

Reactome: Refers to protein interaction pathways database (formerly called the genome knowledge base). ▶protein interaction, ▶genetic networks; <http://www.reactome.org/>.

Read: This is a nucleotide sequence determined in a single gel.

Reading Disability: ▶dyslexia

Reading Frame: The triplet codons can be read in three different registers, starting with the first, second or third, however, only one may spell the correct protein.
 ▶open reading frame, ▶frameshift mutation

Readout: The DNA sequence recognition by proteins may be *direct* (by hydrogen bonding) or *indirect* when the DNA conformation also plays a role. [▶binding proteins](#)

Readthrough: The ribosome continues translation downstream of a stop codon. On an average human hereditary disease is due to the inability to read-through translation-termination nonsense mutation. Some antibiotics (gentamycin) promote readthrough. Unfortunately, it is not useful for clinical purposes because the effective dose produces serious side effects. On the basis of a screening of 800,000 low molecular weight compounds, one report identified PTC124 (3-[5-(fluorophenyl)-[1,2,4]oxadiazol-3yl])-benzoic acid that promoted UGA nonsense suppression at a maximal effective concentration of 3 μM (852 ng mL⁻¹). PTC124 promoted dystrophin production in humans afflicted by muscular dystrophy and in a comparable mutant mice model. Muscle function was restored within 2–8 weeks of exposure to the drug. It was effective to a lesser degree in the case of UAG and UAA nonsense codons. No serious side effects were observed (Welch EM et al 2007 Nature [Lond] 447:87). [▶translation termination](#), [▶autogenous suppression](#), [▶nonsense codon](#), [▶gentamycin](#), [▶genetic medicine](#), [▶muscular dystrophy](#), [▶genetic diseases](#)

Readthrough Protein: This is formed when a suppressor tRNA inserts an amino acid at a site where chain termination is normally expected because of a nonsense codon and thus produces a fusion protein from two different “in-frame” cistrons, separated by a nonsense codon. Readthrough may be brought about by mutation in the anticodon of a tRNA or modification of the tRNA, e.g., selenocysteinyl-tRNA inserts selenocysteine into glutathione oxidase by recognizing the UGA (opal) stop codon. [▶gene fusion](#), [▶transcriptional gene fusion](#), [▶translational gene fusion](#), [▶trapping promoters](#)

Real Time: This means the actual time during which the physical process takes place.

Realized Heritability: [▶gain](#)

Reannealing (reassociation): Double-stranded DNA can be heat denatured (strands separated) and can be restored to double-stranded form, reannealed, when the temperature falls below 60°C. [▶c₀t curve](#)

Rearrangements: These are structural changes of the chromosome(s), e.g., translocation, inversion. [▶chromosomal rearrangements](#)

Reasoning: [▶inference](#)

Reassociation Kinetics: [▶c₀t curve](#)

Reassortant: This is a new virus strain that emerges from a combination of genes of two different strains, e.g., the pandemic influenza strains of 1957 and 1968 contain elements enabling the virus to replicate in humans and the avian segment. The hemagglutinin coding-segment assists in preventing the neutralization of antibodies of humans not previously exposed to the avian flu virus. [▶pandemic](#), [▶hemagglutinin](#), [▶influenza virus](#)

Rec8: This meiotic cohesin is cleaved by separin before chiasma are resolved and meiotic anaphase I can proceed. In vertebrates cohesin is removed during prophase but Scc1 remains associated with the centromeres when separin cleaves this protein and thus facilitates the metaphase-anaphase transition. [▶cohesin](#), [▶separin](#); Buonomo SB et al 2000 Cell 103:387; Waizenegger IC et al 2000 Cell 103:399.

rec: Refers to one or another type of recombination-deficient mutation.

RecA Protein: This is a 38.5 kDa polypeptide involved in homologous recombination by promoting pairing. It is a DNA-dependent ATPase which mediates strand exchange. RecA binds to single-stranded DNA and pre-synaptic nucleoprotein molecules mediate the pairing with the duplex DNA target. The paired DNA is inside a 25 Å hole. Inside this cavity projecting toward the axis of the helix are mobile loops L1 and L2 representing the binding sites. RecA appears to play a role in the segregation of the bacterial chromosomes (Ben-Yehuda S et al 2003 Science 299:532). The RecA protein expressed in transgenic plants substantially increases recombinational repair of DNA damage inflicted by mitomycin. The RecA prokaryotic gene when equipped with the nuclear localization signal and transformed into tobacco cells increases sister chromatid exchange by ~two-threefold. Structural and functional homologs of the bacterial RecA are UvsX (phage), Rad51 (eukaryotes) and RadA (archaea). The RecA protein is required for the maintenance of around 40 proteins necessary for the continuation of replication following DNA damage (Courcelle J, Hanawalt PC 2003 Annu Rev Genet 37:611). [▶recombination molecular mechanism prokaryotes](#), [▶DNA repair](#), [▶RecA-independent recombination](#), [▶RecA1](#); Kowalczykowski SC, Eggleston AK 1994 Annu Rev Biochem 63:991; Gourves A-S et al 2001 J Biol Chem 276:9613; Bar-Ziv R, Libchaber A 2001 Proc Natl Acad Sci USA 98:9068; Robu ME et al 2001 Proc Natl Acad Sci USA 98:8211; Gasior SL et al 2001 Proc Natl Acad Sci USA 98:8411; Lusetti SL, Cox MM 2002 Annu Rev Biochem 71:71.

recA1: A recombination deficient mutation of *E. coli* (map position 58 min) coding for a DNA-dependent

ATPase, a 3522-amino acid residue enzyme. Plasmids carrying it remain monomeric and do not form multimeric circles. When M13 vectors carry it, the foreign passenger DNA has fewer deletions. The *recA* protein mediates the association of double-stranded DNAs by synapsis mainly in the major groove but also in the minor groove of the DNA. The RecA-mediated pairing involves a triplex structure, i.e., along parts of the sequences double-stranded DNA associates transiently with a single strand of the other DNA molecule. The pairing of the DNA molecules may be plectonemic (intertwined) and thus may not require stabilization by proteins. (The paranemic coils are only juxtapositioned and require protein to keep them together.) Experimental data have revealed that ATP hydrolysis is not required for the exchange between paired strands rather the removal of RecA requires ATP hydrolysis. In case the homology between the DNAs is not perfect, ATP is needed for the exchange. RecA is also involved in branch migration but with the assistance of RuvAB and RecG proteins. The extension of the DNA heteroduplex (at the rate of 2–10 bp/sec) in the 5'→3' direction needs ATP hydrolysis. The length of the heteroduplex may increase to 7 kbp. In both prokaryotes and eukaryotes besides RecA (or homologs), a stimulatory exchange protein, binding single strands of the DNA (SSB) is required. The SSB monomers (1/15 base in ssDNA) facilitate synapsis between the heterologous strands. After exchange RecA promotes DNA renaturation. The RecA homologs in yeast, mouse and humans are the RAD51 proteins, and Mei3 in *Neurospora*. (Recombination molecular mechanisms prokaryotes, branch migration, *recB*, other *Rec* genes, DNA repair, RuvABC, RAD).

RecA-Independent Recombination (illegitimate recombination): This may use three pathways (i) simple replication slippage, (ii) sister chromatid-associated replication misalignment, and (iii) single-strand annealing. Single-strand annealing takes place after palindromic sequences within each strand fold into hairpin structures within the strands. When a nuclease (SbcCD) opens the cruciform palindromes resection, followed by annealing of the flanking repeats brings about deletion (see Fig. R16.). RecA-independent recombination occurs at extremely low frequencies and is less responsive to the extent of homology. RecA-independent recombination in *Escherichia coli* is depressed by the redundant action of single-strand exonucleases. In the absence of multiple single-strand exonucleases, the efficiency of RecA-independent recombination events, involving either gene conversion or crossing over, is markedly increased to levels rivaling RecA-dependent events. It seems that RecA-independent recombination is not

intrinsically inefficient but is limited by the single-strand DNA substrate availability. Crossing over is inhibited by exonucleases ExoI, ExoVII, ExoX and RecJ, whereas only ExoI and RecJ abort gene-conversion events. In ExoI– RecJ– strains, gene conversion can be accomplished by the transformation of short single-strand DNA oligonucleotides and is more efficient when the oligonucleotide is complementary to the lagging-strand replication template (Dutra BE et al 2007 Proc Natl Acad Sci USA 104:216). ▶illegitimate recombination, ▶palindrome, ▶exonuclease; Bzymek M, Lovett ST 2001 Proc Natl Acad Sci USA 98:8319.

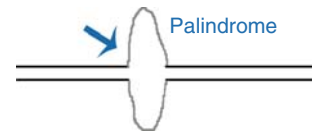


Figure R16. Palindrome

recB: *E. coli* gene (map position 60 min) encoding a subunit of exonuclease, controlling recombination and genetic repair. ▶recombination molecular mechanism prokaryotes, ▶recombination models, ▶DNA repair

RecBCD: An enzyme (ribozyme) complex functioning in recombination of prokaryotes. RecBCD is a helicase and unwinds up to 42,300 bp per molecule, it is a strand specific nuclease. The recognition sequence (also called χ , [chi]) is 5'-GCTGGTGG-3' promotes recombination in its vicinity by recruiting the RecA protein. The enzyme travels along one of the two strands of the DNA in 3'→5' direction. ▶recombination molecular mechanism prokaryotes, ▶recombination models, ▶chi, ▶DNA repair, ▶RecA, ▶AddAB; Jockovich ME, Myers RS 2001 Mol Microbiol 41:949; Taylor AF, Smith GR 2003 Nature [Lond] 423:889; Dillingham MS et al 2003 Nature [Lond] 423:893; crystal structure: Singleton MR et al 2004 Nature [Lond] 432:187.

recC: *E. coli* gene (map position 60 min) encoding a subunit of exonuclease V, controlling recombination and genetic repair. ▶recombination molecular mechanisms, ▶DNA repair; Chen HW et al 1998 J Mol Biol 278:89.

recE: This is the locus of Rac prophage (map position 30 min), encoding exonuclease VIII and promoting homologous binding between single-stranded and double-stranded DNAs. ▶RecA; Muylers JP et al 2000 Genes Dev 14:1971.

RecF: Refers to a single- and double-strand binding recombination protein. (See Nakai H et al 2001 Proc Natl Acad Sci USA 98:8247).

RecG: This unwinds the leading and lagging strands at a damaged replication fork and may contribute to replication restart if it was stalled by the damage. ▶[replication restart](#); McGlynn P, Lloyd RG 2001 Proc Natl Acad Sci USA 98:8227.

RecJ: A single-strand (5'→3') exonuclease used in recombination of *E. coli*. (Hill SA 2000 Mol Gen Genet 264[3]:268).

RecO: A bacterial homolog of the eukaryotic Rad52 protein, which stimulates Rad51 in exchange and mediates single-strand DNA annealing function in recombination. RecO bears functional similarity to bacteriophage T4 protein UvsY. The optimal functioning of RecO necessitates association with the single-strand binding (SSB) proteins in equal proportion of the two. The RecR protein stimulates RecO to facilitate the displacement of SSB by RecA. ▶[Rad51](#), ▶[RecR](#); Kantake N et al 2002 Proc Natl Acad Sci USA 99:15327.

RecQ: Refers to *E. coli* DNA helicase. Homologs of the prokaryotic enzyme exist in eukaryotes and the enzyme resolves secondary structures of the DNA at stalled or broken replication forks. It is a multidomain enzyme. The catalytic core determines the ATPase and helicase functions. The helicase RNase-D-C-terminal domain shows globular fold binding preferentially to single-stranded DNAs and this latter domain apparently determines the specificities of the enzymes found in different organisms (Bernstein DA, Keck JL 2005 Structure 13:1173). ▶[helicase](#); Wu X, Maizels N 2001 Nucleic Acids Res 29:1765; Cobb JA et al 2002 FEBS Lett 529:43; Cui S et al 2003 J Biol Chem 278:1424.

RecR: This mediates DNA renaturation during recombination of *E. coli* (Pelaez AI et al 2001 Mol Genet Genomics 265:663).

RecT: This is encoded by *recE*. It is involved in renaturation of homologous single-stranded DNA and pairing of DNA. ▶[RecE](#), ▶[pairing](#)

RecU: This is a protein in gram positive bacteria. Its absence increases sensitivity to DNA damage, reduces plasmid transformation and affects the segregation of the chromosome in *Bacillus subtilis*. It binds preferentially to single-stranded DNA and cleaves recombination intermediates (Holliday junctions) and anneals single-stranded DNA. ▶[Bacillus subtilis](#), ▶[Holliday junctions](#); Ayora S et al 2004 Proc Natl Acad Sci USA 101:452.

Receptacle: This is the widened end of a flower stalk. It also refers to a container. (See Fig. [R17](#)).

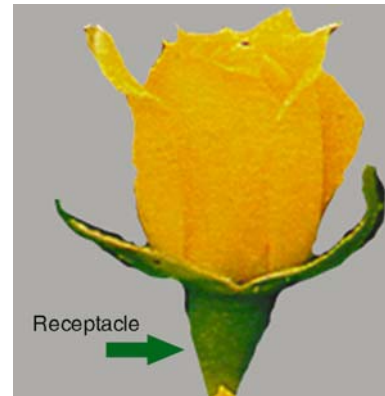


Figure R17. Receptacle

Receptin: This is a natural or engineered microbial protein which can bind to a mammalian protein. It is useful for the identification of individual components of a proteome. It is similar to lectins which bind carbohydrates. ▶[lectins](#), ▶[affibody](#), ▶[monoclonal antibody](#), ▶[MSCRAMM](#); Kronvall G, Jonsson K 1999 J Mol Recognition 12:38–44.

Receptor: This is also called an operator. The site responding to the controlling element (transposase) as originally called by Barbara McClintock the components of the *Spm* transposable systems in maize. ▶[transposable elements of maize receptors](#)

Receptor: Refers to proteins that bind to ligands with cellular signaling functions. Receptors may be located within the plasma membrane (transmembrane proteins) or are intracellular and bind ligands, which penetrate cells by diffusion. Some receptors are ligand-gated ion channels. The number of receptors in a cell may run into hundreds. Several agonists and antagonists may affect their function. Cell surface receptors mediate in some cell to cell and virus–cell interactions. Cell surfaces can be tagged by unnatural, exogenous molecules facilitating the therapeutic targeting of surface glycans and imaging disease progression (Prescher J et al. 2004 Nature [Lond] 431:873). ▶[signal transduction](#), ▶[hormone receptors](#), ▶[transmembrane proteins](#), ▶[serine/threonine kinase](#), ▶[receptor tyrosine kinase](#), ▶[receptor guanylyl cyclase](#), ▶[receptor tyrosine phosphatase](#), ▶[receptors](#), ▶[adaptor proteins](#), ▶[T cell](#), ▶[nuclear receptor](#), ▶[orphan receptor](#), ▶[TCR](#), ▶[ion channels](#), ▶[virus receptor](#); Xu L et al 1999 Curr Opin Genet Dev 9:h 40; Human plasma membrane: <http://receptome.stanford.edu/HPMR/>.

Receptor Down Regulation: Epidermal growth factor (EGF) binding receptors concentrate in coated pits after binding with these growth factors. They enter the lysosomes where degradation of the receptor and

EGF occurs. The cell surface has a reduced number of them because of receptor down regulation. ►endocytosis, ►EGF

Receptor Editing: This mechanism modifies the antigen-specificity of antigen receptors in the variable region of the antibody and may lead to immune tolerance or antibody diversification by V(D)J recombination. This mechanism eliminates the autoreactive B cells when confronted with self-antigens. ►antigen receptor, ►immune tolerance, ►V(D)J, ►immunoglobulins, ►clonal selection; Kouskoff V, Nemazee D 2001 Life Sci 69:1105.

Receptor Guanylyl Cyclase: These transmembrane proteins are associated at the cytosolic end with an enzyme that generates cyclic guanosine monophosphate (cGMP). cGMP activates cGMP-dependent protein kinase (G-kinase) that phosphorylates serine/threonine residues in proteins. ►cGMP, ►serine/threonine kinase; Kusakabe T, Suzuki N 2001 Dev Genes Evol 211[3]:145.

Receptor-Mediated Gene Transfer: Cell surface receptors may internalize their ligands by endocytosis. The ligand (peptides, lectins, sugars, antibody, glycoprotein, etc.) may form a conjugate with a polycation, e.g., polylysine. An expression vector plasmid may bind to a ligand—polycation conjugate. A fusogenic peptide or a disabled adenovirus may facilitate the entry of the complex into the cell by endocytosis and transported with the aid of an endosomal vehicle. From the endosome the DNA (gene) may be transferred to the nucleus where it may have a chance for expression. With the assistance of asialoglycoprotein receptor the gene may be targeted to hepatocytes or with a mannose receptor it may be targeted to macrophages. The transferrin receptor facilitates targeting erythrocytes; polymeric immunoglobulin receptors may aim the gene construct at the lung epithelia; other receptor and ligand combinations permit targeting to other cells or tissues. The advantage of this type of transfection is that it is not infectious, the DNA carrying more than a single gene of almost any size can be targeted. Cell division is not a requisite for expression. The transgene functions in the cytoplasm. Unfortunately, the level and duration of expression vary. The system may elicit an undesirable immune reaction. ►endocytosis, ►asialoglycoprotein receptor, ►transferrin, ►macrophage; Varga CM et al 2000 Biotechnol Bioeng 70:593.

Receptor Protein Tyrosine Phosphatase (RPTP): Refers to signaling molecules required for cell development. It dephosphorylates negative regulatory C-terminal tyrosine residues of the Src family kinases. ►signal transduction, ►Src; Carothers AM et al 2001 J Biol Chem 276:39094.

Receptor Serine/Threonine Kinases: These are the receptors of serine/threonine phosphorylating enzymes. They are the major types of plant receptor kinases, unlike in animals where receptor tyrosine kinases dominate. ►serine/threonine kinase; Choudhury GG 2001 J Biol Chem 276:35636.

Receptor Tyrosine Kinases (RTK): These bind protein tyrosine kinase enzymes (59 genes in humans) such as the receptors for the epidermal growth factor (EGF), insulin, insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGS), nerve growth factor (NGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), macrophage colony stimulating growth factor (M-CSF), RET proteins containing cadherin-like, cysteine-rich extracellular domain. Defects of the RET family of proteins include problems of the glial-cell derived neurotrophic factor, MEN2, Hirschsprung disease, familial medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism and ganglioneuromatosis. Hepatocyte growth factor receptor defects are responsible for the papillary renal cell carcinoma. Platelet-derived growth factor receptor changes activate the KIT oncogene. The insulin receptor anomalies lead to diabetes type II, leprechaunism and Rabson-Mendenhall disease. Hereditary lymphedema receptor disease is due to the vascular endothelial growth factor. Congenital pain with anhidrosis is caused by defects in the neurotrophin receptors. These receptors are transmembrane proteins and when the receptor is associated with the cognate phosphorylase enzyme both the receptor and the target protein receive γ phosphate groups from ATP at certain tyrosine residues. The phosphorylation results in dimerization or dimerization results in phosphorylation and activation. Activation increases the activity of RAS and subsequently the MAP kinases. This eventually leads to the expression of genes. The various regulatory proteins recognize the different phosphorylated tyrosine residues in the receptor. Upon binding to their specific sites they may also be phosphorylated on their own tyrosine residues and become activated. A cascade of events may follow that activate entire signaling pathways. The different receptors and the associated proteins may control the separate or interacting signaling pathways. Mutations or truncation of RTK that permit dimerization without the proper ligand may lead to carcinogenesis. The specificity of RTK (which are involved in diverse metabolic functions) is determined either by the strength or duration of the signal or it may be qualitative. The various cell types may activate RTK signaling in different ways. In craniosynostosis (Crouzon, Pfeiffer, Apert and Jackson-Weiss

syndromes) and some dwarfness (hypochondroplasia, thanatophoric dysplasia) the fibroblast growth factor receptor members of RTK are involved. ▶anoikis, ▶tyrosine kinase, ▶signal transduction, ▶SIRP, ▶RET oncogene, ▶Eph, ▶craniosynostosis syndromes, ▶biomarkers, ▶genetic medicine, ▶cancer therapy; Simon MA 2000 Cell 103:13; Robertson SC et al 2000 Trends Genet 16:265; Madhani HD 2001 Cell 106:9; Haj FG et al 2002 Science 295:1708; Baselga J 2006 Science 312:1175.

Receptor Tyrosine Phosphatase: This binds protein tyrosine phosphates and splits off phosphate groups. (See Bateman J et al 2001 Curr Biol 11:1317).

Receptor-Mediated Endocytosis: This is a very efficient delivery system of macromolecules (such as cholesterol), that adheres to coated pits, into cellular organelles. ▶coated pits

Receptors: These are proteins that bind other molecules (ligands). They can be *extracellular* receptors that respond to outside signals reaching the cells. They may be located on the *surface* of the cell membrane or *within the membrane* but their ligand-binding domains are exposed to the extracellular space. The *intracellular* receptors respond to ligands that diffuse into the cell. ▶ligand, ▶signal transduction, ▶cargo receptors, ▶receptor, ▶adaptor proteins, ▶T cell

Recessive: Such an expression of a gene means that it is not visible in heterozygotes in the presence of the wild type or other dominant alleles of the locus. Recessivity is not necessarily an absolute lack of expression of the gene (except in null alleles) because extremely low level of transcription/translation may not be observed by a particular type of study but may be detectable by a finer analysis. ▶dominance, ▶semidominance

Recessive Allele: This does not contribute to the phenotype in heterozygotes in the presence of the dominant allele. ▶pseudodominance

Recessive Epistasis: ▶epistasis, ▶modified checkerboards

Recessive Lethal: Dies when homozygous, and can be maintained only as heterozygote.

Recessive Lethal Tests, *Drosophila*: ▶*Basc*, ▶*CIB* method, ▶sex-linked recessive lethal, ▶autosomal recessive lethal assay

Recessive Oncogenes: These are tumor-suppressor genes such as encoding p53. ▶tumor suppressors, ▶p53

recF: *E. coli* gene (map position 82 min), also called *uvrF*, controls recombination and radiation repair.

▶recombination molecular mechanisms, ▶DNA repair; Bidnenko V et al 1999 Mol Microbiol 33:846.

recG: *E. coli* gene (map position 82 min) controls recombination. ▶recombination molecular mechanism; Sourcelle J, Hanawalt PC 1999 Mutation Res 435:171.

Recipient: Bacterial cells of the F⁻ state receive genetic material from the donor F⁺ strains. This is also the cell to which genetic material is transferred. ▶conjugation, ▶transformation

Recipient Site: ▶donor site

Reciprocal Crosses: For example, A × B and B × A.

In cases when cytoplasmically determined differences exist between the two parents, the F₁ offspring bears greater resemblance to the female parent that usually transmits the cytoplasm. These reciprocal differences may persist indefinitely in the advanced generations. Although reciprocal differences are normally most obvious in plants, in animal hybrids, e.g., the mule and the hinny they are easily distinguishable. ▶mitochondrial genetics, ▶chloroplast genetics, see Fig. R18.



Figure R18. Reciprocal hybrids of *Epilobium hirsutum* Essen and *Epilobium parviflorum* Tübingen. Parents are 2n = 36. In the cross at the left an *E. parviflorum* female was crossed by an *E. hirsutum* male. The two plants at the right represent the reciprocal cross when the *E. hirsutum* female provided the cytoplasm. (From Michaelis P Umschau 1965 (4):106)

Reciprocal Interchange: This is the same as reciprocal translocation of chromosomes.

Reciprocal Recombination: This is the most common exchange between homologous chromatids at the 4-strand stage of meiosis in eukaryotes. In the case of single crossing over in an interval, two parental types and two crossover strands are recovered. An exception is gene conversion where the exchange is non-reciprocal. In conjugational transfer in bacteria the reciprocal products of the event are not recovered and their fate is unknown. In sexduction and specialized transduction reciprocal recombination may also take place in bacteria (see Fig. R19).
▶crossing over, ▶recombination molecular mechanisms prokaryotes, ▶conjugation, ▶sexduction, ▶specialized transduction

| | |
|------------------------|-------------------------|
| Parental | <i>AB</i> and <i>ab</i> |
| Reciprocal recombinant | <i>Ab</i> and <i>aB</i> |

Figure R19. Reciprocal recombination

Reciprocal Selection: ▶recurrent selection

Reciprocal Translocation: Segments of non-homologous chromosomes are broken off and reattached to each other's place. As a consequence, generally 50% of the gametes of the translocation heterozygotes (formed by adjacent distributions) are defective because they do not have the correct amount of chromatin. ▶translocation

Rec-Mutant: This means deficient in recombination and possibly altered in other functions of the DNA. (See individual Rec entries).

Recoding: This mechanism may translate the same DNA sequence in more than one way. It is a common mechanism in viruses with overlapping genes. There are several other ways this can take place. Some genes utilize multiple promoters and depending on the choice of their utilization, the same RNA may code for more than one protein. Frameshifting may take place: e.g., the mRNA may show slippage on the ribosome, a tRNA^{Leu} with an anticodon GAG may recognize CUUUGA in one frame and in a shift it inserts leucine (UUU) for 4 nucleotides: CUUUGA. Similar frameshifting cassettes may be determined by the *E. coli* gene *SF2* and also in other prokaryotes. In the TY3 transposable element of yeast the GCG AGU U instead of the Ala (GCG) and Ser (AGU) it

may read GCG A GUU Ala (GCG) and Val (GUU). The code words may be interpreted in different ways and stop codons may specify selenocysteine, tryptophan and glutamine. The ribosome may also skip certain sequences, e.g., the T4 phage topoisomerase may bypass 50 contiguous nucleotides and after the long frameshift it continues translation. Variants of phage λ repressor and cytochrome b₅₆₂ when translated from mRNA without a stop codon acquire an unusual COOH end. Co-translation switches the ribosome reading from the defective mRNA to the tRNA-like *ssrA* transcript that is translated into Tyr-Ala-Leu-Ala-Ala (the normal carboxyl end would have been very similar Trp-Val-Ala-Ala-Ala). Recoding may be of importance in some human diseases, e.g., if in the cystic fibrosis transmembrane conductance regulator a glycine codon₅₄₂ or arginine codon₅₅₃ is replaced by an UGA (opal) stop codon, the disease symptoms are alleviated compared with some missense mutations because this opal codon permits some readthrough leakage. ▶overlapping genes, ▶frameshift, ▶selenocysteine, ▶topoisomerase, ▶Ty, ▶cystic fibrosis, ▶set recoding, ▶fuzzy logic; Shigemoto K et al 2001 Nucleic Acids Res 29:4079; Harrell L et al 2002 Nucleic Acids Res 30:2011.

Recoding Signal: This is required for translational recoding. ▶overlapping genes, ▶recoding

Recognition Site of Restriction Enzymes: ▶restriction enzyme

Recoil: This means to bounce back; electromagnetic radiation recoils from glass and metal. ▶Compton effect

Recombinagenic: This may be involved in genetic recombination at an increased frequency.

Recombinant: Refers to an individual with some of the parental alleles reciprocally exchanged. ▶reciprocal recombination

Recombinant Antibody (RAb): This is genetically engineered and usually includes only the variable fragments, which are fused to some other proteins. The appropriate DNA fragments are amplified by PCR and cloned in *E. coli* and a single peptide chain may contain the variable regions of both the light and heavy chains. Animal passage is not required. The antibody gene fragment can be fused to a bacterial signal sequence enabling the direction of the molecule into the periplasmic space where chaperones can properly fold the engineered protein. The

procedure may include selection by phage display. Since RAb is produced without an animal and in vitro, sources of contamination by pathogens can be eliminated. RAb is also monoclonal. Recombinant antibodies can be modified with the battery of tools of molecular biology and different properties can be added to them, e.g., the paratope can be specially targeted to tumor cells (bifunctional antibody). It can be obtained by using human gene fragments, thus precluding an immune response against the RAb. ►PCR, ►immunoglobulins, ►antibodies, ►signal sequence, ►monoclonal antibody, ►paratope, ►phage display, ►polyclonal antibody; Kortt AA et al 2001 *Biomol Eng* 18[3]:95; Karn AE et al 1995 *ILAR J* 37[3]:132.

Recombinant Congenic: An outcross is followed by several generations of inbreeding in order to minimize the background genetic variations. ►recombinant inbred strain panels

Recombinant DNA: This is a DNA that has been spliced in vitro from at least two sources with the techniques of molecular biology or that results from the replication of such molecules. From the viewpoint of safety regulations, synthetic DNA segments, which yield potentially harmful polynucleotide or polypeptide, if expressed within cells, are subject to the same regulations as any harmful natural product. Transposable elements, unless they include recombinant DNA, are not subject to the US National Institute of Health recombinant DNA regulations. ►vectors, ►cloning vectors, ►transformation genetic, ►genetic engineering, ►restriction enzymes, ►splicing; Fed. Regist. [1999] 64:25361; <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>.

Recombinant DNA and Biohazards: Fears of this were expressed by conscientious scientists way back in the 1970s even before the impact of the new techniques could be fully assessed. Since then evidence has accumulated indicating that some of the fears were not entirely justified, except by the wisdom of caution with a hitherto unknown and unused procedure. To avoid safety risks various levels of containments were made mandatory, depending on the organisms used, to prevent the accidental escape of genetically engineered organisms. Certain types of gene transfers were entirely prohibited to avoid contagions and highly toxic products. Cloning vectors were constructed that would not survive outside the laboratory. Bacterial strain X¹⁷⁷⁶ (so designated in honor of the bicentennial anniversary of the national independence of the USA) had an absolute requirement for diaminopimelinic acid, an essential precursor of

lysine and absent from the human gut. Cloning bacterial hosts were made deficient for excision repair (*uvrB*), auxotrophic for thymidine (indispensable for DNA synthesis), mutant for recombination (*rec⁻*) and conjugational transfer of plasmids to other organisms. If reversion frequency of any of, say, 5 defects, each is in the range of 1×10^{-6} , then the joint probability of simultaneous reversion of all 5 would be $(10^{-6})^5 = 10^{-30}$. Since the mass of a single *E. coli* cell is about 10^{-12} g, only in a mass of 10^{11} metric tons of bacteria can one expect to find such a fivefold mutation. Obviously, such a mass of bacteria is not likely to occur because the earth may not support it. To get an idea of what this volume is a comparison can be made: wheat production of the world in 1980 was only 4.5×10^8 tons and the estimated mass of the planet earth 10^{20} tons. To avoid any problem, nevertheless, government authorization is required in all countries where this technology is used, for the release of any genetically engineered species (microbes, plants, animals) for the purpose of economic utilization. Objections to such carefully tested releases are still raised, based not so much on public concern as on personal or political interests and most commonly because of ignorance. During the period spanning more than two decades since recombinant DNA technology has been used, no major accident has been reported and with the guidelines available none is expected. Before recombinant DNA experiments are initiated, the plans are approved by the Institutional Biosafety Committees and Institutional Review Boards. Experiments involving cloning of toxin molecules with LD50 of less than 100 nanograms per kg body weight must be approved by the Office of Biotechnology Activities (National Institute of Health/MSB 7010, 6000 Executive Blvd., Suite 302, Bethesda, MD 20892-7010, Tel. 301-496-9838). Such toxins are botulinum, tetanus, diphtheria and *Shigella dysenteriae* neurotoxin. Specific approval is mandatory for cloning in *Escherichia coli* K12 genes coding for the biosynthesis of toxic substances, which are lethal to vertebrates at 100 ng to 100 mg per kg body weight. Special review and approval by the OBA and the RAC are required for human experimentation or treatment. The OBA sets specific guidelines for different risk categories. Working with plant and animal pathogens requires a permit from the US Department of Agriculture. According to the US National Institute of Health Guidelines, hazardous agents are classified into four groups and the pertinent agents are named according to groups, group 1 is the least hazardous and group 4 is the most dangerous. The principal investigator who is primarily responsible for the observance of the regulations must report all accidents

or any potential hazardous events. ►laboratory safety, ►containment, ►biohazards, ►recombinant DNA evolutionary potentials, ►gene therapy, ►cancer gene therapy, ►Institutional Biosafety Committee, ►RAC, ►OBA, ►GMO; <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>.

Recombinant DNA, Evolutionary Potentials: Using molecular biology techniques genes can be transferred among organisms by means not routinely available in nature. However, it cannot be ruled out that during the process of natural evolution fragments of degraded DNA are taken up by direct transformation and exchanged between taxonomically unrelated species.

Recombinant Inbred Strain Panels: These can be used for mapping in mouse. (For information contact Jackson Laboratory Animal Resources, 600 Main Str., Bar Harbor ME 04609, USA. Phone: 1-800-422 MICE or 207-288-3371. Fax: 207-288-3398).

Recombinant Inbreds (RI): These are generated for physical mapping of DNA by selfing F1 hybrid populations and selecting single seed or animal progenies for about 8 generations until only $(0.5)^8$ (≈ 0.0039) fraction remains heterozygous for a particular marker (linkage ignored). The parental lines are chosen on the basis of differences in their DNA sequences, and from the data the map position of these physical markers can be determined genetically by a combination of molecular and progeny tests. In the case of animals, the calculation is as follows: R (the frequency of discordant individuals) is $R = (4r)/(1 + 6r)$ where r is the recombination in any single gamete. Since interference within very short distances is practically complete, the distance in cM is $d = 100r$. The recombination fraction (\hat{r}) in function of the size of the sample (N) is $\hat{r} = i/(4N - 6i)$ where i is the number of discordant strains and $\hat{d} = 100 \times \hat{r}$ in

cM. In plants, the frequency of recombinant monohybrid gametes is calculated by using the same formula $r = R/(2 - 2R)$ where R is the frequency of homozygous recombinant diploid individuals. ►RAPD, ►congenic resistant lines of mice, ►congenic strains; Bailey DW 1971 Transplantation 11:325.

Recombinant Joint: This is the site of connection of two molecules of DNA in a heteroduplex. ►heteroduplex

Recombinant Plasmid: This is generated either from two different DNAs by using the techniques of molecular biology or by spontaneous or induced genetic recombination. ►plasmid

Recombinant Vaccine: This is produced by in vitro modifications of genes/proteins; it does not carry the full complement of the infectious agent. ►vaccine

Recombinase: Refers to enzyme, mediating recombination. ►FLP/FRT, ►Cre/loxP, ►Rec, ►DMC1, ►Rec51

Recombinase System: ►immunoglobulins

Recombination: It is a process by which the linkage phase (coupling or repulsion) of syntenic genes is altered. In a broad biological sense it means the rearrangement of any molecule. Recombination is most common during meiosis but mitotic recombination also takes place. The mechanism of meiotic and mitotic events is not necessarily identical (see Fig. R20).

Independent segregation and reassortment are outside the realm of this term, according to the original definition given by H.A. Sturtevant, although some textbooks erroneously include these as well (see Fig. R21).

Recombination can be accurately assessed with the aid of sequenced genomes. Data obtained have

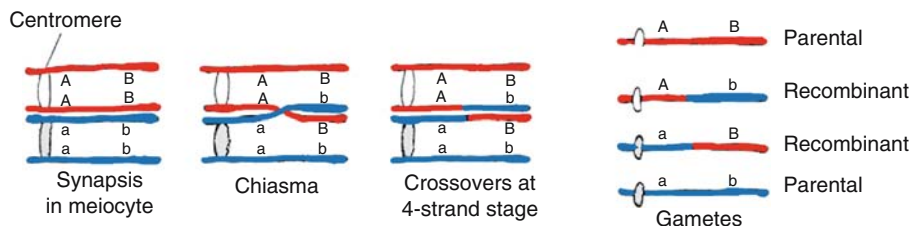


Figure R20. Cytological representation of recombination between homologous chromosomes in coupling phase. Each chiasma leads to crossing over and 50% recombination. The frequency of recombination depends, however, on the distance between the two loci considered. If crossing over takes place in all meocytes between the bivalents, the frequency of recombination is 50%. If only half of the bivalents undergo crossing over in that particular interval, the recombination frequency will be 25% because, say in 4 meocytes with (16 chromatids) $4/16 = 0.25$. If only two of the meocytes display crossing over then $2/16 = 0.125$ is the frequency of recombination. The maximal recombination frequency by a single crossing over is 50%; the minimal may be extremely rare in case the linkage is tight.

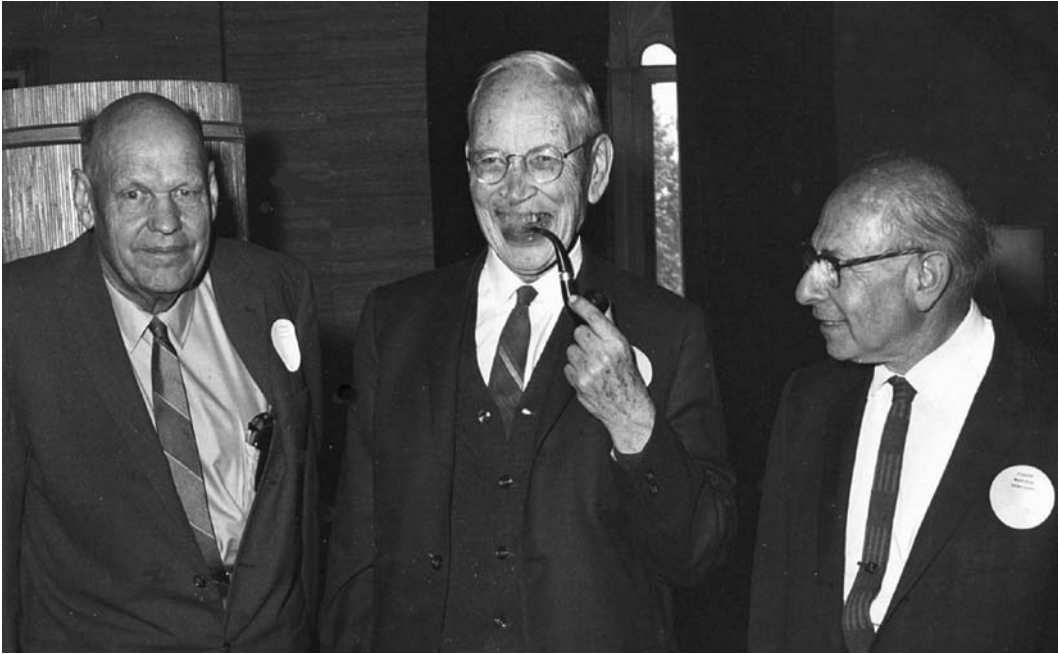


Figure R21. A rare photograph of the three men who independently made basic discoveries in recombination. In the middle is Alfred Henry Sturtevant who as an undergraduate student published the first linkage map of *Drosophila* in 1913 (Science 58:269). On the left is Ernest Gustav Anderson who (with C.B. Bridges in 1925) (Genetics 10:403) demonstrated that crossing over takes place at the four-strand stage. On the right is Curt Stern who demonstrated in 1931 (Biol. Zbl. 51:547) that crossing over involves the physical exchange of chromatids in *Drosophila*. [Harriet B. Creighton and Barbara McClintock also published in 1931 identical proof using maize (Proc Natl Acad Sci USA 17:492)].

revealed considerable (0 to 9 centiMorgan per megabase) variation along each chromosome. The so-called “desert” sequences display low and the “jungle” stretches high recombination and this is depicted in the diagram. (See also other recombination entries, ▶linkage, ▶repulsion, ▶coupling, ▶recombinational probe, ▶flip-flop recombination, ▶site-specific recombination, ▶hot spot, ▶cold spot, ▶sex circle model of recombination, ▶*Cre/loxP*, ▶*FLP/FRT*, ▶*rec*, ▶ectopic recombination, ▶recombination homologous, ▶linkage disequilibrium, ▶centiMorgan, ▶STRP, ▶recombination mechanisms of, ▶retroviral recombination, ▶mitotic crossing-over; Cox MM 2001 Proc Natl Acad Sci USA 98:8173; Sturtevant AH 1913 J Exp Zool 14:43, recombination in populations: Stumpf MPH, McVean GAT 2003 Nature Rev Genet 4:959; <http://www.nslj-genetics.org/soft/>; yeast meiotic recombination hot spots–cold spots: http://www.bioinf.seu.edu.cn/Recombination/rf_dymhc.htm).

Recombination by Replication: At the beginning of the twentieth century William Bateson suggested that recombination is basically associated with the process of replication.

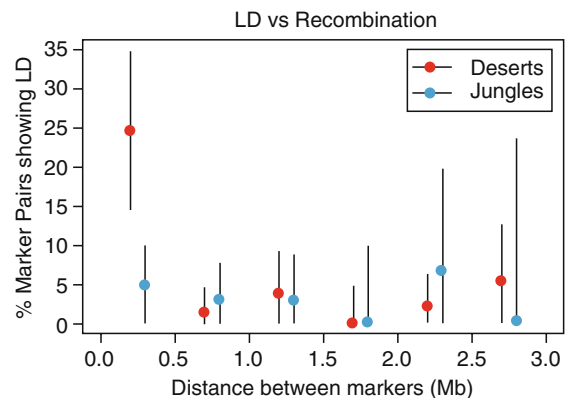


Figure R22. Linkage disequilibrium (LD) among pairs of STRPs (microsatellite repeats) within human autosomal recombination deserts and jungles within 0.25 megabase intervals. (Courtesy of Dr. James L. Weber; see also Yu A et al 2001 Nature [Lond] 409:951)

At that time neither of these phenomena was sufficiently understood or could even be hypothesized meaningfully. On the basis of cytological evidence (1930s) for marker exchange accompanied

by chromosome exchange and later evidence that DNA exchange and phage gene exchange were correlated, the generally accepted view became that recombination does not require replication. However, the discovery of gene conversion remained a puzzling phenomenon although it was observed that about 50% of the gene conversion events involved flanking marker exchange. Holliday and other molecular models of recombination (during the 1960s and 1970s) permitted interpretation of classical crossing over and gene conversion without significant replication. Recently, it has been observed that the mutation or loss of function of the PriA DNA replication protein blocks both replication and recombination in *E. coli*.

The SOS DNA repair activates a replication process that does not require the replicational *oriC* site or the normally functioning DnaA protein but it needs RecA and RecBCD activities. It was assumed and subsequently demonstrated that double-strand breaks may be assimilated into the DNA and result in double D loops in the presence of the nearby *chi* elements. The *chi* elements block nuclease activity and assist the initiation of replication. It appears that PriA and other proteins of the primosome generate a replication fork at the D loop, and relying on the DnaB helicase and the DnaG primase, replication and recombination can be turned on. First, apparently lagging strand synthesis begins by the replisome and the lagging strand then primes the synthesis of the leading strand. Defective PriA may be compensated for by some elements of the primosome. The processes of double-strand break repair and recombination appear the same with the exception that in repair only the defective region has to be corrected whereas in recombination the entire strand must be replicated in order to recover the recombinants. Some observations have indicated the occurrence of joint processes of replicational repair and recombination in eukaryotes. ▶[reduplication theory](#), ▶[breakage and reunion](#), ▶[gene conversion](#), ▶[Holliday model](#), ▶[recombination molecular models](#), ▶[SOS repair](#), ▶[DNA repair](#), ▶[recA](#), ▶[recBCD](#), ▶[chi element](#), ▶[replication fork](#), ▶[D loop](#), ▶[replisome](#), ▶[lagging strand](#), ▶[leading strand](#), ▶[gene space](#); Michel B et al 2001 Proc Natl Acad Sci USA 98:8181.

Recombination by Transcription: Some of the instabilities may be induced by RNA polymerase II, particularly between repeats of the eukaryotic chromosomes. Some yeast mutants may increase the process by over three orders of magnitude. (See Gallardo M, Aguilar A 2001 Genetics 157:79).

Recombination Cloning: This is based on the integration/excision mechanism of the lambda phage and *E. coli* bacterium. Integration involves the λ *attP* site

within the bacterial *attB* site. The bacterial *attL* and *attR* sites flank the integrated phage genome, excision reverses the process. Such a procedure can be used for the generation of vectors with DNA-binding and activation domain sites facilitating the study of protein interaction by analogy of the two-hybrid method. ▶[att sites](#), ▶[two-hybrid method](#); Muyrers JP et al 2001 Trends Biochem Sci 26[5]:325.

Recombination Frequency: Linkage is generally noticed in F₂ when independent segregation of the genes does not occur. Two genes in the homologous chromosomes can be at two different arrangements, repulsion (*Ab/aB*) or coupling (*AB/ab*) (see Table R3). Some scholars have described repulsion as trans and coupling as cis arrangement.

Table R3. Recombination detected

| | Phenotypic Classes Expected | | | |
|---------------------------|-----------------------------|-----------|-----------|-----------|
| | <i>AB</i> | <i>Ab</i> | <i>aB</i> | <i>ab</i> |
| Independent Segregation → | 9/16 | 3/16 | 3/16 | 1/16 |
| Linkage, Repulsion → | less | more | more | less |
| Linkage, Coupling → | more | less | Less | more |

Recombination is commonly calculated as the percentage of recombinants in a test cross population. The maximum frequency is 50% because at this value the frequencies of recombinant and parental chromosomes are equal, i.e., the segregation is independent. Linkage is first observed in F₂ by deviation of the phenotypic proportions from the expectations for independent segregation (see Fig. R23). For example:



Figure R23. Aleurone color (*C*) and shrunken endosperm (*sh*) genes of maize are closely linked in chromosome 9 of maize. On the two ears these markers are in different linkage phase. (From Hutchison CB 1921 J Hered 12:76)

The linkage phase does not affect the frequency of recombination but it affects the frequency of the phenotypic classes (see Table R4). The frequency of recombination is the same in both cases $(5 + 5)/100 = 0.10 = 10\%$ as shown in the table.

Table R4. Phenotypic classes in test crosses in two linkage phases and recombination:

| | (A hypothetical case) | | | |
|--|-----------------------|----|----|----|
| | AB | Ab | aB | ab |
| Repulsion cross (<i>Ab/aB</i>) × <i>ab</i> | 5 | 45 | 45 | 5 |
| Coupling cross (<i>AB/ab</i>) × <i>ab</i> | 45 | 5 | 5 | 45 |

In F_2 recombination frequencies cannot be calculated by such a simple method because in the heterozygotes the genetic constitution of the individual chromosome strands is concealed but may be revealed in F_3 . Nevertheless, recombination frequencies can be calculated (►*F₂ linkage estimation*). Recombination takes place at the four-strand stage of meiosis (see exception of mitotic recombination). The bivalent pair and in the simplest case two chromatids exchange segments. The maximal frequency of recombination within a chromosomal interval is 50%. Recombination frequencies are converted to map units by multiplication with 100. The realistic conversion of recombination frequencies into map units requires *mapping functions* because some of the recombinational events may not be detectable if the frequency of recombination between markers exceeds 15%. In physical measures 1 map unit has a different meaning in different organisms, depending on the size of the genome in nucleotides (nucleotide pairs) and the genetic length of the genome. Thus, 1 map unit in the plant *Arabidopsis* means about 150 kbp, in maize it is around 2,140 kbp and in humans approximately 1,100 kbp. One study reported that in human male autosomes the mean meiotic recombination frequency was 8.9×10^{-3} per megabase. In human chromosome 3 female recombination frequency was 1.43 cM Mb^{-1} and male was 0.85 cM Mb^{-1} (Muzny DM et al 2006 Nature [Lond] 440:1194). Smaller chromosomes have higher rates of recombination (cM/kb) not only among lower compared to higher eukaryotes, but also within one organism (yeast). The frequency of no recombination is a function (f) of the intensity of linkage and the population size; $f = (1 - r)^n$ where r is the recombination fraction and n is the number of test cross progeny. Data on maize (Fu H et al 2002 Proc Natl Acad Sci USA 99:1082) revealed reduced frequency of recombination in regions containing methylated retrotransposons. Recombination frequency may be affected by sex and may vary in different chromosomal regions; it is also influenced by sex in either plus or minus direction. The total recombinational map length may vary in different studies and by the use of different markers. Using

different methods of human recombination, all frequencies corrected by the Kosambi mapping function indicated significantly higher recombination in females than in males ($\sim 1.6:1$) (Matise TC et al 2003 Am J Hum Genet 73:271). In dogs and pigs, female recombination is higher; in cattle the two are about the same whereas in sheep male recombination is higher. Recombination frequencies may vary according to specific chromosomes. In the centromeric region the frequency of chiasma/recombination is lower than in other regions. In the area near the telomeres recombination increases in human males. In trisomy the recombination frequency is reduced. Many human diseases are associated with chromosomal deletions or duplications and in these cases recombination is reduced. ►*mapping*, ►*mapping function*, ►*bacterial recombination*, ►*test cross*, ►*product ratio method*, ►*F₂ linkage estimation*, ►*F₃ linkage estimation*, ►*maximum likelihood method applied to recombination frequencies*, ►*recombination modification of*, ►*recombination variation of*, ►*sperm typing*, ►*chiasma*, ►*hot spot*, ►*map unit*; Lynn A et al 2004 Annu Rev Genomics Hum Genet 5:317; <http://www.nslj-genetics.org/soft/>.

Recombination Frequencies in Bacteria: ►*bacterial recombination*

Recombination, Homologous: ►*recombination*, ►*homologous recombination*

Recombination Hot Spots: Genetic recombinations do not occur uniformly along the physical length of the DNA (chromosomes). In *Arabidopsis*, 1 cM varied from 30 bp to >550,000 bp. Gene-rich regions display more exchanges than gene-poor sequences. Recombination is usually suppressed around or near the centromere or telomere. In some instances recombination near the telomere is increased. In wheat, 1 cM in gene-rich region is estimated to be 118 kb whereas it is 22,000 kb for gene-poor regions. In humans, 1 cM indicates 1 Mb but there are substantial variations. In humans, 50% of all recombination takes place in less than 10% of the DNA sequence and recombination is preferentially outside the boundary of genes (McVeanan GAT et al 2004 Science 304:581). Human crossing over frequencies are clustered into narrow recombination hot spots (Jeffries AJ et al 2005 Nature Genet 37:601). The human genome-wide hot spot numbers vary between 25,000 and 50,000 and they occur preferentially near genes with 50 kb. Hot spots are determined by a CCTCCCT or larger motif. If in the third base T is changed to C, suppression is observed. L1 elements are underrepresented in hot spots (Myers S et al 2005 Science 310:321). ►*coefficient of crossing over*,

►autopolyploids, ►alpha parameter, see Fig. R24; Luo ZW et al 2001 Genetics 157:1369; Wu SS et al 2001 Genetics 159:1339; Hackett CA et al 2001 Genetics 159:1819.

Recombination In Vitro: ►staggered extension process

Recombination, Intrachromosomal: This occurs when homologous tandem or non-adjacent duplications are present in the chromosome. ►intrachromosomal recombination

Recombination, Intragenic: ►intragenic recombination

Recombination Machine: ►recombination molecular mechanisms

Recombination, Mechanisms, Eukaryotes, Yeast: The Sep 1 (strand exchange protein) 132 kDa fragment of a 175 kDa protein of yeast initiates the transfer of one DNA strand from a duplex to a single-stranded circle with 5' to 3' polarity without an ATP requirement. It also has a 5' to 3' exonuclease activity and is probably required for the preparation of 3' end of single- and double-stranded DNA molecules for recombination. Mutation in Sep reduces mitosis, sporulation, meiotic recombination and genetic repair. (The STP β protein, encoded by gene *DST2/KEM1*, is probably identical to Sep 1). One monomer of Sep 1 binds to nearly 12 nucleotides of single-stranded DNA. This requirement is reduced by the presence of the 34 kDa protein, which at a concentration of 1 molecule per 20 nucleotides reduces the requirement for Sep 1 to about 1/100. The DPA protein (120 kDa) of yeast controls DNA pairing and promotes heteroduplex formation in a non-polar manner independently of ATP. It promotes single-strand transfer from double-strand DNA to single-stranded circular DNA if the former has single-strand tails. Protein STP α (38 kDa) increases 15-fold shortly before yeast cells are committed to recombination during meiosis. If the gene encoding it (*DST1*) mutates, meiotic recombination is greatly reduced without an effect on mitotic recombination. The *RAD50* gene product (130 kDa) has an ATP-binding domain and it binds stoichiometrically to duplex DNA. The *RAD51* gene product is homologous to the RecA protein of *E. coli* (►recombination, ►mechanism, ►prokaryotes) and binds single- and double-stranded DNA. The *DMC1* (*disrupted meiotic cDNA*) gene product appears during meiosis and along with the product of *RAD51* performs functions similar to RecA in prokaryotes. Some organisms, *Drosophila melanogaster*, *Caenorhabditis elegans* and *Neurospora* have Rad51 but lack Dmc1 and in yeast mutation in Dmc1 does not prevent recombination. It is assumed that meiotic recombination in yeast involves double-strand breaks of the DNA. The actual site of exchange

may be 25 to 200 kb away from the prominent break (Young JA et al 2002 Mol Cell 9:253). If DNA replication, which normally occurs 1.5 to 2 h before double-strand breaks, is blocked or delayed, recombination does not take place. *Drosophila*: protein Rrp 1 promotes exchanges between single-strand circular and linear duplex DNA. Its C-terminus has homology to *E. coli* exonuclease III and *Streptococcus pneumoniae* exonuclease A. Mammalian Cells: HPP-1 (human pairing protein with 5' to 3' exonuclease activity) binds to the DNA and promotes strand exchange in a 5' to 3' direction and it does not require ATP. The addition of the hRP-A (human single-strand binding) protein stimulates pairing almost 70-fold and reduces the amount of HPP-1 requirement (cf. SF1 in yeast). The precise mechanism by which the Holliday junction (see Holliday model, steps I to L) is resolved is not clear but endonuclease activity is postulated. Bacteriophage T4 gene 49 encodes endonuclease VII that under natural conditions cuts branched DNA structures. Similarly, bacteriophage T7 gene 3 product encodes endonuclease I which cleaves branched DNAs. In yeast, endonuclease XI (Endo XI, $\approx M_r$ 200,000 and other Endo proteins) has been found in cells with mutations in the RAD genes and apparently cuts cruciform DNA of the type expected by the Holliday juncture. ►recombination models, ►recombination molecular mechanisms in prokaryotes, ►recombination models, ►RAD51, ►RAG, ►recombination hot spots, ►Sep 1, ►SRS2, ►STP β , ►synaptonemal complex, ►chiasma, ►sex circle model, ►gene conversion, ►databases; Camerni-Otero RD, Hsieh P 1995 Annu Rev Genet 29:509; Baudat F, Keeney S 2001 Curr Biol 11: R45; Smith GR 2001 Annu Rev Genet 35:243, yeast proteins and models: Krogh BO, Symington LS. 2004 Annu Rev Genet 38:233; exchange of DNA in recombination: Neale MJ, Keeney S 2006 Nature [Lond] 442:153.

R

Recombination Minimization Map: This is based on a skeletal map. The ordering relies on the smallest number of recombinations for single intervals. ►skeletal map

Recombination Models: ►Holliday model, ►Meselson-Radding model, ►Szostak model

Recombination, Modification of: The frequency of recombination may be altered by any means that affect chromosome pairing such as chromosomal aberrations, by DNA inserts introduced through transformation, temperature (either low or high), physical mutagens, rarely by chemicals, *rec*⁻ genes, etc. In the heterogametic sex of *Drosophila* and silkworm meiotic recombination is usually absent although mitotic recombination occurs. In animals,

recombination may be more frequent in females than in males and it is attributed to imprinting. In plants, in the case of a sex difference in recombination its frequency is usually lower in the megaspore mother cell. (See individual entries, ►[coincidence](#), ►[recombination variation of](#), ►[imprinting](#); Singer A et al 2002 Genetics 160:649; Peciña A et al 2002 Cell 111:173).

Recombination, Molecular Mechanisms of: The RecA protein (M_r 37,842) directs homologous pairing by forming a right-handed helix on the DNA and it catalyzes the formation of DNA heteroduplexes. X-ray crystallography indicates that the DNA rests relaxed in the deep groove of this protein to facilitate scanning for homologous sequences. The RecA protein is also involved in DNA repair function (SOS repair). It digests the LexA bacterial repressor and instrumental indirectly in the derepression of over 20 genes involved in recombination and UV mutagenesis. The mechanism(s) of RecA activities can be studied by in vitro reactions. RecA can interact with 3 or 4 DNA strands by wrapping around the paired molecules. DNA-DNA pairing can take place between linear and circular DNA as well. Strand exchange proceeds at a slow pace (2 to 10 base/sec) in a polar fashion (5' to 3'). The transfer begins at the 3' end of the duplex and is transferred to a single strand DNA. Homology is a requisite for the RecA mediated reactions yet it tolerates some mismatches or insertions (up to even 1,000 bases or more) but these slow down the reactions. RecA can mediate pairing between two duplexes as long as there are short single-strand stretches or gaps. Low pH, intercalating chemicals, Z-configuration and other structural changes of the DNA may alleviate the difficulties of binding two duplexes. The RecA protein is a low efficiency ATPase. ATP hydrolysis is not an absolute requirement, for RecA activities in recombination but is more important for the repair reactions. In the presence of ATP the conformation of RecA is altered and in the nucleoprotein complex the DNA is substantially under-wound (the spacing between bases extends from 3.4 Å to 5.1 Å). It is assumed that the paired DNA molecules are not just juxtapositioned, but also one molecule lies in the major groove of the other. The pairing may involve three or four strands.

DNA strand exchange requires that the RecA filament rotates along the longitudinal axis and the DNA molecules are "spooled" inside where they may form the Holliday junction (►[Holliday model](#)). ATP stabilizes the RecA-DNA association and when ATP is split into ADP, the heteroduplex is released and RecA is recycled. Besides the RecA protein, recombination requires the presence

of a single-strand binding protein (SSB), DNA polymerase I, DNA ligase, DNA gyrase, DNA topoisomerase I and the products of genes *recB*, *recC*, *recD*, *recE*, *recF* (binding protein for single-strand DNA), *recG*, *recJ* (exonuclease acting on single-strand DNA), *recN*, *recO*, *recQ*, *RuvB* (helicases), *recR*, *ruvR*, *ruvB* and *ruvC*. RuvC nicks the DNA at the point of strand exchange. RecBCD is a protein-RNA complex encoded by three genes (mentioned earlier), it performs the activities of (i) ATP-dependent double-strand exonuclease, (ii) ATP-dependent single-strand exonuclease, (iii) unidirectional DNA helicase, and (iv) site-specific endonuclease to nick four to six nucleotides downstream of *chi*, a recombinational hot spot (5'-GCTGGTGG-3'). It has been suggested that RecBCD generates 3'-tails that are utilized by protein RecA for DNA strand exchange. RecB and RecC mutations can be suppressed by *sbca* and *sbcb* mutations. Mutations in *sbca* lead to the activation of the product (exonuclease VIII) of *recE*. Mutation in *sbcb* inactivates exonuclease I, an enzyme that digests single-strand DNA, and its inactivation may assist the function of RecA in recombination (►[models of recombination](#)). The precise mechanism by which the Holliday junction (►[Holliday model](#), steps I to L) is resolved is not clear but endonuclease (RuvC) activity is postulated.

Bacteriophage T4 gene 49 encodes endonuclease VII that under natural conditions splits branched DNA structures. Similarly, bacteriophage gene 3 encodes endonuclease I and cleaves branched DNAs. Some of the functions of the *ruv* operon of *E. coli* may be involved in the resolution of the Holliday junctions. *E. coli* also has in vivo systems where the molecular mechanism of resolution of recombination intermediates can be studied. Covalently closed plasmid DNA, DNA polymerase I and DNA ligase are transformed into *E. coli recA* mutants. Both monomeric and dimeric plasmid progenies are seen and the available markers permit the conclusion that crossing over occurs in 50% of the progeny. Recombination is not limited to DNA but viral RNA molecules also recombine.

The molecular mechanisms of recombination in eukaryotes have many features in common with those of prokaryotes. It appears that double-strand breaks can stimulate homologous recombination within one kilobase of the site of the break or it may affect recombination at a distance exceeding 30 kb. At the break a *recombination machine* may gain entry and as the machine moves on a heteroduplex of the DNA may be formed. At the broken ends DNA replication may be primed and there is a potential for recombination. The recombination machine is a complex of many enzymes mediating the recombination process. Recombination requires double-strand

breaks of the DNA after the S phase and ribonucleotide reductase appears to be the rate-limiting factor for double-strand breaks and it is controlled by checkpoints (Tonami Y et al 2005 Proc Natl Acad Sci USA 102:5797). ►recombination mechanisms eukaryotes, ►recombination models, ►recombinational probe, ►recombination by replication, ►chi elements, ►illegitimate recombination, ►recombination RNA viruses, ►ribonucleotide reductase, ►FK506; Camerini-Otero RD, Hsieh P 1995 Annu Rev Genet 29:509; Barre F-X et al 2001 Proc Natl Acad Sci USA 98: 8189; West SC 1992 Annu Rev Biochem 61:603; Cox MM, Lehman IR 1987 Annu Rev Biochem 56:229; Smith GR 2001 Annu Rev Genet 35:243; Krogh BO, Symington LS 2004 Annu Rev Genet 38:233.

Recombination Nodule: Refers to the suspected site of recombination seen through the electronmicroscope as a 100 nm in diameter densely stained structure adjacent to the synaptonemal complex. There are early nodules seen at the association sites of the paired meiotic chromosomes and the late nodules are visible at pachytene when crossovers are juxtaposed. Non-crossovers do not show nodules after mid-pachytene (see Fig. R25). ►synaptonemal complex, ►chiasma, ►pachytene, ►association point, ►meiosis, ►recombination, ►crossing over, ►recombination RNA viruses, ►synapsis; Zickler D et al 1992 Genetics 132:135; Anderson LK et al 2001 Genetics 159:1259.

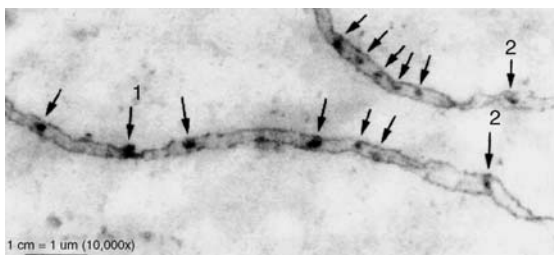


Figure R25. Early recombination nodules on two synaptonemal complexes of *Allium cepa* (onion). At positions marked 2 there is no synapsis yet. (Courtesy of Drs. LK Anderson and SM Stack)

Recombination Proficient: This means that there are no deficiencies involving enzymes mediating recombination. (See *Rec* and *rec* entries).

Recombination Repair: ►DNA repair

Recombination Repeats: These exist in the majority of plant mitochondrial DNAs in 1 to 6 pairs. Recombination can take place between/among these repeats generating various subgenomic DNA molecules.

These repeats (264 bp to >5 kbp in maize) may not be indispensable parts of the mtDNA although they may contain genes for rRNA, cytochrome, etc. ►mitochondrial genetics, ►mtDNA, ►rRNA; Chanut FA et al 1993 Curr Genet 23:234.

Recombination, RNA Viruses: After co-infection of a cell by two different viruses recombination may take place by template switching during replication, thus it is more like a copy choice than a breakage and reunion mechanism. Recombination can take place between homologous and non-homologous strands (illegitimate recombination). The latter mechanism may lead to deletions, duplications and insertions. Among picornaviruses the recombination frequency may be as much as 0.9 in the case of high homology. Recombination in RNA viruses helps to eliminate disadvantageous sequences and can generate new variants. The estimated mutation rate per base is 6.3×10^{-4} and per genome is almost 5. The mutation rate is estimated as mutations per replication. Host genes may suppress or their absence may increase viral recombination (Serviene E et al 2005 Proc Natl Acad Sci USA 103:10545). The double-strand bacteriophages of *Cystoviridae* have their genetic material in three segments. Intra-segment recombination is rare ($\sim 10^{-7}$ /segment/generation) but reassortment between segments is high, even higher than in other taxa (Slander OK et al 2005 Proc Natl Acad Sci USA 102:19009). ►copy choice, ►breakage and reunion, ►illegitimate recombination, ►reverse transcription, ►negative interference; Keck JG et al 1987 Virology 156:331; Kirkegaard K, Baltimore D 1986 Cell 47:433; Negroni M Buc H 2001 Annu Rev Genet 35:275.

Recombination, Targeted: ►Cre/loxP, ►FLP/FRT

Recombination, Variations of: In the heterogametic sex of arthropods (male *Drosophila*, female silkworm) genetic recombination is usually absent or highly reduced. In the latter group of organisms mitotic recombination occurs, and these premeiotic exchanges may account for the observation of recombinants. The most common cause of variation is the presence of *rec-* genes. In Abbott stock 4A × Lindegren's wild type crosses of *Neurospora*, post-reduction frequency was found to be 4.6 ± 1.2 whereas in Lindegren's stock it was 13 ± 1.2 , and in Emerson's × Lindegren's crosses 27.6 ± 3.7 . LJ Stadler, a pioneer of maize genetics, considered recombination as one of the most variable biological phenomena. ►male recombination, ►recombination frequency, ►recombination modification of, ►recombination hot spots, ►tetrad analysis; Browman KW et al 1998 Am J Hum Genet 63:861.

Recombinational Hot Spot: ►hot spot, ►chi site

Recombinational Load: This may emerge from the disruption of favorable, co-adapted gene blocks.

►genetic load, ►fitness-associated recombination

Recombinational Probe: One such short probe is inserted into the 902 bp π VX mini-plasmid containing a polylinker and the *supF* suppressor gene. Lambda phage libraries containing the miniplasmid construct are then propagated. If the phage carries a *supF* suppressible amber mutation, recombination between sequences homologous to the probe can be selectively recovered by forming plaques on an *E. coli* lawn. Recombination may take place even in the absence of perfect homology; less than ca. 8% divergence may be tolerated. Very large populations may reveal recombination within 60 base or longer probes effectively (see Fig. R26). ►*rec*, ►*Rec*, ►mini-plasmid, ►*supF*, π VX, ►lawn, diagram on the use of the π VX microplasmid for the selective

isolation of eukaryotic genes by recombinational probes; Perry MD, Moran LA 1987 Gene 51:227.

Recombinational Repair: ►DNA repair

Recombinator: Refers to cis-acting chromosomal sites promoting homologous recombination. ►*chi*

Recombineering: Refers to genetic engineering by homologous recombination. With the aid of a phage vector large DNA molecules can be cloned into bacterial artificial chromosomes. One such system uses the phage lambda genes Gam (inhibits host RecBCD), Exo, which degrades each DNA in 5'→3' and thus generates single-strand 3' overhangs, Beta protects the overhangs and anneals with complementary sequences. PCR-generated sequences or single-stranded oligonucleotides can be used as recombination substrates. Double-stranded DNA with 3' overhangs may not need Exo. For the

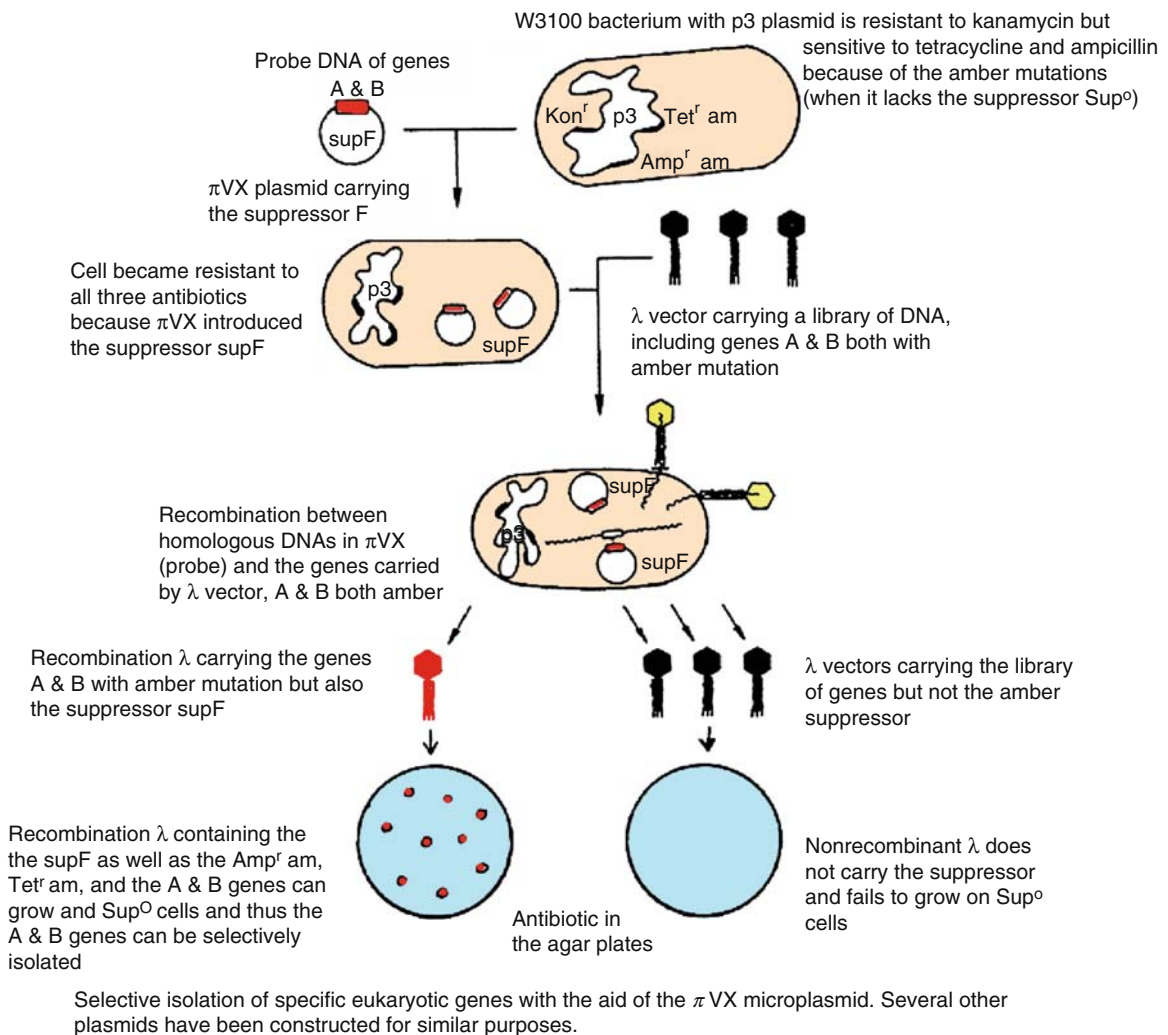


Figure R26. Recombination probe

procedure PCR-amplified linear or double-stranded DNAs are introduced into targeting cassettes that have either short regions of homology at their end or single-stranded oligonucleotides. The inserted DNA may carry any type of mutation or modification and there is no need for restriction enzyme cuts because the insertion is by homologous recombination. The method is simpler and safer than the somewhat unstable YACs and can be applied to functional genomic studies of higher organisms, e.g., mouse. (See terms under separate entries; Copeland NG et al 2001 *Nature Rev Genet* 2:769; Court DL et al 2002 *Annu Rev Genet* 36:351; Yu D et al 2003 *Proc Natl Acad Sci USA* 100:7207).

Recombinogenic: Refers to any agent (mutagen) which increases recombination (also).

Recombinogenic Engineering: ► [recombineering](#)

Recon: This is a historical term for the smallest recombinational unit. Molecular genetics has shown that recombination can take place between two nucleotides within a codon (Benzer S 1957, p 70 In: McElroy WD, Glass B (Eds.) *The Chemical Basis of Heredity*, Johns Hopkins University Press, Baltimore, Maryland).

Recon: This is a comprehensive literature-based genome-scale metabolic reconstruction that accounts for the functions of ORFs, proteins, metabolites and metabolic and transport reactions. The information on systems biology is a step toward individualized medicine and nutrigenomics, the applications, however, need a context to integrate and analyze data, and models resulting from these reconstructions can play a significant role in fulfilling this need. However, the development of cell-type or context-specific models requires the integration of various types of data, including transcriptomic, proteomic, fluxomic and metabolomic measurements (Duarte NC et al 2007 *Proc Natl Acad Sci USA* 104:1777). ► [annotation](#), ► [transcriptome](#), ► [fluxome](#), ► [metabolome](#), ► [nutrigenetics](#), ► [ORF](#), ► [systems biology](#)

Reconstituted Cell: This is produced by fusing cytoplasts and karyoplasts. ► [transplantation of organelles](#), ► [cytoplast](#), ► [karyoplast](#)

Reconstituted Virus: Into an empty viral capsid a complete viral genetic material is introduced, e.g., into the coat of tobacco mosaic virus (TMV) the genome of the related Holmes ribgrass virus (HRV) was introduced and the new particle expressed the characteristic functions of the donor RNA.

This classic experiment proved that the genetic material could also be RNA. Influenza and other viruses can be reconstituted from cloned cDNAs. (See Fig. R27, Fraenkel-Conrat H, Singer B 1957

Biochem Biophys Acta 24:540; Neumann G et al 1999 *Proc Natl Acad Sci USA* 96:9345).

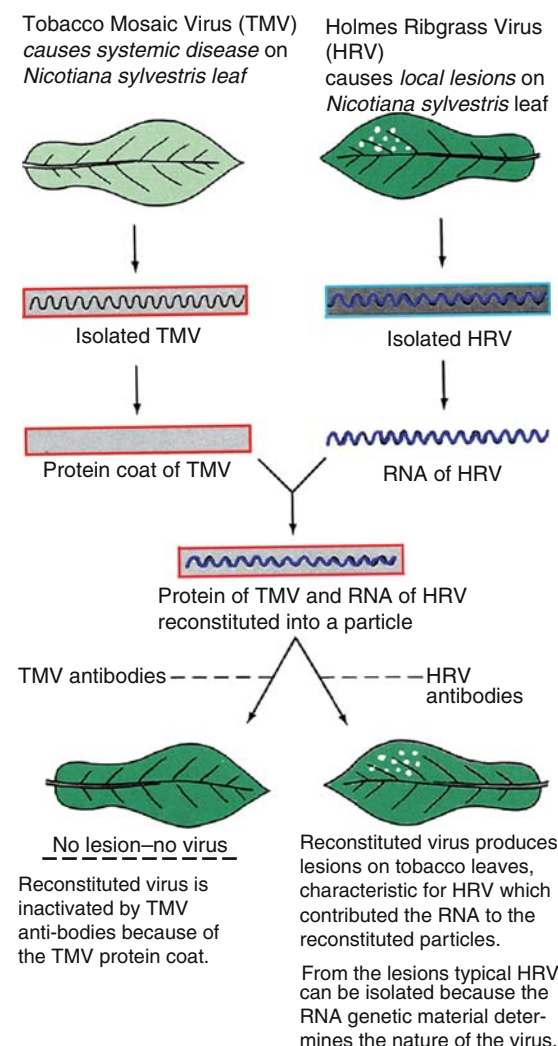


Figure R27. Reconstituted virus

Record: This is a true document of an observation or of a hypothesis which is explicitly stated.

Recoverin: ► [rhodopsin](#)

Recovery of DNA Fragments from Agarose Gel: The fragment is driven by electrophoresis on to DEAE cellulose membrane by cutting a slit in front of the band and placing the DEAE sliver in the slit. Alternatively, electroelution can be used or from agar (at low melting temperature) the DNA can be extracted by phenol and precipitated by ammonium acetate in 2-volume ethanol and collected by centrifugation. ► [electrophoresis](#), ► [DEAE cellulose](#)

RecQ: Denotes a family of helicase proteins. In the case of mutation in the coding gene, chromosomal

instability results in eukaryotes. In prokaryotes the *recQ* is involved in post-replicative repair. ►[chromosomal rearrangements](#), ►[helicase](#), ►[RecA](#), ►[RecB](#) and other *Rec* genes; Enomoto T 2001 J Biochem [Tokyo] 129:501; Wu X, Maizels N 2001 Nucleic Acids Res 29:1765; Cobb JA et al 2002 FEBS Lett 529:43.

RECQL: This is a RecQ-like protein in humans. ►[RecQ](#)

Recruitment: For the initiation of transcription some prokaryotic and eukaryotic genes require activators and the transcriptional complex will operate only if these activators are attracted to the transcriptional target. The GAL1 gene of yeast recruits four units of the GAL4 activator at about 250-base upstream to begin transcription. The GAL4 units are blocked, however, unless galactose is available in the culture medium. The activators make contact with some sites of the RNA polymerase subunits. In bacteria, typical activators are the CAP (catabolite activator protein) and also the λ repressor may bind to the σ^{70} subunit of the polymerase. In yeast, the transcription complex includes more than 30 different proteins. ►[transcription factors](#), ►[transcription complex](#), ►[activator proteins](#), ►[two-hybrid method](#); Francastel C et al 2001 Proc Natl Acad Sci USA 98:12120.

Recruitment of Exons: Evolving genes may acquire coding sequences for functional domains by borrowing exons through recombination. The recruited DNA sequences may occur in several protein genes with different function, e.g., the low-density lipoprotein (LDP) receptor (a cholesterol transport protein) has homology in 8 exons with the epidermal growth factor (EGF) peptide hormone gene. ►[exon](#), ►[LDP](#), ►[EGF](#)

R

Recruitment of Genes: Refers to acquiring new genetic information through recombination or transfection (transformation). ►[transformation](#), ►[transfection](#), ►[recruitment of exons](#)

Rectification, Inward: Through a voltage gated ion channel the current inward exceeds that of the outward. In the case of outward rectification the opposite holds. ►[ion channel](#)

Recurrence Risk: Refers to a couple's chance of having another child with the same defect (see Fig. R28). ►[risk](#), ►[empirical risk](#), ►[genetic risk](#), ►[genotypic risk ratio](#), ► [\$\lambda_s\$](#) , ►[aggregation familial](#), ►[chart](#)

Recurrent Parent: A plant or an animal is mated with selected line(s) in several cycles for one or more backcrosses. ►[recurrent selection](#)

Recurrent Selection (reciprocal recurrent selection): Refers to a variety of methods used for breeding

superior hybrids of plants and animals of high productivity. The general procedure is as follows: lines (inbred or not) A and B are crossed in a reciprocal manner, i.e., A males are crossed to B females and B males are mated with A females. The initial lines are expected to be genetically different to assure the sampling of different gene pools. In this manner several lines are mated, not just A and B. The progenies are tested for performance and only the best parents are preserved. The superior parents are mated again with representatives of their own line. On the basis of their progeny, the parents are re-evaluated. The mating cycle is then repeated. Most commonly, each male is mated with several females of the other line in order to assure the availability of a large population of offspring to be able to conduct statistically meaningful tests. The maintenance of the lines requires that females be mated with selected males within their own lines. This procedure results in inbreeding but enhances the chances of further selection. Therefore, the performance of the selected parental lines is expected to decrease but that of the hybrids will increase. An alternative simplified method involves selection for combining ability in only one set of lines. Thus, line A is mated with a previously inbred tester which has an already known combining ability and the selection is restricted to within line A. This latter modification results in faster initial progress but the final gain may be limited. ►[combining ability](#), ►[hybrid vigor](#), ►[heterosis](#), ►[QTL](#), ►[heritability](#), ►[diallele analysis](#); Hull K 1945 Amer Soc Agron 37:134.

Recursive Partitioning: This is a statistical approach used to classify information into alternative classes, e.g., normal or tumorous. It builds classification rules on the basis of feature information. The underlying principle is that observations of n units represent a vector feature of measurement. (Vector here means a single class matrix.) Or covariates (e.g., data from a type of condition) and a class label. Unlike linear discriminant analysis, it extracts homogeneous strata and constructs tree-based classification rules. (Strata here means a division of the data into parts.) The information is partitioned into increasingly smaller samples (nodes) to facilitate critical discrimination between the classes. ►[matrix algebraic](#), ►[discriminant function](#), ►[cancer classification](#); Zhang H et al 2001 Proc Natl Acad Sci USA 98:6730.

Recursive PCR: This is a method of DNA amplification. Synthetic oligonucleotide primers (50–90 bases) are used which have only terminal complementarity (17–20 bp). They are annealed at 52 °C to 56 °C. The heating cycle is 95 °C and the cooling is at 56 °C. The Vent polymerase is used at 72 °C. This thermostable polymerase has capability not

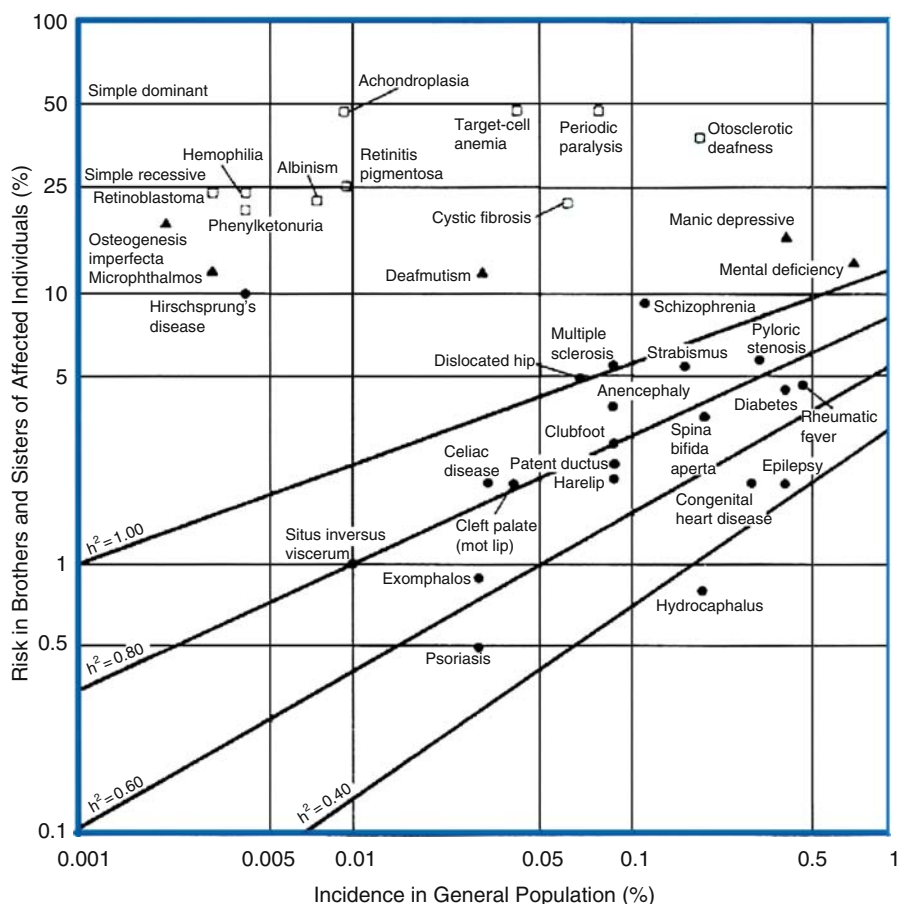


Figure R28. The risk of recurrence of some human abnormalities common to populations of Caucasian descent. The numbers along the horizontal axis refer to the frequency of traits in the population as a whole; the numbers along the vertical axis refer to the risk of occurrence of these defects among brothers and sisters of affected individuals. The heavier lines denote the risk of recurrence according to the nature of the genetic control of these traits. The meaning of dominant and recessive terms is explained in Chapter 4; h^2 stands for heritability in the broad sense (see heritability), indicating the expected inheritance of a trait controlled by several genetic factors. Because the realization of many human genetic anomalies is influenced by a number of factors, estimation of the genetic risk requires an experienced genetic counselor. This consultation will secure peace of mind, for it frequently turns out that the risk is less than feared. Open squares stand for high risks, triangles for medium risks, and solid circles for low risks. Albinism: pigment deficiency of hair, skin, and eye; achondroplasia: a type of dwarfism; anencephaly: a deficiency of brain tissue; celiac disease: an intestinal inflammation; cleft palate: an oral fissure; clubfoot: a deformation of the foot; congenital heart disease: a heart anomaly; cystic fibrosis: fibrous tissue overgrowth with cyst formation; deaf-mutism: loss of hearing and speech; diabetes: a defect of carbohydrate metabolism; dislocated hip: a bone displacement; epilepsy: seizures; exomphalos: a hernia; harelip: upper lip fissure; hemophilia: recurrent bleeding due to lack of blood coagulation; Hirschsprung's disease: a colon enlargement; hydrocephalus: fluid accumulates in the head; manic depressive: obsessive emotional dejection; mental deficiency: deterioration of the mind; microphthalmos: abnormally small eyes; multiple sclerosis: hardening spots in brain and spinal cord; otosclerotic deafness: spongy bones in the ear; osteogenesis imperfecta: brittleness of the bones; patent ductus: fetal blood vessel defect; periodic paralysis: recurrent impairments in motor functions; phenylketonuria: defect in phenylalanine metabolism; psoriasis: scaling skin plaques; pyloric stenosis: obstruction of the distal end of the stomach; retinitis pigmentosa: atrophy and pigmentation in the eyes; retinoblastoma: an eye tumor; rheumatic fever: inflammation of connective tissues; schizophrenia: a mental defect leading to loss of contact with realities; situs inversus viscerum: visceral transposition; spinal bifida aperta: a spinal defect; strabismus: a deviation in the visual axis; target-cell anemia: abnormally thin erythrocytes. (Adapted from Hartl DL 1977. *Our Uncertain Heritage*, J. B. Lippincott, Philadelphia; based on data by Newcombe HB in Fishbein M ed., 1964, 2nd Int. Cont. Congenital Malformations, Int. Med. Congr. Ltd.)

only for strand displacement, but also for exonuclease function and it carries out proofreading and therefore the fidelity of the amplification is very good. During the initial steps each 3' end is extended with the aid of the opposite strand as a template and duplex sections are thus generated. In further cycles one strand of the duplex is displaced by a primer oligonucleotide derived from a neighboring duplex. During the last step high concentration of the terminal oligonucleotides assist in the amplification of the entire duplex. ►polymerase chain reaction, ►Vent; Prodromou C, Pearl LH 1992 Protein Eng 5:827.

red: ►lambda phage, ►Charon vectors

RED613: This is a fluorochrome, a conjugate of R-phycoerythrin and Texas Red. Its excitation maximum is at 488 nm and emission at 613 nm. ►fluorochromes

RED670: This fluorochrome is a conjugate of R-phycoerythrin and a cyanine. Its excitation maximum is at 488 nm from an argon-ion laser, emission is at 670 nm. ►excitation

Red Blood Cell: ►erythrocyte, ►blood, ►sickle cell anemia

Red-Green Color Blindness: ►color blindness

Red King Hypothesis: In mutualistic interaction the slowly evolving species is expected to gain a disproportionate share of the benefits in the population. (See Bergstrom CT, Lachmann M 2003 Proc Natl Acad Sci USA 100:593).

R

Red Queen Hypothesis: If a population does not continue to adapt at the same rate as its competitors, it will lose ecological niches where it can succeed, and if it stays put long enough it may become extinct. The hypothesis suggests that sex evolved so that the species could respond to changes in the biotic environment. Recent analysis, however, does not support the need for sex evolution in all cases of species interactions (Otto SP, Nuismer SL 2004 Science 304:1018). The name RQ was adapted from Lewis Carroll's (pen name of C. L. Dodgson) 1872 fantasy story about a chess game, *Through the Looking Glass*. ►adaptation, ►extinction, ►beneficial mutation, ►equilibrium in populations, ►genetic homeostasis, ►treadmill evolution, ►co-evolution, ►Kondrashov's deterministic model of evolution of sex, ►Muller's ratchet; Van Valen L 1973 Evol Theory 1:1.

Redifferentiation: Refers to organ or organism formation from dedifferentiated cells, such as from callus (see Fig. R29). ►callus, ►regeneration, ►dedifferentiation

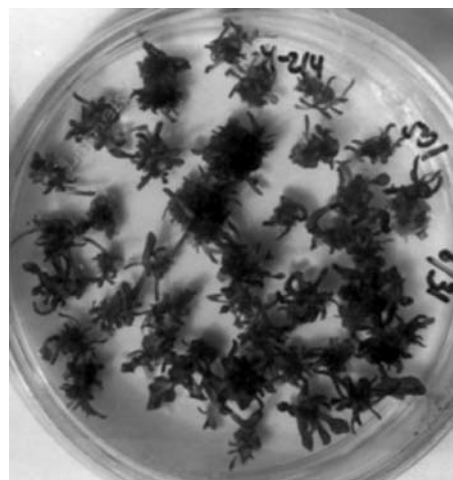


Figure R29. Redifferentiation of leaves from *Arabidopsis* callus (Rédei GP unpublished)

Redox Pair: Refers to an electron donor and the oxidized derivative.

Redox Reaction: ►oxidation-reduction

Reduced Representation Shotgun: ►RRS

Reducing Sugar: Its carbonyl carbon is not involved in glycosidic bond and can thus be oxidized. Glucose and other sugars can reduce ferric or cupric ions, a property that serves for their analytical quantitation (Fehling reaction).

Reductant: An electron donor.

Reduction: Denotes the gain of electrons.

Reductional Division: In meiotic anaphase I half of the chromosomes segregate to each pole and the two daughter cells have n number of chromosomes rather than $2n$ as in the original meiocyte. In the case of uneven numbers of crossing over between the gene and the centromere the numerical reduction of the chromosomes may not result in the separation of different pairs of alleles, i.e., the reduction does not extend to the alleles. The reductional division at meiosis assures the constant chromosome numbers in the species and serves a basis for Mendelian segregation. ►prereduction, ►postreduction, ►tetrad analysis, ►meiosis

Reductional Separation: In meiotic anaphase I the parental chromosomes separate intact because there is

no recombination between the bivalents. ►[equational separation](#)

Reductionism: This refers to the practice of reducing ideas to simple forms or making efforts to explain phenomena on the basis of the behavior of elementary units (molecules). This endeavor is frequently criticized because of the complexities of biological systems. It should be borne in mind that without the analytical approach, science (molecular genetics) would not have progressed to its present level. ►[model organisms](#)

Reductive Evolution: Some obligate intracellular parasites (*Rickettsia*, *Chlamydia*, *Mycobacterium leprae*) lost during evolution a significant portion (up to 76%) of the coding capacity of their genetic material because the host metabolism provided the essential gene products. These organisms may still have many pseudogenes as well as degraded, non-functional DNA tracts. ►[Rickettsia](#), ►[leprosy](#); Pál C et al 2006 Nature [Lond] 440:667.

Redundancy: Refers to repeated occurrence of the same or similar base sequences in the DNA or multiple copies of genes. The repeated gene sequences are considered to have a duplicational origin. About 38–45% of the sampled (ca. 1/3 of all) proteins in *E. coli* are expected to be duplicated and in the much smaller *Haemophilus influenzae* genome, completely sequenced by 1995, 30% appear to have evolved by processes involving duplications. In this small genome some gene families were represented by 10 to over 40 members whereas almost 60% of the genes appeared unique. In yeast almost 60% of the genes are redundant. In the large eukaryotic genomes the repetitious sequences are represented by larger fractions. The number of protein kinases in higher eukaryotic cells may reach 2,000 and that of phosphatases nearly 1,000. Theoretically, true redundancy should succumb to natural selection unless the rate of mutation is extremely low. Besides the shared functions, if the redundant genes have unique roles, they are maintainable. Redundant genes are saved when the *developmental error* rate is high. Redundant genes may affect the fitness of an organism in a very subtle way and may not show a clear independent phenotype. Also, they may serve as an insurance for the loss or inactivation of other members of the gene family. Redundant genes may have the luxury to afford mutation to new functions. Mutation or deletion of redundant genes may not have phenotypic consequences. Some single copy genes can also be removed without any consequences for the phenotype. ►[SINE](#), ►[LINE](#), ►[LOR](#), ►[MER](#), ►[MIR](#), ►[tandem repeat](#), ►[inverted repeat](#), ►[polyploid](#); Goldberg RB 1978 Biochem Genet 1–2:45.

Reduplication Hypothesis: At the dawn of Mendelism, William Bateson postulated that genetic recombination takes place by a differential degree of replication and different associations of genes after they separated at the interphase rather than by breakage and reunion of synapsed chromosomes. ►[breakage and reunion](#), ►[copy choice](#); Bateson W, Punnett RC 1911 J Genet 1:293.

Reelin: This 420 kDa glycoprotein is encoded by the *reeler* gene in mouse and is expressed in the embryonic and postnatal periods. It is similar to extracellular matrix serine proteases involved in cell adhesion. It controls layering and positioning of neurons and mutations in gene impair coordination resulting in tremors and ataxia. In schizophrenia and bipolar psychoses at positions –134 and 139 in the promoter of reelin methylation of cytidine increases as a result of upregulation of methyltransferase (Grayson DR et al 2005 Proc Natl Acad Sci USA 102:9341). ►[ataxia](#), ►[CAM](#), ►[schizophrenia](#), ►[bipolar mood disorder](#), ►[chimpanzee](#); D’Arcangelo G et al 1995 Nature [Lond] 374:719; Keshvara L et al 2001 J Biol Chem 276:16008; Quattrocchi CC et al 2002 J Biol Chem 277:303; see retraction 2004 Science 303:1974.

REF: This RNA-binding nuclear protein facilitates the export of the spliced mRNA from the nucleus to the cytoplasm in cooperation with TAP. ►[TAP](#); Le Hir H et al 2001 EMBO J 20:4987.

Reference Library Database (RLDB): Cosmid, YAC, P1 and cDNA libraries for public use on high-density filters. Information: Reference Library Database, Imperial Cancer Research Fund, Room A13, 44 Lincoln’s Inn Fields, London WC2A 3PX, UK. Phone: 44-71269-3571. Fax: 44-71-269-3479. INTERNET: genome@icrf.icnet.uk, databases.

Refractile Bodies: *Paramecia* may contain bacterial symbionts and the bacteriophages associated with them may appear as bright (refractile) spots under a phase-contrast microscope. ►[symbionts hereditary](#), ►[killer strains](#), ►[Paramecium](#)

Refractory Genes: These interfere with the completion of the life cycle of parasites, e.g., *Plasmodium*, within the insect vector, e.g., mosquitos and can therefore be exploited for the control of malaria and other diseases. ►[Plasmodium](#), ►[malaria](#); Yan G et al 1997 Evolution 51:441.

Refractory Mutation: This may not be revealed through genetic testing although it may lead to a genetic disease, e.g., mutation in introns, promoters or

3'-downstream regulatory sequences that control transcript levels. ►[genetic testing](#)

RefSeq: This is the reference sequence for 2,400 organisms, genomes, transcripts and proteins. (See Pruitt KD et al 2005 Nucleic Acid Res 33:D501; <http://www.ncbi.nlm.nih.gov/RefSeq/>; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>).

Refsum Diseases (10pter-p11.2, 8q21.1, 7q21-q22, 6q23-q24): These autosomal recessive disorders are manifested in adult and early onset forms. Both forms involve phytanic acid accumulation because of the deficiency of an oxidase enzyme in the peroxisomes. The symptoms include polyneuritis (inflammation of the peripheral nerves), cerebellar (hind part of the brain) anomalies and retinitis pigmentosa. The early onset form, in addition, is characterized by facial anomalies, mental retardation, hearing problems, enlargement of the liver, lower levels of cholesterol in the blood and the accumulation of long-chain fatty acids and pipecolate (a lysine derivative). The symptoms of the infantile form overlap with those of the Zellweger syndrome. ►[Zellweger syndrome](#), ►[phytanic acid](#), ►[microbodies](#), ►[retinitis pigmentosa](#); Mukherji M et al 2001 Hum Mol Genet 10:1971; van den Brink DM et al 2003 Am J Hum Genet 72:471.

Refuge: Refers to the area planted with non-transgenic crops (GMO) next to transgenic plants. The purpose is to let non-resistant insects mate with resistant insects and thus dilute out the resistant population. At the moment the best relative size of a refuge is controversial. ►[GMO](#)

Regeneration in Animals: This is more limited than in plants where totipotency is preserved in most of the differentiated tissues. Regeneration can actually be classified into two main groups of functions: one is the regular replacement of cells (e.g., epithelia, hairs, nails, feathers, antlers and production of eggs and sperms) in a wide range of animals, and the other is the capacity to regenerate body parts lost by mechanical injuries. The latter type of regeneration may involve the formation of an entire animal from pieces of the body, such as by morphallaxis in sponges, Hydra, flatworms, annelids (preferentially from the posterior segments), echinoderms, etc. A more limited type of regeneration is found in the higher forms. Arthropods may replace lost appendages of the body. Vertebrate fishes can replace lost fins, gills or repair lower jaws. The Zebrafish is capable of heart regeneration after epicardial injury (Lepilina A et al 2006 Cell 127:607). Some mouse strains (MRL) have an exceptional ability to regenerate heart tissues in vivo. Several amphibians (salamanders, newts) readily regenerate lost limbs,

tails and some internal organs. Reptile lizards can reproduce lost tails although the regenerated one is not entirely perfect. Regeneration of feathers and repair of beaks may take place in birds. In mammals lost blood cells may be replenished by bone marrow activity, or liver cells may regenerate new ones. More limited regeneration may occur in bone, muscle, skin and nerve cells but unlike in plants, complete organisms cannot be regenerated from any part, except the embryonic stem cells or possibly from other stem cells after special treatments. According to recent evidence, mesoderm, endoderm and ectoderm cell lineages can be reprogrammed, e.g., bone marrow cells can regenerate into nerve cells or muscle-derived cells and cells of the central nervous system can reconstitute other cell types. From embryonic stem cells viable, fertile adult mouse can be differentiated (Eggen K, Jaenisch R 2003 Methods Enzymol 365:25). ►[regeneration of plants](#), ►[transdetermination](#), ►[homeotic genes](#), ►[stem cells](#), ►[transplantation of nuclei](#), ►[nuclear transplantation](#), ►[dedifferentiation](#), ►[redifferentiation](#), ►[transdifferentiation](#), ►[Hydra](#), ►[zebrafish](#), ►[planarians](#), ►[newt](#); Leferovich JM et al 2001 Proc Natl Acad Sci USA 98:9830; Alsberg E et al 2002 Proc Natl Acad Sci USA 99:12025; Brockes JP, Kumar A 2005 Science 310:1919; regeneration in planarians: Sanchez AA 2006 Cell 124:241; regeneration of heart review: Laflamme MA, Murry CE 2005 Nature Biotechnol 23:845; comprehensive review of molecular mechanisms involved in regeneration of model organisms: Alvarado AS, Tsonis PA 2006 Nature Rev Genet 7:873.

Regeneration of Plants: Refers to the formation of new organs or entire organisms from dedifferentiated tissues or single cells (see Fig. R30). A higher level of ferredoxin-nitrite reductase quantitative gene locus and nitrate assimilation rice favors regeneration of transgenic plants (Nishimura A et al 2005 Proc Natl Acad Sci USA 102: 11940). ►[embryogenesis somatic](#), ►[embryo culture](#), ►[clone](#), ►[vegetative reproduction](#), ►[totipotency](#), ►[dedifferentiation](#), ►[callus](#), ►[root](#)

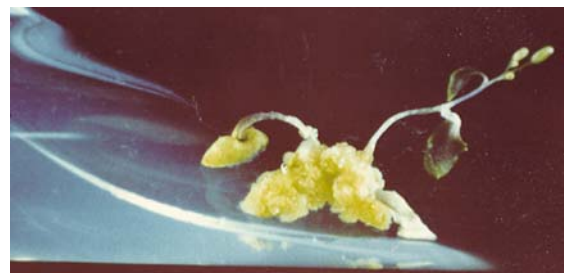


Figure R30. Regeneration of Arabidopsis from callus

Reglomerate: ► [aggregulon](#)

Regression: This is the measure of dependence of one variate on another in actual quantitative terms in contrast to correlation which uses relative terms from 0 to 1. Linear regression involves the independent variate to the first power. Quadratic regression involves the independent variate to the second power and cubic regression to the third power. ► [correlation for the calculation of regression coefficient](#), ► [heritability](#), ► [linear regression](#), ► [cluster analysis](#), ► [multiple regression](#)

Regulated Gene: The expression is conditional and affected by genetic and non-genetic factors. Traits associated with dynamic processes may evolve to some extent more readily through regulatory rather than coding mutations. Indeed, the evolution of complex multicellular organisms would have been all but impossible in the absence of *cis*-regulatory systems that allowed context-dependent transcriptional regulation. The expression of many genes is altered through alternative transcription start sites and splicing and post-translational modifications. Quantitative traits are typically regulated by elements in the vicinity of the gene upstream or downstream. Typical examples of *cis*-regulation are the operons. Certain *duffy* haplotypes segregating in modern human populations offer almost complete resistance to infection with *Plasmodium vivax*. Resistance is due to the lack of Duffy protein expression in erythrocytes, but not in several other cells where it is normally expressed. The causal mutation is a *cis*-regulatory single nucleotide polymorphism (SNP) which disrupts binding of the transcription factor GATA1. Lactose intolerance (LCT) is determined by the presence or absence of an SNP in an intron of minichromosome maintenance deficient 6 homologue (*MCM6*), the next gene 5' of LCT. Experimental tests demonstrate that this SNP elevates LCT transcription (Wray GA 2007 Nature Rev Genet 8:206). ► [housekeeping genes](#), ► [constitutive genes](#), ► [regulation of gene activity](#), ► [operon](#), ► [disaccharide intolerance](#), ► [Duffy blood group](#), ► [SNP](#), ► [GATA](#), ► [MCM1](#), ► [annotation](#), ► [module](#), ► [regulated sequence motifs in humans](#), ► [mouse](#), ► [rat](#); *Caenorhabditis*: <http://www.cisred.org/>; annotated regulatory sequences: <http://www.swissregulon.unibas.ch>; *cis*-regulatory mammalian modules: <http://genomequebec.mcgill.ca/PReMod>.

Regulation of Enzyme Activity: Enzyme activity is characterized by various measures of enzyme kinetics (► [Michaelis-Menten](#), ► [Lineweaver-Burk](#), ► [Eadie-Hofstee](#)). The reaction is controlled by the quantity and/or activity of an enzyme. Enzymes may enhance reaction rates by 10^{10} to 10^{23} relative to uncatalyzed

transformations in aqueous solutions (Kraut DA et al 2003 Annu Rev Biochem 72:517). The quantity of the enzyme depends on protein synthesis/degradation controlled at the level of transcription, translation, processing of the protein, and its instability (► [regulation of gene activity](#)). The substrate of the enzyme may regulate the production of the enzyme protein (► [enzyme induction](#), ► [lac operon](#), ► [catabolite repression](#), ► [attenuation](#)). *Feedback control* means that the accumulation of the product of an enzyme may shut down the operation of a pathway at any step preceding the final product. Feedback control may be simple or multiple, i.e., more than one enzyme may be affected either simultaneously or sequentially or more than a single product of the pathway may act in a concerted manner (► [feedback control](#)). Feedback control may act either at the level of the synthesis (*feedback repression*) or by *inhibition* of the activity of a steady number of enzyme molecules. In general, the inhibitors are either *competitive* (bind to the enzyme and compete with the substrate for the active site) or *non-competitive* (the inhibitors act by attaching to the enzyme at a site other than the active site yet lower enzyme activity [by allosteric effect]). *Uncompetitive inhibitors* operate by binding to the enzyme-substrate complex. *Suicide inhibitors* are converted by the enzyme into an irreversibly binding molecule that permanently damages the enzyme. The inhibitors may simultaneously affect more than one enzyme. *Mechanism-based inhibitors* are highly specific to a single enzyme and as such have great significance for medicinal chemistry. Among these are the *antisense inhibitors* (► [antisense RNA](#)). *Allosteric enzymes* may also be stimulated (*modulated*) by allosteric compounds. The modulator may be *homotropic*, i.e., essentially structurally identical to the substrate or *heterotropic* in case it is not identical to the substrate. The activity of an enzyme may require a proteolytic cleavage of the precursor protein, the *zymogen*. Thermostabilization of an enzyme (cytosine deaminase) by site-directed mutagenesis at sites identified on the basis of crystal structure using computations increased half-life at 50 °C 30-fold without lowering catalytic efficiency. The effects of the three mutations were synergistic and indicated that by purposeful design, industrially or biomedically, more useful enzymes can be produced (Korkegian A et al 2005 Science 308:857). ► [regulation of gene activity](#), ► [protein synthesis](#), ► [signaling](#), ► [allostery](#), ► [allosteric control](#), ► [feedback](#); Wall ME et al 2004 Nature Rev Genet. 5:34.

Regulation of Gene Activity: The various types of cells and differentiated tissues of an organism generally contain the same genetic material (► [totipotency](#),

►regeneration) yet their differences attest that the genes must function in diverse ways in order to bring about the variety of morphological and functional differences. Genetic regulation accounts for this variety. Many genes are expressed in every cell because they determine the metabolic functions essential for life. Another group of genes is responsible for such generally required structural elements as membranes, microtubules, chromosomal proteins. (►housekeeping, ►constitutive genes). Other genes are not constitutive, i.e., they are regulated in response to external and internal control signals; in other words, they are expressed only when they are called up for a duty. The latter group of genes is responsible for the differences within an organism. Today highly sensitive computational methods are available (PHYLONET) for the identification of phylogenetically conserved regulatory motifs by analysis of the promoter sequences of several related genomes. By this approach global regulatory networks can be identified (Wang T, Stormo GD 2005 Proc Natl Acad Sci USA 102:17400).

Pretranscriptional Regulation. The expression of genes is regulated by several means, including the structural organization of the eukaryotic chromosome. Although it was earlier believed that the DNA associated with histones was not or not efficiently transcribed. The nucleosomal organization of the DNA may not prevent transcription yet nucleosomal reorganization may be required for the proper expression of genes (►nucleosomes). For efficient transcription of genes chromatin remodeling (histone acetylation) is required. It has been known since the early years of cytogenetics that, e.g., the heterochromatic regions of the chromosomes were not associated with genes that could be mapped by recombinational analysis. It appears that these tightly condensed regions of the chromosome are not suitable for transcription in general. The coiling of the chromosomes is also genetically regulated. Position effect indicates that gene expression is altered or obliterated by transposition into heterochromatin. Similarly, lyonization of the mammalian X chromosome involves heterochromatinization and silencing of genes (►silencer). The insertion of normal genes (by transformation) into the condensed telomeric region (about 10^4 bp in length) interferes with their expression (►heterochromatin, ►position effect, ►lyonization, ►telomeres). Gene expression depends in some way on the presence of nuclease sensitive sites in the chromatin. At these nuclease hypersensitive sites, apparently the DNA is not wrapped around so tightly and is more accessible to transcription initiation (►nuclease sensitive sites). The effects of the chromatin locale on the expression of genes are clear from the large variations in the

production of a specific mRNA in various transgenic animals and plants which carry a particular gene inserted at different chromosomal locations (►LCR). Also, in order to make the gene accessible to transcription or replication, in bacteria negative supercoils are formed which must be subsequently relaxed. In eukaryotes, DNA in Z conformation may be preferentially available for initiation of transcription (►supercoiling, ►Z DNA). Some genes are regulated by transposition; this mechanism is common in prokaryotes and eukaryotes for generating defense against the immune system of the host (►phase variation, ►antigenic variation), it is also used for sex determination in yeast (►cassette model). At replication the four basic nucleotides are normally used, several nucleoside analogs (e.g., 5-bromodeoxyuridine) may be incorporated into the DNA with some effects on gene expression. In the T-even (T2, T4, T6) phages in place of cytosine 5-hydroxymethyl cytosine is found as a protection against most of the restriction enzymes. In eukaryotes 5 to 25% of the cytosine residues are 5-methylcytosine. Genes with methylated cytosine are generally not transcribed (►methylation of DNA, ►recruitment, ►SRB, ►nuclear receptors).



Figure R31. Genetic regulation

Regulation of Transcription and Transcripts.

The cells have various options for more direct regulation of transcription: (i) control of signal receptor and signal transmission circuits, (ii) construct or take apart assembly lines geared to a particular function, (iii) transcriptional control, (iv) transcript processing and alternative splicing, (v) export of the mRNA to the cytosol in eukaryotes. In prokaryotes and cellular organelles a membrane does not enclose the genetic material and transcription and translation are coupled, and (vi) selective degradation of mRNA or a carboxypeptidase may cleave the transcription factors.

Nucleotide sequences in the DNA (structural gene) specify the primary structure of the transcripts. Upstream cis elements (enhancers, promoters and

other protein binding sequences) control the attachment and function of the DNA-dependent RNA polymerases (►pol I, ►pol II and pol III RNA polymerases). Some eukaryotic genes may have more than one promoter and the tissue or cell type and the physiological conditions select the promoter to be used. Transcript length is dependent on the promoter element used and the upstream, non-translated region contains binding sequences for further regulation of gene expression. Various upstream elements of the same gene may respond differently to cytokines, phorbol esters and hormones (►hormone receptors, ►hormone response elements).

The enhancers may be positioned either upstream or downstream. Inducible genes receive cues through membrane receptors and transmitter cascades, generally regulated by kinases and phosphorylases (►signal transduction). Downstream DNA nucleotide sequences control the termination of transcription and in eukaryotes a polyA tail (exceptions are the histone genes) is added enzymatically without the use of a DNA template (►polyadenylation signals, ►transcription termination in eukaryotes and prokaryotes, ►self-cleavage of RNA, ►RNAi, ►micro-RNA, ►small RNA; Chen K, Rajewsky N 2007 Nature Rev Genet 8:93).

Gene expression begins by the initiation of transcription (►transcription, ►protein synthesis). The DNA displays some specific sequences in the major grooves of the double helix that are recognized by DNA-binding proteins. (►lac operon, for the *E. coli* lac repressor binding site and the CAP site for binding of the catabolite activator protein). In phage λ the *cI* repressor binding element controls by repression several genes (►lambda phage). The consensus sequence of the budding yeast GAL4 upstream element (►galactose utilization), for the mating type $\alpha 2$ consensus (►mating type determination) and for the transcription factor GCN4 (►GCN4) that regulate specific genes. In plants, the core sequence for a transcriptional activator protein is shown under the G-box element. The binding proteins have a short α helix or a β sheet that fits into the major groove of the DNA at the specific sequence motif (►helix-turn-helix, ►Zinc finger, ►leucine zipper, ►helix-loop-helix). Specific activators may also regulate transcription (Spiegelman BM 2004 Cell 119:157). The activation may require a positive or negative control process (►arabinose operon, ►lac operon, ►CAT). For the initiation of transcription in eukaryotes, the presence of a general transcription factor protein complex is essential (►open transcription complex). Additional specific transcription factors may modulate transcription (►transcription factors inducible). In the DNA there are also a number of *response elements* or regulatory sequences that bind

several specific proteins and the proteins in turn may bind additional modules (►response elements, ►hormone response elements). The inducible transcription factors in the eukaryotic nuclei help in the assembly of the transcription complex and activate or repress genes by assembling modules. The interacting elements are responsible for fine-tuning metabolic pathways and regulating morphogenesis. These transcription factors may or may not be syntenic with the genes they act on, and their number may vary depending on the gene concerned. The binding proteins may pile up in a specific way at the promoter after DNA looping brings them to that area. Also, the binding proteins may attract other molecules that act in an activating or silencing manner. In an absolutely abstract form this may be visualized with a few computer symbols.

The bacterial DNA-dependent RNA polymerase (►pol) attaches to the double-stranded DNA, and generates an open promoter complex and proceeds with the transcription (►open promoter complex). The bacterial RNA polymerase may rely on different σ subunits for transcribing various bacterial or viral genes. In some instances bacterial and eukaryotic genes also use activators of transcription to assist the RNA polymerase enzyme to generate the open promoter complex. These proteins may attach to the DNA in an area some distance from the gene (enhancer) and looping may bring the protein to the promoter site (►looping of DNA).

The likelihood of association of two DNA sites by looping reaches an optimum at a distance of about 500 bp and it is considerably reduced when they are very close. Some of the enhancer DNA elements (binding sites for regulatory proteins) may be several thousands of nucleotides apart upstream or downstream of the structural gene (►enhancer). The various binding proteins (symbolized by: \cup , \cap , Ψ , Ω , \clubsuit , \spadesuit , ∇) may associate with the general transcription factors and with each other in different combinations and numbers either to activate or suppress, or to modulate or silence the gene (see Figs. R32, R33, and R34).

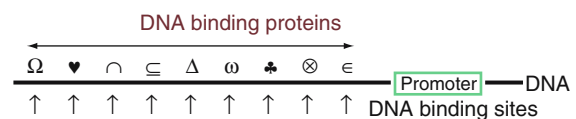


Figure R32. Several different proteins (represented by abstract symbols) can bind upstream of the promoters

The open promoter complex includes the general transcription factors, RNA polymerase II, the TATA box and the transcription initiator (INR). These crude schematic figures do not properly represent the interacting complexes that are required for turning on, turning off and modulating expression as needed

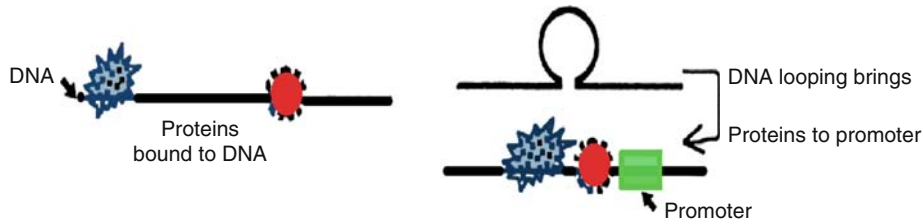


Figure R33. DNA looping

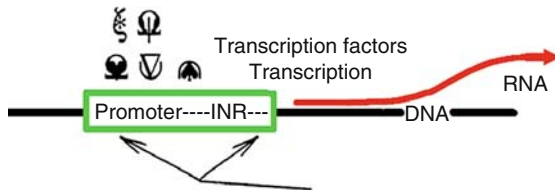


Figure R34. Promoter bound transcription factors regulate transcription

for the orchestration of intricate processes such as the temporal and topological control of morphogenesis ([▶morphogenesis](#)). The transcription factors regulate these processes but the transcription proteins themselves are subject to regulation by metabolic and environmental cues. These processes include conformational changes, combinatorial assembly of subunits, ligand binding, phosphorylation and dephosphorylation, presence of inhibitors and activators ([▶signal transduction](#)). In eukaryotes there may be a need for chromatin remodeling to enable the activators and the TATA box binding protein to access the DNA ([▶nucleosome](#)). For this process a histone acetylase or SWI/SNF complex may have to be recruited in preparation for transcription. In both prokaryotes and eukaryotes special control mechanisms have evolved for the termination of transcription ([▶transcription termination](#)). The regulation of the transcriptional process and the turnover of the transcripts determine the quantity of the transcripts. Many bacterial genes are organized into coordinated regulatory units employing negative, positive or a combination of these two controls of transcription ([▶lac operon](#), [▶arabinose operon](#)). In these operons the genes are either exactly ([▶tryptophan operon](#)) or with some modification ([▶histidine operon](#)) arranged according to the order of the biosynthetic pathway. The amino acid operons use, in addition, *attenuation* for controlling the quantity of the transcripts for maximal economy ([▶attenuator region](#), [▶tryptophan operon](#)). The operons are characterized by coordinated regulation of the transcription of several genes belonging to the same transcriptional unit and transcribe them into a polycistronic mRNA.

Eukaryotes usually do not produce polycistronic mRNAs but the rRNA and tRNA transcripts are processed into functional units post-transcriptionally. Elements of a coordinated unit may not all be juxtapositioned ([▶regulon](#), [▶arabinose operon](#)). The small phage (ϕ X174 [can be found under F]) and retroviral genomes may have overlapping genes that specify more than one protein, depending on the register they are transcribed ([▶overlapping genes](#), [▶recoding](#), [▶retroviruses](#)). The need for the protein products of these overlapping genes transcribed with the aid of the same promoter, may be not the same. Some proteins, e.g., viral coat proteins may be needed in larger quantities than the replicase enzymes. Therefore, mechanisms have evolved to by-pass internal stop signals and produce some fusion proteins that assist in achieving this goal ([▶overlapping genes](#), [▶recoding](#)). In bacterial, plant and animal viruses, another means of regulation of gene activity at different steps has evolved that involves the use of antisense RNA. This mechanism is being explored so as to develop particular drugs for the highly specific regulation of genes with minimal side effects or for the development of new, selective antimicrobial agents and more desirable crop plants without reshuffling the entire genome ([▶antisense technologies](#)). Short RNAs use various means to regulate transcription ([▶repressor](#), [▶RNAi](#), [▶microRNA](#)).

In prokaryotes a special short transcribed stretch of nucleotides, the Shine-Dalgarno box, controls the attachment of the mRNA to the small (30S) ribosomal subunit. For the same task, eukaryotes use “ribosome scanning”, i.e., the mRNA tethers a 40S ribosomal subunit and by reeling locates the first initiator codon. Eukaryotic 40S ribosomal subunits can enter circular mRNAs if they contain internal ribosomal entry sites (IRS).

The primary transcripts are generally not suitable for translation into a protein or for a RNA product (rRNA, tRNA). The transcripts are processed to mRNA and/or other RNA units. Introns are excised and the sequences corresponding to exons are spliced and may even be transspliced with the cooperation of spliceosomes ([▶intron](#), [▶exon](#), [▶spliceosome](#), [▶alternative splicing](#), [▶hnRNA](#), [▶snRNA](#)). The splicing itself

may be genetically and organ-specifically regulated. The transposition of the P element of *Drosophila* is relatively rare in the soma but five times more common in the germ line because one intron is not excised from the transposase transcripts in the somatic cells (►hybrid dysgenesis). Tissue-specificity and function-specificity of many proteins is partly controlled by alternative splicing (►immunoglobulins, ►sex determination). Mitochondrial RNA transcripts may be modified by replacing C residues with Us (►RNA editing).

The eukaryotic mRNAs are capped while still in the nucleus. The transcript is cut at the appropriate guanylic residue and it is then modified (►cap, ►capping enzymes). Capping increases the stability of the mRNA, facilitates its transport to the cytosol and assists in the initiation of translation by being recognized by initiation protein factors eIF-4F, eIF-4B, etc. (►cap, ►eIF).

The tail of the eukaryotic mRNAs (with few exceptions, e.g., histones) is equipped with 50–250 adenylic units to increase their stability. Polyadenylation is controlled separately from transcription because a special enzyme adds these nucleotides after processing of the transcript. Generally, the genes carry a short A-rich consensus (►polyadenylation signal) in the DNA that instructs the RNA polymerase to terminate transcription after the enzyme passes through the signal and also indicates the need for polyadenylation. Eventually, the poly-A tail is reduced to about 30 A units. In eukaryotes, the 3' tail may be substantially regulated by specific, extrinsic genes (Kakoki M et al 2004 Dev Cell 6:597).

Some of the transmembrane proteins have a hydrophobic amino acid sequence in the section that is going to be located within the membrane, whereas the cytosolic end contains a longer hydrophilic carboxyl end. The positioning of the transmembrane proteins shows substantial variations, depending on the intrinsic properties of proteins. The transcript of the same coding sequences is differentially cut in a manner as to assure such a terminus is formed for the membrane-bound proteins whereas a shorter hydrophilic end terminates the otherwise identical circulating immunoglobulin molecules.

After these intricate preparatory processes, the eukaryotic mRNA is transported to the cytosol through the nuclear pores. Prokaryotes do not have membrane-enclosed nuclei but only nucleoids, anchored to the cell membrane, and there the translation proceeds *pari passu* with transcription. (See Carlson M 1997 Annu Rev Cell Dev Biol 13:1; Holstege FC et al 1998 Cell 95:717).

Post-Transcriptional Regulation. The mRNA may be degraded before it is translated into polypeptide chains. About half of the prokaryotic

mRNAs may be degraded within 2–3 min after their synthesis. Eukaryotes have long-lived mRNAs, which usually last for at least three times longer but at times in special dormant tissues of plants they may remain intact for years. The degradation is mediated by special endonucleases that recognize mRNAs. Also, A-U sequences in the non-translated downstream regions may remove the poly-(A) tails and thus stability is reduced in both cases.

Translation in eukaryotes begins with the transport of the capped mRNA outside the nucleus, into the cytosol. The mRNA tethers several ribosomes and the polysomal structures are formed. Some mRNAs are equipped with a signal coding sequence, coding for a special tract of 15 to 35 amino acids. That directs it toward the *signal sequence recognition particle* after only a few dozen amino acids are completed on the ribosome. The *signal peptide* then transports the nascent peptide chain into the lumen of the endoplasmic reticulum, Golgi vesicles, lysosomes and mitochondria, plastids, etc. This mechanism facilitates the subcellular localization of the emerging proteins at places where they are most needed and from where they may be diffused in a gradient as required for embryonic differentiation (►signal sequence, ►signal peptide, ►signal sequence recognition particle, ►morphogenesis in *Drosophila*). Various control mechanisms have been involved in the generation of protein products of genes: (i) translational control, (ii) post-translational modification of the polypeptides, (iii) control of polypeptide assembly into proteins, (iv) regulation of protein conformation, (v) compartmentalization of proteins, (vi) interaction of protein products and ribozymes, (vii) feedback controls at the level of protein synthesis and function, and recently (viii) the wide scale role of small RNAs was discovered (►induction, ►repression, ►attenuation, ►inhibition, ►silencers, ►small RNAs, ►non-coding RNA, etc.). These may be involved before, during and after the final protein products are made.

The state of phosphorylation of the eukaryotic initiation factor, eIF-2 is critical for the translation process. This protein may form a complex with guanosyl triphosphate (GTP) and can assist in the attachment of the initiator tRNA^{Met} to the P site of the small subunit (40S) of the ribosome and scans the mRNA until it finds a methionine codon (AUG). This occurs after the large ribosomal (60S) subunit joins the small subunit to form the 80S ribosome and at the same time one molecule of inorganic phosphate and the inactivated eIF-2 and GDP are released. Then eIF-2 can acquire another GTP and the initiation process is repeated (►protein synthesis).

Although all polypeptide chains start with a formyl-methionine (prokaryotes) or methionine (eukaryotic),

the final product is frequently truncated at both the amino and carboxyl termini. Many proteolytic enzymes are translated as large units and become activated only after cleaving off certain parts of the original protein. To become active insulin is initially made as a pre-proinsulin that must be tailored in steps: first pre-, followed by pro-insulin and finally insulin. Several viral proteins, secreted hydrolytic proteins, peptide hormones and neuropeptides are made as polyprotein complexes which have to be broken down into active units in the trans-Golgi network, secretory vesicles or even in the extracellular fluids to become fully functional. The formation of polyproteins appears to be justified as a protective measure against destruction in the cytosol until they can be sequestered and confined into some vesicles. The loaded vesicles then migrate to predetermined sites where upon receiving the cognate signals they release the active protein. The signals can be chemical, physical (electric potentials) or topological. The release of the members of the polyprotein group may be selective regarding the site of release; different proteins can be released at different anatomical sites.

Some proteins are synthesized in separate polypeptide chains but must be folded and/or assume a quaternary structure, e.g., $\alpha\beta\gamma$ may even have to acquire a prosthetic group such as heme, a vitamin or other organic or inorganic group(s). The folding in prokaryotes begins after completion of the chain. In eukaryotes the folding may begin before the completion of a polypeptide and thus higher complexity is generated in the large proteins. The mRNA may be degraded before it can be translated into polypeptide chains.

Proteins are commonly acetylated after translation, carbohydrate side chains are added (glycoproteins), prenylated, linked by covalent disulfide bonds, special amino acids (serine, threonine, tyrosine) are phosphorylated by kinase enzymes, lysine residues may be methylated, and extra carboxyl groups may be attached to aspartate and glutamate residues.

Engineered Regulation. Using a genetic vector, it is feasible to introduce into somatic cells a structural gene *A* for a protein of a special need. With the aid of another vector it is possible to introduce gene *B* encoding its special transcription factor. The latter transcription factor gene is equipped with a promoter which responds to a specific drug (or to a specific temperature or to any other conditional factor) regulating its transcription. Thus, supplying the drug at variable dosage, the expression of gene *A* can be modulated by the controlled response of gene *B*. Such a system may permit the controls to be fine-tuned and secure compensation for a genetic defect or improve productivity.

According to some estimates, there are about 2,000 different protein kinases and 1,000 phosphatases in a higher eukaryotic cell. They must be regulated in time, space, and for other specificities. This regulation is an extremely complex task and is expected to be mediated by associations with modular, adaptor, scaffold and anchoring proteins working in sequential cooperation through signal transduction pathways. The availability of complete information on nucleotide sequence of both prokaryotic and eukaryotic genomes as well as microarray hybridization permits the assessment of the simultaneous expression of thousands of genes. Eventually, by using appropriate computer technologies the study of the coordinated regulation of the function of entire genomes will become a reality. ▶transcription, ▶transcriptional activator, ▶co-activator, ▶transcriptional modulation, ▶mediator complex, ▶transcription factories, ▶protein synthesis, ▶polysome, ▶endoplasmic reticulum, ▶chromatin, ▶chromatin remodeling, ▶high mobility group of proteins translation initiation, ▶translation, ▶regulation of enzyme activity, ▶axotomy, ▶signal transduction, ▶serine/threonine phosphoprotein phosphatases, ▶cell cycle, ▶LCR, ▶RNA polymerase, ▶DNA looping, ▶insulator, ▶transcription complex, ▶SL1, ▶TBP, ▶TAF, ▶attenuation, ▶open promoter complex, ▶RAD25, ▶signaling to translation, ▶DNA grooves, ▶elongation factors, ▶DNA chips, ▶microarray hybridization, ▶genetic network, ▶networks, ▶regulation of transcription, ▶transcription factors, ▶RNAi, ▶microRNA, ▶combinatorial gene control; Tautz D 2000 Curr Opin Genet Dev 10:575; Lemon B, Tjian R 2000 Genes Dev 14:2551; Rao CV, Arkin AP 2001 Annu Rev Biochem Eng 3:391; Emerson BM 2002 Cell 109:267, reviews in Cell 108:439 ff [2002], Wang W et al 2002 Proc Natl Acad Sci USA 99:16893; Pawson T, Nash P 2003 Science 300:445; Alonso CR, Wilkins AS 2005 Nature Rev Genet 6:709; transcriptional regulation in humans: Maston GA et al Annu Rev Genomics Hum Genet 7:29; <http://www.gene-regulation.com/>; <http://regulondb.ccg.unam.mx:80/index.html>; Gene Resource Locator: <http://www.gene-regulation.com/pub/databases.html#transcompel>; regulatory motif detection tool: <http://159.149.109.16/modtools/>; composite regulatory signatures: <http://140.120.213.10:8080/crsd/>.

Regulator Gene: This controls the function of other genes through transcription. ▶regulation of gene activity, ▶enhancer, ▶silencer, ▶activator, ▶co-activator, ▶operon

Regulatory Elements: These upstream (enhancer) sequences are located within 100 to 400 bp from the translation initiation nucleotide (+1) and control cell and developmental specificities. Some enhancers

may be located at more distant positions and also downstream. The enhancer region provides binding sites for regulatory proteins. ▶[basal promoter](#), ▶[regulation of gene activity](#), ▶[regulator gene](#), ▶[UAS](#)

Regulatory Enzyme: Allosteric or other modifications alter its catalytic activity rate, thus affecting other enzymes involved in the pathway. The Arg5.6 mitochondrial metabolic enzyme can regulate the expression of genes by association with mitochondrial DNA (Hall DA et al 2004 Science 306:482).

Regulatory Sequence in DNA: This binds transcription factors, RNA polymerase and so regulates transcription. The mammalian genomes contain many short (e.g., 8-mer) sequences, which are binding sites to specific proteins. The TGACCTTG sequence occurs in at least 434 human promoters and has been found 162 times in the mouse, rat and dog genomes at a rate of conservation of 37%. The Err- α (estrogen-related receptor) protein binds this octamer (Xie X et al 2005 Nature [Lond] 343:338) or the TNAAGGTCA element (Sladek R et al 1997 Mol Cell Biol 17:5400). An analysis of the 3' untranslated region of the four mammalian genomes has revealed 106 short motifs, which probably mediate post-transcriptional regulation. About 20% of the human genes seem to be regulated by microRNAs. ▶[transcription factors](#), ▶[open transcription complex](#), ▶[enhancer](#), ▶[operon](#), ▶[attenuator site](#), ▶[UAS](#), ▶[nuclear receptors](#), ▶[regulation of gene activity](#), ▶[microRNA](#)

Regulon: This non-contiguous set of genes is controlled by the same regulator gene. The different sections may communicate through looping of the DNA. Proteins mediate the coordination of mRNA (Keene JD 2007 Nature Rev Genet 8:533). ▶[looping of DNA](#), ▶[arabinose operon](#), ▶[regulation of gene activity](#); Manson McGuire A et al 2000 Genome Res 10:744; Huerta AM et al 1998 Nucleic Acids Res 26:55; conserved microbial regulon targets: <http://210.212.212.6/icr/index.html>.

Regulome: Refers to the complete set of transcription factors and their co-regulators.

Reifenstein Syndrome (Xq11-q12): In this condition the individual has XY chromosomal constitution but there is an insufficient production of androgen receptor during fetal development. The individual manifests male pseudohermaphroditism with hypospadias, hypogonadism and gynecomastia yet defective germ cells are present and fertility may be possible by early treatment with testosterone. ▶[androgen-insensitivity](#), ▶[hypospadias](#), ▶[hypogonadism](#), ▶[gynecomastia](#), ▶[testosterone](#), ▶[pseudohermaphroditism](#)

Reinitiation: The eukaryotic ribosomes can terminate an open reading frame and initiate another downstream (at low efficiency). Reinitiation occurs when the translation of one reading frame is completed and the process moves on to the next cistron. In an unfavorable nucleotide context, translation may be reinitiated not at the first AUG codon but at the next one downstream. Translation factor eIF2 may play an important role in the process. ▶[backtracking](#), ▶[regulation of gene activity](#), ▶[transcription](#), ▶[eIF2](#), ▶[translation](#), ▶[cistron](#); Kozak M 1999 Gene 234:187; Park HS et al 2001 Cell 106:723; Kozak M 2001 Nucleic Acids Res 29:5226.

Reinitiation of Replication: The genome of eukaryotes replicates at many points along the chromosomes. To avoid chaos in the nucleus it is important to prevent restart of replication. Reinitiation is prevented by cyclin-dependent kinases (CDKs) by phosphorylation of origin recognition complex (ORC), down-regulation of Cdc6 and the exclusion of MCM2-7 complex from the nucleus. ▶[CDK](#), ▶[Cdc6](#), ▶[ORC](#), ▶[MCM](#); Nguyen VQ et al 2001 Nature [Lond] 411:1068.

Reinitiation of Transcription: For a second cycle of transcription, transcription factors and the RNA polymerase must be re-attracted to the promoter. Reinitiation appears to be a faster process than initiation. TFIID and TFIIA transcription factors do not leave the promoter when the remaining part of the transcription complex is released. The reinitiation intermediate includes TFIID, TFIIA, TFIIF, TFIIE and the Mediator. Subsequently the complete transcription complex, including activators, is reformed depending on ATP and TFIIF. ▶[backtracking](#), ▶[preinitiation complex](#), ▶[transcription factors](#), ▶[mediator](#); Hahn S 1998 Cold Spring Harbor Symp Quant Biol 63:181.

Reiter Syndrome: This is a complex anomaly generally accompanied by overproduction of HLA-B27 histocompatibility antigen. It is characterized by arthritis, inflammation of the eyes and the urethra (the canal that carries the urine from the bladder and in males also serves as the genital duct). The inflammations may be related to sexually transmitted and intestinal infections. ▶[HLA](#), ▶[rheumatic fever](#), ▶[arthritis](#), ▶[connective tissue disorders](#)

Reiterated Genes: These are present in more than one copy, possibly many times.

Rejection: This is an immune reaction against foreign antigens such as may be present in transfused blood or grafted tissue. The rejection of pig organs by humans and Old World monkeys is caused by the presence of α -1,3-galactosyl epitopes on the

pig epithelia. During evolution the rejecters lost the appropriate galactosyltransferase gene and as a consequence developed antibodies against the epitope of the foreign tissue transplant. This immune reaction cannot be satisfactorily mitigated through affinity absorption or complement regulators or other means of immunosuppression (drugs) even in transgenic animals. A better solution appears to be the inactivation of the gene and generation of clones by nuclear transfer into enucleated pig oocytes. When fully developed, this procedure may permit xenotransplantation of pig organs into humans who have serious organ defects. ▶immune reaction, ▶HLA, ▶nuclear transplantation, ▶transplantation of organs, ▶xenotransplantation; Lai L et al 2002 Science 295:1089; Prather R et al 2003. Theriogenology 59:115.

Rejoining: ▶breakage and reunion, ▶breakage-fusion-bridge cycles

rel (REL) Oncogene (2p13-p12, 11q12-q13): This is a turkey lymphatic leukemia oncogene, a transcription factor homologous with NF-κB. c-Rel as a homodimer or as a heterodimer with p50 or p52 is a strong transcriptional activator. In its absence or inactivation, the production of IL-3 and the granulocyte—macrophage colony-stimulating factor is impaired. Rel domains occur in several proteins such as NF-κB, NFAT and another ca. 12. *RelA* encodes the guanosine tetraphosphate synthetase (ppGpp), *RelBE* in *E. coli* encodes the toxin-antitoxin proteins. The toxin severely inhibits bacterial growth as a stringent control whereas the antitoxin is a repressor of the translation of the RelB toxin. ▶NF-κB, ▶NFκB, ▶NFAT, ▶IL-3, ▶GMCSF, ▶oncogenes, ▶morphogenesis in *Drosophila*{3}, ▶p50, ▶stringent response, ▶magic spots; Gugasyan R et al 2000 Immunol Rev 176:134; Christensen SK et al 2001 Proc Natl Acad Sci USA 98:14328; Jaque E et al 2005 Proc Natl Acad Sci USA 102:14635.

Relapsing Fever: ▶Borrelia

Relaxase: ▶relaxosome

Relatedness, Degree of: This term is used in genetic counseling to indicate the probability of sharing genes among family members. In first-degree relatives such as a parent and child half of their genes are in common. In second-degree relatives such as a grandparent and a grandchild 1/4 of their genes are identical. In population genetics, mathematically simpler terms such as the inbreeding coefficient, consanguinity and coefficient of coancestry are preferred. (See these concepts under separate entries, ▶relationship coefficient, ▶MLS; Weir BS et al 2006 Nature Rev Genet 7:771.

Relational Coiling: ▶chromosome coiling

Relationship, Coefficient of: $r = \frac{2F_{IR}}{\sqrt{(1+F_I)(1+F_R)}}$ where F_I and F_R are the coefficients of inbreeding of I and R. If they are not inbred, F_I and F_R equal 0. ▶coefficient of inbreeding, ▶relatedness degree

Relative Biological Effectiveness: ▶RBE

Relative Fitness: ▶selection coefficient

Relative Molecular Mass (M_r): Expresses molecular weight relative to ^{12}C isotope (in $1/12$ units). It is comparable to molecular weight in daltons but it is not identical to molecular weight (MW) represented by the mass of atoms involved. ▶dalton

Relative Mutation Risk: This is equivalent to 1/doubling dose. ▶doubling dose, ▶genetic risk

Relative Sexuality: The intensity of sexual determination may be expressed in degrees in some organisms. In extreme cases a normal female gamete may behave like a male gamete toward a strong female gamete. ▶isogamy, ▶pseudohermaphroditism, ▶intersex

Relaxed Circular DNA: This is not supercoiled because of one or more nicks. ▶nick, ▶supercoiled DNA

Relaxed Control Mutants (*relA*): They have lost stringent control and continue RNA synthesis during amino acid starvation of bacteria. ▶stringent control, ▶fusidic acid

Relaxed Genomes: The organelle DNAs are not replicated in lockstep with the nuclear genome and their replication may be reinitiated during the cell cycle. The distribution of the organelles may not necessarily be equational during cytokinesis. ▶cytokinesis, ▶stringent genomes

Relaxed Replication Control: The plasmids continue to replicate even when the bacterial divisions stop. ▶replication

Relaxin: This water-soluble protein in the corpus luteum mediates the relaxation of the pubic joints and the dilation of the uterine cervix in some mammals. Its two receptors, LGR7 and LGR8, are heterotrimeric G protein binding proteins and are widely distributed among organs indicating their roles in diverse functions. ▶corpus luteum; Hsu SY et al 2002 Science 295:671.

Relaxosome: This DNA protein structure mediates the initiation of conjugative transfer of bacterial plasmids. It contains a *nic* site at the origin of transfer (*oriT*). Relaxase catalyzes the nicking and it becomes covalently linked to the 5' end through a tyrosyl residue. A single strand is then transferred to the recipient by a rolling circle mechanism.

►conjugation, ►rolling circle, ►nick; Xavier Gomis-Rüth F et al 2001 Nature [Lond] 409:637.

Relay Race Model of Translation: A ribosome after passing a chain termination signal of an ORF does not completely disengage from the mRNA and may reinitiate protein synthesis if an AUG codon is within short distance downstream. ►translation, ►regulation of gene activity, ►reinitiation, ►ORF; Ranu RS et al 1996 Gene Expr 5[3]:143.

Release Factor (RF): When translation reaches a termination codon, the release factors allow the polypeptide to be free from the ribosome. In prokaryotes there are two direct release factors RF-1 (specific for UAG/UAA) and RF-2 (specific for UGA/UAA) and a third factor RF-3 stimulates the activity of RF 1 and 2. RF-1 and RF-2 can discriminate between the termination and sense codons by 3 to 6 orders of magnitude effectiveness. In RF-1 a Pro-Ala-Thr and in RF-2 a Ser-Pro-Phe tripeptide, respectively, recognizes the appropriate stop codon. The eukaryotic release factors, eRF and eRF-1 alone can recognize all three stop codons. RF-3 and eRF-3 are GTP-binding proteins. RF-3 is a GTPase on the ribosome in the absence of RF-1 and RF-2; eRF3 requires eRF-1 to act as a GTPase. eRF-1 alone may be sufficient for termination in yeast. It has been suggested that all release factors are homologous to elongation factor G which mimics tRNA in its C-terminal domain and this is the basis of recognition of the RFs of the ribosomal A site. The activity of Class 1 release factors depends on the presence of Gly-Gly-Glu (GGQ) motif in the peptidyl transferase center for the release. In ciliates the stop codons vary and so do the release factors. ►transcription termination, ►protein synthesis, ►regulation of gene activity, ►EF-G, ►eRF; Inagaki Y, Doolittle WF 2001 Nucleic Acids Res 29:921; Zavialov AV et al 2001 Cell 107:115; Ito K et al 2002 Proc Natl Acad Sci USA 99:8494; Klaholz BP et al 2004 Nature [Lond] 427:862.

Releasing Factors: The hormones of the pituitary gland are released under the influence of hypothalamic hormones. ►animal hormones

Relics: These are genes with major lesions (insertions and deletions) in one or more components; they are similar to pseudogenes. ►pseudogenes

REM: An acronym of röntgen equivalent man. It is the product of REB × rad. Generally, 1 rem is considered to be equivalent to 1 rad of 250 kV X-rays; 1 rem is equal to 0.01 Sv (Sievert). ►R unit, ►rad, ►Gray, ►Sievert, ►REB, ►BERT

REM (Ras exchanger motif): This is required in signal transduction for interaction with RAS in GDP exchange for GTP using the GEF motif (Cdc25

homology catalytic unit) of SOS. ►signal transduction, ►RAS, ►SOS, ►GEF, ►Cdc25

REMI (restriction enzyme-mediated integration): An integrating vector is transformed into a cell in the presence of a restriction enzyme that facilitates insertion at the cleavage sites and may bring about insertional mutagenesis. ►insertional mutation, ►restriction enzyme; Thon MR et al 2000 Mol Plant Microbe Interact 13:1356.

Renal Carcinoma, Hereditary Papillary (HPRC): This is frequently caused by triplication (trisomy) and/or mutation of the MET oncogene, a cell surface tyrosine kinase, encoded at human chromosome 7q31.

Renal Cell Carcinoma (RCC): This commonly involves translocation breakage points in human chromosome 3p, each representing a different type. The 3p14.2 region includes the gene for protein tyrosine phosphatase gamma (PTPγ). This region also contains a fragile site, FHIT (fragile histidine triad) and the von Hippel-Lindau syndrome gene. ►hypernephroma, ►papillary renal cell cancer, ►tyrosine phosphatase, ►von Hippel-Lindau syndrome, ►fragile site; Zanesi N et al 2001 Proc Natl Acad Sci USA 98:10250.

Renal-Coloboma Syndrome: Is caused by mutation of the PAX2 (paired-box) gene at 10q24-q25.1 affecting the development of the kidney, eye and ear nerve. ►coloboma; Sanyanusin P et al 1996 Genomics 35:258.

Renal Dysplasia and Limb Defects: This condition is characterized by autosomal recessive underdevelopment of the kidney and the urogenital system, accompanied by defects of the bones and genitalia. ►kidney disease, ►limb defects

Renal Dysplasia and Retinal Aplasia: An autosomal recessive condition kidney developmental anomaly is associated with eye defects. ►kidney disease, ►eye disease

Renal Glucosuria (16p11.2, 6p21.3): Refers to dominant glycosuria which may not be related to diabetes.

Renal-Hepatic-Pancreatic Dysplasia (polycystic infantile kidney disease, ARPKD): Autosomal recessive phenotypes include cystic (sac-like structures) kidneys, liver and pancreas, sometimes associated with other anomalies such as blindness. The polycystic kidney disease of adult type dominant (ADPKD, human chromosome 16) is often associated with internal bleeding or arterial blood sacs (aneurysm). ►kidney disease

Renal Tubular Acidosis: The 17q21-q22 dominant type I defect is primarily in the distal tubules with normal bicarbonate content in the serum. Type II is recessive and the defect is in the proximal tubules and there is a low level of bicarbonate in the urine. Another recessive form involves mutation in the B1 subunit of H^+ -ATPase; in human chromosome 2cen-q13 nerve deafness is present. A proximal type is X-linked recessive. Recessive distal tubular acidosis with normal hearing (rdRTA2) has been assigned to gene ATP6N1B at 7q33-q34. The gene encodes an 840 amino acid subunit of a kidney vacuolar proton pump. The excretion of ammonium is reduced and the urine pH is usually above 6.5 in contrast to types I and II where it is around 5.5. Other variations have also been observed. ▶[kidney diseases](#)

Renal Tubular Dysgenesis: An autosomal recessive defect in the development of kidney tubules. It generally results in perinatal death because of the reduced amount of amniotic fluid (oligohydramnios), absence of urine secretion (anuria) and underdevelopment of the lung (pulmonary hypoplasia) caused by rennin-angiotensin defects. ▶[rennin](#), ▶[angiotensin](#); Gribouval O et al 2005 Nature Genet 37:964; Allanson JE et al 1992 Am J Med Genet 43:811.

Renaturation: Complementary single DNA strands reform double-strand structure by reannealing through hydrogen bonds. ▶[C₀t curve](#), ▶[denaturation](#)

Renilla GFP (from sea pansy): This is a green fluorescent protein with similarities to aequorin but it has only one absorbance and emission peak and its extinction coefficient is higher. ▶[aequorin](#)

Renin (chymosin, rennet): Protein hydrolase reacts with casein in cheese making. It is present in the kidneys and splits pro-angiotensin from α -globulin. ▶[angiotensin](#), ▶[pseudoaldosteronism](#); Kubo T et al 2001 Brain Res Bull 56:23; Krum H, Gilbert RE 2007 J Hypertens 25:25.

Renner Complex: Refers to the chromosomal translocation complex that is transmitted intact. ▶[translocation](#), ▶[translocation complex](#)

Renner Effect: ▶[megaspore competition](#); Renner O 1921 Ztschr Bot 13:609.

Reoviruses: Double-stranded RNA viruses cause respiratory and digestive tract diseases and arthritis-like symptoms in poultry and mammals, in humans, however, the infection usually does not involve serious symptoms. The internal capsid particle transcribes (+)-strand copies from the 10 genomic segments. The transcript carries a cap and it is exported to the cytoplasm of the infected cell. ▶[oncolytic virus](#), ▶[PKR](#), ▶[rotaviruses](#), ▶[cap](#), ▶[plus strand](#); Joklik WK, Roner MR 1996 Progr Nucleic Acid Res Mol Biol 53:249.

REP: Refers to repetitive extragenic consensus of 35 nucleotides, containing inverted sequences, in the bacterial chromosome. There are over 500 copies of it in *E. coli* in intergenic regions at 3' end of the genes. They are transcribed but not translated and appear to be the bacterial version of "selfish" DNA. ▶[selfish DNA](#); Herman L, Heyndrickx M 2000 Res Microbiol 151[4]:255.

Rep: An *E. coli* monomeric or dimeric binding protein and helicase. ▶[binding protein](#), ▶[helicase](#), ▶[monomer](#); Bredeche MF et al 2001 J Bacteriol 183:2165.

rep: The acronym of röntgen equivalent physical, a rarely used unit of X- and γ radiation delivering the equivalent of 1 R hard ionizing radiation energy to water or soft tissues (≈ 93 ergs). ▶[R](#)

Repair Genetic: ▶[DNA repair](#), ▶[unscheduled DNA synthesis](#)

Repairosome: Refers to the protein complex mediating DNA repair. ▶[DNA repair](#)

Repbase: Repetitive DNA database <http://www.girinst.org/>.

Repeat, Direct: This is (tandem) duplication of the same DNA sequence. It may be present at the termini of transposable elements ABC-----ABC. The hexameric CeRep26 repeat of *Caenorhabditis elegans* (TTAGGC) occurs at the telomeres and also at many additional chromosomal regions. The 711 copies CeRep11 are distributed over the autosomes but only one is in the X chromosome. In yeast most of the tandem repeats are in intergenic regions. The majority of them encode cell wall proteins. These repeats recombine frequently with pseudogenes and it is suspected that in pathogenic microbes they contribute to functional diversity of surface antigens, which play an important role in elusion of the host immune defense (Verstrepen KJ et al 2005 Nature Genet 37:986). ▶[transposable element](#), ▶[transposon](#), ▶[interspersed repeats](#), ▶[tandem repeat](#), ▶[homoepitope](#); interspersed repeat [fossile mobile element] tool: <http://repeats.abc.hu/cgi-bin/plotrep.pl>; tool for detection of interspersed repeats: <http://www.repeatmasker.org>.

Repeat-Induced Gene Silencing: ▶[co-suppression](#)

Repeat, Inverted: The double-stranded DNA carries inverted repeats such as transposable elements. The single strands can fold back and form *stem* (by complementarity) and *loop* (no complementarity) structure (see Fig. R35). In the sequenced *Caenorhabditis elegans* inverted repeats represent 3.6% of the genome and occur on an average 1/4.9 kb, introns contain 45% of them and 55% are in intergenic regions. Inverted repeats may increase inter- and

intrachromosomal recombinations by orders of magnitude and are responsible for a large part of the genetic instabilities. Mutation in the *MRE11/RAD50/XRS2* and *SAE2* genes of yeast interferes with the repair of hairpins and contributes to instability of the genome. ▶ **tandem repeats**, ▶ **transposable elements**, ▶ **LIR**; Lobachev KS et al. 1998 Genetics 148:1507; Waldman AS et al 1999 Genetics 153:1873; Lin C-T et al 2001 Nucleic Acids Res 29:3529; Lobachev KS et al 2002 Cell 108:183.

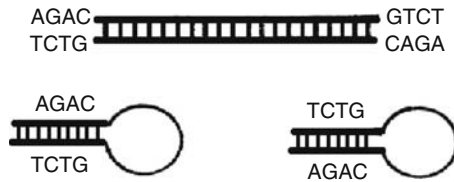


Figure R35. Inverted repeats

Repeat-Associated Short Interfering RNA (rasiRNA): This guides mRNA degradation or chromatin modification and silencing gene expression. ▶ **RNAi**

Repeats, Short Tandem (STR): With the aid of polymerase chain reaction, they serve for individual (forensic) discrimination or for the identification of human cell lines, which may or may not be contaminated. ▶ **PCR**, ▶ **low-copy repeats**; Oldroyd NJ et al 1995 Electrophoresis 16:334; Masters JR et al 2001 Proc Natl Acad Sci USA 98:8012.

Repeats, Trinucleotide: ▶ **fragile sites**, ▶ **trinucleotide repeats**

Repertoire, Antigenic: This is the complete set of antigenic determinants of lymphocytes.

Repertoire Shift: After a secondary immunization with a hapten, following a primary immunization, the variable heavy/variable light (V_H/V_L) immunoglobulin genes show an altered spectrum of somatic mutations. ▶ **immunoglobulins**, ▶ **hapten**; Meffre E et al 2001 J Exp Med 194:375.

Repetitive DNA (repetitious DNA): Refers to similar nucleotide sequences occurring many times in eukaryotic DNA. Some of these sequences represent transposable or retrotransposable elements, others such as ribosomal genes are called to duty when there is a special need for high gene activity, e.g., during embryonal development. More than 40% of the human genome appears highly or moderately repetitive and only about 3% may be genetically functional. ▶ **SINE**, ▶ **LINE**, ▶ **redundancy**, ▶ **pseudogenes**, ▶ **α -satellite DNA**, ▶ **co-suppression**, ▶ **microsatellite**, ▶ **minisatellite**; Britten RJ, Kohne DE 1968 Science 211:667; Toder R et al 2001 Chromosome Res 9[6]:431; Jurka J

et al 2007 Annu Rev Genomics Hum Genet 8:241; Rebase: <http://www.girinst.org>.

Replacement Theory: ▶ **out-of Africa**

Replacement Vector: By homology it recognizes and then replaces a particular segment (gene) of the target. It has a pair of restriction enzyme recognition sites within the region of “non-essential” genes. Non-essential means that their removal and replacement do not impair packaging and propagation in *E. coli* by sequences of interest to the experimenter. ▶ **vectors**, ▶ **stuffer**

Replica Plating: This is designed for efficient selective isolation of haploid microbial mutants. Mutagen-treated cells are spread in a greatly diluted suspension on the surface of complete medium and incubated to allow growth. Because of the dilution, each growing colony represents a single original cell (clone). Then impressions are made of this master plate on minimal medium where only the wild type cells can grow. The absence of growth on the minimal media plates indicates that auxotrophs exist at the spots where no growth was obtained.

The impressions also represent a map of the colonies on the original, complete medium, master plate. Thus, the experimenter can obtain cells from the original colonies and test them for nutritional requirement on differently supplemented media. This procedure thus permits the isolation of mutants and the identification of the nutrient requirement. (See Fig. R36, ▶ **mutant isolation**; Lederberg J, Lederberg EM 1952 J Bacteriol 63:399).

Replicase: This is RNA-dependent RNA polymerase enzyme of viruses encoded by the viral RNA and packed to the progeny capsid so that upon entry to a cell replication of the infective *negative-strand RNA* (influenza, Stomatitisvirus [causing inflammation of mucous membranes]) forms the template for replication but does not code for viral proteins. Without the replicase this negative strand would not be able to function. The *positive-strand RNA* viruses (e.g., poliovirus) are directly transcribed into the protein, including the replicase, and in this form it can be infectious. The DNA-dependent DNA polymerase enzymes are also called replicase. ▶ **replication**, ▶ **RF**, ▶ **positive strand**; Tayon R Jr et al 2001 Nucleic Acids Res 29:3576.

Replicating Vector: ▶ **transformation genetic**, ▶ **yeast**

Replication: ▶ **DNA replication**, ▶ **replication fork**, ▶ **chromosome replication**

Replication Banding: Using sequential 5-bromodeoxyuridine incorporation for the determination of early and late replicating chromosomal regions.

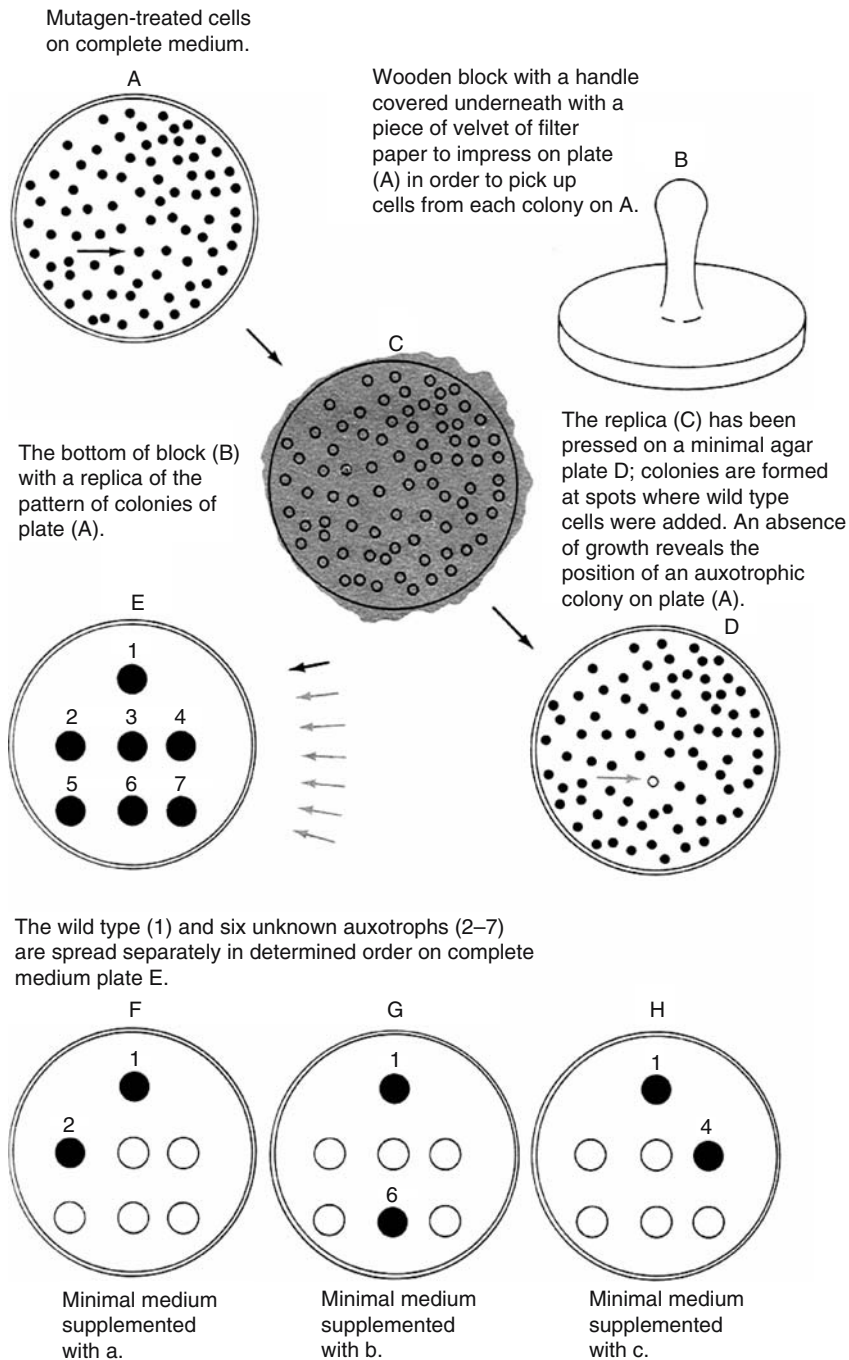


Figure R36. Replica Plating

Replication, Bidirectional: This is the mode of replication in bacteria as well as in the eukaryotic chromosome. Replication begins at an origin and proceeds in the opposite direction on both the old strands of the DNA double helix. The helicase subunits encoded by the xeroderma pigmentosum genes XPB and XPD of the transcription factor TFIIH unwinds the DNA in both

directions. Electron microscope reveals a θ (theta) resembling structure of the circular DNA whereas in the linear eukaryotic DNA bubble-like structures are visible. In prokaryotes this replication is mediated by DNA polymerase III, and in eukaryotes a DNA polymerase α type enzyme. Termination of replication in *E. coli* requires 20 base long Ter elements and the

associated protein Tus (termination utilization complex, M_r 36 K) (see Fig. R37). While replicating the template strand T7 RNA polymerase can by-pass up to 24 nucleotide gaps by making a copy of the deleted sequence using the corresponding non-template tract.

►DNA replication eukaryotes, ►DNA replication prokaryotes, ► θ replication, ►replication bubble, ►pol III, ►pol α , ►replication fork, ►xeroderma pigmentosum, ►transcription factors

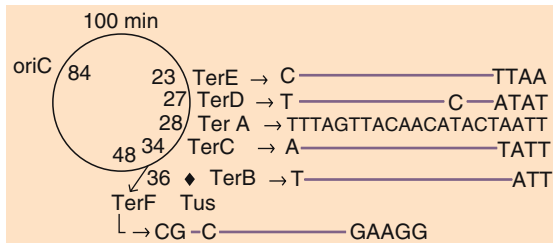


Figure R37. Replication in *E. coli*. (Diagram after Kamada K et al 1996 Nature [Lond] 383:598)

The *TerA*, *D* and *E* stop the replication in an anticlockwise direction and *TerC*, *B* and *F* halt replication of the strand elongated clockwise. The Tus-Ter complex probably blocks the replication helicase. Similar mechanisms operate in most bacteria but replication fork arresting sites are also found in eukaryotes, including humans. (See Hiasa H, Marians KJ 1999 J Biol Chem 274:27244; Abdur-asidova G et al 2000 Science 287:2023; Gerbi SA, Bielinsky AK 1997 Methods 13:271).

Replication Bubble (replication eye): This is an indication of strand separation in a replicon (see Fig. R38). In an eukaryote nucleus an estimated 10^3 to 10^5 replication initiations occur during each cell cycle without any reinitiation per site, thus ensuring that the gene number is maintained. In yeast the dynamics of chromosome replication can be studied with the aid of DNA microarrays and it appears that the two ends of each chromosome replicate rather synchronously but the replication forks move differently in other regions.

►replication bidirectional, ►DNA replication, ►replication fork, ►replicon, ►promoter bubble, ►ORC, ►replication protein A, ►FFA, ►geminin; Diffley JFX 2001 Curr Biol 11: R367; Raghuraman MK et al 2001 Science 294:115.

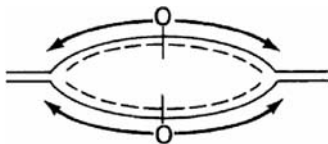


Figure R38. Replication Bubble

Replication, Conservative: A historical model of DNA replication, assuming that the two old (original) DNA strands produce two new copies which then anneal to each other. In other words, double-stranded DNA is not composed of an old and a new strand as revealed by the current and experimentally demonstrated semiconservative replication mechanism.

►semi-conservative replication; Delbruck M, Stent GS 1957, p 699 In: McElroy WD Glass B (Eds.) The Chemical Basis of Heredity, Johns Hopkins Press, Baltimore, MD.

Replication Defective Virus: This is a mutant for the replication function or the lost genes required for producing infective particles.

►replicase

Replication, Dispersive: This refers to an unproven old idea that old and new double-strand DNA tracts alternate along the length of the molecule.

►replication, ►replication fork; Delbruck M, Stent GS 1957, p 699 In: McElroy WD, Glass B (Eds.) The Chemical Basis of Heredity, Johns Hopkins Press, Baltimore, MD.

Replication during the Cell Cycle: Eukaryotic DNA replication takes place predominantly during the S phase of the cell cycle although some repair synthesis (unscheduled DNA synthesis) may occur at other stages. In prokaryotes the replication is not limited to a particular stage and DNA synthesis may proceed without cellular fission. Such a phenomenon (endoreduplication) is exceptional in eukaryotes and is commonly limited to certain tissues only, e.g., to the salivary gland chromosomes of insects (*Drosophila*, *Sciara*) or a rare non-repeating process (endomitosis) that doubles the number of chromosomes. Replication in eukaryotes is an oscillatory process tied to the S phase of the cell cycle. The process of replication shows some variations even among the different eukaryotes and the process described here is modeled after that of *Saccharomyces cerevisiae* (the best known). During the G1 phase, from the pre-origin-of-replication complex (pre-ORC) the ORC (origin of replication complex) is assembled after the cyclosome (APC) proteases degraded the cyclin B-cyclin-dependent kinase (Cyclin B-CDK). The cis-acting *replicator* element and the *initiator* proteins bind at each origin of replication (hundreds or thousands in eukaryotes). The replicator (0.5–1 kb) is a multimeric complex itself and its indispensable component is the A unit but B1, B2 and B3 are also used. The A, B1 and B2 form the core of the replicator and B3 is an enhancer that binds to the *autonomously replicating sequence* (ARS)-binding protein factor 1 (ABF1). The replicator (A + B1) hugs the ORC (origin recognition complex) composed of 6 subunits that form the hub of the replication process and attract

other critical regulatory proteins. The site of the initiation in mammals may extend to 50 kb. At the origin, the nucleosomal structure is remodeled and during S, G2 and early M phase DNase hypersensitive sites are detectable that disappear before the anaphase. It appears that protein Cdc7 is needed for the remodeling. CDC6 (or the homologous Cdc18 protein of fission yeast) is required in G1 or S phase for DNA synthesis (the cells may proceed to an abortive mitosis and aneuploidy in its absence). CDC6 seems to be essential for the formation of the pre-ORC complex. Overexpression of this protein leads to polyploidy. The replication also requires a Replication Licensing Protein (RLF) and members of the MCM (minichromosome maintenance) proteins. Cyclin-dependent kinases (CLB5 and CLB6) are also required to establish the pre-initiation complex but after the assembly is completed some of them may be degraded. Some cyclin-dependent kinases block the reinitiation of the complex until the cell passes through mitosis. Cyclin B5—cyclin-dependent kinase (Clb5-CDK) is inhibited by Sic1 (S phase inhibitory complex) that is removed by ubiquitin-mediated proteolysis at the START point before the S phase is fired on. CDC34, CDC53, CDC4 SKP1, CLN1-Cdc28, CLN2-CDC28 and the APC proteins promote ubiquitination. The initiation of DNA replication may also proceed through another pathway mediated by CDC7 and DNA-binding factor 4 (DBF4). ▶cell cycle, ▶replication fork, ▶CLB, ▶DNA replication eukaryotes, ▶replication protein A, ▶DNA replication prokaryotes, ▶DNA replication in mitochondria, ▶rolling circle replication, ▶ θ (theta) replication, ▶ORC, ▶RNA replication, ▶reverse transcription, ▶bidirectional replication, and other proteins and terms listed under separate entries; Waga S, Stillman B 1998 Annu Rev Biochem 67:721; Kelly TJ et al 2000 Annu Rev Biochem 69:829; Chakalova L et al 2005 Nature Rev Genet 6:669.

Replication Error: This source occurs when a nucleic acid base analog is incorporated into the DNA at the structurally acceptable site but during the following replication, being only an analog, it may cause a replicational error that leads to the replacement of the original base pair by another. E.g., BrU—A base pair in the following replication is converted by error into BrU—G pair which eventually results in the base substitution of C=G at a site that was formerly T=A. Mismatching—in the absence of base analogs—can also occur, e.g., A=C, and the frequency of such errors is within the range of 10^{-4} to 10^{-6} . ▶base substitution, ▶incorporation error, ▶bromouracil,

▶BUdR, ▶hydrogen pairing, ▶ambiguity in translation, ▶error in replication; Ryan FJ 1963 In: Burdette WJ (Ed.) Methodology in basic genetics, Holden-Day, San Francisco, California, p 39; Kunkel TA, Bebenek K 2000 Annu Rev Biochem 69:497.

Replication Eye: ▶replication bubble, ▶DNA replication eukaryotes, ▶replication bidirectional

Replication Factor A: ▶RF-A, ▶helix destabilizing protein

Replication Factor C: ▶RF-C

Replication Factory: This is the same as replication machine. ▶DNA replication prokaryotes

Replication Fork: Represents the growing region of the DNA where the strands are temporarily separated. The simplest diagram of the replication fork is reproduced here showing the new (thin line) facing the polymerase with the 3' end. The leading strand is below and the lagging strand is above (see Fig. R39).

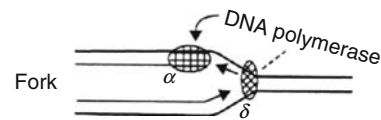


Figure R39. Replication fork

Replication is a very complex process requiring two different polymerases (δ and α for the leading and lagging strand, respectively) and several proteins. ▶DNA replication eukaryotes, ▶chart, ▶DNA replication prokaryotes, ▶nucleoid, ▶GP32 protein, ▶PriA, ▶replication bubble, ▶replication bidirectional, ▶replication licensing, ▶primase, ▶Okazaki fragment, ▶alpha accessory protein, ▶processivity, ▶replication machine; Waga S, Stillman B 1998 Annu Rev Biochem 67:721.

Replication Intermediate: ▶lagging strand, ▶Okazaki fragment, ▶replication fork

Replication Licensing Factor (RLF): The initiation of replication requires two competency signals: the binding of the RLF and S phase promoting factors. The sequential action of these two signals secures the accurate replication of the chromosomes. RLF has two elements: RLF-M and RLF-B. RLF-M is a complex of MCM/P1. RLF-M protein binds to the

chromatin early during the cell cycle but it is displaced after the S phase. ►MCM1, ►MCM3, ►ORC, ►replication, ►cell cycle, ►replication bubble, ►Cdt1, ►geminin; Chong JP, Blow JJ 1996 *Progr Cell Cycle Res* 2:83; Nishitani H et al 2001 *J Biol Chem* 276:44905.

Replication Machine: It has been demonstrated that the *replication machine* of bacteria (*B. subtilis* and probably others) occupies a stationary central position in the cell and initially the twin PolC subunits are located in the replicational origin (O) of the bidirectionally replicating double-stranded DNA ring (see Fig. R40). The simultaneously replicating leading and lagging DNA strands are spooled through the twin machines. The machines contain the polymerase and several accessory proteins (also called replication factory). The eukaryotic replication

bubbles are operated in a similar manner but there are nearly 100 machines per nucleus and each of them handle about 300 replication forks. ►DNA replication prokaryotes, ►DNA replication eukaryotes, ►replication fork, ►clamp-loader; Ellison V, Stillman B 2001 *Cell* 106:655; Bruck I, O'Donnell M 2000 *J Biol Chem* 275:28971; Turner J et al 1999 *EMBO J* 18:771, replicons forming factories: Kitamura E et al 2006 *Cell* 125:1297.

Replication Origin (o): Refers to the point in the genetic material where replication begins. ►CLB, ►replication bubble; isolation of replication origin in complex genomes: Mesner LD et al. 2006 *Mol Cell* 21:719.

Replication Protein A (RPA, RFA, HSSB): A complex of three different polypeptides (~70 kDa, human chromosome 17p13.3; ~32 kDa, 1p35; ~14 kDa,

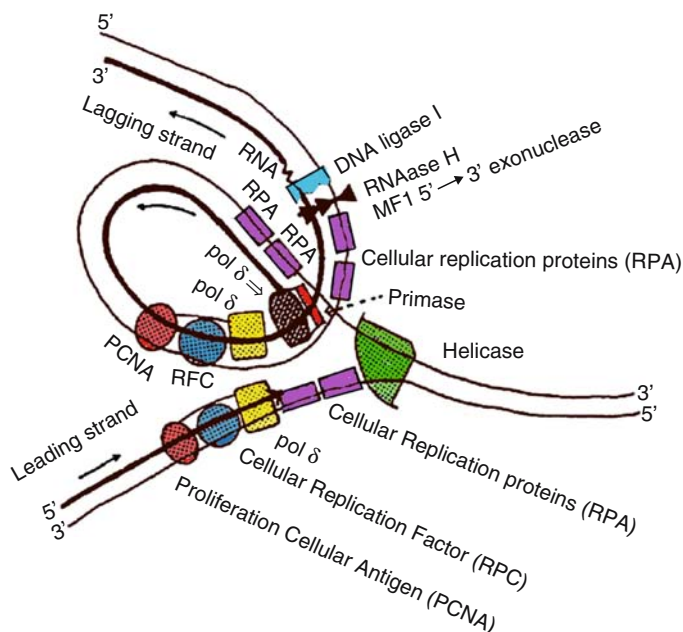


Figure R40. A model of the eukaryotic replication fork based on SV40 studies. Thin lines: old DNA strands; heavy lines: new strands. The replication fork is opened at the replicational origin by helicases. The *cellular replication protein* (RPA) keeps the fork open and brings the pol α DNA polymerase complex to the replication origin. After a short RNA primer is made (not shown on the diagram) at the beginning of the first Okazaki fragment, *cellular replication factor C* (RFC) binds to the DNA and displaces pol α by pol δ. Then RFC, pol δ, and PCNA (proliferating cell nuclear antigen) form a complex on both leading and lagging strands and the two new DNA strands are replicated in concert. The synthesis of the leading strand is straightforward. The lagging strand is made of Okazaki fragments (by "backstitching") because the DNA can be elongated only by adding nucleotides at the 3'-OH ends. After an Okazaki fragment (100–200 bases) is completed, RNase H, MF1 exonuclease remove the RNA primer (jagged line) and DNA ligase I joins the fragment(s) into a continuous new strand. The long arrows indicate the direction of growth of the chain. (Redrawn after Waga S and Stillman B 1994. *Nature* 369:207.)

7p22) binds most commonly to 20–25 nucleotides (with preference for pyrimidines) of single-strand DNA, and may be the first step in DNA replication by participating in DNA unwinding by binding to A-T rich sequences. The size of these subunits varies among different organisms and despite the good homology antigenically not related they cannot be interchanged functionally. The binding to double-stranded DNA is 3–4 orders of magnitude less. RPA binds to other proteins such as the primase subunit of DNA polymerase α , DNA repair proteins. The p53 cancer suppressor gene interferes with its binding to the replication origin. RPA also plays a role in recombination and excision repair. It has affinity to xeroderma pigmentosum damage-recognition protein (XPA) and endonuclease XPG. RPA increases the fidelity of repair polymerases. During the cell cycle RPA is phosphorylated by several kinases such as DNA-PK, CDK proteins, and others. ▶RPA, ▶DNA replication eukaryotes, ▶replication fork, ▶xeroderma pigmentosum, ▶endonuclease, ▶DNA repair, ▶replication bubble, ▶FFA, ▶DNA polymerases, ▶DNA-PK, ▶CDK, ▶somatic hypermutation; Wold MS 1997 Annu Rev Biochem 66:61; Patrick SM, Turchi JJ 2001 J Biol Chem 276:22630; Mass G et al 2001 Nucleic Acids Res 29:3892.

Replication Restart: This is a pathway of the SOS repair system of the DNA bypassing the mismatch and resulting in error-free replication. In bacteria, DNA polymerase II has an important role in the process. After UV irradiation or other damage blocks DNA synthesis, DnaB helicase and in coordination with DnaG primase on both leading and lagging strands provide means to bypass the lesion and a gap is left behind the leading strand in *E. coli* (see Fig. R41). ▶DNA repair, ▶replication of DNA, ▶primase, ▶translesion; Rangarajan S et al 1999 Proc Natl Acad Sci USA 96:9224.



Figure R41. Replication fork is reinitiated after the block leaving a gap behind as primase restarts replication. (Modified after Heller RC and Marians KJ 2006 Nature [Lond] 439:557)

Replication Slippage: One of the several mechanisms generating microsatellite diversity. ▶microsatellite; Viguera E et al 2001 J Mol Biol 312:323.

Replication Speed: kbp/min: *E. coli* 45, yeast 3.6, *Drosophila* 2.6, toad 0.5, mouse 2.2.

Replication Timing: Indicates whether chromosomal sequences replicate early or late during the cell cycle. Early tracts are usually more GC-rich and contain a larger number of genes than the AT-rich late replicating zones. Within the early/late transition regions many cancer genes have been found in human chromosomes 11q and 21q. ▶heterochromatin; Watanabe Y et al 2002 Hum Mol Genet 11:13; Goren A, Cedar H 2003 Nature Rev Mol Cell Biol 4:25.

Replicational Fidelity: Refers to DNA replication error.

Replicative Aging: In yeast the number of cell divisions during the life of the cell may determine aging. ▶chronological aging, ▶longevity, ▶aging

Replicative Form (RF): Double-stranded form of a single-stranded nucleic acid virus that generates the original complementary type of single-strand (+) nucleic acid. The necessity for the double-stranded replicative form is to generate a minus strand that is the template for the plus strand and is complementary to the “sense” molecule. This assures that all the progeny is identical and of one kind. ▶DNA replication, ▶RNA replication, ▶plus strand

Replicative Intermediate: ▶replicative form, ▶replication intermediate, ▶RNA replication

Replicative Segregation: The newly formed cellular organelles display sorting out in the somatic cell lineages in the case of mutation in organelle DNA. ▶sorting out, ▶cell lineage

Replicative Transposition: ▶transposition, ▶transposable elements, ▶cointegrate, ▶Mu bacteriophage

Replicator: Refers to the origin of replication in a replicon. ▶replicon, ▶ARS

Replichore: This is the oppositely replicating half of the *E. coli* genome between the origin and the terminus of replication. ▶*E. coli*

Replicon: A replicating unit of DNA. The size of the replicational unit varies a great deal. In *E. coli*: ≈ 4.7 Mbp, *Saccharomyces cerevisiae*: (yeast): 40 kb, *Drosophila*: 40 kb, *Xenopus laevis* (toad): 200 kb, mouse: 150 kb, broad bean (*Vicia faba*): 300 kb. ▶DNA replication, ▶minireplicon; Jacob F et al 1963 Cold Spring Harbor Symp Quant Biol 18:329; Sadoni N et al 2004 J Cell Sci 117(Pt22):5353.

Replicon Fusion: ▶cointegration

Replisome: Refers to the enzyme aggregate involved in the replication of DNA of *prokaryotes* (PriA, PrB, PriC, DnaC, DnaB and other proteins). The DNA polymerase III holoenzyme consists of two functional enzyme units, one for the leading and the other for the lagging strand. The *polymerase core* contains one α subunit (for polymerization), the ϵ subunit (3'→5' exonuclease for editing repair) and the θ unit. It also includes a ring-like dimer of β *clamp* to hold on leash the DNA strands and a five-subunit *clamp loader* γ complex. There are two subunits that organize the two cores and the clamp loader into a pol III holoenzyme. The asymmetric replication of the leading and lagging strands is determined by the DnaC helicase, unwinding the double helix in front of the replisome. The helicase facilitates the hold of the complex onto the leading strand by the τ unit to make possible the continuous extension of that strand. At the lagging strand, however, the complex goes off and on as the Okazaki fragments are made. ▶[replitase](#), ▶[DNA replication prokaryotes](#), ▶[replication fork in prokaryotes](#), ▶[GP32 protein](#), ▶[DNA polymerases](#), ▶[Okazaki fragment](#); Benkovic SJ et al 2001 Annu Rev Biochem 70:181; Breier AM et al 2005 Proc Natl Acad Sci USA 102:3942; Johnson A, O'Donnell M 2005 Annu Rev Biochem 74:283.

Replitase: Refers to the replicational complex at the DNA fork in *eukaryotes*. ▶[replication fork in eukaryotes](#), ▶[replisome](#), ▶[DNA polymerases](#); Reddy GP, Fager RS 1993 Crit Rev Eukaryot Gene Expr 3[4]:255.

Replum: A central membrane-like septum ↑ inside the silique (fruit) of cruciferous plants bearing the seeds (see Fig. R42). The carpels covering it were removed. Recessive pale mutant cotyledons show through the immature seed coats. At maturity the carpels dehiscence at the base of the fruit (left end here). ▶[silique](#)



Figure R42. Replum

Reporter Gene: This is a structural gene with easily -monitored expression (e.g., luciferase, β -glucuronidase, antibiotic resistance) that reports the function as differentiation progresses, or any heterologous or modified promoter, polyadenylation or other signals attached to the gene by in vitro or in vivo gene fusion. ▶[luciferase](#), ▶[GUS](#), ▶[gene fusion](#)

Reporter Ring: According to the tracking concept of recombination between appropriate *res* (*resolvase*)

points, recombination of two DNA molecules would retain during segregation “reporter rings” catenated to one of the two DNA strands of the DNA recombination substrate during synapse and after its resolution in the product. The “reporter rings” were expected to be limited to one of the catenated product molecules but the experimental data did not support this assumption. ▶[tracking](#), ▶[resolvase](#)

Representational Difference Analysis: ▶[RDA](#)

Repressible: This means subject to potential repression. ▶[repression](#)

Repressilator: This is a synthetic oscillator system composed of several components that may turn on/off as a natural biological clock. In such a system the product of a gene is a repressor for the promoter of the next one and so on. ▶[oscillator](#); Elowitz MB, Leibler S 2000 Nature [Lond] 403:335; Garcia-Ojalvo J et al 2004 Proc Natl Acad Sci USA 101:10955.

Repression: This is the control mechanism interfering with the synthesis (at the level of transcription) of a protein. A general type of repression is attributed to histones, closely associated with the DNA in the nucleosomal structure. When histones are deacetylated they reinforce repression by co-repressors (N-CoR, mSin3). Histone acetyl transferases acylate histones with the assistance of pCAF (chromatin assembly factor) which permits the recruitment of transcription factors to the gene. PCIP = p300/CEP co-integrator associated protein (where CEP is a CREB-binding protein), CREB = cAMP-response element, CBP is a CREB-binding protein, p300 = a cellular adaptor and co-activator of some proteins. This scheme of repression is based on some eukaryotic systems. Other mechanisms are also known. Some repression mechanisms interfere with the translation, e.g., threonyl-tRNA synthetase of *E. coli* represses its own synthesis by binding to the operator. tRNA^{Thr} serves as an antirepressor and the balance between the two mechanisms determines the level of translation (see Fig. R43) (Torres-Larios A et al 2002 Nature Struct Biol 9:343). ▶[feedback control](#), ▶[regulation of gene activity](#), ▶[signal transduction](#), ▶[regulation of enzyme activity](#), ▶[MAD](#), ▶[co-activator](#), ▶[transcription factors](#), ▶[lac repressor](#), ▶[arabinose operon](#), ▶[repressor](#), ▶[tryptophan operon](#), ▶[suppression](#); Maldonado E et al 1999 Cell 99:455; Lande-Diner L, Cedar H 2005 Nature Rev Genet 6:648.

Repressor: This is the protein product of the regulator gene that interferes with the transcription of an operon. The majority of the DNA-binding proteins bind the DNA by their α helices but some of the repressors (*met*, *arc*, *mnt*) bind by β sheets or a combination of both (*trp*). Repression in eukaryotes

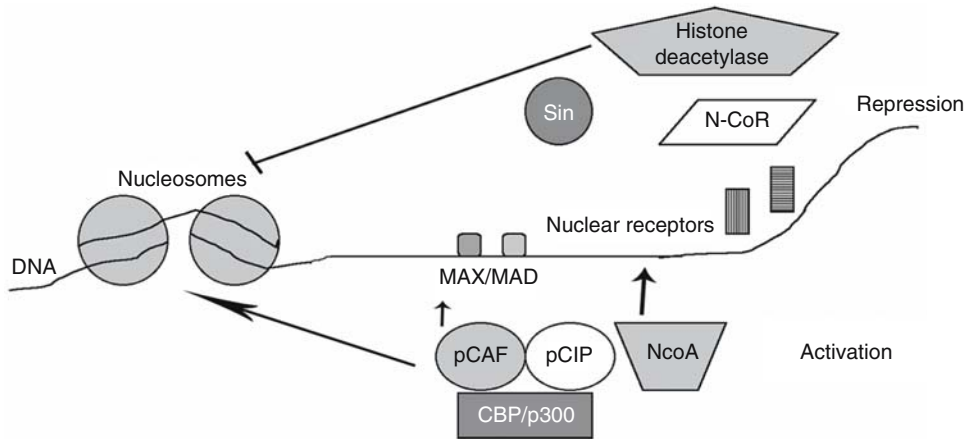


Figure R43. Proteins involved in repression and activation. (Diagram modified after Heinzel T et al 1997 Nature (Lond) 387:43)

has a variety of means for control. The short-range repressors are within 50–150 bp of the transcriptional activators. Since the promoters may be modular (repeating units), the short-range silencers may not affect other than the nearest activators. This organization assures the expression of genes controlling segmentation along the axis of the developing embryo. The long-range repressors may silence the activators from a distance of several kb. The short-range repressor proteins are monomeric whereas the long-range ones are multimeric. The repressors may be either gene-specific or more global. In the latter case in bacteria the repressor binds to the σ subunit of the RNA polymerase. Some of the more recently discovered repressors are not protein molecules but RNAs (ribozymes). In bacteria, glucosamine-6-phosphate (GlcN6P) mRNA encodes within its upstream sequence this ribozyme of ~ 75 nucleotides, which cleaves itself in the mRNA when GlcN6P reaches a sufficient level resulting in decay of the message. The regulatory response is initiated upon binding of GlcN6P to the mRNA (Winkler WC et al 2004 Nature [Lond] 428:281). [►repression](#), [►lac operon](#), [►lac repressor](#), [►arabinose operon](#), [►tryptophan operon](#), [►co-repressor](#), [►morphogenesis in *Drosophila*](#), [►transcription factors](#), [►Gene-Switch](#), [►riboswitch](#), [►tetracycline](#), [►suppression](#), [►suppressor tRNA](#); Pardee A et al 1959 J Mol Biol 1:165; Hummelke GC, Cooney AJ 2001 Front Biosci 6:D1186; Ryu J-R et al 2001 Proc Natl Acad Sci USA 98:12960.

Reproduction: [►asexual](#), [►clonal](#), [►vegetative reproduction](#), [►dioecious](#), [►monoecious](#), [►autogamy](#), [►apomixia](#), [►allogamy](#), [►parthenogenesis](#), [►hermaphroditism](#), [►cytoplasmic transfer](#), [►genetic systems](#), [►conjugation](#), [►conjugation *Paramecia*](#), [►life](#)

[cycle](#), [►breeding system](#), [►fungal life cycle](#), [►social insects](#), [►vivipary](#), [►incompatibility](#)

Reproductive Isolation: Prevents gene exchange between two populations by a hereditary mechanism. Generally reproductive isolation is caused by the inability to mate (pre-mating isolation) but in some instances inviability or sterility of the offspring is the barrier (post-mating isolation). In plants, chromosomal rearrangements normally lead to gametic disadvantage or sterility. In animals, translocated chromosomes are frequently transmitted at fertilization but the duplication-deficiency zygotes are inviable. Mating *Drosophila melanogaster* with *D. simulans* a 3 kb DNA segment is inserted within the *Cyclin E* locus and causes male sterility and inviability but only a low degree of inviability or sterility in females. The *JYAlpha* gene is in chromosome 4 of *Drosophila melanogaster* but during evolution it transposed to the 3rd chromosome of *D. simulans*. In hybrids when this gene is lost hybrid male sterility occurs (Masly JP et al 2006 Science 313:1448). All members of the *Drosophila* species show reproductive isolation from *D. melanogaster*. Reproductive isolation can be associated with the pattern of single nucleotide polymorphism (Payseur BA, Hoekstra HE 2005 Genetics 171:1905). [►incompatibility](#), [►sexual isolation](#), [►isolation genetic](#), [►founder principle](#), [►drift genetic](#), [►effective population size](#), [►translocation](#), [►inversion](#), [►infertility](#), [►transcription](#), [►hybrid inviability](#), [►speciation](#), [►SNP](#); Harushima Y et al 2001 Genetics 159:883.

Reproductive Rate: (R_0) where l_x = probability that female survives to age x and m_x = expected number of female offspring produced by a female of age x .

►age-specific birth and death rate, ►population growth, ►Malthusian parameter, ►parity

$$R_0 = \sum_{X=0}^{\infty} l_X m_X$$

Reproductive Success: ►fitness, ►fertility, ►fecundity

Reproductive Technologies: ►ART

Reprogramming: During development the genome must be selectively turned on and off by epigenetic modifications such as methylation of nucleotides, acetylation and deacetylation of nucleosomes, and recruiting general and specific transcription factors. Such reprogramming which begins after fertilization of the egg is a natural and indispensable process. Problems arise, however, when diploid nuclei of somatic cells are transplanted into the eggs for the purpose of cloning. The somatic nuclei require dedifferentiation to the totipotent/pluripotent state and after transplantation the cloned embryos must be able to redifferentiate for the intended purpose. The transfer of nuclei from embryonic stem cells poses fewer problems yet in vitro culture conditions may not exactly duplicate the normal programming involved in natural fertilization of the haploid egg with the haploid sperm. Generally cloning involves developmental anomalies such as “large offspring syndrome”, various chromosomal anomalies and inviability because of lack of harmony between the donor nucleus and the recipient cytoplasm. Somatic cells may be reprogrammed by transfer into enucleated oocytes or by fusion with pluripotent embryonic stem cells (Tada M et al 2001 *Curr Biol* 11:1553; Ying QL et al 2002 *Nature [Lond]* 416:545). In cell fusion the less differentiated cell reprograms the more differentiated ones to its own features. It seems that reprogramming is a nuclear rather than a cytoplasmic process. It is unclear whether reprogramming by the use of cell extracts would be generally feasible. The cell fusions are not very useful for subsequent cloning because the nuclei are tetraploids. No practical procedure is available for reducing them to diploid level. Various culture conditions can also induce reprogramming. Blastocysts can yield pluripotent embryonic stem cells in vitro. The primordial germ cells of the genital ridge can give rise not only to germ cells (oocyte and sperm), but also to embryonic germ cells when used as explants in vitro or they can dedifferentiate into embryonic carcinoma cells. Spermatogonial stem cells can give rise to spermatzoa or in culture they can be reprogrammed into embryonic stem cell-like tissues. Bone marrow-derived adult multipotent progenitor cells can also be reprogrammed into mesenchymal or blood cells.

The *Nanog* gene (4 exons) in mouse chromosome 6 and human chromosome 12 encodes a 305-amino acid protein in humans (Chambers I et al 2004 *Cell* 113:643). This protein is essential for the maintenance of pluripotency of embryonic stem cells. The name nanog means the land of the ever young in Celtic mythology. Nanog may increase pluripotency of fused cells up to 100% (Silva J et al 2006 *Nature [Lond]* 441:997). Several other genetic factors OCTA4, SOX2 and various transcription factors have also been implicated. Mouse primordial germ cells (PGC) undergo erasure of histone 3 lysine 9 dimethylation (H3K9me2) and upregulation of histone H3 lysine 27 trimethylation (H3K27me3) in a progressive, cell-by-cell manner, presumably depending on their developmental maturation. Before or concomitant with the onset of H3K9 demethylation, PGCs enter G2 arrest of the cell cycle, that apparently persists until they acquire high H3K27me3 levels. PGCs repress RNA polymerase II-dependent transcription, which begins after the onset of H3K9me2 reduction in the G2 phase and tapers off after the acquisition of high level H3K27me3. The epigenetic reprogramming and transcriptional quiescence are independent from the function of Nanos3. Before H3K9 demethylation, PGCs exclusively repress an essential histone methyltransferase, GLP, without specifically upregulating histone demethylases (Seki Y et al 2007 *Development* 134:2627). ►nuclear transplantation, ►epigenesis, ►histone methyltransferase, ►stem cells; Rideout WM III et al 2001 *Science* 293:1093; Häkkelien A-M et al 2002 *Nature Biotechnol* 5:460; Hochedlinger K, Jaenisch R 2006 *Nature [Lond]* 441:1061.

Repolysin: A metalloproteinase involved in the regulation of morphogenesis. ►bone morphogenetic protein

Reptation: A theory about the movement of nucleic acid end-to-end in gels.

Reptin: ►chromatin remodeling

Repulsion: One recessive and one dominant allele are in the same member of a bivalent, such as *A b* and *a B*. ►coupling, ►linkage; Bateson W et al 1905 *Rep Evol Com Roy Soc II*:1.

RER: Denotes rough endoplasmic reticulum (endoplasmic reticulum with ribosomes on top of it).

Resection: Nuclease mediated production of single-strand overhangs in double-strand DNA breaks.

Resequencing: is directed to molecularly known gene(s) in order to determine mutations in the sequence (SNP, insertion, deletion) that have potential role in the expression of the gene and the disease it controls.

Capillary electrophoresis, polymerase chain reaction and automated data analysis may be used for the detection of mutations in the tract. For detection of insertions, labeled nucleotide array is hybridized to the target tract and the increase of signal indicates insertions. Loss of hybridization in a similar approach is the sign of deletion. (See Rijk PD, Del-Favero J 2007 *Methods Mol Biol* 396:331; <http://www.resequencing.mpg.de/>).

Residue: Refers to the elements of polymeric molecules, such as nucleotides in nucleic acids, amino acids in proteins, sugars in polysaccharides and fatty acids in lipids.

Resilin: This is a member of an elastic protein family, including gluten, gliadin and spider silks. ► [glutenin](#), ► [silk fibroin](#); Elvin CM et al 2005 *Nature [Lond]* 437:999.

Resistance Transfer Factors (RTF): Plasmids that carry antibiotic or other drug resistance genes in a bacterial host and are capable of conjugational transfer. ► [plasmid\(s\)](#)

Resistin: This is a 12.5 kDa cysteine-rich protein hormone of adipose tissues. The level of resistin is increased in genetically determined and diet-dependent obesity and it may cause insulin resistance and type II diabetes. ► [adipocyte](#), ► [adiponectin](#), ► [diabetes mellitus](#), ► [insulin](#); Way JM et al 2001 *J Biol Chem* 276:25651.

RESites (related to empty sites): These are genomic sites from where transposable elements moved out but left behind a footprint. Their flanking sequences are similar to insertion targets. (See Le QH et al 2000 *Proc Natl Acad Sci USA* 97:7376).

R

Resolution: Refers to the depth of details revealed by the analysis.

Resolution, Optical: Defines the ability of distinguishing between two objects irrespective of magnification. Magnification helps the human eye but does not improve optical resolution. The power of resolution depends on the wavelength of the light and on the aperture of the lens used. (The achromatic lens is free from color distortion, the apochromatic lens is free from color or optical distortions). The naked human eye may discern details larger than 100 μm , the light microscope with a good oil immersion objective lens may resolve 0.2 μm , the lowest limit for an ideal electronmicroscope is 0.1 nm, i.e., 1 Å. Under practical conditions the resolution of the electronmicroscope is about 2 nm. The resolution of the light microscope is generally defined as $\frac{0.61\lambda}{n \sin \theta}$ where λ is the wavelength of the light (for white light it may be 530 nm), n stands for the refractive index of

the immersion oil or air (when dry lens is used) and θ is half of the angular width of the cone of the light beam focused on the specimen with the condensor of the microscope ($\sin \theta$ is maximally about 1). Then $\sin \theta$ is the *numerical aperture* of the lens and using oil immersion its value may increase to 1.4. The immersion oil should be non-fluorescing, slow drying and of right viscosity for vertical or horizontal inverted views. ► [fluorescence microscopy](#), ► [phase-contrast microscopy](#), ► [Nomarski](#), ► [confocal microscopy](#), ► [electronmicroscopy](#), ► [oil immersion lens](#)

Resolvases: These are endonucleases mediating site-specific recombination and instrumental in resolving cointegrates or concatenated DNA molecules; transposon Tn3 and $\gamma\delta$ encoded proteins promoting site-specific recombination of supercoiled prokaryotic DNA containing replicon fusion, direct end repeats and internal *res* sites (see Fig. R44). ► [site-specific recombination](#), ► [recombination site-specific](#), ► [reporter ring](#), ► [TN3](#), ► [concatenate](#), ► [\$\gamma\delta\$ element](#), ► [EMC](#), ► [phase variation](#), ► [recombination molecular mechanism](#); Kholodii G 2001 *Gene* 269:121; Croomie GA, Leach DR 2000 *Mol Cell* 6:815; $\gamma\delta$ structure: Li W et al 2005 *Science* 309:1210; Kamtekar S et al 2006 *Proc Natl Acad Sci USA* 103:10642.

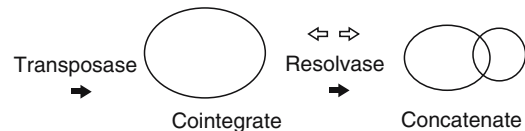


Figure R44. Resolvase functions

Resolving Power: This is the ability to distinguish between two alternatives or detecting an event, the probability of which is expected to be very low, e.g., recombination between two alleles of a gene.

Respiration: Electrons are removed from the nutrients during catabolism and carried to the oxygen through intermediaries in the respiratory chain. Oxygen is taken up and carbon dioxide is produced. ► [fermentation](#), ► [Pasteur effect](#), ► [chlororespiration](#), ► [mitochondria](#)

Respiratory Distress Syndrome: This condition is frequently observed in premature birth and is due to deficiency of pulmonary surfactant protein A (SFTPA2, 10q22.2-q22.3) or PFTP3 (2p12-p11.2).

Responder (*Rsp*): A component of the segregation distorter system in *Drosophila*, a repetitive DNA at the heterochromatic site in chromosome 2–62. ► [hybrid dysgenesis](#), ► [segregation distorter](#)

Response Elements: ►hormone response elements, ►transcription factors, ►inducible regulation of gene activity

Response Regulator: ►two-component regulatory system

Responsiveness: The establishment of a new steady state readily follows a change in the signal(s). ►signal, ►steady state

REST/NRSF (RE1 silencing transcription factor/neural-restrictive silencing factor): This factor blocks the expression of genes in non-neural tissues. It is a component of the histone deacetylase complex. It is involved in the regulation of chromatin and associated protein complexes. (See Kojima T et al 2001 Brain Res Mol Brain Res 90:174; Ooi L, Wood IC 2007 Nature Rev Genet 8:544).

Restenosis (recurrent stenosis): This is usually caused by therapeutic manipulation of the vascular system as an overcompensation for injury repair, e.g., after angioplasty (surgical/balloon opening of stenosis), or coronary/peripheral bypass surgery. Cell cycle inhibitors, antisense technologies, and modifying the expression of particular genes by using genetic vectors targeting particular genes involved in the cell

cycle have been considered for the prevention of this very complex process. ►stenosis, ►cell cycle, ►antisense technologies; Gordon EM et al 2001 Hum Gene Ther 12:1277.

Restitution Chromosomal: Refers to rejoining and healing of broken off chromosomes.

Restitution Nucleus: This is the unreduced product of meiosis.

Restless Leg Syndrome: This age-dependent neurological defect is characterized by compulsive movement of the legs, sleep disorder and increased tendency toward cardiovascular disease. It may affect up to 10% of the population of European descent. A genome-wide association study has revealed that the homeobox gene MEIS1 (chromosome 2p), gene BTBD9 (chromosome 6p), kinase MAP2K5 and transcription factor LBXCOR1 encoded at 15q are involved (Winkelmann J et al 2007 Nature Genet 39:1000).

Restorer Genes: ►cytoplasmic male sterility, ►fertility restorer genes

Restriction Endonuclease: ►restriction enzyme and Table R6.

Table R6. Restriction endonucleases with recognition and cutting sites (Isoschizomers: IS, Cutting site: (')), N: any base, ^m: Methylated base)

| | | | |
|-------------------------|---------------------------------|------------------------------------|---------------------|
| Aal IS Stu I | Bpu AI GAAGAC(N) _{2/6} | Hae III GG'CC | Pma CI IS: Bbr PI |
| Aat II GACGT'C | Bse AI T'CCGGA | Hgi AI IS: Asp HI | Pml IS Bbr PI |
| Acc I GT'(A,C)(T,G)AC | Bse PI IS: Bss H II | Hha I IS: Cfo I | Psp 1406 I AA'CGTT |
| Acc III IS: Mro I | Bsi WI C'GTACG | Hinc II IS: Hind II | Pst I CTGCA'G |
| Acs I (A,G)'AATT(T,C) | Bsi YI CC(N) ₅ 'NNGG | Hind II GT(T,C)'(A,G)AC | Pvu I CGAT'CG |
| Acy I G(A,D)'CG(C,T)C | Bsm I GAATGCN'N | Hind III A'AGCTT | Pvu II CAG'CTG |
| Afl I IS: Ava II | CTTAC'GNN | Hinf I G'ANTC | Rca I T'CATGA |
| Afl II IS: Bfr I | Bsp 12861 IS: Bmy I | Hpa I GTT'AAC | Rsa I GT'AC |
| Afl III A'C(A,G)(T,C)GT | Bsp 14071 IS: Ssp BI | Hpa II C'CGG | Rsr II CG'G(A,T)CCG |
| Age IS: Pin AI | Bsp HI IS: Rca I | Ita I GC'NGC | Sac I GAGCT'C |
| Aha II IS: Acy I | Bsp LU11I A'CATGT | Kpn I GGTAC'C | Sac II IS: Ksp II |
| Aha III IS: Dra I | Bss HII G'CGCGC | Ksp I CCGC'GG | Sal I G'TCGAC |
| Alu I AG'CT | Bss GI IS: Bst XI | Ksp 632 I CTCTTC(N) _{1/4} | Sau I IS: Aoc I |
| Alw 44 I G'TGCAC | Bst 1107 I GTA'TAC | Mae II A'CGT | Sau 3A 'GATC |
| Aoc I CC'TNAGG | Bst BI IS: Sfu I | Mae III 'GTNAC | Sau 96 I G'GNCC |
| Aos I IS: Avi II | Bst EII G'GTNACC | Mam I GATNN'NNATC | Sca I AGT'ACT |
| Apa I GGGCC'C | Bst NI IS: Mva I, Eco RII | Mbo I IS: Nde II | Scr FI CC'NGG |

Table R6. Restriction endonucleases with recognition and cutting sites (Isoschizomers: IS, Cutting site: (')), N: any base, ^m: Methylated base) Continued

| | | | |
|---------------------------------|----------------------------------|---------------------------|-----------------------------------|
| Apo I IS: Acs I | Bst XI CCA(N) ₅ 'NTGG | Mfe I IS: Mun I | Sex AI A'CC(A,T)GGT |
| Apy I IS: Eco RII, Mva I | Cel II GC'TNAGC | Mlu I A'CGCGT | Sfi I GGCC(N) ₄ 'NGGC |
| Ase I IS: Asn I | Cfo I GCG'C | Mlu NI TGG'CCA | Sfu I TT'CGAA |
| Asn I AT'TAAT | Cfr I IS: Eae I | Mro I T'CCGGA | Sgr AI C(A,G)'CCGG(T |
| Asp I GACN'NNGTC | Cfr 10 I (A,G)'CCGG (T,C) | Msc I IS: Mlu NI | Sma I CCC'GGG |
| Asp 700 GAANN'NNTTC | Cla I AT'CGAT | Mse I IS: Tru 91 | Sna BI TAC'GTA |
| Asp 718 G'GTACC | Dde I C'TNAG | Msp I C'C ^m GG | Sno I IS: Alw 44 I |
| Asp EI GACNNN'NNGTC | Dpn I G ^m A'TC | Mst I IS: Avi II | Spe I A'CTAGT |
| Asp HI G(A,T)GC(T,A)'C | Dra I TTT'AAA | Mst II IS: Aoc I | Sph I GCATG'C |
| Asu II IS: Sfu I | Dra II (A,G)G'GNCC(T,C) | Mun I C'AATTG | Ssp I AA'ATT |
| Ava I G'(T,C)CG(A,G) (A,G)G | Dra III CACNNN'GTG | Mva I CC'(A,T)GG | Ssp BI T'GTACA |
| Ava II G'G(A,T)CC | Dsa I C'C(A,G)(C,T)GG | Mvn I CG'CG | Sst I IS: Sac I |
| Avi II TGC'GCA | Eae I (T,C)'GGCC(A,G) | Nae I GCC'GGC | Sst II IS: Ksp I |
| Avr II IS: Bln I | Eag I IS: Ecl XI | Nar I GG'CGCC | Stu I AGG'CCT |
| Bal I IS: Mlu NI | Eam 11051 IS: Asp EI | Nci I CC'(G,C)GG | Sty I C'C(A,T)(A,T)GG |
| Bam HI G'GATCC | Ecl XI C'GGCCG | Nco I C'CATGG | Taq I T'CGA |
| Ban I G'G(T,C)(A,G)CC | Eco 47 III AGC'GCT | Nde I CA'TATG | Tha I IS: Mvn I |
| Ban II G(A,G)GC(T,C)'C | Eco RI G'AATTC | Nde II 'GATC | Tru 9 I T'TAA |
| Bbr PI CAC'GTG | Eco RII 'CC(A,T)GG | Nhe I G'CTAGC | Tth 111 I IS: Asp I |
| Bbs I IS: Bpu AI | Eco RV GAT'ATC | Not I GC'GGCCGC | Van 91 I CCA(N) ₄ 'NTG |
| Bcl I T'GATCA | Esp I IS: Cel II | Nru I TCG'CGA | Xba I T'CTAGA |
| Bfr I C'TTAAG | Fnu DII IS: Mvn I | Nsi I ATGCA'T | Xho I C'TCGAG |
| Bgl I GCC(N) ₄ 'NGGC | Fnu 4 HI IS: Ita I | Nsp I (A,G)CATG'(T,C) | Xho II (A,G)'GATC(T,C |
| Bgl II A'GATCT | Fok I GGATG(N) _{9/13} | Nsp II IS: Bmy I | Xma III IS: Ecl XI |
| Bln I C'CTAGG | Fsp I IS: Avi II | Nsp V IS: Sfu I | Xmn I IS: Asp 700 |
| Bmy G(G,A,T)GC(C,T,A)'C | Hae II (A,G)GCGC'(T,C) | Pin AI AA'CCGGT | Xor II CGAT'CG |

Restriction Enzyme: Endonucleases cut the DNA at specific sites (generally) when the bases are not protected (modified, usually by methylation). Bacteria synthesize restriction enzymes as a defense against invading foreign DNAs such as phages and foreign plasmids. They may facilitate recombination and transposition. Three major types have been identified. Type II enzymes are used most widely for genetic engineering. Type II enzymes have separate endonuclease and methylase proteins. Their structure is simple, cleave at the recognition site(s); the recognition sites are short (4–8 bp) and frequently

palindromic, they require Mg^{2+} for cutting, the methylation donor is SAM. So far more than 3,000 Type II restriction endonucleases have been identified. Type II proteins, unless they have a similar pattern of cleavage, have relatively low sequence homologies.

Type III enzymes carry out restriction and modification with the help of two proteins which share a polypeptide. They have two different subunits.

Cleavage sites are generally 24–26 bp downstream from the recognition site. The recognition sites are asymmetrical 5–7 bp. For restriction, they require ATP and Mg^{2+} . For methylation, SAM, ATP, Mg^{2+}

are needed. *Type I* enzymes are single multifunctional proteins of three subunits, cleavage sites are random and at about 1 kb from specificity sites (crystal structure of the DNA-binding subunit: Kim J-S et al 2005 Proc Natl Acad Sci USA 102:3248). *Type I* restriction enzymes are encoded in the *hsd* (host-specificity DNA) locus with three components: *hsdS* (host sequence specificity), *hsdM* (methylation) and *hsdR* (endonuclease). Their recognition sites are bipartite and asymmetrical: TGA-N8-TGCT or AAC-N6-GTGC. For restriction and methylation, SAM, ATP and Mg^{2+} are required (see Figs. R45 and R46). Restriction enzymes may create a protruding and a receding end or the two ends may be of equal length, e.g.:

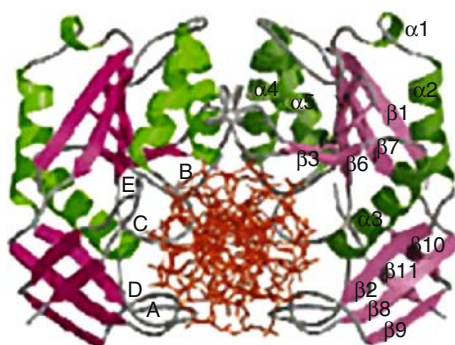


Figure R45. Crystal Structure of *Bgl*/II. In the centre is the DNA and α -helices and β -sheets embrace the DNA. Courtesy of Aggarwal AK; From Lukacs CM et al 2000 Nature Struct. Biol. 7:134



Figure R46. Protruding, receding and blunt ends of restriction fragments

Type II enzymes may be of high specificity, ambiguous, or isoschizomeric, and may be prevented from action on methylated substrates or may be indifferent to methylation. Some restriction enzymes such as *McrA*, *McrBC* and *Mrr* actually cut only methylated DNA. Approximately 3,000 *Type II* restriction enzymes with nearly 200 different specificities are known. Kilo- and Mega-base DNA substrates can be precisely cleaved by combining a DNA-cleaving moiety, e.g., copper-*o*-phenanthroline with a specific DNA binding protein (e.g., CAP). The complex thus cuts at the 5'-AAATGTGATCTAGAT-CACATTTT-3' DNA site of CAP recognition. The great specificity required that the cutting moiety would be attached to an amino acid in such a way that it would bend toward the selected target but not toward unspecific sequences. The *IIS* restriction

endonucleases cleave the DNA at a precise distance outside of their recognition site and produce complementary cohesive ends without disturbing their recognition site. By 2005, over 3,600 restriction endonucleases had been identified representing more than 250 specificities (see Table R6). ▶nucleases, ▶isoschizomers, ▶DNA methylation, ▶restriction-modification, ▶*hsdR*, ▶CAP, ▶antirestriction, ▶RNA restriction enzyme; Roberts RJ, Macelis D 2001 Nucleic Acids Res 29:268; Titheradge AJB et al 2001 Nucleic Acids Res 28:4195; Piungoud A, Jeltsch A 2001 Nucleic Acids Res 29:3705; classification: Roberts RJ et al 2005 Nucleic Acids Res 33: D233; historical perspective: Roberts RJ 2005 Proc Natl Acad Sci USA 102:5905; Brownlee C 2005 Proc Natl Acad Sci USA 102:5909; <http://www.neb.com/nebecomm/products/category1.asp?>; enzymes and genes for restriction and modification: <http://rebase.neb.com/rebase/rebase.ftp.html>.

Restriction Enzymes, Class-IIs (Enases-IIS): These have 4–7 bp, completely or partially asymmetric recognition sites and the cleavage site is at a distance of 1–20 bp. These enzymes are monomeric. They can be employed for precise trimming of DNAs, retrieval of cloned fragments, assembly of genes, cleavage of single-stranded DNA, detection of point mutations, amplification and localization of methylated bases. ▶restriction enzymes, ▶indexer; Szybalski W et al 1991 Gene 100:13.

Restriction Factor: This is a general term for various proteins, proteases, hormones and endonucleases involved in limiting or preventing growth. ▶APOPBEC3G; retrovirus restriction review: Goff SP 2004 Mol Cell 16:849.

Restriction Fragment: Denotes a piece of DNA released after digestion by a restriction endonuclease. The length of the fragments depends on how many nucleotides are situated between the two cleavage sites. From the same genomic DNA, the same enzyme generates fragments of different lengths because the nucleotide sequence varies along the DNA length. ▶restriction enzymes, ▶restriction fragment number, ▶RFLP

Restriction Fragment Length Polymorphism: ▶RFLP

Restriction Fragment Number: This can be predicted on the grounds of the number of bases at the recognition sites. Since the polynucleotide chain has four bases (A, T, G, C), four cutters can have $4^4 = 256$ bp average fragment length and six cutters $4^6 = 4096$. The average frequency of these fragments is

$0.25^4 = 0.0039$ and $0.25^6 = 0.000244$, respectively. However, these predictions are valid only if the distribution of the bases is random, but that is not the case in the coding sequences, e.g., in the ca. 49.5 kb λ DNA 12 EcoRI fragments would have been predicted but only five have been observed. Four, six cutter indicates that the enzyme cleaves the substrate at a 4 or 6 nucleotide-specified site. ►restriction enzymes, ►restriction fragment

Restriction Landmark Genomic Scanning (RLGS): This method detects cleavable restriction enzyme sites (e.g., NotI) in the genome by direct labeling and high-resolution two-dimensional electrophoresis. NotI is methylation sensitive and does not cleave at methylated sites. Tumor tissues usually display chromosomal aberrations and that may alter the restriction sites and the tissue specific differences in RLGS may be characteristic of the cancer. ►restriction enzyme, ►two-dimensional gel electrophoresis; Hirotsune IH et al 1994 DNA Res 1:239.

Restriction Map: ►RFLP

Restriction Mediated Integration: ►REMI

Restriction-Modification: The bacterial restriction enzymes are endonucleases and the modification enzymes are methyltransferases that recognize the same nucleotide sequence as the endonuclease and transfer a methyl group from *S*-adenosyl methionine either to C-5 of cytidine or to cytidine- N^4 or to adenosine- N^6 . For example, HpaII cuts C↓CGG and methylates C^mCGG, TaqI cuts T↓CGA and methylates TGC^mA. The biological purpose of this complex is to destroy invading nucleic acids (phages) by cleaving the foreign DNA with the aid of the restriction endonuclease(s), i.e., restrict the growth of the invader and the same time protect the bacterium's own genetic material by methylation. ►restriction enzymes, ►methylation of DNA, ►anti-restriction, ►methyltransferases, ►DNA uptake sequences; Kobayashi I 2001 Nucleic Acids Res 29:3742; <http://rebase.neb.com/rebase/rebase.html>.

Restriction Point: ►R point, ►checkpoint, ►cell cycle, ►cancer, ►commitment

Restriction Site: Refers to the site where the restriction enzyme cleaves. ►cloning site

Restrictive Conditions: These conditions do not permit the growth or survival of some specific conditional mutants. ►conditional mutation, ►permissive conditions

Restrictive Transduction: ►specialized transduction

Resveratrol (3,5,4'-trihydrostilbene): This is an antioxidant and an anti-inflammatory plant product. The beneficial effect of red wines is attributed to this phytoalexin. Resveratrol is an activator of sirtuin and can rescue polyglutamine-caused symptoms in *Caenorhabditis* as well in the neurons of mice (Parker JA et al 2005 Nature Genet 37:349). Resveratrol improves the health and survival of mice on a high-calorie diet (Baur JA et al 2006 Nature [Lond] 444:337). Resveratrol activates sirtuin and PGC-1 α , improves mitochondrial functions and protects against metabolic disease (Lagouge M et al 2006 Cell 127:1109). ►lipoxygenase, ►phenolics, ►phytoalexins, ►sirtuin, ►PGC

RET Oncogene (Rearranged during transfection): This is in human chromosome 10q11.2. In *Drosophila* its homolog is *tor* (see morphogenesis in *Drosophila*). The protein product is a tyrosine kinase, essential for the development of the nervous system; it is a signaling molecule for GDNF. Mutations at the RET locus may be responsible for familial medullary thyroid carcinoma (FMTc), multiple endocrine neoplasia (MEN2A and MEN2B) and Hirschsprung's disease and may involve a dominant negative effect. The RET gene has five important domains: cadherin-binding, cysteine-rich calcium-binding, transmembrane and two tyrosine kinase (TK) domains. The main course of the RET-activated signal pathway is: RET receptor→Grb2→SOS→RAS→RAF→MAPKK→MAPK→NUCLEUS (transcription factors). The RET regulatory function is preserved between zebrafish and humans without any similarity in sequence (Fischer S et al 2006 Science 312:276). ►oncogenes, ►tyrosine kinase, ►TCR, ►GDNF, ►endocrine neoplasia, ►Hirschsprung's disease, ►phaeochromocytoma, ►papillary thyroid carcinoma, ►Grb, ►SOS, ►RAS, ►RAF, ►MAPKK, ►MAPK, ►dominant negative, ►tyrosine receptor kinase, ►multiple endocrine neoplasia; Manie S et al 2001 Trends Genet 17:580.

Retardation: Denotes slower than normal growth and development. ►mental retardation, ►gel retardation assay

Reticulocyte: An immature enucleate red blood cell displays a reticulum (network) when stained with basic dyes. ►rabbit reticulocyte in vitro translation system

Reticulosis: A complex autosomal recessive disease involving anemia, lowered platelet count, nervous disorders, immunodeficiency, etc. The symptoms may overlap different types of leukemias. The prevalence is about 5×10^{-5} . Bone marrow transplantation and chemotherapy have proved to be beneficial in some cases. (See separate entries).

Reticulosis, Familial Histiocytic: This disorder involves spleen, liver and lymphnode enlargement; it is caused by mutation in the RAG1 or RAG2 genes at human chromosome 11p13. ►[RAG](#), ►[Omenn disease](#)

Retina: This is the inner layer of the eyeball connected to the optic nerve. ►[macular degeneration](#), ►[figure of eye at Iris](#)

Retinal: Refers to vitamin A aldehyde. ►[vitamin A](#)

Retinal Dystrophy (retinopathies): This is caused by defects in the rod photoreceptor—retinal pigment epithelial complex. The incident light activates rhodopsin which transmits the signal to the G protein transducin and then to a phosphodiesterase (PDE) leading to a decrease in the level of cGMP (required for the activity of the transducin) and the closure of Na^+ ion channels and cellular hyperpolarization. Arrestin and rhodopsin kinase regenerate the photoreceptor rhodopsin. Degeneration of the retinal pigment epithelium and the retinal rod receptors may cause blindness because of failure at any step in this system. Low levels of cytosolic cGMP caused by mutation in the cGMP activating protein may be the basis of amaurosis congenita. A defect in the photoreceptor-specific peripherin/RDS protein (located in the rod and cone photoreceptors' outer membranes) also results in retinal dystrophy, presumably because of the damage to anchoring the structures to the cytoskeleton. Another protein ROM1 (rod outer membrane) homologous to peripherin, associates within a tetrameric form and represents the major outer part of the photoreceptor. Peripherin variants have been implicated in some forms of other eye diseases such as retinitis pigmentosa, macular dystrophy and choroidal dystrophy. Injecting peripherin-2 gene using an adeno-associated viral vector can remedy the complex defect. The Bietti corneoretinal dystrophy due to a 32 kDa fatty acid-binding protein defect eventually causes night blindness and has been assigned to 4q25-4qtel.

Apoptosis may account for some retinal degeneration, which can be arrested by growth substances. Retinal damage may be repaired by transplantation of committed progenitor cells from the peak of the rod genesis. These transplanted cells integrate,

differentiate into rod photoreceptors, form synaptic connections and visual function in mice (MacLaren RE et al 2006 Nature [Lond] 444:203). ►[arrestin](#), ►[rhodopsin](#), ►[transducin](#), ►[ion channels](#), ►[peripherin](#), ►[phosphodiesterase](#), ►[signal transduction](#), ►[amaurosis congenita](#), ►[Oguchi disease](#), ►[night blindness](#), ►[Stargardt disease](#), ►[eye diseases](#), ►[cho-roid](#), ►[Usher syndrome](#), ►[apoptosis](#); Rattner A et al 1999 Annu Rev Genet 33:89; Allikments R 2000 Am J Hum Genet 67:793.

Retinitis Pigmentosa (RP): A group of human autosomal recessives (84%), X-linked recessive (6%, Xp11.3 and Xp21.1) or autosomal dominant (10%, 13q14, 8q11-q13) or mitochondrial diseases entailing visual defects and blindness with an onset during the first two decades of life and a prevalence rate in the range of 10^{-4} . The Xp21 (RP6) gene may form a contiguous gene syndrome in that region. Only a small fraction of cases of pigmentary defect is associated with the rhodopsin receptor, a G-protein receptor (RGR). Mutation in the TULP1 gene, expressed only in the retina, may also involve RP. (Tulp-like proteins occur in vertebrates, invertebrates and plants). Several other diseases, e.g., congenital deafness (Usher syndrome), hypogonadism, mental retardation, other neuropathies and mitochondrial deficiencies may also involve similar defects. Nearly 40 genes are probably involved in RP symptoms. A "digenic retinitis pigmentosa" is due to mutations in the unlinked loci of peripherin-2 (6p21-cen) and the ROM1 (retinal rod outer segment protein-1) in chromosome 11q13 (see Fig. R47) (Loewen C et al 2001 J Biol Chem 276:22388). Mutations in the α subunit of a cGMP phosphodiesterase (human chromosome 5q31.2-q34) gene, PDEA (phosphodiesterase A) may also cause retinitis pigmentosa. In the autosomal dominant disease, when there is single amino acid replacement in rhodopsin (His→Pro) ribozymes may discriminate against the mutant rat mRNA and destroy it when the photoreceptors are transduced by adenovirus-associated ribozyme constructs equipped with a rhodopsin promoter. The rhodopsin-like OPN2 gene has been assigned to 3q21-q24. Recessive mutations at 1q31-q32.1 also cause RP12 due to photoreceptor degeneration. The latter gene is homologous to that of *crumbs* in *Drosophila*. The MERTK receptor tyrosine kinase (2q14.1) may also be responsible for RP. A RP GTPase regulator-interacting gene (RPGIP1) has been mapped to 14q11. Dominant mutations at 17p13.3, 1q21.1 and 19q13.4 encode pre-mRNA splicing factors. Inosine monophosphate dehydrogenase gene type 1 (chromosome 7q) deficiency may also be responsible for dominant RP. ►[Lawrence-Moon syndrome](#), ►[Usher syndrome](#),

►Stargardt disease, ►rhodopsin, ►retinoblastoma, ►choroidoretinal degeneration, ►eye diseases, ►ribozyme, ►contiguous gene syndrome; Bennett J 2000 *Curr Opin Mol Ther* 2:420; Phelan JK, Bok D 2000 *Molecular Vision* 6:116; McKie AB et al 2001 *Hum Mol Genet* 10:1555; Vithana EN et al 2001 *Mol Cell* 8:375; Chakarova CF et al 2002 *Hum Mol Genet* 11:87; Kennan A et al 2002 *Hum Mol Genet* 11:547.

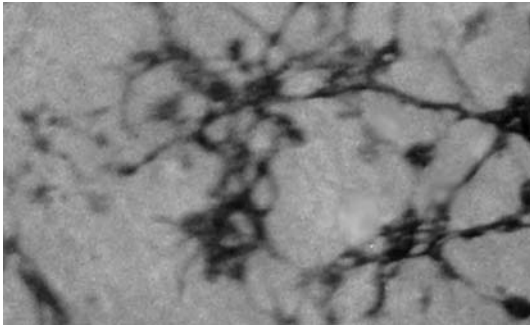


Figure R47. Part of the optic fundus of an eye with dark pigments indicating defects in the photoreceptor cell layer in retinitis pigmentosa. (Courtesy of the March of Dimes Foundation)

Retinoblastoma (RB): This is a tumor arising from the retinal germ cells, a glioma of the retina. The overall incidence is about $1\text{--}6 \times 10^{-5}$ per birth, expressed within the first two years. Almost 40% of the cases are genetically determined. The estimated mutation rate is within the range of 10^{-5} to 10^{-6} . The bilateral form is generally familial whereas the unilateral cases may be due to new mutations. A dominant RB gene has been assigned to human chromosome 13q14. The human RB1 allele may express meiotic drive, detectable by sperm typing. The mouse homolog Rb-1 is in mouse chromosome 14. Apparently RB is more frequently traced to the paternal chromosome 13 than to the maternal one. The incidence of sporadic RB is increasing with parental age. It appears that tumor growth factor B is absent in RB cells. The retinoblastoma protein (or homologs) may play a general role in tumorigenesis upon phosphorylation. RB is frequently associated with small cell lung carcinoma (SCLC), osteosarcoma, bladder cancer, breast cancer, leukemia and other types of malignancies and esterase deficiency (in deletions). Retinoblastoma is the first type of cancer with recognized recessive inheritance in humans. About 5–10% of the retinoblastomas are associated with deletions at chromosome 13q14 and rearrangements

involving that site. RB binding proteins (RBBP), with homology to the E7 transforming protein of a papilloma virus and to the large T antigen of SV40, have been identified. RBBP2/JUMONJI/JARID1A (human chromosome 12p11) demethylates H3K4, a transcriptional regulator histone (Klose RJ et al 2007 *Cell* 128:889). The normal allele of the retinoblastoma protein appears to keep in check abnormal proliferation by limiting the activity of pol III and pol I. Besides mutation in the RB gene, tumor suppressor p53 is also inactivated in retinoblastoma (Laurie NA et al 2006 *Nature [Lond]* 444:61). The retinoblastoma protein stimulates the transcription of several genes primarily by activating the glucocorticoid receptors. RB plays a decisive role at the G1 restriction point decisions (through RAS) in the cell cycle regarding differentiation or continuation of cell divisions. Transcription factor family E2F interacts with RB protein and regulates the cell cycle and cyclins. Retinoblastoma may be unilateral (the majority of the non-hereditary cases) or bilateral (about two-thirds of the hereditary cases). Defect in the RB gene may cause intrauterine death. The normal allele introduced into tumors by adenovirus vectors may slow down cancerous proliferation. Mutations in the retinoblastoma gene homolog of *Arabidopsis* plants cause female and male gametophytic lethality and abnormal nuclear proliferation of the central nucleus of the embryosac (Ebel C et al 2004 *Nature [Lond]* 429:776). ►eye disease, ►oncogenes, ►oncoprotein, ►pol III, ►deletion, ►CAF, ►papova virus, ►Simian virus 40, ►binding protein, ►sporadic, ►MDM2, ►E2F, ►ARF, ►glucocorticoid, ►restriction point, ►cell cycle, ►tumor suppressor, ►p110^{Rb}, ►E2F, ►pocket, ►cyclin, ►p53, ►RAS, ►histone deacetylase, ►papilloma virus, ►adenovirus, ►sperm typing, ►quiescent zone; Nevins JR 2001 *Hum Mol Genet* 10:699; Chan SW, Hong W 2001 *J Biol Chem* 276:28402, test for: Richter S et al 2003 *Am J Hum Genet* 72:253; epigenetic silencers (methyltransferases) and Notch collaborate in developing eye tumors in *Drosophila*: Ferres-Marco D et al 2006 *Nature [Lond]* 439:430; <http://www.es.embnet.org/Services/MolBio/rbgmdb/>.

Retinoid: ►RAR

Retinoic Acid (RA): This is a carboxylic acid derivative of vitamin A; the aldehyde form is retinol (see Fig. R48). The 11-cis retinal is the light absorbing chromophore of the visual pigments (carotenoids). Retinoic acids belong to a nuclear receptor family (RARE, RJR) and act as ligand-inducible transcription factors. Retinoids play a role in the anterior-posterior pattern of development of the body axis and

limbs of vertebrates (Vermot J et al 2005 Science 308:563). It may also have anti-cancer effects. RA activates RARE and PPAR β/δ , if it acts with RARE it may cause cell growth inhibition and if it acts with PPAR it induces pro-survival genes. A balance between CRABP-II (cellular retinoic acid binding protein) and PPAR (peroxisome proliferator activated receptor) determines these two opposing functions (Schug T et al 2007 Cell 129:723). ►transcription factors, ►RARE, ►opsin, ►PPAR

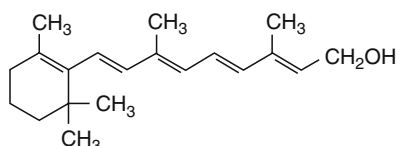


Figure R48. All-trans-retinol (vitamin A)

Retinol: Serum retinol-binding protein 4 contributes to insulin resistance and obesity and type 2 diabetes (Yanjg Q et al 2005 Nature [Lond] 436:356). ►retinoic acid, ►diabetes, formula given here.

Retinopathy: A disease of the retina. ►eye diseases

Retinoschisis: Refers to autosomal dominant, recessive or X-linked (Xp22.3-p22.1) degeneration of the retina involving splitting of that organ. ►eye diseases; Wang T et al 2002 Hum Mol Genet 11:3097.

Retra Genes: These are associated with retroviral sequences and/or transposons in the vertebrate genomes. ►retroviruses, ►transposon; Zdobnov EM et al 2005 Nucleic Acids Res 33:946.

Retroelements: ►retroposon, ►retrotransposon, ►processed pseudogene

Retrogene: This is a pseudogene with a transcriptionally active promoter. Retrogenes may be situated within the retroposon and have no introns. ►pseudogenes, ►SINE

Retrograde: This means backward. ►anterograde

Retrograde Evolution: The deletion of DNA sequences leads to adaptation to new function. Many pathogens lose genes upon becoming pathogenic. Pathogens and symbionts generally have smaller genomes than non-pathogenic or non-symbiotic relatives/ancestors. The reduction in genome size is probably the

consequence of lack of need for maintenance of metabolic functions that are available in the host. Pseudogenes represent relics of genes that are no longer required. ►pseudogenes; van Ham RCHJ et al 2003 Proc Natl Acad Sci USA 100:581.

Retrograde Regulation: The expression of nuclear genes is also controlled by mitochondrial and chloroplast factors. Genes in the cellular organelles (mitochondria and plastids) are coordinated in expression. Nuclear genes encode the overwhelming majority of functions in these organelles. In plants, the photosynthetic machinery, other plastid genes, primarily Mg-protoporphyrin IX synthetic complex and the chloroplast-localized pentatricopeptide-repeat protein GUN1 (genomes uncoupled 1) is a node where different chloroplast retrograde signals converge. The GUN complex comprises nearly 450 members and is present across the various plant species. GUN1 is the central mediator of communication with the nucleus. GUN2, 3, 4 and 5 control the MG-protoporphyrin IX system. GUN1 collects the signals and conveys them to the nuclear gene ABI4 and by binding to promoters in the DNA regulates RNA in the nucleus. Defect(s) or stress in the chloroplast leads to repression of some nuclear genes (Koussevitzky S et al 2007 Science 316:715). Similar retrograde regulation is also expressed through the mitochondria. ►chloroplasts, ►chlorophyll, ►pentatricopeptide, ►protoporphyrin, ►photosynthesis; Surpin M et al 2002 Plant Cell 14:S327; retrograde mitochondrial signaling in yeast: Liu Z, Butow RA 2006 Annu Rev Genet 40:159.

Retrohoming: ►intron homing

Retroid Virus: This has a double-stranded DNA genome (e.g., cauliflower mosaic virus, hepadnaviruses) which replicates the DNA with the aid of a RNA intermediate. ►cauliflower mosaic virus, ►hepatitis B virus, ►retroviruses

Retromer: A complex of five proteins: Vps35p, 29p, 26p, 17p and 5p. These proteins are involved in sorting endosomes to the trans-Golgi network and retrieval of the cation-independent mannose-6-phosphate receptor. Nexins are involved in the process of sorting. Retromers are essential for mammalian development. Retromers also function in yeast. ►endosome, ►Golgi; Griffin CT et al 2005 Proc Natl Acad Sci USA 102:15173.

Retron: This is responsible for the synthesis of msDNA. Retrons have several elements: the transcriptase *ret*,

the coding regions of msDNA, msdRNA and also requires RNase H. RNase HJ is needed for the maintenance of the proper structure and the termination of the transcription. ▶[msDNA](#), ▶[RNase H](#), ▶[reverse transcriptase](#), ▶[rettronphage](#); Lampson B et al 2001 *Progr Nucleic Acids Res Mol Biol* 67:65.

Retronphage: These retrons are parts of different proviruses, e.g., one in *E. coli* inserts within the selenocysteyl gene (*SecC*). ▶[retron](#), ▶[selenocysteine](#)

Retroposon (non-LTR retrotransposon): This transposable element is mobilized through the synthesis of RNA that is again converted to DNA by reverse transcription before integration into the chromosome. Some of the retroposon-derived elements acquired essential functions during evolution. An in silico assay of human genes for transcriptional activity revealed that more than 1,000 retrocopies were transcribed and ~120 developed into bona fide genes (Vickensbosch N et al 2006 *Proc Natl Acad Sci USA* 103:3220). The *Peg10* (paternally expressed, imprinted gene) of retroposon origin in the mouse is essential for placental development and embryo survival beyond day 10.5 post coitum (see Fig. [R49](#)). This gene is present in a wide variety of animals, except chicken and the *Fugu rubripes* fish (Ono R et al 2006 *Nature Genet* 38:101).

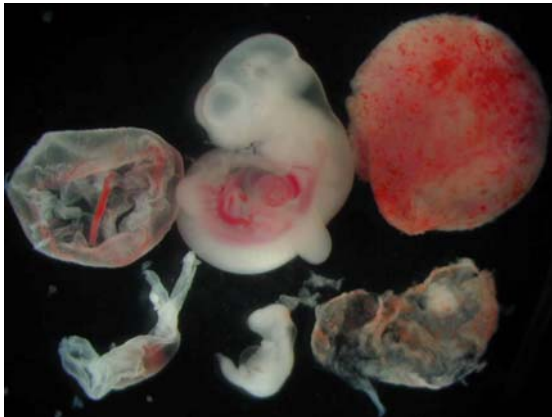


Figure R49. The expression of the *Peg10* gene (10.5. p.c.) wild type (upper row) and the knockout in mouse embryonic development (yolk sac, embryo, placenta). Courtesy of Drs. Fumitoshi Ishino and Ryuichi Ono

The retroposon may be a viral element or it may have originated from an ancient viral element. Retroposons are the long interspersed elements (▶[LINE](#)) and the short interspersed elements (▶[SINE](#)), the

copia elements in animals and several others of the hybrid dysgenesis factors, and they also occur in several species of plants. The majority of the plant retroposons have lost their ability to move. Retroposons can be distinguished from retrotransposons, the former do not have long terminal repeats (LTR) whereas the latter do. ▶[retroviruses](#), ▶[reverse transcriptase](#), ▶[copia](#), ▶[hybrid dysgenesis](#), ▶[transposable elements](#), ▶[LINE](#), ▶[SINE](#), ▶[processed pseudogene](#), ▶[knockout](#), ▶[post coitum](#); Wilhelm M, Wilhelm FX 2001 *Cell Mol Life Sci* 58:1246.

Retro-Proteins: These have inverse folding. Although folding should theoretically depend only on the amino acid sequence, they may have altered stability. The majority of genetic inversions are detrimental but the deleterious effect may not be the consequence of misfolding of proteins. ▶[inversions](#)

Retropseudogene: ▶[processed pseudogene](#)

Retroregulation: RNase III may degrade mRNA from the 3' end; some mutations in temperate phages may prevent this degradation and thus permit the translation of the mRNA. This control, operating from the end (downstream) forward (upstream), is known as retroregulation. ▶[retroviruses](#), ▶[regulation of gene activity](#), ▶[ribonuclease III](#)

Retrosequence: This is transcribed by reverse transcriptase.

Retrospective Study: This study involves the history of diseased individuals or individuals exposed to disease in the past and compares them to concurrent control cohorts. ▶[prospective study](#)

RetroTet-Art Vector: This has been designed to modulate the expression of the transgene by employing the tetracycline inducible system as well as the p16 growth arrest protein (Activators and repressors expressed together) so that during gene therapy the expression can be varied according to requirement. ▶[gene therapy](#), ▶[tetracycline](#); Rossi EM et al 1998 *Nature Genet* 20:389.

Retrotranslocation: Refers to the ejection of misfolded proteins from the endoplasmic reticulum back into the cytoplasm where they are subject to proteasome-mediated degradation. The dislocation is mediated by several Derlin proteins and p97 (Lilley BN, Ploegh HL et al 2005 *Proc Natl Acad Sci USA* 102:14296).

Retrotransposon: Refers to retrovirus-like transposable elements with long terminal repeats and position within the genome as retroviruses, however, they lack extracellular lifestyle, i.e., they cannot move from cell to cell. In *Arabidopsis* transposon Tag1, a 98 bp 5' terminal fragment containing a 22 bp inverted repeat and four copies of the AAACCX 5' subterminal repeat is sufficient for transposition, but a 52 bp 5' fragment with only one subterminal repeat is not. At the 3' end, a 109 bp fragment containing four copies of the most terminal 3' TGACCC repeat, but not a 55 bp fragment, which has no subterminal repeats is sufficient for transposition (Liu D et al 2001 Genetics 157:817).

Usually retrotransposons lack introns because they are propagated through a RNA intermediate and the introns are removed. The *Penelope* retrotransposon of *Drosophila viridis* shows a 75 bp intron with GT/AG donor/acceptor site in the 5' untranslated region. Similar elements have also been identified in some flatworms, roundworms, crustaceans, fishes and amphibians (Arkhipova IR et al 2003 Nature Genet 33:123).

Retrotransposons are common in the eukaryotic genomes and are apparently not distributed at random in the chromosomes. In mice oocytes retrotransposons, carrying promoters, can developmentally regulate the expression of multiple genes by serving as alternate promoters (Peaston AE et al 2004 Dev Cell 7:597). The VL30 retrotransposons in mice and humans are suppressors of leukemia oncogenes and also play a normal role in steroidogenesis (Song X, Garen A 2005 Proc Natl Acad Sci USA 102:12189).

The five *Ty* elements of *Saccharomyces* congregate in regions about 750 bp upstream of tRNA genes and *Ty5* is found at the telomeres.

Usually the sites of insertion are methylated and not transcribed and that protects the genome from insertional mutations. In a 280 kb region flanking the maize alcoholdehydrogenase gene (*Adh1*, chromosome 1L-128) 10 different retroelements were

found crowded with repetition and inserted within each other. The repetitive elements of the maize genome largely represent retrotransposons and constitute at least 50% of the total nuclear DNA. The size of the repeats varies from 10 to 200 kb and they are distributed throughout the genome. The maize retrotransposons with a very high copy number (10,000 to 30,000) usually do not cause insertional mutations. The elements with a small copy number (1–30) preferentially move into genic sequences. The *Arabidopsis* genome, which is about 1/20th of that of maize, contains almost 20 retrotransposons but only with 5–6 copies. In *Vicia faba* plants with a genome size of 13.3 pg (about 1.3×10^{10} nucleotide pairs), 10% of the genome comprises retrotransposable elements but in related species their number is much smaller. In *Allium* and other plants the elements are mainly in the centromeric and telomeric heterochromatin regions whereas in other organisms they may be dispersed (see Table R7). The plant retrotransposons (with the exception of the *Tnt1* of tobacco) fail to move because their transposase is pseudogenic. The major difference between retrotransposons and retroviruses is that the former do not produce envelope (Env) protein. ▶retroviruses, ▶insertion elements, ▶retroposon, see Figs. R50 and R51, ▶transposable elements, ▶transposons, ▶hybrid dysgenesis, ▶methylation of DNA, ▶Ty, ▶copia. It was expected that retrotransposons and retrotransposons (retroelements) would constitute about 5 to 10% of the human genome but the sequencing data revealed a substantially higher proportion. ▶retrotransposons, ▶SINE, ▶LINE, ▶Ty, ▶transposable elements, ▶processed pseudogene; Kumar A, Bennetzen J L 1999 Annu Rev Genet 33:479; Wang J et al 2006 Human Mutat 27:323; long terminal repeat (LTR) finder: http://tlife.fudan.edu.cn/ltr_finder/; retrotransposon and L1 signature finder: <http://www.riboclub.org/cgi-bin/RTAnalyzer/index.pl>.

Table R7. Retrotransposon and retrotransposon-like elements in *Drosophila* (*copia*), *saccharomyces cerevisiae* (*TY912*), and *Arabidopsis* (*tag-3*) all make 5 bp target site repeats. Their long direct terminal repeats are of different length yet they have highly conserved sequences (aligned in bold). Their internal domains of different length still has a few similarities although *copia* is highly mobile, whereas *tag-3* is no longer moving because its transposase gene underwent too many changes (pseudogenic). (After Voytas & Ausubel 1988 Nature [Lond] 336:242)

| Element | 5'Long terminal repeat | Internal domain | 3'Long terminal repeat |
|---------|------------------------------------|---|------------------------------------|
| Copia | TGTTGGA...TACAACA 276 bp | GGTTATGGGCCAGTC...TTGAGGGGGCG 4190 bp | TGTTGGA...TACAACA 276 bp |
| TY912 | TGTTGGA...TTTCTCA 334 bp | TGGTAGCGCCCTGTGCT...TATGGGTGGTA 5250 bp | TGTTGGA...TTTCTCA 334 bp |
| Tag-3 | TGTTGGA...GGTAACA 514 bp | AGTGGTATCAGAGCCA...AAGGTGGAGAT 4190 bp | TGTTGGA...GGTAACA 514 bp |

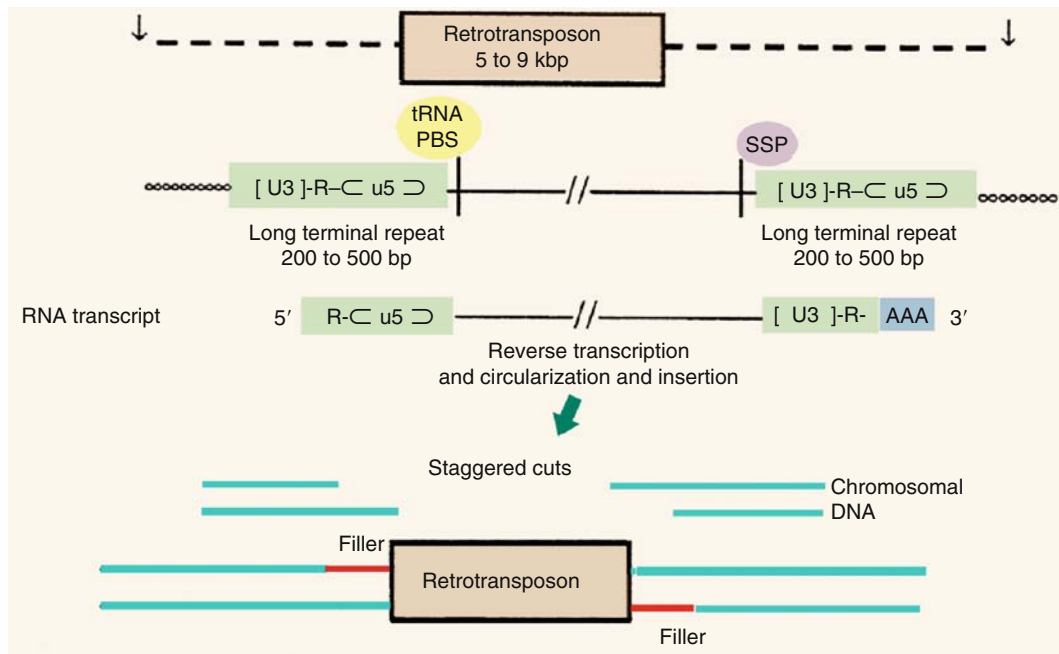


Figure R50. A DNA copy of a retrotransposon in the chromosome is replicated through a RNA transcript. The replication begins at the R segment of the 5' long terminal repeat (LTR) and proceeds through segment U5 and the non-repetitive internal region of the element (shown within the vertical lines) toward the 3' boundary of the R segment of the long terminal repeat. The first strand of the DNA is synthesized by the reverse transcriptase, encoded within the retrotransposon and is primed by the CCA-3'-OH end of one or another kind of host tRNA that pairs by complementarity to the upstream LTR. The reverse transcription also employs a protein-tRNA complex that binds to the tRNA-protein site (tRNA-PPS). The second strand is primed at the SSP site (second strand primer). At the target site, duplication occurs

Retroviral Recombination: Retroviruses have dimeric RNA genomes which are transcribed into double-stranded DNA after productive infection. Recombination occurs during the synthesis of the plus and minus strands. Complementarity between the palindromic sequences at the dimerization initiation sites of the hairpins is required for the two RNA chromosomes. The 5' untranslated sequence forms a kissing-loop structure (Figure R51) that contains essential replication elements. Increased homology and proximity of the homology tracts promote template switching. The diagram depicts a perfect

palindrome but the strands may not be perfectly complementary along their entire length. Circles indicate markers. ▶retrovirus, ▶kissing loop, ▶palindrome; Mikkelsen JG et al 2004 Nucleic Acids Res 32:102.

Retroviral Restriction Factors: These mammalian proteins interfere with effective infection or propagation of the retrovirus in the mammalian host cell. The APOBEC3G and ZAP inhibit the replication of the viral nucleic acid. The Friend virus susceptibility factor (Fv1) targets the incoming retroviral leukemia virus capsid. The TRIM5 factor group protects against HIV-1 and murine leukemia virus by acting after the entry of the virus into the host cell. ▶retrovirus, ▶TRIM, ▶leukemia inhibitory factor, ▶APOBEC3G, ▶ZAP; Hatzioannou T et al 2004 Proc Natl Acad Sci USA 101:10774.

Retroviral Vectors: These are capable of insertion into the chromosomes of a wide range of eukaryotic hosts. The expected important features are: (i) efficiency and selectivity for the target, (ii) safety, (iii) stable maintenance, and (iv) sufficient expression for the purpose employed. Generally, the *gag*, *pol* and *env* genes are removed but all other elements required for

R

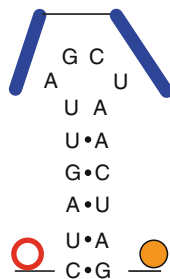


Figure R51. Kissing loop

integration and RNA synthesis and the ψ packaging signal are retained. Usually a selectable marker neomycin [*neo*], or dehydrofolate-reductase [*dhfr*] resulting in methotrexate resistance (MTX), or bacterial hypoxanthine-phosphoribosyltransferase [*hprt*], or guanine-hypoxanthine-phosphoribosyltransferase [*gpt*], or mycophenolic acid (MPA) resistance is inserted in such a way that its initiation codon (ATG) falls into the same place as the ATG of the group-specific antigen protein (*gag*) gene. Transcription will be initiated at the 5' long terminal repeat (5'LTR) and translation will proceed from the ATG that is at the same place as that of *gag* (see Fig. R52).

The generalized vector shown here is non-infectious and requires superinfection by a helper virus. There are several other types of vector designs. After the DNA has been packaged into a virus particle the transfer of the gene is almost fully efficient as long as the cell has the appropriate receptor. By engineering the knob on the viral surface, the vector may be targeted to special cells. The recombinant DNA integrates into the host as a provirus with aid of the *integrase* protein encoded also by the *pol* gene. The most commonly used murine leukemia virus vector (MuLV) has about 6–8 kb carrying capacity. It is desirable to target the integrase to sites where the danger of insertional mutation is minimized in case the vector is used for therapeutic purposes. This goal may be difficult to achieve. Targeting to the sites of RNA polymerase III attachment with the aid of the yeast *Ty* transposons has been considered. This polymerase (pol III) transcribes ribosomal RNA genes that are present in multiple copies and thus pose a lower risk for deleterious mutations. A better approach may be using targeted homologous recombination. Targeting the transgene may be refined by the use of a cell-specific promoter.

The provirus is generally present in a single copy per cell but this *producer cell* will proceed with the production of recombinant retrovirions. The production of the recombinant virus is enhanced if initially the cell is also co-infected by a wild type proviral plasmid. However, such a system has a disadvantage because of the presence of a helper virus, which competes with a pseudovirion, and it may also be hazardous by being pathogenic. The problems related to the helper virus can be eliminated if it retains all the viral genetic sites except the packaging site (ψ) and is

therefore unable to produce infectious particles. There are several means of preventing reconstitution of an infectious viral particle which can cause disease.

Broad host range (amphotropic) viral vectors can be constructed by replacing a narrow range (ecotropic) viral envelope protein with another of an amphotropic virus. The Env protein mediates the virus/vector entry into the cell through the Pit-2 receptor. Env determines the host range. The host range may be extended by pseudotyping, i.e., co-infection of the cells with two different viruses, which results in a mixed envelope glycoprotein. Improved targeting of the retrovirus may be achieved by attaching cell specific ligands or antibodies to Env. Some of the Env proteins may elicit spongiform encephalomyelopathy. Caution must be exercised because the vector or host cell DNA and the helper virus genetic material may recombine and give rise to infectious particles. By genetic engineering additional modifications have been made in the helper virus to prevent the formation of infectious single recombinants. This has been achieved by replacing, e.g., the 3' LTR with a termination stretch of the SV40 eukaryotic virus DNA.

The *retroviral expression vectors* are more useful because they not only prove that the viral vector is present in the cell, but also propagate desirable genes (e.g., growth hormone genes and globin genes). Since retroviral vectors may carry strong promoters and enhancers within the LTR region, they can over-express some genes. They may also be employed for insertional mutagenesis because they can insert at different chromosomal locations and can be used as tools to study animal differentiation and morphogenesis. The most commonly used retroviral vectors have been derived from the Moloney murine leukemia virus (MoMuLV). In some instances the retroviral vectors within the host are silenced because the viral promoter in the 5' LTR is methylated by the host enzymes. This *promoter shutoff* may be avoided by using eukaryotic promoters. In some instances the inclusion of a locus control region (LCR) of the host may boost the expression of the transgene. The use of insulators may protect the transgene from host repressors. Also, a heterologous promoter that may drive more efficient expression (SIN vector, double copy vector) may replace the viral promoter. Retroviral vectors may permit the utilization of internal ribosomal entry sites (IRES) to drive the expression

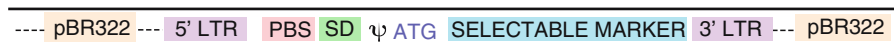


Figure R52. Retroviral vector. pBR322: bacterial plasmid, 5' LTR: long terminal repeat, PBS: binding site for primer to initiate first-strand DNA synthesis, SD: splicing donor site, ψ : packaging signal for the virion, ATG the first translated codon (Met) of the selectable marker (e.g., antibiotic resistance), 3' LTR: long terminal repeat

of more than one gene. By using tissue-specific promoters the expression of the transgene may be limited to a certain cell type, e.g., in tumor cells. The promoter may also be selected for inducibility so that the expression may be regulated by the supply of glucocorticoids or a metal, or tetracycline, etc. Retroviral vectors are useful for gene therapy because they integrate stably into human and animal cells and are normally transmitted through mitoses. ▶**vectors**, ▶**retroviruses**, ▶**viral vectors**, ▶**double-targeted vector**, ▶**epitope**, ▶**SV40**, ▶**mycophenolic acid**, ▶**MoMuLV**, ▶**lentiviral vectors**, ▶**foamy viral vectors**, ▶**ψ**, ▶**SIN vector**, ▶**E vector**, ▶**double-copy vector**, ▶**IRES**, ▶**packaging cell lines**, ▶**gene therapy**, ▶**gene marking**, ▶**pseudotyping**, ▶**Ty**, ▶**pol III**, ▶**LCR**, ▶**insulator**, ▶**inducible gene expression**, ▶**cancer gene therapy**, ▶**biohazards**, ▶**laboratory safety**; Yee J-K 1999, p 21 In: Friedmann T (Ed.) *Development of Human Gene Therapy*, Cold Spring Harbor Laboratory Press; Smyth TN (Ed.) 2004 *Gene and Gene Therapy*, Marcel Dekker, New York; Somia N 2004 *Methods Mol Biol* 246:463.

Retroviruses (Retroviridae): These include onco-, lenti- and spumaviruses. In eukaryotes they contain dimeric single-stranded RNA, which is processed by a stringent switch (Badorrek CS et al 2006 *Proc Natl Acad Sci USA* 103:13640) as the genetic material that is replicated through a double-stranded DNA intermediate with the aid of a reverse transcriptase enzyme. Retrovirus reverse transcription usually takes place after the host has been infected. In the human foamy virus (spumavirus), the infectious particles already carry a double-stranded DNA, indicating that reverse transcription precedes infection. Besides the polymerase gene (*pol*), they all carry group-specific antigen (*gag*) and envelope (*env*) protein genes. These three viral components are

active in trans whereas the other elements require cis position. A provirus introduced into a cell by retroviral infection may become a retrotransposon (e.g., Ty element in yeast, copia in *Drosophila*). They are characterized by long terminal repeats (LTR), measuring a few thousand nucleotides in length. For infection to proceed, the viral capsid protein fiber and knob must find an appropriate receptor on the surface of the target cell.

When the virus enters the host cell its RNA genetic material is converted into double-stranded DNA, and it may be covalently integrated into a host chromosome. Although the targets for integration are spread all over the genome, transcriptionally active regions are preferred. Integration “hot spots” in chicken cells may be used by RSV a million times more often than expected by chance alone, and some sequences in mouse cells (e.g., the HGPRT gene) may be avoided. After a cell is infected by a single virion, in a day, thousands of viral particles may be produced.

Retroviruses are considered to be diploid (dimeric) because they have a pair of genomes, two identical size RNAs of 7 to 9 kb. All retroviruses minimally encode a protease, a polymerase, ribonuclease H activity of the reverse transcriptase and an integrase function. A generalized structure of retroviruses is presented in Figure R53 (individual types may display variations of this scheme):

The three proteins: gag (group-specific antigen) a polyprotein, pol (polymerase, reverse transcriptase), env (envelope protein) are transcribed in different, overlapping reading frames and then for RNA packaging into virion. The genomic subunits are the same as the mRNA, i.e., they are (+) strands. The transcript RNA has a 7-methyl-guanylate group at the 5' end and a 100 to 200 polyA tract at the 3' end, similar to eukaryotic mRNAs. The different retroviruses code for various proteins with known or yet to be identified functions. The gag-pol polyprotein complex contains



Figure R53. At the two ends of the viral genome are the *long terminal repeats* (LTR) of 2 to 8 kb. At the left and right termini of the LTRs are *attU3* and *attU5*, respectively for the attachment of the U3 (170 to 1,200 nucleotides) and U5 (80 to 120 nucleotides) direct repeats of the provirus in the host DNA. The *att* sequences at the 3' end of U5 and at the 5' end of U3' contain usually imperfect, inverted repeats where viral DNA joins the host DNA at 2 nucleotides from these ends. The terminal repeats represented by *R* (10 to 230 nucleotides) are used for the transfer of the DNA during reverse transcription. *E*: transcriptional enhancer, *P*: promoter, *PA*: signal for RNA cleavage and polyadenylation. *PBS*: binding site for tRNA primer for first strand DNA synthesis (different retroviruses use the 3'-OH end of different host tRNAs for initiation). *PPT*: polypurine sequences, which prime the synthesis of the second strand of DNA. *SD*: splice donor (the site where *gag* and *pol* and *env* messages are spliced). *SA*: splice acceptor site (the site where the second splice site joins to the first [donor] site)

information on proteolytic activities that generates a *protease* from the carboxyl end of gag and some other proteins. *Reverse transcriptase* (RT) and *integrase* (IN) and a *protease* are generated by proteolysis from the translated *pol* gene product. The SU product of the *env* gene recognizes the retroviral receptors which are transmembrane proteins of the host. The nucleocapsid proteins remain attached to the proviral DNA and facilitate the integration of the viral DNA into the host DNA. Some of the murine leukemia viruses can enter the cell nucleus only when the nuclear membrane breaks down during mitosis. Some of the lentiviruses can enter the nucleus with the assistance of the integrase and other proteins. In the human foamy virus the pol protein is translated by splicing mRNA that does not include the gag domain. The reverse transcriptase varies among the different retroviruses. The Rous sarcoma virus RT contains a RNA and DNA-directed polymerase, a RNase H as well as a tRNA-binding protein. It works with either RNA or DNA primers and synthesizes up to 10 kDa molecules from single RNA priming sites. For transcription of the viral proteins, the host RNA polymerase II is utilized. The host machinery translates the viral transcripts. The proteins may be processed in different ways by proteolysis to become functional.

Actinomycin D inhibits the replication on the DNA but not on the RNA template. Azidothymidine (AZT) inhibits polymerization and viral replication. The RNase H activity removes RNA in both 5' to 3' and 3' to 5' and digests the cap, tRNA and the polyA tail. All

retroviruses have an integrase protein derived from the C end of the gag-pol polyprotein complex. Integrase (30 to 46 kDa protein with Zn fingers) inserts the virus into the eukaryotic chromosomes (see Fig. R54).

At the site of integration there is target-duplication as the recessed ends of the target filled in by complementary nucleotides (*in italics*) (see Fig. R55). Inside the chromosomes of the host the retroviral *provirus* still carries the LTRs at both ends. After transcription, viral RNAs are produced. Following proteolytic cleavage, the polyproteins can be converted into viral proteins with the assistance of the cellular machinery. Viral particles (virions) may be assembled from the viral RNA and viral proteins at the surface of the cell and virions can exit from the cell membrane by “budding” and can infect new cells with two single-stranded RNA copies through appropriate cellular receptors.

The retroviral genome has 10^5 times increased mutability compared to cellular genes. Retroviral genomes recombine with a frequency of 10 to 30% during each cycle of replication. Integration may have a profound effect on cellular genes; it may inactivate suppressor genes controlling cellular proliferation or it may activate the transcription of cellular genes with the same effect and thus initiate carcinogenesis.

The major types of retroviruses are: (i) bird's (avian) sarcoma and leukosis viruses such as Rous sarcoma virus (RSV), avian leukosis virus (ALV) and Rous-associated viruses (RAV 1 and 2), (ii) reticuloendotheliosis viruses (hyperplasia of the net-like

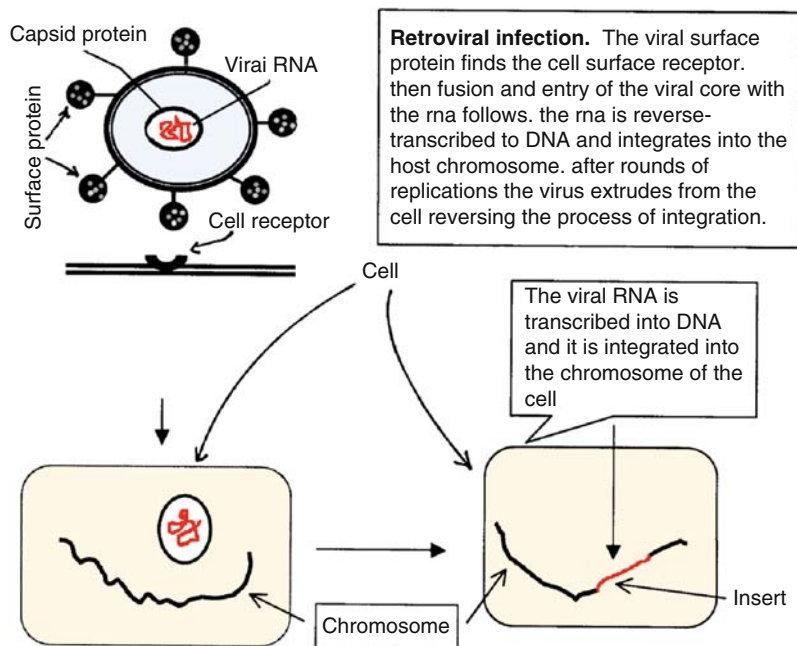


Figure R54. Retroviral integration

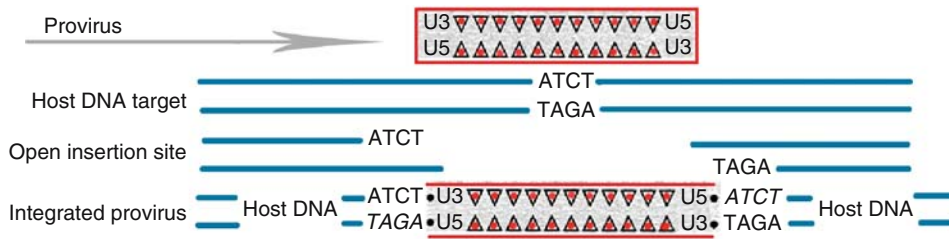


Figure R55. Integration of the provirus into the host DNA

and endothelial [tissues lining organ cavities]), e.g., spleen necrosis virus (SNV), (iii) mammalian leukemia and sarcoma viruses, e.g., Moloney murine sarcoma virus (Mo-MSV), Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (Ha-MSV), Friend spleen focus-forming virus (FSFFV), feline leukemia virus (FLV), and simian sarcoma-associated virus (SSAV), (iv) mammary tumor viruses (MMTV), (v) primate-type D viruses, e.g., Mason-Pfizer monkey virus (MPMV) and simian retrovirus (SRV-1), (vi) human T-cell leukemia-related viruses (HTLV-1 and HTLV-2), simian T cell leukemia virus (STLV) and bovine leukemia virus (BLV), (vii) immunodeficiency and lentiviruses, e.g., human immunodeficiency viruses (HIV-1 and HIV-2), Visna virus, simian immunodeficiency virus (SIV), caprine (goat) arthritis - encephalitis virus (CAEV) and equine (horse) infectious anemia virus (EIAV). (Classification provided by Varmus H, Brown P 1989). About 1% of the human genome includes retroviral sequences (human endogenous retroviruses [HERV]). During evolution these elements presumably inserted themselves and have been extensively modified. These HERV elements gave rise to transposable elements or their pseudogenic forms in the modern genome. The endogenous viruses synthesize the gag and env proteins that not only enables them to become infective, but may also prevent their transposition. The Env protein may also interfere with the viral receptors and thus limit reinfection. The HERV do not seem to have much significance for the genome at present; however, retrotransposition may lead to mutation and loss of gene function, including loss of cancer gene suppression. The resistance alleles block the integration of the viral RNA. The HIV-1 retrovirus usually integrates within the transcriptional unit of a gene. In contrast the murine leukemia virus (MLV) preferentially integrates into or around the promoter of the gene rather than into the translational unit. Typical retroviruses do not occur in plants, however the *Athila* elements of *Arabidopsis* and the *SIRE-1* of soybean come close to retroviruses in as much as they harbor envelop-like genes. ▶overlapping

genes, ▶retroposon, ▶retrotransposon, ▶retrogene, ▶hybrid dysgenesis, ▶copia elements, ▶LINE, ▶reverse transcription, ▶retroviral vectors, ▶oncogenes, ▶tumor viruses, ▶cancer, ▶HTDV, ▶animal viruses, ▶plant viruses, ▶pararetrovirus, ▶nucleocapsid, ▶knob; Knipe DM, Howley PM (Eds.) 2001 Fundamental Virology, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania.

Retrovirus Resistance: In general this is controlled by dominant genes in the animal host. In mice a major gene is *Fv1*, which has the *Fv1ⁿ* allele permitting the replication of the NIH Swiss mice N-tropic viruses but blocking the replication of the B-tropic (Balb/c mouse) viruses. The *Fv1^b* allele allows the replication of the B-tropic virus strains but blocks the N-tropic strains. The *n* and *b* alleles are codominant and their difference is only at two positions of their sequence. The *Fv1⁰* allele does not restrict any virus strains. The resistance genes block the integration of the cDNA of the viral genome into the host nucleus or host chromosome. Tropism may depend on a single amino acid difference of a domain of the group-specific antigen. High infection titer may, however, overcome the restriction. In human and some animal cells REF1 gene is credited with a function similar to that of *Fv1*. TRIM5α family of proteins controls simian resistance to HIV or other lentiviruses. Gene Lv2 provides resistance against HIV-2. APOBEC3G (apolipoprotein B mRNA-editing complex) fights the virus by deaminating the cytosine residues to uracil in the DNA and U-glycosylase generates an abasic site. The deficient provirus fails to code for the required proteins. An active *Vif* gene can, however, deactivate APOBEC3G. The BAF protein (barrier to autointegration factor) may prevent the viral DNA integration into the host chromosome.

Cyclophilin may have the opposite effect and can facilitate retroviral infection. Importin 7 protein may facilitate the access of HIV-1 to the nucleus. A number of other proteins may affect the infection process. ▶acquired immunodeficiency, ▶tropic, ▶provirus, ▶cyclophilins, ▶APOBEC3, ▶RNA editing; Goff SP 2004 Annu Rev Genet 38:61.

Rett Syndrome (dominant, RTT, Xq28, Xp22): This is a neurological disorder with onset after a period of normal early development. Loss of speech, motor skills, constant wringing of the hands, seizures and mental retardation are observed predominantly in girls. The prevalence rate is $\sim 1\text{--}2 \times 10^{-4}$ among girls, and in 99.5% cases is caused by new mutations occurring predominantly in the paternal X chromosome. The biochemical basis is missense or nonsense mutation in the meCP2 gene encoding a methyl-CpG-binding protein, which regulates BDNF and thus controls the syndrome (Martinowich K et al 2003 Science 302:890). MeCP2 interacts with transcriptional activators and silencers, chromatin remodeling factors—histone deacetylase and histone methyl transferase. In Rett syndrome homologous pairing in the 15q11-13 (imprinted site of Angelman's syndrome) is impaired (Thatcher KN et al 2005 Hum Mol Genet 14:785). In some atypical cases cyclin-dependent kinase 5 gene is involved (Guy J et al 2001 Nature Genet 27:322). ▶autism, ▶BDNF, ▶meCP2, ▶methylation of DNA, ▶Angelman's syndrome, ▶imprinting; Wan M et al 1999 Am J Hum Genet 65:1520; Meloni I et al 2000 Am J Hum Genet 67:982; Trappe R et al 2001 Am J Hum Genet 68:1093; Chen RZ et al 2001 Nature Genet 27:327; Shahbazian MD et al 2002 Hum Mol Genet 11:115; Bienvenu T, Chelly C 2006 Nature Rev Genet 7:415.

REV1, REV3, REV7: These are subunits of DNA polymerase ζ . REV1 is involved in DNA repair mutagenesis. This polymerase—unlike others—uses aginine³²⁴ for template after the guanine at its place is ejected and joins it by complementary hydrogen bond to deoxycytidine triphosphate (Nair DT et al 2005 Science 309:2219). Rev1 translesion DNA polymerase is functional primarily during the G₂/M phase of the cell cycle rather than during the S phase (Waters LS, Walker G C 2006 Proc Natl Acad Sci USA 103:8971). ▶DNA polymerases, ▶translesion, ▶SOS repair, ▶Y-family DNA polymerases; Lawrence CW, Hinkle DC 1996 Cancer Surv 28:21; Murakumo Y et al 2001 J Biol Chem 276:35644; Masuda Y, Kamiya K 2002 FEBS Lett 520:88.

Rev: This splicing element was originally identified in viruses. It assists exports through the nuclear pore. ▶RNA export, ▶nuclear pore

Reversal of Dominance: ▶dominance reversal

Reverse Array: This is a tissue lysate (rather than cells) blotted on a solid support for protein analysis. ▶protein

Reverse Dot Blot: ▶colony hybridization

Reverse Endocrinology: Using orphan receptors new hormones and ligands may be searched for and studied. ▶orphan receptors, ▶endocrinology

Reverse Genetics: ▶reversed genetics

Reverse Ligase-Mediated Polymerase Chain Reaction (RL-PCR): When the beginning target mRNA is cleaved at a known location the RL-PCR method generates a product of a predictable length in the presence of an appropriate linker and a nested primer. The linker is a probe for synthesized strand. ▶polymerase chain reaction, ▶nested primer, ▶RACE; Bertrand E et al 1997 Methods Mol Biol 74:311.

Reverse Linkage: ▶affinity

Reverse Mosaicism: Secondary mutation(s) restore(s) wild type function to a nucleotide sequence without returning to the wild type nucleotide or amino acid sequence. Such somatic mosaicism may also be produced by intragenic mitotic recombination, gene conversion frameshift mutation or some type of compensatory sequence alterations in the gene as shown in the box. The substituted nucleotides are in lower case, the “mutant” is in bold and the “revertant” alteration in outline letters (see Fig. R56) (Data after Waisfisz Q et al 1999 Nature Genet 22:379).

| | |
|--------------------|----------------------------------|
| Wild type | DNA...TTC.CTG.CTC.TGG.GCT |
| Amino acids | F L L W A |
| Mutant | DNA TTC.CTG. CgC .TGG.GCT |
| Amino acids | F L R W A |
| Revertant | DNA TTC.CTG. tgC .TGG.GCT |
| Amino acids | F L C W A |

Figure R56. Reverse mosaicism

Reverse Mutation (backmutation): This is a change from mutant to wild type allele, $a \rightarrow A$. In the experiment shown in the photo thiamine prototrophs were selected on soil among thiamine auxotrophs (see Fig. R57). The thiamine mutants died in the absence of thiamine but the revertants grew normally. The material was genetically marked at both flanks 5 and 9 map units, respectively to verify that the apparent revertants were not contaminants. The progeny of the revertants were genetically analyzed. They segregated for auxotrophy and prototrophy in the proportion of 5:3 because at the time of the reversion the diploid germ line consisted of two diploid cells. One of the cells remained

homozygous for thiamine requirement and the other became heterozygous and segregated for 3 wild type (2 heterozygotes) and for one homozygous for thiamine auxotrophy. ►Ames test, ►mutant isolation, ►mutation, ►suppressor gene



Figure R57. Reverse mutation of *Arabidopsis* thiamine mutant

Reverse-Phase Protein Array (RPPA): Samples to be assessed are robotically spotted, and an antibody is used to measure the amount of a particular protein present in the sample. In contrast to 2D-PAGE and antibody arrays, the reverse-phase methodology assesses only one protein per slide, but its advantage is that all the cell or tissue samples can be analyzed side by side in a single array. This is particularly useful in functional studies where protein levels are compared across samples rather than samples compared across protein types. This method—with modifications—has been successfully used for the study of cancer and normal cells and the progression of cancer development as well as prognosis. ►gel electrophoresis, ►microarray hybridization; Nishizuka S et al 2003 Proc Natl Acad Sci USA 100:14229.

Reverse Transcriptases: These enzymes transcribe DNA on a RNA template. An outline of the function of the enzymes within the protein coat using the diploid template is presented here. A similar process is followed in in vitro assays. Reverse transcriptases are commercially available from purified avian myeloblastosis (cancer of the bone marrow) cells or as cloned Moloney murine leukemia virus (MoMLV) gene product. The avian enzymes are dimeric and have strong reverse transcriptase and RNase H activities. The murine polymerase is monomeric

and exhibits only weak RNase H activity. Therefore, the murine enzyme is preferred when mRNA is transcribed into cDNA. Also, RNase H can degrade DNA and may reduce the efficiency of cDNA synthesis. The temperature optimum of the avian enzyme is 42° C (pH 8.3) and at this temperature the murine enzyme is already degraded. The pH optimum for the murine enzyme is 7.6. Both enzymes have much lower activity slightly below or above the pH optima. The avian enzyme more efficiently transcribes structurally complex RNAs. Reverse transcriptases are used for generating DNA from mRNA for vector construction or generating labeling probes, for primer extension, and for DNA sequencing by the dideoxy chain termination method. Since reverse transcriptase does not have an editing (exonuclease) function, it may make errors at the rate of 5×10^{-3} to 1×10^{-6} per nucleotide. This rate is orders of magnitudes higher than the error rate of most eukaryotic replicases. The HIV-1 reverse transcriptase can use as template either RNA or DNA; in the latter case it makes double-stranded DNA. Nucleoside analog-induced inhibition is effective for fighting HIV proliferation. This treatment, however, increases mutation in mtDNA because it also inhibits DNA polymerase γ (Martin AM et al 2003 Am J Hum Genet 72:549). ►retroviruses, ►cDNA, ►central dogma, ►msDNA, ►error in replication. Reverse transcriptase action is given in Figure R58.

Reverse transcription of the retroviruses follows the generalized scheme. A single-stranded viral RNA (vvvv) serves as template for the synthesis of the first strand DNA ($\rightarrow\rightarrow\rightarrow$). The synthesis is primed by a tRNA attached to the PBS (primer-binding site of the retroviral [-] strand). The host tRNA is base-paired by 18 nucleotides to a sequence next to U5. The first strand DNA (also called strong stop minus DNA) is extended at the rate of about 2 kb per h until the last part of the primer-binding site is copied. When the synthesis is extended, the copying of the second DNA strand ($\leftarrow\leftarrow\leftarrow$) begins. The process is practically the same in the cell and in vitro conditions. DNA polymerases β and γ also have some reverse transcriptase function in as much as they can copy poly(rA) by using oligo-dT primer. ►retroviruses, ►telomerase, ►transposon, ►DNA polymerases, ►mtDNA, ►HIV; Whitcomb JM, Hughes SH 1992 Annu Rev Cell Biol 8:275; Gao G, Goff SP 1998 J Virol 72:5905; Vastmans K et al 2001 Nucleic Acids Res 29:3154.

Reverse Transfection: Specific cDNAs or RNAs encapsulated in lipid are placed at defined locations on a glass slide and cells are layered on top. The cells can be transfected by the genes or by silencing RNAs. The cells isolated can then express mRNAs or

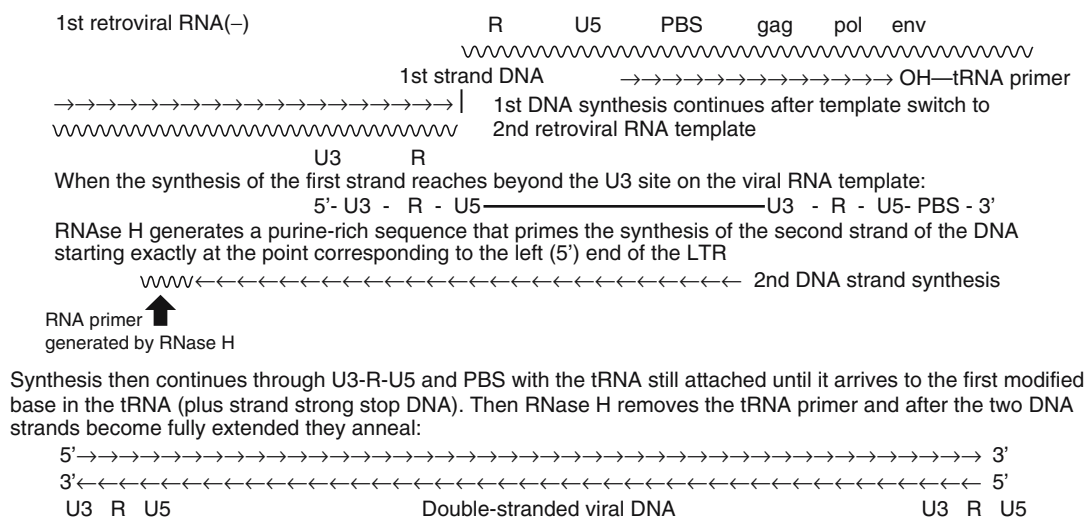


Figure R58. Reverse transcription

the silencing RNAs on microarrays. Nucleic acids when labeled by fluorescent tags can be specifically recognized. This procedure assists in the identification of drug targets or specific gene products controlling metabolism. ▶[transfection](#), ▶[RNAi](#), ▶[microarray hybridization](#); Ziauddin J, Sabatini DM 2001 Nature [Lond] 411:107.

Reverse Translation: If the protein is sequenced and the amino acids of a short segment are coded by non-degenerate or moderately degenerate codons, it is possible to synthesize a few RNAs on the basis of the presumed codon sequences, and one of them may be complementary to the DNA. This short RNA sequence can be hybridized to the DNA that codes for this particular protein. By reversing the translation and generating an appropriate probe, the gene can be isolated. ▶[probe](#), ▶[synthetic probe](#)

Reverse Two-Hybrid System: The system monitors disruptions of protein-protein interactions. ▶[two-hybrid system](#)

Reversed Genetics (inverse genetics): Nucleic acids and proteins, etc. are first isolated and characterized in vitro by molecular techniques and subsequently their hereditary role is identified. Also, gene expression can be studied by introducing into cells, by transformation, reporter genes with truncated upstream or downstream signals, in vitro generated mutations, site-specific recombination, targeting genes, etc., thereby determining the functional consequences of these alterations. Briefly stated, reversed genetics starts with molecular information and then deals with its biological role. Classical (forward) genetics recognizes genes when mutant forms become available and then studies their transmission, chromosomal location,

mechanism of biochemical function, their fate in populations and evolution. Reversed genetics is sometimes called surrogate genetics. ▶[genetics](#), ▶[inheritance](#), ▶[heredity](#); Masters PS 1999 Adv Virus Res 53:245.

Reversion: Refers to backmutation either at the site where the original forward mutation took place or in another (tRNA) gene that may act as a suppressor tRNA or the reversion is caused by correcting the frameshift. The possibility of reversion is frequently considered as evidence that the original forward mutation was not caused by a deletion. Suppressor mutation outside the mutant locus, however, may restore the non-mutant phenotype. Reversion may also take place when the mutation was caused by a duplication and a deletion evicted the duplicated sequence. ▶[backmutation](#), ▶[base substitution](#), ▶[suppressor](#), ▶[sup](#), ▶[suppressor tRNA](#), ▶[frameshift](#), ▶[reverse mutation](#), ▶[Ames test](#)

Reversion Assays in *Salmonella* and *E. coli* in Genetic Toxicology: The *Salmonella* assay has been described by the Ames test. The most commonly used *E. coli* test employs strains WP2 and WP2_{uvrA} that are deficient in genetic repair and are auxotrophic for tryptophan. They detect base substitution revertants but the assay does not respond to most frameshift mutagens (unlike some of the *Salmonella* strains TA97, TA98, TA2637 and derivatives). The *E. coli* systems do not offer any advantage over that of the *Salmonella* assay of Ames. ▶[Ames test](#), ▶[bioassays in genetic toxicology](#), ▶[mutation detection](#)

Rex Color: Refers to the color of rodent (rabbit) hair which appears in the presence of the recessive fine fur gene, *r*, in certain combinations with black (*B/b*), agouti (*A/a*) and intensifier (*D/d*).

Rex1p, Rex2p, Rex3p: These are exoribonuclease members of ribonuclease D family. ▶[ribonuclease D](#)

Rexinoids: These are agonists of RXR retinoid X receptor and regulate cholesterol absorption and bile acid metabolism/transport. ▶[agonist](#), ▶[retinoic acid](#)

Reye's syndrome: This disorder is characterized by non-genetic inflammation of the brain in infants and may lead to fever, vomiting, coma and eventually death. The use of aspirin is contraindicated in this condition. ▶[acetyl-CoA dehydrogenase deficiency](#)

Reynaud Disease: ▶[Raynaud's disease](#)

Reynolds Number: Characterizes the flow of a liquid from laminar to turbulent flow or the other way around. Reynolds number is a characteristic of the viscous drag (resistance) on a structure through a fluid medium like the cellular plasma.

RF (release factor): A protein which mediates the release of the peptide chain from the ribosome after it recognizes the stop codons. ▶[translation termination](#), ▶[release factors](#), ▶[protein synthesis](#), ▶[transcription termination in prokaryotes](#), ▶[transcription termination in eukaryotes](#); Dontsova M et al 2000 FEBS Lett 472:[2–3]:213.

RF: A replicative form of single-stranded nucleic acid viruses (DNA or RNA) where the original single strand makes a complementary copy that serves as a template to synthesize replicas of the first (original) genomic nucleic acid chain. ▶[replicase](#), ▶[plus strand](#); Buck KW 1999 Philos Trans R Soc Lond B Biol Sci 354:613.

Rf: Refers to fertility restorer genes in cytoplasmic male sterility. ▶[cytoplasmic male sterility](#)

R

Rf Value: In paper or thin-layer chromatography, the distance from the baseline of the migrated compound divided by the distance of migration of the solvent (mixture) is the Rf value. This value which is always less than 1 is characteristic of a particular compound within a defined system of chromatography. ▶[paper chromatography](#), ▶[thin-layer chromatography](#), see Fig. [R59](#).

RF-A: Replication factor A is a human single-stranded DNA binding protein, auxiliary to pol α and pol δ .

▶[pol](#), ▶[helix destabilizing protein](#), ▶[replication](#), ▶[replication fork eukaryotes](#)

RFA (replication factor A): This is the same as replication protein A (RPA). ▶[DNA replication eukaryotes](#)

Rfam: This is the database of non-coding RNAs. ▶[non-coding RNA](#); <http://rfam.janelia.org/>.

RF-C: Denotes the DNA replication factor C, a primer/template binding protein with ATPase activity. It plays a primary role in replicating the leading strand DNA in eukaryotes. RF-C loads PCNA on the DNA that tethers the DNA polymerase to the replication fork. RF-C is also called Activator I. ▶[replication fork](#), ▶[PCNA](#); Mossi R, Hubscher U 1998 Eur J Biochem 254:209.

RF-C (also RF-C): This is a cellular replication factor. ▶[DNA replication eukaryotes](#); Schmidt SL et al 2001 J Biol Chem 276:34792.

RFLP (restriction fragment length polymorphism): Restriction endonuclease enzymes cut the DNA at specific sites and thus generate fragments of various sizes in their digest, depending on the distances between available recognition sites in the genome. During evolution when base changes occurred at the recognition sites through mutation, the length of fragments (within related strains) may have changed. After electrophoretic separation, a polymorphic pattern may be distinguished. These fragments may constitute co-dominant molecular markers for genetic mapping. Restriction fragment maps can also be generated by strictly physical methods. If a small circular DNA is completely digested by a restriction enzyme yielding fragments, say A, B, C, D, E but incomplete digestion with the same enzyme produces ABD, DB, AD, BC and CE triple or double fragments, respectively but never AB, BE, DC or AC. Thus, the fragment sequence must be ADBCE because the double fragments must be neighbors. Another procedure is to digest by at least two enzymes and determine the overlaps by hybridization in a sequential manner. The overlapping fragments indicate which fragments are next to each other (see Fig. [R60](#)).

$$R_f = \frac{\text{distance} - B}{\text{distance} - A}$$

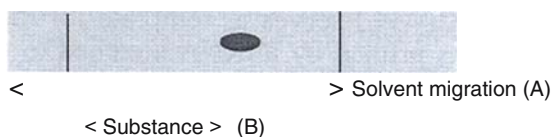


Figure R59. Definition of Rf



Figure R60. Restriction fragment length of the same DNA depending of the enzyme used

Restriction fragments can be used in genetic linkage analysis. They represent “dominant” physical markers because the DNA fragments can be recognized in heterozygotes. RFLP markers are useful for following the inheritance of linked genetic markers, which have variable expressivity and/or penetrance under unfavorable conditions. *Long-range restriction map* (macro-restriction map) represents the cutting sites of restriction enzymes along the chromosome. ▶restriction enzymes, ▶restriction fragment number, ▶restriction fragment length, ▶physical map, ▶T-RFLP; Sharma RP, Mohapatra T 1996 *Genetica* 97[3]:313; Wicks SR et al 2001 *Nature Genet* 28:160.

RFLP Marker: A restriction enzyme-generated DNA fragment which has been or can be mapped genetically to a chromosomal location and can be used for determining linkage to it. They are codominant and always expressed. Their inheritance and recombination can be determined in relatively small populations. ▶restriction enzyme, ▶RFLP, ▶physical map, ▶integrated map

RFLP Subtraction: A selective technique for the enrichment of particular polymorphic, eukaryotic genomic unique segments. Small restriction fragments are isolated and purified from one genome containing sequences that are in large fragments in another related genome of mouse. By subtractive hybridization the segments with shared sequences by both genomes are removed. Thus, small fragments unique to one or the other strain are obtained. These sequences then become mappable genetic markers. ▶genomic subtraction; Rosenberg M et al 1994 *Proc Natl Acad Sci USA* 91:6113.

RFLV: This is a RFLP variant. ▶RFLP

RFX: A human DNA binding protein that promotes dimerization of MYC and MAX and thus stimulates transcription. A group of transcription factors for the major histocompatibility complex is also designated as RFX. RFX binds cooperatively with NF-Y and X2BP. RFX has four complementation groups (CIITA [16p13], RFX5 [1q21.1-q21.3], RFXAP [13q14], RFXANK [19p12]). Their defects may be responsible for autosomal immunodeficiency syndrome. The RFX factor binds to X-boxes (5'-GTNRCC[0-3N] RGYAAC-3'] where N = any nucleotide, R = purine and Y = pyrimidine. The human RFX1 is a helix-turn-helix protein, which uses a β -hairpin (called also a wing) to recognize DNA. ▶MYC, ▶MAX, ▶MHC,

▶immunodeficiency, ▶bare lymphocyte syndrome, ▶helix-turn-helix, ▶MYC, ▶MAX, ▶NF-X, ▶X2BP; Katan-Khaykovich Y, Shaul Y 2001 *Eur J Biochem* 268:3108.

RGD: An amino acid sequence Arg-Gly-Asp in the extracellular matrix and in fibronectin is recognized by, and bound to, integrin. RGD peptides can activate caspase-3 and initiate the apoptotic pathway. RGD peptides may facilitate cell adhesion, uptake of viral vectors or polycationic synthetic vectors. ▶fibronectin, ▶integrin, ▶apoptosis, ▶amino acid symbols in protein

RGE (rotating gel electrophoresis): The gel is rotated 90° at switching the cycle of the electric pulses. ▶pulsed field gel electrophoresis

rGH (rat growth hormone): A thyroid hormone. ▶animal hormones, ▶hormone receptors, ▶hormone-response elements

RGR: A yeast gene regulating transcription by RNA polymerase II. ▶NAT, ▶RNA polymerase

RGR (retinal G protein-coupled receptor): An opsin protein encoded at human chromosome 10q23. (See Chen XN et al 1996 *Hum Genet* 97:720).

RGS (regulator of G protein signaling): RGS is actually the same as GAP (GTP-ase activating protein). The different RGS proteins have different specificities for the different $\alpha\beta$ and γ subunits of the trimeric G proteins. In mammals there are at least 19 members of this family of proteins with a common core, the RGS box. ▶G proteins, ▶GAP, ▶signal transduction, ▶conductin; Kehrl JH, Sinnarajah S 2002 *Int J Biochem Cell Biol* 34:432.

RH: ▶radiation hybrid

Rh Blood Group: The name comes from a misinterpretation of the early study, namely that this human antigen would have the same specificity as that of rhesus monkey red cells. It is now known that this was incorrect; the animal antigen is different but the name was not changed. Despite over half a century of research the Rh antigen is not sufficiently characterized. The antigen may be controlled by three closely linked chromosomal sites—C, D and E—and on this basis eight (2^3) different allelic combinations were conceivable; the triple recessive *cde* being a null combination. The eight combinations are also designated as R or r with superscripts: *CDe* (R^1 or $R^{1,2,-3,-4,5}$), *cde* (r , or $R^{-1,-2,-3,4,5}$), *cDE* (R^2 or $R^{1,-2,3,4,-5}$), *CDe* (R^0 or $R^{1,-2,-3,4,5}$), *cDe* (r' or $R^{-1,-2,3,4,-5}$), *Cde* (r' or $R^{-1,2,-3,-4,5}$), *CDE* (R^2 or $R^{1,2,3,-4,-5}$) and *CdE* (r^y or $R^{-1,2,3,-4,-5}$). The first three of these occur at frequencies about 0.42, 0.39, and 0.14, respectively in England, and the others

are quite rare. In some oriental populations, R^1 (0.73%) and R^2 (0.19%) predominate and the recessives have a combined frequency of about 2%. This is in contrast to Western populations where they occur in over 40% of people. Clinically the most important is the D antigen because 80% of the D⁻ individuals, in response to a large volume of D⁺ blood transfusion, make anti-D antibodies. The *d* alleles are amorph. The Rh genes are in human chromosome 1p. In addition, regulatory loci have also been identified in chromosome 3. For phenotypic distinction antisera anti-D, anti-C, anti-E, anti-c, and anti-e are used, and on the basis of the serological reactions 18 phenotypes can be distinguished. Anti-D antibodies are usually immunoglobulins of the G class (IgG). They develop only after immunization by Rh⁺ type blood. Anti-C antibodies are generally of IgM type and they occur along with IgG after an Rh⁻ person is immunized with Rh⁺ blood. Anti-E antibodies (IgG) are elicited in E negatives after exposure to E⁺ blood. Anti-c antibodies (IgG) occur in CDe/CDe individuals after transfusion with c⁺ erythrocytes. Anti-e antibodies are very rare (0.03). The major types of Rh antigens have several different variations. The Rh antigens are probably red blood cell membrane proteins. About 50 different Rh antigens have been identified. An Rh deficiency may also arise by the activity of a special suppressor gene in human chromosome 6p11-p21.1 or by CD47 protein, encoded at human chromosome 3q13.1-q13.2. The RG gene is situated at 1p34.3-p36.1.

It is clinically very significant that about 15% of Western populations are *cde/cde*. In Oriental populations the frequency of this genotype is very low. This type of individuals—called Rh negatives—may respond with erythroblastosis when exposed to Rh positive blood. If an Rh negative female carries a fetus with Rh positive blood type, antibodies against the fetal blood may be produced by the mother. This may then cause severe anemia with a high chance of intrauterine death and abortion. Generally, during the first pregnancy, this hemolytic reaction is absent but the chance in the following pregnancies, by when sufficient immunization has taken place by the fetal blood entering into the maternal bloodstream, the probability of erythroblastosis becomes high. Thus pregnancies of Rh negative females are monitored and appropriate serological treatment provided if antibody production is detected to prevent fetal erythroblastosis. Erythroblastosis may also occur if an Rh negative individual is transfused with Rh positive blood. The rodent antibodies responding to rhesus monkey red cells are now called the LW blood group. The physiological role of the Rh antigens is apparently in the CO₂ gas channel. ▶erythroblastosis fetalis, ▶blood groups, ▶immunoglobulins, ▶antibodies,

▶schizophrenia, ▶eclampsia; Avent ND 2001 J Pediatr Hematol Oncol 23:394; Stockman JA 3rd, de Alarcon PA 2001 J Pediatr Hematol Oncol 23:385, evolution of the Rh proteins: Huang C-H, Peng J 2005 Proc Natl Acad Sci USA 102:15512.

Rhabdomere: A rod-shaped element of the compound eye of insects. There are eight R1 to R8 neuronal photoreceptors in each of the ca. 20 cells of the *Drosophila* eyes, containing about 800 ommatidial clusters. ▶compound eye, ▶ommatidium, ▶*Drosophila*, ▶sevenless

Rhabdomyosarcoma: A type of cancer involving chromosome breakage in the Pax-3 gene 2q35 and 13q14 (Rhabdomyosarcoma-2) or other translocations involving chromosome 3 and 11 (Rhabdomyosarcoma-1). These break points may also be related to the Beckwith-Wiedemann syndrome or WAGR syndrome. The malignant rhabdoid tumor is associated with deletions in human chromosome 22q11.2 encoding the homologue (hSNF5/INI1) of the yeast chromatin remodeling protein SWI/SNF. Embryonal rhabdomyosarcoma is due to a defect at 11p15.5. Isochromosome 3q has the same effect as mutation at the ATR (ataxia telangiectasia and rad3-related site), i.e., inhibiting MyoD (myogenesis), causing cell cycle abnormalities and predisposition to cancer. ▶Pax, ▶Beckwith-Wiedemann syndrome, ▶WAGR, ▶ataxia, ▶Wilms tumor, ▶chromatin remodeling, ▶SWI, ▶nucleosome, ▶histone, ▶nuclease-sensitive sites

Rhabdoviridae: Oblong or rod-shaped (130–380 × 70–85 nm), single-stranded RNA (13–16 kb) viruses with multiple genera and wide host ranges. ▶CO₂-sensitivity in *Drosophila*

Rhalloc: The sequences mapped by radiation hybrid methods by various mapping groups. ▶radiation hybrids

Rhdb: A database containing the mapping information obtained by radiation hybrids. ▶radiation hybrids

Rheology: The study of elasticity, change of shape, viscosity and flow of materials such as blood through the vascular system of veins and heart.

Rhesus Blood Group: ▶Rh blood group, ▶LW blood group

Rhesus monkey (Macaque, *Macaca mulatta*, 2n = 42, genome size ~2.87 Gb): A representative of mainly South-East Asian and North African species of long-tail monkeys. These small intelligent animals have been used extensively for biological and behavioral studies. Rhesus monkeys separated from the human lineage about 25 million years ago and yet they retained about 93% of their identity to humans. The

sequenced genome has revealed 100 different families of DNA transposons and more than half a million recognizable copies of endogenous retroviruses (ERVs). The analysis revealed more than 1,000 rearrangement-induced break points through the HCR (Human-Chimpanzee-Rhesus) lineages, of which 820 occur between rhesus and the reconstructed human-chimpanzee ancestor. As with humans and chimpanzees, the analysis of the macaque assembly revealed an enrichment of segmental duplications near gaps, centromeres, and telomeres. Some segmental duplications contain genes of high biological significance. The statistical approach revealed that 1,358 genes were gained by duplication along the macaque lineage. The average human gene differs from its ortholog in the macaque by 12 nonsynonymous and 22 synonymous substitutions, whereas it differs from its ortholog in the chimpanzee by fewer than three nonsynonymous and five synonymous substitutions. Similarly, 89% of human-macaque orthologs differ at the amino acid level, as compared with only 71% of human-chimpanzee orthologs. Thus, the chimpanzee and human genomes are in many ways too similar for characterizing protein-coding evolution in primates, but the added divergence of the macaque helps substantially in clarifying the signatures of natural selection. Important evolutionary differences from human genes responsible for the diseases, have been detected (Gibbs RA et al 2007 Science 316:222). ►Rh blood group, ►LW blood group, ►Cercopithecidae, ►primates, ►chimpanzee

Rheumatic Fever (rheumatoid arthritis, RA, 6p21.3):

Rheumatic fever consists of ailments affecting mainly the connective tissues and joints, but it may cause also heart and nervous system anomalies. The HLA region accounts for most of the susceptibility but regions associated with other autoimmune diseases (lupus erythematosus, inflammatory bowel disease, multiple sclerosis, ankylosing spondylitis) are also implicated. The disease is complex because environmental and susceptibility factors heavily confound the direct genetic determination. For example, certain streptococcal infections can precipitate rheumatic fever. The familial forms are attributed to dominant genetic factor(s) and susceptibility has been attributed to recessive genes(s). Several antigens have been identified which appeared to be more predominant within affected kindred. One monoclonal antibody, D8/17, was present in 100% of the patients affected with the disease whereas two other monoclonal antibodies showed up between 70% to 90% coincidence and with 17% to 21% presence even among the unaffected people. One susceptibility factor is linked to IL-3. Simultaneously, blocking both B and T cell

receptors by the signaling molecule BlyS (B lymphocyte stimulator) and TACI (transmembrane/T-cell-activator and calcium-modulating and cyclophilin ligand interactor) prevented the development of arthritis in mice (Wang H et al 2001 Nature Immunol 2:632; Yan M et al ibid 638). Peptidylarginine deiminases (encoded at 1p36) post-translationally convert arginine into citrulline. Citrullinated epitopes are common targets of arthritis-specific autoantibodies directed against perinuclear factor/keratin and against the Sa system (Suzuki A et al 2003 Nature Genet 34:395). Sa is a hapten-carrier antigen in which vimentin is the carrier and citrulline is the hapten. Various forms of tumor necrosis factor (TNF) inhibitors such as TNF monoclonal antibodies and methotrexate therapy (Keystone EC et al 2004 Arthritis Rheumatism 50:1400) and recombinant TNF receptor (TNFR) and immunoglobulin-G1 fragment crystalline (Fc) fusion protein have been successfully used for clinical treatments (Morteland LW et al 1997 New England J Med 337:141). Injecting an interleukin-1 receptor antagonist (IL-1 Ra) cDNA in a retroviral vector (derived from Moloney leukemia virus) in synovial fibroblasts was beneficial without side effects (Evans CH et al 2005 Proc Natl Acad Sci USA 102:8698). In mice who have been exposed daily to 10% ethanol in drinking water the development of erosive arthritis was almost totally abrogated and they did not display any liver toxicity. In contrast, the antibody-mediated effector phase of collagen-induced arthritis was not influenced by ethanol exposure. Also, the major ethanol metabolite, acetaldehyde, prevented the development of arthritis. This anti-inflammatory and anti-destructive property of ethanol was mediated by (1) down-regulation of leukocyte migration and (2) up-regulation of testosterone secretion, with the latter leading to decreased NF- κ B activation (Jonsson I-M et al 2004 Proc Natl Acad Sci USA 104:258). ►arthritis, ►rheumatoid, ►pseudorheumatoid dysplasia, ►ankylosing spondylitis, ►HLA, ►Coxsackie virus, ►IL-3, ►IL-32, ►autoimmune disease, ►citrullinemia, ►urea cycle, ►hapten, ►vimentin, ►keratin; Jawaheer D et al 2001 Am J Hum Genet 68:927; Okamoto K et al 2003 Am J Hum Genet 72:303.

Rheumatoid: Resembling a rheumatic condition.
►rheumatic fever

Rhinoceros: *Ceratotherium simum*, 2n = 84; *Rhinoceros unicornis*, 2n = 82; *Diceros bicornis*, 2n = 134.

Rhizobium: ►nitrogen fixation

Rhizofiltration: ►bioremediation

Rhizoid: A structure resembling plant roots.

Rhizome: An underground plant stem modified for storage of nutrients and propagation (see Fig. R61).



Figure R61. Rhizome

Rhizomorph: ►hypha

Rhizosphere: The environment around the roots of plants. ►microbiome

RHKO (random homozygous knockout): ►knockout

RhIB: A helicase of the DEAD-box family. ►helicase, ►DEAD-box, ►degradosome

RHMAP (radiation hybrid mapping): A multipoint radiation mapping procedure. It analyzes the minimal number of breaks (RHMINBRK) and may provide mapping information and by the use of the maximum likelihood procedure (RHMAXLIK) linkage information. ►radiation hybrid; Am J Hum Genet 49:1174.

RHMAXLIK: ►RHMAP

RHMINBRK: See ►RHMAP

Rho: A GTPase homolog of the RAS oncogene. It relays signals from cell-surface receptors to the actin cytoskeleton. It regulates myosin phosphatase and Rho-associated kinase. In yeast cells, a RHO protein is involved in the stimulation of cell wall β (1→3)-D-glucan synthase and the regulation of protein kinase C, and in mediation of polarized growth, morphogenesis and cell migration (metastasis). Actually, Rho is a subunit of the glucan synthase enzyme complex. Serine-threonine protein kinase and protein kinase N (PKN) are apparently activated by Rho. Rho also mediates endocytosis. Rho, in cooperation with RAF, seems to induce p21^{Waf1/Cip1} protein, which blocks the transition from the G₁ to the S phase of the cell cycle. In human chromosomes, Rhos are designated as ARH6: 3pter-p12, ARH12: 3p21, ARH9: 5q 31-qter. The Rho family includes Rac, CDC42, RhoG, RhoE, RhoL, and TC10 proteins. Increase of RhoC activity accompanies metastasis of melanoma cells. Members of the Rho family of proteins are also involved in the regulation of photoreception and developmental events mediated by light. ►RAS oncogene, ►metastasis, ►melanoma, ►RAF, ►cytoskeleton, ►receptor, ►photoreceptors, ►RAC, ►CDC42, ►endosome, ►CNF, ►p21, ►citron, ►ROCK, ►ROK, ►Yersinia; Kaibuchi K et al 1999 Annu Rev Biochem 68:459; Etienne-Manneville S,

Hall A 2002 Nature [Lond] 420:629; Katoh H, Negishi M 2003 Nature [Lond] 424:461.

rho (ρ): A designation of density; high G+C content of DNA increases it while high A+T content decreases it. ($\rho = 1.660 + [0.098 \times \{G+C\}]$ fraction in DNA). The density is determined on the basis of ultracentrifugation in CsCl and refractometry of the bands. ►buoyant density

rho Factor: A protein involved in the termination of transcription in (rho-dependent) prokaryotes. It is about 46 kDa and is a hexamer (~275 kDa). For maximal efficiency it is present in about 10% of the molecular concentration of the RNA polymerase enzyme. It is basically an ATP-dependent RNA-DNA helicase. Rho can stop elongation of the transcript only at specific termination sites in the RNA. In mitochondria, the mtTERM protein can stop transcription on both DNA strands. In yeast, the REB-1 protein terminates transcription and releases RNA from the ribosome. In mouse, the TFF-1 protein terminates the action of RNA polymerase I whereas the La protein controls RNA polymerase III. ►transcription termination in prokaryotes, ►transcription termination in eukaryotes, ►N-TEF, ►antitermination; Yu X et al 2000 J Mol Biol 299:1279; Kim D-E, Patel SS 2001 J Biol Chem 276:13902; crystal structure: Skordalakes E, Berger JM 2006 Cell 127:553.

rho Gene: The *rho* gene is responsible for the suppressive petite (mtDNA) condition in yeast. ►mtDNA

rho⁻ Mutants: The rho mutants of yeast lost from their mitochondrial DNA most of the coding sequences. They are very high in A+T content (the buoyant density of the DNA is low). ►mtDNA

rho-Dependent Transcription Termination: Actually, none of the rho-dependent bacterial strains absolutely require this protein factor for termination. ►rho factor, ►transcription termination, ►rho-independent; Konan KV, Yanofsky C 2000 J Bacteriol 182:3981.

Rhodamine B: A fluorochrome used for fluorescent microscopy; its reactive group forms a covalent bond with proteins (immunoglobulins) and other molecules. It is also a laser dye. Its absorption maxima is 543 (355) nm. Caution: It is carcinogenic. ►fluorochromes

Rhodospseudomonas palustris: A rather ubiquitous purple photosynthetic bacterium containing 5,459,213 bp in the chromosome and one plasmid of 8,427 bp. The estimated gene number is 4,835 (Larimer FW et al 2004 Nature Biotechnol 22:55).

Rhodopsin: A light-sensitive protein (opsin, $M_r \approx 28,600$, human chromosome 3q21-q24) coupled with a chromophore, 11-cis retinal, which isomerizes to all-trans retinal immediately upon the receipt of the first photon.

It functions as the light receptor molecule in the disks of the photoreceptive membrane of the photoreceptor cells of the animal retina of the eye. Rhodopsin has seven short hydrophobic regions that pass through the endoplasmic reticulum (ER) membrane in seven turns. The amino end (with attached sugars) is within the ER lumen and the carboxyl end points out into the cytosol. In the rod shape photoreceptor cells, rhodopsin is responsible for monochromatic light perception at low light intensities. In the cone shape photoreceptor cells color vision is mediated by it in bright light. The photoreceptor cells transmit a chemical signal to the retinal nerves that initiate then the visual reaction series. When the receptor is activated, the level of cyclic guanylic monophosphate (cGMP) drops by the activity of cGMP and bind phosphodiesterase and it is quickly replenished in dark by *guanylyl cyclase*. The activated opsin protein is transducin, an α , G protein subunit, that activates cGMP phosphodiesterase. When one single photon of light hits rhodopsin, through an amplification cascade, 500,000 molecules of cGMP may be hydrolyzed, 250 Na^+ channels may close, and more than a million Na^+ are turned back from entering the cell through the membrane within the time span of a second. In the dark, the sodium ion channels are kept open by cGMP; in the light the channels are closed. The sodium-calcium channels being shut, in light, the intake of Ca^{2+} is reduced and that leads to the restoration of the cGMP level through the action of the recoverin protein that cannot function well when it is bound to Ca^{2+} . Recoverin is a calcium sensor in the retinal rods. The rhodopsin gene has been assigned to human (see

Fig. R62) chromosome 3q21-qter and to mouse chromosome 6. *Drosophila* has three rhodopsin loci (*Rh2* [3-65], *Rh3* [3-70], *Rh4* [3-45]). In flies, too, the *nina* loci are involved in the synthesis of opsins affecting the ommatidia and ocelli. ▶phytochrome, ▶signal transduction, ▶G-proteins, ▶retinitis pigmentosa, ▶retinoblastoma, ▶color blindness, ▶color vision, ▶ommatidium, ▶ocellus, ▶opsins, ▶circadian rhythm, ▶night blindness, ▶proton pump; Yokoyama S 1997 Annu Rev Genet 31:315; Palczewski K et al 2000 Science 289:739; Bartl FJ et al 2001 J Biol Chem 276:30161; Sakmar TP 2002 Current Opin Cell Biol 14:189; Garriga P Manyosa J 2002 FEBS Lett 528:17; xanthorodopsin proton pump antenna: Balshov SP et al 2005 Science 309:2061, G protein-coupled receptor: Palczewski K 2006 Annu Rev Biochem 75:743.

Rhoeo discolor: An ornamental plant with large chromosomes (see Fig. R63), $2n = 12$; genome $x = 14.5 \times 10^9$ bp.



Figure R63. Rhoeo haploid set

rho-Independent Transcription Termination: Also it is called intrinsic transcription termination. The original model visualized the involvement of an RNA hairpin followed by a 15-nucleotide T (thymidine-rich)

R

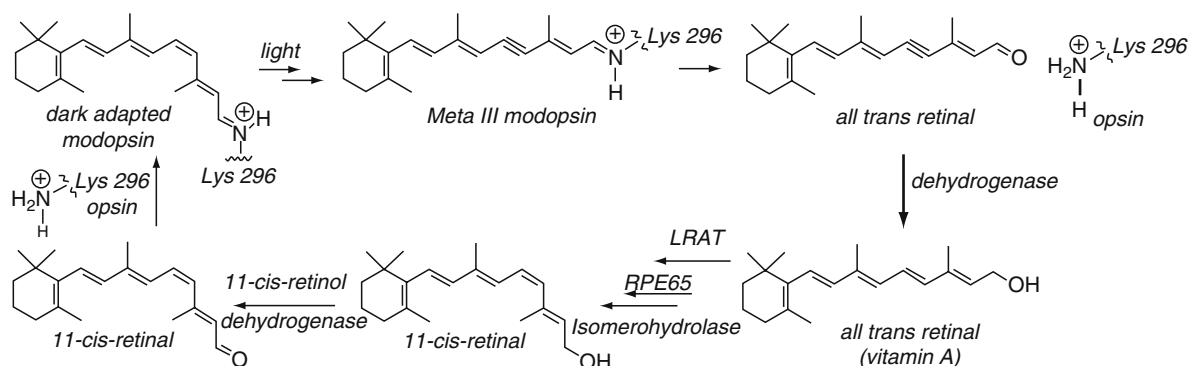


Figure R62. The visual cycle of the rhodopsin pathway in mammals. (From Gollapalli DR, Rando RR 2004 Proc Natl Acad Sci USA 101:10030. Copyright by the National Academy of Sciences USA, 2004)

region. The hairpin may be separated from the T sequences by a 2-nucleotide spacer. Since the *E. coli* genome has been fully sequenced, 135 terminators were identified and 940 putative terminators were found. Some of these are up to 60 nucleotides away from the 3'-end of the transcription units. ▶**transcription termination**; d'Aubenton Carafa Y et al 1990 J Mol Biol 216:835; Lesnik EA et al 2001 Nucleic Acids Res 29:3583.

Rhombcephalon: ▶**hindbrain**

Rhomboid Protease: Phylogenetically widespread membrane/mitochondrial intramembrane serine proteases that activate the epidermal growth factor receptor. In yeast, one rhomboid acts on cytochrome c peroxidase and a dynamin-like GTPase. γ -secretase is also an intramembrane proteolytic enzyme (Urban S, Wolfe MS 2005 Proc Natl Acad Sci USA 102:1883). ▶**EGF**, ▶**secretase**; McQuibban GA et al 2003 Nature [Lond] 423:537; Koonin EV et al 2003 Genome Biol 4:R19; crystal structure of *E. coli* GlpG intramembrane serine protease: Wang Y et al 2006 Nature [Lond] 444:179.

Rhombomeres (neuromeres): Metameric units of eight subdivisional partition of the neuroepithelium of the hindbrain. ▶**metamerism**

Rhoptry (toxosome): Generally, a club-shaped apical organ of apicomplexan protozoa; it mediates infection by sporozoites. ▶**malaria**, ▶*Plasmodium*, ▶**apicomplex**, ▶**sporozoite**

Rhubarb (*Rheum* spp): The plant has about 50 species; $2n = 2x = 44$. It is an accessory food plant and some species are used as medicinal herbs (cathartic [laxative]).

R

Rhynchosciaras: *Rhynchosciaras* are dipteran flies with very clearly banded polytenic chromosomes in the salivary gland nuclei. ▶*Sciara*, ▶**polytenic chromosomes**

Ri: ▶**recombinant inbreds**

Ri Particle: These particles are formed in cold in vitro during the 30S ribosomal subunit reconstitution experiment of rRNA and about 15 proteins. Upon heating, to assume the proper conformation, they become RI* particles. ▶**ribosome**, ▶**ribosomal RNA**, ▶**ribosomal protein**

Ri Plasmid: A root-inciting plasmid of *Agrobacterium rhizogenes*. It can be used for genetic engineering to the same way as the Ti plasmid of *Agrobacterium*

tumefaciens. The bacterium is responsible for the hairy root disease of plants. Its T-DNA contains two segments. The right T-DNA (T_R) contains genes for the production of opines, mannopine and agropine, and also for auxin. These auxin genes are highly homologous to the comparable genes in the Ti plasmid of *Agrobacterium tumefaciens*. The left portion of the T-DNA (T_L) includes 11 open reading frames with organization similar to eukaryotic genes; however this segment is different from that of the Ti plasmid. ▶**Ti plasmid**; Moriguchi K et al 2001 J Mol Biol 307:771.

RIA: ▶**radioimmunoassay**

Ribavirin: An antibiotic; its 5'-phosphate inhibits inosine monophosphate (see Fig. R64). ▶**inosine**

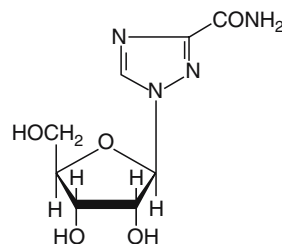


Figure R64. Ribavirin

Ribbon Diagram of Polypeptide Structure: An X-ray structure of a α -helix (at left) and a short β -sheet (at right ending with an arrow) (see Fig. R65). Typically, the protein structure is more complex and contains several of these elements forming multiple domains. ▶**protein structure**

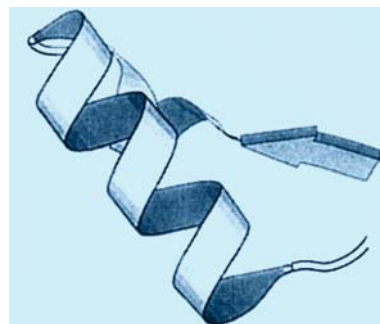


Figure R65. Ribbon diagram of polypeptide structure

Riboflavin (lactoflavin, vitamin B₂): A vitamin precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) oxidation coenzymes. Riboflavin is heat stable but rapidly decomposes in light (see Fig. R66). (See Ritz H et al 2001 J Biol Chem 276:22273).

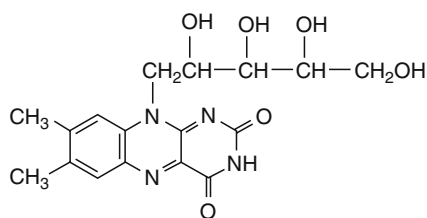


Figure R66. Riboflavin

Ribocyte: An evolutionarily ancestral cell with RNA genetic material. ▶[RNA world](#)

Ribo-gnome: Small regulatory RNAs, such as micro-RNA, RNAi, etc. (Zamore PD, Haley B 2005 Science 309:1519).

Riboflavin Retention Deficiency: A riboflavin retention deficiency may prevent hatching of eggs in “leaky auxotrophic” chickens. The defect is not in absorption but the vitamin is rapidly excreted by a genetic default, and the *rd/rd* eggs have only about 10 µg of the vitamin rather than the normal level of about 70 µg. If 200 µg is injected into the eggs before incubation, hatching occurs.

Ribonuclease (RNases): Ribonuclease occur in a large number of specificities and they digest various types of ribonucleic acids. The bovine pancreatic ribonuclease is a small (124 amino acids) and very heat-stable enzyme. The pancreatic ribonuclease was the first enzyme chemically synthesized in the laboratory. An autoradiogram (see Fig. [R67](#)) permits the

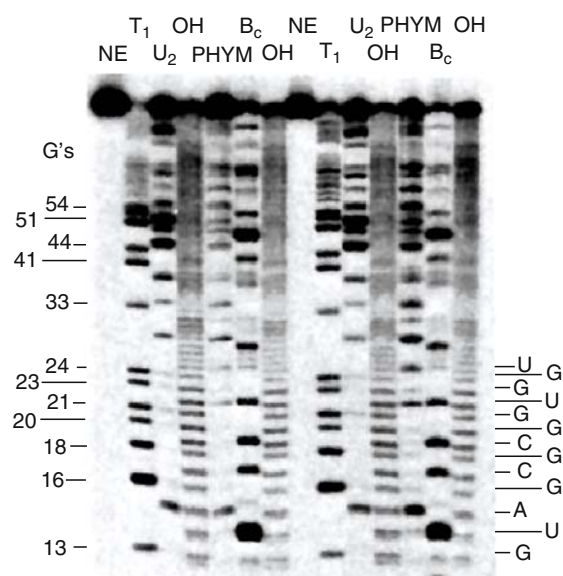


Figure R67. Ribonucleases

distinction of the digestion enzyme control, T₁: G-specific enzyme; U₂: ribonuclease is A-specific; Phy M: *Physarum* enzyme M, specific for U + C; OH: random alkaline digest; and B_c: *Bacillus cereus* enzyme with U + C specificity. On the left side guanosine positions are indicated from the 5'-end, and on the right side the nucleotide sequences are shown as read from the gel. (Courtesy of P-L Biochemicals, Inc.). ▶[RNases](#), ▶[ribonucleases](#), ▶[angiogenins](#); Condon C, Putzer H 2002 Nucleic Acids Res 30:5339.

Ribonuclease 1: Degrades RNA I. ▶[RNA I](#); Cunningham KS, et al 2001 Methods Enzymol 342:28.

Ribonuclease II: Ribonuclease II is similar in action to Ribonuclease D; its role is not just limited to processing; it can also degrade an entire tRNA and mRNA molecule. It is an exonuclease. The enzyme has four domains: two cold-shock domains, the catalytic RNB domain, and one S1 domain. The enzyme contacts RNA in the “anchor” and “catalytic” regions. The catalytic RNB domain includes four conserved sequence motifs. This catalytic pocket is accessible only to single-stranded RNA. The structural features, shown in the Figure [R68](#), are probably characteristic for other members of this family of proteins (Frazão C et al 2006 Nature [Lond] 443:110). ▶[ribonuclease D](#); Donovan WP, Kushner SR 1986 Proc Natl Acad Sci USA 83:120.

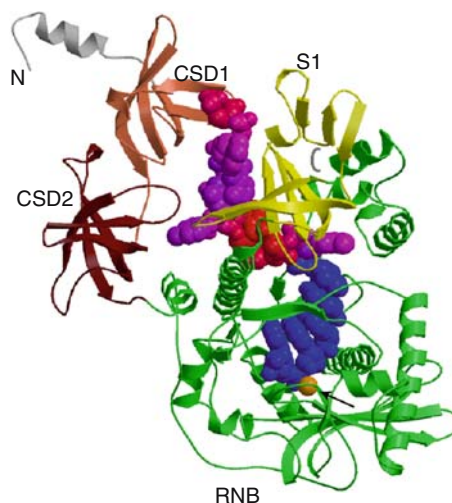


Figure R68. Crystal structure of *E. coli* RNase II. CSD1, CSD2, S1 are oligonucleotide-binding domains. RNB is the catalytic domain. Mg²⁺ is at arrow. The docked RNA is colored from red to blue, according to atomic displacement parameters. (Courtesy of Drs. Carlos Frazão and Maria Arménia Carrondo)

Ribonuclease III (RNase III): A homodimeric phosphodiesterase; an endonuclease cutting double-strand RNA from the 3' or 5' end. It cleaves prokaryotic and eukaryotic pre-rRNA at a U3 snoRNP-dependent site. RNase III controls the maturation of cellular and phage RNAs and may determine the translation and half-life of mRNAs. In prokaryotes its cleaving action may be restricted by antideterminants. In yeast, RNA tetraloops (AGNN) are located 13–16 bp from the RNase III recognition sites (see Fig. R69). ▶trimming, ▶snoRNP, ▶antideterminant, ▶Dicer; Grunberg-Manago M 1999 Annu Rev Genet 33:193; Conrad C, Rauhut R 2002 Int J Biochem Cell Biol 34:116; crystal structure: Gan J et al 2005 Structure 13:1435; Gan J et al 2006 Cell 124:355.

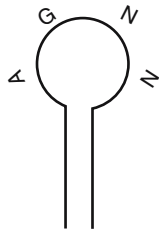


Figure R69. Tetraloops of four nucleotides

Ribonuclease A: A family of RNA digesting enzymes, including pancreatic, brain ribonucleases as well the related eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP) and angiogenin, involved in defense functions. ▶eosinophil, ▶angiogenesis, ▶Prp75; Sheraga HA et al 2001 Methods Enzymol 341:189; Cho S et al 2005 Genomics 85:208.

Ribonuclease B: RNase B cuts at U+C sequences of RNA. (See Zapun A et al 1998 J Biol Chem 273:6009).

Ribonuclease BN: An exonuclease that cuts tRNA. ▶exonuclease; Callahan C et al 2000 J Biol Chem 275:1030.

Ribonuclease D: RNase D processes tRNA primary transcripts at the 3' end into mature tRNA. ▶tRNA, ▶primary transcript, ▶RNAi; crystal structure: Zuo Y et al 2005 Structure 13:973.

Ribonuclease E: RNase E cleaves RNAs with secondary structure within single-stranded regions rich in A and U nucleotides, e.g., RNA I. The N-terminal domain of 1,061 amino acids functions as an endonuclease involved in mRNA and rRNA processing and degradation in *E. coli* and other bacteria. The catalytic activity of RNase E (and RNase G) is enhanced in the multimeric forms by having a monophosphate at the 5' end despite the fact that mRNA degradation begins

endonucleolytically (Jiang X, Belasco JG 2004 Proc Natl Acad Sci USA 101:9211). This enzyme also shortens the polyA and polyU tails of RNA molecules. Its C-terminus may associate with a 3'→5' exoribonuclease and other proteins in the degradosome complex. ▶RNA I, ▶*E. coli*, ▶endonuclease, ▶exonuclease, ▶degradosome, ▶tmRNA, ▶protein repair, ▶mRNA, ▶tRNA; Grunberg-Manago M 1999 Annu Rev Genet 33:193; Walsh AP et al 2001 Nucleic Acids Res 29:1864, crystal structure: Callaghan AJ et al 2005 Nature [Lond] 437:1187.

Ribonuclease G (CafA): RNase G processes the 5' end of 16S rRNA with RNase E (Feng Y et al 2002 Proc Natl Acad Sci USA 99:14746).

Ribonuclease H: RNase H digests RNA when paired with DNA but it does not cut single-strand RNA or double-strand RNA or double-strand DNA. This family of proteins includes transposases, retroviral integrase, Holliday structure resolvase and the RISC nuclease Argonaute. RNase H specifically recognizes the A form of RNA and the B form of a DNA strand (Nowotny M et al 2005 Cell 121:1005). RNase HI, as an endonuclease, can remove RNA primers (except 1 nucleotide) from the 5'-end of the Okazaki fragments. RNase H may also cleave "irrelevant sites", i.e., RNA that is imperfectly bound to DNA. RNase H can be used to prevent the translation of mRNA by recruiting it to phosphorothioated DNA. ▶DNA replication eukaryotes, ▶Rad27/Fen1, ▶Okazaki fragment, ▶antisense technologies, ▶phosphorothioate, ▶RNA I, ▶microRNA, ▶transposase, ▶integrase, ▶resolvase, ▶Aicardi-Goutières syndrome; Wu H et al 2001 J Biol Chem 276:23547, folding of RNase H: Cecconi C et al 2005 Science 309:2057.

Ribonuclease J: An exoribonuclease that can cut 5' to 3' both ribosomal and mRNA of *Bacillus subtilis*. RNase J1 plays a role in maturation and 5' stability of mRNA (Mathy N et al 2007 Cell 129:681).

Ribonuclease L: In dimeric form, RNase L cleaves single-stranded RNA. Its product may reduce viral replication in interferon-exposed cells and suppress prostate cancer. It may be induced by interferon. For activity it depends on 2',5'-oligoadenylates (2–5A). RNase L may be involved in apoptosis. The RNase L inhibitor plays important role in ribosome biogenesis and HIV capsid assembly (Karcher A et al 2005 Structure 13:649). Compounds bound to the 2–5A-binding domain of RNase L induce RNase L dimerization and activation. Low-molecular-weight activators of RNase L had broad-spectrum antiviral activity against diverse types of RNA viruses, including the human parainfluenza virus type 3, yet these compounds by themselves were not cytotoxic at

the effective concentrations (Thakur CS et al 2007 Proc Natl Acad Sci USA 104:9585). ▶**apoptosis**, ▶**RNAi**, ▶**Ire**, ▶**interferon**; Stark GR et al 1998 Annu Rev Biochem 67:227; Carpten J et al 2002 Nature Genet 30:181; Malathi K et al 2005 Proc Natl Acad Sci USA 102:14533.

Ribonuclease MRP (9p21-p12): A mitochondrially-localized enzyme involved in cleavage of pre-mRNA and pre-rRNA. Its defect affects the cell cycle, hair hypoplasia, immunodeficiency, hematological abnormalities and the assembly of the ribosomes and the degree of bone dysplasia, respectively (Thiel CT et al 2007 Amer J Hum Genet 81:519).

Ribonuclease P: RNase processes the 5' end of transfer RNA transcripts (and cleaves some other RNAs). It may process some pre-tRNAs at the 3'-end. Its catalytic subunit is a ribozyme in bacteria, a 377-nucleotide RNA that can do the processing even without the ~120-amino acid protein. However, the protein may enhance specificity and is required for ribosomal translocation. For catalytic activity the enzyme requires divalent cations (Mg^{2+}). The chloroplast enzyme is not a ribonucleoprotein but is only a protein. The size of the protein subunits in bacteria is about 14 kDa, but in eukaryotes it may exceed 100 kDa. Although at least 10 proteins are associated with RNase P, either protein Rpp29 or C5 are essential for activation of the core RNA and substrate recognition as well as for catalysis (Sharin E et al 2005 Nucleic Acids Res 33:5120). Eukaryotic RNase P RNA is also able to cleave its substrate in the absence of protein(s) although with relatively low efficiency; this suggests that the catalytic activity resides in the RNA subunit of RNase P (Kikowska E et al 2007 Proc Natl Acad Sci USA 104:2062). ▶**ribozyme**, ▶**external guide sequences**, ▶**KH domain**, ▶**RNase**, ▶**RNA maturases**, ▶**MRP**; Kurz JC, Fierke CA 2000 Curr Opin Chem Biol 4:553; Tous C et al 2001 J Biol Chem 276:29059; Gopalan V et al 2002 J Biol Chem 277:6759; Xiao S et al 2002 Annu Rev Biochem 71:165; specificity domain: Krasilnikov AS et al 2003 Nature [Lond] 421:760; structural diversity: Krasilnikov AS et al 2004 Science 306:104; crystal structure of the RNA component: Torres-Larios A et al 2005 Nature [Lond] 437:584; crystal structure of *Bacillus stearothermophilus* P RNase RNA: Kazantsev AV et al 2005 Proc Natl Acad Sci USA 102:13392; structure and function: Marquez SM et al 2006 Mol Cell 24:445.

Ribonuclease R: An RNase II homolog 3'→5' exoribonuclease of *E. coli*. RNase R and polynucleotide phosphorylase are essential for the proper assembly of ribosomes by eliminating defective rRNA monomers. ▶**ribonuclease II**, ▶**rRNA**, ▶**polynucleotide**

phosphorylase; Cheng A-F, Deutscher MP 2002 J Biol Chem 277:21624; Cheng Z-F, Deutscher MP 2003 Proc Natl Acad Sci USA 100:6388.

Ribonuclease S: RNase S enzymes are associated with self-incompatibility of plants (Ma R-C, Oliviera MM 2002 Mol Genet Genomics 267:71).

Ribonuclease T: An exonuclease of tRNA, cutting at the amino acid accepting end (CCA). ▶**tRNA**; Zuo Y, Deutscher MP 1999 Nucleic Acids Res 27:4077; Zuo Y et al 2007 Structure 15:417.

Ribonuclease T₁: RNase T₁ is specific for G (guanine) linkages in RNA. (See Kumar K, Walz FG Jr 2001 Biochemistry 40:3748).

Ribonuclease U1: A guanine-specific RNase. (See Takahashi K, Hashimoto J 1988 J Biochem [Tokyo] 103:313).

Ribonuclease U2: RNase U2 is specific for A+U nucleotides in RNA. (See Taya Y et al 1972 Biochim Biophys Acta 287:465).

Ribonuclease Z (3' tRNase): A zinc-dependent metallo-hydrolase; an endonuclease, which processes the 3'-end of most prokaryotic, cytoplasmic, and mitochondrial tRNAs (Dubrovsky EB et al 2004 Nucleic Acids Res 32:255; crystal structure: Li de la Sierra-Gallay I et al 2005 Nature [Lond] 433:657).

Ribonucleic Acid: ▶**RNA**

Ribonucleoprotein (RNP): A ribonucleic acid associated with a protein. ▶**RNP**

Ribonucleotide: A ribonucleotide contains one of the four nitrogenous bases (A, U, G, C), ribose and phosphate. It is a building block of RNA. ▶**deoxyribonucleotide**

Ribonucleotide Reductase (RNR): A ribonucleotide reductase converts ribonucleotide di- and triphosphates into deoxyribonucleotide di- and triphosphates. It is required for DNA synthesis, the completion of the cell cycle and malignancy. RNR proteins might have been instrumental in generating DNA in the RNA world. The allotetramer enzyme has a large subunit, R1, which regulates the maintenance of a deoxynucleotidetriphosphate pool; its level is constant throughout the cell cycle. The R2 subunit converts ribonucleotides to deoxyribonucleotides and it appears in G1 and vanishes at early S phase. The 351-amino acid R2 subunit is the product of the p53R2 gene, activated by p53. Gene p53R2 apparently has a DNA repair function. ▶**cell cycle**, ▶**malignant**, ▶**CDC22**, ▶**RNA world**, ▶**p53**, ▶**recombination molecular mechanism of**; Jordan A, Reichard P 1998 Annu Rev Biochem 67:71; Tanaka H et al 2000 Nature 404:42; Chimpoy K,

Mathews CK 2001 J Biol Chem 276:7093; Högbom M et al 2004 Science 305:245; Nordlund P, Reichard P 2006 Annu Rev Biochem 75:681.

Ribose: An aldopentose sugar, present in ribonucleic acids with an OH group at both 2' and 3' positions. Its deoxyribose form lacks the O at the 2' position and it is present in DNA (see Fig. R70). ▶**aldose**, formula given here

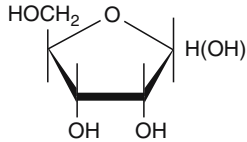


Figure R70. D-ribose

Ribose Zipper: When two RNA strands of opposite polarity are situated in close vicinity to each other hydrogen bonds may form between the 2'-OH groups of consecutive riboses in both strands. (See Klostermeier D, Millar DP 2001 Biochemistry 40:37).

Ribosomal DNA: The codes for ribosomal RNAs. ▶**ribosome**

Ribosomal Filter: A hypothesis proposing that cis-regulatory sequences in the mRNA modulate its binding to the 40S ribosomal subunit by complementarity to the 18S or 28S ribosomal subunits or by affinity to specific ribosomal proteins. This binding may filter, i.e., influence the translation in a (+) or (−) manner and may be a factor in differential translation in a tissue- or development-specific manner. ▶**ribosomes**, ▶**translational control**; Mauro VP, Edelman GM 2002 Proc Natl Acad Sci USA 99:12031.

R

Ribosomal Frame Shifting (translational recoding): ▶**overlapping genes**, ▶**recoding**

Ribosomal Genes: ▶**rrn**, ▶**ribosomes**, ▶**rRNA**

Ribosomal Proteins: Ribosomal proteins are generally designated with an S or L indicating whether it is part of the small or large ribosomal subunit. The size of these 55 proteins in *E. coli* range from 6 kDa to 75 kDa. They bind to the RNAs at specific binding sites, either directly or through their association. In *E. coli* the genes for these proteins are scattered among other genes in the chromosome. One of the bacterial ribosomal proteins is present in several copies whereas the other ones occur only once per ribosome. In eukaryotes, about 80 ribosomal proteins exist encoded by a larger number of genes generally occurring in a single or a few copies. Transcription factor Ifh1 of yeast is a key regulator by association

with the promoters by the aid of the forkhead-associated factor RAP1 (Wade JT et al 2004 Nature [Lond] 432:1054). The ribosomal proteins assure the proper structural conditions on the ribosomes for translation. About 35% of the bacterial ribosomes are protein. Two-thirds of the chloroplast ribosomal proteins are imported from the cytoplasm and even larger fractions of the mitochondrial proteins are coded by the nucleus. The number of ribosomal proteins in organelles is higher than in prokaryotes. The mitochondrial ribosomes (mitoribosomes) are ~69% protein and ~31% RNA whereas the prokaryotic ribosomes are ~33% protein and ~67% RNA. The number of proteins in the mammalian mitochondrial ribosomes is about 85 and nearly all are imported. The number of ribosomal proteins in the large mitochondria of higher plants is about 65. Proteins bind only single-stranded sequences of RNA. ▶**nucleolus**, ▶**ribosomes**, ▶**RAP1**, ▶**protein synthesis**, ▶**Diamond-Blackfan anemia**; Nomura N et al 1984 Annu Rev Biochem 53:75; Kenmochi N et al 2001 Genomics 77:65; Uechi T et al 2002 Nucleic Acids Res 30:5369; Lecompte O et al 2002 Nucleic Acids Res 30:5382; <http://ribosome.miyazaki-med.ac.jp/>.

Ribosomal RNA: About 65% of the bacterial ribosomes are RNA. The 16S bacterial rRNA (1.54 kb) has short double-stranded domains and single stranded loops and about ten of the bases near the 3'-end are methylated. The 16S ribosomal RNA undergoes conformational changes (switches) before translation of the mRNA (Lodmell JS, Dahlberg AE 1997 Science 277:1262).

The 16S rRNA is frequently used for taxonomic classification. Actually, both types of base pairings have been found with physiological activity although mutations that favored the Type II conformation favored fidelity of the translation (see Fig. R71). Proteins S5 and S12 facilitate these switches that seem to also play a role in tRNA selection in algae and fungi.

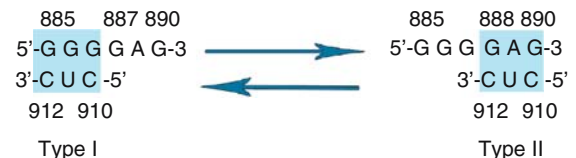


Figure R71. Ribosomal RNA

The 23S rRNA (3.2 kb) carries about 20 methylated bases. The 18S mammalian rRNA (1.9 kb) has more than 40 and the 28S (4.7 kb) has more than 70 methylations. The ribosomal RNAs provide not just a niche for translation, they also interact directly with translation initiation. The 16S rRNA cooperates with

the anticodon at both the A and P sites and the 23S rRNA interacts with the CCA end of the tRNA. The ribosomal exit channel (E) plays a regulatory role in peptide elongation (Nakatogawa H, Ito K 2002 Cell 108:629). In the 23S rRNA, two guanine sites are universally conserved (G2252, G2253), and the Cytosine 74 site of the acceptor end of the tRNA (CCA) is required for their functional interaction at the P site of the ribosome for protein synthesis. Methylated sequences in the rRNA mediate, probably, the joining of the small ribosomal subunit to the large subunit after translation is initiated, and holds on to the initiator tRNA^{fMet}. Some mutations in the 16S RNA may cause an override through the stop codon and failure of termination of the translation; mutations in the 23S RNA may disturb the A and P ribosomal sites. T 23S ribosomal RNA has six domains (see Fig. R72).

Of these, domain V, in an isolated form, can perform peptide elongation even better than the intact 23S molecule. It seems that ribosomal RNA alone (without protein) is required for peptide elongation (see Fig. R73). Ribosomal ribozymes mediate peptidyl transferase functions. The prokaryotic 23S ribosomal RNA contains the pentapeptide, coding minigene (GUGCGAAUGCUGACAUAAGUA) with a canonical ribosome-binding site and appears to mediate resistance to the antibiotic erythromycin. The 5S bacterial rRNA contains 120 nucleotides and binds three proteins (L25, L18, L5). 5S RNA is also present in eukaryotes where it forms a complex with the L5 ribosomal protein. L25 binds to the E loop of 7 hydrogen-paired nucleotide pairs stabilized by Mg²⁺. The 3'-end of the small ribosomal subunit is highly conserved from prokaryotes to plants and mammals. For example, in *E. coli*, GAUCACCUCUUA-OH, in yeast, GAUCA—UUA-OH, in maize, GAUCA—UUG-OH, and in rat, GAUCA—UUA-OH, occur (the - signs are inserted for alignment). The function of rRNA synthesis is regulated by homeostasis, feedback, and by many other protein factors. Among them is *dksA*, a multicopy suppressor of a wide range of apparently unrelated functions. ▶nucleolus, ▶ribosomes, ▶ribosomal genes, ▶class I genes, ▶class

III genes, ▶rrn, ▶discriminator region, ▶introns, ▶ribosomal proteins, ▶protein synthesis, ▶aminoacyl-tRNA synthetase, ▶tRNA, ▶gene size, ▶tmRNA, ▶RNase, ▶rRNA MRP; Noller HF 1991 Annu Rev Biochem 60:191; Liang W-Q, Fourmier MJ 1997 Proc Natl Acad Sci USA 94:2864; Gutell RR et al 2002 Current Opin Struct Biol 12:301; Moore PB, Steitz TA 2002 Nature [Lond] 418:229; Paul BJ et al 2004 Annu Rev Genet 38:749; 5S ribosomal RNA: <http://biobases.ibch.poznan.pl/5SDData/>; diagnostics by 16S rDNA: <http://www.ridom.de>; post-transcriptionally modified bases in the small subunit ribosomal RNA: <http://medlib.med.utah.edu/SSUmods/>; rRNA genes: <http://rdp.cme.msu.edu>; server for 16S ribosomal RNA alignment in prokaryotes: http://greengenes.lbl.gov/cgi-bin/nph-NAST_align.cgi.



Figure R73. Transcription of ribosomal RNA in the nucleolar organizer region of the chromosomes of *Acetabularia*. The genes are separated by non-transcribed intergenic spacers. One transcription unit is about 1.7 μm. The ribosomal operons in *E. coli* use the proteins S4, L3, L4, and L13 for antitermination with functions similar to the *Nus* genes (Torres M et al 2001 EMBO J 20:3811). (The electronmicrograph is courtesy Spring H et al J Microsc Biol Cell 25:107.)

Ribosome Binding: ▶Shine-Dalgarno sequence, ▶ribosome, ▶mRNA, ▶ribosome scanning

Ribosome Binding Assay: The ribosome binding assay was used in the mid 1960s to identify several codons. RNA oligonucleotides that bound to ribosomes attached to those charged tRNA molecules which had the specific anticodons and carried the appropriate amino acids. This way, the relationship between RNA codons and amino acids was revealed. ▶genetic code, ▶decoding

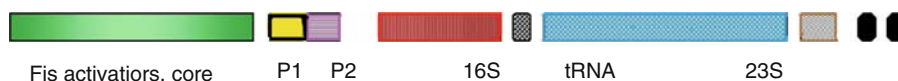


Figure R72. Ribosomal RNA operon in *E. coli*; Fis (factor for inversion stimulation [an old terminology]), core: core promoter, P: promoters, 16S: 16S rRNA genes, tRNA is an intercalated transfer RNA gene, 23S: 23S ribosomal RNA genes, 5S: 5S rRNA, t1, t2 termination signals. Only 120 bp separates the stronger P1 promoter from P2. The core promoter is the landing site of the RNA polymerase and it includes several hexamers for the recognition of the σ^{70} RNA polymerase holoenzyme. Upstream of the promoters are A-T-rich sequences (UP) that enhance polymerization. The carboxyterminal domain (CTD) of the α subunit also recognizes this area. Promoters in the different systems show variations from the main scheme.

Ribosome Display: The same as RNA-peptide fusions. ►[display technologies](#); Hanes J et al 2000 Nature Biotechnol 18:1287.

Ribosome Hopping: The bypassing of the coding gaps in phage T4 genes with the assistance of a special protein factor. (See Herr AJ et al 2001 J Mol Biol 311:445).

Ribosome Recycling (RRF): After the termination of the translational process, the ribosome is disassembled into the small and large subunits. The post-termination complex in prokaryotes contains release factors RF1, RF2 and RF3, the 70S ribosome with the mRNA still attached to it, a deacylated tRNA at the P site, and an empty A site. This complex is split up by RRF (ribosome recycling factor, Agrawal RK et al 2004 Proc Natl Acad Sci USA 101:8900) and the elongation factor G (EF-G) by GTP hydrolysis. RRF structurally mimics tRNAs, except the amino acid-binding 3'-terminus. This indicates that RRF interacts with the post-termination complex in a manner similar to that of a tRNA responding to the ribosome. ►[ribosomes](#), ►[protein synthesis](#), ►[A site](#), ►[P site](#), ►[EF-G](#), ►[aminoacylation](#); Kisselev LL, Buckingham RH 2000 Trends Biochem Sci 25:561; Inokuchi Y et al 2000 EMBO J 19:3788; Hirokawa G et al 2002 J Biol Chem 277:35847.

Ribosome Scanning: Eukaryotic mRNAs do not have a Shine-Dalgarno consensus for ribosome binding. They are probably attached by the 5'-m⁷G(5')pp. The (5')mRNA sequence reels on the ribosome until the initiator methionine codon is found. Circular viral or eukaryotic RNAs, if they contain internal ribosome entry sites (IRES), may be translated without a need for a free 5'-end. The RNA helicase eIF4E and the other translation initiation factor eIF4G, as well as the cap-binding protein eIF4E and the tail-binding protein Pab1, are instrumental in a cooperative manner in the initiation of translation. ►[Cap](#), ►[Shine-Dalgarno](#), ►[protein synthesis](#), ►[IRES](#), ►[dicistronic translation](#), ►[Kozak rule](#), ►[eIF](#), ►[elongation initiation](#), ►[translation](#), ►[ribosome shunting](#); Kozak M 1989 J Cell Biol 108:229; Sachs AB 2000 Cell 101:243; Kozak M 2002 Gene 299:1.

Ribosome Shunting: The long leader sequence of viral DNA (adenovirus, cauliflower mosaic virus, etc.) may contain several short open reading frames, which usually interfere with the translation of the downstream ORFs. These impediments may be bypassed (jumped) by the formation some internal structure, e.g., stem-loop structure. It seems that for the proper scanning of the ribosome the ~100 nucleotides at the 5' and 3' ends are most essential. ►[adenovirus](#), ►[cauliflower mosaic virus](#), ►[ORF](#), ►[stem-loop](#),

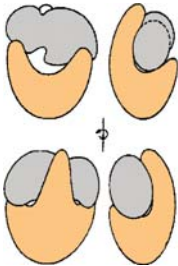
►[ribosome scanning](#); Pooggin MM et al 2001 Proc Natl Acad Sci USA 98:886.

Ribosome Skipping: The same as translational bypassing.

Ribosomes: Ribosomes provide the workshop and some of the tools for protein synthesis in all cellular organisms, including the subcellular organs, mitochondria, and chloroplasts. A yeast cell contains about 200,000–2,000,000 ribosomes. The chloroplastic ribosome genes are situated in the characteristic inverted repeats, except in some *Fabaceae* and conifers. The prokaryotic and organellar ribosomes are similar and their approximate molecular weight is 2.5×10^6 Da with a sedimentation coefficient of 70S. The higher eukaryotic ribosomes, excluding the organellar ones, have a molecular weight of about 4.5×10^6 Da, and they are ~80S. The ribosomes have both a minor and a major subunit built of RNA and protein (see Fig. R74).

The prokaryotic 30S subunit includes 20 proteins, assembled through several steps of conformational transitions as detected by pulse and chase monitored with the aid of quantitative mass spectrometry (Talkington MWT et al 2005 Nature [Lond] 438:628). The crystal structure of the 70S ribosome complexed with mRNA and tRNA has been determined (Selmer M et al 2006 Science 313:1935).

Hrr25 protein kinase-dependent phosphorylation regulates the organization of the pre-40S eukaryotic ribosomal subunit (Schäfer T et al 2006 Nature [Lond] 441:651). The large subunit, 50S is connected to the small subunit, 30S by an RNA-protein bridge. From the middle of the large subunit a tunnel runs toward the small subunit. The formation of the 80S ribosome requires the mediation of eIF5. The mitochondrial ribosomes do not contain 5S subunits but chloroplasts do have them. The number of ribosomes may greatly increase when protein synthesis is very rapid. During early embryogenesis in amphibia, the rRNA gene number may increase three orders of magnitude by a process of amplification and the extra copies of the genes are sequestered into minichromosomes forming micronuclei. Their number in some higher plants regularly runs into thousands. The bacterial ribosomes are about 65% RNA and 35% protein. On the ribosomes, several active centers can be distinguished. The A and P sites receive the tRNAs. This area extends to both the small and the large subunits. The tRNA after unloading of the amino acids leaves the ribosome at the exit site (E) of the large subunit. Some of the peptide chains exit through the tunnel of the large subunit. The translocation factor EF-G seems to occupy a space in between the two subunits. The complex crystal structure of the *E. coli* ribosome is



| | | |
|-----------------------------|---|--|
| | Prokaryotic | Eukaryotic |
| Small subunit | 30S | 40S |
| rRNA types | 16S (1.54 kb) | 18S (1.9 kb) |
| protein, kinds of molecules | 21 | ~33 |
| Large subunit | 50S | 60S |
| rRNA types | 23S (3.2 kb) 5S (0.12 kb) | 28S (4.7 kb) 5S (0.12 kb) 5.8S (0.16 kb) |
| Protein, kinds of molecules | 34 | ~49 |
| Ribosomes, number/cell | 15,000–70,000 (<i>E. coli</i>) | more and variable |
| Ribosomes, gene number | in 7 operons 200 genes in <i>Drosophila</i> /genome | |

Figure R74. 70S prokaryotic ribosome viewed from different angles (Courtesy Tischendorf GW et al 1975 Proc Natl Acad Sci USA 72:4870). The ribosome structure is much more complex than shown in the diagram (see Brimacombe R, p 41 In: Eggleston RA et al (Eds.) The Many Facets of RNA. 1998 Academic Press, San Diego, CA, USA). By the use of crystallography, nuclear magnetic resonance, neutron diffraction and cryo-electron microscopy more detailed three-dimensional structures have been revealed. Also chemical foot printing, mutation and other probes have identified the links between ribosomal components and ribosomal sites of tRNA and mRNA.)

described at 3.5 Å resolution (Schuwirth BS et al 2005 Science 310:827). The *classical* model of translation is discussed under the protein synthesis entry. Binding of the anticodon stem-loop of P-site tRNA to the ribosome is sufficient to lock the head of the small ribosomal subunit in a single conformation, thereby preventing movement of mRNA and tRNA before mRNA decoding (Berk V et al 2006 Proc Natl Acad Sci USA 103:15830).

The newer hybrid-states model is given in the diagram. The elongation factor EF-TU may be located on the small subunit but it communicates with EF-G. The EF-Tu.GTP.tRNA ternary complex is instrumental in the delivery of the aminoacyl-tRNA to the A/T hybrid site of the peptidyl tRNA-ribosome in complex. (A is the amino acid, P the peptidyl, and T is the corresponding large subunit site.) In prokaryotes, then, the anticodon binds to the A site of the 30S ribosomal subunit. Hydrolysis of GTP is followed by the release of the elongation factor EF1A/EF-Tu. After this, the CCA end of the amino acid-charged tRNA moves to the A site of the large (50S) subunit. Peptidyl transferase (located at the end of the tunnel closest to the small subunit) then mediates peptide bond formation between the nascent peptide chain and the next incoming amino acid. After the peptide bond is initiated the peptidyl-tRNA is deacylated and is transferred to the P site on the large subunit. The anticodon stays for a while at the A site of the small subunit while the CCA end is on the P site of the large subunit. Then the anticodon moves to the P site of the large subunit and the CCA site goes to the E site of the large subunit (see Fig. R75) (Márquez V et al 2004 Cell 118:45). Meanwhile, after the recognition of the cognate codon by the

anticodon, the EF1A·GTP complex moves to the GTPase center of the ribosome, and EF1A·GDP and the tRNA are released at the E site. After the translocation from the A site to the P site, the elongation factor EF1B mediates the conversion of the inactive EF1A·GDP into the active EF1A·GTP. This and other more recent models indicate that the movement on the ribosomes involves the tRNA, but the peptidyl moiety moves very little. If the A site of a prokaryotic ribosome is unoccupied, water may carry out a nucleophilic attack on the peptidyl-tRNA at the P site. In the absence of an appropriate A-site substrate, the peptidyltransferase center can position the ester link of the peptidyl-tRNA in a conformation that prevents the nucleophilic attack by water. Protein factors may also assist in the protection (Schmeing TM et al 2005 Nature [Lond]:438:520).

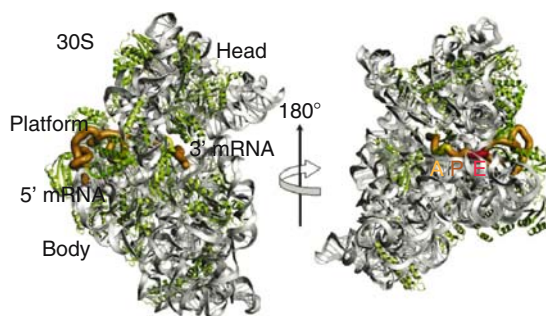


Figure R75. mRNA on the ribosome. Left: Solvent site view of the 30S subunit with 5'-end (position -36) and 3'-end (position +12) of the mRNA. Right: interface view of the 30S subunit with A, P and E codons of the mRNA. Courtesy of Dr. Marat Yusupov, IGBMC, Illkirch, France; see also Yusupov, G et al. 2006 Nature [Lond] 444:391

Chloramphenicol, erythromycin, lincomycin, streptomycin, spectinomycin, kanamycin, hygromycin, etc., normally inhibit prokaryotic ribosomes. Eukaryotic ribosomes are sensitive to cycloheximide, anisomycin, puromycin, tetracyclines, etc. The ribosomes play an important role in the regulation of protein synthesis. It appears that the availability of active ribosomes is controlled at the level of the transcription of the rRNA genes. When the supply of ATP and GTP is adequate, rRNA genes are activated for transcription. In case the level of these nucleotide triphosphates is low, rRNA transcription is reduced or halted. An abundance of free ribosomal proteins may feedback-inhibit ribosomal production. The ribosome-associated Rel-A protein may mediate the formation of ppGpp from GTP (and possibly from other nucleotides). Then, ppGpp (or pppGpp) may shut off rRNA and tRNA synthesis by binding to the promoter of the RNA polymerase or to its anti-termination signal. ▶nucleolus, ▶protein synthesis, ▶ribosomal proteins, ▶E site, ▶A site, ▶P site, ▶Sec61 complex, ▶ribosomal RNAs, ▶EF-G, ▶EF-TU-GTP, ▶translocation hypothesis, ▶antibiotics, ▶discriminator region, ▶ribosome recycling, ▶ribonuclease R, ▶chloroplasts; Green R, Noller HF 1997 *Annu Rev Biochem* 66:679; Venema J, Tollervey D 1999 *Annu Rev Genet* 33:261; for crystalline structure of the small and the large subunits of bacterial ribosomes: Clemons WM Jr et al 1999 *Nature (Lond.)* 400:833; Ban N et al *ibid.* 841; Cate JH et al 1999 *Science* 285:2095; Wimberly BT et al 2000 *Nature (Lond.)* 407:327; Ban N et al 2000

Science 289:905; Yusupova GZ et al 2001 *Cell* 106:233; Ogle JM et al 2001 *Science* 292:897; LaFontaine DLJ, Tollervey D 2001 *Nature Rev Mol Cell Biol* 2:514; Moss T, Stefanovsky VY 2002 *Cell* 109:545; Doudna JA, Rath VL 2002 *Cell* 109:153; Fatica A, Tollervey D 2002 *Current Opin Cell Biol* 14:313; Moore PB, Steitz TA 2003 *Annu Rev Biochem* 72:813; <http://rdp.cme.msu.edu>; small subunit: <http://www.psb.ugent.be/rRNA/ssu/>; large subunit: <http://www.psb.ugent.be/rRNA/lssu/>.

Riboswitch: In certain mRNAs there are untranslated receptor elements for target metabolites. Highly selective binding of the metabolite permits a conformational switch (somewhat similar to attenuation) that may lead to modulation in the synthesis of a protein or by cutting up mRNA with the aid of a ribozyme (see Fig. R76).

In some instances, tandem riboswitches control complex regulation (Sundarsan N et al 2007 *Science* 314:300). In some cases, RNase P cleaves the riboswitch (Altman S et al. 2005 *Proc Natl Acad Sci USA* 102:11284). The crystal structure of *Arabidopsis* thiamine pyrophosphate riboswitch provides information on its basic function (Thore S et al 2006 *Science* 312:1208). More than 2% of the genes in some species are regulated by riboswitches. Riboswitches have high specificities and can discriminate even among guanine (G), adenine (A) or hypoxanthine. A more complex binding pattern has been identified in the thiamine pyrophosphate (TPP) riboswitch (Serganov A et al 2006

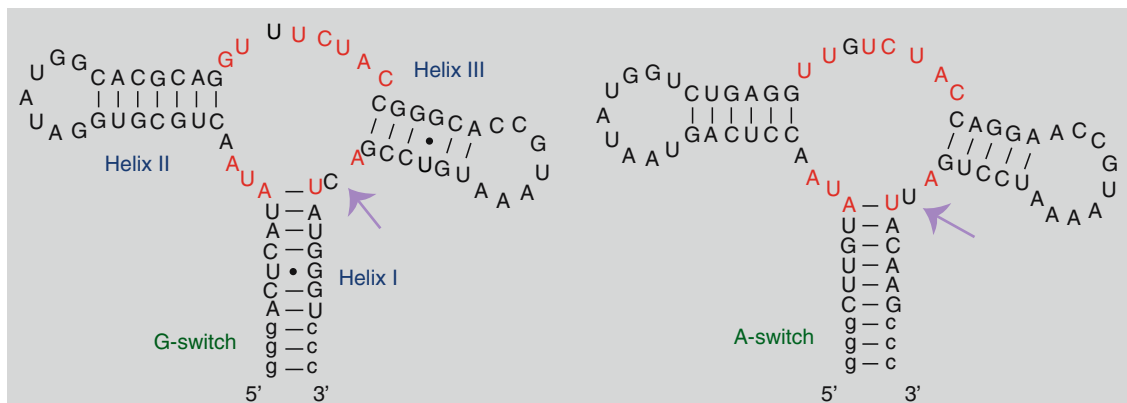


Figure R76. Riboswitch. Secondary structure guanine (G) and adenine (A) switches. The two switches appear highly similar, almost identical, and yet they have high specificity. The red core sequences are well conserved, except the bases represented at purple arrows. The lower-case letters represent residues not found in the original and which are introduced here to facilitate in vitro transcription. (Modified from Noeske J et al 2005 *Proc Natl Acad Sci USA* 102:1372.)

Nature [Lond] 441:1167) or *S*-adenosylmethionine riboswitch (Montange RK, Batey RT 2006 Nature 441:1172). ▶repressor, ▶attenuator region, ▶aptamer, ▶ribonuclease P; Winkler WC et al 2002 Proc Natl Acad Sci USA 99:15908; Mandal M et al 2003 Cell 113:577; Mandal M, Breaker R 2004 Nature Rev Mol Cell Biol 5:451; purine-specific riboswitch structure: Batey RT et al 2004 Nature [Lond] 432:411; riboswitches in genomes: Hammann C, Westhof E 2007 Genome Biol 8:210; alternative splicing: Cheah MT et al 2007 Nature [Lond] 447:497.

Ribothymidine: A thymine in the tRNA which is attached to ribose rather than to deoxyribose as it occurs in the DNA. ▶tRNA

Ribotype: The RNA pool (similar to genotype for DNA); the information content of the RNA. It is different from the genotype because by differential processing, splicing, editing, etc., it may convey different meanings. The processed variations—during the course of evolution—may be integrated into the DNA genetic material with the aid of reverse transcriptases and become part of the “hard heredity”. (See Herbert A, Rich A 1999 Nature Genet 21:265).

Ribozyme: A catalytic RNA possessing enzymatic activity such as splicing RNA transcripts, cleavage of DNA, amide and peptide bonds, polymerization and limited replication of RNA, etc. Thus, these ribonucleic acids carry out functions similar to those of protein enzymes. Ribozymes are generally metalloenzymes, commonly using Mg^{2+} for catalysis and stabilization.

Some viral ribozymes do not require metal ions to cleave phosphodiester bonds. Most commonly they cleave phosphodiester bonds but they can also synthesize nucleotide chains. The ribozymes are generally large molecules yet the shortest ribozyme is only UUU and it acts on CAAA. A two-base ribozyme may catalyze the formation of 3',5' phosphodiester linkages 36,000-fold faster (Reader JS, Joyce GF 2002 Nature [Lond] 420:841). Ribozymes commonly have an internal guide for substrate recognition near their 5' terminus and a *splice site* (self-cleavage or catalytic site) where they cleave and splice the molecules. Frequently, ribozymes are classified into groups such as the hammerhead ribozymes (see Fig. R78) that are used mainly by plant RNA viruses, the RNase P, the delta, group I, and hairpin ribozymes (see Fig. R77). The hammerhead ribozymes cut at the UCX sequence if the neighboring sequences are complementary and pair.

Tertiary contacts distant from the active site prime hammerhead ribozymes for catalysis (Martick M, Scott WG 2006 Cell 126:309). The hairpin ribozymes must have at least ~50 nucleotides in the catalytic domain and ~14 in the substrate domain. The two domains pair in a two-stem form separated with an unpaired loop of the ribozyme and substrate, most commonly containing a 5'-AGUC-3' sequence. Cleavage is usually between A and G of the substrate.

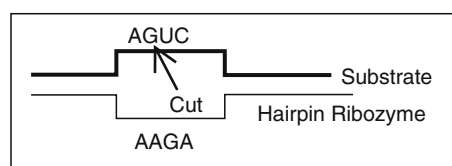


Figure R77. Hairpin ribozyme

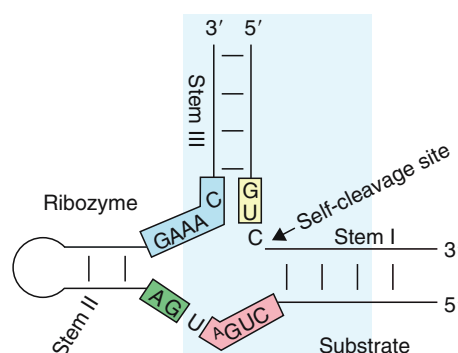


Figure R78. The critical sequences in the hammerhead ribozymes (boxed nucleotides) are conserved

RNA-catalyzed RNA polymerization has also been identified. Various proteins may affect the substrate binding by base-pairing and cleavage product release. Although ribozymes may cleave molecules in trans, their efficiency is usually better for cis substrates. Ribozymes functioning as ligases or polynucleotide kinases in mRNA repair by trans-splicing. Isomerases as well as self-alkylating catalysts have also been isolated from large pools (10^{14}) of diverse RNAs.

From an evolutionary point of view these diverse ribozyme functions lend support to the ideas of the prebiotic RNA world (see Fig. R79). Ribozymes can be engineered to recognize specific mRNAs and by cleaving them prevent the expression of a particular protein. They have an advantage over protein enzymes because it is less likely that they would incite an immune reaction. Because of their small

size, their introduction into the cell is facilitated with the aid of transformation vectors. Small RNA transcription units that may accumulate up to 106 copies per cell can propagate them. Transcription units for tRNA, U6 snRNA have been used. Although these units produce high ribozyme titer in the cell, polymerase II transcribed units target the ribozymes more effectively to the desired location. In such Pol II units the ribozyme motif is inserted into the 5' untranslated sequences. Evolution of ribozymes may be a much faster process than that of protein enzymes. A single polynucleotide sequence may fold into two different conformations and display two different catalytic activities such as the Hepatitis Delta Virus self-cleaving ribozyme and a class III self-ligating ribozyme. These ribozymes may not share more than 25% (random) nucleotide identity and yet their folding pattern may satisfy the requirements of the two functions (Schultes EA, Bartel DP 2000 Science 289:448). Both hammerhead and hairpin ribozymes were introduced into human cells infected with HIV and the ribozymes reduced the level of the gag protein. Ribozyme gene therapy has been considered for malignancies caused by the human papilloma virus, Epstein-Barr virus, and hepatitis viruses. Ribozymes thus have various therapeutic potentials if an appropriate targeting system (e.g., retroviral, adenoviral vectors, cationic liposomes) is available. Ribozymes may inactivate tyrosine kinases, transcription factors, cell adhesion molecules, growth factors, telomerase, etc. The ribozyme may recognize complementary RNA targets. Problems may include low efficiency of transfection, poor target recognition, transcriptional silencing, instability, etc. Inadequate target recognition can apparently be remedied by adding a biosensor to the ribozyme, the absence of which the ribozyme is in an inactive conformation. When the sensor recognizes a specific substrate, the ribozyme conformation is changed and it is activated, and it cleaves the specific target (Bergeron LJ, Perrault J-P 2005 Nucleic Acids Res 33:1240). Ribozymes may be used in the same way as antisense constructs but with the special advantage of catalytic activity. ▶introns, ▶ribonuclease P, ▶peptidyl transferase, ▶CBP2, ▶deoxyribozyme, ▶ligase RNA, ▶kinase, ▶alkylation, ▶RNA world, ▶RNA restriction enzyme, ▶gene therapy, ▶cancer gene therapy, ▶HIV, ▶SELEX, ▶liposomes, ▶cytofectin, ▶lipids cationic, ▶viral vectors, ▶transfection, ▶antisense technologies, ▶transdominant molecules, ▶leadzyme, ▶DNA-zyme; Wadekind JE, Mckey DB 1998 Annu Rev Biophys Biomol Struct 27:475; Doherty EA, Doudna JA 2000 Annu Rev Biochem 69:597; Ferbeyre G et al

2000 Genome Res 10:1011; Takagi Y et al 2001 Nucleic Acids Res 29:1815; Doudna JA, Cech TR 2002 Nature [Lond] 418:222; hairpin ribozyme: Nahas MK et al 2004 Nature Struct Mol Biol 11:1107; structure-function of hammerhead ribozymes: Blount KF, Uhlenbeck OC 2005 Annu Rev Biophys Biomol Struct 34:415.

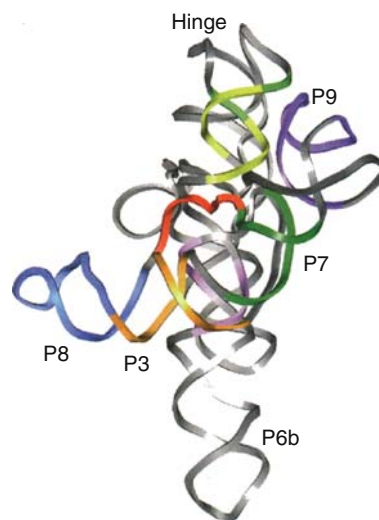


Figure R79. The crystal structure of a 247-nucleotide *Tetrahymena* ribozyme of an rRNA intron. The conserved helical elements are identified by P1 TO P9. (Courtesy of Dr. Tom Cech. From Golden BL et al 1998 Science 282:259)

Ribulose 1,5-Bisphosphate Carboxylase-Oxidase

(Rubisco): A chloroplast-located enzyme, generally the largest amount of protein in that organelle. Its large subunit is encoded and translated by the chloroplast system; the small subunit is coded for by a nuclear gene, translated in the cytosol, and imported into the plastids. The abundance of the small subunit affects the translation of mRNA of the large subunit. Rubisco is involved in early steps of photosynthesis and works through an intermediate 3-phosphoglycerol and it is involved in oxidative and reductive carboxylation. In dinoflagellates, Rubisco is encoded by the nucleus. ▶chloroplast genetics, ▶photosynthesis, ▶Rubisco; Suss K et al 1993 Proc Natl Acad Sci USA 90:5514; Taylor TC et al 2001 J Biol Chem 276:48159; Spreitzer RJ, Salvucci ME 2002 Annu Rev Plant Biol 53:449.

Rice (*Oryza*): Gramineae, x = 12, genome size ~430 Mbp; the species is either diploid or tetraploid. The genome size was revised to 389 Mb in 2005 (see Fig. R80).



Figure R80. *Oryza*

Over 2,000 molecular markers are available in this small genome. The generation time is 90–140 days. Two genomes were sequenced by 2002 (Science 296:79 and 92) and seem to have more open reading frames (32,000–55,000) than other organisms. After sequencing the genome the total nontransposable element-related and protein-coding gene number was revised to 37,544, and 29% of them are clustered in families. 2,859 of the genes appear unique to rice and other cereals. A transcription map of 35,970 (81.9%) of the genes and the existence of 54,564 transcribed intergenic sequences is available for *indica* rice (Li L et al 2006 Nature Genet 38:124). Homologues to *Arabidopsis* appear to be 71% and 90% of the *Arabidopsis* genes are homologous to those in rice. Of the 11,487 *Tos17* retroposon sites, 3,243 are within genes. The nuclear genomes showed organellar DNA fragments in 0.38% to 0.43%. There are 80,127 polymorphic sites which distinguish the two cultivated rice subspecies, *japonica* and *indica*. Single nucleotide polymorphism was high, 0.53% to 0.78%, about 20 times higher than in *Arabidopsis* (Matsumoto T et al 2005 Nature [Lond] 436:793).

Two groups of quantitative gene loci (QTL) have been successfully identified with regard to biochemical activity and their significance in breeding more productive crops. A 383-bp deletion of a gibberellin oxidase gene (*Ph1*, plant height) lead to high-yielding short-stem strains (Sasaki A et al 2002 Nature [Lond] 416:701). Gene *Gn1*, encoding cytokinin oxidase/dehydrogenase enzyme at reduced expression and increased cytokinin level in the reproductive organs and increased grain number per panicle by 44% and consequently increased yields. Several *Gn* genes were scattered over five chromosomes (Ashikari M et al 2005 Science 309:741). The completely sequenced chromosomes 11 and 12 contain 289

disease resistance-like and 28 defense-response genes (BMC Biology 2005, 3:20). *O. sativa* cultivars die if completely submerged in water for two weeks. The *Sub1A* allele, near the centromere of chromosome 9, is an ethylene-response-factor-like gene and can convey tolerance to flooding and increases crop security (Xu K et al 2006 Nature [Lond] 442:705). ▶cytokinin, ▶gibberellins, ▶QTL, ▶candidate gene, ▶*Magnaporthe grisea*; Shimamoto K, Kyojuka J 2002 Annu Rev Plant Biol 53:399; Sasaki T et al 2002 Nature [Lond] 420:312; Feng Q et al 2002 Nature [Lond] 420:316; Kikuchi S et al 2003 Science 301:376; sequenced genome of the pathogen *Xanthomonas oryzae*: Lee B-M et al 2005 Nucleic Acids Res 33:577; Molecular Biological Encyclopedia: <http://cdna01.dna.affrc.go.jp/cDNA/>; <http://rgp.dna.affrc.go.jp/giot/INE.html>; <http://www.tigr.org/tdb/tgi/>; annotation database: <http://www.tigr.org/tdb/e2k1/osa1/>; reverse genetics: <http://orygenesdb.cirad.fr/>; annotations: <http://rapdb.lab.nig.ac.jp/>; mutants: <http://rmd.ncpgr.cn/>; annotation database: <http://rad.dna.affrc.go.jp/>; LTR retrotransposons: <http://www.retroryza.org/>; <http://rice.tigr.org>.

Richner-Hanhart Syndrome: ▶tyrosine aminotransferase

Ricin: An extremely toxic, ribosome-inactivating, dimeric toxin produced by the plant, castor bean (*Ricinus*). The estimated lethal dose is 1–10 µg/kg when delivered as an injection or aerosol to humans. It may be significant in cancer therapy research. The deglycosylated ricin toxin A chain (dgRTA)—when containing three-amino acid mutations (xAspyat, position 97) where x can be Leu, Ile, Gly or Val and y could be Val, Leu, Ser—causes practically no liver damage and shows much reduced vascular leak syndrome. Liver damage and vascular leakage in the lung would be the major obstacles requiring the therapeutic use of this toxin (Smallshaw JE et al 2003 Nature Biotechnol 21:387). Limited trials indicate that an effective and low-risk vaccine can be produced against ricin. By using recombinant DNA technology changes can be created at the ribotoxic A chain that can prevent vascular leak effects of ricin. Tests show that 100 µg of the modified antigen provided 100% protection when injected at monthly intervals into five human volunteers (Vitetta ES et al 2006 Proc Natl Acad Sci USA 103:2268). ▶magic bullet, ▶RIP, ▶biological weapons, ▶castor bean; Lord JM et al 1991 Semin Cell Biol 2:15; Day PJ et al 2001 J Biol Chem 276:7202.

Ricinosome: A protease precursor vesicle formed from the endoplasmic reticulum in senescing plant tissues. It contains large quantities of a 45 kDa cystin

endoprotease and other proteins required for apoptosis. ►**apoptosis**, ►**protease**; Schmid M et al 2001 Proc Natl Acad Sci USA 98:5353.

Rickets: Anomalies in bone development caused by defects of calcium and phosphorus absorption and/or vitamin D deficiency. Human autosomal recessive conditions may be caused by defects in the synthesis of calciferol (vitamin D) from sterols; in such cases vitamin D₃ can correct the dependency. In some forms the receptor is defective and vitamin D cannot alleviate the hereditary condition (12q12-q14). Deficiency of pseudovitamin D (25-hydroxycholecalciferol-1-hydroxylase) is also at about the same chromosomal area. Hypophosphatemia (Xp22.2-p22.1) may also cause vitamin D unresponsive rickets. Rickets may then have multiple phenotypic consequences such as alopecia, epilepsy, etc. ►**hypophosphatasia**, ►**hypophosphatemia**, ►**vitamin D**, ►**spermine**, ►**Dent disease**

Rickettsia: Small rod-shape or roundish, obligate intracellular, Gram-negative bacteria. They may carry typhus (typhoid fever, accompanied by eruptions, chills, headaches and high mortality) and spotted fever, a tick-borne disease of cerebrospinal meningitis (brain inflammation) from animals to humans by infected arthropods (ticks, lice, fleas). The mammalian receptor for *R. conorii* is Ku70 and the *Rickettsia* protein rOmpB is a ligand for the internalization process. Ubiquitin ligase c-Cbl is also recruited to the entry foci to block invasion by partial destruction of Ku70 (Martinez JJ et al 2005 Cell 123:1013). The genome of *Rickettsia prowazekii* contains 1,111,523 bp and it shows the closest similarity to mtDNA of eukaryotes (Andersson SG et al 1998 Nature [Lond] 396:109). ►**mtDNA**, ►**mitochondria**, ►**endosymbiont theory**, ►**Wolbachia**, ►**Ku70**, ►**OMP**, ►**ubiquitin**; Nature [Lond] 396:133 for complete physical map; ►**reductive evolution**, ►*Anaplasma marginale*; Ogata H et al 2001 Science 293:2093.

Rictor: A rapamycin-insensitive mTOR. ►**rapamycin**, ►**TOR**

RID (random insertion/deletion): A technique by which certain bases of the DNA can be deleted and/or replaced at various positions, thus generating mutations. ►**targeting genes**, ►**mutagenesis**; Murakami H et al 2002 Nature Biotechnol 20:76.

RIDGE (region of increased gene expression): The highly expressed genes appear to be clustered in the chromosome as detected by SAGE. These domains have high G-C content, high SINE and low LINE repeat density and shorter introns. Antiridge domains display opposite characteristics.

►**SAGE**, ►**clustering of genes**; Versteeg R et al. 2003 Genome Res 13:1998.

Rieger Syndrome: An autosomal dominant eye, tooth and umbilical hernia syndrome. Its chromosomal location (just as the Nazi discoverer of the disease) was controversial. Human chromosomes 21q22, 4q25, 13q14 and several others have been implicated. The basic cause is also unclear; epidermal growth factor, interleukin-2, alcohol dehydrogenase, fibroblast growth factor deficiencies appear to be involved in chromosome 4. The chromosome 4 gene (RIEG) has now been cloned and it encodes a transcription factor with similarities to the *bicoid* gene of *Drosophila*. Vertebrate homologs *Pitx*, *Potxlx* and *Apr-1* mediate the left-right development of visceral organs in concert with a number of other genes such as *Sonic hedgehog*, *Nodal*, etc. ►**eye diseases**, ►**tooth agenesis**, ►**morphogenesis in *Drosophila*** {8}, ►**left-right asymmetry**; Saadi I et al 2001 J Biol Chem 276:23034.

Rifampicin: An antibiotic that inhibits prokaryotic DNA-dependent RNA polymerase (but not the mammalian RNA polymerase) and inhibits replication in *E. coli* and other prokaryotes. Rifamycin has similar effects. The antibiotic effects of the different rifamycins may vary. ►**antibiotics**, ►**maytanisoids**; Campbell EA et al 2001 Cell 104:901.

Rifins (repetitive interspersed family): Rifins are *Plasmodium falciparum* proteins in high copy number, involving antigenic variation. They are instrumental in the infection by the parasite. ►*Plasmodium falciparum*, ►**antigenic variation**

Rigens: A translocation complex in *Oenothera muricata*. If during meiosis this complex goes to the top end of the megaspore tetrad, it may overcome its topological disadvantage and this megaspore may develop into an embryo sac because the other complex, *curvans*, is not functional in the megaspores. ►**megaspore competition**, ►*Oenothera*, ►**zygotec lethal**

RIG Oncogene: The RIG oncogene is probably required for all types of cellular growth and it is active in a very wide variety of cancers. The C-terminal domain of RIG-1 binds double-stranded RNA and thus senses infectious viruses. It also stimulates the expression of transcription factors such as NF-κB, IRF3, ATF2, and provides protection against virus infection. The overexpression of MAVS (mitochondrial antiviral signaling) boosts the protection by IFN-β stimulation. ►**oncogenes**, ►**NF-κB**, ►**IRF3**, ►**ATF2**; Seth RB et al 2005 Cell 122:669; McWhirter SM et al 2005 Cell 122:645; detection of viral RNA by RIG-1:

Hornung V et al 2006 Science 314:994; RIG-1 response to single-strand RNA: Pichlmair A et al 2006 Science 314:997.

RIGS (repeat-induced gene silencing): An apparently epigenetic phenomenon caused by the methylation of cytosine residues. An alternative process is that locally paired regions of homologous sequences are flanked by unpaired heterologous sequences in transgenic plants. Silencing and variegation occurs when transgenes are inserted either in trans or cis position to heterochromatin. The degree of silencing is proportional to the distance between the transgene and the heterochromatin. ▶methylation of DNA, ▶RIP, ▶silencing, ▶epigenesis, ▶co-suppression, ▶heterochromatin, ▶position effect; Selker EU 1999 Cell 97:157.

Riken (Genome Exploration Research Group, Genome Science Laboratory): Technologies, cDNA encyclopedias, etc. (<http://genome.gsc.riken.jp>).

Riley-Day Syndrome (dysautonomia): A human chromosome 9q31-q33 recessive neuropathy involving emotional instability, lack of tearing, feeding difficulties, unusual sweating, cold extremities, etc. The prevalence in Ashkenazic Jews is about $2-3 \times 10^{-4}$ but it is quite rare in other ethnic groups. Defects in the nerve growth factor receptor are suspected. ▶neuropathy, ▶nerve growth factor, ▶IkB, ▶pain-insensitivity; Slaugenhaupt SA et al 2001 Am J Hum Genet 68:598.

Ring Bivalent: A ring bivalent has terminalized chiasmata in both arms (see Fig. R81) and thus in early anaphase I the homologous chromosomes appear to be temporarily connected at the telomeric regions of the four chromatids (see Fig. R82). This, however, is not a ring chromosome. ▶translocation ring

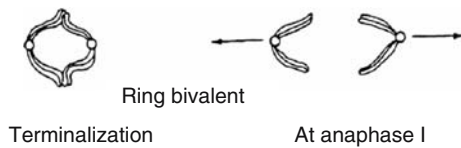


Figure R81. Terminalization of ring bivalents



Figure R82. Ring and rod bivalents

Ring Canal: Ring canals are intercellular bridges during cytotblast differentiation (see Fig. R83). They

transport mRNA and proteins from nurse cells to the oocytes. They are composed of actin, the hts (hui-li tai shao), and the kelch proteins. ▶cytotblast, ▶maternal effect genes, ▶RNA localization



Figure R83. Ring chromosome

Ring Chromosome: A circular chromosome without free ends (o)—such as the bacterial chromosome—as the ring DNAs in mitochondria and plastids. Ring chromosomes may result by different types of chromosome breakage. Simultaneous breaks across the centromere and the chromosome ends (telomeres) may result in the fusion of the two broken termini generating one or two ring chromosomes. Also, crossing over between two ends of the same chromosome may give rise to a centric ring and acentric fragments. Sister chromatid exchange within a ring chromosome may result in a dicentric ring chromosome, which at anaphase separation may break at various points and generate unequal size ring chromosomes and genetic instability (see Fig. R84). ▶dicentric ring chromosome, ▶ring bivalent, ▶translocation ring, ▶sister strand exchange, photomicrograph by Dr. D. Gerstel.

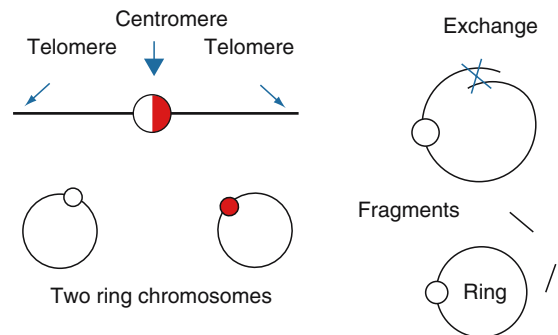


Figure R84. Left: A simultaneous breakage at both the centromere and at the telomeres may result in fusion between the broken ends and the generation of ring chromosomes from both of the arms of the normal chromosome generating two new ring chromosomes. Right: Exchange between the two ends yields a ring chromosome and two acentric fragments. For the sake of simplicity the chromatids of the chromosomes are not represented in the diagrams

RING Finger: A cysteine-rich amino acid motif such as Cys-X2-Cys-X(9–27)-Cys-X(1–3)-His-X2-Cys-X2-Cys-X(4–48)-Cys-X2-Cys. X stands for any amino acids in the numbers shown in parenthesis. These are protein-protein, protein-membrane, protein-DNA interacting elements involved in the regulation of transcription, replication, recombination, restriction, development, cancerous growth, etc. The RING fingers may also bind Zinc and are thus related to Zinc fingers. The name comes from the human gene RING—carrying such a motif—located in the vicinity of HLA. ▶ [Zinc finger](#), ▶ [DNA-binding protein domains](#), ▶ [autoimmune disease](#); Saurin AJ et al 1996 Trends Biochem Sci 21:208.

Ring Species: Ring species are reproductively isolated, yet some connections exist between them (Irwin DE et al 2005 Science 307:414).

Ringer Solution: A ringer solution is prepared in somewhat different concentrations depending on type of tissues it is used for. It is used as a sterilized physiological salt solution, in 100 mL water mg salts: NaCl 860, KCl 30, CaCl₂ 33; some formulations also add NaHCO₃ 20, NaH₂PO₄ and glucose 200.

RIP: A term for “recombination induced premeiotically” and, alternatively, “repeat induced point mutation”. When repeated (generally longer than 400 bp) DNA is introduced into fungi (*Neurospora* and others) by transformation or by other means, and the replicated sequence may be lost premeiotically. Alternatively, the duplications are methylated to reduce recombination or mutations are induced. In *Ascobolus* and *Coprinus*, the repeats may be methylated without mutations to follow. The mutations are attributed to cytidylic acid methylation of 5'-CpG sequences as a defense against duplication introduced by transformation to silence the superfluous genetic material. The methylation results primarily in transition mutations, GC→AT. The distribution of the mutations in the DNA is not random but most commonly occurs 5' of adenine sites but somewhat less frequently take place 5' to thymine or guanine but rarely at site 5' to other cytosines. Generally, within the same chromosome, either C→T or G→A changes occur, but not both. The majority of the RIP mutations are missense or nonsense but occasionally functional alleles also arise. The RIP mutations are frequently unstable and the longer duplications revert at a frequency of about 10⁻⁴ in the vegetative cells. ▶ [co-suppression](#), ▶ [ripping](#), ▶ [RNAi](#), ▶ [RIGS](#), ▶ [methylation of DNA](#), ▶ [MIP](#), ▶ [position effect](#), ▶ [suppressor genes](#), ▶ [integration](#); Selker EU 1997 Trend Genet 13:296; Hsieh J, Fire A 2000 Annu Rev Genet 34:187; Miao VP et al 2000 J Mol Biol

300:249; Freitag M et al 2002 Proc Natl Acad Sci USA 99:8802.

RIP (ribosome-inactivating protein): Antiviral proteins in plants and animals with glycosylase activity. Thus, they may depurinate RNA of susceptible ribosomes and block protein synthesis. RIPs protect plants against pathogens. ▶ [depurination](#), ▶ [glycosylases](#), ▶ [saporins](#), ▶ [ricin](#), ▶ [abrin](#); Nielsen K, Boston RS 2001 Annu Rev Plant Physiol Plant Mol Biol 52:785.

RIP (RNAIII inactivating peptide): ▶ [RNAIII/rnaiii](#)

RIP (regulated intramembrane proteolysis): It may control cell differentiation, lipid metabolism and various proteins in prokaryotes and eukaryotes. The targets included are proteins of the endoplasmic reticulum, sterol regulatory element binding proteins (SREBP), and amyloid precursor protein (APP), Notch). ▶ [SREBP](#), ▶ [Alzheimer disease](#); Notch, Brown MS et al 2000 Cell 100:391.

Rip1: ▶ [RNA export](#)

Ripping: The process generated by RIP mutations. RIP may also generate point mutations primarily by G-C → A-T transitions. ▶ [RIP](#)

RISC (RNA-induced silencing complex): RISC is composed of siRNA as well as Argonaute 2, VIG, FXR and the Tudor-SN proteins. ▶ [RNAi](#), ▶ [named proteins](#), ▶ [miRNP](#), ▶ [P body](#); Caudy AA et al 2003 Nature [Lond] 425:411.

Rise: ▶ [one-step growth](#)

Risk: A combination of the degree of a hazard with its potential frequency of occurrence, e.g., if a recessive gene causes a particular malformation in 30% of the fetuses, the probability of its homozygosity among the progeny of heterozygous parents is 0.25. Thus, the risk of this malformation is $0.3 \times 0.25 \approx 0.075$, i.e., 7.5%. If an individual is known to be heterozygous for a recessive lethal gene and marries a first cousin, the risk of them having a stillborn child may be as high as $0.5 \times 0.25 = 0.125 = 1/8$. If, however, the carrier marries an unrelated person from the general population, where the frequency of this gene is only 0.005, the risk will be $0.5 \times 0.005 = 0.0025 = 1/400$. In some cases, the calculation of the genetic risk is not quite as simple. Let us assume that the penetrance of a dominant gene is 80% but non-transmissible factors (somatic mutation not included into the germline, environmental effects) may also evoke the same symptoms; in this case members of the family do not display the defect. For example, when new dominant germline mutations are responsible for 15% of the cases, in this instance the ancestors are not affected.

The offspring of such a mutant individual, however, has a 0.8 (penetrance) $\times 0.5$ (expected gametic transmission) = 0.4 chance of being affected. The risk of all their offspring not being affected is $1 - 0.15 = 0.85$, and if not inherited (0 inheritance), the chance is $0.85 \times 0 = 0$. The probability of inherited (0.15) \times penetrance (0.8) is $\cong 0.12$ (12%). Further considerations are necessary for proper genetic counseling if the proband has already normal, not-affected offspring. We designate the hereditary status of the proband, the probability of being a hereditary case: $P(H) = 0.15$, as specified above. The probability that the first child being normal (not affected), despite the defective parental gene is $P(N/H) = 1 - 0.4 = 0.6$. The probability that the proband does not have this defective gene in the germline is $P(H^-) = 0.85$. The conditional probability that an offspring would be normal is $P(N/H^-) \cong 1$. From Bayes' Theorem the probability that the first child inherited but did not express the trait is:

$$P(H/N) = \frac{P(H)P(N/H)}{P(H)P(N/H) + P(H^-)P(N/H^-)}$$

$$= \frac{[0.15][0.6]}{[0.15][0.6] + [0.85][1]} = \frac{0.09}{0.94} \cong 0.096$$

With two not-affected children $P(N/H) = 0.6^2 = 0.36$, and for n offspring 0.6^n is the probability of the parent being normal in phenotype although having the defective gene.

The second child being normal although carrying the defective gene is:

$P(N/H) = 0.096 \times 0.4 \cong 0.0384$ and after substitution into the Bayes' formula

$$P(H/N) = \frac{[0.15][0.0384]}{[0.15][0.0384] + [0.85][1]} = 0.0067$$

Attributable risk (AR) reveals the risk of genetically susceptible individuals relative to those who are not susceptible. It is estimated as $AR = \{P_{Aa}(1 - 2q[1 - P_{aa}])\} / (P_{Aa}[1 - 2q])$ where P is the frequency and A and a are the dominant and recessive alleles, respectively, at a locus. The relative risk can also be estimated by the contingency chi square using an association test. Absolute risk is the excess risk of an agent which causes a difference between exposed and unexposed populations. Background risk is the chance of being afflicted in a population with a certain frequency of disease-causing allele(s). Usually, confounding factors also influence the risk—age, sex, addictions, etc.—and when this is the case more elaborate statistical procedures are required. Life expectancy may be reduced by several factors in a complex manner (smoking a cigarette [10 min], accidents [95 days], obesity [by 20% or

2.7 years], 1 mrem of radiation [1.5 min], medical X-rays [6 days]).

It is of great recent interest to determine the risk of disease by genome-wide association studies (risk engine) (Editorial 2005 *Nature Genet.* 37:1153). [►Bayes' theorem](#), [►genetic risk](#), [►recurrence risk](#), [►empirical risk](#), [►genetic hazards](#), [►genotypic risk ratio](#), [► \$\lambda_s\$](#) , [►association test](#), [►mutation in human populations](#), [►utility index for genetic counseling](#), [►confidence intervals](#), [►radiation hazard assessment](#), [►cosmic radiation](#), [►linkage](#)

RITS (RNA-induced transcriptional silencing): RITS contains Dicer-generated siRNA and it is required for heterochromatin silencing by attaching to histone-3 methylated at lysine 9 residues. [►RNAi](#), [►heterochromatin](#), [►histones](#); Ekwall K 2004 *Mol Cell* 13:304; Noma K et al 2004 *Nature Genet* 36:1174; Bühler M et al 2006 *Cell* 125:873.

RIZ (retinoblastoma-interacting zinc finger protein, 220 kDa with 8 Zn-finger domains): RIZ has a common loss at human chromosomal site 1p36 and may be responsible for colorectal cancer, breast cancer, and endometrial neoplasias. RIZ also appears as a downstream effector of estrogen action. [►retinoblastoma](#), [►Zinc finger](#), [►estradiol](#), [►colorectal cancer](#), [►effector](#); Steele-Perkins G et al 2001 *Genes Dev* 15:2250.

RK: Rank of utility.

RK2 Plasmids: These plasmids represent a family of broad host-range plasmids (56.4 kb), resistant to tetracycline, kanamycin, and ampicillin. The size and selectability of other members of the family varies. (See Pogliano J et al 2001 *Proc Natl Acad Sci USA* 98:4486).

RKIP (Raf kinase inhibitor protein): [►RAF](#)

RLDB: [►reference library database](#)

RLGS (restriction landmark genomic scanning): The goal of the procedure is to determine the methylation status of genes that may have undergone epigenetic changes (such as oncogenic transformation) or are imprinted. It also detects tissue-specific methylation patterns in the genome. It is based on digestion of DNA by a rare-cutter restriction endonuclease such as *NotI*, which does not cleave methylated CpG islands. The fragments are then radioactively end-labeled at the *NotI* cut sites and further reduced in size by another restriction enzyme, e.g., *EcoRV* (GAT↓ATC). The fragments are then separated by agarose gel electrophoresis and further cleaved with a third restriction enzyme, e.g., *HinfI* (G↓ANTC) in the gel. The small fragments are then subjected to electrophoresis in a second dimension in an

acrylamide gel and the fragments containing the radioactive label are identified. The procedure thus identifies the difference between methylated and not methylated status at a specific site. The method holds promise for mass scanning potential cancer genes. It has also been used for determining allele-specific methylation of imprinted genes (Plass C et al 1996 *Nature Genet* 14:106). ▶[epigenesis](#), ▶[imprinting](#), ▶[electrophoresis](#), ▶[restriction enzymes](#), ▶[methylation of DNA](#); Costello JF et al 2000 *Nature Genet* 25:132; Costello JF et al 2002 *Methods* 27:144.

RLK: A Tec family kinase involved in T cell receptor signaling. ▶[T cell receptor](#), ▶[Tec](#); Yang WC et al 2000 *Int Immunol* 12:1547.

R-Loop: A quasi three-stranded structure consisting of a double-stranded DNA and a single-stranded RNA, which displaces, at a short section, one of the DNA strands. Such a structure may occur primarily at the replication forks of DNA of prokaryotes and eukaryotes. ▶[D loop](#); Nossal NG et al 2001 *Mol Cell* 7:31; Clayton DA 2000 *Hum Reprod* 15(Suppl. 2):22; Tracey RB, Lieber MR 2000 *EMBO J* 19:1055.

RLP (ribosome landing pad): ▶[IRES](#)

RL-PCR: ▶[reverse ligase-mediated polymerase chain reaction](#)

RMCE (recombinase mediated cassette exchange): A procedure for large-scale screening of recombinants under selective conditions. Variations exist. The diagram was redrawn after Tsin E et al 2005 *Nucleic Acids Res* 33(17):e147 (see Fig. R85). ▶[Cre/LoxP](#), ▶[hygromycin](#), ▶[gancyclovir](#), ▶[tetracycline](#), ▶[green fluorescent protein](#), ▶[luciferase](#), ▶[targeting genes](#), ▶[gene replacement](#)

RME1: An inhibitor of yeast meiosis and sporulation. ▶[mating type determination](#); Shimizu M et al 1998 *Nucleic Acids Res* 26:2320.

RMGR (recombinase-mediated genomic replacement): ▶[gene replacement](#)

RMSA-1 (regulator of mitotic spindle assembly): A protein which is phosphorylated only during mitosis and is a substrate for CDK2 kinase; it is required for the assembly of the spindle. ▶[spindle](#), ▶[CDK](#); Yeo JP et al 1994 *J Cell Sci* 107:1845.

RNA: Ribonucleic acid is a polymer of ribonucleotides. There are three main classes of RNAs in the cell: the mRNA, which provides the instructions for protein synthesis, the various ribosomal RNAs, and the tRNAs. Other RNAs are involved in splicing, editing, post-transcriptional modification, ribonucleoproteins that insert proteins into membranes and mediate telomere synthesis, replication priming RNAs, inhibitory RNAs (RNAi), ribozymes, and the noncoding RNAs involved in dosage compensation and imprinting. Maps of nuclear and cytosolic polyadenylated [poly(A)⁺] RNAs longer than 200 nucleotides (nt) (long RNAs, lRNAs) and whole-cell RNAs less than 200 nt (short RNAs, sRNAs) are transcribed over the entire nonrepetitive portion of the human genome. The potential biological function of an appreciable portion of long unannotated transcripts is to serve as precursors for sRNAs. These maps reveal three classes of RNAs that have specific genomic localization at gene boundaries. The biological relevance of these classes of RNAs is supported by a strong correlation with the expression state of the genes they associate with, as well as their syntenic conservation between humans and mouse (Kapranov P et al 2007 *Science* 316:1484). ▶[RNA I](#), ▶[mRNA](#), ▶[tRNA](#), ▶[rRNA](#), ▶[rrn](#), ▶[nucleic acid chain growth](#), ▶[non-canonical bases](#), ▶[telomerase](#), ▶[RNA editing](#), ▶[replication](#), ▶[RNAi](#), ▶[microRNA](#), ▶[ribozymes](#),

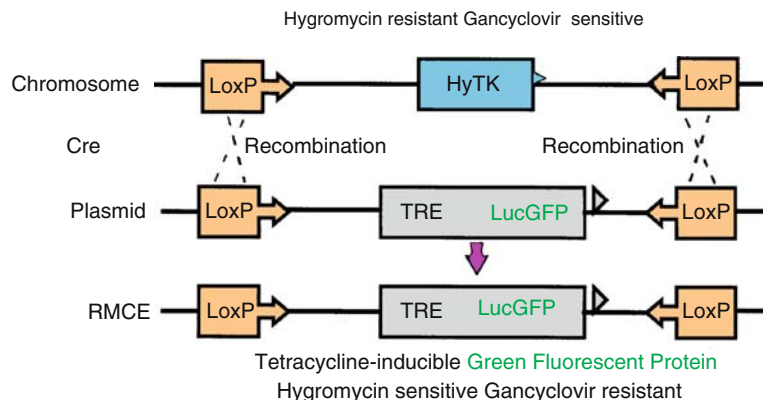


Figure R85. Recombinase-mediated cassette exchange

►dosage compensation, ►imprinting, ►Xist; <http://prion.bchs.uh.edu/>; structure and motifs: <http://uther.otago.ac.nz/v5g.html>; RNA structure, function, sequence alignment: <http://www.ccrmp.ncifcrf.gov/~bshapiro>; RNA secondary structure, folding, neighbors: <http://bioinformatics.bc.edu/clotelab/RNABor/>; RNA folding design: <http://www.bioinf.uni-freiburg.de/Software/INFO-RNA/start.html>; RNA secondary structure predictor: <http://compbio.cs.sfu.ca/taverna/>.

RNA I: An untranslated bacterial RNA controlling the maturation of RNA II that serves as a primer for plasmid DNA synthesis. RNA I and RNA II are synthesized on opposite DNA strands. RNA I binds to RNA II and thereby prevents its folding into a cloverleaf that is necessary for the formation of a stable DNA:RNA hybrid between RNA II and the plasmid DNA. This binding is promoted by the Rop protein (63 amino acid residues) coded for by 400-base downstream from the origin of replication. A single G → A transition mutation in Rop or upstream from it may contribute to plasmid amplification (see Fig. R86). RNA I, RNA II, and Rop also control plasmid incompatibility. RNase H cuts off the pre-primer section and prepares the primer for the actual DNA synthesis. RNA I may be polyadenylated and then its decay hastened in a way similar to mRNA. RNA I and RNA II may interact initially by base pairing between their 7-nucleotide complementary loops. The Rom/Rop protein may also bind to the transient complex and assures a more stable duplex of the two RNAs causing failure of replication initiation. ►polyadenylation, ►plasmid, ►RNA polymerase, ►ROM; Mruk I et al 2001 Plasmid 46:128.

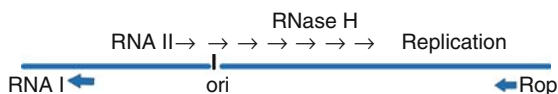


Figure R86. RNA I and RNA II synthesis

RNA II: ►RNA I

RNA Binding Proteins: These proteins modify the RNA structure locally or globally; they may affect RNA trafficking, mRNA biosynthesis, translation, splicing, polyadenylation, differentiation and diseases. They may be part of the combinatorial tagging of mRNA and may control the localization, translation, and decay of mRNA in the global expression program (Gerber AP et al 2004 PLoS Biol 2:342). The length and composition of the binding domains may vary. A human RNA-binding protein is encoded in chromosome 8p11-p12 (RBP-MS). ►DNA-binding protein domains, ►hnRNP; Burd CG, Dreyfuss G 1994

Science 265:615; Dreyfuss G et al 2002 Nature Rev Mol Cell Biol 3:195; Hall KB 2002 Current Opin Struct Biol 12:283; RNA binding site predictor: <http://bindr.gdcb.iastate.edu/RNABindR/>.

RNA Cap: ►cap, ►capping enzymes

RNA, Catalytic: ►ribozyme

RNA Chaperone: ►chaperones

RNA Codons: ►genetic code

RNA Computer: See Faulhammer D et al 2000 Proc Natl Acad Sci USA 97:1385; ►DNA computer

RNA Dependent RNA Polymerase (RdRP): This polymerase replicates the RNA genome of viruses. The RNA-directed RNA polymerase, primed by siRNA, amplifies the interference by RNAi. ►RNAi; Ahlquist P 2002 Science 296:1270; Ortin J, Parra F 2006 Annu Rev Microbiol 60:305.

RNA Display: A procedure for the enrichment of specific RNAs. In in vitro the translation system uses a synthetic mRNA, which carries the peptidyl acceptor antibiotic puromycin at the 3' end. The protein synthesis proceeds until the end of the open reading frame and the translation stalls at the RNA-DNA junction. The puromycin enters the A site of the ribosome and accepts the nascent peptide. Affinity chromatography and immunoprecipitation permit purification of the fused mRNA-peptide from the complex mixture. The RNA serves as a tag for specifying the peptide. ►protein synthesis, ►puromycin, ►affinity chromatography, ►immunoprecipitation, ►phage display; Roberts RW, Szostak JW 1997 Proc Natl Acad Sci USA 94:12297.

RNA, Double-Stranded: A double-stranded RNA is usually a minor fraction of the total cellular RNA (unlike to DNA). It appears that if double-stranded RNA, with sequences homologous to an open reading frame of a gene, is introduced into the cell, the antisense RNA more effectively blocks the function of that gene (in *Caenorhabditis*). It is a surprising fact that even at very low abundance this RNA is a highly effective inhibitor. A double-stranded RNA-binding protein is apparently required for gene activation in the mammalian germ cells. dsRNA is common in virus-infected cells and it is an inducer of interferon. It inhibits the transcription of about one-third of the genes and stimulates the rest to a variable degree.

A substantial fraction of the pairing of RNA molecules is not in compliance with the Watson-Crick model. Hoogsteen and "sugar edge" pairing also occur. The edge indicates the relative orientation of the glycosidic and hydrogen bases. The four RNA bases (A, C, G, U) may associate in 4² matrices.

These steric associations may be evolutionarily better preserved than the base positions themselves. They facilitate long-range RNA-RNA interactions and create binding sites for proteins and small ligands. ►antisense RNA, ►targeting genes, ►RNAi, ►Watson-Crick model, ►Hoogsteen pairing, ►RNA helicase; Geiss G et al 2001 J Biol Chem 276:30178; Leontis NB et al 2002 Nucleic Acids Res 30:3497.

RNA Driven Reaction: In a DNA-RNA hybridization experiment, the RNA is far in excess compared to single-stranded DNA. This assures that hybridization will take place at all potential annealing sites. ►DNA hybridization, ►nucleic acid hybridization

RNA Editing: A means of posttranscriptional or co-transcriptional altering of the RNA transcript (mRNA, tRNA, rRNA, 7 SLRNA). It is a very common process in the mitochondria of *Trypanosomes* (►*Trypanosoma brucei*). A separately transcribed 40–80-base “guide RNA” with homology to the 5′-end of the RNA to be modified pairs with the target. Then, uracil residues from the 3′-end tract of the guide are transferred into the target sequences. Two enzymes are primarily involved in the editing of exonuclease 1 (REX1) and (REL) RNA ligases (Kang X et al 2005 Proc Natl Acad Sci USA 102:1017). This editing thus changes the content of the message and the amino acids of the translated protein. In the mitochondria of this protozoan, thousands of U nucleotides may be inserted into different pre-mRNAs. Us may also be removed at a 10-fold lower frequency. It has been hypothesized that the U replacements are provided by the 3′-end of the gRNA, but recent experimental evidence indicates that they come from free UTPs. In the mitochondria of plants, in about 10% of the transcripts, U may replace C or C replaces U. The editing of four to 25 RNAs may take place in the chloroplasts. Transacting factors psbE and petB bind to five nucleotides cis upstream from the editing site (Miyamoto T et al 2004 Proc Natl Acad Sci USA 101:48). Although there is no conserved consensus around the edited sequences in plant chloroplasts, in tobacco a 27-nucleotide sequence at the RpoB-2C target plays a critical role (Hageman CE et al 2005 Nucleic Acids Res 33:1454). Editing appears to be rare but not limited to higher animals. One C residue deamination in the apolipoprotein-B results in a U replacement and the creation of a stop codon, and consequently a truncated protein. Another similar deamination in the middle of the transcripts alters the permeability of a Ca²⁺ channel. Thus editing produces two different mRNAs from one. Although C→U is the common change, U→C may also occur exceptionally. Simple deamination, addition

or co-transcriptional errors, such as stuttering of the polymerase may also bring about the changes. RNA editing also takes place in different RNA viruses. In HIV-1, G→A editing also occurs besides C→U. Mammalian nuclear RNA editing may involve the deamination of adenosine into inosine in the double-stranded pre-mRNA of the glutamate-receptor subunits. The enzyme responsible for the process is dsRAD (double-stranded RNA adenosine deaminase, also called DRADA or ADAR). The ADAR1 and ADAR2 proteins are associated with spliceosomal components of a 200 S large ribonucleoprotein complex (InRNP). The deficiency of ADAR in *Drosophila* results in behavioral anomalies during the advanced developmental stages. There are differences in editing among animals. Fruit flies, mosquitoes, and butterflies have similar editing sites within a single exon of the synaptotagmin genes. Honeybees, beetles and roaches, however, do not edit this synaptotagmin site. Comparative genomics of 34 species indicates that complex, multidomain, pre-mRNA structures (e.g., pseudoknots) determine the specificity of adenine editing in synaptotagmin (Reenan RA 2005 Nature [Lond] 434:409).

In the tRNA^{Asp} of marsupials, the GCC anticodon is found that can only recognize the glycine codon. In 50% of these tRNAs the middle base is edited to U, and thus the regular Asp anticodon is generated. The marsupial mitochondria also have the regular tRNA^{Gly} with anticodon GGN that recognizes all four glycine codons, but the edited codon can match up with only two of the glycine codons. Why among the only 22 tRNAs there are two for glycine (normal and edited) is a puzzling observation. RNA editing occurs through the plant kingdom (with few exceptions), in mitochondria as well as in chloroplasts, albeit at lower frequency in the latter. In the plastids there are about 25 editable sites, while in the mitochondria their number may exceed 1,000. RNA editing may generate new initiation and termination codons in plant organelles and thus new reading frames. No U→C editing was observed in the mitochondria or chloroplasts of gymnosperms or in the chloroplasts of angiosperms. The site of editing is apparently selected on the basis of the flanking sequences.

RNA editing also occurs in nuclear genes and contributes to the regulation at an additional level. It appears that the neurofibromas are determined by editing in the neurofibromatosis gene (NF1). Editing may also regulate the mRNA of the serotonin-2C receptor. In the immune system, T cell-independent B cells (B1) also diversify their surface receptors by RNA editing. Defects in RNA editing may potentiate tumorigenesis. ►mtDNA, ►apolipoproteins, ►kinetosome, ►gRNA, ►genetic code, ►stuttering, ►wobble, ►DRADA, ►ADAR, ►Z DNA,

►anticodon, ►mooring sequence, ►serotonin, ►editosome, ►B cell, ►RNA ligase, ►synaptotagmin, ►pseudoknot; Gott JM, Emeson RB 2000 *Annu Rev Genet* 34:499; Raitskin O et al 2001 *Proc Natl Acad Sci USA*:6571; Aphasizhev R et al 2002 *Cell* 108:637; Bass BL 2002 *Annu Rev Biochem* 71:817; Maas B et al 2003 *J Biol Chem* 278:1391; Blanc V, Davidson O 2003 *J Biol Chem* 278:1395; <http://bioinfo.au.tsinghua.edu.cn/dbRES>; http://biologia.unical.it/py_script/search.html.

RNA Enzyme: ►ribozyme

RNA Export: From the nucleus, mRNA requires the presence of the nuclear export factor NES and a cellular cofactor Rip1/Rab. The NES function is part of the Gle1 yeast protein (M_r 62K). Gle1 interacts with Rip1 and nucleoporin (Nup 100) in the nuclear pore. The Rev splicing factor can substitute the Gle1 function. Protein Aly of metazoans is involved in pre-mRNA slicing and mRNA export. The export of unspliced mRNA may be prevented by nuclear retention factors (RF), however some intron-less mRNAs can be exported and efficiently translated in the cytoplasm. The export of mRNA also requires PIP₂ and PIP₃. The abundant hnRNPs (hnRNP C and hnRNP K) have also been implicated in mediating RNA export. It seems, some TAP elements are also involved in the export. tRNA and U snRNA export may require members of the importin β family of proteins. The export of tRNAs may be mediated by the aminoacyl-tRNA synthetases after processing of transcripts. This involves the removal of the not needed 5' and 3' sequences, introns, addition to 3' end of the CCA sequence, and modification of some nucleotides. Some mRNA export protein factors coordinate the export of transcriptionally co-regulated functional classes of transcripts. Thus, the yeast export proteins, Yra1 and Mex67, bind 1,000 (20%) and 1,150 (36% of the total) mRNAs, respectively, and usually their specificity does not overlap (Hieronymus H, Silver PA 2003 *Nature Genet* 33:155). ►RNA transport, ►REV, ►nuclear pore, ►transport elements constitutive, ►export adaptors, ►nuclear export sequences, ►importin, ►TAP, ►aminoacyl-tRNA synthetase, ►Ipk1, ►cell-penetrating peptides; Michael WM 2000 *Trends Cell Biol* 10:46; Zenklusen D, Stutz F 2001 *FEBS Lett* 498:150; Sträßer K et al 2002 *Nature [Lond]* 417:304.

RNA Extraction: An essential requisite that RNase activity be eliminated or prevented during all operations. The glassware can be made RNase free by baking for 8 h or by chloroform washing. A 1% diethyl pyrocarbonate (DEPC [carcinogen!]) washing

(2 h, 37 °C) may also be useful. RNase activity in the extraction media can be inhibited by vanadium or by the clay, Macaloid. These are subsequently eliminated by water-saturated phenol extraction. RNases can also be blocked by 4 M guanidium thiocyanate and β -mercaptoethanol. RNA is extracted from the tissues in a buffer containing a detergent (0.5% Nonidet) and a reducing agent (dithiothreitol). Proteins may be removed by proteinase K digestion. RNase-free DNase removes DNA. Finally, chilling in cold ethanol (containing Na-acetate) precipitates RNA. The RNA is taken up in a TE, pH 7.6 buffer. Its quantity can be measured spectrophotometrically at 260 nm. Several variations of these general procedures are being used to isolate RNA. ►DNA extraction, ►RNase-free DNase, ►TE

RNA Factory: The complex associated with RNA polymerase II. It carries out transcription, splicing, and cleavage-polyadenylation of the mRNA precursor. ►mRNA; McCracken S et al 1997 *Nature [Lond]* 385:357.

RNA Finger: An RNA element (e.g., CCCH) binding to Zn-finger proteins. It controls various cellular processes. ►DNA binding protein domains

RNA Fingerprinting: The purpose is to identify the differential expression of the total array of genes that constitutes about 15% (or less) of all at a particular time in a mammalian genome. To attain this goal partial cDNAs are amplified by reverse transcription using PCR from a subset of mRNAs. The short sequences are then displayed on a sequencing gel (differential display). Pairs of primers are selected in such a way that each will amplify 50 to 100 mRNAs. One of the primers (5'-TCA) is anchored to the TG upstream of the poly(A) tail of the mRNA. This primer will recognize 1/12 (4!/2!) of the mRNAs with different combination of the last two 3' bases omitting T as the penultimate base. The primer will then only amplify this subpopulation. As 5' primers, 6–7 bp arbitrary sequences are used. Such a procedure can be used not just for molecular analysis of development. Eventually the genes producing the transcripts can be cloned. ►PCR, ►reverse transcription, ►DNA fingerprinting, ►fingerprinting of macromolecules, ►differential display, ►RDA, ►microarray hybridization, ►proteomics, ►SAGE, ►TOGA; Gill KS, Sandhu D 2001 *Genome* 44:633.

RNA Folding: There is a requirement for Mg²⁺ in maintaining the tRNA tertiary structure but other RNAs also need potassium or magnesium ions for folding. The ionic environment influences the folding of macromolecules and their function depends on the appropriately folded state. RNA folding proceeds through a number of intermediate states. For protein

synthesis on the ribosome in the cells the tRNA is aminoacylated in the tertiary fold (see Fig. R87). ▶aminoacyl-tRNA synthetase, ▶ribozyme, ▶RNA structural; Draper DE et al 2005 Annu Rev Biophys Biomol Struct 34:221; single RNA molecule folding: Zhuang X 2005 Annu Rev Biophys Biomol Struct 34:399; Pan T, Sosnick T 2006 Annu Rev Biophys Biomol Struct 35:161; detection of thermodynamically stable and evolutionarily conserved RNA secondary structures in multiple sequence alignments: <http://rna.tbi.univie.ac.at/cgi-bin/RNAz.cgi>.

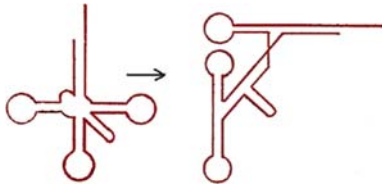


Figure R87. RNA folding

RNA G8: RNA G8 contains about 300 nucleotides and it is associated with the ribosomes in *Tetrahymena thermophila*. It is transcribed by RNA polymerase III and conveys thermal tolerance to the cells. ▶thermal tolerance

RNA Helicases: RNA helicases unwind double-stranded RNAs to facilitate transcription. They have two double-stranded RNA domains and have a cis-acting transactivation response (TAR) element binding and a dsRNA activated protein kinase (PKR) domain. TAR enhances the transcription of HIV-1. It appears that the helicase activity resides within the ribosome and that the ribosomal proteins S3, S4 and S5 encircle the incoming RNA on the 30S ribosomal unit and play a role in processivity (Takayar S et al 2005 Cell 120:49). The NPH-II RNA helicase has specificity for the ribose moiety of the loading strand and for a section of the 3'-overhang. Yet, under less stringent conditions it also acts on DNA (Kawaoka J, Pyle AM 2005 Nucleic Acids Res 33:644). ▶eIF4A, ▶helicase, ▶DEAD-box, ▶breast cancer, ▶acquired immunodeficiency, ▶double-stranded RNA; Lüking A et al 1998 Crit Rev Biochem Mol Biol 33:259; Fujii R et al 2001 J Biol Chem 276:5445.

RNA, Heterogenous: ▶hnRNA

RNA Insertion Element: An RNA insertion element can be generated by in vitro combination of an endoribonuclease ribozyme with a R3C ribozyme with RNA ligation function. The conjoined bifunctional ribozymes can integrate into a target RNA. Several mutations had to be isolated and selected to generate an efficient modular system. Such structures may be useful for insertional mutagenesis of mRNA.

▶insertion element, ▶insertional mutagenesis, ▶ribozymes; Kumar RM, Joyce GF 2003 Proc Natl Acad Sci USA 199:9738.

RNA Interference: In *Caenorhabditis* nematodes, fed on double-stranded RNA-containing bacteria, gene expression is transiently but specifically suppressed, as long as the dsRNA is available. The interfering dsRNA may be generated by inserting T7 phage RNA polymerase genes at the opposite ends of specific genes in a plasmid. Alternatively, a single copy of the polymerase may be used on inverted duplication of a specific gene. *Note:* some of the papers by Taira, K. had to be corrected (Nature [Lond] 431:211) and another (Nature 423:838) was retracted (Nature 426:100). ▶*Caenorhabditis*, ▶RNAi, ▶inhibition of transcription, ▶posttranscriptional gene silencing; Moss EG 2001 Curr Biol 11:R772.

RNA Ligase: An RNA ligase catalyzes the joining of RNA termini, such as generated during the processing of tRNA transcripts, in a phosphodiester bond and may need ATP for the reaction. It is an essential enzyme for RNA editing. ▶ligase DNA, ▶ligase RNA; Stage-Zimmermann TK, Uhlenbeck OC 2001 Nature Struct Biol 8:863; Ho KC, Shuman S 2002 Proc Natl Acad Sci USA 99:12709; deoxyribozyme RNA ligase: Prior TK et al 2004 Nucleic Acids Res 32:1075.

RNA Localization: Embryonic development is an asymmetric process and the local distribution and enrichment of special RNAs play decisive roles. The RNA transcribed from the bicoid locus of *Drosophila*, encoding a transcription factor, specifies anterior cell fates in the oocytes and embryos. The germcell-less nuclear pore associated factor participates in the definition of posterior development. The growth factor encoded by gurken affects anterior-dorsal differentiation whereas the prospero encoded transcription factor controls apical/basal development in the neuroblasts. In mammals, the transcript of the β -actin genes is involved in the definition of the cytoskeleton and it is localized primarily at the periphery of epithelial cells, fibroblasts, and myoblasts. The different RNAs appear at the predestined locations immediately following transcription. Some of the rather uniformly distributed RNAs are degraded, except at the locations where they exercise morphogenetic function(s). The localization seems to be mediated by signals (usually a few hundred bases or less), generally in the untranslated 3'-end (3'-UTR) of the mRNAs. The mRNAs are not translated until properly localized. Translation without prior localization might cause developmental anomalies. Besides the cis-acting element (e.g., 3'-UTR), trans-acting factors encoded by other genes may also affect

localization (e.g., influence the cytoskeletal motor proteins or RNA binding proteins). Localization of the RNA may also be assured by alternative splicing of the transcripts. The pattern of distribution may change as the microtubule-organizing center develops and motor proteins become available. At a later stage, before the nurse cells decay, they dump large amounts of RNA into the oocyte through the ring canals. Later, ooplasmic streaming somewhat mixes up the previously laid down distribution pattern. When the early syncytial blastoderm (~6,000 nuclei) is converted into a cellular blastoderm, the anterior-posterior and the dorsal ventral polarization begins, upon the expression of the genes, specifying the morphogenetic pattern. At this stage the control shifts toward the zygotic effect genes from the maternal effect ones. Another control involved the diffusion pattern of the morphogenetic gene products. ►*morphogenesis in Drosophila*, ►*maternal effect genes*, ►*MTOC*, ►*ring canal*, ►*METRO*, ►*motor proteins*; Bashirullah A et al 1998 *Annu Rev Biochem* 67:335; Palacios IM, St Johnston D 2001 *Annu Rev Cell Dev Biol* 17:569; Bullock SL, Ish-Horowicz D 2001 *Nature [Lond]* 414:611; Saxton WM 2001 *Cell* 107:707.

RNA Maturases: Ribosomal transcripts are processed to size by the U3, U8, U13 independently transcribed small RNAs (snoRNA, small nucleolar RNAs). The U13-U14 snoRNAs and E3 are encoded by the introns of protein-coding genes participating in the process of translation. They are co-transcribed with the pre-mRNA and removed during the processing of the genes. By the intron of the U22 host gene (UHG) seven U RNAs are transcribed. These U RNAs display 12–15 base complementary sequences to rRNAs. ►*splicing*, ►*introns*, ►*ribonuclease P*; Delahodde A et al 1989 *Cell* 56:431; Claros MG et al 1996 *Methods Enzymol* 264:389.

RNA Mimicry: ►*translation termination*

RNA Mimics: 2'-modified oligodeoxynucleotides such as the 2'-O-methyl-modified ones that have enhanced binding affinity to complementary RNA and are resistant to some nucleases. ►*antisense technology*; Putnam WC et al 2001 *Nucleic Acids Res* 29:2199.

RNA, Micro (miRNA, mir): A 22-nucleotide inhibitory RNA. ►*RNAi*; Zeng Y et al 2002 *Mol Cell* 9:1327.

RNA, Noncoding (ncRNA): There are many mRNA-like-yet-not-translated molecules in the cell. They are polyadenylated and spliced but lack long open reading frames. They have regulatory or signal functions (Szymanski M, Barciszewski J 2003 *Int Rev Cytol* 231:197). A noncoding RNA transcribed

in an intergenic region upstream from the *SER3* gene of yeasts can interfere with the binding of activators to the *SER* promoter and thus regulates its transcription (Martens JA et al 2004 *Nature [Lond]* 429:571). Noncoding RNAs are the tRNAs, ribosomal RNAs, the snRNAs, microRNAs, and snoRNAs. In whole genome microarrays of *E. coli*, besides 4,052 coding transcripts, 1,102 apparently noncoding transcripts were found in the intergenic regions. In humans, about 98% of the transcripts are noncoding. There are also the tiny noncoding RNAs (tncRNA) that resemble microRNAs but are not transcribed as short hairpin RNA precursors and yet they play regulatory roles in development (Ambros V et al 2003 *Current Biol* 13:807). The development of the neural stem cells may be modulated by a small double-stranded RNA and protein interaction (Kuwabara T et al 2004 *Cell* 116:779). On the basis of secondary structure and thermostability, coding and noncoding RNAs can be rapidly identified by a computational procedure (Washietl S et al 2005 *Proc Natl Acad Sci USA* 102:2454). ►*microRNA*, ►*RNAi*, ►*antisense RNA*, ►*RNA regulatory*, ►*small RNA*, ►*Xist*, ►*Rfam*; Erdmann VA et al 2001 *Cell Mol Life Sci* 58:960; Eddy SR 1999 *Curr Opin Genet Dev* 9:695; Storz G 2002 *Science* 296:1260; Kiss T 2002 *Cell* 109:145; Fahey ME et al 2002 *Comp Funct Genomics* 3:244; Tjaden B et al 2002 *Nucleic Acids Res* 30:3732; Griffith-Jones S et al 2003 *Nucleic Acids Res* 31:439; <http://biobases.ibch.poznan.pl/ncRNA/>; <http://www.sanger.ac.uk/Software/Rfam/>; <http://rfam.wustl.edu/>; mammalian non-coding RNA: <http://research.imb.uq.edu.au/RNAdb>; <http://bioinfo.ibp.ac.cn/NPInter/>; plants: <http://www.prl.msu.edu/PLANTncRNAs/database.html>.

RNA Nucleotides, Modified: There are four basic nucleotides in the cell but several others are produced by posttranscriptional modification as needed for tRNAs and various coenzymes. ►*modified bases*; <http://medlib.med.utah.edu/RNAmods>.

RNA Plasmids: RNA plasmids exist in some mitochondria that are not homologous to the mtDNA. ►*mtDNA*

RNA Polymerases (RNAP): DNA-dependent RNA polymerases synthesize RNA on a DNA template. The T7 RNA polymerase is a relatively simple molecule (100 kDa). As a rule, this polymerase directs the incorporation of the first nucleotide in a template-directed manner with a single nucleotide primer. First, it produces several pieces of short RNAs and then these 10–12 nucleotide units polymerize into an elongation complex and exits from the promoter.

Between the DNA template and the 3'-proximal RNA transcript at least a 9-nucleotide long hybrid is formed for efficient processivity during the elongation of the RNA.

The RNA products then separate from the template and the duplex of the DNA is restored. The T7 phage promoter has a binding domain (−17 to −6) and an initiation domain (−6 to +6). After the binding domain of the polymerase recognizes the DNA, melting of the duplex takes place. During the elongation phase, about 200 nucleotides are added per second. The termination is rho independent in T7 and the end forms a stem-loop structure and a stretch of U bases. The termination seems to be a reverse process of the initiation, i.e., a stable isomerization is followed by an unstable sequence. In many respects, the phage enzyme despite its simple structure functions similarly to more complex polymerases. In prokaryotes a single polymerase synthesizes all cellular RNAs. The prokaryotic pol enzyme contains four subunits α , β , β' , and σ . The large β subunits are evolutionarily highly conserved and they are the main instruments of polymerization with the other subunits.

The prokaryotic RNA polymerases are of about 500 kDa in size whereas the T7 enzyme is only about 40 kDa. The *E. coli*, α subunits (36.5 kDa) recognize the promoter, the β' subunit (155.2 kDa) binds DNA, and the β (150.6 kDa) is active in RNA polymerization. The σ is essential to start transcription in a specific way by opening the double helix for the action of the RNA polymerization. The eukaryotic organelles contain prokaryotic type RNA polymerases. The eukaryotic RNA polymerase II—transcribing protein-encoding genes—has about 12 subunits and is somewhat larger but highly homologous across wide phylogenetic ranges. The two largest subunits are similar to the β' and β subunits of the prokaryotic enzyme. The carboxy-terminal domain (CTD) of the largest subunit of the eukaryotic RNAP II carries up to 52 amino acid repeats (YSPTSPS) which are liable to phosphorylation (Meinhart A, Cramer P 2004 Nature [Lond] 430:223). Only the CTD unphosphorylated form participates in a transcription initiation complex but it is phosphorylated when it begins to elongate the RNA transcript. After transcription, the CTD phosphates are removed by phosphatase Fcp1 (Kamenski T et al 2004 Mol Cell 15:399). The CTD repeat is not essential for transcription initiation by RNAP II but for the stability of the initiation complex (Lux C et al 2005 Nucleic Acids Res 33:5139). When transcription is arrested the carboxy-terminal domain of Pol II is ubiquitinated (Somesh BP et al 2007 Cell 129:57). The complex of transcription includes the Mediator

and a total of about 60 proteins with a combined mass of 3.5 MDa. In an *E. coli* cell there are about 2,000 core RNA polymerase molecules. The number of protein factors affecting transcription in *E. coli* is about 240–260.

In eukaryotes, there are three different DNA-dependent RNA polymerases (I, II, III) that display substantial homology. Polymerase IV of plants assists in the production of siRNA. It targets de novo methylation of cytosine and contributes to the formation of facultative heterochromatin (Onodera Y et al 2005 Cell 120:613). Besides RNA polymerase II, a single polypeptide nuclear RNA polymerase (spRNAP-IV) alternatively transcribed from the mammalian mitochondrial RNA polymerase gene (*POLRMT*) can also transcribe mRNA. This polymerase lacks terminal 262 amino acids in the nucleus (compared to the mitochondrially located form) and the mitochondrial targeting signal. It is resistant to α -amanitin but remains sensitive to *POLRMT*-specific RNAi. Its promoter is substantially different from that of Pol II and does not respond to transcriptional enhancers. It transcribes several nuclear genes (Kravchenko JE et al 2005 Nature [Lond] 436:735).

TRNA polymerases replicate the genome of the RNA viruses. Mammalian RNA polymerase II may also carry out RNA-dependent RNA synthesis by switching to the RNA genome of the hepatitis delta virus (Chang J, Taylor J 2002 EMBO J 21:157). The viral enzymes—in contrast to the DNA polymerases—lack a proofreading function and, consequently, their error rate may be within the 10^{-3} to 10^{-4} range per nucleotide leading to the extreme diversity of the RNA viruses. The prokaryotic RNA polymerase moves along the DNA at a speed exceeding 10 nucleotides/second. Termination is basically the reverse process of the transcription initiation. In the haploid yeast cell there are 2,000 to 4,000 RNA polymerase II molecules and about ten times more general transcription factor molecules. In 2006, Roger D. Kornberg received the Nobel Prize for his basic study of RNA polymerase structure and function. (See Figs. [R88](#), [R89](#), and [R90](#), [▶pol](#), [▶ \$\sigma\$](#) , [▶sigma factor](#), [▶promoter](#), [▶open promoter complex](#), [▶promoter melting](#), [▶transcription](#), [▶transcription factors](#), [▶transcription termination](#), [▶terminator](#), [▶antitermination](#), [▶error in replication](#), [▶error in transcription](#), [▶pausing transcriptional](#), [▶arrest transcriptional](#), [▶transcript cleavage](#), [▶transcription complex](#), [▶inchworm model](#), [▶nucleic acid chain growth](#), [▶processivity](#), [▶repression](#), [▶mediator complex](#), [▶SRB](#), [▶protein synthesis](#), [▶transcript elongation](#), [▶elongator](#), [▶RNA dependent RNA polymerase](#), [▶RNAi](#), [▶ \$\alpha\$ -amanitin](#),

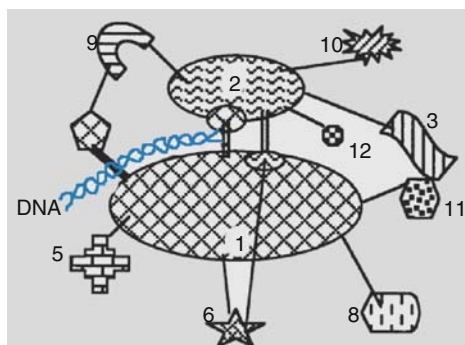


Figure R88. Schematic drawing of the 10/12 subunits of the yeast RNA polymerase II. Subunits 1, 5 and 9 grip the DNA below the active center of the enzyme. Pores below the active center form the entry of the nucleotides and the exit of the polymerized RNA. (Redrawn after Cramer P et al 2000 *Science* 288:640)

►heterochromatin, ►transcription factories; Archambault J, Friesen JD 1993 *Microbiol Rev* 57:703; Barberis A, Gaudreau L 1998 *Biol Chem* 379:1397; Mooney RA, Landick R 1999 *Cell* 98:687; Ishihama A 2000 *Annu Rev Microbiol* 54:499; Cramer P et al 2001 *Science* 292:1863; Gnatt AL et al 2001 *Science* 292:1876; Vassilyev DG et al 2002 *Nature [Lond]* 417:712; Bushnell DA, Kornberg RD 2003 *Proc Natl Acad Sci USA* 100:6969; single-molecule analysis of transcription: Bai L et al 2006 *Annu Rev Biophys Biomol Struct* 35:343; structure of human RNA polymerase II: Kostek SA et al 2006 *Structure* 14:1691; historical steps in the discovery of the yeast RNA polymerase II: Landick R 2006 *Cell* 127:1087; chromatin and transcription: Li B et al 2007 *Cell* 128:707; molecular and structural bases of transcription: Kornberg RD 2007 *Proc Natl Acad Sci USA* 104:12955.

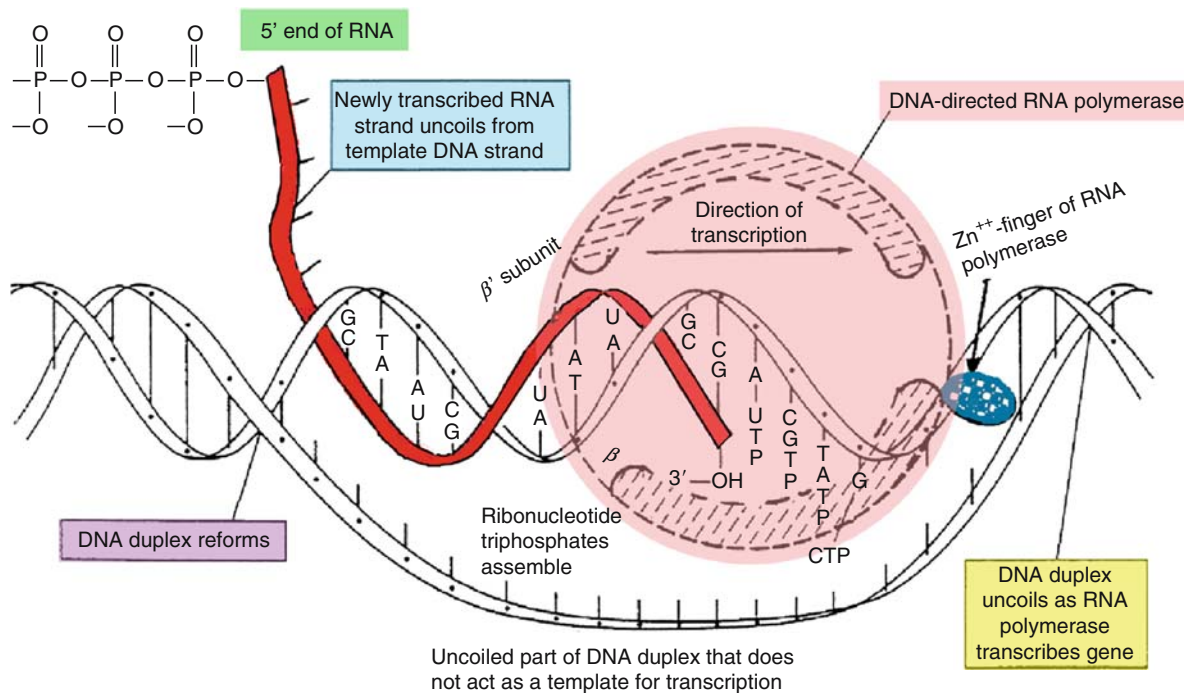


Figure R89. Conceptualization of the general process of transcription of RNA on DNA template from ribonucleoside 5'-triphosphates. The first 5'-nucleotide retains the three phosphates; the following ones split off a pyrophosphate and are then hooked up to the 3'-OH ends. In this process a ternary complex involving DNA, RNA, and protein is involved. The RNA-protein has been located to about 9 bp from the DNA fork into the transcription bubble where the DNA template forms an approximate 8 bp heteroduplex (HBS, heteroduplex-binding site). The RBS (RNA-binding site) together with HBS extends to approximately 14–16 RNA nucleotides from the 3'-OH end. About 7–9 nucleotides further downstream, RBS, HBS, and DBS (DNA-binding site) are situated and stabilize transcription. The DNA entry and the RNA exit sites on the polymerase are in close vicinity to each other. This diagram does not show the general transcription factors and the numerous other proteins regulating the process. (Diagram is modified after Page DS, *Principles of Biological Chemistry*. Willard Grant, Boston MA; see also Nudler E, et al 1998. *Science* 281:424.) For the structure of initiation complex of the T7 enzyme at 2.4 Å resolution, see Cheetham GMT and Steitz TA 1999. *Science* 286:2305.

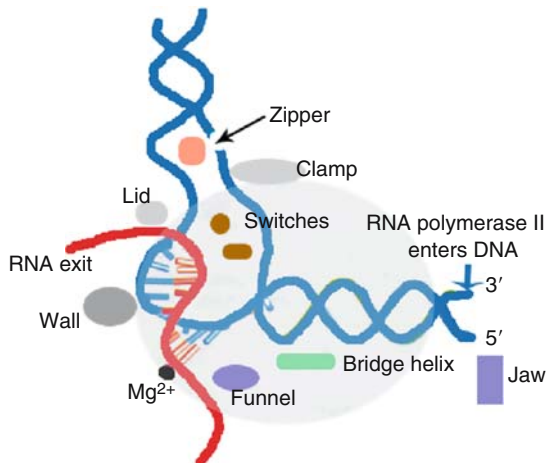


Figure R90. The structures of RNA polymerase II has been determined at 3.3 Å resolution. The schematic of the major functional elements is shown above. The enzyme enters DNA at right and holds onto it by the element designated as **JAW**. The **CLAMP** domain keeps the protein on the DNA. The **Switches** turn on the function. A large protein subunit, the **WALL** causes an approximately 90° turn of the DNA template. This then facilitates the addition of nucleotides to the RNA. The RNA building blocks, the nucleotide triphosphates, enter the complex through the **FUNNEL**, which ends in a **PORE**. Magnesium (or other metals) is required for the polymerization. The RNA chain is symbolized by a dotted line. The DNA and RNA from a 9-base duplex. The **RUDDER** (not shown here) prevents the extension of the DNA—RNA hybrid to go beyond the 9 base pairs and facilitates the separation of the duplex. The synthesized RNA exits under the **LID**. The **BRIDGE HELIX** under the coding strand of the DNA apparently promotes the addition of nucleotides. (Modified after Gnatt AL, et al 2001 *Science* 292:1876.)

R

RNA Polymerase Holoenzyme: A complex of RNA Pol II, transcription factors and other regulatory proteins including Srb. It is a general transcriptional regulator of eukaryotes. ▶transcription factors, ▶co-activators, ▶TBP, ▶TAF, ▶RNA polymerase

RNA Polymerase I: It generates ribosomal RNA. In yeast, the UAF includes histones H3 and H4 and four non-histone proteins as essential factors (Tangaonkar P et al 2005 *Proc Natl Acad Sci USA* 102:10129). ▶transcription factors

RNA Polymerase II: ▶RNA polymerases

RNA Polymerase III: RNA polymerase III mediates the transcription of tRNAs and other small RNAs. It has efficient proofreading ability and reduces transcriptional errors by 10^3 (Alic N et al 2007 *Proc Natl Acad Sci USA* 104:10400). This enzyme may be

suppressed by ARF (Morton JP et al 2007 *Nucleic Acids Res* 35:3046). ▶transcription factors, ▶ARF

RNA Polymerase IV (nuclear RNA polymerase D1A): A plant enzyme which, with RNA-dependent RNA polymerase 2, provides a substrate for Dicer-like 3 endoribonuclease in generating siRNA. It also mediates RNA-dependent methylation of DNA (Matzke M et al 2006 *Cold Spring Harbor Symp Quant Biol* 71:449). ▶Dicer, ▶RNA dependent RNA polymerase, ▶siRNA, ▶epigenesis; Zhang X et al 2007 *Proc Natl Acad Sci USA* 104:4536.

RNA Polymerizations: ▶pol

RNA Primer: ▶DNA replication

RNA Processing: Eukaryotic genes are “in pieces”, although the DNA is continuous, in between the protein-coding nucleotide sequences (exons), non-translated additional nucleotide sequences, introns occur. The long sequences are transcribed into a long RNA tract but the introns are removed and the exons are spliced to make the mRNA. Similar processing is carried also out with the rRNA and tRNA. The vast majority of prokaryotic genes do not require these processes. These cutoffs, the mRNA, and the primary transcripts constitute the pool of the hnRNA (heterogeneous nuclear RNA). The primary RNA transcripts are coated with different proteins and thus form hnRNP, i.e., hnRNA-protein particles. These particles are instrumental in cutting the transcripts and splicing the exons into mRNA. After the splicing is completed, the methylated guanylic cap and the polyA tail are added and then the mRNA exported into the cytosol. ▶introns, ▶hnRNA, ▶spliceosome, ▶post-transcriptional processing, ▶exosome; Varani G, Nagai K 1998 *Annu Rev Biophys Biomol Struct* 27:407.

RNA-Protein Interaction: A common phenomenon in the regulation of transcript elongation, attenuation, and in antitermination and several other functions in the cell. (See Nagai K, Mattaj IW 1994 *RNA-Protein interactions*, Oxford University Press; ▶antitermination; Xia T et al 2005 *Proc Natl Acad Sci USA* 102:13013).

RNA, Regulatory: See antisense RNA, B2 RNA, Csr, guide RNA, microRNA, noncoding RNA, noncoding sequences, plasmid maintenance, hok-sok-mok, RNAi, 6S RNA, shRNA, siRNA, signal sequence recognition particle, 7SK RNA, snoRNA, SRA RNA, telomerase, U RNA, Xist. (See Storz G et al 2005 *Annu Rev Biochem* 74:199).

RNA Repair: Among the ~62 naturally occurring RNA modification, 20 involves methylation. Modified RNAs play important roles in the control of gene

expression and RNA folding and RNA-Protein interactions, and may affect cellular defenses. The human demethylases AlkB (14q24) and an AlkB-like protein, ABH3 (encoded at 11q11), repair both RNA and DNA. ▶DNA repair, ▶methylation of DNA, ▶methylation of RNA, ▶ribozyme; Wei YE et al 1996 Nucleic Acids Res 24:931; Aas PA et al 2003 Nature [Lond] 421:859.

RNA Replication: Some bacteriophages (R17, MS2, fd2, f4, Q β , M12) and some animal viruses such as the polio virus, the vesicular stomatitis virus, rhinoviruses (influenza viruses) and the vast majority of the plant viruses have RNA genetic material. This RNA is either single- or double-stranded. One of the best known is the Q β replicase system. The tetramer (210 kDa) is encoded one viral (β subunit about 65 kDa) and three bacterial genes (translation factors). The replicase enzyme does not have an editing exonuclease function. These replicases do not replicate or transcribe host RNAs. The replication of the RNA is similar to the replication of DNA inasmuch as all nucleic acid strands are elongated at the 3'-OH ends. (The retrovirus replication is discussed under reverse transcription.) Most of the bacterial RNA viruses and many animal viruses have the same genetic material as their mRNA (+ strand viruses). They use a replicative intermediate (RI) for the synthesis of the first new (−) strand.

The (−) strand can then generate as many (+) strands as needed. Some viruses are, however (−) strand viruses because their genetic material is not identical to the mRNA but complementary to it. The polio virus (+) strand is the genetic material that is associated with a protein at the 5'-end through a phosphodiester linkage to a tyrosine residue. The (−) strand lacks this feature. Apparently, the OH group of the tyrosine primes the synthesis of the (+) strand but the (−) strand can get by without it. The reoviruses of vertebrates contain 8–10 short double-stranded RNA molecules. When the virus enters the host cell the coat protein is shed and its RNA polymerase is activated and works conservatively and asymmetrically. A virion enzyme copies the (−) strand and a new (+) is released. The original RNA duplex is conserved. On the new (+) strand a (−) strand is made and the double-stranded RNA is reconstituted. ▶DNA replication, ▶RNA dependent RNA replication, ▶replicase, ▶replicative intermediate, ▶plus strand, ▶retroviruses; Tang H et al 1999 Annu Rev Genet 33:133; Knipe DM, Howley PM (Eds.) 2001 Fundamental Virology, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania.

RNA Restriction Enzyme: In ribozymes restriction functions may exist. ▶restriction enzyme, ▶ribozyme

RNA Rewriting: ▶RNA editing

RNA, Ribosomal: ▶ribosomes

RNA, 4.5S: A bacterial RNA of 114 nucleotides. It targets signal peptide-equipped proteins to the secretory apparatus where it forms the signal-recognition particle with protein Ffh. It also binds to the translation elongation factor G. It is homologous to the eukaryotic 7S RNA. ▶Ffh, ▶secretion system, ▶RNA 7S, ▶elongation factors; Nakamura K et al 2001 J Biol Chem 276:22844.

RNA, 5S; RNA, 5.8S: ▶ribosomes; <http://biobases.ibch.poznan.pl/5SData/>.

RNA 6S: A regulator of the RNA polymerase of *E. coli*. (See Wassarman KM, Storz G 2000 Cell 101:613).

RNA, 7S: A cytoplasmic class of RNA of ~300 nucleotides, present in prokaryotes and eukaryotes. It participates in the function of RNA polymerase III and in the sequence signal recognition particle to direct proteins to the endoplasmic reticulum. The 7S RNA, which is part of the eukaryotic 35S pre-rRNA, is also a precursor of the 5.8S ribosomal RNA and the small GTPase RAN processes it. ▶RAN, ▶DNA 7S, ▶signal sequence recognition particle; Luehrsen KR et al 1985 Curr Microbiol 12:69; Suzuki N et al 2001 Genetics 158:613.

RNA, 10Sa (SsrA/tmRNA): When an mRNA is truncated at the 3'-end and has no stop codon, the ribosome may switch from one RNA to another to terminate the translation. The switching results in the generation of an 11-amino residue at the carboxyl end that destines the protein for degradation. The last 10 amino acids are translated from a stable so-called 10Sa RNA (363 nucleotides). So far, these 10 amino acids were found on murine interleukin-6 translated in *E. coli*, λ phage *cI*, cytochrome b-562, and polyphenylalanine translated on polyU. The 10Sa RNA is similar to a tRNA and it is charged with alanine. This alanine is found as the first amino acid of the tag. This saves the ribosome from the “unfinished” mRNA and permits its quasi-normal operation. The mechanism carries out the same task as ubiquitin does in eukaryotes. ▶translation non-contiguous, ▶ubiquitin, ▶lambda phage, ▶tmRNA; Gillet R, Felden B 2001 EMBO J 20:2966; Zwieb C, Wower J 2000 Nucleic Acids Res 28:169; <http://www.indiana.edu/~tmrna>.

RNA, 20S: A naked, single-stranded RNA phage-like replicon of about 2,500 nucleotides in yeast, encoding a 95 kDa RNA polymerase-like protein. Its termini are 5'-GGGGC and GCCCC-3' and therefore may circularize. (See Rodriguez-Cusino N et al 1998 J Biol Chem 273:20363).

RNA Sequencing: RNA sequencing can be done by digesting RNAs with different ribonuclease enzymes that cut the phosphodiester linkages at the specific nucleotides and then separate the fragments by gel electrophoresis (ca. 20% polyacrylamide) in one or in two dimensions. The RNA is generally labeled by ^{32}P in order to autoradiograph the dried gels. T_1 ribonuclease (from *Aspergillus oryzae*) generates fragments with 3' guanosine monophosphate ends. U_2 ribonuclease (from *Ustilago sphaerogena*) cleaves at purine residues (intermediates 2',3'-cyclicphosphates). RNase CL 3 (from chicken liver) has about 16-fold higher activity for cytidylic than uridylic linkages. RNase B (from *Bacillus cereus*) cuts Up↓N and Ap↓N bonds. RNase Phy M (from *Physarum polycephalum*) has the specificity Ap↓N and Up↓N. When several of these enzymes are employed, from the separate electrophoretic patterns, the sequences from the positions of the fragments with different termini can be deduced. In many ways the sequencing of RNAs with the aid of enzymatic breakage is very similar in principle to the Maxam and Gilbert method of DNA sequencing. Recently, RNA was sequenced by first converting it using reverse transcriptase into cDNA and then using the much easier DNA sequencing methods to determine the RNA nucleotide sequences. ▶DNA sequencing, ▶ribonucleases; Gilham PT 1970 Annu Rev Biochem 39: 227; Bachellerie J-P, Qu L-H 1993 Methods Enzymol 224:349; Kuchino Y, Nishimura S 1989 Methods Enzymol 180:154; Lane DJ et al 1988 Methods Enzymol 167:138; sequences and motifs: <http://uther.otago.ac.nz/Transterm.html>.

RNA Silencing: ▶RNAi, ▶microRNA

RNA 7SL: An approximately 300-base long molecule forming the signal recognition particle (SRP) with six proteins of 10 to 75 kDa size. (See Müller J, Benecke BJ 1999 Biochem Cell Biol 77:431).

RNA, Small: ▶snRNA

RNA Splicing: The primary RNA transcript is much larger than required for particular functions and is, therefore, cut up during processing and the transcripts corresponding to introns removed. The remaining pieces are then reattached (spliced together) to form the mature RNA molecule. ▶introns, ▶RNA processing; Weg-Remers S et al 2001 EMBO J 20:4194.

RNA, Structural: Structural RNA may have a noncoding, regulatory function in the genome (Washietel S et al 2007 Genome Res 17:852). Several computational methods are available for their analysis. ▶AlifoldZ, ▶EvoFold, ▶RNAz, ▶RNA folding

RNA Structure (SCOR): See Noller HF 2005 Science 309:1508; ▶MS2 phage; structural classification:

<http://scor.lbl.gov>; non-canonical base-base interactions: <http://prion.bchs.uh.edu/1/>; <http://www.rna.icmb.utexas.edu/>; RNA tertiary structure server: <http://bioinfo3d.cs.tau.ac.il/ARTS/>; structural homology search: <http://bioinfo.csie.ncu.edu.tw/~rnamst/>; regulatory motif prediction: <http://regrna.mbc.nctu.edu.tw/>.

RNA Surveillance: RNA surveillance monitors for the presence of RNAs that have stop codon mutations, which might lead to the synthesis of truncated proteins. The nonsense mRNA is directed to P bodies for degradation by the NMD (nonsense-mediated decay) pathway (Sheth U, Parker R 2006 Cell 125:1095). In yeast, the NMD process begins by recruiting the Upf1 protein to the ribosomes. Ubf1p can bind ATP. It can also bind nucleic acids without ATP and can hydrolyze ATP in a nucleic-acid-dependent manner. Ubf1p is also an ATP-dependent 5'→3' RNA/DNA helicase. Upf32p is probably a signal transducer from Ubf1 to Ubf3, and the latter then enlists the nonsense mRNA to the NMD complex. Ubf3p is located mainly in the cytoplasm but it can shuttle between the nucleus and the cytoplasm. In yeast proteins eRF1 and eRF3, termination factors are also required for the abortion of translation. The complex also mediates the decay of the defective polypeptide if any is made. NMD systems operate in a wide range of eukaryotes and may have roles to play in some cancers and hereditary diseases of humans. ▶Pab1p, ▶Xrn1p, ▶exosome, ▶degradosome, ▶SMG, ▶SR motif, ▶P body; Culbertson MR 1999 Trends Genet 15:74; Maquat LE, Carmichael GG 2001 Cell 104:173; Ishigaki Y et al 2001 Cell 106:607; Frischmeyer PA et al 2002 Science 295:2258; Lewis BP et al 2003 Proc Natl Acad Sci USA 100:189; Chang Y-F et al 2007 Annu Rev Biochem 76:51.

RNA, Therapeutic: Therapeutic RNAs may be used in medicine as a gene function inhibitory means such as in antisense technologies and RNAi. Ribozymes may cleave pathogenic RNA molecules of infectious agents (e.g., HIV). Trans-splicing of transcripts may correct defective functions (e.g., sickle-cell disease, tumor suppressor transcripts). RNA may be used to prevent the binding of pathogenesis proteins to target (e.g., HIV-1 TAR, REV). Transfection of dendritic, antigen-presenting cells with DNA that generate mRNA for tumor antigens may boost the effectiveness of cytotoxic T lymphocytes. ▶decoy RNA, ▶RNAi, ▶aptamer, ▶ribozyme, ▶acquired immuno deficiency, ▶transsplicing, ▶CTL, ▶antigen presenting cell, ▶tumor antigen, ▶tumor suppressor; Sullenger BA, Gilboa E 2002 Nature [Lond]: 418:252.

RNA Transcript: An RNA copy of a segment of DNA.

RNA Transport: mRNA, snRNA, U3 RNA, and ribosomal RNA (but not tRNA) are exported from the nucleus by RCC1 (yeast homolog is PRP20/MTR1). This nuclear protein is a guanine nucleotide exchange factor for the RAS-like guanosine triphosphatase (GTPase). Some plant virus RNAs spread through plasmodesmata to a distance from the site of infection with the aid of protein transporters. Plants can move their own mRNAs through the phloem cells at great distances. ►**RAN**, ►**RCC1**, ►**nuclear pore**, ►**plasmodesma**, ►**phloem**, ►**transport elements constitutive**, ►**TAP**, ►**RNA export**, ►**export adaptors**; Yang J et al 2001 Mol Cell 8:397.

RNA Trap (RNA tagging and recovery of associated proteins): The purpose of the procedure is to test the mechanism of action on gene expression exerted by enhancers, which are distant from a genic site. To this goal, the unprocessed RNA transcript of a specific locus with labeled oligonucleotides is hybridized to isolated cell nuclei. Horseradish peroxidase-conjugated antibodies are localized to the oligonucleotide probe. Peroxidase-activated biotinyl-tyramide covalently labels the electron-rich protein moieties by biotin in this region. From the sonicated cell fragments the biotin-conjugated chromatin is isolated by affinity to a streptavidin column. The specific sequences are then enriched by quantitative PCR. Enrichment of the locus control region—specifically the DNase hypersensitive sites—indicated by immunofluorescence analysis that one of the hypersensitive sites becomes physically associated with the gene transcribed. This technology thus supports the role of DNA looping in gene function. ►**biotin**, ►**enhancer**, ►**LCR**, ►**PCR**, ►**regulation of gene activity**, ►**streptavidin**, ►**DNA looping**; Carter D et al 2002 Nature Genet 32:623.

RNA Trimming: ►**trimming**

RNA, Ubiquitous: ►**U RNA**

RNA Viruses: ►**viruses**, ►**retroviruses**, ►**animal viruses**, ►**plant viruses** TMV, ►**MS2**, ►**paramyxovirus**, ►**viral vectors**, ►**reovirus**, ►**togavirus**, ►**ebola virus**, ►**rabies**; virus database: <http://www.ncbi.nlm.nih.gov/ICTVdb/ictvdb.htm>.

RNA World: RNA world existed in the pre-biotic era when RNA carried out auto- and heterocatalysis without DNA. There is evidence now that ribozymes can even catalyze nucleotide synthesis giving further support to the RNA world concept. In addition, evidence shows that RNA is involved in the catalysis of protein synthesis: (i) by encoding amino acid sequence in protein; (ii) activation of amino acids; (iii) synthesis of aminoacyl-tRNA by a reaction analogous to the aminoacyl-tRNA synthetases; and (iv) formation of peptide bonds. Highly reactive aminoacyl phosphate oligonucleotide adaptors and

RNA guides facilitate di- and tripeptide synthesis in a single guide sequence-dependent manner without ribosomes or ribozymes (Tamura K, Schimmel P 2003 Proc Natl Acad Sci USA 100:8666). ►**origin of life**, ►**ribozyme**, ►**autocatalytic function**, ►**heterocatalysis**, ►**peptide nucleic acid**, ►**protein synthesis**; Kumar RK, Yarus M 2001 Biochemistry 40:6998; Joyce GF 2002 Nature [Lond] 418:214; Szabó P et al 2002 Nature [Lond] 420:340; Yarus M 2002 Annu Rev Genet 36:125; Spirin AS 2002 FEBS Lett 539:4; Gilbert W 1986 Nature [Lond] 319:P618.

RNA-Dependent RNA Polymerase: ►**RNA-dependent RNA polymerase**

RNA-Directed DNA Methylation (RdMD): A sequence-specific silencing of DNA. The methylation may be limited to as short as 30-base sequences but it extends generally to longer stretches (Pélissier T, Wassenegger M 2000 RNA 6:55). Argonaute 4 plays both catalytic and non-catalytic roles in DNA methylation through the RNAi pathway (Qi Y et al 2006 Nature [Lond] 443:1008). Transcriptional silencing via RNA-directed DNA methylation and chromatin modification involves two forms of nuclear RNA polymerase IV (Pol IVa and Pol IVb), RNA-dependent RNA polymerase 2 (RDR2), DICER-LIKE3 (DCL3), ARGONAUTE4 (AGO4), the chromatin remodeler, DRD1, and the de novo cytosine methyltransferase, DRM2 (Pikaard CS 2006 Cold Spring Harbor Symp Quant Biol 71:473). ►**methylation of DNA**, ►**epigenetics**, ►**argonaute**, ►**RNAi**; Wassenegger M et al 1994 Cell 76:567; Mette MF et al 2000 EMBO J 19:5194.

RNAi (RNA-mediated genetic interference): Single or double-stranded RNA, formed or introduced into the cell, may interfere with the translation of the endogenous genes of *Caenorhabditis* or plants, *Drosophila* or mammals. Apparently, *Saccharomyces cerevisiae* lacks miRNA and RNAi capabilities. The miRNAs (~22 nucleotides) are very similar to RNAi but they are produced from foldback DNA. They can cleave hundreds of mRNAs or repress their translation and thereby regulate the function of genes involved in the regulation of plant and animal development (Bartel DP 2004 Cell 116:281). Short synthetic RNAs may also evoke interference. The double-stranded RNA is at least an order of magnitude more potent. In the nematode, the most effective exogenous delivery, to any part of the body, is through the intestines. The effective pre-RNAi length is 2,000—1,000 nucleotides. RNAi is ATP-dependent, but it is not linked to mRNA translation. There is now evidence that the effect of RNAi is enzymatic (RNAi nuclease) and involves the degradation of the mRNA rather than some kind of antisense mechanism. The nascent dsRNA, generated

by RNA-dependent RNA polymerase, is degraded to eliminate the incorporated mRNA and new cycles of dsRNAs are produced that yield new siRNAs (short interfering RNAs), and secondary siRNAs (Lipardi C et al 2001 Cell 107:297). The secondary siRNAs are the products of the action of RNA-directed RNA polymerase versus the primary siRNAs, which are the products of the action of Dicer nuclease. The secondary siRNAs, in contrast to the primary siRNAs, do not have mismatches to their target (Sijen T et al 2007 Science 315:244). The siRNA (21–22 nucleotides) combines with proteins (RISC [RNA-induced silencing complex]) that degrade the RNAs recognized by siRNA (Martinez J et al 2002 Cell 110:563). siRNA is also involved in chromatin remodeling by the nucleolar RNA processing center (localized in the Cajal bodies) involving RNA-dependent RNA polymerase, DICER-LIKE3, ARGONAUTE4 and the largest subunit RNA polymerase IV b (Pontes O et al 2006 Cell 126:79; Li CF et al 2006 Cell 126:93). RNA silencing by siRNA in both plants and animals may be mediated by the methylation of DNA and histone H3 lysine⁹ (Kawasaki H, Taira K 2004 Nature [Lond] 431:211).

For high effectiveness of RNAi in the mammalian system the antisense strand should have A/U at the 5' end and the 5' end should have a 7-base pair AU-rich sequence. At the 5' end of the single-strand there should be G/C. There should be no more than a 9 bp long GC stretch present (Ui-Tei K et al 2004 Nucleic Acids Res 32:936). The secondary siRNA may spread 5' to the original target sequence of the mRNA and this new RNA has been called transitive RNAi. This phenomenon may lead to the silencing of many genes with each siRNA and provide a means for revealing their function (Chi J-T et al 2003 Proc Natl Acad Sci USA 100:6343). Genome-wide analysis of growth and viability of *Drosophila* cells using high throughput RNAi screen with 19,470 double-stranded RNAs identified ~91% of the genes involved in these functions. Many of these genes had no known mutant alleles before (Boutros M et al 2004 Science 303:832).

Theoretically, siRNA appear ideal for therapeutic purposes but their practical application faces several hurdles. Although invertebrate cells readily take up siRNA, the majority of cells of vertebrates do not absorb it efficiently enough to bring about gene silencing (see Fig. R91). Direct injection or delivery

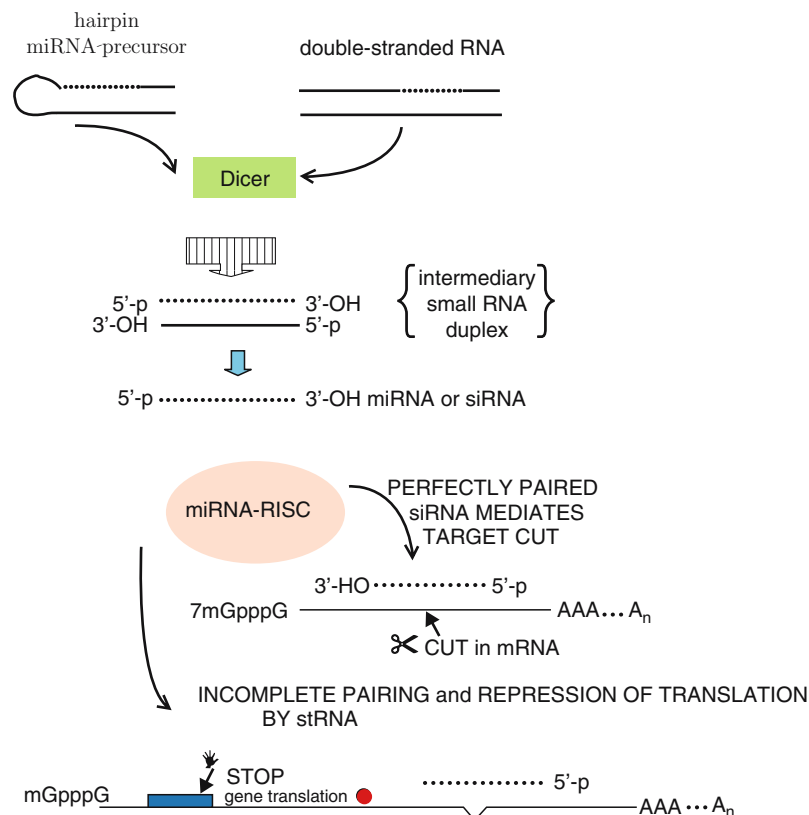


Figure R91. A model of the roles in gene silencing by miRNA, stRNA and RNAi (Modified after Hutvagner G and Zamore PD 2002 Science 297:2056)

by cationic lipids into the retina or into the genital tract seems to be more successful and may provide help in age-related macular degeneration or in viral infections, e.g., corona virus (SARS) in the lung. There are promises for treatment of local inflammatory lesions. New vehicles of delivery to internal organs are under exploration; these include liposomes or nanoparticles. siRNA-binding antibody fragments with fusion proteins may target special cells (tumors, HIV-infected lymphocytes). The free siRNA has a very short half-life in the body but once it is incorporated into the RISC complex it may survive for weeks. Unintended targets may be adversely silenced by siRNA. Chemical modification of the second residue in the active siRNA strand may prevent off-target problems. Other problems may involve triggering inflammatory, immune or interferon reactions by the body to the siRNA resembling viral RNA. The cells may become resistant to siRNA if the viral or cancer targets undergo mutational changes. siRNA may also adversely affect endogenous microRNAs (see, for excellent reviews, Dykxhoorn DM, Lieberman J 2006 Cell 126:231; Kim DH, Ross JJ 2007 Nature Rev Genet 8:173)

An shRNA/siRNA library targeting 9,610 human and 5,563 mouse genes is also available (Paddison PJ et al 2004 Nature [Lond] 428:427; see also Berns K et al 2004 *ibid*:431). In organisms, which have not been sequenced or annotated there are, in some cases, difficulties with the use of the RNAi technology. To overcome these problems, siRNA libraries were constructed containing all possible permutations. These were obtained by the use of a plasmid vector containing two convergent RNA III polymerase promoters. This procedure facilitated the construction of 5×10^7 siRNA-encoding plasmids in a single vessel. Such a library permitted genome-wide screening on the basis of phenotype (Chen M et al 2005 Proc Natl Acad Sci USA 102:2356). RNA polymerase II can synthesize a short hairpin RNA with a special green fluorescent protein coupled marker and good function (Zhu H et al 2005 Nucleic Acids Res 33(6):262). A pDECAP vector, expressing double-stranded RNA from an RNA polymerase II promoter that lacks the 5'-cap and the 3'-polyA tail transcript is not exported to the cytoplasm where it would encounter interferons, which would destroy it. The induction of an interferon response may cause general rather than specific silencing. The introduction of double-strand RNAs activates protein kinase PKR in the animal cell which phosphorylates and inactivates the eukaryotic translation initiation factor eIF2a. This causes general inactivation of many genes in the same way as an antiviral response. By keeping it within the animal nucleus it can be used to knock down specific genes by the double-stranded

RNA transcript of a transcriptional corepressor gene (Shinagawa T, Ishii S 2003 Genes Dev 17:1340). In cases when RNAi inactivates more than the target gene, the rescue of the critical gene is feasible by transforming the cell with the aid of a bacterial artificial chromosome carrying an RNAi-resistant transgene from a related species (Kittler R et al 2005 Proc Natl Acad Sci USA 102:2396). If a gene-specific siRNA sequence is inserted between two opposing promoters such as the mouse U6 and human H1, sense and antisense strands of the same template results in the mammalian cell after transfection. The construction of siRNA expression cassettes can be used in a high-throughput manner to scan targets genome-wide (Zheng L et al 2004 Proc Natl Acad Sci USA 101:135). siRNAs can be generated efficiently by restriction enzymes (Sen G et al 2004 Nature Genet 35:183; Shirane D et al 2004 Nature Genet 36:189). In *Caenorhabditis* genes, *rde-1*, *-2*, *-3*, *-4* control this interference. RDE-1 and RDE-4 proteins seem to practice surveillance for the presence of double-stranded RNA, and transposons and RDE-2 and RDE-3 (and MUT-7) degrade these RNA molecules as a defense mechanism. The mut-7 gene controls RNA interference and transposon silencing in *Caenorhabditis*. The two strands of the targeted double-stranded RNA are cleaved into 21–23- (or 25-) nucleotide long segments (siRNAs [short interfering RNAs] and stRNA [small temporal RNA]). The siRNA degrades its target whereas the regulatory stRNA represses translation of its target mRNA. There appear to be two RNase III motif enzymes involved in their processing from precursors RNAs. One, the initiator enzyme, Dicer, generates a ~22 nucleotide guide that marks the mRNA for further degradation by the RISC (RNA-induced silencing complex), an effector ribonuclease complex. Dicer-1 has specificity for single-stranded RNA and Dicer-2 (R2D2) cuts double-stranded RNA. R2D2 also selects the proper strand for association with the Argonaute component of RISC (Tomari Y et al 2004 Science 306:1377). The silencing is highly specific and yet the interference may affect related genes too; the effect may vary in degree in the various tissues. The dsRNA precursor of RNAi is transported within the body by the transmembrane protein SID-1 (Feinberg EH, Hunter CP 2003 Science 301:1545). The interference can also be transmitted to the progeny although, most probably, posttranslational events are involved. The protein product of the gene is homologous with the 3'-5' exonuclease domains of RNaseD and the Werner syndrome protein. By establishing a library of DNA clones in a bacterium, which produces double-stranded RNA (RNAi/shRNA) and fed to post-embryonic *Caenorhabditis*, the function of a large number of hitherto unknown

ORF could be identified by the silenced phenotype. Or, in case of genes controlling cell division by the use of in vivo, time-lapse differential interference contrast microscopy. The *eri-1* mutants of *Caenorhabditis* encode an evolutionarily conserved protein domain, homologous to nucleic acid-binding and exonuclease proteins. The *ERI-1* gene product (and its human homolog) degrades siRNA and thus negatively regulates RNAi (Kennedy S et al 2004 Nature [Lond] 427:645). A genome-wide study of *Caenorhabditis* revealed 90 proteins, including Piwi/PAZ, DEAH helicases, DNA binding/processing factors, chromatin-associated factors, DNA recombination proteins, nuclear export/import factors and 11 known components of the RNAi machinery within the interference pathway (Kim JK et al 2005 Science 308:1164). A genome-wide library of *Drosophila melanogaster* RNAi transgenes, extending to 88% of the genome, enables the conditional inactivation of gene function in specific tissues of the intact organism (Dietzl G et al 2007 Nature [Lond] 448:151).

In plants, the same mechanism can account for co-suppression and VIGS. In plants, two types of mechanism account for viral RNA silencing: (i) The helper component-proteinase (HC-Pro) derived from the potyviruses, which is very efficient and can silence a broad range of plant viruses and transgene-induced as well as VIGS silencing; (ii) The potato virus X (PVX) p25, which is much less effective and its action targets systemic silencing. *Arabidopsis* has four Dicer enzymes. The Dicer-like 4 (DCL4) complex confers antiviral immunity but it can be suppressed by a viral factor. Both DCL4 and DCL2 have to be suppressed for a suppressor-deficient virus to achieve systemic infection and cause bleaching (see Fig. R92) (Deleris A et al 2006 Science 313:68).



Figure R92. Photobleaching

These small RNAs may fight (HIV, Hepatitis viruses, cancer) and suppress transposons. The viral suppression of miRNAs may be responsible for some

of the disease symptoms (Kasschau KD et al 2003 Dev Cell 4:205). Some endogenous proteins can also mediate gene silencing in plants and in *Caenorhabditis* or *Drosophila*. RNAi technology may also be applied to human pathogenic viruses such as HIV (Jacque J-M et al 2002 Nature [Lond] 418:435). The therapeutic application of RNAi technology appears promising. Systemic delivery of siRNA in liposomes by intravenous injection into nonhuman primates seems very effective. Within 24–48 h after injection it showed precise targeting of apolipoprotein B and the biological effect lasted for 11 days at the highest dose (Zimmermann TS et al 2006 Nature [Lond] 441:111). Interfering RNAs have sequence-specificity for silencing but the specificity is not absolute. The siRNA technology combined with targeting specific dominant disease alleles (Machado-Joseph/spinocerebellar ataxia type 3 or Pick disease/tau) can specifically inhibit a disease symptom in a highly discriminating manner (Miller VM et al 2003 Proc Natl Acad Sci USA 100:7195). RNAi can specifically eliminate new single nucleotide mutations in the SOD1, amyotrophic lateral sclerosis alleles (Ding HG et al 2003 Aging Cell 2:209).

siRNA microbicides targeted to the Herpes simplex virus 2 envelope glycoprotein and DNA-binding protein. siRNA microbicides targeted to Herpes simplex virus 2 envelope glycoprotein and DNA-binding protein and thymidine kinase provided effective protection by vaginal application against the lethal effects of Herpes in mice. The treatment protected the animals even if applied one day after the infection and provided protection for several days. No adverse interferon effects occurred. This approach appears promising in the fight against sexually transmitted diseases (Palliser D et al 2006 Nature [Lond] 439:89). Although targeting of siRNAs to the proper disease sites and their maintenance in the cells is difficult, chemical modifications substantially improve their therapeutic potential (Soutschek J et al 2004 Nature [Lond] 432:173). Recently, reservations emerged concerning the specificity of siRNAs for effective medical treatment because the RNA molecules also hit unintended targets in some studies (Jackson & Linsley 2004 Trends Genet. 20:521). Certain mismatches between siRNA and the target abolish silencing effects. This may be due either to the failure of accessing the RISC complex or the inability of base recognition in the target. A study of the 57 all possible single-nucleotide mutations in the CD46 siRNA (siCD46) revealed that in this case mismatches between A and C bases as well in the G:U wobble pair were well tolerated, but alterations at other sites involved degradation of the target mRNA (Du Q et al 2005 Nucleic Acids Res 33:1671). The RNAi-induced silencing may be transmitted to

several generations of *Caenorhabditis* although the penetrance may not be more than 30% and the expressivity may vary (Vastenhouw NL et al 2006 Nature [Lond] 442:882).

The average silencing activity of randomly selected siRNAs is as low as 62%. Applying more than five different siRNAs may lead to saturation of the RNA-induced silencing complex (RISC) and to the degradation of untargeted genes. Therefore, selecting a small number of highly active siRNAs is critical for maximizing knockdown and minimizing off-target effects. To satisfy these needs, a publicly available and transparent machine learning tool is available that ranks all possible siRNAs for each targeted gene. Support vector machines (SVMs) with polynomial kernels and constrained optimization models select and utilize the most predictive effective combinations, thermodynamic, accessibility and self-hairpin features. This tool reaches an accuracy of 92.3% in cross-validation experiments (Ladunga I 2007 Nucleic Acids Res 35:433; <http://optirna.unl.edu/>).

Curiously, 21-nt dsRNAs targeted to selected promoter regions of human genes of E-cadherin, p21, and VEGF boost the expression of the genes rather than dampen it. The dsRNA mutation at the 5' end of the antisense strand, or "seed" sequence, is critical for activity. Mechanistically, the dsRNA-induced gene activation requires the Argonaute 2 (Ago2) protein and is associated with a loss of lysine-9 methylation on histone 3 at dsRNA-target sites (Li LC et al 2006 Proc. Natl. Acad. Sci. USA 103:17337). Multiple duplex RNAs complementary to the progesterone receptor (PR) promoter increase the expression of both PR protein and RNA after transfection into cultured human breast cancer cells. Upregulation of PR protein reduced the expression of the downstream gene encoding cyclooxygenase 2 but did not change concentrations of the estrogen receptor. This demonstrates that activating RNAs can predictably manipulate physiologically relevant cellular pathways. Activation decreased over time and was sequence specific. Chromatin immunoprecipitation assays indicated that activation is accompanied by reduced acetylation at histones H3K9 and H3K14 and by increased di- and trimethylation at histone H3K4 (Janowski BA et al 2007 Nature Chem Biol 3:166).

The 2006 Nobel Prize for physiology and medicine was awarded to Andrew Z. Fire and Craig C. Mello for their pioneering research on interfering RNA. ▶co-suppression, ▶microRNA, ▶shRNA, ▶siRNA, ▶rasiRNA, ▶piRNA, ▶tncRNA, ▶Dicer, ▶RNA non-coding, ▶antisense RNA, ▶small RNA, ▶self-cleavage of RNA, ▶argonaute, ▶PAZ domain, ▶heterochronic RNA, ▶antisense technologies, ▶heterochromatin, ▶methylation of DNA, ▶deletion

mapping, ▶posttranscriptional silencing, ▶RNA interference, ▶DEAH box proteins, ▶apolipoproteins, ▶liposome, ▶interferon, ▶quelling, ▶inhibition of transcription, ▶host-pathogen relation, ▶epigenesis, ▶Cajal body, ▶Werner syndrome, ▶Machado-Joseph syndrome, ▶Pick's disease, ▶ribonuclease D, ▶viral encephalitis, ▶Nomarski differential phase contrast microscopy, ▶RISC, ▶VIGS, ▶methylation of DNA, ▶amyotrophic lateral sclerosis, ▶SOD, ▶support vector machine; Fire A 1999 Trends Genet 15:358; Tabara H et al 1999 Cell 99:123; Grishok A et al 2000 Science 287:2494; Grishok A et al 2001 Cell 106:23; Elbashir SM et al 2001 Nature [Lond] 411:494; Vance V, Vaucheret H 2001 Science 292:2277; Hutvagner G et al 2001 Science 293:834; Matzke M et al 2001 Science 293:1080; Hammond SM et al 2001 Science 293:1146; Ruvkun G 2001 Science 294:797; Plasterk RHA 2002 Science 296:1263; Zamore PD 2002 Science 296:1265; Mlotshwa S et al 2002 Plant Cell 14:S289; Hutvagner G Zamore PD 2002 Current Opin Genet Dev 12:225; Hannon GJ 2002 Nature [Lond] 418:244; McManus MT, Sharp PA 2002 Nature Rev Genet 3:737; Tijsterman M et al 2002 Annu Rev Genet 36:489; analysis of function of the genome: Kamath RS et al 2003 Nature [Lond] 421:231; Novina CD, Sharp PA 2004 Nature [Lond] 430:161; design and validation RNAi effectors: Huppi K et al 2005 Mol Cell 17:1; Matzke MA, Birchler JA 2005 Nature Rev Genet 6:24; Voinnet O 2005 Nature Rev Genet 6:206; in mammals: Martin SE, Caplen NJ 2007 Annu Rev Genomics Hum Genet 8:81, high-throughput techniques: Echeverri CJ, Perrimon N 2006 Nature Rev Genet 7:373; http://dnaseq.med.harvard.edu/rnai_database.htm; human siRNA: <http://itb1.biologie.hu-berlin.de/~nebulus/sirna/>; RNAi web site: http://www.rnaiweb.com/RNAi/RNAi_Web_Resources/siRNA_Collections_Databases/; RNAi Codex: <http://codex.cshl.org/scripts/newmain.pl>; *Drosophila* cell culture RNAi: <http://www.flight.licr.org>; http://flyrnai.org/cgi-bin/RNAi_screens.pl; RNAi probes: <http://rnai.dkfz.de>.

RNAIII/rnaiii: A bacterial virulence-controlling molecule. It is induced by the RNAIII activating protein (RAP). The RIP protein produced in non-pathogenic strains competes for activation of rnaIII and the production of *Staphylococcus aureus* toxin. ▶RAP; Balaban N et al 2001 J Biol Chem 276:2658.

RNA-IN: The leftward transcript of the bacterial transposase gene in transposable elements, transcribed from the pIN promoter. ▶RNA-OUT, ▶Pin

RNA Interference: ▶RNAi

RNA-Mediated Gene Activation: ▶RNAi

RNA-Mediated Recombination: RNA-mediated recombination is thought to be involved in the exchange between the reverse transcript and the corresponding cellular allele. The Ty element-mediated recombination is supposed to involve RNA. ▶Ty; Derr LK et al 1991 Cell 67:355.

RNA-OUT: A transcript originating from the strong pOUT promoter of bacterial transposable elements. It opposes pIN and it directs transcription toward the outside end of the IS10 element. ▶RNA-IN, ▶pIn, ▶pOUT, ▶Tn10

RNAP: RNA polymerases; in prokaryotes there is only one DNA-dependent RNA polymerase whereas in eukaryotes RNA Pol I, Pol II, and Pol III are found. ▶RNA polymerases

RNA-PCR: A polymerase chain reaction may amplify rare RNAs after the RNA is reverse-transcribed into DNA. ▶polymerase chain reaction, ▶reverse transcripts

RNA-Peptide Fusions: Synthetic mRNAs can be fused to their encoded polypeptides when the mRNA carries puromycin, a peptidyl acceptor antibiotic at the 3'-end. After in vitro enrichment, proteins can be selected in a directed manner. ▶directed mutation, ▶evolution; Roberts RW, Szostak J 1997 Proc Natl Acad Sci USA 94:12297.

RNA-Protein Interactions: RNA-protein interactions are ubiquitous in all cells in the formation of ribosomes, spliceosomes, in several ribozymes, in posttranscriptional regulation, in translation machinery (in tRNAs, elongation factors), and viral coat proteins. (See Jones S et al 2001 Nucleic Acids Res 29:943).

RNase: ▶ribonucleases

RNase-free DNase: Heat, at 100 °C for 15 min, 10 mg RNase A per mL and 0.01 M Na-acetate (pH 5.2). Then cool and adjust pH to 7.4 (1 M Tris-HCl) and store at -20 °C. ▶DNase free of RNase

RNase MRP: A ribonuclease that cleaves rRNA transcripts upstream of the 5.8 rRNA. In the mitochondria it cleaves the primers of DNA replication. ▶U RNPs, ▶cartilage hair dysplasia; Ridanpää M et al 2001 Cell 98:195.

RNASIN: A ribonuclease inhibitor.

RNAz: A computer program which combines comparative sequence analysis and structure prediction for noncoding RNAs. The measure for RNA secondary structure conservation is based on computing a consensus secondary structure and a measure for thermodynamic stability, which, in the spirit of a z score, is normalized with respect to both sequence length and base composition but can be calculated

without sampling from shuffled sequences (Washietl S et al 2005 Proc Natl Acad Sci USA 102: 2454; <http://www.tbi.univie.ac.at/~wash/RNAz>). ▶AlifoldZ, ▶EvoFold, ▶Z score

RNKP-1: A homolog of ICE and fragmentin-2. ▶apoptosis, ▶ICE, ▶fragmentin-2

RNP: A ribonucleoprotein; any type of RNA associated with a protein particle as in the hnRNA or in the ribosomes. Proteins bind only single-stranded sequences of RNA. In the recognition of the bases, the shape and charge distribution of the RNA are also important. ▶RNA, ▶hnRNA, ▶ribosomes

RNR: ▶ribonucleotide reductase

RNS (reactive nitrogen species): ▶nitric oxide, ▶ROS

Roadmap: A project of the National Institute of Health. It was initiated in 2002 for the purpose of promoting medical research and its application for the benefit of public health. It provides technical information, support for high-risk research, and other funding (<http://nihroadmap.nih.gov>).

ROAM Mutation (regulated overproducing alleles under mating signals): Activates yeast Ty elements through the influence of the MAT gene locus. Such a system may operate if the Ty insertion takes place at the promoter of a gene and then the Ty enhancer may be required for the expression of that gene. These genes are expressed only in the *a* or *a* mating type cells but not in the diploid *a/a* cells. ▶Ty, ▶mating type determination in yeast; Rathjen PD et al 1987 Nucleic Acids Res 15:7309.

Roan: A fur color (cattle, horse) with predominantly brown-red hairs interspersed with white ones. It is common sign of heterozygosity for the *R* and *r* alleles of a gene locus. ▶co-dominance

Roberts Syndrome: The Roberts syndrome actually overlaps with the *SC phocomelia* (= absence or extreme reduction of the bones of extremities located proximal to the trunk of the body; see Fig. R93) and with the TAR syndrome involving thrombocytopenia (reduction in the number of blood platelets), mental retardation, cleft palate, etc. These three syndromes are all autosomal recessive and seem to be basically the same. They are caused by chromosomal instability. Although linkage to chromosomes 1q, 4q and 8p has been detected, the strongest linkage (lod score 13.4) pointed to 8p12-p21.2. In this tract, gene ESCO2 controls sister chromatid cohesion and the protein supposedly expresses acetyltransferase activity (Vega H et al 2005 Nature Genet 37:468). ▶chromosome breakage, ▶thrombocytopenia, ▶Holt-Oram syndrome, ▶Wiskott-Aldrich syndrome, ▶mental retardation

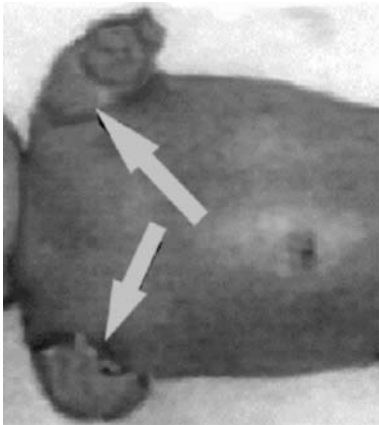


Figure R93. Roberts syndrome

Robertsonian Translocation (Robertsonian change):

Two nonhomologous telocentric chromosomes fused at the centromere. Or, more likely, the translocation between two nonhomologous acrocentric chromosomes. The outcome is a replacement of two telo- or acrocentric chromosomes with one clearly bi-armed chromosome. These translocated chromosomes may have preserved the centromeres of both acrocentrics and remain cytologically stable because one of the centromeres is inactivated. Robertsonian translocations are very common in mouse cell cultures but they also occur in wild natural populations, resulting in an apparent change in chromosome morphology and numbers. The telomeric region of different mouse chromosomes include a contiguous linear order of T₂AG₃ repeats that share considerable identity in the centromeric minor satellite DNA, ranging from 1.8 to 11 kb (see Fig. R94). This telomeric domain shows the same polarity and more than 99% identity

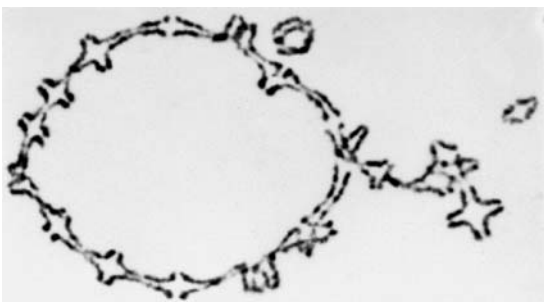


Figure R94. Late diakinesis/early metaphase I in the mouse, heterozygous for different Robertsonian translocations; 15 metacentrics in a superchain, 1 Trivalent, 2 Bivalents. The sex chromosomes are not involved in Robertsonian changes. (Courtesy Capanna E et al 1976 Chromosoma 58:341)

between nonhomologous chromosomes and may explain both the maintenance of the telomeric state and Robertsonian translocations (see Fig. R95) (Kalitsis P et al 2006 Proc Natl Acad Sci USA 103:8786). If this translocation occurs, generally a minute piece of the acrocentric chromosome is lost, but being genetically inert, it has no consequence for fitness. Robertsonian translocation may affect 1/843 human neonates. ▶translocations, ▶acrocentric, ▶telocentric, ▶fitness, ▶dicentric chromosome; Pardo-Manuel de Villena F, Sapienza C 2001 Cytogenet Cell Genet 92:342; Bandyopadhyay R et al 2002 Am J Hum Genet 71:1456.



Figure R95. Robertsonian translocation

Robinow Syndrome (RRS): A rare autosomal dominant phenotype involving, usually but not always, short stature, normal virilization but micropenis, hypertelorism of the face, etc. In the Robinow-Sorauf syndrome the main characteristic is the flattened and almost doubled big toe. An autosomal recessive Robinow syndrome included the same facial and genital features but, in addition, multiple ribs and abnormal vertebrae were present. The basic defect of the recessive RRS (9q22) is due to premature chain termination in an orphan receptor tyrosine kinase (ROR2). It is allelic to brachydactyly type B. ▶limb defects, ▶Chotzen syndrome, ▶limb defects, ▶stature in humans, ▶brachydactyly, ▶micropenis

Robo (roundabout): A *Drosophila* gene determining the straight movement of axons along the embryonal axis and preventing crossing back over the midline once a cross-over is made. Homologs exist in other eukaryotes. ▶axon, ▶slit; Simpson JH et al 2000 Cell 103:1019.

Robot Scientist: Implementing the technology of artificial intelligence makes it possible to originate hypothesis, devise experiments for their testing, carry out physical experiments in the laboratory, interpret the results, and falsify hypotheses inconsistent with test. Upon actual trials involving genes, proteins, and metabolites in the aromatic amino acid pathway of yeast, the system appeared competitive with the human performance and proved a cost decrease three-fold to 100-fold. ▶artificial intelligence; King RD et al 2004 Nature [Lond] 427:247.

Robotic Technologies: Machine operations for the performance of routine tasks in order to carry out analytical methods on a large scale and in a precise manner. For example, the robotic spotting of

thousands of nanoliter or picoliter volumes on microscope slides to an area of 1 cm². DNA that can be structurally programmed can be inserted within a two-dimensional crystalline DNA array and facilitates the construction of a nanorobotic system. Atomic force microscopy demonstrated that a rotary device was fully functional after insertion (Ding B, Seeman NC 2006 *Science* 314:1583). ▶ [atomic force microscope](#)

Robustness: A statistical concept that indicates the justification of an assumption concerning the procedures applicable to the data at hand (e.g., normal distribution). A robust statistical method is less liable to violations of the assertion. Usually, but not necessarily, the parametric methods are more robust than the nonparametric ones (because of, e.g., subjective scales). Robustness is also used in physiology to characterize the stability of the steady state under variable conditions; robustness is invariance of the phenotype despite perturbations. Robustness is inherent in all evolvable biological systems (Kitano H 2004 *Nature Rev Genet* 5:826). Genetic robustness can be associated with redundancy, epistasis, and with the function of genetic networks. The “ordered systems” of the cell are very resistant to perturbations whereas the “chaotic” systems are very susceptible to perturbations (Shumulevich I et al 2005 *Proc Natl Acad Sci USA* 102:13439). Robustness against mutation can be explained by multiple solutions to specific biological problems. Mutations can be neutral in a “neutral space” where alternative configurations can solve the same biological need. ▶ [parametric methods in statistics](#), ▶ [non-parametric methods](#), ▶ [epistasis](#), ▶ [redundancy](#), ▶ [genetic networks](#), ▶ [canalization](#); Albert R et al 2000 *Nature [Lond]* 406:378; Stelling J et al 2004 *Cell* 118:675; Wagner A 2005 *Robustness and Evolvability in Living Systems*. Princeton University Press, Princeton, New Jersey.

Rock: An RHO-associated protein serine/threonine kinase involved with microtubules of nuclear division. It induces the phosphorylation of cofilin by LIM-kinase. Caspase-3 removes an inhibitory domain of Rock 1 and that then phosphorylates the light chain of myosin. This is the main cause of the blebs on cells undergoing apoptosis. ▶ [RHO](#), ▶ [microtubules](#), ▶ [ROK](#), ▶ [LIM](#), ▶ [citron](#), ▶ [cofilin](#), ▶ [myosin](#), ▶ [apoptosis](#), ▶ [immunological surveillance for blebs](#); Sebbagh M et al 2001 *Nature Cell Biol* 3:346.

Rock-Paper-Scissors Model: An ecological dispersal, movement and interaction model based on a children's game by the same name. A rock crushes the scissors, the scissors cut paper, and the paper covers the rock. There is a complex facultative interaction here

that determines the survival of colicin-producing, colicin-sensitive and colicin-resistant strains of *E. coli* bacterium. ▶ [E. coli](#), ▶ [colicin](#); Kerr B et al 2002 *Nature [Lond]* 418:171.

Rocks: ▶ [scaffolds in genome sequencing](#)

Rocket Electrophoresis: A type of immunoelectrophoresis where antigens are partitioned against antisera. ▶ [immunoelectrophoresis](#), ▶ [antigen](#), ▶ [anti-serum](#), ▶ [electrophoresis](#); Hansen SA 1988 *Electrophoresis* 9:101.

Rodents (order *Rodentia*): A large number of species (mouse, rat, hamsters, rabbit) that have been extensively used for genetic research because of the small size of these multiparous mammals and short generation time. Mice and rats reach their sexual maturity in 1 or 2 months, and their gestation period is 19 and 21 days, respectively. They have been exploited as laboratory models for the study of cancer, antibodies, population genetics, behavior genetics, radiation and mutational responses, etc. Rodents are carriers of several human pathogens (bubonic plague [*Pasteurella pestis*], tularemia [*Pasteurella tularensis*], etc.). Several inbred strains of mice have contributed very significantly to the understanding of immunogenetics. ▶ [animal models](#), ▶ [mouse](#), ▶ [rat](#); <http://www.niehs.nih.gov/crg/cprc.htm>.

Roentgen (röntgen): A unit of ionizing radiation (X-rays). ▶ [R unit](#), ▶ [Röntgen machine](#)

Rogers Syndrome (TRMA): ▶ [megaloblastic anemia](#) (human chromosome 1q23)

Rogue: An off-type of unknown (genetic) determination.

ROI (reactive oxygen intermediates): ROI are by-products of oxidative metabolism of mitochondria, peroxisomes, and may be formed by ionizing radiation. ▶ [ROS](#); Ono E et al 2001 *Proc Natl Acad Sci USA* 98:759.

ROK: One of the multiple RHO-associated protein kinases regulating the microtubules of the spindle. ▶ [RHO](#), ▶ [spindle](#), ▶ [ROCK](#), ▶ [citron](#)

Rolling Circle: Replication is common among circular DNAs (such as conjugative plasmids [e.g., the F plasmid], double-stranded [λ phage] and single-strand phages [M13, ϕ X174], amplified rDNA minichromosomes in the amphibian oocytes). A protein nicks one of the DNA strands and remains attached to the 5'-end. The free 3'-OH terminus serves as the point of extension by DNA polymerase in such a way that the opened old strand is displaced from the circular DNA while the new strand is formed and is immediately hydrogen bonded to the old template strand (see Fig. [R96](#)). Thus, the rolling circle remains

intact and may generate new single-stranded DNAs that may be doubled later. The displaced single strand may be formed in just a single unit length of the original duplex circle or it may become a single- or double-stranded concatamer. It may also circularize in a single- or double-stranded form with the assistance of a DNA ligase to join the open ends.

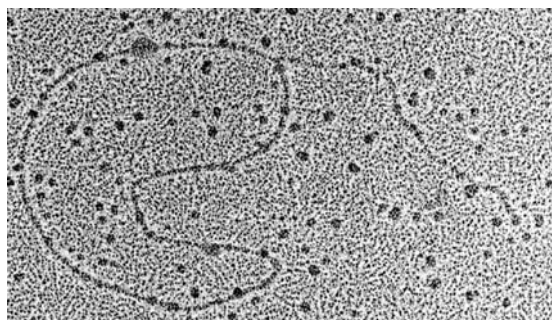


Figure R96. Rolling circle replication. The (-) strand is the template for the (+) strand. The → indicates the direction of growth. The 5' end of the (+) strand attaches to the membrane (□5'). (Diagram is courtesy Gilbert W, Dressler D 1968 Cold Spring Harbor Symp Quant Biol 33:473. Electronmicrograph is the courtesy of Dr. Nigel Godson)

Rolling circle mechanisms have been identified in the transposition of bacterial insertion elements but they are more common in eukaryotes. The transposons of eukaryotes that utilize rolling circle transposition are called Helitrons. These elements may be quite abundant in eukaryotes but are hard to detect by the common computer programs because they do not generate target site duplications like the majority of transposable elements. Many of them are non-autonomous in transposition. Helitrons do not have inverted terminal repeats. Their 5' end begins with TC nucleotides and the 3' end is CTRR [R stands for purine]. Near the 3' end they have a characteristic 16—20-nucleotide palindrome, which does not have a conserved sequence. Helitrons can pick up several genes and transpose them to other locations and thus gene collinearity is altered within the same species (Lal SK, Hannah C 2005 Proc Natl Acad Sci USA 102:9993). The *Arabidopsis*, rice, and *Caenorhabditis* Helitrons may encode about 1,500 amino acids that embed a 5' → 3' helicase-like protein and a replication A protein besides some other gene products. For transposition several host proteins are also required. Evolutionarily Helitrons may have originated from geminiviruses. (See Fig. R97) ▶conjugation, ▶conjugation mapping, ▶concatamer, ▶padlock probe, ▶insertion element, ▶palindrome, ▶replication protein A, ▶geminivirus;

del Pilar Garcillan-Barcia M et al 2001 Mol Microbiol 39:494; Kapitonov VV, Jurka J 2001 Proc Natl Acad Sci USA 98:8714; Feschotte C, Wessler SR 2001 Proc Natl Acad Sci USA 98:8923.



Figure R97. Rolling circle (see Figure R96 for explanation)

Rolling Circle Amplification (RCA): A short DNA primer, which is complementary to a segment of a circular DNA, and an enzyme generate many single-stranded, concatameric copies of DNA in the presence of deoxyribonucleotide (see Fig. R98). It can produce sufficient material for microarray analysis from specific locations and can detect single-nucleotide differences. ▶microarray hybridization, ▶concatamer; Nallur G et al 2001 Nucleic Acids Res 2001 29[23]:e118.

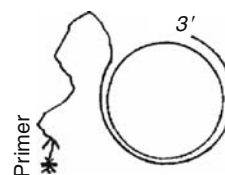


Figure R98. Rolling circle amplification

ROM (RNA-one-Modulator): A protein of 63-amino acid residues which affects the inhibitory activity of an antisense-RNA. A transacting inhibitor of plasmid replication is also named Rop/Rom. ▶RNA I, ▶antisense technology, ▶Fanconi's anemia; Lin-Chao S et al 1992 Mol Microbiol 6:3385.

ROMA: Representational oligonucleotides microarray analysis. ▶RDA

ROMA (Romani): ▶gypsy

Roman and Arabic Numerals: See Fig. R99.

I = 1, II = 2, III = 3, IV = 4, V = 5, VI = 6, VII = 7, VIII = 8, IX = 9, X = 10, XX = 20, XXX = 30, XL = 40, L = 50, LX = 60, LXX = 70, LXXX = 80, XC = 90, C = 100, CC = 200, CCC = 300, CD = 400, D = 500, DC = 600, DCC = 700, DCCC = 800, CM = 900, M = 1000

Figure R99. Roman and Arabic numerals

Romanovs: The last Tsar of Russia, Nicholas II, and his wife and three children were executed and buried near Ekaterinburg, Russia, on 16 July 1918 after the

Bolshevik take-over of power. Seventy-five years later the bodies were exhumed and from the bone tissues, the identities of the remains were determined on the basis of mitochondrial and nuclear DNAs. Tsarina Alexandra was granddaughter and Prince Philip (husband of the present Queen of England, Elizabeth) the great grandson of Queen Victoria. Their mitochondrial DNA should be identical, as well as those of the three daughters of Alexandra. Forensic DNA analysis confirmed the expectation. Sex was determined from the bone samples by identifying the X-chromosomal amelogenin gene that is expressed in the enamel of the teeth. It is rich in GC (51%) and codes for a proline-rich protein (24%). The nuclear DNA samples confirmed the identity. The Tsar and his paternity and his mtDNA tied him to his brother (by the exhumed remains of Grand Duke Georgij) on the basis of heteroplasmy. The four other skeletons did not belong to royal family members but were of the physician and other people of the court. The two youngest children, Anastasia and Alexis, were not found in the grave. The purported identity of Anastasia with Anna Anderson was not confirmed by DNA analysis. The results of these studies have been questioned (Stone R 2004 Science 303:753), and the controversy regarding the identity of the skeletal remains continues (Science 306:407 [2004]).
 ▶DNA finger-printing, ▶heteroplasmy, ▶Tsarevitch Alexis, ▶Queen Victoria; Gill P et al 1994 Nature Genet 6:130.

ROMK: A potassium ion channel family member; it is encoded in human chromosome 11 and alternative splicing generates its isoforms. ▶ion channels, ▶isoform, ▶splicing, ▶Bartter syndrome

Ron: A cell-membrane tyrosine kinase and receptor of the macrophage stimulating protein. Both are located in human chromosome 3p21. ▶macrophage-stimulating protein, ▶HGF

Röntgen Machine: An X-ray machine (invented by WK Röntgen), producing ionizing radiation (used for induction of mutation, mainly deletions) and medical examination of the body. The dose delivered is measured by R, Rad, Rem, rep, Sv, Gy. ▶R, ▶roentgen, ▶radiation hazard, ▶radiation effects, ▶radiation threshold, ▶radiation protection, ▶radiation measurement

RO[•], ROO[•]: Reactive oxygen, hydroperoxide radical. ▶ROS

roo: ▶copia

Roof Plate: An organizing center for dorsal neural development in the embryo. ▶floor plate, ▶organizer

Root: Refer a segment of the transverse cross section in Figure R100. Roots secrete a great variety of

chemicals through their roots and transgenic plants may eventually be used to manufacture, in hydroponic cultures, various needed chemicals (see Fig. R101). The advantage of the hydroponic cultures is that the purification of the secreted substances is easier. The Rho GTPase GDP dissociation inhibitor, RhoGDI, regulates root hair development at special sites (Carol RJ et al. 2005 Nature [Lond] 438:1013). Root regeneration is mediated by auxin distribution and the expression pattern of three transcription factors (Xu J et al 2006 Science 311:385). ▶quiescent zone, ▶seed germination, ▶hydroponic culture, ▶transgenic, ▶trichostatin, ▶rho; Ryan PR, Delhaize E 2001 Annu Rev Plant Physiol Plant Mol Biol 52:527; Xie Q et al 2002 Nature [Lond] 419:1676.

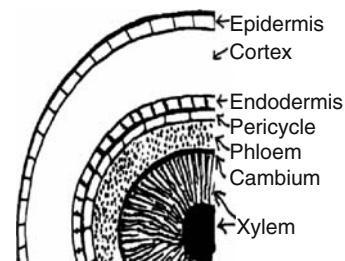


Figure R100. Root cross section segment

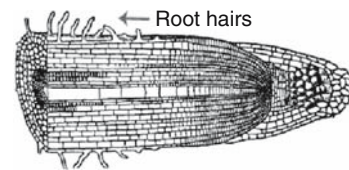


Figure R101. Root cross section segment

Root Cap: A thin membrane-like protective shield at the tip of the roots. Genetic ablation with the aid of transformation by diphtheria-toxin transgene, driven by a root cap-specific promoter showed that transgenic plants are viable without several root tip cell layers and develop more lateral roots.

Root Nodule: ▶nitrogen fixation

Root Pressure: The guttation of a wounded stem caused by osmosis in the roots of plants.

Rooted Evolutionary Tree: The evolutionary tree indicates the origin of the initial split of divergence. ▶evolutionary tree, ▶unrooted evolutionary tree

Rop Protein: ▶RNA I

ROP (RhoGEF GTP-binding protein): ROP increases nucleotide dissociation (1,000 x) from Rop (RAS-related GTP binding protein) and associates tightly with nucleotide-free Rop. It functions as a molecular

switch in plant growth and development (Berken A et al 2005 Nature [Lond] 436:1176). ►RAS, ►GEF

ROR (retinoid-related orphan receptor): RORs are animal hormone receptors regulating *Bcl* and thus the survival of lymphocytes. They are, however, involved in the regulation of several other developmental processes too. The ROR response elements (RORE) have the AGGTCA consensus, preceded by a 5 bp A/T-rich sequence. ►*Bcl*, ►survival factors, ►IL-17; Jetten AM et al 2001 Progr Nucleic Acid Res Mol Biol 69:205.

RoRNP: A ribonucleoprotein involving the so-called Y RNA (transcript of RNA polymerase III), the 60 kDa Ro60 protein and, in some cases, also the La protein (regulator of pol III). RoRNP has been identified in all eukaryotes examined and it appears to be the target of the autoimmune diseases of lupus erythematosus and Sjögren syndrome. ►autoimmune disease; Labbe JC et al 1999 Genetics 151:143.

ROS: The reactive oxygen species that may play a detrimental role in radiation damage, modification of DNA, degenerative human diseases, plant disease, etc. Mitochondrial oxidative phosphorylation, lipid peroxidation, and induced nitric acid synthase (NOS) may produce large amounts of reactive NO (nitric oxide) and thus generate ROS. NO is a known deaminating mutagen. The production of antioxidants (vitamin C, vitamin E, glutathione, ferritin, β carotene) is the defense against ROS damage. A PPAR γ coactivator (PGC-1 α) is required for the induction of several ROS-detoxifying enzymes (such as GPx1, SOD2); it protects against neurodegeneration by ROS (St-Pierre J et al 2006 Cell 127:397). The cells may also use SOD, catalases, and peroxidases to degrade ROS. Reactive oxygen may be responsible for half of the human cancer cases. Also, deficiency of ROS (by supplying 2-methoxyestradiol) may trigger the demise of leukemia cells because cancer cells have increased aerobic metabolism. The redox enzyme p66^{Shc} generates mitochondrial hydrogen peroxide and is a signal to apoptosis. Electron transfer between cytochrome c and p66^{Shc} contributes to ROS formation, apoptosis, and aging (Giorgio M et al 2005 Cell 122:221). ►SOD, ►hydrogen peroxide, ►PPAR, ►hydroxyl radical, ►RO $^{\bullet}$, ►ROO $^{\bullet}$, ►oxidative DNA damage, ►nitric oxide, ►Fenton reaction, ►oxidative deamination, ►aging, ►host-pathogen relationship, ►photodynamic effect, ►singlet oxygen, ►ROI, ►apoptosis, ►aging; Möller IM 2001 Annu Rev Plant Physiol Plant Mol Biol 52:561; Lee D-H et al 2002 Nucleic Acids Res 30:3566.

ROS oncogene: The ROS oncogene is in human chromosome 6q22 and it is the c-homolog of the

viral v-ros. It appears to be the same as MCF. ►oncogenes

Rosa spp: Ornamentals with $2n = 14, 21, 28$. ►*Rosa canina*

Rosa canina (dog rose): A pentaploid species with 35 somatic chromosomes (see Fig. R102). Unlike other pentaploids it is fertile. In meiosis, the plants produce seven bivalents and 21 univalents. The univalents are lost at gametogenesis in the male and so the sperms contain only seven chromosomes, derived from the seven bivalents. During formation of the megaspore all the 21 univalents and the seven chromosomes from the seven bivalents are incorporated into the embryo sac. The addition of the seven male and the 28 female chromosomes to the zygote restores the 35 somatic chromosome number. The female contributes more chromosomes to the offspring; it is therefore matroclinous. Recombination is limited to the seven bivalents. Its breeding system is a unique mixture of generative and apomictic reproduction. ►pentaploids, ►apomixis, ►matroclinous, ►univalent; Gustafson Å 1944 Hereditas 30:405.



Figure R102. *Rosa canina*

Rosacea: A skin disease caused by inflammation due to persistent reddening of the skin (erythema). The antimicrobial peptides cathelicidine and serine protease levels seem to be elevated, which are involved in innate immunity, dilation of the blood vessels, leukocyte migration and wound healing responses. It may be due to candidiasis, Sjögren syndrome and other causes (Bevins, Yamasaki K et al 2007 Nature Med 13:975). ►candidiasis, ►Sjögren syndrome

Rosetta Stone Sequences: Rosetta stone sequences aid in deciphering the function of simple polypeptide sequences. Prokaryotic proteins frequently carry out the same functions as the corresponding eukaryotic ones. In eukaryotes, the homologous proteins are

frequently fused with other proteins that are required for their function whereas in prokaryotes they may appear separately as single proteins. Once the function of the fused eukaryotic proteins is known, the function of both the prokaryotic counterparts can also be inferred. For example, in *E. coli*, gyrase A and B are encoded separately but in yeast they have homology to different domains of topoisomerase II. In a sequential manner, then, functional connections can be revealed to other proteins too. ▶[phylogenetic profile method](#), ▶[gene neighbor method](#); Marcotte EM et al 1999 Science 285: 751.

Rosette: Plant shoots with greatly reduced internodes commonly found in dicots before the stem bolts after induction of flowering; any anatomical structure in animals arranged in a form resembling the petals of a rose (see Fig. [R103](#)).



Figure R103. Leaf rosette

ROSI: Also called the round spermatid injection or round spermatid nucleus injection (ROSNI). This and the elongated spermatid injection (ELSI) involve injection of haploid germ cells retrieved from testicular biopsies into recipient oocytes. These procedures help overcome male infertility when the spermatozoon is unable to penetrate the egg (Jurisikova A et al 1999 Mol Hum Reprod 5:323). ▶[ART](#)

Rossellini-Guienetti Syndrome: ▶[ectodermal dysplasia](#)

Rossmann Fold: An NAD(P)-binding domain (Gly-XXXGlyXGly) near the N-terminus, encoded by a large number of eukaryote and prokaryote genes. ▶[NADP⁺](#)

Rostral: In the direction of the beak, mouth or nose rather than toward the hind position.

***r*₀t:** In a RNA-driven DNA-RNA hybridization reaction, it is the concentration of RNA × the time of the reaction (analogous to *c*₀t in reassociation kinetic

studies with DNA). *r*₀t sheds information on the RNA complexity of different cells during development. ▶[c₀t](#), ▶[RNA driven reaction](#)

Rotamase: A group of enzymes catalyzing cis-trans isomerization. ▶[cyclophilin](#), ▶[immunophilins](#)

Rotamer: A rotational isomer involving a side chain, i.e., not the backbone of the molecule. The place of atoms is altered by rotation around single bonds.

Rotational Diffusion: A process wherein membrane proteins travel within the membranes by rotation perpendicular to the plane of the lipid bilayer. ▶[cell membrane](#)

Rotaviruses (*Reoviridae*): Their genomes consist of 10–12 double-stranded RNA and each particle carries a single copy of this genome (see Fig. [R104](#)). The terminal sequences control replication and packaging. Through internal deletions the RNAs may become aberrant, called DI RNA (defective interfering), resulting in lower infectious capacity. The rotaviruses may cause gastroenteritis (stomach and intestinal inflammation) and diarrhea in human babies and animals. The introduction of recombinant vaccinia virus T7 RNA polymerase into rotavirus generates artificial viral mRNA and can induce mutation (Komoto S et al 2006 Proc Natl Acad Sci USA 103:4646). ▶[reovirus](#), ▶[vaccinia](#)

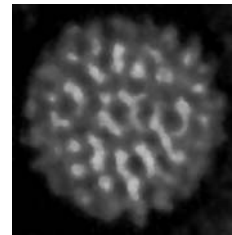


Figure R104. Rotavirus

Rothmund-Thomson Syndrome: An autosomal recessive human disorder involving dermal (skin) lesions (see Fig. [R105](#)), dark pigmentation, light-sensitivity, early cataracts, bone and hair problems, and premature aging. It may lead to squamous (scaly) carcinomas. Autosomal dominant genes determine some similar types of diseases. One form is assigned to human chromosome 8q24.3 and another to 17q25. Both genes encode helicases; the homologs of what control recombination in yeast. ▶[cancer](#), ▶[light-sensitivity diseases](#); helicase: Sangrithi MN et al 2005 Cell 121:887).



Figure R105. Rothmund syndrome skin lesions. (From Bergsma D (Ed.) 1973 Birth Defects. Atlas and Compendium. By permission of the March of Dimes Foundation)

Rotor Syndrome: ▶Dubin-Johnson syndrome

Rough Draft of the Syndrome: A not complete sequence of a genome and yet it displays the sequences of about 90% of the euchromatic parts, containing the coding units. ▶human genome, ▶genome projects

Rough ER: ▶endoplasmic reticulum rough, ▶RER

Round of Matings: After bacteriophages have been replicated within the host cell, the newly formed molecules of “vegetative DNAs” may recombine with each other several times. Because of the multiple exchanges (in agreement with the Poisson distribution expectations), it appears that the maximal recombination between markers cannot exceed 30–40%. ▶mapping function, ▶negative interference, ▶coefficient of coincidence; Visconti N, Delbrück M 1953 Genetics 38:5.

Rous Sarcoma: Rous sarcoma was originally detected as a viral RNA cancer in chickens. The protooncogene homolog was detected in rats and other mammals. ▶RAS and homologs, ▶oncogenes, ▶TV/RCAS

Rowley-Rosenberg Syndrome: An autosomal recessive growth retardation, different from dwarfism, and characterized by aminoacidurias. ▶dwarfism, ▶aminoacidurias

RPA: A single-strand DNA-binding protein (of subunits of 70, 34 and 14 kDa) participating in replication, nucleotide excision repair, repair of double-strand breaks by recombination. ▶replication protein A, ▶DNA replication eukaryotes, ▶NER, ▶BER, ▶UNG2; Davis AP, Symington LS 2001 Genetics 159:515.

RPB: Subunits (differently numbered, each) of RNA polymerase II. ▶RNA polymerase

RPD3/Sin3: A histone deacetylase and a component of the Mad/N-CoR/Sin3/RPD transcriptional protein repressor complex. It may also block the position effect exerted by centromeric and telomeric heterochromatin. ▶position effect, ▶PEV, ▶histone, ▶histone deacetylase, ▶Mad, ▶N-CoR, ▶signal transduction, ▶repression, ▶transcription, ▶Sin3; Fazio TG et al 2001 Mol Cell Biol 2001 21:6450.

R-Phycocerythrin: A phycobiliprotein fluorochrome isolated from algae. Maximal excitation is at 545 and 565 nm but it is also excited at 480 nm. Maximal emission is at 580 nm and hence the red color.

rpo: RNA polymerases such as A, B, C₁, C₂ in (organelles) plastids and mitochondria and resembles bacterial RNA polymerases. ▶RNA polymerase, ▶σ

RPPA: ▶reverse-phase protein array

r-Proteins: Ribosomal proteins. ▶ribosome

RPTK (ROS receptor protein tyrosine kinase): A sperm receptor protein tyrosine kinase that may bind to the ZP3 (zona pellucida) protein of the egg matrix. These proteins, in various stages of cooperation, affect several cellular processes. ▶sperm, ▶egg, ▶fertilization; Zeng L et al 2000 Mol Cell Biol 20:9212.

RRAS: ▶RAS oncogene

RRE (Rev response element): An RNA export adaptor promoting the export of the HIV-1 transcripts from the nucleus. If an RRE is inserted into an intron (which normally retained within the nucleus), even that could be exported to the cytoplasm. ▶export adaptors, ▶acquired immunodeficiency; Zhang Q et al 2001 Chem Biol 8:511.

rrn: In *E. coli* there are seven ribosomal transcription units, *rrn-A*, *-B*, *-C*, *-D*, *F*, *-G*, *-H* including the 16S-23S-5S RNAs, spacers and intercalated tRNA genes within the spacers. Maturation involves trimming of the co-transcript (cleavage by RNase III) and processing by other RNases, RNases P and D (See Fig. R106). The number of rRNA genes in eukaryotes is very variable and subject to amplification. At the developmental stages of very active protein synthesis the number of ribosomal genes may be amplified to several thousands, and, e.g., in the amphibian oocytes may be sequestered into mini-nuclei. Eukaryotic rRNA genes are transcribed in a ca. 45S precursor RNA, containing the 18S-5.8S-28S (in this order) and



Figure R106. Segment of a eukaryotic rRNA gene cluster in transcription. (Courtesy Spring H et al 1976 J Microsc Biol Cell 25:107)

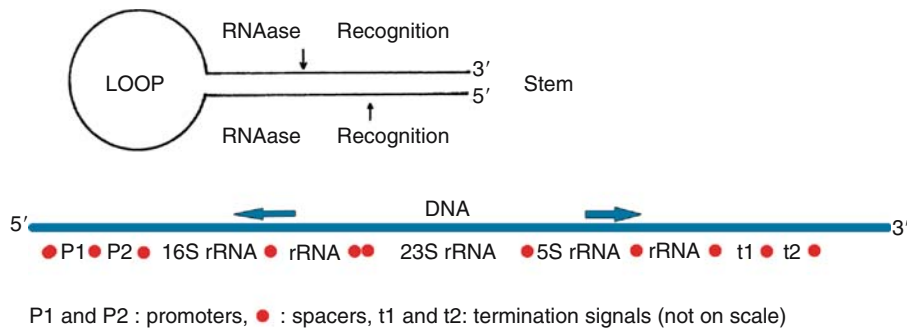


Figure R107. The DNA region of the rRNA and tRNA gene cluster (*rrn*) in *E. coli* is transcribed into longer than 30S primary transcripts, interrupted by spacers. The ribosomal and transfer RNA genes are clustered and co-transcribed in the order 5' - 26S-23S-5S-3' and within the intergenic spacers the tRNA genes are situated. RNase III at the duplex stems trims the individual gene transcripts. The different loops contain ca. 1,600, 2,900 and 120 nucleotides, corresponding to the 16S, 23S and 5S ribosomal RNAs, respectively. (The 1,600 and the 2,900 base sequences are also called p16 and p22, respectively). RNase P further trims each of these rRNA precursors and the tRNA precursors are processed by RNase P at the 5' and by RNase D at the 3' end

spacer sequences. The pathway of trimming may vary among the different species. The 18S rRNA is immediately methylated at about 40 sites and a few more methyl groups are added in the cytoplasm after maturation. The 28S rRNA is methylated immediately after transcription at over 70 sites and these methylated sites are saved during the process of maturation. The cleavage takes place at the 5' side of the genes and between the spacers. The 5.8S rRNA eventually associates with the 28S rRNA by base pairing. (See Fig. R107, ►ribosomal RNA, ►ribosomal proteins, ►ribosomes, ►stringent response, ►stringent control, ►RNA maturases; Hirvonen CA et al 2001 J Bacteriol 183:6305).

rRNA: Ribosomal RNA; a structural component of the ribosomes. rRNAs may be preferentially amplified in the oocytes of amphibians and other organisms. ►ribosome, ►ribosomal RNA

RRS (reduced representation shotgun): A method for mapping single nucleotide polymorphism in a genome. ►SNIPS; Altshuler D et al 2000 Nature [Lond] 407:513.

RS Domain: The RS domain is rich in arginine (R) and serine (S); RS proteins are parts of the spliceosomes. ►spliceosome

RSC (remodel structure of chromatin): ►chromatin remodeling

r-Scan Statistics: Detects anomalous spacing of oligonucleotides and peptides. (Jeff AR et al 2001 Genes, Chromosomes Cancer 32:144).

RSF: ►hybrid dysgenesis I-R system

RSF: A 400–500 kDa protein complex of a 325 kDa protein and the 135 kDa hSNF2h/ISWI. ►chromatin

remodeling, ►SNF2; Labourier E et al 1999 Genes Dev 13:740.

RSK (ribosomal protein S6 kinase, RSK-3 at Xp22.2-p22.1, RSK-2 at 6q27, RSK-1 in human chromosome 3, there is also an RSK-4): An epidermal growth factor-regulated protein kinase phosphorylating histone 3; RSK-3 defect is involved in the Coffin-Lowry syndrome. MAPK-phosphorylated RSK prevents parthenogenetic development of unfertilized eggs. RSK integrates MAPK and PDK1 signaling pathways. ►Coffin-Lowry syndrome, ►EGF, ►histones, ►MAPK, ►PDK, ►S6 kinase, ►chromatin remodeling

R-Spondin: A family of proteins binding Wnt ligands to the Frizzled (Fzd) receptor and the low-density lipoprotein-related receptor (LRP) 5 or LRP6 coreceptor. They initiate downstream signaling events leading to gene activation by β -catenin and the T-cell factor (TCF)-lymphoid enhancer factor (LEF) family transcription factor complex (Nam J-S et al 2006 J Biol Chem 281:13247). ►Wingless, ►lipoprotein, ►T cell receptor, ►T cells, ►LEF, ►catenins

RSR: The relative survival rate.

RSS (recombinational signal sequence): V(J)D recombinase mediates recombination only in gene segments flanked by tripartite recombination signal sequences consisting of a highly conserved heptamer (7mer), an AT-rich nonamer (9mer), and 12 or 23 base-long intervening nucleotides. ►immunoglobulin, ►V(J)D recombinase, ►RAG

Rst (*R-st*): The stippled, paramutable allele of *R* locus of maize in the long arm of chromosome 10. ►paramutation, ►R locus. (See Fig. R108).



Figure R108. Rst Kernel

R_{ST}: The same as F_{ST} but it is based on variation in microsatellites. ▶F_{ST}, ▶microsatellite

r₀t Value: The measure of RNA-DNA or RNA-RNA hybridization; the product of the concentration of single-stranded RNA and the time elapsed since the beginning of the reaction. ▶c₀t value

RTF (resistance transfer factor): Bacterial plasmids carrying various antibiotic and other resistance genes. ▶resistance transfer factors, ▶conjugation in bacteria, ▶plasmid mobilization

Rth: ▶Rad 27

RTK: ▶receptor tyrosine kinase

RTP (replication termination protein): The RTP is functionally, but not structurally, similar to Tus. ▶replication bidirectional, ▶Tus gene product; Gautam A et al 2001 J Biol Chem 276:23471.

RT-PCR: A reverse transcription-polymerase chain reaction. The purpose of the procedure is similar to the PCR in general. In this instance it amplifies the small amounts of RNA transcripts as cDNA. The reaction requires reverse transcriptase, mRNA, deoxyribonucleotides and primers that can be random DNA sequences, oligodeoxythymidine or antisense sequences. The method is very sensitive and the RNA of a single cell can be amplified and thus localized gene expression studied. Under well-controlled conditions it can be semi-quantitative. It is now used for clinical diagnostic purposes too. ▶RNA fingerprinting, ▶PCR, ▶in situ PCR, Barlič – Maganja D, Grom J 2001 J Virol Methods 95:101; <http://web.ncicrf.gov/rtp/gel/primerdb/>.

rtTA (reverse transactivator tetracycline): Basically a tTA system containing a nuclear localization signal at the 5'-end. It binds efficiently the *tetO* operator—but only in the presence of tetracycline derivatives such as doxycycline or anhydrotetracycline. ▶tTA, ▶tetracycline; Pacheco TR et al 1999 Gene 229:125.

rtTA-nls: The same as rtTA.

RU486 (mifepristone/mifeprex): A pregnancy prevention drug. It chemically induces abortion. Recently, a small number of women developed excessive bleeding and ectopic pregnancies after its use. Misopristol, the most common vaginally administered drug, in rare cases lead to deadly infection by *Clostridium sordelli* bacteria by weakening the immune system. These drugs are in wide use in Europe. RU486 has been approved in the USA since 2000. ▶hormone receptors; Mahajan DK et al 1997 Fertil Steril 68:967; DeHart RM, Morehead MS 2001 Ann Pharmacother 35:707; Schulz M et al 2002 J Biol Chem 277:26238.

RU Maize: RU maize carry plasmid-like elements in their mitochondria and yet they are not male sterile. ▶cytoplasmic male sterility, ▶mtDNA

Rubella Virus (a toga virus): The Rubella virus causes the disease of German measles. Infection during early pregnancy may cause intrauterine death of the human embryo and/or developmental anomalies in the newborn. ▶teratogenesis

Rubinstein Syndrome (Rubinstein-Taybi syndrome, RSTS, 16p13.3): The Rubinstein syndrome is characterized by dominant defects in the heart valve of the pulmonary aorta, collagen scars on skin wounds, an enlarged passageway between the skull and the vertebral column, mental retardation, and broad thumbs (see Fig. R109).



Figure R109. Rubinstein Syndrome

This condition has very low recurrence risk (1%) and about 0.2–0.3% of the inmates of mental asylums are afflicted by it. Haplo-insufficiency for the CBP transcription factor seems to be involved in the abnormal differentiation. Many afflicted individuals have break points at chromosome 16p13.3, and this is the site of the human cyclic AMP response element-binding protein (CBP/CREB). The syndrome may also be elicited by a continued requirement for CREB co-activation and histone acetylation of the CREB-binding protein (Alarcón JM et al 2004 Neuron 42:947). In addition, the p300 protein encoded by the EP300 gene (22q132) is also similar in structure to CBP and can be responsible for RSTS (Roelfsema JH et al 2005 Am J Hum Genet 76:572). ▶mental retardation, ▶CREB, ▶CBP, ▶GLI3 oncogene, ▶epigenesis; Murata T et al 2001 Hum Mol Genet 10:1071.

Rubisco: Ribulose biphosphate carboxylase-oxygenase (M_r 550,000), a chloroplast enzyme.

The eight large subunits (each M_r 56,000) are coded for by chloroplast DNA and the small subunits (each M_r 14,000) are under nuclear control (see Fig. R110). The carboxylase function catalyzes the covalent attachment of carbon-dioxide to ribulose-1,5-bisphosphate and then splits into two molecules of 3-phosphoglycerate. The oxygenase function mediates the incorporation of O_2 into ribulose-1,5-bisphosphate and the resulting phosphoglycolate re-enters the Calvin cycle. ▶chloroplast, ▶chloroplast genetics, ▶photosynthesis, ▶ribulose biphosphate carboxylase; Douce R, Neuberger M 1999 Curr Opin Plant Biol 2:214; Spreitzer R, Salvucci ME 2002 Annu Rev Plant Biol 53:449.

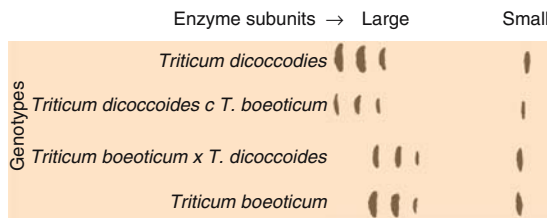


Figure R110. Genetic and electrophoretic evidence that the large subunits of RUBISCO are maternally inherited, whereas the small subunit is transmitted biparentally. Molecular studies mapped the large subunits in the chloroplast DNA. (After Chen K, Gray JC, and Wildman SG. See also 1975. *Science* 190:1304.)

Rudiment: Either the beginning stage of a developing structure or the remains of a decayed or reduced one.

Rule 12/23: ▶immunoglobulins, ▶V(D)J, ▶RAG

Rumex hastatulus: A North-American herbaceous plant which has variable chromosomal sex determination. The plants found in North Carolina have three pairs of autosomes, one X and two Y chromosomes. The form prevalent in Texas has four pairs of autosomes and one X and one Y chromosome. The middle line connects the positions of the centromeres. ▶sex determination, ▶chromosomal sex determination, see Fig. R111.

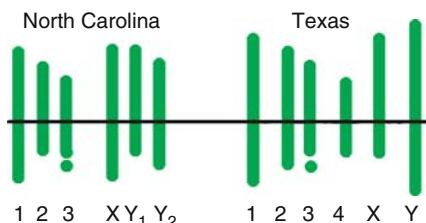


Figure R111. (Redrawn after Smith BW 1964. *Evolution* 18:93.)

Runaway Plasmids: At lower temperature (30 °C) runaway plasmids are present in relatively low copy number and do not interfere with the growth of the host cell. At above 35 °C their copy number rises substantially and so does the DNA they contain. Only after about 2 h (by the time they account for 50% of the DNA of the cell) do they suppress cellular growth. ▶vectors, ▶copy-up mutation; Uhlin BE et al 1983 Gene 22:255.

Runaway replication: The replication is not restricted to the normal manner. (See Chao YP et al 2001 Biotechnol Progr 17:203).

Run-off Transcription: The inducer of gene activity (e.g., light signal) is withdrawn and the tapering off of transcription is monitored by incorporation of labeled nucleotides. (See Delany AM 2001 Methods Mol Biol 151:321).

Run-on Transcription: Once the transcription is turned on in isolated nuclei it proceeds without further need for enhancers as measured by the incorporation of labeled nucleotides into mRNA. ▶transcription, ▶regulation of gene activity; Hu ZW, Hoffman BB 2001 Methods Mol Biol 126:169.

Run1 (run, 1–65): A *Drosophila* pair-rule gene encoding a DNA-binding protein/transcription factor with homologies to, e.g., CBFA1, -2, -3 core-binding factor subunits of human and mouse genes. ▶leukemia, ▶pair rule genes, ▶tandem repeats

Runx: Transcription factors, which may either activate or suppress tumorigenesis. *Runx3* may also aid the proliferation of B lymphocytes and autoimmune disease. The mouse *Shox2* gene upstream of *Runx2* is a key regulator of chondrogenesis and long-bone development (Cobb J et al 2006 Proc Natl Acad Sci USA 103:4511). In hematopoietic stem cells, Smad6, an inhibitor of Bmp4 signaling, binds and inhibits Runx1 activity, whereas Smad1, a positive mediator of Bmp4 signaling, transactivates the *Runx1* promoter. Three key determinants of HSC development are the Scl (small cell lung) transcriptional network, Runx1 activity, and the Bmp4/Smad signaling pathway (Pimanda JE et al 2007 Proc Natl Acad Sci USA 104:840). Runx2 is also involved in the control of RNA polymerase I promoter and associated proteins (Young DW et al 2007 Nature [Lond] 445:442). During mitosis, when transcription is shut down, Runx2 selectively occupies target gene promoters, and Runx2 deficiency alters mitotic histone modifications (Young DW et al 2007 Proc Natl Acad Sci USA 104:3189). ▶lymphocytes, ▶mesenchyma, ▶osteoblast, ▶Smad, ▶Bmp, ▶small cell lung carcinoma; Spender LC et al 2005 Oncogene 24:1873; Sato T et al 2005 Immunity 22:317.

Rupert: The hemophiliac grandson of Leopold of Albany (a hemophiliac himself), son of Queen Victoria. ▶[hemophilias](#), ▶[Queen Victoria](#)

Russell-Silver Syndrome (RSS): Most commonly autosomal recessive (7p11.2-p13, 17q23-24, 15q26.1-qter, 11p15), but X-linked or sporadic cases with low birth-weight dwarfism, frequently with asymmetric body and limbs, deformed fingers, relatively large skull and mental retardation are common. The 7p site is closely associated with the location of the genes encoding growth factor receptor-binding protein 10 and the insulin-like growth factor-binding proteins 1 and 3. Maternal disomy, at least for a 35 Mb sequence, appears to account for the symptoms. ▶[dwarfism](#), ▶[stature in humans](#), ▶[imprinting](#), ▶[uniparental disomy](#); Hannula K et al 2001 *Amer J Hum Genet* 68:247; Nakabayashi K et al 2002 *Hum Mol Genet* 11:1743.

Rust: Disease of grasses (cereals) caused by *Puccinia graminis*. *Puccinia* fungi display rust color pustules (see Fig. R112). Resistance in barley is based on a receptor-like serine/threonine kinase protein (Nirmala J et al 2006 *Proc Natl Acad Sci USA* 103:7518). New aggressive variants of *Puccinia graminis* are threatening existing resistant wheat varieties. ▶[host-pathogen relations](#); Staples RC 2000 *Annu Rev Phytopath* 38:49.

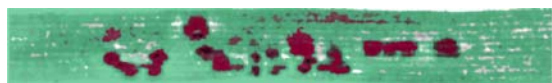


Figure R112. *Puccinia trititica* (Courtesy of Dr ER Sears)

Rut: ▶[oestrus](#)

RuvABC: A protein complex operating in the Holliday structure of recombination. The RuvAB helicase/ATPase and motor protein complex mediates branch migration (also through nucleosomes in eukaryotes) and replication. RuvC is an endonuclease. ▶[branch migration](#), ▶[Holliday juncture](#), ▶[recombination molecular mechanisms in prokaryotes](#), ▶[recA](#), ▶[endonuclease](#), ▶[AAA proteins](#); West SC 1997 *Annu Rev Genet* 31:213; Constantinou A et al 2001 *Cell* 104:259; Yamada K et al 2001 *Proc Natl Acad Sci USA* 98:1442.

RVs: ▶[BIN](#)

RXR: ▶[RAR](#)

Ryanodine (ryanodol 3-[1H-pyrrole-2-carboxylate]): A toxic extract (insecticide) from the new world tropical shrub *Ryania speciosa*. It regulates calcium ion channels in muscles. The mutation of deletion of the ryanodine receptor gene (RYR1, 19q13.1) may lead to malignant hyperthermia. ▶[ion channels](#),

▶[central core disease](#), ▶[hyperthermia](#); Zalk R et al 2007 *Annu Rev Biochem* 76:367.

Rye (*Secale cereale*): $2n = 2x = 14$ is an outbreeding crop plant used for the production of bread, biscuits, starch, and alcohol.

Its taxonomy is somewhat controversial. Rye can be crossed with a number of other cereals; among them the allopolyploid *Triticale* (wheat \times rye hybrids, $2n = 42$ and $2n = 56$) are most notable. Addition lines and transfer lines carrying rye chromosomes or chromosomal segments have been made. Rye belongs to those exceptional grain crops where autotetraploid varieties have agronomic value. Trisomic lines are known. Some varieties harbor a variable number of B chromosomes (see Fig. R113). Rather unusually, some of the plastids are also transmitted through the pollen. ▶[chromosome banding](#), ▶[Triticale](#), ▶[alien addition](#), ▶[chromosome substitution](#), ▶[alien substitution](#), ▶[transfer lines](#), ▶[holocentric](#), ▶[ergot](#); <http://www.tigr.org/tdb/tgi.shtml>.



Figure R113. Giemsa-stained rye karyotype displaying an isochromosome (⇔) and the corresponding arm in a normal chromosome (→). (Courtesy Dr. Gordon Kimber)

Ryegrass: *Lolium multiflorum* and *L. perenne*, both $2n = 14$ (see Figs. R114 and R115).



Figure R114. Rye ear



Figure R115. Ryegrass ear

Historical vignettes

George W. Beadle recollections (Stadler Genetics Symp. 2:114) about Archibald E. Garrod discoveries of inborn errors of metabolism beginning in 1899 and Richard Goldschmidt's classical book of *Physiologische Theorie der Vererbung* 1927 (Springer, Berlin).

"I recall giving a lecture at the University of California, Berkeley, in the mid-forties in which I recounted this remarkable story of the neglect of GARROD's work. RICHARD GOLDSCHMIDT, then on the faculty of that university was in the audience. He told me after the lecture that he could not understand how he had omitted mention of GARROD's work in his well-known book *Physiological Genetics* and that he had indeed been well aware of it, but had forgotten about it when he wrote the book. That seems to me a pretty good indication that he had not really appreciated its significance, much as de VRIES had not properly assessed the work of MENDEL when he first read about it."

At the January 6-8, 1909 meeting of the American Breeder's Association the above paper was presented in Columbia, Missouri.

AMERICAN BREEDERS' ASSOCIATION. 365

WHAT ARE "FACTORS" IN MENDELIAN EXPLANATIONS?

BY PROF. TH MORGAN.

Columbia University, New York, N. Y.

In the modern interpretation of Mendelism, facts are being transformed into factors at a rapid rate. If one factor will not explain the facts, then two are invoked; if two prove insufficient, three will sometimes work out. The superior jugglery sometimes necessary to account for the results may blind us, if taken too naively, to the common-place that the results are often so excellently "explained" because the explanation was invented to explain them. We work backwards from the facts to the factors, and then, presto! explain the facts by the very factors that we invented to account for them. I am not unappreciative of the distinct advantages that this method has in handling the facts. I realize how valuable it has been to us to be able to marshal our results under a few simple assumptions, yet I cannot but fear that we are rapidly developing a sort of Mendelian ritual by which to explain the extraordinary facts of alternative inheritance. So long as we do not lose sight of the purely arbitrary and formal nature of our formulae, little harm will be done; and it is only fair to state that those who are doing the actual work of progress along Mendelian lines are aware of the hypothetical nature of the factor-assumption. But those who know the results at second hand and hear the explanations given almost invariably in terms of factors, are likely to exaggerate the importance of the interpretations and to minimize the importance of the facts.

S

S (such as in 5S RNA): ►sedimentation coefficient

s: ►selection coefficient

s: Standard deviation of a set of experimental observations. ► σ parametric

σ : The measure of superhelical density of DNA.

σ : A subunit of prokaryotic RNA polymerase enzyme, essential to start transcription in a specific way. This factor opens the double helix for the action of the RNA polymerase. Also, the σ^{70} is involved in pausing of transcription. The σ^{70} recognition sites consist of two hexamers located at -10 and -35 positions from the transcription start point. The sigma factor can melt promoter independently from the RNAP (polymerase) protein (Hsu H-H et al 2006 Cell 2006 127:317). The σ^{70} s are in excess of the polymerase enzyme and there is a competition for the enzyme molecules among the σ^{70} units (Grigorova I et al 2006 Proc Natl Acad Sci USA 103:5332). The σ^{38} subunits are used at the stationary phase of growth. σ^{28} is a minor subunit transcribing only less than two dozen genes. σ^{54} , another minor subunit binds to the promoter even in the absence of the core polymerase. In the synthesis of stress proteins σ^{32} and σ^{24} are used. Usually the σ^{70} is released from the polymerase (RNAP) at the beginning of the elongation of the transcript or shortly afterwards. However, some of them stay on throughout elongation and regulate gene expression depending on the cellular circumstances. The σ elements are complexed with anti- σ proteins when not in use. In some algae the protein present in the chloroplast is encoded by the nucleus. In several plant species, the same polypeptide is coded for by the chloroplast DNA. ►RNA polymerase, ►open promoter complex, ►sigma factor, ►chloroplast, ►chloroplast genetics, ►rpo, ►Pribnow box, ►transcription factors, ►UP elements, ►DnaJ; Dartigalongue C et al 2001 J Biol Chem 276:20866; Marr MT et al 2001 Proc Natl Acad Sci USA 98:8972; Bar-Nahum G, Nudler E 2001 Cell 106:443; Kuznedelov K et al 2002 Science 295:855; Mekler V et al 2002 Cell 108:599; Nickels BE et al 2005 Proc Natl Acad Sci USA 102:4488; review: Mooney RA et al 2005 Mol Cell 20:335; anatomy of *E. coli* σ^{70} : Shultzaberger RK et al 2007 Nucleic Acids Res 35:771.

σ : The parametric designation of standard deviation. ►standard deviation, ►standard error

σ : Yeast transposable element. ►Ty

σ : A viral infectious hereditary agent of *Drosophila*. ►CO₂ sensitivity, ►infectious heredity

σ : 387 bp region intercalated between the two S elements in opposite orientation of the complex R locus of maize. ►paramutation, ►tissue specificity, ►R locus of maize

S8: A ribosomal protein with binding site at the 597–599/640–643 at the hairpin of the 16S rRNA and it is required for the assembly of the 30S small ribosomal subunit (see Fig. S1). ►ribosomes

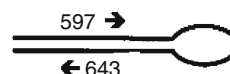


Figure S1. Hairpin

S-9: ►microsomes, ►Ames test

S³⁵ or ³⁵S: Sulfur isotope. ►isotopes

S49: A mouse lymphoma cell line.

S Alleles: Control self-sterility in plants. ►self-incompatibility, ►incompatibility alleles

S Cytoplasm: Present in some cytoplasmically male sterile lines. ►cms

S Factor: A mitochondrial plasmid-like element in male sterile plants. ►cms

S6 Kinase (RSK, S6K): The collective name for the cytosolic p70^{S6K} and the nuclear p85^{S6K} kinases that phosphorylate the S6 ribosomal protein before the initiation of translation. The supply of amino acids affects the process. Mutation in the genes results in reduced cell and body size. Mice deficient for S6K are glucose intolerant and hypoinsulinemic. S6K is an effector of mammalian TOR. The carboxyl end of S6 and the phosphorylation sites within are highly conserved from *Drosophila* to humans. ►translation initiation, ►platelet-derived growth factor, ►phosphatidylinositol, ►S6 ribosomal protein, ►5'-TOP, ►cell size, ►insulin, ►TOR; Duffer A, Thomas G 1999 Exp Cell Res 253:100; Um SH et al 2004 Nature [Lond] 431:200.

S Locus: ►selfsterility alleles

S1 Mapping: When genomic DNA is hybridized with the corresponding cDNA or mRNA the non-homologous sequences cannot find partners to anneal with, and the single-stranded loops can be digested with S1 nuclease (see Fig. S2). The remaining DNAs that formed double-stranded structure can then be isolated by gel electrophoresis or their position and length can be

determined by autoradiography if appropriately labeled material was used. Thus, intron positions are revealed. ►introns, ►S₁ nuclease, ►DNA hybridization, ►genomic DNA; Favaloro J et al 1980 Methods Enzymol 65:718; Dziembowski A, Stepien PP 2001 Anal Biochem 294:87.

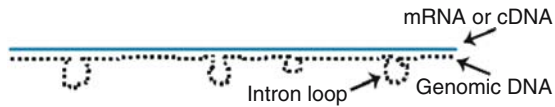


Figure S2. S₁ mapping

S₁ Nuclease: S₁ Nuclease from *Aspergillus oryzae* cleaves single-stranded DNA (preferentially), and single-stranded RNA. Double-stranded molecules and DNA–RNA hybrids are quite resistant to it unless used in very large excess. The enzyme produces 5′-phosphoryl mono- and oligonucleotides. S₁ has many applications in molecular biology: mapping of transcripts, removal of single-stranded overhangs from double-stranded molecules, analysis of the pairing of DNA–RNA hybrids, opening up “hairpin” structures. Its pH optimum is 4.5 and this may cause unwanted depurination. ►nucleases, ►S₁ mapping, see figure of hairpin structure; Kormanec J 2001 Methods Mol Biol 160:481.

S Phase: S phase of the cell cycle when regular DNA synthesis takes place. ►cell cycle

S Protein: ►vitronectin

S1 Ribosomal Protein: Binds to U-rich sequences upstream of the Shine-Dalgarno sequence and may promote translation. ►Shine-Dalgarno sequence, ►translation; Boni IV et al 2001 EMBO J 20:4222.

S6 Ribosomal Protein: Phosphorylated at about 5 serine residues near its C terminus, and the phosphorylated state is correlated with the activation of protein synthesis on the ribosomes; the phosphorylation is stimulated by mitogens and growth factors. ►ribosome; Recht MI, Williamson JR 2001 J Mol Biol 313:35.

5S RNA: ►ribosomal RNA, ►ribosomes; Artavanis-Tsakonas S et al 1977 Cell 12:1057.

6S RNA: Binds σ^{70} RNA polymerase in response to limited nutrient supply of bacteria and represses its transcriptional activity (Wassarman KM, Storz G 2000 Cell 101:613) and assures cell survival (Trotochaud AE, Wassarman KM 2004 J Bacteriol 186:4978). ►B2 RNA, ►7SK RNA, ►SRA RNA, ►RNA regulatory

7S RNA: ►RNA 7S

SAA: Serum amyloid A. ►amyloidosis

SABE (serial analysis of binding elements): A method for identification of DNA-binding transcription factors. ►SAGE; Chen J, Sadowski I 2005 Proc Natl Acad Sci USA 102:4813.

S-Adenosylmethionine (SAM): A methyl donor for restriction-modification methylase enzymes, and general methylation of DNA; synonymous with Adomet. Folic acid and other compound contribute indirectly to SAM synthesis and methylation. ►methylation of DNA

S-Adenosylmethionine Decarboxylase (AdoMetDC): An enzyme involved in the biosynthesis of spermidine and spermine. For its activity, it is essential to contain a covalently bound pyruvoyl end group to the α -subunit of the dimeric enzyme (see Fig. S3). This enzyme is found in both prokaryotes and eukaryotes. ►spermidine, ►spermine; Li Y-F et al 2001 Proc Natl Acad Sci USA 98:10578.

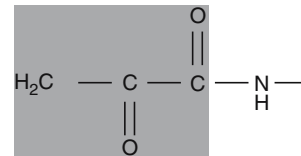


Figure S3. Pyruvoyl

SAC: A regulator of nuclear export and the cell cycle. ►nuclear pore, ►nuclear export factors

Saccades: Abrupt changes in the fixation of the eyes during scanning objects directed by the reflex center of the brain (superior colliculus).

Saccharin: A non-caloric sweetener; hundreds of times sweeter than sucrose. Oral LDLo for humans is 5 g/kg; it has been a suspected carcinogen and mutagen but later studies did not confirm its classification as a carcinogen. ►LDLo, ►aspartame, ►fructose

Saccharomyces cerevisiae: The eukaryotic budding yeast has chromosome number $n = 16$, its genome sizes is about 1.2×10^7 bp, approximately three times that of the prokaryotic *E. coli*. Recent sequencing and knockout information contradicted earlier estimates that less than 10% of its genome would be repetitive. A newer study estimates gene duplication (concerted evolution) and gene conversion rate to be about 25 million years and about 28 times of the mutation rate (Gao L-Z, Innan H 2004 Science 306:1367). In chromosome III of 55 open reading frames only 3 appeared indispensable for growth on a rich nutrient medium. Of 42 other genes, only 21 displayed

a phenotype. This information points to redundancy even in this small genome. This conclusion may be misleading, however, because some genes are called to duty only under specific circumstances. Its entire genome was sequenced by 1996. The 5885 open reading frames are encoded by 12,068 kb. About 140 genes code for rRNA, 40 for snRNA and for 270 tRNA. About 11% of the total protein produced by the yeast cells (proteome) has metabolic function, 3% is involved in DNA replication and energy production, respectively; 7% is dedicated to transcription, 6% to translation and 3% (ca. 200) are different transcription factors. About 7% is concerned with transporting molecules. About 4% are structural proteins. The original gene number estimate has been since reduced to 6128 or fewer, and some studies consider the number only 5726 (Kellis M et al 2003 Nature [Lond] 423:241). Promoters, terminators, regulatory sequences and intergenic sequences with unknown functions occupy about 22% of the genome. The majority of yeast genes are not absolutely essential for survival or function (Giaever G et al 2002 Nature [Lond] 418:387). Many proteins are involved with membranes. In rich nutrient media its doubling time is about one and half-hour. The organism has regular meiosis and mitosis. The vegetative multiplication is by budding (budding yeast), i.e., the new (daughter) cell is formed as a small protrusion (bud) on the surface of the mother cell. Haploid cells may fuse to generate diploidy and the diploid cells may undergo meiosis (sporulation), and the four haploid products are retained in an ascus as an unordered tetrad. The haploid cells may have α or a mating type. Although budding yeast is eukaryotic it can be cultured much like prokaryotes, and thus it combines many of the advantages of both groups of organisms.

The yeast cell can be spherical (oblong) as represented in Figure S4 or they may become pseudohyphal (filament-like) in appearance. MAPK,

PKA and AMPK proteins mediate this switch of growth type. Approximately 25–30% of the human genes have significant homology with a yeast gene. The present genome might have evolved through extensive duplications. Baker's yeast is not a pathogen but may be harmful for immune-compromised individuals (Wheeler RT et al 2003 Proc Natl Acad Sci USA 100:2766) and it is considered to be an opportunistic pathogen. ►mating type determination in yeast, ►fungal life cycles, ►mtDNA, ►tetrad analysis, ►YAC, ►duplication, ►yeast vectors, ►yeast transformation, ►yeast transposable elements, ►gene replacement, ►synthetic genetic array, ►synthetic lethal, ►transcript mapping, ►*Schizosaccharomyces*, ►databases, ►MAPK, ►PKA, ►AMPK; sequencing: <ftp://ftp.ebi.ac.uk/pub/databases/yeast>; protein coding sequences: <ftp://ftp.ebi.ac.uk/pub/databases/lista>; <http://genome-www.stanford.edu/Saccharomyces>; <http://www.yeastgenome.org/>; <http://mips.gsf.de/genre/proj/yeast/>; yeast introns: http://www.cse.ucsc.edu/research/compbio/yeast_introns.html; Triples: <http://bioinfo.mbb.yale.edu/e-print/genome-transposon-nature/text.htm>; phenome: <http://prophecy.lundberg.gu.se>; transcriptional regulation: <http://www.yeasttract.com>; protein–protein interaction: <http://mips.gsf.de/genre/proj/impact>; proteomics, fluorescence microscopy: <http://www.yeastrc.org/pdr/>; Dwight SS et al 2001 Nucleic Acids Res 30:69; Barnett JA, Robinow CF 2002 Yeast 19:151 and 745; Mackiewicz P et al 2002 Yeast 19:619; 4000 interactions among 1000 genes: Tong AHY et al 2004 Science 303:808.

SACO (serial analysis of chromatin occupancy): Detects the binding sites of proteins along the chromosome. (See Impey S et al 2004 Cell 119:1041).

Sacral Agensis (Currarino triad): A malformation of the caudal (tail) end of the notochord. Genes at human chromosomes 7q36 and 1q41-q42 may affect its rare dominant expression. ►Currarino triad, ►notochord

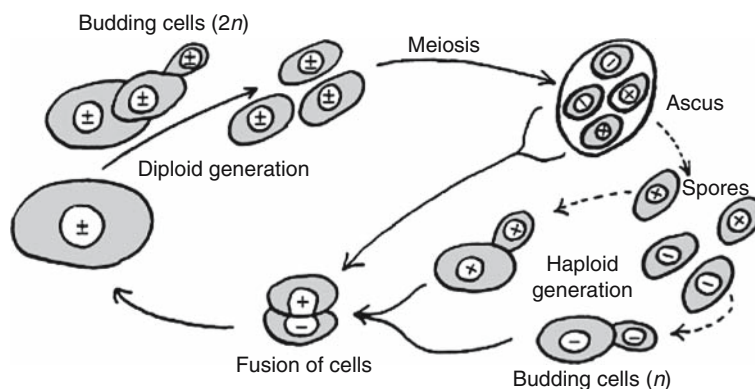


Figure S4. Life cycle of budding yeast

SAD Mouse: An animal model for human sickle cell anemia. It produces polymerized hemoglobin due to mutations in β globin, Hb^{SAD}. ▶[sickle cell anemia](#); Martinez-Ruiz R et al 2001 *Anesthesiology* 94:1113.

SADDAN (severe achondroplasia with delayed development and acanthosis nigricans): ▶[achondroplasia](#), ▶[acanthosis nigricans](#)

SADR (serious adverse drug reaction): Considered the fourth leading cause of human death, it claims 100,000 fatalities and affects about 2,000,000 persons each year in the USA due to marketed medicine. Individual reaction to specific drugs varies and certain ethnic groups include more vulnerable genotypes than others. Besides beneficial effect, many drugs have unknown side effects. It is highly desirable to develop test that would predict the genetic bases of SADR. With the progress of genomic information there are potentials for clinical application of such tests. The European pharmacogenomics project EUDRAGENE, the Canadian Genotypic Adjustment of Therapy in Childhood (GATC) and various programs of the US National Institute of Health (Pharmacogenetics Research Network) are seeking solutions for the problems. ▶[drug development](#), ▶[metabonomics](#), ▶[genetic medicine](#), ▶[pharmacogenetics](#), ▶[pharmacogenomics](#); Giacomini KM et al 2007 *Nature [Lond]* 446:975.

Saethre-Chotzen Syndrome: ▶[Chotzen syndrome](#)

SAF: SKP-associated factors, F-box proteins. ▶[SKP](#), ▶[F-box](#)

Safety: ▶[laboratory safety](#), ▶[chemicals hazardous](#), ▶[recombinant DNA and biohazards](#), ▶[radiation hazard assessment](#), ▶[cosmic radiation](#), ▶[gloves](#), ▶[environmental mutagens](#). (See Fleming DO, Hunt DL (Eds.) 2000 *Biological Safety. Principles and Practices*, ASM Press, Washington DC).

Safflower (*Carthamus tinctorius*): An oil crop of warmer climates, $2n = 24$; other related species have $2n = 20$ or $2n = 44$ chromosomes.

SAGA: A histone acetyltransferase complex of about 20 different proteins that interact with TBP (TFIID) and with gene-specific transcriptional activators. In yeast SAGA, SLIK and TFIID complexes appear to have some redundant functions. The Chd1 (chromo-ATPase/helicase-DNA binding domain) links histone (H3, H2B) methylation with SAGA and SLIK-dependent acetylation (Pray-Grant MG et al 2005 *Nature [Lond]* 433:434). ▶[histone acetyltransferase](#), ▶[histones](#), ▶[TBP](#), ▶[bromo-domain](#), ▶[transcription](#), ▶[transcription factors](#), ▶[chromatin](#)

[remodeling](#), ▶[SNF/SWI](#); Sterner DE et al 1999 *Mol Cell Biol* 19:86.

SAGE (Serial Analysis of Gene Expression): A procedure that permits the analysis of the function of many genes by a sweeping procedure. The first step is to isolate all the mRNAs that are produced in a single organ, at a particular developmental stage. By reverse transcription they are converted into cDNA. The 3' ends are then tagged by biotin. The cDNAs are digested by a restriction enzyme and the end fragments are trapped on streptavidin beads. After that, a second restriction enzyme is applied which cuts at least 9 bp from the fragments. In a following step, each short (9 bp or longer) tag is amplified by PCR and the tagged pieces are linked into a single DNA molecule. Then each tag is sequenced by an automatic sequencer and the tags are counted. In this sweeping manner 20,000 genes can be monitored in a month. The same effort would require years if it would be conducted on separate genes. This procedure reveals not just the number of expressed genes in that organ but reveals also the level of their activity. Some may be expressed in a single copy, others may be very active and are represented by multiple copies. Long SAGE is a variant of the SAGE procedure (Saha H et al 2002 *Nature Biotechnol* 20:508). ▶[genome project](#), ▶[genomics](#), ▶[biotin](#), ▶[streptavidin](#), ▶[DNA sequencing automated](#), ▶[electrospray MS](#), ▶[laser desorption MS](#), ▶[DNA chips](#), ▶[expressed-sequence tag](#), ▶[microarray hybridization](#), ▶[microarray analysis](#), ▶[SABE](#), ▶[RIDGE](#); Lash AE et al 2000 *Genome Res* 10:1051; Polyak K, Riggins GJ 2001 *J Clin Oncol* 19:2948; review: Wang CM 2007 *Trends Genet* 23:42; <http://www.sagenet.org>; 5' end SAGE tags: <http://5sage.gi.k.u-tokyo.ac.jp>; DEGSAGE, accurate mapping of SAGE tags: <http://dna.bio.puc.cl/SAGEExplore.html>.

SAGE Genie: An innovative new bioinformatics tool based on SAGE but providing a single platform for acquiring, annotating and interpreting large sets of gene expression data. The new technology measures gene expression by the frequency of 3' signature SAGE tags of 10 bases specific and unique to each transcript. The method permits the analysis of gene expression that are up- or down-regulated and allows automatic matching of SAGE tags to known transcripts. The incorrectly linked or those occurring only once or obtained by sequencing errors are filtered out from millions of tags. Then *confident SAGE tags* (CST) are obtained. The SAGE Genie permits *horizontal comparisons* (e.g., normal versus cancerous expression) and in addition *vertical comparisons* (e.g., expression profiles in different tissues or organs) under any desired conditions. This technology appears simpler and has far greater specificity than microarrays. The SAGE Genie

provides an automatic link between gene names and SAGE transcript levels accessible by the Internet: <http://cgap.nci.nih.gov/SAGE>. ► **SAGE**, ► **microarray hybridization**; Boon K et al 2002 Proc Natl Acad Sci USA 99:11287.

Sagittal (adjective): In the anterior-posterior body plan.

Saguenay—Lac-Saint-Jean Syndrome (2p16): A rare, recessive, morbid cytochrome oxidase deficiency with symptoms similar to Leigh disease. ► **Leigh's encephalopathy**

SAHA (suberoylanilide hydroxamic acid): An inhibitor of histone deacetylase.

Saimiri (squirrel monkey): ► **Cebidae**

Sainfoin (*Onobrychis viciifolia*): A leguminous forage plant; $2n = 14$ or 28 (see Fig. S5).



Figure S5. Onobrychist

Sal I: Restriction endonuclease with recognition site $G\downarrow TCGAC$.

Salamander: *Salamandra salamandra*, $2n = 24$, *Ambystoma mexicanum*, *A. tigrinum tigrinum* ($n = 14$). The estimated genome size of the ambystomas is 7291 map units, the largest known. (See Voss SR et al 2001 Genetics 158:735).

Salicylic Acid (*O*-hydroxybenzoic acid): A painkiller, keratolytic and fungicidal agent; it also mediates the expression of disease defense-related responses in plants (see Fig. S6). Its methylsalicylate derivative, a volatile compound, may carry out airborne signaling after infection of plants by pathogens. The PAD genes

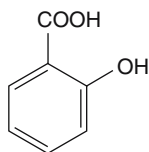


Figure S6. Salicylic acid

encode lipase-like molecules involved in salicylic signaling. Salicylic acid activity may be modulated by desaturation. ► **host-pathogen relation**, ► **hypersensitivity reaction**, ► **desaturase**, ► **aspirin**; Dempsey DM et al 1999 Crit Rev Plant Sci 18:547; Wildermuth MC et al 2001 Nature [Lond] 414:562.

Saline: The water solution of NaCl; the “physiological saline” is 0.9% salt solution for humans.

Salivary Gland Chromosomes: These are polytenic and because of their large size and clear landmarks, have been used extensively for cytogenetic analyses of *Drosophila* and other flies. The cultures to be used for this type of studies should be less crowded and moist. Third instar larvae can be used as they crawl out of the medium before the cuticle hardens. The larvae are placed in aceto-orcein or into 7% aqueous NaCl on microscope slides. A needle is used to hold the larva in place, and with a second needle placed behind the mouth parts the larva is decapitated and the salivary gland is pulled out. In aceto-orcein on a clean slide, the nuclei are stained in 5 to 10 min. The chromosomes may be spread by gentle pressure on the cover slide and after sealing the edge with wax, they can be examined under a light microscope. ► **polytenic chromosomes**, ► *Drosophila*, see Fig. S7; Lifschytz E 1983 J Mol Biol 164:17; Cold Spring Harb Symp Quant Biol 38 1974.

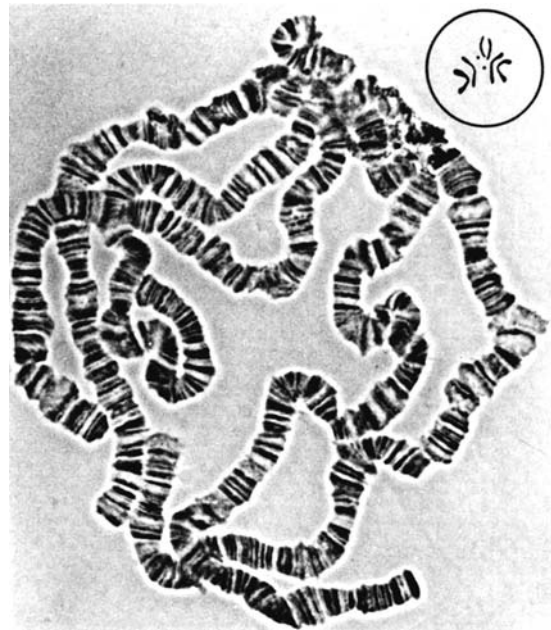


Figure S7. Salivary gland chromosomes of *Drosophila* (Courtesy of Dr. HK Mitchell). Upper right (circled) a regular mitotic set of chromosomes at about the same scale. (Redrawn after Painter TS 1934 J Hered 25:465)

Salivary Gland Chromosomes and Mapping: Since the salivary chromosomes display clear topological markers (bands), they can be used to locate deletions, duplications, inversions, translocations and can be used to associate mutant phenotypes with physical alterations. The genetic and cytological maps are collinear yet they are not exactly proportional by distance. ►coefficient of crossing over, ►*Drosophila*; Painter TS 1943 J Hered 25:465; Bridges CB 1935 J Hered 26:60.

Salla Disease: ►sialic acid, ►sialuria

Salmon: *Salmo gairdneri*, $2n = 58-65$. A transgenic Atlantic salmon strain carrying the growth hormone of the Pacific chinook salmon (*Oncorhynchus tshawytscha*) and the promoter of the eel-like ocean pout (*Macrozoarces americanus*), for an antifreeze protein grows twice as fast as its normal counterpart and actually thrives on less food. Some other transgenic strains do not perform as well (see Fig. S8). ►animal hormones, ►antifreeze protein; <http://pewagbiotech.org/research/fish>.



Figure S8. Coho Salmon (*Oncorhynchus kisutch*)

Salmonella: A member of the enteric Gram-negative bacteria and as such related to *E. coli*, and its handling ease is similar to it. It is a human pathogen and even in the laboratory it requires some caution when manipulated. Several of the related species contaminate food and feed supplies and create health hazards. F⁺, F' and Hfr strains are available. Its best known transducing phage is P22. The 4,809,037 bp genome of *Salmonella enterica* CT18 and two plasmids, pHCM1 (multiple-drug-resistance incH 218,159 bp) and the cryptic plasmid pHCM2 (106,516 bp) have been sequenced. It includes >200 pseudogenes and hundreds of insertions and deletions. *Salmonella enterica* serovar Typhimurium LT2 contains 4857 kb chromosome and a 94 kb virulence plasmid. *Salmonella cholerae suis* genome of 4.7 Mb has been sequenced. This bacterium primarily infects swine but is also pathogenic to humans (Chiu C-H et al 2005 Nucleic Acids Res 33:1690). ►histidine operon, ►Ames test, ►phase variation; Parkhill J et al 2001 Nature [Lond] 413:848; McClelland M et al 2001 Nature [Lond] 413:852; Edwards RA et al 2002 Trends Microbiol 10:94; <http://www.salmonella.org>.

Salpiglossis variabilis (Solanaceae): A plant species with the rather unusual characteristics where the four pollen grains, product of a single meiosis, stick together and, therefore can be used for tetrad analysis and gene conversion in higher plants. ►tetrad analysis, ►gene conversion

Salpingectomy: The sterilization of mammals by removal of the Fallopian tube (salpinx) leading to the uterus. ►sterilization humans, ►vasectomy, ►tubal ligation, ►birth control, ►uterus

Salt Bridges: Non-covalent ionic bonds in multimeric proteins.

Saltation: The unproven evolutionary proposition that species (and even higher taxonomic categories) arise by non-Darwinian sudden, major alterations. ►hopeful monster

Saltatory Replication: The sudden amplification of DNA segments during evolution.

Salt-Tolerance: Salt-tolerance of plants is regulated by the HKT1 (high affinity potassium [K⁺] transporter). This protein is actually a Na⁺ and K⁺ cotransporter and at high K⁺ level results in low level of Na⁺ uptake thus conveying some salt tolerance. Ca²⁺ is beneficial for salt tolerance supposedly under the control of a protein sensor displaying about 50% similarity to calcineurin and neuronal calcium sensors. The Na⁺/H⁺ antiport protein (NHX) mediates another salt control. Low proline content in the cells causes high salt-sensitivity whereas an increase in the level of sugar alcohols favors salt tolerance. Another potential mechanism for salt tolerance would be the improved elimination of the salt from the cells. *Arabidopsis* plants carrying a mutant NHX1 gene displayed higher tolerance for sodium and, in addition, because of the accumulation of NaCl in the vacuoles acquired better exploitation of the soil moisture through osmosis. Having salt tolerant crops may extend the usage of alkaline soils and may make it possible to use seawater for irrigation. Increased glyoxylase activity improves salt tolerance (Singla-Pareek SL et al 2003 Proc Natl Acad Sci USA 100:14672). Tobacco plant transgenic for the pea DNA helicase 45 (a homolog of the translation initiation factor eIF-4A) increased salt tolerance without reducing yield (Sanan-Misra N et al 2005 Proc Natl Acad Sci USA 102:509). The overlapping gene pair of *Arabidopsis* encoding Δ^1 -pyrroline-5-carboxylate dehydrogenase (*P5CDH*) and *SRO5* of unknown function can generate a 21-nucleotide siRNA that can increase salt tolerance (Borsani O et al 2005 Cell 123:1279). ►ion channels, ►calcium signaling, ►calcineurin, ►glyoxylate cycle, ►eIF-4a,

► *Priformospora indica*, ► overlapping genes, ► RNAi; Zhang H-X, Blumwald E 2001 Nature Biotechnol 19:765; Zhu J-K 2002 Annu Rev Plant Biol 53:247; Shi H et al 2003 Nature Biotechnol 21:81.

Salvage Pathway: A recycling pathway, in contrast to the de novo pathway, e.g., nucleotide synthesis from nucleosides after removal of the pentose followed by phosphoryborylation. ► phosphoribosyl transferase, ► HGPRT, ► HAT medium

SAM (significance analysis of microarrays): Permits statistical distinction between microarray signals. ► microarray hybridization; Tusher VG et al 2001 Proc Natl Acad Sci USA 98:5116.

SAM: ► S-adenosyl-L-methionine, ► substrate adhesion molecules

SAM68 (SRC-associated in mitosis): A phosphoprotein and a target of SRC, FYN and ITK kinases during mitosis. It also binds to the SH domains of the Grb adaptor protein of the cytoplasm and NCK in the nucleus. When SAM68 is tyrosine dephosphorylated, it binds RNA. A homolog of SAM68 is ÉTOILE. ► STAR, ► signal transduction, ► Src

SAM (system for assembling markers): <http://www.sanger.ac.uk/Software/sam/>.

Sampling Distribution: The probability distribution of a statistic estimated from a random sample and a certain size. The sampling distribution is somewhat different from the normal distribution that is characterized by the mean (μ) and the standard deviation (σ) inasmuch as mean (M) has a standard deviation of σ/\sqrt{n} .

Sampling Error: Can occur when the population is too small or when few individuals are sampled. The proper sample size n can be statistically estimated as shown in the formula. $n = \frac{2(z_\alpha - z_\beta)^2 \sigma^2}{(\mu_1 - \mu_2)^2}$ where z_α is the normal deviate for a level of significance α , and z_β is the normal deviate for β and $1 - \beta$ is the power required, σ^2 is the variance of each population with means μ_1 and μ_2 chosen or whenever the selection is not random. ► drift genetic, ► genetic drift, ► effective population size, ► founder principle, ► normal deviate, ► normal deviation, ► Z distribution

Sancho: A non-viral retrotransposable element. ► transposable elements

Sandhoff's Disease: Characterized either by the absence of both β -hexosaminidase α and β activity or by β -hexosaminidase β subunit only. This autosomal recessive hereditary defect has very similar symptoms to those of the Tay-Sachs disease that is caused by β -hexosaminidase α subunit deficiency.

β -Hexosaminidase β subunit defect blocks the degradation of β -galactosyl-*N*-acetyl-(1→3)-galactose-galactose-glucose-ceramide to β -(1→4)-galactosyl-galactose-glucose-ceramide and hexosaminidase α normally converts GM₂ ganglioside (neuraminic-*N*-acetyl-galactose-4-galactosyl-*N*-acetyl-glucose-ceramide) into GM₃ ganglioside (neuraminic-*N*-acetyl-galactose-glucose) ceramide. The genes for β -hexosaminidase α and β are in human chromosomes 15q23-q24 and 5q13, respectively. Their structural similarity indicates evolution by duplication. ► sphingolipidoses, ► sphingolipids, ► gangliosides, ► Tay-Sachs disease

Sandwich-Like Protein: Two β -sheets of 3–5 β -strands packed face-to-face.

Sanfilippo Syndrome: ► mucopolysaccharidosis

Sanger Method of DNA Sequencing: ► DNA sequencing

SANT (SWI3, ADA-2, N-COR, TFIIB): The chromatin remodeling complex sharing among them an ATPase and transcription and chromatin remodeling domains. ► chromatin remodeling, ► SWI, ► ADA, ► N-COR, ► TFIIB

Santa Gertrudis Cattle: Originated by a cross between the exotic-looking Brahman x shorthorn breeds (*Bos taurus*). The Brahman cattle descended from *Bos indicus*. ► cattle

SAP-1 (stress activated protein): SAP-1 is involved in the activation of MAP kinases in binding to their serum response factor (SRF). SAP is required for the activation of SLAM. ► MADS box, ► MAP, ► SRF, ► Epstein-Barr virus, ► SLAM, ► Elk, ► lymphoproliferative diseases X-linked, ► XPL; Latour S et al 2001 Nature Immunol 2:681; Cannons JL et al 2004 Immunity 21:693.

SAPK: A stress-activated protein kinase of the ERK family. SAPK can be activated by SEK a protein kinase, related to MAP kinase kinases. The signaling cascade involved is targeted to JUN. ► signal transduction, ► ERK, ► MAPKK, ► MEKK, ► JUN, ► JNK, ► Ire

Saponification: Alkaline hydrolysis of triacylglycerols to yield fatty acids. ► triacylglyceride, ► fatty acids

Saponins: Glycosylated triterpenoid or steroidal alkaloids in plants where they may be protective against fungal pathogens. Some fungal pathogens detoxify this defense molecule in a two-step process. ► host-pathogen relation; Bourab K et al 2002 Nature [Lond]: 418:889.

Saporins: Plant glycosidases, which remove adenine residues from RNA and DNA but not from ATP or dATP. ▶RIP

Saposins (10q22.1): Glycoproteins involved in the activation of galactosylceramidase. Pro-saponins are precursors of the endosomal lipid transfer proteins, which in association with CD1 present lipid antigens to the natural killer lymphocytes (NKT). ▶leukodystrophy, ▶shingolipids, ▶killer cell, ▶CD1; Qi X, Grabowski GA 2001 J Biol Chem 276:27010.

Saprophytic: Lives on non-living organic material. ▶biotrophic

SAR (structure-activity relationship): A field of study in carcinogen, mutagen and drug research. Structural modifications may or may not affect activity and it would be important to know what are the decisive factors and how to design more effective drugs. The biological assays of inhibition not only permit classification of the compounds (potential drugs) but also provide information on the structure of the proteins they interact with (Fliri AF et al 2005 Proc Natl Acad Sci USA 102:261). ▶TD₅₀, ▶CASE, ▶MULTICASE, ▶biophore

SAR (systemic acquired resistance): SAR may be induced in plants by pathogens, salicylic acid, ethephon, a compound releasing ethylene. The SAR-related genes may be members of regulons under common promoters binding specific transcription factors. Inactivation of MAP kinase 4 by the maize *Ds* transposon increased SAR and salicylic acid level and boosted the expression of pathogenesis-related proteins in *Arabidopsis*, although it reduced the size of the plants. In *Arabidopsis* for the expression of SAR a protein secretory pathway, including many genes, requires activation (Wang D et al 2005 Science 308:1036). Salicylic acid binding protein (SABP2) can convert methylsalicylic acid to salicylic acid and activates SAR (Forouhar F et al 2005 Proc Natl Acad Sci USA 102:1773). ▶host-pathogen relationship, ▶ethylene, ▶salicylic acid, ▶MAPK, ▶desaturase; Maleck K et al 2000 Nature Genet 26:403; Petersen M et al 2000 Cell 103:1111; Maleck K et al 2000 Nature Genet 26:403.

SAR: ▶scaffold

SAR1: A low activity GTPase, related to Arf. It regulates the traffic between the endoplasmic reticulum and the Golgi apparatus. ▶endoplasmic reticulum, ▶Golgi, ▶GTPase, ▶Arf, ▶GTPase; Takai Y et al 2001 Physiol Rev 81:153.

SAR by NMR (structure-activity relationship by nuclear magnetic resonance-based methods): An essential and sophisticated method to synthetic drug design. Natural or synthetic molecules are screened and

optimized analogs are synthesized to identify high-affinity ligands to develop effectively targetable drugs. ▶SAR, ▶NMR

SARA (Smad anchor for receptor activation): Recruits SMADs to the TGF- β receptor and thus regulates TGF signaling. ▶SMAD, ▶TGF

SarA: A pleiotropic staphylococcal accessory regulator of virulence. It binds to multiple AT-rich sequences. (See Schumacher MA et al 2001 Nature 409:215).

Saran Wrap: A thin sheet of plastic that clings well to most any surface and suitable for covering laboratory dishes, gels, etc.

Sarcoglycans (SGCA, 17q12-q21.33; SBCB, 4q12): A part of the dystrophin—glyco-protein complex in the sarcolemma. The complex protects the muscles and connects the cytoskeleton and the extracellular matrix. Sarcoglycan mutations may cause dystonia and myoclonous. ▶dystroglycan, ▶muscular dystrophy, ▶dystonia, ▶myoclonous; Zimprich A et al 2001 Nature Genet 29:66.

Sarcoidosis (susceptibility locus at 6p21.3, HLA-DRB1, BTNL2 [butyrophilin-like 2], Löfgren syndrome): A polygenic disorder of the immune system affecting lung, lymph nodes and eyes. Prevalence is $\sim 1.2 \times 10^{-4}$ among the majority of people of European extraction, except Swedes whose risk is about 5 times larger. The relative risk of first-degree relative is 2.8 to 18. ▶HLA; Valentonyte R et al 2005 Nature Genet 37:357.

Sarcolemma: Membranes covering the striated muscle fibers. ▶caveolin, ▶dystrophin

Sarcoma: A solid tumor tissue with tightly packed cells embedded in a fibrous or homogeneous substance; sarcomas are frequently malignant. Sticker sarcoma is canine transmissible venereal tumor. ▶Rous sarcoma, ▶RAS, ▶oncogenes; Bonnicelli JL, Barr FG 2002 Curr Opin Oncol 14:412.

Sarcomere: Muscle units of thick myosin, thin actin filaments between two plate-like Z discs. These units are repetitive. ▶titin, ▶nebulin, ▶myosin

Sarcoplasmic Reticulum: The membrane network in the cytoplasm of muscle cells containing high concentration of calcium, which is released when the muscle is excited.

Sarcosinemia: Sarcosine (methylglycine, CH₃NHCH₂-COOH) is normally converted to glycine (NH₂CH₂-COOH) by the enzyme sarcosine dehydrogenase. A defect at this step increases the level of sarcosine in the blood and in the urine (hypersarcosinemia), and may result in neurological anomalies but it may have almost no effect at all. Glutaric aciduria and defects in folic acid metabolism may also cause hypersarcosinemia. ▶glycine, ▶folic acid

Sarin: A nerve gas, which inhibits acetylcholinesterase.
 ►organophosphates

Sarkosyl (*N*-lauroylsarcosine): A detergent for solubilizing membranes and is used for extraction of tissues.

SARS (severe acute respiratory syndrome): The disease symptoms resembling flu develop by exposure to a corona virus of about 30,000-nucleotide, positive single-stranded RNA genome (see Fig. S9) (Marra MA et al 2003 Science 300:1399). The genome displays regional variations at several sites. The different strains show essential variations in the proteins decorating the capsid that determine virulence. During the first week high fever occurs without much additional symptoms. During the following four days, pneumonia develops in the lung that subsequently may become destructive to this organ. Protection is prevention, hygiene, avoiding breathing the airborne particles but no effective drug therapy exists. It is a zoonosis. Apparently the Himalayan palm civet (*Paguma larvata*) and the raccoon dog (*Nyctereutes procyonoides*) transmitted the virus to humans. In these animals the genomic sequence of the virus is 99.8% identical to that found in human (Song H-D et al 2005 Proc Natl Acad Sci USA 102:2430). Mortality rate is 5 to 15%. In mice DNA vaccine is effective (Yang Z-y et al 2004 Nature [Lond] 428:561). Angiotensin-2 converting enzyme (ACE2) is the only known receptor for this virus. L-SIGN is similar to SIGN/DC-SIGNR (dendritic cell specific ICAM-3 grabbing non-integrin) is expressed in the lymph nodes and placenta is encoded by *CLEC4M* gene in mouse. L-SIGN and DC-SIGN bind to high-mannose oligosaccharides of viruses including the SARS virus. Human individuals heterozygous for the *CLEC4M* tandem repeats are less susceptible to SARS. L-SIGN homozygotes bind even better the virus and degrade it and show lower capacity for trans infection (Chan VSF et al 2006 Nature Genet 38:38; the conclusions of this paper were questioned by Teng NL-S et al 2007 Nature Genet 39:691; Zhi L et al 2007 Nature Genet 39:692; Chang KVK et al 2007 Nature Genet 39:694 did not concede). The coronavirus variants SARS-CoV and other coronaviruses encode two RNA-dependent replicases, a specific spike protein, a small envelope protein, a membrane protein, a nucleocapsid protein and nine unidentified other proteins. Diagnostic approaches involve RT-PCR, ELISA and an IIFT kit for the detection of IgG antibody response and all of them display some advantage and shortcomings for diagnosis. A microarray-based technology appears rapid, sensitive and accurate and it is adaptable to other viral infections (Zhu H et al 2006 Proc Natl Acad Sci USA 103:4011). ►zoonosis, ►immunization

genetic, ►plant vaccine, ►angiotensin, ►ICAM, ►dendritic cell, ►RT-PCR, ►ELISA, ►immunoglobulins, ►Newcastle disease; Navas-Martin S, Weiss SR 2003 Viral Immunol 16(4):451; Webby RJ, Webster RG 2003 Science 302:1519; antiviral drugs: Wu C-Y et al 2004 Proc Natl Acad Sci USA 101:10012.

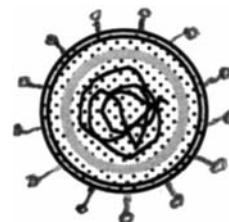


Figure S9. Corona virus

SAS (statistical analysis system): A computer software for the many types of data analyses.

SAS (switch-activating site): ►*Schizosaccharomyces pombe*

SAT: ►satellited chromosome

SATB1 (special AT-rich sequence binding protein 1): Regulates chromatin folding and anchors special DNA sequences (ATC) into its network. It facilitates histone acetylation at many specific loci and it controls tissue-specific gene expression. ►tissue-specificity, ►chromatin remodeling; Cai S et al 2003 Nature Genet 34:42; controlling cytokine gene expression: Cai S et al 2006 Nature Genet 38:1288.

SAT-DAC (satellite-DNA-based artificial chromosome): SAT-DAC of mammals is expected to replicate independently from the genome and to express its gene content as a huge vector. It may serve also for transferring any gene into mammals (humans) without the risk of disruption resident genes. SAT-DACs composed mainly of AT sequences may be readily isolated from the rest of the genome. Such a structure was stably inherited in mice. (See Hadlaczky G 2001 Curr Opin Mol Ther 3:125).

Satellite Cells: Surround each myofiber beneath the basal lamina and are precursors of muscle growth and repair. As few as seven satellite cells, associated with myofibers, are sufficient sources of muscle regeneration (Collins CA et al 2005 Cell 122:289; Montarras D et al 2005 Science 309:2064). ►basement membrane, ►myofibril, ►stem cells

Satellite DNA: DNA fraction with higher or lower density (during ultracentrifugal preparations) than the bulk DNA (see Fig. S10). Generally, it contains substantial repetitive DNA (in up to 5 Mb tracts). These satellite sequences generally pose problems

in genome sequencing because of their instability in the cloning vectors. Very little information is available regarding the function of SAT DNA. Dimeric oligopyrroles-imidazoles target adenine-thymine-rich satellite sequences and the scaffold-associated region (SAR) of *Drosophila*. Unexpectedly these polyamides induce gain- or loss-of-function phenotypes. It is assumed that these chemicals facilitate accessibility to chromatin. ▶repetitious DNA, ▶ultracentrifugation, ▶heterochromatin, ▶α-satellite, ▶polyamides, ▶satellite, ▶pyrrole, ▶imidazole; Janssen S et al 2000 Mol Cell 6:999; Janssen S et al 2000 Mol Cell 6:1013.

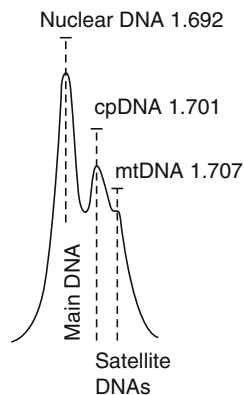


Figure S10. Satellite DNAs are identified by ultracentrifugation on the basis of their densities in CsCl

Satellite RNA: The transcript of satellite DNA: ▶satellite DNA

Satellite Virus: A defective virus co-existing with another (helper) virus to correct for its insufficiency. The unrelated helper is required for infection.

S

Satellited Chromosome: Carries an appendage to one arm by a constriction (see Fig. S11). The bridge between the main body of the chromosome and appendage is the site of the nucleolar organizer. It was named originally SAT as an abbreviation for *sine acido thymonucleinico*, i.e., a place where there was, then, no detectable DNA (= thymonucleic acid, as it was called in the 1930s) in that part of the chromosome. The appendages were also called trantabs.



Figure S11. Satellited chromosome

Satsuma Mandarin: A pollen sterile citrus variety that, if no foreign pollen can reach the flowers, produces seedless oranges. This is the characteristic also for navel oranges although some navel oranges have many seeds because in those the abnormal carpel development may interfere with pollination but they are not basically self-sterile. ▶seedless fruits

Saturated Fatty Acids: All their chemical affinities satisfied, have higher energy content than the unsaturated fatty acids that contain one or more double bonds. ▶fatty acids, ▶cholesterols, ▶omega-3 fatty acids

Saturation Density: of a mammalian cell culture before contact inhibition takes place. ▶cancer, ▶malignant growth, ▶contact inhibition

Saturation Hybridization: One component in the nucleic acid annealing reaction mixture has excessive concentration to allow finding all possible sites of homology and hybridization. ▶nucleic acid hybridization

Saturation Mutagenesis: Induce mutations at all available sites to reveal the relative importance of these sites. ▶mutagenesis, ▶localized mutagenesis, ▶linker scanning, ▶GAMBIT

Saturation of Molecules: The carbon-carbon attachments of single covalent bonds (no double bonds when entirely saturated). ▶saturated fatty acids

Sau 3A: Restriction endonuclease with recognition sequence ↓GATC; *Sau* 96 I: G↓GNCC.

SAUR (small auxin-up RNA): RNAs encoded by several genes that are induced by auxins. ▶auxins; Guilfoyle TJ 1995 ASGSB Bull 8:39.

SBD: Single-strand DNA binding domains of ~120 amino acids in the large subunits (and possibly in the small) of the RPA protein of eukaryotes. ▶DNA replication in eukaryotes, ▶RPA

SBF (Saccharomyces binding factor): Composed of Swi4 and Swi6 along with MBF (composed of Swi4 and Mbp1) initiate the transcription of genes cyclin 1 (*CLN1*) and cyclin 2 (*CLN2*) required for activation of Cdc28 enabling the progress of the cell cycle from G1 to S phase. ▶cell cycle, ▶cyclin, ▶Cdc28, ▶Swi, ▶MBF

Sbf1 (SET-binding factor 1): A myotubularin-like protein (but without phosphatase activity) binding to SET domains. ▶SET, ▶myopathy

SBMA: ▶Kennedy disease

sc: Indicating *Saccharomyces cerevisiae* (budding yeast) DNA, RNA or protein as a prefix.

SC1: An immunoglobulin superfamily cell adhesion molecule, it is transiently expressed during avian embryogenesis by a variety of cell types.

SC Phocomelia: ▶ [Roberts syndrome](#)

SC35: An SR protein. ▶ [SR motif](#)

SCA: ▶ [spinocerebellar ataxia](#), ▶ [ataxin](#), ▶ [ataxia](#)

SCA (statistical coupling analysis): Maps energetic interactions in proteins and measures the statistical interactions between amino acid positions in order to shed light on folding patterns (Lockless SW, Ranganathan R 1999 Science 286:295). ▶ [protein folding](#)

Scaffold: The cytoskeleton of the cell or residual protein fibers left in the chromosome after the removal of histones. The bulk of the scaffold is of two proteins, Sc1 (a topoisomerase II) and Sc2. The scaffold is attached to SAR (scaffold attaching regions) of the chromatin. Cytoskeletal scaffolds facilitate the transport of various molecules along its network and secure them at the proper cellular positions. Scaffold proteins—in connection with other molecules—can also fine tune quantitatively input-output properties (Bhattacharyya RP et al 2006 Science 311:822). Artificial polymer scaffolds have been constructed and used as an alternative to viral vectors to deliver therapeutic proteins or gene constructs to cells with defective or deleted genes and release their cargo in their target environment. In animal models, implanted platelet-derived growth factor greatly enhanced vascularization. ▶ [cytoskeleton](#), ▶ [topoisomerase](#), ▶ [loop domains model](#), ▶ [genetic engineering](#), ▶ [MAR](#), ▶ [WGS](#); Dietzel S, Belmont AS 2001 Nature Cell Biol 3:767.

Scaffold Protein: A platform that accepts, assembles and delivers cofactors to biological targets.

Scaffolds in Genome Sequencing: A set of ordered, oriented contigs, assembled relative to each other

by mate pairs in adjacent contigs. For assembling the over 99% accurate sequences of the *Drosophila* genome, Celera group used 8 Compaq Alpha ES40 computers with 32 gigabyte memory. In the assembly, the repetitive sequences pose real challenges because the overlaps can be *true overlaps* that belong together or the overlaps are parts of repeated sequences that may occur multiple times and being scattered in the genomes and therefore, do not belong together. A collection of fragments whose arrangement is uncontested by overlaps from other fragments are *unitigs*. The unitigs that represent unique (non-repetitive) sequences—although some extending into repeats—are called *U-unitigs*. In Figure S12 X' and X'' represent repeated sequences and in the box, they are “overcollapsed” in a unitig because they consistently subassemble as the interior of the repeats. In the repeat boundary box, A and B or B and C do not overlap and they are computationally resolved and help in extending of the assembly of the U-unitigs into scaffolds (see Fig. S13).

If mate pairs and overlaps consistently appear in bundles, the ordering of the non-repetitive euchromatic segments is facilitated. Usually gaps appear between the U-unitigs and scaffolds. Smaller fragments called *rocks*, *stones* and *pebbles* fill in these gaps. The shorter unitigs still have two or one mate links. The correct *tiling path* (a minimally overlapping DNA fragment map spanning that length of the genome) is also verified by statistics. The *reads* (base sequences) are verified also by multiple *base-calls* (identifying the correct nucleotide in a sequence) and the sets are evaluated by Bayesian statistics.

The *Drosophila* genome was sequenced and assembled in 838 *firm scaffolds* (containing at least one U-unitig). As of 2000, the WGS still has 1887 gaps with a total length of 2322 Mbp varying in size up to 150 Mbp and zero. The number of U-unitigs was 7164 (8.007 Mbp), rocks 1787 (0.927 Mbp), stones 132 (0.118 Mbp) and pebbles 25,101. STS (sequence-tagged site) mapping and BAC/P1/cosmid clone tiling

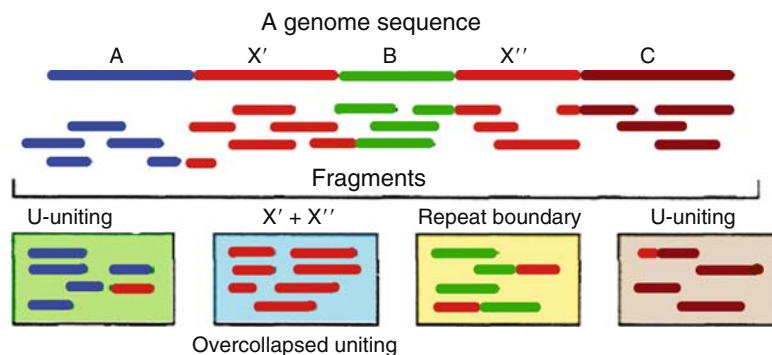


Figure S12. Scaffold. (Modified after Myers EW, et al. 2000 Science 287:2196)

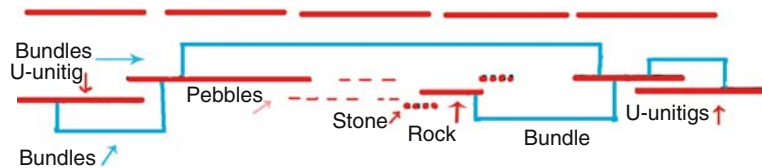


Figure S13. Scaffold of a collection of ordered contigs built of unitigs. (Modified after Myers EG et al. 2000 Science 287:2196)

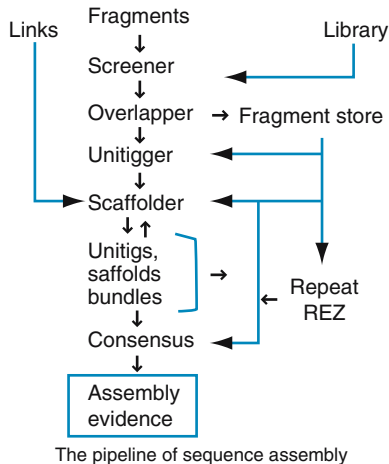


Figure S14. The overall strategy of the Celera operations. (Modified after Myers EW et al. 2000 Science 287:2196)

path (CTP) has validated the WGS map. Yet some refinement will continue, especially in the heterochromatic regions (around the centromere, etc.). ►WGS, ►genome projects, ►contig, ►mate pair, ►Bayes' theorem, ►STS, ►BAC, ►P1, ►cosmid, ►tiling, ►DNA sequencing, see Fig. S14; Myers EW et al 2000 Science 287:2196.

Scaffold-Mediated Activation: The assembly of a molecular platform in response to death stimuli and the recruitment of pro-caspases. It is initiated through cell surface receptors such as the Fas receptors, TNF α receptors and their bound ligands leading to the formation of caspases and ending up in apoptosis. ►caspase, ►TNF, ►apoptosis; Earnshaw WC et al 1999 Annu Rev Biochem 68:383.

SCAIP (single condition amplification/internal primer sequencing): Amplifies large number of exons at a single set of PCR temperatures. Sequencing specificity is gained by uniform use of a second, internal set of sequencing primers. After purification of the DNA sequencing requires three days at low cost (Flanigan KM et al 2003 Am J Hum Genet 72:931).

Scale-Free Networks: networks.

Scaling: ►quarter-power scaling, ►synaptic scaling

SCAM (substituted-cysteine accessibility method): The method used for studying cysteine substitution and covalent modification on the structure-function relationship of proteins.

SCAMP (secretory carrier membrane proteins): Integral membrane proteins of secretory and transport vesicles, like the synaptic vesicles, etc. (See Wu TT, Castle JD 1998 Mol Biol Cell 9:1661).

Scanning Electronmicroscopy (SEM): In contrast to transmission electron microscopy, the electron beam is reflected from the surface of the specimen, coated with a heavy metal vaporized in a vacuum, through a process called *shadowing*. As the electron beam scans the specimen, secondary electrons are reflected according to the varying angles of the surface of the object and generate a *three-dimensional image* corresponding to the grade of reflections. The maximal resolution is 50–100 times less than with the transmission electronmicroscopy but the image obtained can be highly magnified. It is an important technique for developmental studies. ►electronmicroscopy, ►stereomicroscopy, ►scanning tunneling microscopy, ►SPM, for picture see ►petals

Scanning Force Spectroscopy (SFS): Measures association and dissociation constants of biological molecules. ►optical tweezer; Bonin M et al 2002 Nucleic Acids Res 30(16):e81.

Scanning, Genetic: Genetic scanning.

Scanning Linker Mutagenesis: The transposon is inserted within the gene in-frame at an appropriate restriction enzyme recognition site (see Fig. S15). After transcription and translation of the construct the target protein carries a new peptide of a size depending on the size of the insertion. The procedure has been applied to both prokaryotes and eukaryotes. ►transposon, ►restriction enzyme, ►insertional mutation; Hayes F 2003 Annu Rev Genet 37:3.

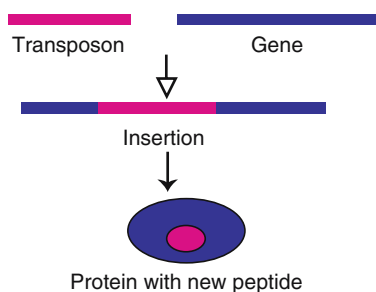


Figure S15. Scanning linker mutagenesis

Scanning Mutagenesis: ▶homolog-scanning mutagenesis, ▶linker scanning

Scanning of mRNA: The eukaryotic mRNA does not have a special consensus (such as the Shine-Dalgarno box in prokaryotes) for attachment to the ribosomes, so the mRNA leader adheres by its methylated guanylic cap to the ribosomes and the ribosome runs on it until it finds an initiation codon (generally AUG) to start translation. A preferred sequence, however, may be around the AUG codon AG—CCAUGG. The 3' terminus of the 18S rRNA of mammals bears some similarity to the prokaryotic 16S terminus:

$$A^{Me2} A^{Me2} CCUGC GGAAGGAUGA—UUA-3'-OH.$$

The presence of the m⁷G-cap facilitates the initiation but is not absolutely indispensable. The average length of the 5'-untranslated (50–70 nucleotides) sequence and its structure may favor translation but only large differences from it (very short tracts) decrease substantially the initiation. A ~12-nucleotide hairpin secondary structure between the cap and AUG improves the efficiency of translation. Similarly, the polyA tail is advantageous for translation possibly by facilitating the recycling of the ribosomes on the same mRNA. *Leaky scanning* indicates that more than one initiator codons or only the second or a later AUG is used for translation and the preceding one(s) are skipped (Chen A et al 2005 Nucleic Acids Res 33:1169). In this case different polypeptides may result. ▶Shine-Dalgarno sequence, ▶eIF, ▶initiation codon; Kozak M 1989 J Cell Biol 108:229; Samuel CE 1989 Progr Nucleic Acid Res Mol Biol 37:127.

Scanning Tunneling Microscope (STM): STM can resolve biological molecules at the atomic level; its use has been proposed for DNA sequencing. With STM, vibrational spectroscopy is possible permitting the analysis of molecules adsorbed on a surface. The vibrational energies may reveal adsorption sites, orientation and adsorption changes. ▶electrospray MS, ▶laser desorption, ▶nanotechnology, ▶SPM

SCAP (SREBP cleavage-activating protein): Regulates cholesterol metabolism by promoting the cleavage of transcription factors SREBP-1 and -2 (sterol regulatory element binding proteins). In low-sterol cells, discrete proteolysis cuts of the amino-terminal of SREBPs. As a consequence, these proteins enter the nucleus and activate the LDL receptor and cholesterol and fatty acid biosynthetic enzymes. The system can be studied by mutant CHO cells that either cannot synthesize cholesterol or LDL receptors in response to sterol depletion, or are sterol resistant and cannot terminate the synthesis of sterols or their LDL receptor. ▶sterol, ▶LDL, ▶CHO, ▶Niemann-Pick disease, ▶lipodystrophy; Shimano H 2001 Progr Lipid Res 40(6):439.

SCAR (sequence-characterized amplified region): Physical markers obtained by polymerase chain reaction-amplified RAPD bands. ▶amplification, ▶RAPD, ▶PCR; Iturra P et al 2001 Heredity 84:412.

SCAR: The suppressor of cAMP receptor. ▶cAMP

SCARMD: ▶muscular dystrophy

Scatter Diagram: A two-dimensional graphic representation of the characteristics of two variables, two traits, which may be or may not be correlated, e.g., people with a certain eye and hair color.

Scatter Factor (hepatocyte growth factor): Cellular responses of scatter factor are mediated by the Met tyrosine kinase receptor. It has multiple cell targets and it is probably involved in mesenchym-alepithelial interactions and liver, kidney development, organ regeneration, metastasis, etc. ▶hepatocyte growth factor, ▶metastasis, ▶macrophage-stimulating protein; Tacchini L et al 2001 Carcinogenesis 22:1363.

Scattering: Deflection of electrons by collision(s). ▶Compton effect

Scavenger Molecules: They clean up the cells of substances that are no longer needed.

SCC: Yeast integral membrane protein with partial structural homology to cyclophilins. ▶cyclophilins, ▶double-strand breaks

Sccl1: ▶separin, ▶Rec8

SCD25: A suppressor of gene *cdc25* mutations in yeast; increases the dissociation of Ras•GDP but does not affect Ras•GTP. ▶cell cycle, ▶cdc25

SCE: ▶sister chromatid exchange

Scent: ▶fragrances

SCEUS (smallest conserved evolutionary unit sequences): Reveal evolutionary similarities of the DNA in the genomes across taxonomic boundaries. ▶unified genetic map

SCF (Skp1—CDC53—F-box protein): A complex of ubiquitination function. The SCF protein complexes have regulatory role in the cell cycle and development. ▶Skp, ▶CKS1, ▶CDC53, ▶F-box, ▶ubiquitin, ▶jasmonic acid, ▶E1, ▶E2, ▶E3, ▶cell cycle, ▶von Hippel-Lindau syndrome, ▶glucose induction; see also Patton EE et al 1998 Trends Genet 14:237; Schwab M, Tyers M 2001 Nature [Lond] 413:268; Zheng N et al 2002 Nature [Lond] 416:703.

SCF: ▶stem cell factor

ScFv (single chain fragment variable): A variable portion of the antibody molecule that may still be expressed, e.g., in plantibodies or bacteria or other cells. ▶antibody, ▶plantibody, ▶single-chain Fv antibody; Norton EJ et al 2001 Hum Reprod 16:1854.

Scheie Syndrome: ▶Hurler syndrome

Schiff Base: α -amino groups of amino acids may react reversibly with aldehydes and form a Schiff base; these are labile intermediates in amino acid reactions. ▶Schiff reagent

Schiff's Reagent: Retains a blue color in the presence of aldehydes. Aldehydes are exposed to a fuchsin solution (0.25 g/L H₂O) and decolorized by SO₂. ▶aldehyde, ▶fuchsin

Schimke Immuno-Osseus Dysplasia (SIOD): An apparently recessive disease displaying spondyloepiphyseal dysplasia, lentigines and progressive immune and other defects. The basic anomaly is due to mutation of chromosomal matrix-associated protein (SMAR-CAL1, 2q34-q36) controlling chromatin remodeling. The gene contains 17 exons and encodes a 954 amino acid protein. Variant forms exist. ▶spondyloepiphyseal dysplasia, ▶lentigines, ▶chromatin remodeling; Boerkoel CF et al 2002 Nature Genet 30:215.

Schindler Disease: An α -N-acetylgalactosaminidase deficiency (human chromosome 22), a lysosomal storage abnormality(?) leading to a neurological disease with onset before age one and progressive deterioration of motor and talking skills. ▶Kanzaki disease

Schinzel Syndrome (ulnar-mammary syndrome, 12q24.1): An autosomal dominant ulnar-mammary syndrome shows complex symptoms including malformation of the hand and shoulder, mammary glands, delayed puberty, obesity, etc. The T box gene TBX3 causes it. ▶ulna

Schinzel-Geidion Syndrome: An autosomal recessive malformation of the face and head, heart, growth retardation, telangiectasia, supernormal hair development. ▶hypertrichosis, ▶telangiectasis

Schistosomiasis: The state of disease of animals and humans seized by one or another species of the

parasitic flatworms *Schistosoma* (fluke). The parasites infect the blood vessels through contact with contaminated waters in warm climates of the world. In these species, the male carries the female in a ventral sac (gynecophoral canal) (see Fig. S16). Intermediate hosts are snails and molluscs. The *S. haematobium* is primarily a human parasite.

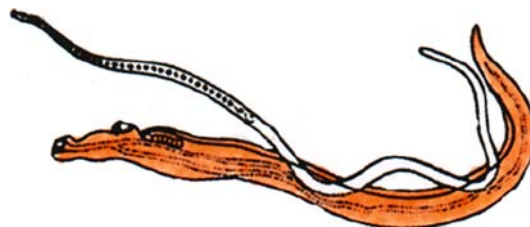


Figure S16. *Schistosoma haematobium* male carrying the female

The *S. japonicum* infects several animals as well. The symptoms of the disease may vary according to the various species and may include systemic irritations, cough, fever, eruptions, tenderness of the liver, diarrhea, and bladder carcinoma, etc. Without medication, the infected intestines, liver, kidneys, brain, etc., may be seriously damaged. The therapeutic antimony derivatives are highly toxic to humans. The parasite is present in millions of people of the tropics including the ancient Egyptian mummies. A codominant locus in human chromosome 5q31-q33 provides some protection against *Schistosoma mansoni*. The interferon- γ receptor (IFN- γ R1) locus (6q22-q23) also controls *S. mansoni* infection. Vaccination with attenuated larvae is feasible. ▶IFN; <http://www.tigr.org/tdb/tgi/>; Verjovski-Almeida S et al 2003 Nature Genet 35:148; Hu W et al 2003 Nature Genet 35:139.

Schizencephaly (10q26.1): A very rare brain disorder. The hemisphere is partly missing and cerebrospinal fluid fill the void. Type one is mild but type II is severe involving mental retardation, seizure, lack of speech and blindness. EMX2 linkage and EMX2 independent case are known (Tietjen I et al 2005 Am J Med Genet 135:166).

Schizocarp: A fruit where the carpels split apart in order to free the seeds.

Schizophrenia (dementia praecox): A behavioral disorder. The afflicted individuals cannot distinguish well reality from dreams and imagination. Hallucinations and paranoid behavior, delusions, inappropriate emotional responses, lack of logical thought and concentration are common symptoms. The precise mechanism of inheritance is unknown yet in about 13% of the children of afflicted parents it reoccurs, and ~45% of

the identical twins are concordant in this neurological disease but only ~15% of dizygotic twins.

The general incidence in the population varies from 1 to 4%. Both autosomal, pseudoautosomal single and multiple recessive and dominant loci were implicated. There were some indications that schizophrenia genes are in chromosomes 1q32.2 (?), 4q34.3, 5q33.2, 6q21.31, 6q25.2, 6pter-p22, 7p15.2, 7q11, 8p21-p22, 9q21, 10p, 10q22.3, 12q24, 13q34, 14q13, 15q11.2, 17p11-q25.1, 20, 21q21.2, 22q12.1-q11.23 (proline dehydrogenase), 22q21, 4q31 and in the long and short arms of chromosome 5. The 22q11 site encodes catechol-*O*-methyltransferase (COMT) and its deletion involves velocardiofacial syndrome and high incidence (20–30%) of psychiatric diseases, including schizophrenia. COMT controls the metabolism of catecholamine neurotransmitters (Shifman S et al 2002 Am J Hum Genet 71:1296). Some evidence indicates chromosomal sites 13q34 and 8p21-p22 as the most important for the determination of susceptibility. A schizophrenia locus was assigned to human chromosome 1q21-q22 with a lod score of 6.5 (Brzustowicz LM et al 2000 Science 288:678). This gene encodes the selenium-binding protein (SELENBP1) of unknown function and its upregulation is the most consistent biomarker of the disease (Glatt SJ et al 2005 Proc Natl Acad Sci USA 102:15533). DISC1 (disrupted in schizophrenia) is a major factor in developing this affective disorder. DISC1 is disrupted either by balanced translocation t(1;11)(q42;q14), or t(1;16)(p31.2;q21). The 1p31.2 breakpoint disrupts the B1 isoform of phosphodiesterase 4B gene (PDE4B). The N-terminal domain (amino acids 219-283) of DISC1 binds PDE4B. PDE4B apparently inactivates adenosine 3',5' cyclic monophosphate (cAMP), which has important function in learning, memory and mood. DISC1 interacts with the UCR2 domain of PDE4B and a raise in cAMP disrupts the association of PDE4B and DISC1; concomitantly this increases PDE4B activity (Millar JK et al 2005 Science 310:1187). *Disc1* missense mutations in mice give rise to phenotypes related to depression and schizophrenia, thus supporting the role of *DISC1* in major mental illness and can serve as an animal model for the disease (Clapcote SJ et al 2007 Neuron 54:387).

The various manifestations of schizophrenia have strong environmental components. Maternal malnutrition during the first trimester, maternal influenza during the second trimester, perinatal complications, intrauterine fetal hypoxia, or maternal pre-eclampsia may substantially aggravate the risk (Tsuang T 2000 Biol Psychiatry 47:210). Maternal-fetal incompatibility due to the presence of the Rh D protein in the pregnancy increases the chance for the psychiatric condition by a factor of ~2.6 (Palmer CGS et al 2002 Am J Hum

Genet 71:1312). Retroviral sequences have been detected in the cerebrospinal fluid in ~28% of the patients with recent onset and in ~5% of patients with chronic affliction (Karlsson H et al 2001 Proc Natl Acad Sci USA 98:4634). *Oligodendrocyte lineage transcription factor 2* (OLG2) abnormality increases susceptibility to schizophrenia by itself and by affecting other genes namely CNP, NRG1 and ERBB4 (Georgieva L et al 2006 Proc Natl Acad Sci USA 103:12469).

MAO (monoamine oxidase) level is reduced in the afflicted individuals. MAO enzyme removes amino groups from neurotransmitters. The overproduction of dopamine (3,4-dihydroxyphenyl-ethylamine), a precursor of neurotransmitters may be suspected in causing it. Glutamate decarboxylase 67 (GAD67), a marker for this system has been found by many studies to show decreased expression in schizophrenia and bipolar disorders. In the latter, suppression of transcription factors involved in cell differentiation may contribute to GABA dysfunction (Benes FM et al 2007 Proc Natl Acad Sci USA 104:10164). Chlorpromazine (a peripheral vasodilator, antiemetic drug) and reserpine (alkaloid) may alleviate the psychological symptoms by inhibiting dopamine receptors. According to the glutamate-dysfunction hypothesis the disease is caused by an imbalance between dopamine and glutamate or the glutamate receptor NMDA. In schizophrenia and other affective disorders frequently an expansion of trinucleotide repeats is detectable. Schizophrenia, other mental illnesses and drug addiction predispose to violent crime 2–6 times in excess of normal individuals (Friedman RA 2006 N Engl J Med 355:2064).
 ►paranoia, ►psychoses, ►affective disorders, ►neurological disorders, ►pseudoautosomal, ►concordant, ►twinning, ►trinucleotide repeats, ►obsessive-compulsive disorder, ►cataplexy periodic, ►eclampsia, ►Rh blood factor, ►hypoxia, ►MAO, ►NMDA; Baron M 2001 Am J Hum Genet 68:299; Gurling HMD et al 2001 Am J Hum Genet 68: 661; neuregulin and susceptibility: Stefansson H et al 2002 Am J Hum Genet 71:877; Chumakov I et al 2002 Proc Natl Acad Sci USA 99:13675; Levinson DF et al 2003 Am J Hum Genet 73:17; Lewis CM et al 2003 Am J Hum Genet 73:34; review: O'Donovan MC et al 2003 Hum Mol Genet 12:R125; research forum: <http://www.schizophreniaforum.org>.

Schizosaccharomyces pombe (fission yeast): The 3 chromosomes are of 5.7, 4.7 and 3.5 Mb size, respectively (see Fig. S17). It has the lowest number of genes among eukaryotes, 4944. The cells are 7 × 3 µm. This eukaryote, an ascomycete, has both asexual (by fission) and sexual life cycles (each meiosis producing 8 ascospores). Under good growing conditions it reproduces by mitotic divisions.

At starvation (for any factors of growth) the plus (P) and minus (M) type cells fuse and meiosis follows. The mitotic cell cycle (2.5 h) has the typical G₁, S, G₂ and M phases. The G₂ phase takes 70% of the total time whereas the other phases equally share the rest. Under severe nutritional limitations instead of sexual development, the cells are blocked in either of the G phases and this dormant state is called “GO”.



Figure S17. *S. pombe*

The mating type is determined by which of the *P* or *M* alleles is switched (transposed) from their silent position to the *mat1* locus where they are expressed. Actually both *P* and *M* genes have two alleles with different number of amino acids in their polypeptide products: *Pc* (118), *Pi* (159) and *Mc* (181) and *Mi* (42). The *c* alleles (required for meiosis and conjugation) are transcribed rightward from the centromere when nitrogen is available, and the *i* alleles (required only for meiosis) are transcribed in the opposite direction in N starvation. The product of the *Pi* allele has a protein-binding domain, whereas that of *Mc* shows some homology to the *Drosophila Tdf* (testis-determining factor) and the mouse *Tdy*. Homothallic strains can switch between mating types but the heterothallic ones are either *P* or *M*. The *MAT* site is comparable to the disk drive of a computer (or the slot of a tape player) where either the *P* or the *M* disk (or tape cassette) is plugged in and that determines whether the mating type in the heterothallic strain will be *P* or *M*. The *P* (1113 bp) and *M* (1127 bp) sites are actually the storage sites for the *P* and *M* mating type information, respectively. The recombination-promoting complex contains proteins Swi2 and Swi5 that are located near the silent mating type region and exercise long-range effects (Jia S et al 2004 Cell 119:469).

The mating type region in the right arm of chromosome II can be represented as shown in Figure S18.

The *DSB* (double-strand break) near the *MAT* site—in about 25% of the cells—is probably required so

that the chromosome would permit the insertion of one or the other cassette. This breakage is probably transient and quickly restored so that the continuity of the chromosome would not be compromised. According to new data the break at the *mat1* site is actually an artifact arising during purification of alkali-labile DNA due to a genetic imprint occurring while the lagging strand is synthesized. The imprints are one or two RNA nucleotides in the DNA (Vengrova S, Dalgaard JZ 2004 Genes Dev 18:794). This imprint may then reverse the *mat1* locus or introduce an origin of replication. The ~15 kb *L* and *K* sequences are spacers where meiotic recombination is not observed. The H₁ (59 bp) and H₂ (135 bp) homology boxes are flanking the disk drive (*MAT*) and both floppy disks while the H₃ (57 bp) only occurs at left of the *P* and *M* sequences. It has been supposed that the reason why the *P* and *M* elements are silent at the storage sites is because of the H₃ presence there but not at the *MAT* site where they are expressed. The switching (transposition) is controlled by *SAS1* and *SAS2* (switch-activating sites) right of *DSB* (within 200 kb). In addition, at least 11 other transacting (*swi*) loci regulate switching (transposition). Mating type determination in the budding yeast (*Saccharomyces cerevisiae*) is also controlled by transposition, albeit in a different way, and the homology of the DNA sequences in the elements is low. Fission yeast has contributed to learning many aspects of the cell cycle control. Its genome sequence (Wood V et al 2002 Nature [Lond] 415:871) revealed 4824 protein-coding genes, so far the smallest number in eukaryotes. Its promoter sequences are longer than those in budding yeast indicating extended control of functions. About 43% of the genes contain introns. About 50 genes seem homologous to some extent to human genes controlling disease and half of these are cancer-related. ▶*Saccharomyces cerevisiae*, ▶mating type determination, ▶SWI, ▶cell cycle, ▶imprinting; Vengrova S et al 2002 Int J Biochem Cell Biol 34:1031; http://www.sanger.ac.uk/Projects/S_pombe/; <http://pingu.salk.edu/~forsburg/pombeweb.html>.

Schneckenbecken Chondrodysplasia: Autosomal recessive, lethal defect of the cartilage. It bears similarity to thanatophoric dysplasia.

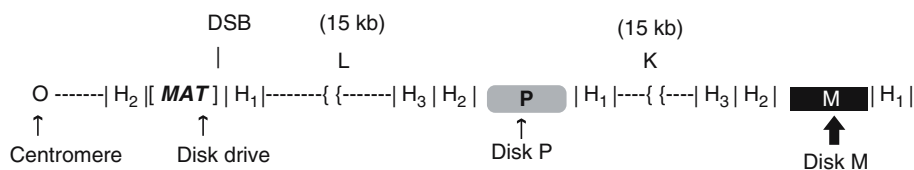


Figure S18. Mating type controls in *Schizosaccharomyces*

Schnipsel Database: Facilitates the identification of protein relationships by using Schnipsels (fragments) using SMART. ►[SMART](#)

Schwachman-Diamond Syndrome (human chromosome 7q11): Involves recessive pancreatic lipomatosis, bone marrow dysfunction and skeletal anomalies. (See Goobie S et al 2001 *Am J Hum Genet* 68:1048; Boocock GRB et al 2003 *Nature Genet* 33:97).

Schwann Cell: A glial cell (forms myelin sheath for the peripheral nerves). Its differentiation requires the Oct-6 POU factor, Ca^{2+} /calmodulin kinase, MAPK, cAMP response element-binding protein, expression of *c-fos* and *Krox24* genes. ATP arrests the differentiation of the Schwann cells before myelination. ►[myelin](#), ►[Oct-1](#), ►[POU](#), ►[calmodulin](#), ►[MAPK](#), ►[cAMP](#), ►[fos](#), ►[Krox-24](#)

Schwannoma: ►[neurofibromatosis](#)

Schwartz-Jampel Syndrome (chondrodystrophic myotonia, 1p34-p36.1): A rare recessive failure to relax muscles, reduced height, skeletal dysplasia (abnormal development). The affection is due to an altered proteoglycan (perlecan) of the basement membranes. ►[basement membrane](#); Arikawa-Hirasawa E et al 2002 *Am J Hum Genet* 70:1368.

Scianna Blood Group (Sc): Represented by antigenic groups Sc-1 and Sc-2, located in human chromosome 1. ►[blood groups](#)

Sciara: Dipteran flies with polytenic, giant chromosomes in their salivary glands. The basic chromosome number in *Sciara coprophylla* is 3 autosomes and 1 X chromosome but there are also the heteropycnotic so called *limited chromosome(s)*, which are present only in the germ-line. They are eliminated from the nuclei during the early cleavage divisions. The egg pronucleus contains three autosomes, an X chromosome and one or more limited chromosomes. The sperm contributes three autosomes, two X chromosomes and some limited chromosomes that are all of maternal origin. The first division of the spermatocyte is monocentric and separates the maternal chromosome set from the paternal one. The maternal chromosomes move to a single pole whereas the paternal set is positioned away from the pole and are never transmitted to the progeny. The single secondary spermatocyte displays an unusual unequal type division. The X-chromosome divides longitudinally and both copies are included into the same cell, and only this cell survives. From the cleavage nuclei first the limited chromosomes are eliminated and subsequently, from the cells that become male one of the X-chromosomes is also evicted thus the males become XO and the females are XX. ►[Rhynchosciara](#), ►[polytenic chromosomes](#), ►[salivary gland](#)

►[chromosomes](#), ►[sex determination](#), ►[chromosomal sex determination](#)

SCID (severe combined immunodeficiency): A heterogeneous group's genetically determined diseases. It involves defective V(J)D recombination of immunoglobulin genes. Several frameshifts, point mutations or deletions in the IL-2R γ (γc) chain (human chromosome Xq13) were found to be associated with SCID-X1. Actually, this part of the γ -chain is shared by the receptors of IL-4, IL-7, IL-9 and IL-15. Because of the deficiency, the T cells and the natural killer cells also become abnormal. The anomaly may involve also the Jak/STAT and other signaling pathways. Jak3 defects cause SCID symptoms. Introduction of genetically engineered macrophages expressing IFN- γ into the lung of mice provided marked protection against infection. IFN- γ upregulates the expression of major histocompatibility class I and class II molecules that lead to the activation of killer lymphocytes. Apparently after successful gene therapy, using IL2RG interleukin-2 receptor component in genetically engineered vector, caused lymphoma in several cases. Ora1 protein (encoded at 12q24) controls CRAC channel function, i.e., Ca^{2+} -release-activated Ca^{2+} influx. Sustained calcium supply is essential for the adaptive immune response. Some SCID patients have defect in CRAC and consequently loss of immune protection (Feske S et al 2006 *Nature [Lond]* 441:179). In a mouse model with ablated *Arf* tumor suppressor and IL-2R γ high frequency of insertional mutations occurred near or within several protooncogenes; thus this strain could be used as a model for testing potential risks of human gene therapy for XSCID constructs (Shou Y et al 2006 *Proc Natl Acad Sci USA* 103:11730). ►[adenosine deaminase deficiency](#), ►[severe combined immunodeficiency](#), ►[gene therapy](#), ►[signal transduction](#), ►[immunoglobulins](#), ►[RAG](#), ►[DNA-PK](#), ►[T cell](#), ►[killer cell](#), ►[MHC](#), ►[Jak/STAT](#), ►[IL-2](#), ►[IL-4](#), ►[IL-7](#), ►[IL-9](#), ►[IL-15](#), ►[gene therapy](#), ►[calcium signaling](#); Wu M et al 2001 *Proc Natl Acad Sci USA* 98:14589; French Gene Therapy Group 2003 *J Gene Med* 5:82.

Science: A systematic study of natural phenomena with the explicit purpose to prove or negate a working hypothesis or hypotheses by experimental means. According to K.R. Popper (1962 *Conjectures and Refutations*, Basic Books, New York, p 218), for science the “criterion of potential satisfactoriness is thus testability, or improbability: only a highly testable or improbable theory is worth testing and is actually (and not merely potentially) satisfactory if it withstands severe tests—especially those tests to which we could point as crucial for the theory before they were ever undertaken. I refuse to accept the view

that there are statements in science which we have, resignedly, accept as true merely because it does not seem possible...to test them". Science seeks to store, classify and evaluate certainties. Research is exploring uncertainties to provide facts for science. Applied science seeks to find economic use of the principles discovered by basic or pure science. Gathering information is one of the tools of science. The information becomes science when it can be integrated into a proven theoretical framework. The framework may need modification as information accrues. Science should never be subjected to ideology, politics and unproved or improvable ideas. Such influences are disastrous for science as the famous Galileo trial had shown in 1663 when the great scientist was forced to recant his valid thesis that the Earth is not the center of the Universe: "I abjure, curse, and detest the aforesaid errors and heresies, and generally every other error". Using big words and overcomplicated sentences are against the aim of sciences, which calls for lucidity. Coining new terms unless they facilitate communication must be avoided. It is important to explore the exact contents and meanings of terms before application in communication to be sure they are not preempted. ►experiment, ►genetics, ►misconduct scientific, ►lysenkoism, ►creationism; theory of scientific discovery: Koshland DE Jr 2007 Science 317:761.

Scientific Freedom: The right to pursue researches and publish the outcome. This right is limited, however, by the need to regulate activities that are directed against the well-being of humans, human economic activities and specifically the freedom to create biological and chemical terror weapons and publishing papers that may jeopardize public safety. Serious concerns arise about how to implement the regulation without fettering scientific inquiry and safeguarding society. ►bioterrorism, ►informed consent, ►bioethics; Fraser CM, Dando MR 2001 Nature Genet 29:253.

Scientific Misconduct: According to the NSF (National Science Foundation, USA) "fabrication, falsification, plagiarism, or other serious deviation from accepted practices." ►publication ethics, ►ethics, ►misconduct scientific; Federal Register 18, March, 2002.

Scintigraphy: The photographic location of radionuclides within the body after introduction of radioactive tracers. ►radioactive label, ►radioactive tracer

Scintillation Counters: Can be liquid scintillation counters or crystal scintillation-counters for solids. The counter is an electronic appliance where the sample is placed in a solution of organic compounds (cocktail). The radiation coming from the isotopes (even from the weak β -emitters) causes flashes in the fluorescing cocktail that are directed to a photoelectric

cell. The cell then releases electrons that are amplified and registered (counted). Each flash corresponds to a disintegration of an atom of the isotope so the equipment displays (or prints out) the disintegrations per minute (dpm) or counts per minute (cpm), generally with background radiation subtracted. This information provides measures of the quantity of the label (or labeled compound). In the crystal scintillation counter, the radiation (usually energetic γ -rays, X-rays or β -rays) emitted by the isotope hits a crystal of sodium iodide containing traces of thallium iodide, and again the disintegrations are registered similarly to the liquid scintillation counter. ►radioisotopic tracers, ►radiolabeling, ►isotopes, ►dpm, ►radiation hazard assessment

Scission: Cuts in both strands of a DNA molecule at the same place. ►nick

Scissors Grip: ►Max

Scissors, Molecular: ►Cre/loxP, ►excision vector, ►targeting genes

Scj1: A 40 kDa budding yeast chaperone in the endoplasmic reticulum, inducible by tunicamycin antibiotic but not by heat. ►chaperones; Nishikawa S, Endo T 1997 J Biol Chem 272:12889.

SDK: A protein with phosphotyrosine binding domain but different from the SH2 domain of SRC. ►SRC, ►SH2, ►PTB; Kojima T et al 2001 Biochem Biophys Res Commun 284:1039.

SCLC: ►small cell lung carcinoma

Sclerenchyma: Plant tissues with tough, hard cell walls.

Scleroderma: A probably autosomal dominant disease involving scaly hardening of the skin and increased frequency of chromosome breakage. ►skin diseases; Whitfield ML et al 2003 Proc Natl Acad Sci USA 100:12319.

Scleroids: Cells with unusually hardened walls.

Sclerosis: The hardening caused by inflammation or hyperplasia of the connective tissue.

Sclerosteosis (SOST/BEER, 17q12-q21): A rare recessive dysplasia of the bones displaying progressive sometimes-massive overgrowth distinct from osteopetrosis. It may distort the face and may be accompanied by syndactyly. Its highly conserved glycoprotein product, sclerostin appear to be an antagonist of the bone morphogenetic protein and other members of the TGF β family. It contains cystine-rich "knots." ►BMP, ►syndactyly, ►TGF, ►van Buchem disease; Brunkow ME 2001 Am J Hum Genet 68:577; Balemans W et al 2001 Hum Mol Genet 10:537.

Sclerotia: ►hypha, ►ergot

Sclerotome: Mesenchymal embryonic precursor of the vertebral column and ribs.

SCMRE: A cis-acting element in the c-fos protooncogene and it is responsible for induction by some mitogens. ►FOS, ►protooncogene, ►cis, ►mitogen

SCN: Sodium ion channel.

scnDNA: A single-copy nuclear DNA.

Scoliosis: In this condition, the spine is not straight but laterally curved (see Fig. S19); it may be due to polygenic causes or it can be part of skeletal syndromes. Its incidence is about 1–6% of the adult human populations. Kyphoscoliosis is a similar condition in mice. ►horizontal gaze palsy, ►lordosis, ►kyphosis; Blanco G et al 2001 Hum Mol Genet 10:9.



Figure S19. Scoliotic pig

S-Cone Syndrome (ESCS, encoded by PNR/NR2E3 gene in human chromosome15q23): A night blindness and blue light hypersensitivity because of defect in the retinal cones in the eye. ►eye diseases

SCOP: The structural classification of proteins. (See Murzin AG et al 1995 J Mol Biol 247:536; Przytycka T et al 1999 Nature Struct Biol 6:672; <http://scop.mrc-lmb.cam.ac.uk/scop>).

Scopes Trial: In 1925, John Scopes was convicted for breaking Tennessee state law (repealed in 1967) by teaching evolution in a public school. The verdict was later overturned on a technicality. ►intelligent design, ►creationism

Scopolamine: ►Datura, ►alkaloids

Score Test (Wald-Wolfowitz test): A non-parametric test to compare unmatched samples and all information is paired with a numerical score. It is assumed that the scores represent a continuous distribution. The null hypothesis is that the runs represent identical populations. (See Hays WL, Winkler RL 1971 Statistics: Probability, Inference and Decision. Holt. Rinehart and Winston, New York).

Scotomorphogenesis: The differentiation of plants in the absence of light, e.g., etiolated growth. ►brassinosteroids

SCP₂: A sterol carrier protein 2; probably the same as nsL-TP. ►sterol

Scrapie: ►encephalopathies, ►Creutzfeldt-Jakob disease, ►prion, ►kuru

Scratchy: An in vitro method of combinatorial protein engineering independent of sequence identity. It involves incremental truncation of protein coding genes and then reshuffling and DNA fusion. The purpose is to improve protein function. ►iterative truncation; Lutz S et al 2001 Proc Natl Acad Sci USA 98:11248.

Screening: Selective classification of cell cultures for mutation or for special genes, conveying auxotrophy, antibiotic or other resistance, selecting antibodies by cognate antigens, plant populations for disease- or chemical-resistance, animal progenies for blood groups, etc. Narrow sense screening may not involve selective isolation but special criteria are used to distinguish in the growing population those individuals who have a special trait. Genetic screening in animals is feasible by the use of RNAi. The RNA is introduced into pronuclear cells by injection and it is transmitted for several generations. The RNAi can knock down important genes and thus their function is revealed (Peng S et al 2006 Proc Natl Acad Sci USA 103:2252). ►genetic screening, ►genetic testing, ►knock-down, ►RNAi; Forsburg SL 2001 Nature Rev Genet 2:659; Jorgensen EM, Mango SE 2002 Nature Rev Genet 3:356.

Screwworm: ►Cochliomya hominivorax, ►genetic sterilization, ►myiasis

Scribble: ►PDZ

Scripton (transcripton): A unit of lambda phage transcription. ►lambda phage

scrRNA: Small cytoplasmic RNAs. ►snRNA

scrNAP: Small cytoplasmic ribonucleoprotein.

Scrotum: The pouch containing the testes and accessory sex organs of mammals.

Scrunching (according to the Oxford Dictionary squeezing into a compact shape): At abortive or productive initiation of transcription RNA polymerase (RNAP) “scrunches” the DNA at a stationary stage to unwind DNA and pulls it into itself. The process requires RNA synthesis. Promoter escape also involves scrunching. (See Revyakin A et al 2006 Science 314:1139; Kapanidis AN et al 2006 Science 314:1144).

Scutellum: The single cotyledon of the grass embryo (see Fig. S20).



Figure S20. S = scutellum, E = embryo

SD: ► *Segregation distorter*, ► *standard deviation*

Sdc25: A guanine-nucleotide release factor, similar to Cdc25. ► *RAS*, ► *Cdc25*, ► *EF-Tu*

SDF-1 (stromal cell-derived factor): A chemokine and natural ligand of fusin. With its receptor CXCR-4 it mobilizes and promotes the proliferation of CD34⁺ cells. ► *CD34*, ► *fusin* [*LESTR*], ► *chemokines*, ► *CXCR*; Weber KS et al 2001 *Mol Biol Cell* 12:3074.

S-DNA: A mechanically stretched DNA that might have been extended 1.7 times of its normal contour length. ► *slipped-structure DNA*, ► *trinucleotide repeats*; Cluzel P et al 1996 *Science* 271:792.

SDP: ► *short-day plants*

SDR (short dispersed repeats): Organellar DNA sequences of 50–1000 bp that may occur in direct or inverted forms and may represent more than 20% of the chloroplast genomes of *Chlamydomonas reinhardtii* alga and various land plants. Similar or shorter redundant sequences occur in the mitochondria of plants, animals and fungi. In *Saccharomyces cerevisiae* eight 200–300 bp *ori* and *rep* sequences and 200 G + C sequences of 20–50 bp may be clustered into several mtDNA gene families. Similar mobile G + C elements may occur in other fungi. SDRs have been exploited for forensic population studies. ► *chloroplasts*, ► *mtDNA*, ► *mobile genetic elements*, ► *organelle sequence transfers*; Seidl C et al 1999 *Int J Legal Med* 112(6):355.

SDR: ► *strain distribution pattern*

SDS (sodium dodecyl sulfate): A detergent, used for electrophoretic separation of protein and lipids.

Sds: A leucine-rich protein and regulates protein phosphatase 1C during mitosis of yeast. ► *protein phosphatases*; Peggie MW et al 2002 *J Cell Sci* 115:195.

SDS-PAGE: ► *SDS-polyacrylamide gel*

SDS-Polyacrylamide Gels: Electrophoretic gel containing sodium dodecyl sulfate (SDS, also called sodium lauryl sulfate [SLS], detergents) and polyacrylamide. This medium dissociates proteins into subunits and

reduces aggregation. Generally, the proteins are denatured with heat and a reducing agent before loading on the gel. The polypeptides become negatively charged by binding to SDS and are separated in the gel according to size (rather than by charge). On the basis of the mobility, the molecular weight of the subunits can be estimated with the aid of appropriate molecular size markers (ladder) but caution is required because glycosylated proteins may not reflect the molecular mass of the protein. The concentration of the polyacrylamide determines the size of the polypeptides that can be separated. Polyacrylamides (bisacrylamide: acrylamide, 1:29) separates [kDa proteins] as follows: 15% [12–43], 10% [16–68], 7.5% [36–94], 5% [57–212]. ► *gel electrophoresis*, ► *electrophoresis*

SDT Test: A non-parametric sign test used in pedigrees to compare the average number of candidate alleles between affected and non-affected siblings. ► *TDT*, ► *sib TDT*; Rieger RH et al 2001 *Genet Epidemiol* 20(2):175; <http://www.sdtcorp.com/companyprofile.html>.

SE: ► *standard error*

Sea Lion (*Eumetopias jubatus*, *Zalophus californianus*): Other species occur also in Australia and New Zealand and other parts of the coastal oceans of the world. The chromosome numbers are 2n = 32 to 36 in the different species. Some of the species form hybrids (see Fig. S21).



Figure S21. Sea lion

Sea Oncogene: An avian erythroblastosis virus oncogene. The human homolog is at human chromosome 11q13 in very close vicinity to INT2 and BCL1. ► *oncogenes*

Sea Urchins: *Strongylocentrotus purpuratus* (see Fig. S22) and *Toxopneustes lividus*, both 2n = 36, and other echinodermata have been favorable objects of cell cycle studies, fertilization, embryogenesis, development and evolution. They have very long life (>100 years) and produce annually millions of gametes. Their large-size eggs can be easily collected

and handled in the laboratory. Their non-adaptive immune system includes a highly complex system of receptors. The 814 megabase includes ~23,300 genes. The average transcript length is 8.9 kb and the average gene length is 7.7 kb. The average exon were about 100–115 nucleotides whereas the introns ~750 nucleotides. Most of the genes are in regions of 35 to 39% GC regions. Cytogenetic maps are not available. This outbreeding species is highly heterozygous and individuals display ~5% single nucleotide polymorphism (SNP), about ten times higher than that in humans. The sequenced *S. purpuratus* genome has orthologs of vertebrate genes for vision, hearing, chemosensation and several human diseases. genome: 2006 Science 314:941; immune system: Rast JP et al 2006 Science 314:952; transcriptome: Samanta MP et al 2006 Science 314:960; for genome: http://www.ncbi.nlm.nih.gov/genome/guide/sea_urchin/; for embryology: <http://www.stanford.edu/group/Urchin/>; proteins: <http://www.expasy.org/cgi-bin/get-entries?OC=Strongylocentrotus>.

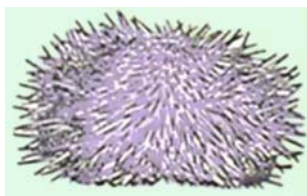


Figure S22. *Strongylocentrotus*

Seal: *Callorhinus ursinus*, 2n = 36; *Zalophus californianus*, 2n = 36; *Cystophora cristata*, 2n = 34; *Erignatus barbatus* 2n = 34; *Helichoereus grypus* 2n = 32.

Search Engine: Uses the Internet as a source for finding keywords and documents. Frequently used search engines are Google, Yahoo, AltaVista and others.

Sebastian Syndrome: ► [May-Hegglin anomaly](#)

Sec6/8: A multiprotein complex that mediates cell-to-cell contacts and transport vesicle delivery. ► [Golgi apparatus](#); Matern HT et al 2001 Proc Natl Acad Sci USA 98:9648.

Sec63 (NPL1/PTL1): A 663-amino acid yeast transmembrane chaperone protein with partial homology at the near-N-end of DnaJ. It interacts with Kar2, Ces61, Sec71, and Sec72 proteins. ► [chaperones](#), ► [DnaK](#), ► [Kar2](#), ► [Sec61 complex](#), ► [Mtl1](#); Young BP et al 2001 EMBO J 20:262.

Sec61 Complex (Sec Y complex): Built of the three Sec subunits (α , β , γ) and other proteins form a protein-conducting channel across the endoplasmic reticulum (ER) membrane. It associates with the large subunit of the ribosome of prokaryotes and eukaryotes and transports some of the nascent proteins into the lumen of the ER. A small molecule, cotransin (see Fig. S23), inhibits protein translocation into ER in a discriminatory manner of signal sequence (Garrison JL et al 2005 Nature [Lond] 436:285). ► [Sec proteins](#), ► [protein-conducting channel](#), ► [ribosomes](#), ► [endoplasmic reticulum](#), ► [protein synthesis](#), ► [Sec63](#), ► [endoplasmic reticulum-associated degradation](#), ► [unfolded protein response](#), ► [CAM](#), ► [chloroplast import](#); Mori H, Ito K 2001 Proc Natl Acad Sci USA 98:5128; Beckmann R et al 2001 Cell 107:361; van den Berg B et al 2004 Nature [Lond] 427:36.

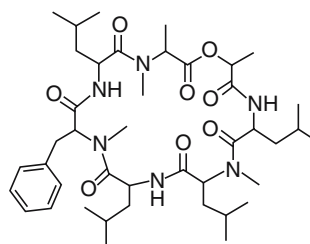


Figure S23. Cotransin

SecA (α) Protein: (seven-component complex): A peripheral membrane domain of the translocase enzyme and it is the primary receptor for the SecB/pre-protein complex by recognizing the leader domain of the pre-protein. Hydrolyzes ATP, GTP, promotes cycles of translocations and pre-protein release. ► [membranes](#), ► [translocase](#), ► [Mss](#), ► [Ypt](#), ► [Rab](#), ► [translocase](#), ► [translocon](#), ► [protein targeting](#), ► [SRP](#), ► [ARF](#), ► [protein synthesis](#), ► [endoplasmic reticulum](#), ► [exocytosis](#); Hsu SC et al 1999 Trends Cell Biol 9:150; Jilaveanu LB 2005 Proc Natl Acad Sci USA 102:7511.

SecB (β) Protein: A 17-subunit chaperone involved in translocation of pre-proteins by complexing and keeping them in the right conformation and binding to membrane surface of the endoplasmic reticulum. Recognizes both the leader and mature protein domains. ► [chaperones](#), ► [membranes](#), ► [endoplasmic reticulum](#), ► [SRP](#), ► [translocon](#), ► [translocase](#), ► [protein targeting](#); Driessen AJ 2001 Trends Microbiol 9:193.

Secis: The selenocysteine regulatory element in coding and non-coding regions of selenocystein genes in prokaryotes and eukaryotes (Mix H et al 2007 Nucleic Acids Res 35:414).

Seckel's Dwarfism (bird-headed dwarfism, 3q22.1-q24): A microcephalic autosomal recessive condition with reduced intelligence. The basic defect is in a phosphatidylinositol 3-kinase-like kinase. ▶[dwarfism](#), ▶[microcephaly](#), ▶[phosphatidylinositol](#); O'Driscoll M et al 2003 *Nature Genet* 33:497.

Second Cycle Mutation: Caused by the excision or movement of a transposable element and leave behind a footprint which still causes some type of alteration in the expression of the gene. This type of alterations may be connected with the defective nuclear localization of a transcription factor. ▶[transposon footprint](#), ▶[transposable elements](#), ▶[nuclear localization sequences](#)

Second Division Segregation: ▶[tetrad analysis](#), ▶[post-reduction](#)

Second-Harmonic Imaging Microscopy: Visualizes biomolecular arrays in cells, tissues and organisms. ▶[microscopy](#); Campagnola PJ, Loew LM 2003 *Nature Biotechnol* 21:1356.

Second-Male Sperm Preference: ▶[last-male sperm preference](#)

Second Messenger: Molecules with key roles in signal transduction pathways such as cyclic-AMP, cyclic-GMP, and others. Animal physiologists call hormones first messengers. In animal and plant cells Ca^{2+} is also considered to play the role of second messenger. Inositol triphosphate is also a second messenger. ▶[cAMP](#), ▶[cGMP](#), ▶[mRNA](#), ▶[PIK](#), ▶[PIP](#), ▶[signal transduction](#), ▶[G proteins](#)

Second Site Non-Complementation: ▶[non-allelic non-complementation](#)

Second Site Reversion: A suppressor mutation at a site different from that of the original lesion but is capable of restoring the normal reading of the mRNA. ▶[suppressor tRNA](#), ▶[suppressor gene](#), ▶[reversion](#), ▶[compensatory mutation](#)

Second Strand Synthesis: ▶[reverse transcriptase](#)

Secondary Constriction: ▶[nucleolar organizer](#), ▶[satellited chromosome](#), ▶[SAT](#)

Secondary Immune Response: An immune reaction conditioned by the memory cells when antigenic exposure occurs repeatedly. ▶[immunological memory](#)

Secondary Lymphoid Tissues: The lymph nodes and spleen (in contrast to primary lymphoid tissues, the bone marrow and thymus). ▶[immune system](#)

Secondary Metabolism: Produces molecules that are not basic essentials for the cells and their products occur only in specialized tissues, e.g., anthocyanin, hair pigments. Many of the secondary plant metabolites,

e.g., phytoalexins, phenolics, flavone, pterocarpan, chlorogenic acid, sesquiterpenes, diterpene, saponins, furanoacetylene, alkaloids, indole-derivatives, etc., are defense molecules against microbial pathogens. Jasmonate-mediated genetic reprogramming of the transcriptome may reveal some basic aspects of the complex processes (Goossens A et al 2003 *Proc Natl Acad Sci USA* 100:8595). (See Dixon RA 2001 *Nature [Lond]* 411:843).

Secondary Nondisjunction: ▶[nondisjunction](#)

Secondary Response Genes: Their transcription is preceded by protein synthesis; probably primary response genes are involved in their induction. They are stimulated by mitogens alone without cycloheximide. ▶[mitogens](#), ▶[primary response genes](#), ▶[signal transduction](#)

Secondary Sex Ratio: The proportion of males to females at birth. ▶[age of parents](#), ▶[sex ratio](#), ▶[primary sex ratio](#)

Secondary Sexual Character: Usually accompany the primary sexual characters but they are not integral part of the sexual mechanisms, e.g., facial hair in human males, red plumage of the male cardinal birds, increased size bosoms in females and higher pitch voice, etc. ▶[primary sexual characters](#), ▶[accessory sexual characters](#)

Secondary Structure: The steric relations of residues that are next to each other in a linear sequence within a polymer such as α -helix, a pleated β -sheet of amino acids. ▶[protein structure](#); http://cmgm.stanford.edu/WWW/www_predict.html.

Secondary Trisomic (isotrisomic): The third chromosome has two identical arms, originated by misdivision of the centromere or by the fusion of identical telochromosomes. ▶[trisomics](#), ▶[misdivision](#), ▶[telosome](#)

Secondary-Ion Mass Spectrometry: A focused ion beam removes neutral and ionized atoms and molecules from a solid surface. These secondary ions are then accelerated and separated according to mass-to-charge ratio in a mass spectrometer. ▶[mass spectrum](#)

Secretagogue: A compound or factor that stimulates secretion. ▶[ghrelin](#); Pombo M et al 2001 *Horm Res* 55 (Suppl. 1):11.

Secretases: α -secretase enzyme cleavage of APP (amyloid precursor protein) interferes with the production of α amyloids whereas cleavage by β - and γ -secretase contributes to the formation of amyloid plaques. γ -Secretase (transmembrane aspartyl protease) activity requires the presence of the protein nicastrin, which binds presenilin near the

active site, and there is an interaction among these and the fragment generated by β -secretase. The γ -secretase complex has four components: presenilin, nicastrin, aph-1 and pen-2 (Kimberly WT, Wolfe MS 2003 J Neurosci Res 74:353). The cytoplasmic tail of APP, released intracellularly by secretase γ , teams up with histone acetyl transferase and other proteins and may promote gene expression. Cleavage of APP by β -secretase at the N-end releases APPs β (~100 kDa, N-terminal fragment) and a membrane-bound 12 kDa C-end fragment (C99). Cleavage by α -secretase generates the N-end APPs α and a membrane-bound 10 kDa piece (C83). C99 and C83 can be further split by secretases and yield 4 kDa A β (Alzheimer plaque material) and the harmless 3 kDa p3 peptides, respectively. γ -Secretase generates the 40-residue and in smaller proportion, 42-residue A β fragments. The latter forms the tangled brain fibers and the 40-residues accumulate as brain plaques. β -Secretase cuts at Asp1, Val3 and Glu11 and most commonly, A β begins with Asp. Met \rightarrow Leu replacements favor the generation of amyloid plaques common in the early onset Alzheimer disease. Pin1 prolyl isomerase binds the phosphorylated Thr 668-Pro motif in APP and increases its polymerization by three orders of magnitude. Overexpression of Pin1 reduces A β secretion but knockout of Pin1 increases its secretion. Pin1 knockout increases amyloidogenic APP processing and selectively elevates the insoluble and toxic A β 42 (Pastorino L et al 2006 Nature [Lond] 440:528). The BACE transmembrane aspartic protease is a β -secretase. Secretase γ has a role also in Notch-controlled developmental processes. **▶Alzheimer disease, ▶ β -amyloid, ▶BACE, ▶TACE, ▶ADAM, ▶presenilins, ▶memapsin, ▶nicastrin, ▶rhomboid protease, ▶CD147, ▶Notch**; Kopan R, Goate A 2000 Genes Dev 14:2799; Cao X, Südhof TC 2001 Science 293:115; Esler WP, Wolfe MS 2001 Science 293:1449; Fortini ME 2002 Nature Rev Mol Cell Biol 3:673; Takasugi N et al 2003 Nature [Lond] 422:438.

Secretion Machine (injectisome): The bacterial pathogens of both animals and plants secrete about 20 different proteins mediating infection of the host. Of these, nine are conserved across phylogenetic boundaries and appear to have a universal mRNA targeting signal. **▶host-pathogen relation**; Lee VT, Schneewind O 1999 Immunol Rev 168:241; injectisome structure: Merlovits TC et al 2006 Nature [Lond] 441:637.

Secretion Systems: Type III (~20 proteins) is a contact-dependent mechanism of transfer of bacterial pathogenicity island genes and toxins to other organisms. Type III secretion system (T3SS) has a complex needle structure (Galán JE, Wolf-Watz H 2006 Nature [Lond] 444:567). Bacterial plasmids may encode the

pathogenicity island. Type IV/V: the autotransporters are the bacterial conjugation and the agrobacterial T-DNA transfer systems. Type II (12–14 proteins) is the general secretion system. The Type I system requires three proteins and it is encoded in pathogenicity islands or plasmids. **▶pathogenicity island, ▶T-DNA, ▶conjugation bacterial**; Galán JE, Collmer A 1999 Science 284:1322; Burns DL 1999 Curr Opin Microbiol 2:25; Cornelis GR, Van Gijsegem F 2000 Annu Rev Microbiol 54:735; Fadoulglou VE et al 2004 Proc Natl Acad Sci USA 101:70; secretion type III system assembly: Yip CK et al 2005 Nature [Lond] 435:702; secreted protein database: <http://spd.cbi.pku.edu.cn>.

Secretion Trap Vector: Inserts a reporter gene, which is expressed in a transmembrane region. The constructs may carry a region of the CD4 gene fused in-frame to the 5'-end of the reporter, e.g., *LacZ*, which can be then identified by Xgal at the membrane. **▶CD4, ▶Xgal**; Shirozu M et al 1996 Genomics 37(3):273.

Secretion Vector: Besides an expressed structural gene, it carries a secretion signal to direct the gene product to the appropriate site. (See Bolognani F et al 2001 Eur J Endocrinol 145:497).

Secretome: Type III secretion system of bacteria serve as effectors for causing disease. **▶secretion systems, ▶effector**; Guttman DS et al 2002 Science 2002 295:1722.

Secretor: Secretes the antigens of the ABH blood group into the saliva. Fucosyltransferase, FUT is the same gene locus as SEC/SE but there is a difference in tissue-specific expression. **▶ABH antigen, ▶fucosyltransferase**; D'Adamo PJ, Kelly GS 2001 Altern Med Rev 6(4):390.

Secretory Immunoglobulin A: An IgA dimer with a secretory component. **▶immunoglobulins**

Secretory Proteins: Mainly glycoproteins that are released by the cell after synthesis, such as hormones, antibodies and some enzymes. Secretory proteins (~1400) are located in the endoplasmic reticulum (~64%) and in the Golgi-derived COP transport vesicles (~14%); about 29% occur in both (Gilchrist A et al 2006 Cell 127:12165).

Secretory Vesicle (secretory granule): Releases stored molecules such as hormones within the cell. Chromogranin A appears to control the biogenesis of the granules. **▶Golgi apparatus, ▶endocytosis**; Kim T et al 2001 Cell 106:499.

Sectioning: A generally required procedure for the preparation of biological specimens for histological examination. The material may need embedding before they are cut either free hand or by microtomes. Some

microtomes cut tissues frozen by CO₂. The 1–20 µm thin sections are subsequently placed on microscope slides and subjected to a series of manipulations (paraffin wax removal, dehydration, staining) before examination. ▶microtome, ▶embedding

Sectorial-Spore Colonies: The colonies arise when the haploid spores carried heteroduplex DNA with different alleles in the heteroduplex region (see Fig. S24). ▶heteroduplex

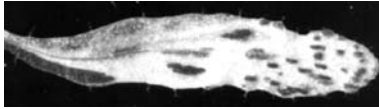


Figure S24. Sectorial plant leaf

Sectorial: Displays sectors, e.g., mitotic recombinant, sorting-out of organelles, somatic mutation, etc. ▶mosaic, ▶chimeric

Securins: They control the onset of the separation of sister chromatids during mitosis. The anaphase-promoting complex (APC) destroys securin before the sister chromatids can separate. Deletion of securin leads to chromosomal instability as it is common in cancer cells. ▶sister chromatid cohesion, ▶APC, ▶cohesin, ▶separin, ▶meiosis I, ▶CDC2, ▶spindle; Sjögren C, Nasmyth K 2001 Curr Biol 11:991; Jallepalli PV et al 2001 Cell 105:445; Zhou Y et al 2003 J Biol Chem 278:462.

SecY Protein: An integral membrane component of bacteria involved in chaperoning the assembly of membrane and some soluble proteins. ▶membrane; Veenendaal AK et al 2001 J Biol Chem 276:32559; Osborne AP et al 2007 Cell 129:97.

SecY/E Protein: The membrane embedded domain of translocase enzyme consisting of SecY and SecE polypeptides. Stabilizes and activates SecA and facilitates membrane binding. ▶membrane, ▶SecY

SED: Spondyloepiphyseal dysplasia, bone diseases.

Sedimentation Analysis: ▶satellite DNA

Sedimentation Coefficient: The rate by what a molecule sediments in a solvent. It is characterized by the Svedberg unit (S) that is a constant of 1×10^{-13} . S is derived from the equation $s = (dx/dt)/\omega^2 x$, where x = the distance from the axis of rotation in the centrifuge, ω is the angular velocity in seconds ($\omega = \theta/t$, where θ is the angle of rotation and t is time). At a constant temperature (20 °C) in a solvent s depends on the weight, shape and hydration of a molecule. The S value is used for the characterization of macromolecules, e.g., RNA such as 16S ($= 16 \times 10^{-13}$).

Seed: ▶microRNA

Seed Alignment: Uses only one of each pair of homologs represented by a CLUSTAL W-obtained phylogenetic tree linked by a branch length <0.2. ▶CLUSTAL W, ▶phylogenetic tree, ▶MOST

Seed Coat: ▶integument

Seed Development: ▶embryogenesis in plants, ▶endosperm; seed biology: <http://www.seedbiology.de/index.html>.

Seed in Genome Sequencing: ▶genome projects

Seed Germination: Requires the activation of >2000 genes. The process begins by activation of the root apical meristem, followed by activation of the cotyledons, the shoot apical meristem and secondary meristems. Six D-type and two A-type cyclins have important roles. ▶meristem, ▶root, ▶cyclins, ▶abscisic acid; Masubelele NH et al 2005 Proc Natl Acad Sci USA 100:15694.

Seed Size: In *Arabidopsis*, seed size is controlled by at least 3 genes acting in the same pathway regulated by a kinase (Luo M et al 2005 Proc Natl Acad Sci USA 102:17531).

Seed Storage: Generally viability (germination and survival) of seed can be maintained by storage below –20 °C and low moisture content (<7–8%) well beyond the conditions of normal ambient temperature and humidity. ▶freeze drying, ▶artificial seed; Buitink J et al 2000 Proc Natl Acad Sci USA 97:2385.

Seeding: To use a set of DNA fragments (in e.g., BACs) as the beginning points for chromosome walking. ▶BAC, ▶genome projects, ▶chromosome walking, ▶parking

Seedless Fruits: May be the result of different genetic mechanisms. Aneuploids, triploids, self-incompatibility or gametic sterility genes may be most commonly responsible for this condition. ▶seedless watermelon, ▶bananas, ▶pineapple, ▶navel orange, ▶stenospermocarp, ▶seedless grapes, ▶parthenocarp

Seedless Grapes: The result of a gene that causes early embryo abortion although fertilization occurs normally (stenospermocarp). ▶seedless fruits

Seedless Watermelons: Triploids (produced by crossing tetraploids with diploids). They are more convenient to eat since seeds do not have to be removed. Their flavor and sweetness may make them superior to conventional varieties. ▶seedless fruits, ▶watermelon

Segment Polarity of the Body Genes: Segment polarity of the body genes in *Drosophila* mutations are

involved in the alteration of the characteristic body pattern and are often accompanied by inverted repetition of the remaining structures. By cell-cell communication, they maintain the pattern imposed on them through subsequent developmental processes. ▶ [morphogenesis in *Drosophila*](#)

Segmental Aneuploid: Contains an extra chromosomal fragment(s) in addition to the normal chromosome complement; it is a partial hyperploid. ▶ [hyperploid](#), ▶ [aneuploid](#)

Segmental Interchange: ▶ [translocation chromosomal](#)

Segmentation Clock: An ensemble of numerous cellular oscillators located in the unsegmented pre-somitic mesoderm, controls segmentation as it travels anteriorly in the embryo (Horikawa K et al 2006 Nature [Lond] 441:719).

Segmentation Genes: Control the polarity of body segments in animals. ▶ [morphogenesis in *Drosophila*](#), ▶ [metamerism](#); Zákány J et al 2001 Cell 106:207; Dubrulle J et al 2001 Cell 106:219; Tautz D 2004 Dev Cell 7:301.

Segmentation of Microarray Spots: The separation of the not entirely circular signal spots from the background.

Segmented Genomes: For example, the DNA of T5 phage is in four linkage groups, the RNA genetic material of alfalfa mosaic virus is in four segments.

Segregation: The separation of the homologous chromosomes and chromatids at random to the opposite pole during meiosis and carrying in them the alleles to the gametes. Independent segregation of non-syntenic genes (or ones, which are more than 50 map units apart within a chromosome) is one of the basic Mendelian rules. In the haploid products of meiosis of diploids, the 1:1 segregation of the alleles may be identified. Sometimes “x-segregation” is distinguished when after mitotic crossing over at the four-strand stage, each of the daughter cells carries one recombinant and one parental strand, and this is most common. At “z-segregation” the distribution of the chromosomes into the daughter cells is biased inasmuch as one of them carries two parental and the other two recombinant strands. Mitotic nondisjunction has been called “y-segregation.” ▶ [Mendelian laws](#), ▶ [autopolyploid](#), ▶ [tetrad analysis](#), ▶ [segregation distorter](#), ▶ [preferential segregation](#), ▶ [epistasis](#), ▶ [meiosis](#), ▶ [mitotic crossing over](#), ▶ [nondisjunction](#), ▶ [chromosome segregation](#), ▶ [partitioning](#), ▶ [condensin](#), ▶ [cohesin](#), ▶ [separin](#); Ghosh SK et al 2006 Annu Rev Biochem 75:211.

Segregation Analysis: The analysis reveals the pattern of inheritance whether it is autosomal recessive,

autosomal dominant, X-linked recessive or dominant, multifactorial, penetrance, expressivity of a gene(s). This the first, sometimes laborious step, especially in human genetics where controlled matings are not available, before gene frequencies, genetic risk, recombination, etc. can be meaningfully estimated. (See mentioned terms at separate entries; <http://hasstedt.genetics.utah.edu/>).

Segregation, Asymmetric: The differentiation and morphogenesis require that the progeny cells would differ from the mother cell after cell division. This difference is brought about by the unequal distribution of cellular proteins. ▶ [morphogenesis in *Drosophila*](#)

Segregation Distorter: A dominant mutation (*Sd*, map position 2-54 in *Drosophila*). When it is present, the homologous chromosomes (and the genes within) are not recovered in an equal proportion after meiosis. The second chromosomes that carry it are called SD and may be involved in chromosomal rearrangement and other (lethal) mutations. At the base of the left arm they may have *E(SD)* [*enhancer of Sd*] or *Rsp* (*Responder of SD*, at the base of the right arm), and more distally *St(SD)*, *Stabilizer of SD* and other components of the system. *SD*+/+ males transmit the *SD* chromosome to about 99% of the sperm. When *Rsp* is in the homologous chromosome, *Sd* is preferentially recovered. *Sd* is actually a tandem duplication of a 6.5 kb segment, and transformation by a 11.5 kb stretch of its DNA confers full *Sd* activity to the recipient flies. The sequence carries two nested genes, (*dHS2ST*), a homolog of the mammalian heparan-sulfate 2-sulfotransferase and *dRanGAP*, a guanine triphosphatase activator of the Ras-related Ran protein. It appears that the truncation of RanGAP is responsible for the poor transmission of the spermatids. Some of the other elements of the system act in a modifying manner and may cause recombination in the male. In many species of insects, the infection of males by the bacterium *Wolbachia* kills the offspring of the infected males x uninfected females but the viability of the infected eggs is normal. In mice, the transmission ratio distorter system (TRD) that impairs sperm flagellar motility and the *Tcr* (*t complex responder*) in cooperation with other genes located within chromosome 17 (t haplotype) affects chromosome segregation. The chromosome carrying the *Tcr* gene (even as a transgene at another location) enjoys high transmission in the presence of *Tcd*. The *Tcd* genes can act in both cis and trans position whereas *Tcr* (80 kb protein kinase) acts in cis position. *Tcr* represents a fusion between a part of the ribosome S6 protein kinase (*Rsk3*) and another gene of the microtubule affinity-regulating (MARK) Ser/Thr protein kinase family. The *Tcr* gene appears to have descended from a rearrangement

between a member of the *Smok* (sperm motility kinase) family and a *Rsk* allele. Eventually, a practical method can be devised to increase one or the other sex by moving *Tcr* either to the X or to the Y chromosome of farm animals without relying on sperm sorting and artificial insemination. ▶lethal factors, ▶meiotic drive, ▶transmission disequilibrium, ▶certation, ▶preferential segregation, ▶polarized segregation, ▶megaspore competition, ▶tetrad analysis, ▶gene conversion, ▶epistasis, ▶pollen-killer, ▶infectious heredity, ▶RAS, ▶RAN, ▶RSK, ▶heparan sulfate, ▶sex-ratio, ▶spirochetes, ▶dosage compensation; Powers PA, Ganetzky B 1991 Genetics 129:133; Schimenti J 2000 Trends Genet 16:240; Pardo-Manuel De Villena F, Sapienza C 2001 Mamm Genome 12:331.

Segregation Index: The gene number in quantitative traits, also called effective number of loci. ▶gene number in quantitative traits

Segregation Lag: The mutation or transformation is expressed only by third division of the bacteria until all chromosomes are sorted out. ▶phenotypic lag; Angerer WP 2001 Mutation Res 479:207.

Segregation Ratio: The phenotypic (genotypic) proportions in the progeny of a heterozygous mating. ▶segregation, ▶Mendelian segregation, ▶modified Mendelian ratios, ▶ascertainment test

Segregational Petite: ▶petite colony mutants, ▶mtDNA

Segregational Sterility: A heterozygote produces unbalanced gametes. ▶inversion, ▶translocation, ▶gametophyte factor, ▶hybrid dysgenesis, ▶segregation distorter

Seip Disease: ▶lipodystrophy familial

Seitelberger Disease: A degenerative encephalopathy (infantile neuroaxonal dystrophy). ▶encephalopathies

Seizure: A sudden attack precipitated by a defect in the function of the nervous system. *Audiogenic seizures* are due to multifactorial mutations in the mouse, upon exposure to loud high-frequency sound. ▶epilepsy, ▶double cortex, ▶periventricular heterotopia

Sek1 (MKK): A tyrosine and threonine dual-specificity kinase involved in the activation of SAPK/JNK families of kinases and it protects T cells from Fas and CD3-mediated apoptosis. ▶SAPK, ▶JNK, ▶Fas, ▶CD3, ▶apoptosis, ▶T cell; Yoshida BA et al 1999 Cancer Res 59:5483.

Seladin-1: A mediator of Ras-induced senescence. ▶RAS, ▶senescence; Wu et al 2004 Nature [Lond] 432:640.

Selaginella (club moss): Primitive green plant with small genome size (~132 Mb) (see Fig. S25). It is a suitable model plant for evolutionary and developmental studies. It has both female and male gametophytes but rather than producing seed, the fertilized megaspore (embryo) remains embedded in the vegetative tissue of the female gametophyte and starts its development at that place. (See http://www.genome.arizona.edu/BAC_special_projects/).



Figure S25. *Selaginella*

SelB: A prokaryotic translation factor homologous to eIF-2A and eIF-2γ. ▶eIF-2A

SELDI-TOF (surface enhanced laser desorption/ionization–time of flight spectrophotometry): A special form of MALDI-TOF procedure for the study of protein–protein interactions. ▶MALDI-TOF; Bane TK et al 2000 Nucleic Acids Res 30(14):e69.

Selectable Marker: Permits the separation of individuals (cells) that carry it from all other individuals, e.g., in an ampicillin or hygromycin medium (of critical concentration) only those cells (individuals) can survive that carry the respective resistance genes (selectable markers). The aequorin gene equipped with an appropriate promoter may light up the tissue of expression in insects. Many different genes may serve as selectable markers (mutant dihydrofolate reductase [DHFR]), methylguanine methyltransferase [MGMT] multidrugresistance [MDR1]). Selectable markers such as antibiotic (used in medical practice) resistance are undesirable in producing transgenic crops. ▶aequorin

Selectins: These are cell surface carbohydrate-binding, cytokine-inducible, transmembrane proteins. They also bind to endothelial cells in the small blood vessels along with integrins and enable white blood cells and neutrophils to ooze out at the sites of small lacerations to combat infection. L-selectin facilitates the entry of lymphocytes into the lymph nodes by

binding to CD34 cell adhesion molecules. The ESL-1 selectin ligand is a receptor of the fibroblast growth factor. The selectins contain an amino-terminal lectin domain, an element resembling epidermal growth factor and a variable number of complementary regulatory repeats and a cytoplasmic carboxyl end. The P (1q23-q25) and E (1q23-q25) selectins recruit T helper-1 but not T helper-2 cells to the site of inflammation. L-selectin may promote metastasis of cancer cells. ▶[integrins](#), ▶[cell adhesion](#), ▶[cell migration](#), ▶[FGF](#), ▶[EGF](#), ▶[lectins](#), ▶[T cell](#), ▶[TACE](#), ▶[leukocyte adhesion deficiency](#), ▶[metastasis](#), ▶[integrins](#); Dimitroff CJ et al 2001 J Biol Chem 276:47623.

Selection: The unequal rate of reproduction of different genotypes in a population. Bacteria are particularly well suited for the study of the consequences of long-term selection because on simple culture media the evolving population after 20,000 generations can be compared to the ancestral ones. In an experiment of similar nature, two genes affecting DNA supercoiling (*topA*, *fis*) proved competitive. DNA supercoiling affects cell viability, replication, repair, transcription, recombination and transposition (Croizat E et al 2005 Genetics 169:523). In the constant environment of a chemostat a bacterial population substantially diverged in several directions within less than a month (Maharjan R et al 2006 Science 313:514). ▶[selection coefficient](#), ▶[allelic fixation](#), ▶[genetic load](#), ▶[fitness of hybrids](#), ▶[selection and population size](#), ▶[mutation pressure and selection](#), ▶[genetic drift](#), ▶[selection types](#), ▶[non-Darwinian evolution](#), ▶[selection conditions](#), ▶[selection purifying](#), ▶[screening](#), ▶[natural selection](#), ▶[chemostat](#); Brookfield JFY 2001 Curr Biol 11:388.

Selection and Population Size: In very small population, chance (random drift) may be more important than the forces of selection in determining allelic frequencies. When the selection pressure becomes very large, even in small populations there is a good chance for the favored allele to become fixed. ▶[allelic fixation](#), ▶[random drift](#), ▶[genetic drift](#); in human populations: Kreitman M 2000 Annu Rev Genomics Hum Genet 1:539.

Selection, Balanced: ▶[balanced polymorphism](#)

Selection Coefficient: The measure of fitness of individuals of a particular genetic constitution relative to the wild type or heterozygotes in a defined environment. If the fitness is zero the selection coefficient is 1. In other words, if an individual does not leave offspring (fitness is zero), the selection against it in a genetic sense is 1 (100%). The selection coefficient is generally denoted as (*s*) or (*t*), where the former indicates the selection coefficient of the recessive class and (*t*) indicates the selection coefficient of the homozygous dominants. The meaning and relation of fitness and selection coefficients in a population complying with the Hardy-Weinberg theorem is best illustrated in Table S1.

In case we take the fitness of one genotype as unity (in this case we choose the heterozygotes, e.g., $w_2 = 1$), then the *standardized fitness* becomes:

$$\frac{w_1}{w_2} = 1 - s \text{ and } s = 1 - \frac{w_1}{w_2}$$

$$\text{similarly } \frac{w_3}{w_2} = 1 - t \text{ and } t = 1 - \frac{w_3}{w_2}$$

▶[fitness](#), ▶[allelic frequencies](#), ▶[Hardy-Weinberg theorem](#), ▶[advantageous mutation](#)

Selection Conditions: Selection may operate at different levels beginning in meiosis (distorters, gametic factors) or at any stage during the life of the individual beginning with the zygote through the entire reproductive period. The intensity of the selection depends on the genes, the overall genetic constitution of the individual and the environment, including the behavioral pattern of the population (e.g., protecting the young and infirm). The formulas representing the various means of selection were derived from the Hardy-Weinberg theorem $p^2 + 2pq + q^2 = 1$ (see Table S2) and their use is exemplified.

The genotypic contributions to the *AA*, *Aa* and *aa* phenotypes are p^2 , $2pq$ and $q^2(1 - s)$, respectively, where *s* is the selection coefficient (▶[selection coefficient](#) for derivation of *s*).

The total contribution is now reduced from 1 to $1 - sq^2$ because sq^2 individuals are eliminated by selection. Thus, the new frequency of the recessive alleles becomes q_1 and the

S

Table S1. Selection and fitness in a Hardy-Weinberg population

| Genotypes | AA | Aa | aa | Total |
|---------------------|----------------------|----------------------|----------------------|-------|
| Zygotic frequencies | p^2 | $2pq$ | q^2 | 1 |
| Fitness | w_1 | w_2 | w_3 | |
| Gametes produced | $(w_1) \times (p^2)$ | $(w_2) \times (2pq)$ | $(w_3) \times (q^2)$ | 1 |

Table S2. Formulas to calculate the change in allelic frequencies per generation at various conditions of selection. In case s or q is very small, omission of the sq product from the denominator may be of very little consequence for the outcome

| Type of selection | Increase (+) or decrease (-) in the rate of change of an allele (Δq) per generation |
|--|---|
| 1. Selection against gametes | $-\frac{sq(1-q)}{1-sq}$ |
| 2. Differential selection in males and females (without sex linkage) | $q^2[1 - \frac{1}{2}(s_{\text{male}} + s_{\text{female}})]$ |
| 3. Selection at X-chromosome linkage | gametic in the heterogametic and zygotic in the homogametic sex |
| 4. Selection against recessive lethals | $-\frac{q^2}{1+q}$ |
| 5. Selection against the allele in absence of dominance | $-\frac{1}{2}\frac{sq(1-q)}{1-sq}$ |
| 6. Selection against dominant lethals | $+(1-q)$ |
| 7. Partial selection against homozygous recessives in case of complete dominance | $-\frac{sq^2(1-q)}{1-sq^2}$ |
| 8. Partial selection against completely dominant alleles | $+\frac{sq^2(1-q)}{1-s(1-q)^2}$ |
| 9. Selection against recessives in autotetraploids | $-spq^4$ |
| 10. Selection against intermediate heterozygotes | $-\frac{sq(1-q)}{1-2sq}$ |
| 11. Selection against heterozygotes | $+2spq(q - \frac{1}{2})$ |
| 12. Selection against both homozygotes (heterozygote advantage) | $+\frac{pq(s_1p - s_2q)}{1-s_1p^2 - s_2q^2}$ |

$$q_1 = \frac{q^2[1-s] + pq}{1-sq^2}$$

change in the frequency of q , is $\Delta q = \frac{q^2[1-s] + pq}{1-sq^2} - q$ which reduces to $\frac{sq^2(-q)}{1-sq^2}$. The effectiveness of the selection also depends on the frequency of the allele involved. Selection against rare recessive alleles may be very ineffective because only the homozygotes are affected. Selection most frequently works at the level of the phenotype and the recessives may not influence the fitness of the heterozygotes. At low values of q the majority of the recessive alleles is in the heterozygotes and thus sheltered from the forces of selection. Dominant, semidominant and codominant alleles may be, however, very vulnerable if they lower the fitness of the individuals. As an example let us assume that the frequency of a recessive allele is $q = 0.04$ and by using formula 4 shown in Table S2 the change in allelic frequency per generation is $\Delta q = -\frac{[0.04]^2}{1+0.04} \cong -0.00154$ and after $n = 25$ generations, the initial frequency of the gene, $q_0 = 0.04$ changes to: $q_n = \frac{q_0}{1+nq_0} = \frac{0.04}{1+[25 \times 0.04]} = 0.02$ meaning that complete

elimination of all homozygotes ($s = 1$) for 25 generations reduces only to half the frequency of that recessive allele. The initial zygotic frequency of $(0.04)^2 = 0.0016$ (1/625) will thus change to $(0.02)^2 = 0.0004$ (1/2500).

If the same deleterious allele would be semidominant and it conveys a fitness of 0.5 relative to the homozygotes for the other allele, according to formula 5 in Table S2, the change of the frequency of this semidominant allele in a generation becomes: $\Delta q = -\frac{[1/2][0.5][0.04][0.96]}{1 - \{[0.5] \times [0.04]\}} \cong -0.0098$. Thus, a semidominant allele with 0.5 selection coefficient will be selected against more than six times as effectively as a recessive lethal factor because $0.0098/0.00154 \cong 6.4$ in these examples.

The number of generations required to bring about a certain change in gene frequencies can be calculated in the simple case when the homozygous recessives are lethal, i.e., the selection coefficient is, $s = 1$: $T_{\text{generations}} = \frac{q_0 - q_T}{q_0 q_T} = \frac{1}{q_T} - \frac{1}{q_0}$ where q_0 is the initial frequency of the allele and q_T is its frequency after T generations. If it is assumed that the genotypic frequency is $(q_0)^2 = 0.0001$ and $q_0 = 0.01$ then the

number of generations required to reduce the initial frequency to $q_T = 0.005$ is $T = \frac{1}{0.005} - \frac{1}{0.01} = 100$. After 100 generations then the frequency of the recessive lethal allele becomes $(q_T)^2 = (0.005)^2 = 0.000025 = 1/40,000$ compared to the initial frequency of $1/10,000$. The effectiveness of selection is much influenced by the heritability of the allele concerned. In complex cases more elaborate computations are required that cannot be illustrated here. ▶selection coefficient, ▶balanced polymorphism, ▶mutation pressure opposed by selection, ▶selection and population size, ▶allelic fixation, ▶genetic load, ▶fitness of hybrids, ▶gametophyte, ▶QTL, ▶heritability, ▶gain, ▶mutation neutral

Selection, Cyclic: Different phenotypes are selected depending on seasonal variations in the environment.

Selection Differential: ▶gain

Selection Index in Breeding: ▶gain

Selection Inferred from DNA Sequences: Different types of natural selection (negative selection, recurrent positive selection, balancing selection) affect the pattern of variation in DNA sequences although recent population growth, bottlenecks and population subdivisions confound the pattern of genetic variation and may mimic the effects of natural selection. If synonymous mutations are neutral then natural selection at non-synonymous sites can be effectively tested. A non-parametric test can compare allele frequency spectrum of segregating sites among regions of functional classes. Because of being non-parametric the comparisons encounter difficulties in biological interpretation with other methods. A maximum likelihood method can infer, however, both selection and demographic changes. Assuming that non-coding single nucleotide polymorphism (SNP) is selectively neutral and correction can be made to determine selection among non-synonymous changes. Experimental data indicate negative selection on non-synonymous alterations (as expected) and the strength of selection is most explicit when the amino acid substitutions involve radical changes (Williamson SH et al 2005 Proc Natl Acad Sci USA 102:7882). ▶non-parametric test, ▶non-synonymous codon, ▶maximum likelihood, ▶selection types, ▶SNIPs, ▶McDonald-Kreitman hypothesis

Selection Intensity: ▶gain

Selection—Medical Care: The progress of effective medical care saves increasing number of human lives. Some of the saved individuals will have a chance to transmit deleterious genes to their offspring so eventually some increase in detrimental alleles is expected. Non-synonymous mutations reduce fitness

by an average of 4.3% and selection acting against non-synonymous polymorphism is $\sim 9 \times 10^{-5}$. This also indicates that medical care may not affect the extent of fitness too much but it is very difficult to identify the gene involved in complex diseases. (Eyre-Walker A et al 2006 Genetics 173:891). ▶selective abortion, ▶genetic risk, see Fig. S26.

Selection, Long Term: Plant and animal breeders carry on selection for many generations and the effectiveness is reduced less than expected based on selection for single desirable genes/traits. The cause of the effectiveness is that multiple interacting genes determine the majority of traits of agricultural interest (Carlborg Ö et al 2006 Nature Genet 38:418). ▶polygenic inheritance, ▶QTL, ▶gain

Selection, Negative: Maintains disadvantageous alleles. The term is also used in the sense of elimination disadvantageous alleles. ▶drift genetic, ▶hitchhiking, ▶selection purifying

Selection, Natural: ▶natural selection

Selection Positive: Maintains the advantageous alleles. (See selection motif tool: <http://oxytricha.princeton.edu/SWAKK/>).

Selection Pressure: The intensity of selection affecting the frequency of genes in a population. ▶volatility

Selection, Purifying: Acts against the heterozygotes of a new allele with lower fitness. Asexual reproduction favors the accumulation of deleterious mutations. Mitochondrial mutations in asexual lineages of microcrustacean *Daphnia pulex* accumulated deleterious mutation four times the rate compared to sexual lineages (Paland S, Lynch M 2006 Science 311:990). ▶hitchhiking, ▶genetic drift, ▶Muller's ratchet

Selection Response: (heritability) \times (selection differential). ▶heritability, ▶gain

Selection Types: (i) *Stabilizing* favors the intermediate forms that have ability to survive under the most common but opposite conditions (such as cold and heat, draught and excessive precipitation). (ii) *Directional selection* shifts the mean values of a population either toward higher or lower values than the current mean. (iii) *Disruptive selection* breaks up the population into two or more subpopulations that each has adaptive advantage in particular niches of a larger habitat. (iv) *Frequency-dependent selection* favors an allele when it is relatively rare and may turn against it when it becomes abundant. Common examples are found in host-parasite, predator-prey relationships or in resource utilization (see Fig. S27) (Carius HJ et al 2001 Evolution 55:1136).

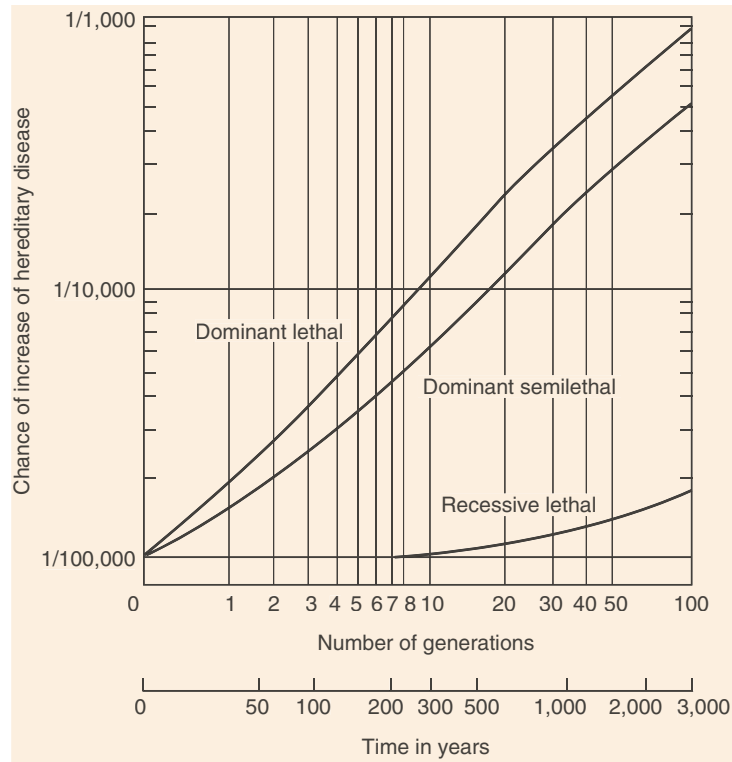


Figure S26. The effect of medical care on the incidence of human diseases. Thus the improvement of medical services may lead to deterioration of the gene pool. If the initial frequency of a detrimental recessive allele is 0.001 or less, the consequences of the selection may not be evident for about 300 years. Even after thousands of years of selection the increase of incidence is relatively modest. The frequency of dominant lethal or dominant semi-lethal alleles may increase much faster. (Redrawn after Bodmer WF, Cavalli-Sforza LL 1976 *Genetics, Evolution, and Man*. Freeman, San Francisco, California)

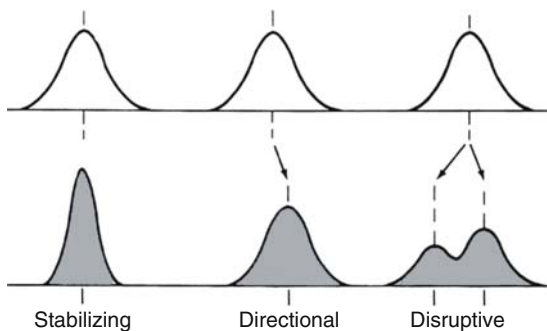


Figure S27. Top: Original frequency distribution of populations. Below: The shifts in distribution after selection. (After Mother K 1953 *Symp Soc Exp Biol* 7:66)

When the number of predators increase beyond a point there will not be enough prey to maintain the predators and their number will decrease. Similarly, when animals overgraze in the natural habitat, ultimately their population decreases. Similarly, highly

virulent viruses may outcompete the less aggressive types even when they may kill the host faster. ►fitness, ►selection apostatic selection, ►selection cyclic, ►competition, ►artificial selection

Selection Value: ►selection index, ►gain

Selective Abortion: The termination of a pregnancy by precocious removal of the fetus from the womb if the condition of the mother or of the fetus medically justifies it and the legal system permits it. The genetic constitution or condition of the fetus may be tested with the aid of amniocentesis or sonography. From the viewpoint of genetics, selective abortion may pose biological problems. If all families would compensate for the abortions elected based on genetic defects, the frequency of these defective genes may actually rise in the population. This may happen because it assists heterozygotes for genetic abnormalities to leave offspring that—although may not display the morbid trait—can again transmit the undesirable genes to future generations. If all carriers would refrain from reproduction, the frequency of the deleterious genes

may sink to the level of new mutations. Selective abortion may involve also ethical, moral and political problems but these are beyond the scope of genetics. ▶abortion spontaneous, ▶abortion medical, ▶pregnancy unwanted, ▶amniocentesis, ▶counseling genetic, ▶selection and medical care, ▶sterilization humans, ▶ethics, ▶bioethics, ▶genetic screening

Selective Advantage: In population genetics, selective advantage is expressed by the relative fitness of bearers of (two) genotypes. Generally the wild type has greater fitness (W_N) than a mutant type (W_M) and their relative fitness is $(W_N)/(W_M)$. W (fitness) is the reproductive success. Usually, $(W_N)/(W_M) = 1 - s$, where s is the selection coefficient indicating the disadvantage of the mutant type. In case the fitness of a genotype exceeds 1 it has an advantage in survival. ▶selection coefficient, ▶fitness, ▶beneficial mutation, ▶codon usage

Selective Fertilization: Some sperms, because of their gene content, may be at a disadvantage in competition with other sperms for penetrating the egg, or where multiple eggs or megaspore cells are formed, their success depends on their genetic constitution. Because of this, the genetic segregation may deviate from the standard Mendelian expectation. ▶gamete competition, ▶certation, ▶megaspore competition, ▶meiotic drive, ▶sperm

Selective Medium: Only permits the propagation of individuals or cells that carry a selectable marker, such as high or low temperature, antibiotic, drug resistance, etc. (see Fig. S28) ▶selectable marker

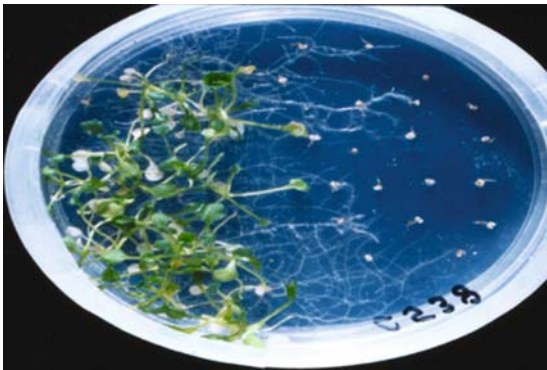


Figure S28. Hygromycin medium. Left: *Arabidopsis* plants transgenic for resistance; right: Wild type fails to grow (Rédei, unpublished)

Selective Neutrality: Assumes that random drift is responsible for the allelic frequencies in a particular population, i.e., all alleles at a locus have the same selective value. ▶random genetic drift, ▶allelic frequencies

Selective Peak: Determined by the genetic homeostasis of a population, i.e., the gene frequencies are maintained at this optimum as long as catastrophic changes in the environment do not occur. ▶homeostasis, ▶adaptive landscape

Selective Screening: ▶screening, ▶selective medium, ▶mutation detection

Selective Sieve, Extent of: The rate of substitution at a gene site/mutation rate for the gene.

Selective Sweep: The rapid establishment of advantageous allele(s) in a population. Such alleles may carry along other linked genes too by a mechanism of hitchhiking. Less advantageous mutations may also be swept along with linked advantageous ones. The selective sweep may reduce the genetic variation in the population. ▶hitchhiking, ▶selection types, ▶selective advantage, ▶mutation beneficial; Nurminsky DI et al 1998 Nature [Lond] 396:572.

Selective Value: ▶fitness, ▶selection coefficient

Selectivity Factor (SF): A human general transcription factor homologous to TFIIB of other eukaryotes. ▶transcription factors

Selectivity Filter: Functions as a gatekeeper to allow or prevent the access of another (small) molecule into a structural pocket of a protein. Aromatic amino acids (being relatively bulky) permit the access of larger structures whereas smaller amino acids are more restrictive. Selective filters have significance for the development and effectivity of special drugs.

Selector Genes: These are supposed to specify segmental differences during morphogenesis, such as anterior/posterior or dorsal/ventral. The selector genes after receiving morphogenetic signals may team up with the relevant other transcription factor genes and recruit a number of specific activators to turn on the transcription of specific morphogenetic genes (see Fig. S29). The process of differentiation of an organ may take place by two major steps. First, the body position is specified and then the pattern of differentiation is determined. Selector genes are used also for genes that facilitate selection of transformed cells, e.g., neomycin, kanamycin, hygromycin resistance and others. ▶morphogenesis, ▶morphogenesis in *Drosophila*, ▶signal transduction, ▶differentiation, ▶imaginal disc; Affolter M, Mann R 2001 Science 292:1080; Guss KA et al 2001 Science 292:1164; Ao W et al 2004 Science 305:1743.

Selenium-Binding Protein Deficiency (SP56, 1q21-q22): Causes neurological disorder and sterility due to the deficiency of a 56 kDa protein and other selenoproteins. Selenium may have anticarcinogenic property.

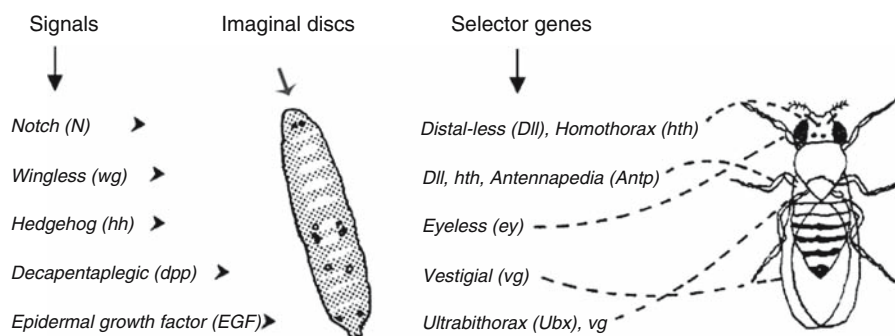


Figure S29. Selector gene responses and expression

► **selenocysteine**; Martin-Romero FJ et al 2001 J Biol Chem 276:29798.

Selenocysteine (SC, $C_6H_{12}N_2O_4Se_2$): A reactive, very toxic, oxygen-labile amino acid. Selenophosphate is the donor of selenium for the synthesis of selenocysteyl-tRNA, which has the UCA anticodon and SC incorporation is directed by the UGA (usually a stop) codon. In bacteria, a special mRNA fold immediately following UGA mediates the incorporation of SC, carried by its own tRNA. The loop binds the SelB protein, which acts like a somewhat unusual elongation factor. In mammals, the loop (called SECIS) is locked at the end of the mRNA. Two proteins carry out the function of SelB. SBP2 binds the SECIS element whereas eEFSec binds the selenocysteine tRNA. Incorporation of selenocystein into proteins requires a selenocystein-specific translation elongation factor (eEFSec) and a SECIS binding protein (SBP2). SBP2 associates with the 28S RNA of the ribosome (Kinzy SA et al 2005 Nucleic Acids Res 33:5172). Thus, SC is the 21st “natural” amino acid. A putative selenocysteine synthase had been identified as a pyridoxal phosphate-containing protein called soluble liver antigen. The activity of this synthase was characterized using selenophosphate and a tRNA aminoacylated with phosphoserine as substrates to generate selenocysteine. Identification of selenocysteine synthase allowed the delineation of the entire pathway of biosynthesis in mammals. Selenocysteine synthase is present only in those archaea and eukaryotes that make selenoproteins (Xu X-M et al 2007 PloS Biol 5(1):e4).

Selenocysteine-containing proteins (glutathione peroxidase, 5'-deiodinases, formate and other dehydrogenases, glycine reductase) may have substantially higher or lower catalytic activity and may have theoretical and applied interest. Selenoproteins may be scavengers of heavy metals and may favor survival of cultured neurons. Removal of the selenocysteine tRNA^{Sec} causes embryonic lethality in mice. Deiodination enzymes catalyze deiodination of thyroid

hormones and modulate the level of these hormones. Selenoprotein-binding protein binds to deiodinase 2 and causes thyroid disease (Dumitrescu AM et al 2005 Nature Genet 37:1247). In a marine gutless worm, *Olavius algarvensis* 99 selenoprotein genes that clustered into 30 families were found. In addition, several pyrrolysine-containing proteins were identified in this dataset. Most selenoproteins and pyrrolysine-containing proteins were present in a single deltaproteobacterium, $\delta 1$ symbiont (Zhang Y, Gladyshev VN 2007 Nucleic Acids Res 35:4952).

► **code genetic**, ► **antideterminant**, ► **protein synthesis**, ► **SelB**, ► **SECIS**, ► **unnatural amino acids**, ► **pyrrolysine**; Gladyshev VN, Kryukov GV 2001 Biofactors 14:87.

Selenoproteins: They appear to have roles in antioxidant defenses (protection against UV, peroxides), against tumor formation, viral resistance, thyroid and reproductive functions. The selenoprotein phospholipid, hydroperoxide glutathione peroxidase (PHHGPx) is an active, soluble enzyme during sperm maturation but in mature spermatozoa, it is enzymatically inactive and insoluble. There its role is structural, securing the stability of midpiece where mitochondria are abundant. The human genome may encode 25 selenoproteins. Deficiency of selenoproteins may accelerate the development of cancer (Diwadkar-Navsariwala V et al 2006 Proc Natl Acad Sci USA 103:8179). ► **selenocysteine**, ► **UV**, ► **sperm**, ► **glutathione peroxidase**; Copeland PR, Driscoll DM 2001 Biofactors 14:11; Kryukov GV et al 2003 Science 300:1439.

SELEX (systematic evolution of ligands by exponential enrichment): A method of aptamer selection from random oligonucleotide sequences (10^{15} to 10^{18}) resulting in the isolation of aptamers and ligands. The oligonucleotide library is synthesized by commercial DNA synthesizers and used in 20–30 or 200 base long sequences ($4^{20} \sim 10^{12}$ whereas $4^{75} \sim 1.4 \times 10^{45}$ combinations). The phage R17 coat protein provides an excellent RNA recognition site. It binds to a loop

(AUUA) and a four-base stem structure with a bulged A residue. The synthetic nucleotide sequence may use modified ribose residues such as 2' F (fluoride) or 2'NH₂ in the triphosphate nucleotides. This makes the oligonucleotides stable for several hours whereas unmodified RNA may be degraded by nucleases immediately. By "partition" (gel electrophoresis, nitrocellulose filtration) the few good sequences must be separated from the large pool. The aptamers may be truncated to limit to the minimal effective binding sites and may be further modified by extra nucleotide analogs for increased stability. The technology may be applied to the search for new drugs, diagnostic compounds and ribozymes of diverse functions. ▶aptamer, ▶nitrocellulose filter, ▶gel electrophoresis, ▶ribozyme, ▶DNA binding proteins; Wilson DS, Szostak JW 1999 Annu Rev Biochem 68:611; <http://www.mgs.bionet.nsc.ru/mgs/systems/selex/>.

Self-Antigen: Antigens synthesized within the system that may stimulate autoimmune reaction by the T cells although normally there is no immune response to the self-antigens. ▶T cells, ▶autoantigen, ▶MHC, ▶self-tolerance, ▶immune tolerance

Self-Assembly: A process of reconstituting a structure from components when there is enough information within the pieces to proceed without outside manipulation, e.g., the self-assembly of ribosomes from RNA and protein subunits.

Self-Cleavage of RNA: Some ribozymes may cleave more than 99% of the mRNAs and thereby preventing gene expression. By genetic engineering, effective ribozymes can be introduced into vectors and thus prevent transcription of functional mRNA or its translation. ▶ribozyme, ▶RNAi; Yen L et al 2004 Nature [Lond] 431:471.

Self-Compatibility: Self-fertilization can take place and the offspring is normal. ▶self-incompatibility, ▶incompatibility alleles

Self-Cross: A misnomer for self-fertilization. ▶cross

Self-Deleting Vector: A lentiviral vector may integrate into the cell and deliver a gene (Cre), which is expressed in the target and subsequently deleted in a Creb-dependent manner. The undesirable effect of the vector is thus avoided. ▶viral vectors, ▶lentivirus, ▶Cre/LoxP; CREB Pfeifer A et al 2001 Proc Natl Acad Sci USA 98:11450.

Self-Destructive Behavior: ▶Lesch-Nyhan syndrome, ▶Smith-Magenis syndrome

Self-Fertilization: Can take place between the gametes in hermaphroditic individuals; autogamy is the strictest means of inbreeding. Self-fertilization occurs in ~20% of plant species and ~33% are intermediates

between selfing and outcrossing (Vogler DW, Kalisz S 2001 Evolution 55:202). The sperm of XO males preferentially fertilizes *Caenorhabditis elegans* hermaphrodites. ▶autogamy, ▶inbreeding, ▶*Caenorhabditis*; Herlihy CR, Eckert CG 2002 Nature [Lond] 416:320.

Self-Immunity: Mediated by protein factors that bind to, for e.g., Moloney virus and thus prevent the integration into the sequences by another viral element. ▶cis-immunity, ▶phage immunity

Self-Inactivating/Self-Activating Vector: ▶E vector

Self-Incompatibility: The failure of fusion of male and female gametes produced by the same individual or lethality of the embryo formed by such fusion. Self-incompatibility may be controlled either by the sporophyte or by the gametophyte. The incompatibility for effective pollination is determined by secreted glycoproteins (SLG, on the surface of the stigma) and membrane-bound receptor protein kinases (SRK, attached to the stigma cells). The stigma cells preferentially synthesize these proteins and only low level of expression is found in the anthers of cruciferous plants. In several solanaceous plants (tomato, *Nicotiana glauca* and *Petunia inflata*), an S (self-compatibility) RNase may attack in the style the RNA in self-pollen. The S-RNase is normally compartmentalized in vacuoles of the pollen tube. Primarily protein HT-B keeps S-RNase sequestered. When HT-B is degraded RNase is released and incompatibility is established (McLure B 2004 Plant Cell 16:2840; Goldraij A et al 2006 Nature [Lond] 439:805).

In poppy plants, a receptor on the pollen recognizes a stylar protein. The binding between this ligand and receptor leads to release of calcium ions that in turn inhibit pollen-tube growth. Two soluble inorganic pyrophosphatases regulate the incompatibility reaction (de Graaf BHJ et al 2006 Nature [Lond] 444:490). In *Brassica* plants self-incompatibility is overcome if the aquaporin gene was disrupted. This indicates that functional water channels are one of the requirements for the manifestation of self-incompatibility in *Brassica*. Recent information indicates that in the stigma cell membranes of crucifers the single *S* locus encodes an *S* locus glycoprotein (SLG) and a single-pass transmembrane serine/threonine *S* receptor kinase (SRK). The latest evidence indicates that SRK and not SLG is responsible for the haplotype specificity and SLG reinforces the self-incompatibility. Transfer of the SRK and SCR genes from *Arabidopsis lyrata* to *A. thaliana* confers self-incompatibility to the latter species, which is normally autogamous (Nasrallah ME et al 2002 Science 297:247). The secretion of a cysteine-rich protein (SCR, encoded also at the

S locus) by the self-pollen catalyzes the autophosphorylation of the SLG—SRK complex. The SRK protein then interacts with ARC1 (autorejection component) stigma protein and as a consequence, through a series of events the self-pollen is incapacitated on the stigma by ubiquitination (Stone SL et al 2003 Plant Cell 15:885). It has been shown that an S-RNase with another component is responsible for the pollen tube breakdown in the incompatible combinations. The factor PiSNF encoding 389 amino acids ~161 kb downstream of the S₂ allele may protect the pollen from the decay (Sijacic P et al 2004 Nature [Lond] 429:302). In poppy, a caspase-3 type protein prevents self-fertilization in self-incompatibility (Thomas SG, Franklin-Tong VE 2004 Nature [Lond] 429:305). Accordingly, self-incompatibility in the different species may have different controls.

Self-incompatibility is usually determined by a large array of alleles in the populations (~100 haplotypes in *Brassicas*) and there are substantial differences among the species regarding the number of such alleles maintained depending on the effective population size. Heteromorphic self-incompatibility is based on mechanical barriers to self-fertilization. The stigma is located to a higher position in the flowers than the anthers, and the pollen usually does not reach the stigmatic surface. In such cases, artificial pollination is successful. Sporophytic incompatibility means that the incompatibility factors operate not at the gametophyte (pollen - egg) level but the pistil or pollensac tissues and control the growth of the pollen tube. In *Brassica rapa* sporophytic selfincompatibility is controlled methylation of the promoter of the recessive allele in the tapetal tissues (Shiba H et al 2006 Nature Genet 38:297). Selfincompatibility may break down by epigenetic mechanisms; in *Arabidopsis* species hybrids the S-locus receptor kinase transcript may be aberrantly processed and in *Capsella* hybrids the S-locus cysteine-rich protein may be suppressed (Nasrallah JB et al 2007 Genetics 175:1965). ▶incompatibility alleles, ▶S alleles, ▶HLA, ▶unilateral incongruity, ▶population effective size, ▶gametogenesis, ▶Ribonuclease-S, ▶RNA I, ▶ligand, ▶gametophyte, ▶pistil, ▶pollen, ▶tapetum, ▶aquaporin; Nasrallah JB 2005 Trends Immunol 26:412; McClure B 2006 Curr Opin Plant Biol 9:639; Dickinson HG 2000 Trends Genet 16:373; Kachroo A et al 2001 Science 293:1824; Takayama S et al 2001 Nature [Lond] 413:534; Tong N 2002 Trends Genet 18:113; Kachroo A et al 2002 Plant Cell 14: S227; Stone JL 2002 Q Rev Biol 77:17; Takayama S, Isogai A 2005 Annu Rev Plant Biol 56:467; self/nonself discrimination in pre- and post-zygotic systems: Boehm T 2006 Cell 125:845.

Self-Regulation: The process of regeneration of embryos from bisected (cut into halves) blastulas. This can take place in lower and higher animals including human, when identical twins are formed by spontaneous events. The dorsal-ventral morphogenetic gradients in the two halves are mediated by the bone morphogenetic proteins (BMP) and extracellular proteins such as Chordin, Sizzled and Bambi and others, which are situated at opposite poles and are under opposite transcriptional regulation (Reversade B, De Robertis EM 2005 Cell 123:1147).

▶Spemann's organizer, ▶organizer

Self-Renewal: An ability of cells to also produce stem cells that are not just able to divide mitotically and generate progenitor cells. ▶stem cells, ▶progenitor; Smith AG 2001 Annu Rev Cell Dev Biol 17:435.

Self-Reproduction: The general property of living systems. It means that the system can produce detached self-reproducing copies of itself. Self-reproducing machines—if they can function—may have special human interest for working in environments hazardous to humans such as outer space, mutagenic conditions, etc. Important requirement would be not just self-assembly, which would make only a copy of itself from parts but would continue—if parts provided—making additional copies continuously. The self-reproducing feature has now been achieved in principle by the use of a four-module system. It is still very far from generating a system comparable to a biological unit, which can generate 10²⁰ amino acid combinations not to consider the many other biological elements of a living organism (Zykov V et al 2005 Nature [Lond] 435:163).

Selfing: Self-fertilization; it is symbolized by ♂.

Selfish DNA: An assumption for certain DNA sequences (introns, repetitive non-coding sequences, transposable elements) that they have no selective (adaptive, evolutionary) value for the carrier, therefore, the presence of such sequences is of no advantage to the cells concerned, and are propagated only for selfish (parasitic) purposes. Some of the originally “selfish DNAs” (1979–80) turned out to have some functions, e.g., as maturases, and others represent transposable elements and continuously reshape the genome and are thus significant for mutation and evolution. Alu sequences appear to be more common within the generic GC regions hinting some regulatory functions. The minisatellite DNAs and the trinucleotide repeats are implicated in an increasing number of hereditary diseases. The majority of the Y-chromosomal sequences of *Drosophila* do not seem to have any identifiable function yet male fertility may be impaired if they are deleted. ▶junk DNA, ▶introns, ▶ignorant DNA, ▶copia, ▶trinucleotide repeats, ▶REP, ▶plasmid addiction, ▶transposable elements, ▶Alu;

van der Gaag M et al 2000 *Genetics* 156:775; Hurst GDD, Werren JH 2001 *Nature Rev Genet* 2:597; Hammerstein P, Hagen EH 2006 *Genes in Conflict. The Biology of Selfish Genetic Elements*. Harvard University Press, Cambridge, Massachusetts.

Selfish Genes: These have selective advantage over comparable ones and ensure their own propagation. The selfishness contrasts altruism when genes of the non-reproductive casts of social insects promote the welfare of the colony at the expense of their own work although they themselves are sterile. ▶ [altruism](#)

Selfish Replicon: The small circular plasmids in eukaryotic nuclei (maize) without any apparent function beyond perpetuating themselves.

Self-Organizing Map: ▶ [cluster analysis](#)

Self Protein: ▶ [self antigen](#), ▶ [molecular mimics](#), ▶ [bystander activation](#), ▶ [immune system](#)

Self-Primed Synthesis: The synthesis from single-strand DNA obtained through reverse transcription, one primer may be used at the 5' end to produce the second strand by extension at the 3'-end in a hairpin like structure. The synthesis by self-priming is slow (see Fig. S30).



Figure S30. Self-priming

Self-Replicating DNA: A replication mechanism for short double-stranded molecules that do not require assistance by proteins. Similar mechanisms may have operated during prebiotic evolution, and it can be reproduced in the laboratory. ▶ [replication](#), ▶ [self-assembly](#)

Self-Replicating Peptide: An autocatalytic molecule capable of assembling amino acids into oligopeptides. The yeast transcription factor GCN4 leucine-zipper domain can promote its own synthesis of 15–17 amino acid residues. ▶ [GCN4](#), ▶ [leucine zipper](#)

Selfrestriction: Self restriction lymphocyte recognizes foreign antigen bound to self MHC molecule. ▶ [lymphocyte](#), ▶ [MHC](#)

Self-Splicing Introns: Group I and group II introns can fold into catalytic structures capable of removing their own sequences from the RNA transcripts of genes. ▶ [intron](#)

Self-Tolerance: The unresponsiveness of the immune system to self-antigens. Apoptosis is a means for the maintenance of self-tolerance; lymphocytes and dendritic cells play an important role (Chen M et al

2006 *Science* 311:1160). *Central self-tolerance* may be caused by death of the lymphocytes when encountering autoantigens. Peripheral self-tolerance takes place among the mature lymphocytes in the peripheral lymphatic organs. *Clonal ignorance* fails to recognize the autoantigens because of their sequestration or the failure to stimulate the indispensable secondary signals, such as cytokines, etc. ▶ [immune tolerance](#), ▶ [self-antigen](#), ▶ [autoimmune diseases](#), ▶ [immune system](#), ▶ [at least one hypothesis](#); Rubin RL, Kretz-Rommel A 2001 *Crit Rev Immunol* 21:29.

Selvin: A rarely used unit of absorbed radiation dose. ▶ [Sievert](#)

SEM (scanning electronmicroscopy): ▶ [electronmicroscopy](#)

SEM-5: A homolog of *Grb2* in *Caenorhabditis* nematodes. ▶ [Grb2](#)

Semantics: The differentiating meaning of words and sentences. Also used by information-extraction programs for interpreting the correct meaning.

Semaphorin: A family of membrane-associated, secreted protein factors, required for axonal pathfinding in neural development. Semaphorin 5A can be bifunctional, promontory and inhibitory, to axon guidance depending on heparan and chondroitin sulfate proteoglycans (Kantor DB et al 2004 *Neuron* 44:961). Transduction by semaphorin III is mediated by the neuropilin-1 receptor. Semaphorins also regulate the development of the right ventricle and the right atrium of the heart as well as various cartilaginous and other tissues. Human semaphorins IV and V genes reside at the 3p21.3 chromosomal site; it is deleted in small cell lung carcinoma. Semaphorin 4A primes T cells and regulates Th1/Th2 (Kumanogoh A et al 2005 *Immunity* 22:305). Semaphorin 7A controls both axon guidance and T cell reaction (Czopik AK et al 2006 *Immunity* 24:591) and initiates T cell-mediated inflammation through α 1 β 1 integrin (Suzuki K et al 2007 *Nature [Lond]* 446:680). Semaphorin 4D links axon guidance and tumor-induced angiogenesis (Basile JR et al 2006 *Proc Natl Acad Sci USA* 103:9017). ▶ [axon](#), ▶ [col-lapsin](#), ▶ [neuropilin](#), ▶ [netrin](#), ▶ [neurogenesis](#), ▶ [small cell lung carcinoma](#), ▶ [plexin](#), ▶ [fasciclin](#), ▶ [axon guidance](#), ▶ [integrin](#); Tessier-Lavigne M, Goodman CS 1996 *Science* 274:1123; Pasterkamp RJ, Verhaagen J 2001 *Brain Res Rev* 35:36; Serini G et al 2003 *Nature [Lond]* 424:391; Pasaterkamp RJ et al 2003 *Nature [Lond]* 424:398.

SEMD: ▶ [PAPS](#)

Semelparity: The organism reproduces only once during its lifetime, e.g., *Palingea longicauda*

(Ephemeroptera) or some marsupials, which die after one mating season.

Semen: The viscous fluid in the male ejaculate composed of the spermatozoa and secreted fluids of the prostate and other glands. The seminal fluid of *Drosophila* reduces the propensity of the females to mate with another male. Its higher quantity lowers the viability of the females. Thus, the semen per se may have a role in fitness. ►testis, ►prostate

Semenogelin: A protein in the seminal fluid that promotes the viscosity of the ejaculate. It tends to prevent successful, additional insemination in promiscuous females (Dorus S et al 2004 Nature Genet 36:1326).

Semiconductor: The materials of germanium, silicon and others are characterized by increased electric conductivity as temperature increases to room temperature. These materials are called semiconductors because their conductivity is much lower than that of metals. In metals, the increase in temperature lowers conductivity. In the semiconductor material, the electronic motion is turned on through the crystal lattice structure. (The crystal lattice is a complex of atoms and molecules held together by electrons and atomic nuclei into an extremely large molecule-like structure.) The energy states are in so-called bands. When all the sites in an energy band are completely occupied by electrons, there is no flowing electric current because none of the electrons can accept increased energy even if exposed to an electric field of ordinary magnitude. This is thus a non-conductor state. When the energy gap between two bands is small, the electrons can be thermally excited into a conduction band and the electrons under the influence of an external electric source can initiate an electric current. This state of the crystal is an *intrinsic semiconductor*. The carriers of the current are called positive holes. Transistors (electronic amplifying devices utilizing single-crystal semiconductivity) operate by the principles of conduction electrodes and mobile positive holes. Industrially used semiconductors are *extrinsic semiconductors*, which mean that when small amounts of other material is introduced into them, it results in enhanced conductive properties. These devices are essential components of electronic laboratory equipments and communication systems, computers and television sets.

Semi-Conservative Replication: The regular mode of DNA replication where one old strand serves as template for the synthesis of a complementary new strand and this then with an old strand becomes the daughter double helix. ►DNA replication,

►replication, see Table P3 at ►pulse-chase entry and Fig. W4 in ►Watson and Crick model

Semi-Dominant: The dominance is incomplete, and therefore such genes may be useful because the heterozygotes can be phenotypically recognized. ►incomplete dominance, ►codominance

Semigamy: Occurs when the egg and sperm do not fuse, rather they contribute separately to the formation of the embryo that may become thus a paternal-maternal chimera. ►apomixis, ►androgenesis, ►parthenogenesis

Semi-Lethal: Genes that reduce the viability of the individual, and may cause premature death. ►lethal equivalent, ►lethal factors, ►LD50, ►LD₀

Seminal Fluid: ►semen, ►sperm

Seminal Root: The root of the embryo in plant seeds. ►root

Seminoma: Same as spermatocytoma.

Semio: In association with additional terms indicates signals or symptoms, e.g., semiochemicals such as pheromones or semiology, i.e., symptomatology.

Semi-Ortholog: The duplicated copy of a single copy ortholog. ►orthologous loci

Semiotics: The study of signs and symbols. It is used in bioinformatics and communication. Organisms interpret their environment by the signs encountered. Medicine makes diagnoses on the bases of signs.

Semisynthesis of Proteins: Non-natural amino acids, e.g., norvaline and homoserine can be inserted at specific protein sites to explore the conformational and functional consequence of the alteration. Similarly, photoactivatable cross-linkers, fluorophores, alteration of the active site of enzymes by specific amino acid replacement, cassette mutagenesis, introduction of stable isotopes have been accomplished. Selective chemical ligation of unprotected peptides may be useful to preserve solubility. Proteins can be changed posttranslationally by removing inteins and religation the flanks through different chemical reactions. Protein transsplicing can use inteins that were split into N- and C-terminal sections, which are separately inactive but activity is gained by ligation. By chemical synthesis, the D and L enantiomorphs of the HIV-1 proteases have been prepared displaying reciprocal chiral specificity as a proteases and similar specificity for enzyme inhibitors (Milton RC et al 1992 Science 256:1445). Ligation via an intein permits the production of new types of proteins from different elements and insertion of amino acid analogs may result in a cytotoxic molecule (Evans TC et al 1998 Protein Sci 7:2256). Sequential steps can link

more than two elements. These engineered proteins have great theoretical and applied utility. ▶[homoserine](#), ▶[norvaline](#), ▶[active site](#), ▶[fluorophore](#), ▶[in-tein](#), ▶[cassette mutagenesis](#), ▶[expressed protein ligation](#), ▶[HIV-1](#), ▶[enantiomorph](#), ▶[chirality](#); Wallace CJ, Clark-Lewis I 1997 *Biochemistry* 34:14733; Muir TW 2003 *Annu Rev Biochem* 72:249.

Semisterility: Indicates that in an individual some gametes or gametic combinations are not viable when others are normal. Semisterility is common after deletion and duplication in the offspring of inversion and translocation heterozygotes but it may be caused by self-incompatibility, incompatible non-allelic combinations, cytoplasmic factors, fungal or viral infections, adverse environmental conditions, etc. ▶[chromosomal aberrations](#), ▶[mtDNA](#)

Semisynthetic Compounds: Natural products but chemically modified.

Semliki Forest Virus: A member of the alphavirus group. ▶[alphavirus](#)

Sendai Virus: A parainfluenza virus. In an ultraviolet light-inactivated form, it has been used to promote fusion of cultured mammalian cells or uptake of liposomes by its modifying effect on the lipids of the plasma membrane. ▶[cell genetics](#), ▶[cell fusion](#), ▶[cell membranes](#), ▶[polyethylene glycol](#), ▶[fusigenic liposome](#), ▶[alpha viruses](#)

senDNA: Mitochondrial DNA (ca. 2.5 kb), excised from the first intron of the *cox1* gene (cytochrome oxidase) and amplified in *Podospira anserina*. This and similar structures appear to be responsible for aging in vegetative cultures. ▶[aging](#), ▶[killer plasmids](#)

Senescence: The process of aging of organisms. At the cellular level, it has a somewhat different meaning. Cell senescence indicates how many cell divisions are expected on an average from isolated mammalian cells. Generally, cell senescence is correlated with the age of the individual and organism from where it was explanted. Human fibroblast cells under normal conditions cease to proliferate after about ± 50 divisions although individual lineages may vary. Normal human mammary epithelial cells are different as they fail to senesce as fibroblasts do but eventually they develop telomerase problems and chromosomal anomalies. It has been suggested that the activity of the telomerase enzyme slows down and causes this phenomenon. The irreversible arrest of proliferation is *replicative senescence*. The tumor-suppressor protein p53, the retinoblastoma protein (Rb1), cyclin-dependent kinase (Cdk) inhibitors such as p21^{CIP1/WAF1} and p16^{INK4a} are also involved. The disruption of p21^{CIP1/WAF1} leads to an escape of senescence by human fibroblasts. Some rodent cell

lines (glia oligodendrocyte precursor cells) may not senesce. In addition, cancer cells and human fibroblast cells fused to cancer cells may divide indefinitely. Hyper-replication of the DNA induced by oncogenes may also invoke senescence (Micco RD et al 2006 *Nature [Lond]* 444:638). Senescence involves the upregulation of genes that are clustered in the chromosomes (Zhang H et al 2003 *Proc Natl Acad Sci USA* 100:3251). Plant cells when provided with an appropriate regime of phytohormones may be maintained continuously and can even be regenerated into differentiated organisms. Senescence of plant cells is regulated by cytokinins, and the increase in cytokinin level inhibits the process of senescence. ▶[aging](#), ▶[agonescence](#), ▶[monoclonal antibody](#), ▶[apoptosis](#), ▶[tissue culture](#), ▶[embryogenesis somatic](#), ▶[cell cycle](#), ▶[hybridoma](#), ▶[senDNA](#), ▶[killer plasmids](#), ▶[Hayflick's limit](#), ▶[telomerase](#), ▶[telomeres](#), ▶[p53](#), ▶[p21](#), ▶[p16^{INK4a}](#), ▶[Ets oncogene](#), ▶[Id proteins](#), ▶[Cdk](#), ▶[retinoblastoma](#), ▶[mole](#), ▶[plant hormones](#); Romanov SR et al 2001 *Nature [Lond]* 409:633; Karlseder J et al 2002 *Science* 295:2446; He Y, Gan S 2002 *Plant Cell* 14:805.

Senescence, Replicative: After a certain number of replications due to dysfunction of the telomeres, proliferation ceases. When this process goes out of control, it may involve tumorigenesis.

Senior-Loken Syndrome (NPHP1, 2q13; NPHP3, 3q22; NPHP4, 1p36; IQCB1, 3q13.31-q21.2): A heterogeneous syndrome involved in chronic kidney disease of children. NPHP1 encodes nephrocystin protein. NPHP3, responsible for nephronophtosis recessive kidney disease, encodes a 1330 amino acid protein interacting with nephrocystin. NPHP4 encodes the 1426 amino acid nephroretinin protein, which interacts with nephrocystin. IQCB1/NPHP5 also encodes nephrocystin and the patients display simultaneously retinitis pigmentosa. (See Otto EA et al 2005 *Nature Genet* 37:282.

Sense-Antisense Genes: Overlapping genes. ▶[overlapping genes](#)

Sense Codon: Specifies an amino acid. ▶[genetic code](#)

Sense Strand: The DNA strand that carries the same nucleotide sequences as the mRNA, tRNA and rRNA (of course in the RNAs U stand in place of T). It does not carry an absolute meaning because of some cases both strands are transcribed although in context of a particular RNA it is correct. ▶[template strand](#), ▶[coding strand](#)

Sense Suppression: ▶[co-suppression](#), ▶[quelling](#), ▶[RNAi](#)

Sensillum: A cuticular sensory element; *sensilla campaniformia* are small circular structures along longitudinal veins of *Drosophila* wings (see Fig. S31). ▶*Drosophila*



Figure S31. Sensillum

Sensitivity: The percentage of correct identification of (carcinogens) on the basis of the (mutagenicity or other rapid) assay system. In DNA sequencing: the correctly predicted bases divided by total length of the cDNA. ▶accuracy, ▶specificity of mutagen assays, ▶predictability, ▶bioassays for environmental mutagens

Sensor Gene: Responsible for perceiving a signal. ▶signal transduction

Sensoryneural: Affecting the nerve mechanism of sensing.

Sensory Neuropathy 1 (HSN1): A dominant (human chromosome 9q22.1-q22.3) de-generative disorder of the sensory neurons, ulcerations and bone defects. A serine palmitoyltransferase subunit maps within the HSN1 gene and it is expressed in the dorsal root ganglia. ▶neuropathy, ▶pain-insensitivity, ▶hypomyelination, ▶ganglion; Bejaoui K et al 2001 Nature Genet 27:261.

Sensory Transduction: Mediates touch, heat and pain responses in the skin. Sensory neurons of A β , A δ or differently myelinated C fibers respond to the stimuli. Thermosensation is mediated through Transient Receptor Potential (TRP) families among them is the TRPV1 vanilloid transducer protein of capsaicin (present also in pungent peppers). Neuronal fibers evoke heat and pain sensation (nociception). TRPV2 is activated at temperatures above 52 °C. Other TRPVs respond to chemical stimuli. Cooling sensation (below 32 °C) is transduced by other TRPVs, TRPA (ankyrin family) and TRPNs. Mechanotransduction (touch responses) are sensed by A β or A δ nociceptors, depending on intensity of the stimulus and other factors. Different channels exit for osmolarity, stretch, different chemicals, auditory (stereocilia) and other functions. Keratinocytes, Merkel (tactile) cells respond also to shape and texture. Some of the mechanisms have polymodality and are integrated into circuits. Many of these functions can be now be studied by mutations (Lumpkin EA, Caterina MJ 2007 Nature [Lond] 445:858).

▶nociceptor, ▶capsaicin, ▶ion channel, ▶osmolarity, ▶deafness

Sentinel Phenotypes: These are used in human genetics to detect newly occurring mutations. These traits are supposed to be relatively easily detectable by direct appearance or clinical laboratory data can be obtained through routine examinations. Their frequencies are statistically evaluated for epidemiological information regarding possible increase in mutagenicity/carcinogenicity in an environment. ▶mutation in human populations, ▶epidemiology; Czeizel A 1989 Mutat Res 212:3.

Sentrin: A ubiquitin-carrier protein (known also under other names). ▶ubiquitin, ▶UBL, ▶SUMO, ▶PIC; Kahyo T et al 2001 Mol Cell 8:713.

Seq 1: A pleiotropic eukaryotic (yeast) strand exchange protein. ▶recombination in eukaryotes, ▶STP β

Sepal: The whorl of (usually green) leaves below the petals in a flower (see Fig. S32). ▶flower differentiation

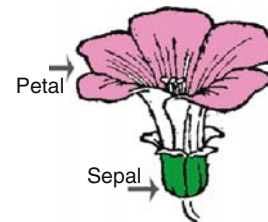


Figure S32. Sepal

Separins (Scc1, separase): Ubiquitous Esp1/Cut1-like proteins (~180–200 kDa), which are removed from their inhibitory association with securin by APC in order to separate the sister chromatids at anaphase. Separins may have endopeptidase-(cysteine proteases) like function. The Rec8 subunit of cohesin is cleaved by separin and consequently the meiotic chiasmata are resolved. The disjunction of the homologous chromosomes takes place during meiosis I. Separase also cleaves the kinetochore-associated protein Slk19 at the onset of anaphase. Slk stabilizes the anaphase spindle and assures an orderly exit from anaphase. The inner centromere-like protein–Aurora complex is regulated by the CDC14 phosphatase (Pereira G, Schiebel E 2003 Science 302:2120). ▶sister chromatid cohesion, ▶co-orientation, ▶Rec8, ▶Scc1, ▶mitosis, ▶chiasma, ▶cohesin, ▶securin, ▶shugoshin, ▶APC, ▶anaphase, ▶Aurora, ▶CDC14, ▶kinetochore, ▶spindle, ▶FEAR; Hauf S et al 2001 Science 293:1320; Sullivan M et al 2001 Nature Cell Biol 3:771.

Sephadex: An ion exchanger or gel-filtration medium on cross-linked dextran matrix. ▶[dextran](#), ▶[gel filtration](#)

Sephardic: Jews who moved to Spain after the Roman occupation of Israel and then in the Middle Ages to Western European countries. ▶[Ashkenazim](#), ▶[Jews and genetic diseases](#)

Sepharose: The anion exchanger of agarose matrix such as DEAE (diethylaminoethyl) sepharose.

Sepsis: Bacteria or bacterial toxins in the blood stream, resulting in potentially fatal condition. Sepsis induces apoptosis of the lymphocytes by the action of caspases. Caspase inhibitors or introduction or stimulation of Bcl-2 may improve survival. Caspase 12 exists in both short and long forms by genetic determination. The long form may be less effective in controlling the innate reaction of inflammation and thus in sepsis. Inflammation is the first step in the immune reaction and it is controlled by cytokines. Bacterial clearance and sepsis resistance is found in mice deficient in caspase-12 (Saleh M et al 2006 Nature [Lond] 440:1064). ▶[apoptosis](#), ▶[Bcl](#), ▶[lymphocyte](#), ▶[caspase](#), ▶[sepsis](#), ▶[caspase](#); Hotchkiss RS et al 2000 Nature Immunol 1:496; Saleh M et al 2004 Nature [Lond] 429:75.

Septal: The adjective for septum (dividing structure, a wall).

Septate: Separated by cross walls (septa) (see Fig. S33).



Figure S33. Septate fungal mycelium

Septation: ▶[tubulins](#)

Septic Shock: A bacterial lipopolysaccharide endotoxin-induced hypotension leading to inadequate blood supply to several organs; it is potentially fatal. Neutralizing MIF may alleviate it. The inflammatory responses are amplified by the triggering receptors (TREM) on neutrophils and monocytes. ▶[MIF](#); Patel BM et al 2002 Anesthesiology 96:576.

Septins: Rather ubiquitous polarizing GTPase (38–52 kDa GTP-binding) proteins, found in organisms from fungi to humans. In yeast, septins form hourglass-shaped pure proteins in between mother and daughter cells and mechanically mediate cytokinesis and growth (see Fig. S34) (Vrabioiu AM, Mitchison TJ 2006 Nature [Lond] 443:466). A human septin gene is at 17q25.3. Septin deficient spermatozoa are defective in movement because the kinesin-mediated

intraflagellar transport of sperm stalls in this case, although fertility is rescued if the spermatozoa are injected into the oocytes (Ihara M et al 2005 Dev Cell 8:343). ▶[congression](#), ▶[cytokinesis](#); McIlhatton MA et al 2001 Oncogene 20:5930.



Figure S34. Hourglass-shaped septin

Septooptic Dysplasia (SOD, De Morsier syndrome, 3p21.2-p21.1): A relatively rare disorder involving optic nerve and pituitary gland hypoplasia and absence of the septum pellucidum (the double membrane separating the anterior horn and the lateral ventricles of the brain in the median plane bounded by the corpus callosum). A phenotype is quite variable. The molecular basis is deficiency in pituitary hormone production due to mutation in the HESX1 gene. ▶[pituitary](#); Carvalhjo LR et al 2003 J Clin Invest 112:1192.

Sequatron: An automated high performance DNA sequencing apparatus (Hawkins TL et al 1997 Science 276:1887). ▶[sequenator](#), ▶[DNA chips](#), ▶[SAGE](#), ▶[DNA sequencing](#)

Sequenase: A genetically engineered DNA polymerase. It combines the 85 kDa protein of phage T7 gene 5 and the 12 kDa *E. coli* thioredoxin protein (the latter keeps it associated with the template). The 3' → 5' exonuclease activity is suppressed. It synthesizes about 300 nucleotides per second, and it is used for DNA sequencing and oligolabeling. ▶[DNA sequencing](#), ▶[oligo-labeling probes](#)

Sequenator: An automated equipment that breaks up a protein sequentially, starting at the NH₂ terminus, into amino acids, identifies them by chromatography, and thus determines their sequence. ▶[amino acid sequencing](#)

Sequence Alignment: ▶[CLUSTAL](#), ▶[Sequin](#); multiple sequence alignments algorithm: <http://msa.cgb.ki.se/cgi-bin/msa.cg>; multiple alignment tools: <http://www.igs.cnrs-mrs.fr/Tcoffee/>; multiple alignment including codons, mismatches, pseudogenes: <http://coot.embl.de/pal2nal/>; multiple alignment tool with shuffled and repeated sequences: <http://aba.nbcr.net/>.

Sequence Analysis Toolkit, for genes: <http://www.migenas.org/home/index.jsp>.

Sequence Logo: A sequence logo graphically represents DNA and amino acid sequence patterns from a set of aligned sequences (see Fig. S35). A column of

stacked symbols represents each position of the alignment with its total height, reflecting the information content in this position by the Delila Software package. It displays aligned base sequences in bits, at each position by the height of the symbols <http://biodev.hgen.pitt.edu/enologos/>. (Diagram redrawn after Shaner M et al from web site: <http://www-lecb.ncifcrf.gov/~toms/logoprograms.html>).

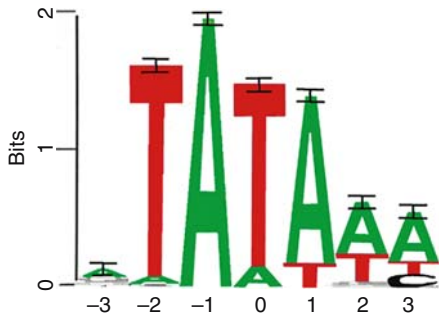


Figure S35. Sequence logo of 40 yeast TATA sites

Sequence Saturation Mutagenesis (SeSaM): To carry out SeSaM: 1. Generate DNA fragments of random length, 2. With the aid of terminal transferase add to the tails universal bases, 3. Elongate the fragments in a PCR to full length genes using a single-strand template and replace the universal base by standard one. Random mutations occur because the universal bases are promiscuous in pairing. ▶[terminal deoxynucleotidyl transferase](#), ▶[universal bases](#), ▶[polymerase chain reaction](#), ▶[mutagenesis](#); Wong TS et al 2004 Nucleic Acids Res 32(3):e26.

Sequence Skimming: In sequence skimming, a long DNA fragment is probed with some known genes in order to test whether the probes have homology and thus, a site within this long fragment chosen at random. ▶[probe](#); Elgar G et al 1999 Genome Res 9:960.

Sequence Space: The number of possible sequences of a particular length.

Sequence-Based Taxonomy: <http://www.ncbi.nlm.nih.gov/Taxonomy/taxonomyhome.html>.

Sequence-Tagged Connector (STC): ▶[genome project](#); Mahairas GG et al 1999 Proc Natl Acad Sci USA 96:9739.

Sequence-Tagged Site: ▶[sequenced tagged sites](#)

Sequenced Tagged Sites: Single-copy DNA regions (100–500 bp), for which polymerase chain reaction (PCR) primer pairs are available and can be used for DNA mapping. ▶[PCR](#), ▶[primer](#), ▶[expressed-sequence tag](#); Venichanon A et al 2000 Genome 43:47.

Sequencing: ▶[DNA sequencing](#), ▶[survey sequencing](#), ▶[protein sequencing](#), ▶[RNA sequencing](#), ▶[genome projects](#), ▶[deep sequencing](#)

Sequest: A software package for the analysis of mass spectral data of proteins/peptides (<http://fields.scripps.edu/sequest/>).

Sequester: To lay away or separate (into a compartment).

Sequin: A software tool for submitting nucleic acid sequence information to GenBank, EMBL, or DDBJ. It can be reached at <http://www.ncbi.nlm.nih.gov/Sequin/index.html>. ▶[GenBank](#), ▶[EMBL](#), ▶[DBJ](#)

SER (smooth endoplasmic reticulum): An internal flat vesicle system in the cytoplasm, involved in lipid synthesis. ▶[RER](#)

Serca: Sarcoplasmic reticulum Ca^{2+} ATPase. ▶[Brody disease](#), ▶[Darier-White disease](#)

SEREX (serological analysis of tumor antigens by recombinant expression cloning): SEREX screens cancer patients' own sera for (autologous) tumor cells in order to determine antigens (cDNAs), which may be used for antibody-mediated immunotherapy. ▶[cancer gene therapy](#), ▶[immunotherapy](#); Okada H et al 2001 Cancer Res 61:2625.

Serial Analysis of Gene Expression: In the serial analysis of gene expression, short DNA sequence tags are prepared from many cDNA clones and after forming concatamers the entire cDNA is sequenced.

Serine (Ser, S): An amino acid (β -oxy- α -amino-propionic acid, MW 105.09); it is soluble in water. RNA codons: UCU, UCC, UCA, UCG, AGU, AGC. Serine is derived from the glycolytic pathway (see Fig. S36).

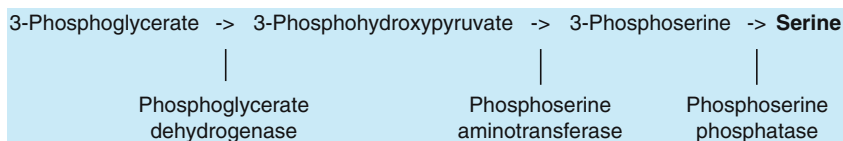


Figure S36. Serine biosynthetic path

Serine dehydratase enzyme, with pyridoxal phosphate prosthetic group, degrades serine into pyruvate and NH_4^+ . ▶amino acids, ▶amino acid metabolism, ▶oxalosis, ▶3-phosphoglycerate dehydrogenase

Serine Kinase: ▶MCF2 oncogene for serine phosphoprotein

Serine Protease: Serine protease degrades proteins in extracellular matrix and the family includes about 98 members and regulates many physiological reactions. ▶matrix, ▶kallikrein; Stoop AA, Craik CS 2003 Nature Biotechnol 21:1063.

Serine/Threonine Kinase: Serine kinase phosphorylates serine and tyrosine residues in proteins. Their receptors are transmembrane proteins and the kinases attach to the cytosolic carboxyl end of the receptors. ▶transforming growth factor β , ▶PIM oncogene, ▶PKS oncogene, ▶activin, ▶bone morphogenetic protein, ▶membrane proteins, ▶protein kinases, ▶receptor guanylyl cyclase, ▶signal transduction, ▶SMAD

Serine/Threonine Phosphoprotein Phosphatases: Serine phosphoprotein phosphatases remove phosphate from serine and threonine residues of proteins. *Protein phosphatase-I* is inhibited by cAMP by promoting the phosphorylation of a *phosphatase inhibitor protein* through protein kinase A. *Protein phosphatase IIA* is the enzyme most widely involved in dephosphorylation of the products of serine/threonine kinases. *Protein phosphatase-IIB* (calcineurin) is most common in the brain where Ca^{2+} activates it. *Protein phosphatase-IIC* plays only a minor role in the cells. The catalytic subunit of the first three is homologous but they also contain special regulatory subunits. *Phospholipase C* (PLC) may be coupled to G-proteins and upon its activation the level of Ca^{2+} increases. This cation mediates numerous cellular reactions. ▶serine/threonine kinases, ▶phosphorylases, ▶signal transduction, ▶regulation of gene activity

Serine/Threonine Protein Kinase: ▶serine/threonine kinase

Seripauperines (PAU): A large group of proteins in eukaryotes, conspicuously low in serine and having amino-terminal signal sequence. Their function is still unknown. They are encoded at subtelomeric sites in all yeast chromosomes. ▶signal sequence; Coissac E et al 1996 Yeast 12:1555.

Seroconversion: As per seroconversion, new antibody production against an antigen alters the serological state.

Serodeme: A particular type of antigen produced by a clone. ▶antigen

Serology: Serology deals with antibody levels and with the reactions of antigens. ▶serum; serological classification: <http://fred.bioinf.uni-sb.de/sepacs.html>.

Seronegative: A seronegative fails to display antibodies against the antigen in question.

Seropositive: In a seropositive, reactive antibody to an antigen is present in the serum.

Seroswitch Vector: In a seroswitch vector, the epitope of the viral coat protein can be changed to evade the adverse serological reaction against it, in cases when the same passenger DNA must be used repeatedly, e.g., in cases of adenoviral vectors. ▶adenovirus, ▶epitope, ▶serotype

Serotonin (5-hydroxytryptamine): A tryptophan-derived neuro-transmitter modulates sensory, motor, and behavioral processes (including also feeding behavior) controlled by the nervous system (see Fig. S37). Hydroxytryptamine 2B receptor also regulates the cell cycle by interacting with the tyrosine kinase pathway through the phosphorylation of the retinoblastoma protein and the activation of cyclin D1/Cdk4 and cyclin E/Cdk2. Cyclin D1, in concert with other proteins, induces also the MAPK pathway. The 5-hydroxytryptamine receptor 5-HT_{1B} binds protein p11 and in a mouse model seems to alleviate depression. Triptan drugs used for treatment of migraine seem to act as a 5-HT_{1B} agonist (Sharp T 2006 Science 311:45; Svenningsson P et al 2006 Science 311:77). Serotonin transporter (SERT) is a polytopic membrane transporter with 12 transmembrane domains. The 5-HT_{3A} receptor is a large-conductance neuronal serotonin channel. Low activity of 5-HT serotonin transporter may cause a propensity to psychiatric disorders (Ansorge MS et al 2004 Science 306:879). ▶neurotransmitters, ▶glucocorticoid, ▶obesity, ▶substance abuse, ▶alcoholism, ▶cocaine, ▶cyclins, ▶Cdk, ▶MAPK, ▶retinoblastoma, ▶migraine

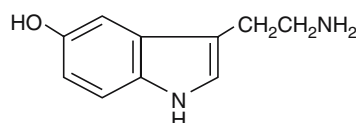


Figure S37. Serotonin

Serotype: A serotype is distinguished from other cells by its special antigenic properties. ▶antigenic variation, ▶capsule

Serovar: Same as serotype.

Serpentine Receptors: Seven-membrane spanning receptors. ▶seven membrane proteins

Serpines (serine-protease inhibitors, 14q32.1): Serpines, when mutated, may be responsible for emphysema, thrombosis, and angioedema. Viral infection may counteract them. The accumulation of neuroserpin caused by mutation leads to a familial encephalopathy with neuroserpin inclusion bodies (FENIB), a dementia. There are about 500 serpins of 350–500 amino acid residues. They occur in all organisms from mammals, to plants, to viruses. Serpin, SRPN6 seems to control innate resistance in *Anopheles* against *Plasmodium* (Abraham EG et al 2005 Proc Natl Acad Sci USA 102:16327). ▶maspin, ▶C1 inhibitor, ▶Hsp [Hsp47], ▶L-DNase II, ▶emphysema, ▶thrombosis, ▶angioedema, ▶encephalopathy, ▶antitrypsin, ▶malaria, ▶*Plasmodium*; Atchley WR et al 2001 Mol Biol Evol 18:1502; Silverman GA et al 2001 J Biol Chem 276:33293; Crowther DC 2002 Hum Mut 20:1; Lomas DA, Carrell RW 2002 Nature Rev Genet 3:759.

Serprocidin: ▶antimicrobial peptides

Sertoli Cells: ▶Wolffian ducts

Serum: The clear part of the blood, from which the cells and the fibrinogen have been removed; the clear liquid that remains of the blood after clotting. The immune serum contains antibodies against specific infections. It differs from plasma, which is the non-particulate portion of cells. ▶plasma, ▶antibody production, ▶serology

Serum Dependence: As per serum dependence, animal cells may grow or differentiate only or preferentially in cultures containing serum.

Serum Response Element (SRE): A DNA tract that assures transcriptional activation in response to growth factors in the serum. ▶SRE, ▶CARG box

Server (web server): The server delivers information available on the internet with the aid of computer programs.

S

Sesame (*Sesamum indicum*): An oil seed crop with about 37 related species; the cultivated form is $2n = 2x = 26$ but related species may have $x = 8$ and different levels of ploidy.

Sesquidiploid: A sesquidiploid contains a diploid set of chromosomes derived from one parent and a higher-number set from the other. ▶allopolyploid, ▶allopolyploid segmental

Sessile: A sessile plant is attached directly to a base without a stalk.

SET Motifs (Su[var3-9]-enhancer-of-zeste-trithorax): originally named after the three *Drosophila* regulatory proteins where they occur and modulate chromatin structure and thus gene expression. Set2 is a methyltransferases enzyme. So far the products of

at least 20 genes display such a domain with an apparent role in epigenesis/development. The *polycomb* gene of *Drosophila*, yeast telomeric silencing, heterochromatin-mediated gene silencing, variegation position effects (PEV), as well as, the Mll factors involve SET domains. ▶chromodomain, ▶integration, ▶transcription, ▶Mll, ▶w locus, ▶Polycomb, ▶Sbfl, ▶epigenesis, ▶methyltransferase; Baumbusch LO et al 2001 Nucleic Acids Res 29:4319.

Set Point, Viral: The level of circulating virus in the plasma during the nonsymptomatic phase preceding the progression to AIDS (Fellay J et al 2007 Science 317:944). ▶acquired immunodeficiency

Set Recoding: ▶fuzzy inheritance

Seta: Bristles, stiff hairs of animals or plants.

SETGAP (selectable expression of transient growth-arrest phenotype): A system suitable for the isolation of genes that interfere with the expression of certain other genes or genetic pathways. ▶negative regulator; Pestov DG, Lau LF 1994 Proc Natl Acad Sci USA 91:12549.

Sevenless (sev): X-chromosomal gene (1-33.38) of *Drosophila* controlling the R7 rhabdomeres and thus altering the photoreceptivity of the eye. The carboxy terminal of the protein product of the wild type allele shows homology to the tyrosine kinase receptor of *c-ras*, *v-src*, and EGF. ▶photoreceptor, ▶rhodopsin, ▶signal transduction, ▶ommatidium, ▶compound eye, ▶daughter of sevenless, ▶RAS, ▶EGF, ▶BOSS, ▶rhabdomere

Seven-Membrane Proteins (7tm): Integral parts of the plasma membrane that span the membrane by seven helices; they are important in signal receptor binding and in association with G-proteins. More than 800 genes encode these most versatile receptors of chemokines, hormones, neurotransmitters, odorants, and taste and light signals. Heteromeric G proteins, β -arrestin, and GRK family of proteins mediate the signal transmission to 7tm protein receptors. ▶signal transduction, ▶G-protein, ▶transmembrane receptors, ▶arrestin, ▶GRK; Pierce KL et al 2002 Nature Rev Mol Cell Biol 3:639.

Seven-Pass Transmembrane Proteins: Same as seven membrane protein.

Severe Combined Immunodeficiency (SCID): A less frequently occurring (0.00001-0.00005) autosomal disease than the X-linked agammaglobulinemia, but it is generally lethal before age two. The thymus is abnormally small and therefore there is a severe deficiency of the T- and sometimes also the B-lymphocytes. The afflicted infant cannot overcome infections. SCID-X1 may be effectively treated by

gene therapy but cancerous growth may ensue when the retroviral vector is inserted in the vicinity of the promoter of the LMO2 proto-oncogene (Hacein-Bey Abina S et al 2003 Science 302:415). In some cases, viral infection may severely damage the thymus, and this non-hereditary disease may closely mimic the symptoms of SCID. The DNA-dependent kinase (p350), encoded in human chromosome 8q11, is most likely responsible for SCID-1. A gene in chromosome 10p of humans interferes with the V(D)J recombination system and thus prevents normal function of both B- and T-lymphocytes (Moshous D et al 2001 Cell 105:177). Several other gene loci may also be involved in the development of the disease. SCID mouse devoid of T and usually also B-lymphocytes can accept human grafts and can be used to create a partial human immune system in the mouse. The most common form of it is X-chromosome-linked (Xq13). In about 40% of the cases, there is adenosine deaminase deficiency. T cell deficiency may be treated by the transplantation of hematopoietic cells. ADA may be corrected by gene therapy (Fischer A et al 2001 Immunity 15:1). In some cases, transplantation of thymus tissues may lead to improvement. ►[agam-maglobulinemia](#), ►[hypogammaglobulinemia](#), ►[immunodeficiency](#), ►[SCID](#), ►[DNA-PK](#), ►[adenosine deaminase deficiency](#), ►[gene therapy](#)

Sewall Wright Effect: Same as drift genetic.

Sex: In eukaryotes, sex makes possible the production of two kinds of gametes and it is the requisite of syngamy. By recombination and by promoting linkage equilibrium, sex facilitates selection of adaptive variation and provides a means for elimination of deleterious genes. In prokaryotes and viruses, “sex” is recombination. The majority of species reproduce sexually and the relatively few asexual species seem to represent dead ends in evolution. The tiny *Bdelloid* freshwater rotifers are exceptional because they survived and evolved for 35–40 million years without sex. The *genetic sex* in the female is determined by the X chromosome(s) whereas the Y chromosome carries the male determining genes. The *gonadal sex* is represented by the ovarian differentiation in the female and the testicular differentiation in the male. *Somatic sex* is gonadally controlled. Female differentiation takes place—irrespective of the chromosomal constitution—if the gonads are removed during early fetal development. The anti-Müllerian hormone synthesized by the Sertoli cells and the fetal androgens (testosterone, androstenedione) synthesized by the Leydig cells normally suppress female differentiation. The fetal female gonads have no effect on the female somatic sex development. In the gonadless genital tract of both sexes, the Müllerian ducts are maintained but the Wolffian ducts degenerate. Estrogen synthesized by the

female may adversely affect the male type differentiation. The anti-Müllerian hormone apparently blocks, however, an enzyme (aromatase) required for feminization and in this case the somatic sex shifts towards the direction of masculinization. ►[gender](#), ►[sex cell](#), ►[syngamy](#), ►[copulation](#), ►[sex determination](#), ►[recombination](#), ►[linkage](#), ►[meiosis](#), ►[Wolffian ducts](#), ►[Müllerian ducts](#), ►[gonads](#), ►[sex hormones](#)

Sex Allocation: The variation in sex ratio in favor of males or females due to non-chromosomal sex-determining mechanisms such as exist in social insects, and are caused by colony size, mating behavior, and available resources. ►[sex determination](#), ►[sex ratio](#)

Sex Bias in Disease Phenotype: As per the sex bias, one or the other sex is more likely to express the disease. ►[Rett syndrome](#), ►[imprinting](#)

Sex Bias in Mutation: ►[mutation rate](#)

Sex Bivalent: In the sex bivalent, the X and Y chromosomes have homology only in the short common segment where they can pair and recombine. ►[pseudoautosomal](#)

Sex Body (XY body): A structure associated with both the X and the Y chromosomes. For its formation, the H2AX (a histone 2A variant) is required apparently for chromatin remodeling. The sex body inactivates both the X and Y chromosome during the pachytene stage of sperm formation and is involved in gene silencing. The sex body presumably protects against illegitimate chromosome association and thus, aneuploidy (McKee BD, Handel MA 1993 Chromosoma 102:71). ATR localizes, under BRCA1, to the XY chromatin and after phosphorylating histone H2AX, the sex body is formed (Turner JMA et al 2004 Curr Biol 14:2135). In H2AX deficiency the males but not the females are infertile. ►[ATR](#), ►[breast cancer](#), ►[Meisetz](#), ►[histone variants](#), ►[pachytene](#); Fernandez-Capetillo O et al 2003 Dev Cell 4:497.

Sex Cell: A gamete that can fuse with another sex cell of the opposite mating type (sperm, egg) to form a zygote. ►[zygote](#), ►[mating type](#), ►[gamete](#), ►[isogamy](#)

Sex Chromatin: ►[Barr body](#)

Sex Chromosomal Anomalies in Humans: Sex chromosomal anomalies are of various types and they may occur at a frequency of 0.002 to 0.003 of all births. *Females:* X0, XXX, XXXX, XXXXX, X0/XX, X0/XXX, X0/XXX/XX, XX/XXX, X0/XXY, XXX/XXXX, XXX/XXXX/XX and *males:* XX, XYY, XXY, XXYY, XXXY, XXXYY, XXY/XY, XYY/XYYY, X0/XXY/XY, XXYYY/XY/XX, XXXY/XXXXY. Other, even more complicated types have been reported. The most common mechanism by

which these anomalies occur is nondisjunction in meiosis and mitosis. The more complex type mosaics (indicated by /) are the result of repeated non-disjunctional events. The XO condition is called *Turner syndrome*, the XXX is *triplo-X*, while XXY and other male conditions with multiple X and Y(s) are generally referred to as Klinefelter syndrome along with the XX males, which have a Y-chromosome translocation to another chromosome. Similar sex-chromosomal anomalies have been identified in various other mammals. The XO condition results in an abnormal female in humans and mice but in a normal male in grasshopper or *Caenorhabditis*, and in an abnormal male in *Drosophila*. ▶*trisomy*, ▶*chromosomal sex determination*, ▶*Turner syndrome*, ▶*Klinefelter syndrome*, ▶*triplo-X*, ▶*XX males*, ▶*gynandromorph*, ▶*testicular feminization*

Sex Chromosome: The sex chromosome is unique in number and/or function to the sexes (such as X, Y or W, Z); see ▶*chromosomal sex determination*. In the heterogametic sex, the X and Y chromosomes pair and may recombine in a relatively short terminal region although in the heterogametic sex in insects recombination is practically absent, except when transposable elements function. ▶*PAR*, ▶*sex determination*

Sex Circle Model of Recombination: The basic tenets of the sex circle model of recombination in fungi, according to F.W. Stahl (1979 Genetic Recombination. Freeman, San Francisco, California), are: 1. Any marker can recombine either by reciprocal exchange or by gene conversion. 2. Close markers are more likely to recombine non-reciprocally. 3. Gene conversion observes the principle of parity. 4. Gene conversion is polar. 5. In half of the cases, gene conversion is accompanied by classical exchange of outside markers. 6. Reciprocal recombination is always accompanied by exchange of outside markers. 7. Conversion that does not involve outside exchange shows no interference of flanking genes. 8. Gene conversion accompanied by outside marker exchange may also involve interference. 9. Conversion asci (5:3, 6:2) obey the principles listed under 1 to 8. 10. All markers (except deletions, and a small fraction of conversion alleles) can segregate post-meiotically. 11. The very rare aberrant 4:4 conversion asci may be the results of two events. ▶*recombination*, ▶*gene conversion*

Sex Comb: Special structures on the metatarsal region of the foreleg of *Drosophila* male (see Fig. S38). ▶*Drosophila*



Figure S38. Sex comb

Sex Controlled (sex influenced): The degree of expression of a gene is determined by the sex (e.g., baldness is more common in human males than females). ▶*Hirschsprung's disease*, ▶*Huntington's disease*, ▶*imprinting*

Sex Determination: In dioecious animals and plants, sex is usually determined by the presence of two X (female) and XY (male) chromosomal constitution, respectively. In other words, the females are homogametic (i.e., the eggs all carry an X chromosome) and the males are heterogametic (i.e., they can produce sperm with either X or Y chromosomes). Exceptionally XX individuals may be males if the sex-determining section of the Y chromosome is translocated to an X. An XY individual can be a female if from the Y chromosome the sex-determining part of her Y chromosome was lost. In some species, e.g., birds and moths, the females are heterogametic (WZ) and the males are homogametic (ZZ). In the nematode *Caenorhabditis*, some grasshoppers, and some fishes, the females are XX and the males are of XO (single X) constitution. In *Drosophila*, the proportion of the X chromosome(s) and autosomes (A sets) determines sex. Normally, if the ratio is 1 X:2 sets of autosomes, the individual is male; if there are 2 Xs:2 sets of autosomes, the fly is female. All individuals with a sex ratio above 1 are also females and those with a ratio between 0.5 and 1 are intersexes. XO human and mouse individuals are females, however, and irrespective of the number of X chromosomes, as long as there is at least 1 Y chromosome, they appear male. In hermaphroditic plants the development of the gynoecia and androecia are determined by one or more gene loci. Actually, in *Drosophila* three major and some minor genes are known to control sex. *Sexlethal* (*Sxl*, 1-19.2) can mutate to recessive *loss-of-function* alleles that are deleterious to females but inconsequential to males. The dominant *gain-of-function* mutations do not affect appreciably the females but are deleterious to males. The *Sxl* locus may produce ten different transcripts. Three transcripts (4.0, 3.1 and 1.7 kb) are expressed at the blastoderm stage. Adult females have four transcripts (4.2, 3.3, 3.3, and 1.9 kb); the latter two are missing or reduced if the germline is defective. Adult males display three transcripts (4.4, 3.6 and 2.0 kb). The *Sxl* transcripts are alternatively spliced and functional in the

female and are non-functional in the male. The *Sxl* gene product is apparently required for the maintenance of sexual determination and the processing of the downstream *tra* (*transformer*, 3-45) gene product. The *Sxl* protein (354 amino acids) controls alternative splicing of the *tra* pre-messenger RNA by binding to a polypyrimidine tract (UGUUUUUUU) of a non-sex-specific 3' splice site of one *tra* intron. This binding then prevents the binding of the U2AF general splicing factor binding to the site, and U2AF is forced then to a female-specific 3' splice site. The *Sxl* protein binds also to its own pre-mRNA and promotes its female-specific splicing. The *Sxl* locus is regulated by other known genes: *da* (*daughterless*, 2-41.5) is a positive activator of *Sxl*, and it is suppressed by the gain-of-function mutations of the latter gene. The expression of *da*⁺ is necessary for the proper development of the gonads of the female in order to form viable eggs. In both sexes, the product of *da*⁺ is required also for the development of the peripheral and central nervous systems and the formation of the cells that determine the adult cuticle. Thus, the *da*⁺ gene has both maternal and embryonic influence. Females heterozygous for the *da*¹ mutations produce sterile or intersex males and masculinize the exceptional daughters, which are homozygous for *male* (*maleless*, 2-55.2); *male* is lethal to single X males but has no effect on XX females. The *DA* gene product is a helix-loop-helix protein with extensive homology to the human κE2 enhancer (human chromosome 19p13.3-p13.2) of the κ-chain family of immunoglobulins. Chromosomally, female (XX) flies homozygous for the third-chromosome recessive *tra* mutations become sterile males. XXY *tra/tra* individuals are also sterile males but XY *tra/tra* males are normal males. A 0.9 kb transcript of the locus is female-specific and is required in the female, and another 1.1 kb RNA is present in both sexes but no functions are known and is probably not essential. The splicing of the *tra* transcripts is controlled by *Sxl* gene products. When the 0.9 transcript is expressed in a XY fly, the body resembles that of a female. Another *tra* locus (*transformer 2*, 2-70) regulates spermiogenesis and mating in normal males. Null mutations of *tra2*, when homozygous, transform XX females into sterile males. Actually, the *tra2* gene products seem to mediate the splicing of the *dsx* (*double sex*, 3-48.1) transcripts. Dominant mutations at the *dsx* locus when heterozygous with the wild type allele change XX individuals into sterile males but they have no effect on XY males. Null alleles of *dsx*, when homozygous, transform XX flies into intersexes. The recessive allele *dsx11* transforms XY flies into intersexes, and the null alleles change both XX and XY flies into intersexes. Germline sexual differentiation is not affected by the normal allele of this gene but it is controlled by the X: autosome

ratio. A 3.5 kb female-specific transcript is present in the larvae and adults. In the larvae, 3.8 and a 2.8 kb male-specific transcripts are detectable and by adult stage, in addition, a 0.7 kb RNA also appears. The *ix* (*intersex*, 2-60.5) mutations when homozygous also change the XX flies into intersexes. Homozygous *ix* XY males appear normal morphologically but their courtship and mating behavior is altered. Thus, sex determination in *Drosophila* appears to follow the cascade and *fru* regulates mating behavior and sexual orientation through the *tra* and *tra2* genes:

In summary: the X:autosome ratio is the trigger mechanism for the alternate sex developmental pathways. In the males, the *Sxl* and *tra* genes are expressed but their transcript is not spliced to functional forms (see Fig. S39). The critical male sex-determining function is attributed to locus *dsx*, which in the wild type produces a protein blocking the genes required for female development. In the females, with a chromosomal constitution of 2X:2A sets, a functional *Sxl* product is manufactured that mediates the female-specific splicing of its own transcripts. The *Sxl* protein mediates then the splicing of the *tra* transcripts, leading to the synthesis of a Tra protein, which along with the Tra2 protein directs the female-specific splicing of the *dsx* transcript. The synthesized DSX protein blocks then all the genes with functions that would be conducive to male development. Sex determination in *Caenorhabditis* is different from that in *Drosophila*, probably because the XX individuals are hermaphrodites and the nondisjunctive gametes lead to the development of the rare XO males. The level of expression of the known sex-determination genes is shown in Figure S40.

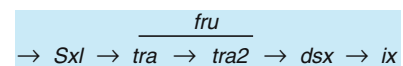


Figure S39. Major sex genes in *Drosophila*

Early in the pathway, *fox* (female X) acts as a numerator of the X-chromosomes, and 5 X-linked *dpy* (*dumpy*) alleles regulate dosage compensation. The hermaphroditic XX females of *Caenorhabditis* originally may produce sperm, oocyte production is then switched on. The *fem-3* gene turns on sperm production in the XX animals. The 3'-untranslated region of the mRNA of the *fem-3* gene mediates the switch after the cytoplasmic binding factor FBF protein binds to this region.

Six *mog* genes are important regulators of female ⇌ male switching. In XX *Caenorhabditis*, the sex determination complex protein (SDC-2) blocks the expression of the male-determining gene *her-1* and in that state hermaphrodites are formed. The SDC-2

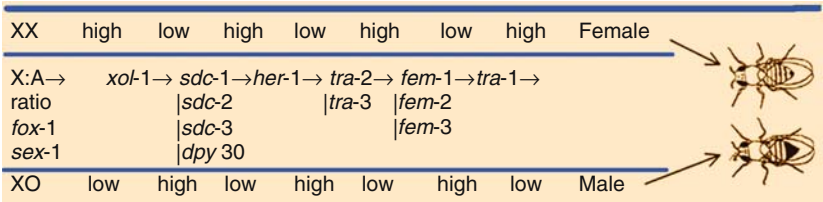


Figure S40. Sex chromosome: autosome ratio. (Diagram modified after Kuwabara, PE & Kimble, J 1992. *Trends Genet* 8:164.)

recruits to the X chromosome SDC-3, DUMPY (dpy), MIX-1 (mitosis and X), and other proteins, resulting in the reduced expression of the X chromosomal genes; thus, dosage compensation is realized. In the XO males, *her-1* is transcribed and the SOC complex does not attach to the single X chromosome and all its genes are expressed normally. Sex determination in mammals is much more complex and the pathway is not entirely clear. For a number of years, the H-Y antigen was thought to have a major role but this turned out to be an incorrect notion. A major critical difference was found in an 11 amino acid segment of SMCX (structural maintenance chromosome X) and SMCY proteins encoded within the X and Y homology region. The genes DMRT1 and 2 in the short arm of human chromosome 9 have homologs in other mammals. Also, the Z chromosomes in chicken, alligators, *Drosophila*, and *Caenorhabditis* display higher expression in the male gonads than in the female gonads and appear to be basic regulators of sexual dimorphism. Sex chromosomal anomalies in humans generally also lead to mental retardation. In several reptiles, sex is determined by the temperature the eggs are exposed to during incubation in the sand they are laid in. Thus climate change and vegetation change can affect population structure in these animals (Kamel SJ, Mrosovsky N 2006 *Ecol Appl* 16:923). The actual manifestation of sex may be deeply affected by endocrine hormones directly or indirectly through environmental pollutants. In *Plasmodium* (causing malaria), induction of blood formation favors an increased production of the male parasite. In both plants and some hermaphroditic animals, stress conditions promotes maleness (Hughes RN et al 2003 *Proc Natl Acad Sci USA* 100:10326). ▶mating type determination in yeast, ▶freemartins, ▶hormones in sex determination, ▶fru, ▶gynandromorphs, ▶chimera, ▶intersex, ▶fat body, ▶hermaphrodite, ▶testicular feminization, ▶sex hormones, ▶pheromones, ▶accessory sexual characters, ▶sex phenotypic, ▶mental retardation, ▶chromosomal sex determination, ▶X-chromosome

counting, ▶mealy bug, ▶dosage compensation, ▶Msl, ▶Mle, ▶transsexual, ▶H-Y antigen, ▶SRY, ▶sex-selection, ▶mating type determination in yeast, ▶Schizosaccharomyces pombe, ▶F plasmid, ▶sex plasmid, ▶Hfr, ▶sex-chromosomal anomalies in humans, ▶social insects, ▶Sciara, ▶schistosomiasis, ▶sex determination in plants, ▶Rumex, ▶sex-reversal, ▶pseudoautosomal, ▶amelogenin test, ▶arrhenotoky, ▶complementary sex determination, ▶numerator, ▶Plasmodium, ▶mealy bug, ▶haploid; for sex determination in *Caenorhabditis* see Meyer BJ 2000 *Trends Genet* 16:247; Mittwoch U 2001 *J Exp Zool* 290:484; Koopman P 2001 *Cell* 105:843; Vilain E 2000 *Annu Rev Sex Res* 11:1; Goodwin EB, Ellis RE 2002 *Curr Biol* 12:R111; Hodgkin J 2002 *Genetics* 162:767; detailed review of the molecular mechanism of sex determination in *Drosophila*: Black DL 2003 *Annu Rev Biochem* 72:291; sex chromosome evolution in mammals: Marshall Graves JA 2006 *Cell* 124:901.

Sex Determination in Plants: In dioecious plants, sex determination is very similar to that in animals (▶sex determination). In monoecious and hermaphroditic plants, sex is controlled without the presence of special chromosomes and a number of genes (nuclear, mitochondrial, and plastidic) involved in morphogenesis, phytohormone synthesis, and environmental responses determine the differentiation of the flowers and the oogenesis (female) and microsporogenesis (male), and therefore, sexuality. Genes are known that are similar to those of sex reversal in animals and feminize or masculinize, respectively, the monoecious or hermaphroditic flowers (e.g., *tassel seed*, *silkless* [in maize], *superman*, *gametophyte female* [in *Arabidopsis*], etc.). *Tasselseed 2* encodes a short-chain alcohol dehydrogenase that is involved in stage-specific floral organ abortion. Gibberellic acids, brassinosteroids, ethylene, chromosome-breaking agents, and mutagens may also influence the expression of sexual development as well as temperature regimes and other environmental factors. ▶gametophyte, ▶gametophyte factors, ▶vernalization,

►photoperiodism, ►self-incompatibility, ►flower differentiation, ►phytohormones; Juarez C, Banks JA 1998 *Curr Opin Plant Biol* 1:68.

Sex Differences: Sex differences vary among phylogenetic groups in both morphology and function. In humans, the chromosomal constitution (XX, XY) is different. The more than single X chromosome generally undergoes lyonization. The ribosomal protein RPS4Y encoded by the Y chromosome is different from the X chromosome RPS4X. The relative level of hormones depends on sex; the ovaries produce more estrogen and progesterone (correlated with incidence of breast cancer). Reduction of the natural supply of estrogen may involve reduced memory and increase autoimmune disorders in females. Other, phenotypic differences are obvious. A survey of the expression of 13,977 mouse genes in males and females indicated differences besides the reproductive tissues; differences were also found in the kidney and liver genes involved in drug and steroid metabolism and osmotic regulation (Rinn JL et al 2004 *Dev Cell* 6:791). Sex hormones quantitatively affect the expression of many genes involved in different metabolic functions and disease (Weiss LA et al 2006 *Nature Genet* 28:218). ►sex, ►sex determination, ►lyonization, ►estrogen, ►androgen, ►autoimmune diseases, ►gender; human sex differences between men and women: Federman DD 2006 *N Engl J Med* 354:1507.

Sex Differentiation: ►sex, ►sex determination

Sex, Evolutionary Significance: It has generally been assumed that sex facilitates the purging of linked deleterious parental genes by recombination. But Keightley, P.D. and Eyre-Walker, A. (*Science* 290:331) arrived to the conclusion that sex is not maintained by its ability to purge deleterious mutations. Sex may be disadvantageous for evolution. Experimental evidence in yeast supports the advantage of sex in selective environment (Goddard MR et al 2005 *Nature [Lond]* 434:636). Sex selects for robustness and evolutionary advantage (Azevedo RBR et al 2006 *Nature [Lond]* 440:87). Acquisition of sex led to the evolution of diploidy, which is protective against the consequences of deleterious recessive mutations. ►sex, ►Kondrashov's deterministic model of evolution of sex; Rice WR, Chippindale AK 2001 *Science* 294:555; Kondrashov FA, Kondrashov AS 2001 *Proc Natl Acad Sci USA* 98:12089; Bachtrog D 2003 *Nature Genet* 34:215.

Sex Factor: A transmissible plasmid in bacteria that carries the fertility factor(s) F. ►F⁺, ►Hfr, ►F plasmid

Sex Hormones: Sex hormones have either estrogenic (female) or androgenic (male) influence. These are

steroids of the ovaries and placenta (estradiol, progesterone), the testes (testosterone), or of the adrenal cortex (cortisol and aldosterone). Gene expression patterns of the uterine luminal epithelial cells might be regulated by estradiol-17 β and inhibited by progesterone. Progesterone rapidly downregulated about 20 genes associated with DNA replication. Among the down-regulated group were all six minichromosome maintenance proteins (MCM), suggesting that replication licensing is a key in sex steroid hormone regulation of cell proliferation in the uterus (Pan H et al 2006 *Proc Natl Acad Sci USA* 103:14021). Testosterone is also required in females, although in smaller amounts. Androgens control the reproductive organs but also affect hair growth (beard) and the early death of the hair follicles causing preferential male baldness. Androgens promote bone and increased muscle growth as well. Some of the synthetic "anabolic hormones," without androgenic effects, are used (illegally) by athletes to boost performance. Testosterones are also precursors of estrogens. Estrogens are formed in the female-specific organs and their targets include the mammary glands, bones, and fat tissues. Estrogen synthesis is regulated by the follicle-stimulating hormone (FSH) of the anterior pituitary. The pituitary luteinizing hormone mediates the release of the egg, and progesterone is required for the maintenance of pregnancy. The administration of exogenous estrogens and progestins inhibit ovulation and can be used as contraceptives. Other compounds act by prevention of the fusion of the sperm with the egg or implantation of the egg in the uterus, e.g., the drug RU486. Before the development of the contraceptive pills, in the ancient world herbal medicine had been used, prepared from plants (berries of *Juniperus sabina*, gentiana) (see Fig. S41) that contained estrogens. Sperm production may be stopped by injection of progestin and androgen combinations, while inhibiting epididymal functions can prevent sperm maturation or may interfere with the release of enzymes required for breaking through the protective coat of the egg. Antiprogestins, antiestrogens, or other inhibitors of steroid biosynthesis and non-peptide antigonadotropin-releasing hormone antagonists may serve as female contraceptives. The steroid hormone-controlled sexual behavior is also mediated by neuronal activity. Prolonged use of steroid contraceptives or androgenic or anabolic steroids may increase the risk of liver, ovarian, or uterine carcinomas. There are several diseases or conditions (heart diseases, thromboses, embolism, diabetes, skin irritations, *Chlamydia* infection, etc.) where contraceptive drugs are not or conditionally permissive. In some conditions (ovarian and endometrial cancer, uterine myoma, rheumatoid arthritis, etc.), oral

contraceptives may be beneficial. Ethinylestradiol may occur in human females taking oral contraceptives and if they become pregnant accidentally (3%), the fetus is exposed to this compound. Bisphenol leached out from resin-coated lining of food and beverage containers, dental sealers, and polycarbonate plastic is also an estrogen. Male mouse fetus, when exposed to these substances, develops prostate duct abnormalities (Timms BG et al 2005 Proc Natl Acad Sci USA 102:7014). ▶animal hormones, ▶hormone receptors, ▶RU486, ▶bisphenol, ▶estradiol, ▶progesterone, ▶MCM, ▶hyperlipoproteinemia, ▶epididymis, ▶transsexual, ▶sex, ▶fertilization, ▶fertility, ▶infertility, ▶ART, ▶contraceptives



Figure S41. *Juniper*

Sex Influenced: ▶sex-influenced, ▶sex controlled, ▶imprinting

Sex Linkage: In sex linkage, various genes in the sex chromosomes are inherited with the transmission of that chromosome. Sex linkage in females is generally partial because the two X-chromosomes may recombine. The recombination between the X and Y chromosomes is limited only to the homologous (pseudoautosomal) regions. In some insects (*Drosophila*, silkworm), recombination even between autosomes is usually absent in the heterogametic sex. ▶recombination frequency, ▶recombination mechanisms, ▶crossing over, ▶hemophilia, ▶autosexing, ▶genetic equilibrium, ▶pseudoautosomal, ▶criss-cross inheritance; Morgan TH 1910 Science 32:120; Morgan TH 1912 Science 36:719.

Sex Mosaic: The sex-chromosomal constitution in the body cells may vary in a sectorial manner. Typical examples are the gynandromorphs in insects, which have body sectors with both XX and XO constitution. Sex mosaicism also occurs in humans with variable numbers of X and Y chromosomal sectors. The mosaicism is generally the result of non-disjunction or chromosome elimination. ▶sex determination, ▶non-disjunction, ▶gynandromorphs

Sex, Phenotypic: The phenotypic manifestations of the influence of the steroid sex hormones, such as facial hair, increased phallic size in males, horns or

special plumage in animals, and enlarged breast and mammary glands development in females. ▶sex determination, ▶animal hormones

Sex Pilus: ▶pilus

Sex Plasmid: The bacterial F plasmid. ▶F element, ▶F plasmid

Sex Proportion: The proportion of male individuals in a population. ▶sex ratio

Sex Ratio: The *primary sex ratio* is the number of male conceptuses relative to that of females. The *secondary sex ratio* indicates the number of females:males at birth. The *tertiary sex ratio* states the ratio among adult males and females. Since XX females are mated with XY males, the proportion—just as in a testcross—should be 1:1. In the United States, at birth the proportion is about 105–106 males:100 females. In the West Indies the proportion is about 1:1 or the number of females is slightly more. In China and Korea, the sex ratio in newborns is about 115 males to 100 females. Generally the female:male ratio shifts in favor of females by progressing age. By about 21–22, in the USA, the female:male proportion becomes about 1:1, and because of mortality differential of the sexes, by age 65 there are about 145 females for 100 males. In dioecious plants, the sex ratio may vary a great deal because of modifier genes and physiological factors (hormone supply). Since the 1930s, population geneticists have repeatedly considered the problem whether infanticide alters the sex ratio by selection. Infanticide generally biases the childhood ratio against females. This might have the consequence that the genes of families producing males would be favored, would have greater fitness, and the secondary sex ratio would tend to be biased in favor of males. The problem is more complicated, however, in human societies because systems of mating and the socio-economical conditions have a substantial influence. Statistical data seems to indicate that under stressful living conditions, women preferentially abort male fetuses and this reduces the secondary sex ratio (Catalano R, Bruckner T 2006 Proc Natl Acad Sci USA 103:1639).

In some *Drosophila* stocks, infection by filiform bacteria results in female offspring. The *sex-ratio* genes in the *Drosophila* X chromosome cause an excess of females in the progeny of the males carrying this gene(s). Usually, drive suppressors in the autosomes and in the Y chromosome balance the sex-ratio gene expression. Some gynandromorphs with very small XO sectors may also survive. Triploid intersexes live, as do females sex-transformed by *tra*, *ix*, and *dsx* genes (i.e., phenotypically males, although XX). The sex ratio in the Seychelles warbler's (*Acrocephalus sechellensis*) eggs may vary according

to the availability of food supply; in low-food territories they may have 77% male offspring, whereas with high food supply the proportion of sons may be only 13%. This difference is not due to the different viability of the eggs. In some species of the *Cyrtodiopsis* flies in Malaysia, the sex ratio may be biased either toward the females or toward the males. In the cases of female bias, the males carry a *driver-X* chromosome that by some means eliminates from fertilization most of the Y-bearing sperms resulting in predominantly female (XX) offspring. In the male biased stocks, the Y chromosome carries a suppressor for the driver-X and actually somewhat increases the chances of function for the Y-bearing sperms, resulting in more than 50% male progeny. Irrespective of the actual mechanism of sex determination, natural selection tends to promote the 1:1 proportion of the two sexes because as long as sexual reproduction is maintained, both males and females contribute to the offspring. ▶hermaphroditism, ▶sex determination, ▶sex-reversal, ▶spirochete, ▶infectious heredity, ▶sex proportion, ▶gynandromorph, ▶age of parents and secondary sex ratio, ▶male-stuffing, ▶sex selection, ▶segregation distorter, ▶meiotic drive, ▶dosage compensation, ▶*Wolbachia*; Jaenike J 2001 Annu Rev Ecol Syst 32:25; Hardy ICW (Ed.) 2002 Sex Ratios. Concepts and Research Methods. Cambridge University Press, Cambridge, UK.

Sex Realizer: A substance that determines whether male or female gonads would develop.

Sex Reversal (sex change): Sex reversal involves sex phenotypes that do not match the expectation based on chromosomal sex determination. Gene *fru* splices differently in males and females of *Drosophila*. If the splicing in males is according to the female pattern or in the females in the male pattern, the sexual behavior (courtship) is reversed and males and females court the same sex (Demir E, Dickson BJ 2005 Cell 121:785) because of altered response to pheromones through the olfactory system (Stockinger P et al 2005 Cell 123:795). It has been suggested that a certain number of trinucleotide repeats (glutamine) in the *Sry* gene would be responsible for this reversal but other studies could not confirm the mechanism in mice and it appears that alteration in the function of autosomal regulator genes may be involved. There are apparently sex-determining autosomal (17q24.3-q25.1 and 9p24) factors, which may cause sex reversal in 46XY individuals. Other autosomal and X-chromosomal genes (Xp21.3-p21.2) may also be responsible for sex reversal. In young mice with knockout for the estrogen receptors α and β ($\alpha\beta$ ERKO), the development of the sexual organs is near normal. By adult stage in the ovaries of the females, seminiferous

tubule-like structures develop, Müllerian inhibitory substance is formed at an elevated level, and Sox9 protein has been found indicating that the estrogen receptors (ER) are essential for the maintenance of the normal ovarian phenotype. The $\alpha\beta$ ERKO males displayed some spermatogenesis but also became sterile. In both males and females, the α ER is most essential for normal sexuality. Male-to-female sex change in mice seems to be controlled by fibroblast growth factor 9. Defect in the nuclear localization of SRY may lead to gonadal dysgenesis in humans. Mutation in the R-spondins family of human growth gene results in a recessive syndrome in the absence of the testis-determining SRY gene, characterized by complete XX sex reversal, palmo-plantar hyperkeratosis, and predisposition to squamous cell carcinoma of the skin (Parma P et al 2006 Nature Genet 38:1304). R-spondins are ligands interacting with Fzd/LRP (Frizzled/Lipoprotein related) receptor complexes and inducing beta-catenin-T cell factor (TCF) gene activation in different species both in vitro and in vivo. ▶SRY, ▶*tra*, ▶sex determination, ▶campomelic dysplasia, ▶hermaphroditism, ▶pseudohermaphroditism, ▶homosexual, ▶testicular feminization, ▶SF-1, ▶estradiol, ▶SOX, ▶knockout, ▶gonads, ▶Müllerian ducts, ▶*Wingless*, ▶adrenal hypoplasia congenital, ▶FGF, ▶gonadal dysgenesis, ▶thrombospondin, ▶R-spondin; Ostrer H 2000 Semin Reprod Med 18:41; Colvin JS et al 2001 Cell 104:875; Li B et al 2001 J Biol Chem 276:46480; sex reversal—sex determination review: Camerino G et al 2006 Curr Opin Genet Dev 16:289.

Sex Selection: Sex selection is possible with the use of cell sorters, followed by artificial insemination. Sex determination is feasible also by FISH or PCR before implantation. The mammalian X-chromosome-bearing sperm has 2.8 to 7.5% more DNA than the Y bearing sperms. The sperm can be classified and selected with high efficiency and at high speed (18 million sperm/h). It is used in animal husbandry for artificial insemination and its effectiveness is 85–95%. It would be technically feasible also in human artificial insemination and ethically less objectionable than the preimplantation selection of fertilized eggs. Sex selection involves not just ethical problems but it may also affect the sex ratio in the population. It has been estimated that in China the males exceed females by ~30% because of selective abortion. This also leads to a social imbalance because many males may not find mates. ▶cell sorter, ▶segregation distorter, ▶sex determination, ▶ART, ▶PGD, ▶social selection, ▶sex ratio; Garner DL 2001 J Androl 22:519; Johnson LA 2000 Anim Repr Sci 60–61:93; van Munster EB 2002 Cytometry 47:192; Welch GR, Johnson LA 1999

Theriogenology 52:1343; international survey of frequency: Sermon K et al 2005 Hum Reprod 20:19.

Sex Vesicle (XY body): The meiotically paired mammalian sex chromosomes in the males may be heterochromatinized and form the sex vesicle, a special, visible structure. ▶sex chromosomes, ▶heterochromatin

Sexduction (F-duction): F-duction takes place when genes carried in the bacterial sex element (F' plasmid) recombine with the bacterial chromosome. ▶F' plasmid, ▶Hfr, ▶conjugational mapping, ▶transduction; Jacob F et al 1960 Symp Soc Gen Microbiol 10:67; Lederberg EM 1960 Symp Soc Gen Microbiol 10:115; see Fig. S42.

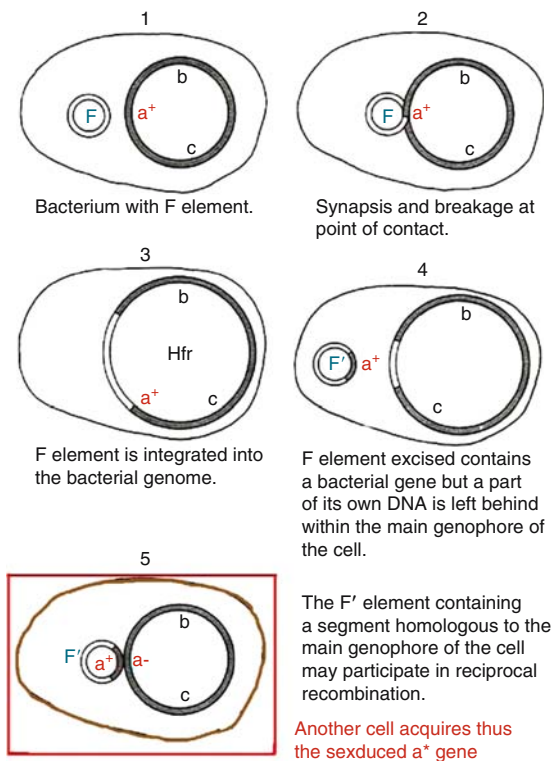


Figure S42. Sexduction

Sex-Influenced: A sex-influenced trait is that, which has a different degree of expression in male and female individuals, e.g., facial hairs in humans, color of plumage in birds, horns in deer, etc. ▶hare lip, ▶pyloric stenosis, ▶Hirschsprung's disease, ▶lupus erythematosus, ▶imprinting

Sexing: Distinguishing female from male forms of animals. This procedure may be difficult in young birds because the genitalia may appear ambiguous to those who do not have special expertise (▶autosexing). The avian males are homogametic (WW) and

the females are heterogametic (ZW). Sexing may be carried out also by the karyotyping of the tissues or Barr body detection. Molecular sexing may make possible the identification of sex on the basis of DNA markers from any tissue sample. On the Z chromosomes, there are both the CHD-W and the CHD-NW genes whereas the W chromosome carry only the CHD-NW gene. The base sequences of these two genes are very similar, except in a short tract. When a restriction enzyme cuts within this segment of CHD-W, the females display three electrophoretic bands but the males show only one.

A non-invasive sexing may be carried out on preimplantation embryos by inserting a green fluorescent transgene into the X chromosome. The male offspring of green fluorescent mammalian males will not display fluorescence. Such transgenic animals are apparently normal. ▶sex determination, ▶autosexing, ▶genetic sexing lines, ▶aquorin

Sex-Limited: The expression of a sex-limited trait is limited to one sex (e.g., lactation in females, Wildervanck syndrome).

Sex-Linked Lethal Mutations: Sex-linked lethal mutations in *Drosophila* served as the first laboratory test to quantitate mutation frequency and assess the mutagenic properties of physical and chemical agents. The old procedure was called the *CIB* test (C stands for crossover exclusion brought about by the presence of usually three inversions, *I* is a recessive lethal gene, and *B* indicates the dominant *Bar* eye mutation.) The principle of the techniques is diagrammed at *CIB*. If any new recessive mutation takes place in the X chromosome of a male, then in the F_2 only females may occur because the original recessive *I* gene present in the inverted *B I* chromosome will kill the hemizygous male progeny. If a new lethal mutation occurs, it may kill (or much reduce the proportion) of the other type of males in F_2 . Nowadays instead of the *CIB* method, generally the improved *Basc* chromosome is used (*B*: *Bar*, *a*: *apricot* eye color [*w* locus] and *sc*: *scute* inversions). Any recessive lethal mutation in the X-chromosome of the grandfather's sperm results in the death of one of the grandsons. Rarely, some exceptional females are also found, which are the result of unequal sister chromatid exchange in the inversion heterozygote mother. Somewhat similar manner autosomal recessive lethals can also be detected in *Cy L/Pm* stocks. ▶bioassays in genetic toxicology, ▶autosomal recessive lethal assay, ▶*Basc*, ▶*Cib* and diagrams there.

Sex-Reversal: As per sex-reversal, the sex by karyotype does not always correspond to sex phenotype. By translocation, a testis-determining factor (TDF/SRY) may move from the Y chromosome to an X

chromosome, and thus 46 autosome XX males can occur. Also, it has been claimed that an autosomal testis-determining factor (TDFA) may be responsible for some of the intersexes and sex reversion cases. Terminal deletions of human chromosome 9p and 10q may result in sex-reversal. ▶intersexes, ▶H-Y antigen, ▶SRY, ▶hermaphroditism, ▶pseudohermaphroditism, ▶testicular feminization, ▶Swyer syndrome, ▶gonadal dysgenesis, ▶sex determination, ▶campomelic dysplasia, ▶DSS, ▶Polycomb; Osterer H 2001 J Appl Physiol 91:2384; Li B et al 2001 J Biol Chem 276:46480.

Sex-Selection: As per sex selection, X-bearing sperms can be separated with reasonably good efficiency from their Y-bearing counterparts with the aid of cell sorters and fluorescent labeling, on the basis of the increased DNA content of X-bearing sperms. This process then can be used in artificial insemination in animal breeding. For humans, sex-selection is primarily an ethical issue. ▶sex determination, ▶sex ratio; Johnson LA 2000 Anim Reprod Sci 60–61:93; Welch GR, Johnson LA 1999 Theriogenology 52:1343.

Sexual Conflict: In sexual conflict, the enhanced reproductive success of one of the sexes reduces the fitness of the other, e.g., polyspermic fertilization. The seminal fluid of the male (mating success) may be toxic to the female and reduces the lifespan of the female *Drosophila*. ▶polyspermic fertilization, ▶sexual selection; Rice WR 1996 Nature [Lond] 381:232.

Sexual Differentiation: The realization of sex-determination (gonads) and development of secondary sexual characters, such as facial hair in men, differential plumage in birds, etc. In *Drosophila*, for the male gonad differentiation and normal sexual development the expression of the JAK-STAT signal transduction pathway is required in the somatic cells. For the female gonads, JAK-STAT activity is not necessary (Waversik M et al 2005 Nature [Lond] 436:563). ▶gonad, ▶signal transduction; Wedell A et al 2000 Lakartidningen 97:449; Burtis KC 2002 Science 297:1135; Reiner WG, Gearhart JP 2004 N Engl J Med 350:333; gonadal and functional abnormalities: MacLaughlin DT, Donahoe PK 2004 N Engl J Med 350:367.

Sexual Dimorphism: As per sexual dimorphism, the two sexes are morphologically distinguishable. In some species, the differences appear only during later development or by the time of sexual maturity. The differences are not limited to morphology but also various functions may differ. In the males, the language centers are localized in the left inferior frontal gyrus region of the brain, while in females both left and right regions are active. Conversion of

testosterone to estradiol by neuronal tissue critically affects sexual differentiation of the brain. GABA and calcium-binding proteins are more abundant in the newborn male rats relative to females. This difference appears to be a switch from excitatory action in the males to inhibitory signals in the females. GABA would increase phosphorylation of CREB at Ser¹³³ by protein kinase A, calcium-activated calmodulin kinase, ribosomal S6 kinase 2, and mitogen-activated kinase-activated protein kinase 2 in the brain of the male. This appears to be the initial signal to sexual dimorphism. Wnt-7a regulates sexual dimorphism of mouse by controlling the Müllerian inhibitory substance. ▶human intelligence, ▶autosexing, ▶sex determination, ▶GABA, ▶protein kinases, ▶calmodulin, ▶CREB, ▶wingless, ▶Müllerian duct, ▶gonads; Auger AP et al 2001 Proc Natl Acad Sci USA 98:8059; Vincent S et al 2001 Cell 106:399.

Sexual Dysfunction: ▶erectile dysfunction, ▶priapism, ▶Peyronie disease, ▶vaginismus

Sexual Incompatibility: ▶incompatibility

Sexual Isolation: Sexual isolation has significance in speciation by, either preventing mating (isolation by life cycle, behavior or generative organs) between certain genotypes, or because of gametic or zygotic death or inviability of their offspring. A very common form of sexual isolation is the inviability of the recombinants of chromosomal inversions. The cross-breeding at the incipient speciation may be prevented by pheromone gene(s) responsible for the production of differences in the female cuticular hydrocarbons in *Drosophila*. ▶incompatibility, ▶inversions, ▶speciation, ▶fertility, ▶pheromone; Majestic J 2001 FEMS Lett 199:161; Fang S et al 2002 Genetics 162:781.

Sexual Maturity: The developmental stage by which reproductive ability is attained. It varies in different organisms (m: month, y: year): cat 6–12 m, cattle 6–12 m, chimpanzee 8–10 y, dog 9 m, elephant 8–16 y, horse 12 m, humans 12–14 y, mouse 1 m, rabbit 3–4 m, rat 2 m, sheep 6 m, swine 5–6 m. Sexual maturity is affected also by environmental factors. ▶gestation

Sexual Orientation: ▶homosexual

Sexual Reproduction: The production of offspring by mating of gametes of opposites sex or mating type. Sexual reproduction seems to have evolved because it facilitates segregation of alleles and recombination among linked loci, resulting in increased fitness in different environments. The fungus *Cryptococcus neoformans* has both *a* and *α* mating types, yet the majority of the populations are represented by *a* mating type only. In these cases, the same mating type

spores may fuse, undergo meiosis and produce four α spores (see Fig. S43) (Lin X et al 2005 Nature [Lond] 434:1017). ►meiosis, ►gametogenesis; <http://www.germonline.org/index.html>.

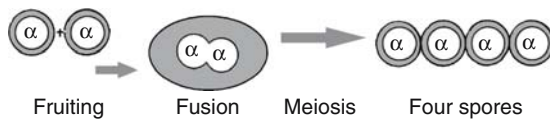


Figure S43. Sexual reproduction between same mating type

Sexual Selection: Competition among mates of the same sex or gametes or preferential choice of one or another type of mates. The general purpose of sexual selection is to find mates with selective advantage for the offspring. Some body ornaments of the male birds may increase their sexual attractiveness to females and provides a selective advantage in mating and producing offspring. Some body features may be associated with high viability genes and are evolutionarily advantageous to the bearer as a means of higher chances of leaving offspring by mate choice. A quantitative analysis of the correlation between body-ornament (white head-spot) of the male flycatcher bird (*Ficedula albicollis*) indicated that the ornament did not evolve by hitchhiking with genes of otherwise higher fitness but by its own merit (see Fig. S44) (Qvarnström A et al 2006 Nature [Lond] 411:84). In some instances, the actual value of the selected trait, e.g., the fancy tail of the peacock may not easily be rationalized (see Fig. S45). The gynogen Sailfin Molly fish females reproduce clonally, yet they rely on sperm of heterospecific males to initiate embryogenesis; thus, it appears that the males do not contribute to the progeny. Yet the sexual forms of the females prefer those males, which mate with the gynogens. Consequently, the males exploited by the gynogens still benefit from the unusual sexual selection. Although sexual selection most frequently involves the selection of the males, in the sand lizard (*Lacerta agilis*), the females achieve selection. The



Figure S44. *Ficedula albicollis*



Figure S45. Peacock, Chinese handiwork

females may copulate with several closely or distantly related males but it appears that the share of offspring sired by the remotely or unrelated males is higher in the same clutch. Thus, the females select apparently the sperm of the more distantly related males. Females of feral fowl may eject the sperm acquired through coerced mating by inferior males. Mate preference in male and female rats whose progenitors had been treated with the antiandrogenic fungicide vinclozolin (LD₅₀ 10 mg/kg, rat) has been observed. This effect is sex-specific, and females three generations removed from the exposure discriminate (transgenerational effect) and prefer males who do not have a history of exposure, whereas similarly epigenetically imprinted males do not exhibit such a preference (Crews D et al 2007 Proc Natl Acad Sci USA 104:5942). Polymorphism exists in binding a protein that facilitates the attachment of the sperm to the egg and that may affect male selection by the egg. In some instances, the sexual selection is based on meiotic drive. In *Drosophila* species, mate recognition/preference is influenced by cuticular hydrocarbon composition. In guppy fish, sexual attractiveness of the males is positively

correlated with ornamentation (encoded in the Y chromosome) but negatively correlated with survival. Asexual populations may have higher fitness than the sexual ones because every individual has a chance to reproduce, especially when the deleterious mutation rate is higher in males than in females, as is most commonly the case. ►meiotic drive, ►sexual dimorphism, ►certation, ►megaspore selection, ►assortative mating, ►disassortative mating, ►gynogenesis, ►heterospecific, ►conflict evolutionary, ►sexual conflict, ►transgenerational effect; mate choice: Chenoweth SF, Blows MW 2006 *Nature Rev Genet* 7:681; Swanson WJ et al 2001 *Proc Natl Acad Sci USA* 98:2509; Snook RR 2001 *Curr Biol* 11:R337; Knight J 2002 *Nature [Lond]* 415:254; Pizzari T, Birkhead TR 2002 *Biol Rev* 77:183.

Sexual Swelling: A large, conspicuous reddish structure in between the vulva and the anus of the females of many Old World primates at the time of ovulation. It is a mating attractant for the males and has a value in sexual selection. ►vulva, ►anus, ►sexual selection

Sexuparous: The sexual production of offspring in species where parthenogenetic reproduction co-exists with sexual reproduction. ►parthenogenesis

SF: ►hybrid dysgenesis I-R system. Also ►splicing factor protein. ►introns

SF1 (stimulatory factor): A yeast protein (33 kDa) reducing the binding requirement (at the concentration of 1 SF/20 nucleotides) of protein Sep 1 to DNA during recombination, by two orders of magnitude. It probably has a role in DNA pairing. ►synapsis

SF1 (splicing-transcription factor): SF1 represses transcription. (See Goldstrohm AC et al 2001 *Mol Cell Biol* 21:7617).

SF-1 (Ftz-F1, fushi tarazu factor homolog, nuclear receptor subfamily 5 group A member 1 [NR5A1]): The steroidogenic factor (adrenal 4 binding protein [Ad4bp]) at human chromosome 9q33 (30 kb genomic DNA) regulates cytochrome 450 steroid 21-hydroxylase, aldosterone synthase, anti-Müllerian hormone (MIS), XY sex reversal, and adrenal failure and plays key role in steroid biosynthesis. SF-1 function is modulated by phospholipids through mediating ligand binding (Li Y et al 2005 *Mol Cell* 17:491). ►steroid hormones, ►fushi tarazu, ►Müllerian ducts; Whitworth DJ et al 2001 *Gene* 277:209; crystal structure: Wang W 2005 *Proc Natl Acad Sci USA* 102:7505.

SF2/ASF: ►SR protein, ►SR motif

SFF: A cell cycle regulating yeast protein. ►cell cycle

SFK: A group of tyrosine protein kinases, SFKs, reside on the interior part of the cell membrane and respond to external signals. They are members of the Src family. When phosphorylated by Csk or other kinases, the proteins assume an inactive conformation and their activation requires phosphatases. Cbp attracts Csk to the membrane. The active SFK then phosphorylates other proteins. Rafts localized on the outer surface of the membrane modify SFKs. ►CBP, ►Csk, ►RAFT, ►Src; Vara JA et al 2001 *Mol Biol Cell* 12:2171.

SFM: Serum-free medium.

Sfp1: A protooncogene; probably the same transcription factor as PU.1 and Spi1. ►Spi1, ►PU.1

SGLT (sodium/glucose co-transporter): A defect in SGLT results in Glucose-Galactose Malabsorption (GGM), a potentially fatal neonatal (human chromosome 22) recessive disorder, unless the diet is made sugar-free. (See Xie Z et al 2000 *J Biol Chem* 275:25959).

SGP-1: The syntenic gene predictor in homologous sequences of genomes. ►gene predictor; Wiehe T et al 2001 *Genome Res* 11:1574; <http://soft.ice.mg.de/spg-1>.

SGT1: A proteolysis factor controlled by ubiquitin. ►ubiquitin; Tor M et al 2002 *Plant Cell* 14:993.

SH₂ (src homology domain): An about 100 amino acid long binding site for tyrosine phosphoproteins. These phosphoproteins such as the SRC and ABL cellular oncogenes, phosphotyrosine phosphatases, GTPase activating protein, phospholipase C, and the Grb/Sem 5 adaptor protein have important role in signal transduction. In the human genome, there are about 115 SH₂ domains. ►SH₃, ►SRC, ►WW, ►PTB, ►pleckstrin, ►signal transduction

SH₃ (src homology domain): The binding site for the proline-rich motif (Arg-X-Leu-Pro-Pro-Z-Pro [the latter is Leu for the Src oncoprotein and Z is Arg for phosphoinositide kinase] or it can be X-Pro-Pro-Leu-Pro-X-Arg) in an adaptor or mediator protein in the signal transduction pathway through RAS. By binding, conformational and functional changes take place. The activity of the cellular SRC protein increases during normal and neoplastic mitoses. Protein p68, closely related to the GAP-associated p62, is bound to the SH₃ domain of SRC. The SH₃ binding is specific in vivo, yet of low affinity. The human genome encodes about 250 SH₃ domains (see Fig. S46). ►SH₂, ►SRC, ►RAS, ►signal transduction, ►GAP; SH₃ site detection: <http://cbm.bio.uniroma2.it/SH3-Hunter/>.



Figure S46. Structure of the SH3 domain. From Alm E and Baker D 1999 Proc. Natl. Acad. Sci. USA 96:11305

Shade-Avoidance Syndrome: The shade-avoidance syndrome of plants results in elongated stem, reduced leaf expansion, and accelerated flowering under reduced light. Several phytochrome genes mediate it. ▶[phytochrome](#), ▶[floral evocation](#); Cerdán PD, Chory J 2003 Nature [Lond] 423:881.

Shadow Bands: Same as stutter band.

Shadowing: An electronmicroscopic preparatory procedure by which the surface of the specimen is coated with a vaporized metal, such as platinum. The shadowed objects display a three-dimensional effect in scanning, but in some cases, even in transmission electronmicroscopy. ▶[scanning electronmicroscopy](#)

Shadowing, Phylogenetic: A cross-species base sequence comparison in order to find important functional, structural, and regulatory elements in different evolutionary categories. (See Boffelli D et al 2003 Science 299:1391).

Shah-Waardenburg Syndrome (SOX10/WS4, 22q13; EDN3/ET3 20q13.2-q13.3): The Shah-Waardenburg Syndrome involves the endothelin-3 signaling pathway; it shows the combined symptoms of the Hirschsprung disease and the Waardenburg syndrome. The embryonic neural crest appears to have recessive (EDN3) or dominant (SOX10) defects. ▶[Hirschsprung disease](#), ▶[Waardenburg syndrome](#), ▶[endothelin](#), ▶[RET oncogene](#), ▶[SOX](#); Touraine RL et al 2000 Am J Hum Genet 66:1496.

Shaking (shak): Alleles at several chromosomal locations in *Drosophila* cause shaking of the legs under anesthesia to a variable degree, depending on the locus and allele involved. Some mutants may display

hyperactive behavior in a temperature-dependent manner. Some may be viable, while others are homozygous lethals. The *shakB* mutants may cause a defect in the synapse between the giant fiber neuron, postsynaptic interneuron, the dorsal longitudinal muscle, and the nerves operating the tergotrochanter (back-neck) muscle (see illustrations at ▶[Drosophila](#)). The shaking may be caused by a defect in a protein of a potassium ion channel. ▶[ion channel](#)

Shannon-Weaver Index: ▶[diversity](#)

Shark Cartilage: Sharks, mainly sea-inhabiting cartilaginous fishes, are presumably rarely afflicted by tumors. The prevailing assumption was that their cartilage protects from cancer. Experimental evidence—contrary to some early studies—indicates, however, that shark cartilage products are ineffective against advanced cancer (Loprinzi CL et al 2005 Cancer 104:176).

SHARP (SMRT and histone deacetylase-associated repressor protein): A regulator of PPAR. ▶[PPAR](#), ▶[SMRT](#); Shi Y et al 2002 Proc Natl Acad Sci USA 99:2613.

Shasta Daisy (*Chrysanthemum maximum*): An ornamental plant; $2n \approx 90$ (see Fig. [S47](#)).



Figure S47. Shasta daisy

SHC: An adaptor protein involved in RAS-dependent MAP kinase activation after stimulation by insulin, epidermal (EGF), nerve (NGF), platelet derived growth factor (PDGF), interleukins (IL-2,-3,-5), erythropoietin and granulocyte/macrophage colony-stimulating growth factor (CSF), and lymphocyte antigen receptors. It binds to tyrosine-phosphorylated receptors and when phosphorylated at tyrosine it interacts with the SH2 domain of Grb2, which interacts with SOS in the RAS signal transduction pathway. The phosphotyrosine-binding (PTB) domain can also recognize the tyrosine-phosphorylated protein. The latter is similar to the pleckstrin homology domain and most likely binds the acidic phospholipids of the cell membrane. SHC is also an oncogene, involved in the development of phaeochromocytoma neoplasias. ▶[signal transduction](#), ▶[phaeochromocytoma](#),

►adenomatosis endocrine multiple, ►neoplasia, ►insulin, ►EGF, ►NGF, ►PDGF, ►SOS, ►interleukins, ►CSF, ►pleckstrin domain; Ravichandran KS 2001 *Oncogene* 20:6322.

Shearing: Cutting DNA to fragments by mechanical means, e.g., by rapid stirring or brusque pipetting.

Sheats: Any tube-like structure surrounding another, also the part of a leaf that wraps the stem.

Sheep, Domesticated (*Ovis aries*): $2n = 54$; some wild sheep have higher number of chromosomes. A medium-density linkage map of 1062 unique loci became available by 2001 and has helped in mapping the cattle and goat genomes (Maddox JF et al 2001 *Genome Res* 11:1275; Cockett NE et al 2001 *Physiol Genomics* 7:69; <http://www.wool.com.au/LivePage.aspx?pagel=116#mainBody>; <http://www.angis.org.au/Databases/BIRX/mis/>; <http://www.ncbi.nlm.nih.gov/genome/guide/sheep>).

Sheep Hybrids: Domesticated sheep (*Ovis aries*, $2n = 54$) forms fertile hybrids with muflons but the goat x sheep hybrid embryos rarely develop normally. ►transplantation nuclear; Ruffing NA 1993 *Biol Reprod* 49:1260.

Sheldon-Hall Syndrome (distal arthrogryposis): ►Freeman-Sheldon syndrome

Shelterin: ►telosome

Sherman Paradox: The various recurrence risks among relatives caused by expansion of fragile X sites transmitted by non-symptomatic males. ►mental retardation, ►recurrence risk, ►fragile X, ►trinucleotide repeats; Sherman SL et al 1985 *Hum Genet* 69:289; Fu YH et al 1991 *Cell* 67:1047.

Shift: An internal chromosomal segment, generated by two break points, translocated within the same or into another chromosome, within a gap opened by a single break. It is a rare phenomenon. Shifting of the relative proportion of mitochondrial recombination products commonly occurs in plants. ►transposition, ►reciprocal interchange, ►translocation

Shifting-Balance Theory of Evolution: According to the Shiftin-balance theory of evolution, polymorphism in a population is determined by a dynamic interplay of the forces of pleiotropy, epistasis, genotypic values, fitness, and population structure. Alternative ideas would be the discredited neo-Lamarckian internal drive or the well-documented neutral mutation concepts. ►polymorphism, ►pleiotropy, ►genotype, ►fitness, ►neo-Lamarckism, ►neutral mutation, ►population structure; Wade MJ, Goodnight CJ 1991 *Science* 253:1015.

Shigella: A group of gram-negative enterobacteria causing dysentery (intestinal inflammation and

diarrhea) in humans and higher monkeys. Butyrate treatment effectively mitigates shigellosis by up-regulation of a natural antibiotic (LL-37/cathelicidin) in the intestinal epithelium (Raquib R et al 2006 *Proc Natl Acad Sci USA* 103:9178). ►primates; database: <http://www.mgc.ac.cn/ShiBASE/>.

Shikimic Acid: An intermediate in aromatic amino acid-, flavonoid-, fragrance-, alkaloid- and plant pigment biosynthesis (see Fig. S48).

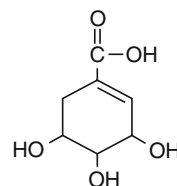


Figure S48. Shikimic acid

Shine-Dalgarno Sequence: Nucleotide consensus (AGGAGG) in the non-translated 5' region of the prokaryotic mRNA (close to the translation initiation codon), complementary to the binding sites of the ribosomes. The terminus of the 16S ribosomal RNA is generally:

$A^{Me2} A^{Me2} CCUGCGGUUGGAUGACCUCCUUA-3'-OH$. The eukaryotic mRNAs do not have this sequence and the mRNA attaches to the ribosomes by means of ribosomal scanning. In the polycistronic messages, each cistron generally has a Shine-Dalgarno sequence. Mitochondrial and ribosome mRNAs, generally but not always, have this or a modified Shine-Dalgarno. ►anti-Shine-Dalgarno, ►ribosome scanning, ►IF, ►initiation codon, ►polycistronic mRNA; Shultzaberger RK et al 2001 *J Mol Biol* 313:215.

Shingles: The herpes (varicella-zoster) virus responsible for chicken pox may emerge from a latent stage, later in the life of an individual when immunity has waned. It then causes shingles (sore eruptions) in parts of the body innervated by ganglions harboring the earlier latent virus (see Fig. S49). About 20% of adults become affected. Chickenpox is highly contagious but shingles are transmitted only from the open eruptions and not by sneezing or casual contact and the risk of infection is very low. Hand washing is helpful to prevent infection from afflicted individuals. Guanosine analogs (acyclovir) are commonly used for treatment, which interfere with replication by viral DNA or RNA polymerases (see Fig. S50). ►herpes, ►chickenpox, ►Varicella zoster virus, ►ganglion; Dwyer DE, Cunningham AL 2002 *Med J Austral* 177(5):267; vaccine: Vázquez M et al 2005 *N Engl J Med* 352:439.

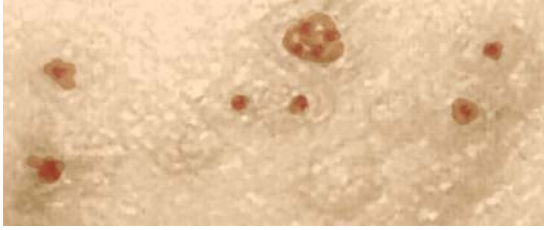


Figure S49. Shingles

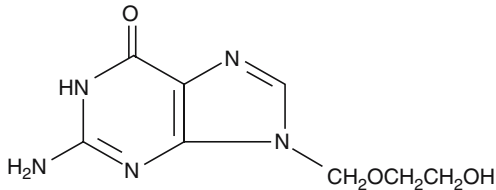


Figure S50. Acyclovir

SHIP: Inositol phosphatase with SH₂ domain. SHIP proteins in tyrosine phosphorylated form signal to hematopoiesis, cytokines, PTEN, etc. ▶SH₂, ▶inositol, ▶cytokines, ▶hematopoiesis, ▶PTEN, ▶ITIM; Rohrschneider LR et al 2000 Genes Dev 14:505.

SHIRPA: A protocol for phenotypic characterization of mutation in mice (Rogers DC et al 1997 Mammalian Genome 8:711).

SHIV: A simian immunodeficiency virus (SIV) engineered to carry an HIV coat protein and thus capable of infection of, and symptoms of AIDS in macaque monkeys. ▶HIV, ▶SIV, ▶acquired immunodeficiency syndrome, ▶primates

SHMOOs: Mating projections in yeast.

S

SHOM (sequencing by hybridization to oligonucleotide microchips): One of the automated (robotic) procedures developed for nucleotide sequence diagnostics. (See Yershov G et al 1996 Proc Natl Acad Sci USA 93:4913; ▶DNA chips, ▶microarray hybridization).

Shoot: The plant part(s) above ground or a branch of a stem.

Shope Papilloma: A viral disease of rabbits causing nodules under the tongue. The double-stranded DNA virus of about 8 kbp has 49 mole percent G + C content. ▶bovine papilloma

Short-Day Plants: Short-day plants require generally less than 12–15 h daily illumination for flowering; at longer light periods they usually remain vegetative. ▶photoperiodism, ▶long-day plants

Short Dispersed Repeats: ▶SDR

Short Patch Repair: An excision repair removing, and then replacing, about 20 nucleotides. ▶DNA repair, ▶excision repair, ▶mismatch repair; Mansour CA et al 2001 Mutat Res 485:331.

Short RNA (sRNA): ▶microRNA, ▶RNAi

SHORT Syndrome: An autosomal recessive phenotype characterized by the initials of the SHORT acronym: short Stature, Hyperextensibility of joints and hernia, Ocular depression, Rieger anomaly (partial absence of teeth, anal stenosis [narrow anus], hypertelorism [increased distance between organs or parts], mental and bone deficiencies, and Teething delay). ▶stature in humans, ▶dwarfism, ▶pseudoautosomal

Shortstop Promoter: The shortstop promoter mediates the transcription of only some of the exons although some repeats within the exons may be expanded.

Shotgun Cloning: In shotgun cloning, the DNA of an entire genome is cloned without aiming at particular sequences. From the cloned array of DNA fragments (library), the sequences of interest may be identified by appropriate genetic probes. ▶cloning, ▶DNA probe, ▶DNA library; Matsumoto S et al 1998 Microbiol Immunol 42:15.

Shotgun Sequencing: In shotgun sequencing, random samples of cloned DNA, e.g., the segments of a cosmid are sequenced at random. *Whole-genome pairwise shotgun* procedure sequences paired ends of cloned DNAs of varying sizes and fragmented them into a larger number of contigs ordered with the aid of high-power computers. If there are still gaps between the contigs those are filled in by “finishing.” The *hierarchical shotgun sequencing* procedure is based on mapped clones generated by BACs. The *Double-barrel shotgun* sequences the DNA from both ends. The short sequences are arranged into longer tracts by computers. The *Full shotgun sequence* indicates that the cloned inserts have been covered about 8–10 times. *Half shotgun coverage* is only 4–5-fold random sequence. ▶DNA sequencing, ▶first-draft sequence, ▶contig, ▶completion, ▶WGS, ▶scaffolds in genome sequencing, ▶human genome, ▶genome projects; Bankier AT 2001 Methods Mol Biol 167:89; whole genome shotgun (WGS) products: <http://www.ncbi.nlm.nih.gov/projects/WGS/WGSprojectlist.cgi>.

Shoufflons: Clustered (generally 6 to 7) recombination/inversion sites and a shoufflon-specific recombinase in bacteria. These elements determine the nature of the bacterial pili, thick rigid or thin pilus. A typical

shoufflon is plasmid R64, a 120.8 kb conjugative plasmid encoding streptomycin and tetracycline resistance and at least 49 genes in the 54 kb transfer region. Various types of shoufflons occur in different bacteria. ▶[site-specific recombination](#), ▶[pilus](#); Komano T 1999 *Annu Rev Genet* 33:171.

SHP-1 (synonymous with SH-PTP1, PTP1C, HCP): Tyrosine phosphatase; it contains the SRC homology domain SH2. Upon activation of T cells, it binds to the kinase ZAP-70 resulting in increased phosphatase activity but in a decrease in ZAP-70 kinase activity. It is a negative regulator of the T cell antigen receptor. It is activated by radiation stress. ▶[T cell](#), ▶[ZAP-70](#), ▶[ITIM](#); Kosugi A et al 2001 *Immunity* 14:669.

Shprintzen-Goldberg Syndrome: ▶[Marfanoid syndromes](#)

SHREC: A multienzyme effector complex, which regulates nucleosome positioning to assemble higher-order chromatin structures critical for heterochromatin functions and gene silencing (Sugiyama T et al 2007 *Cell* 128:491).

Shrew: The smallest insectivorous mammals; *Blarina brevicauda*, 2n = 50; *Cryptotis parva*, 2n = 52; *Neomys fodiens*, 2n = 52; *Notiosorex crawfordi*, 2n = 68; *Sorex caecutiens*, 2n = 42; *Suncus murinus*, 2n = 40; *Tupaia belangeri* tree shrew, 2n = 62 (see Fig. S51).



Figure S51. Tree shrew

Shrinkage: Shrinkage occurs when multiple regression data are applied to new information and the regression decreases. ▶[correlation](#), ▶[multiple regression](#)

shRNA (short heterochromatic RNA): shRNA is instrumental in the formation of heterochromatin and the epigenetic remodeling of chromatin. ▶[heterochromatin](#), ▶[epigenesis](#), ▶[RNAi](#); Jenuwein T 2002 *Science* 297:2215.

shRNA (short hairpin RNA): shRNA can be used for global identification of genes involved in certain functional pathways by blocking their expression

(Moffat J et al 2006 *Cell* 124:1283). By intravenous infusion of 49 Adeno-associated virus vectors carrying different shRNAs, 36 caused dose-dependent liver injuries and 23 caused death in adult mice. Liver-derived microRNA pathway was down-regulated by nuclear karyopherin/exportin-5. (Grimm D et al 2006 *Nature [Lond]* 441:537). Reversible gene inactivation was attained by expression of an insulin receptor (*Insr*)-specific shRNA. Upon induction by doxycycline, mice developed severe hyperglycemia within seven days. The onset and progression of the disease correlates with the concentration of doxycycline, and the phenotype returns to the baseline, shortly after the withdrawal of the inductor doxycycline (Seibler J et al 2007 *Nucleic Acids Res* 35(7):e54). ▶[RNAi](#), ▶[microRNA](#), ▶[karyopherin](#); Paddison PJ 2002 *Genes Dev* 8:948.

sHsp (small heat-shock proteins): Diverse ubiquitous proteins (15–80 kDa) formed in response to heat or other stress. Their transcriptional activation requires three inverted repeats of NNGAAN motif (HSE) where the heat shock transcription factor (HSF) binds. Their regulation may require other factors (e.g., estrogen, ecdysterone, etc.). The homology among the different types resides in the COOH-terminal half (α -crystalline domain). They may form large oligomers. Their role is heat and chemical protection of cells. Plant sHSP chaperones respond to various stresses to resist irreversible protein denaturation. ▶[heat-shock proteins](#), ▶[ibp](#); Haley DA et al 2000 *J Mol Biol* 298:261.

Shuffling: ▶[DNA shuffling](#)

Shufflon: A region in the chromosome with structural rearrangements.

Shugoshin: The shugoshin cohesin keeps sister chromatids together during anaphase I of meiosis. At meiosis I, Rec8, which replaces SCC1/RAD21 in meiosis, mediates the separation of the chromatids in the chromosome arms but keeps cohesion intact around the centromere until meiosis II. In yeast and probably in other eukaryotes as well, shugoshin protects the separation of chromatids from separase cleavage in meiosis I. Shugoshin is associated with serine/threonine protein phosphatase 2A (PP2A) protein in humans. Shugoshin and PP2A protect the separation of chromatids at the centromere. Shugoshin probably dephosphorylates cohesin and protects separation at the centromere (see Fig. S52). ▶[meiosis I](#), ▶[meiosis II](#), ▶[cohesin](#), ▶[separin](#); Kitajima TS et al 2006 *Nature [Lond]* 441:46; Riedel CG et al 2006 *Nature [Lond]* 441:53.

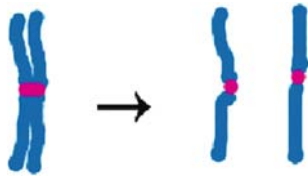


Figure S52. Sister chromatids separated at the centromere

Shunting: In shunting, during scanning the 40S ribosomal subunit jumps from the region of capture of the mRNA at the 5' m7 GpppN cap or at another sequence until it locates the translation initiation codon. Thus, the ribosome bypasses the 5' leader. For efficient translation of the mRNA with an internal ribosomal entry site (IRES), the homeodomain protein Gtx translated from IRES and a 9 to 7 nucleotide long sequence complementary to a site in the 18S eukaryotic ribosomal subunit was necessary (Chappell SA et al 2004 Proc Natl Acad Sci USA 101:9590). The presence of the Gtx translation element and the complementary 8 nucleotide sequence facilitates shunting even across an upstream uAUG codon in the leader and across a hairpin structure in the leader (Chappell SA et al 2006 Proc Natl Acad Sci USA 103:9488). ▶scanning, ▶translational hopping, ▶IRES, ▶leader sequence, ▶Cap

Shuttle Vector: A “promiscuous” plasmid that can carry genes to more than one organism and can propagate the genes in different cells, e.g., in *Agrobacterium*, *E. coli*, and plant cells. ▶vectors, ▶cloning vectors, ▶transformation genetic, ▶promiscuous DNA; Perez-Arellano I et al 2001 Plasmid 46:106.

Shwachman-Diamond Syndrome (Shwachman-Bodian-Diamond syndrome, 7q11): Pancreatic insufficiency, blood and bone abnormalities, and increased hematological cancer risk; probably recessive. The yeast ortholog, Sdo1 is critical for the release and recycling of the nucleolar shuttling factor Tif6 (ribosome biogenesis factor) from pre-60S ribosomes, a key step in 60S maturation and translational activation of ribosomes and its defect predisposes to bone marrow failure and leukemia (Menne TF et al 2007 Nature Genet 39:486).

SI: The unit of absorbed dose (1 Joule/kg) of electromagnetic radiation; it is generally expressed in Gray (Gy) or Sievert (Sv = 1 rem) units. Earlier rad (= 0.01 Gy) was used. ▶r, ▶rem, ▶Gray, ▶Sievert, ▶Curie, ▶Becquerel

Sialic Acid: An acidic sugar such as *N*-acetylneuraminic acid or *N*-glycolylneuraminic acid; it is present in the gangliosides (see Fig. S53). Polysialic acid is involved

in cell and tissue type differentiation, learning, memory, and tumor biology. The synthesis is mediated by polysialyl transferase under the regulation of neural cell adhesion molecules. The recessive sialic acid storage diseases (e.g., Salla disease, 6q14-q15) involve hypotonia and cerebellar ataxia, while mental retardation is caused by a family of anion/cation symporters.

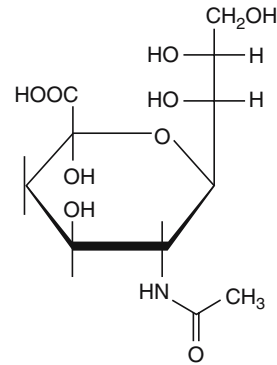


Figure S53. Sialic acid

The enzyme CMP-sialic acid hydroxylase changes *N*-acetylneuraminic acid into *N*-glycolylneuraminic acid. This enzyme is active in all mammals, except humans, where the 6p22.3-p22.2 locus suffered a 92-base deletion in the 5' region after the separation of humans from the primate lineage of evolution. Also, the human lineage—in contrast to that of chimpanzee—has only pseudogenes for the receptor (Siglec-L1) of *N*-glycolneuraminic acid. ▶gangliosides, ▶gangliosidosis, ▶CAM, ▶neuraminidase deficiency, ▶fusogenic liposome, ▶lysosomal storage disease, ▶symport, ▶sphingolipids, ▶cytidylic acid, ▶sialuria; Chou H-H et al 1998 Proc Natl Acad Sci USA 95:11751; Angata T et al 2002 J Biol Chem 277:24466; Aula N et al 2000 Am J Hum Genet 2000 67:832.

Sialidase Deficiency: ▶neuraminidase deficiency

Sialidosis: ▶neuraminidase deficiency

Sialolipidosis: ▶mucopolidosis IV

Sialuria (9p12-p11): Sialuria is caused by a semidominant/recessive gene defective in the feedback-sensitivity of uridine diphosphate *N*-acetylglucosamine 2-epimerase enzyme by cytidine monophosphate-neuroaminic acid. The afflicted have defects in bone (dysostosis) and psychomotor [movement and psychic activity] development and infantile death may occur. Salla disease (6q14-q15) is a sialic acid storage disease with mental and psychomotor retardation. ▶neuroaminidase deficiency

Siamese Cat: A Siamese cat displays darker fur color at its extremities because during slow blood circulation, more pigment develops at specific locations of the body. This is due to the presence of a temperature-sensitive gene, similar to Himalayan rabbits and other animals. The pattern distribution is due to a transition mutation from G→A in the 2nd exon of a tyrosinase gene, resulting in replacement of glycine by arginine (Lyons LA et al 2005 *Anim Genet* 36(2):119). The mutant allele produces pigment at the lower temperature of the extremities; it is thus a modification of albinism when pigment formation is absent in the entire body. Normal function of tyrosinase is required for the production of melanin, a pigment of fur color. ▶pigmentation of animals, ▶Himalayan rabbit, ▶temperature-sensitive mutation, see Fig. S54.



Figure S54. Siamese cat

Sib: Same as sibling. ▶full sib, ▶half sib

Sib Pair Method: ▶affected-sib-pair method

Sib TDT (s-TDT): A transmission disequilibrium test to detect genetic linkage/association on the basis of analysis of close genetic markers and disease among sibs. ▶SDT; Spielman RS, Ewens WJ 1998 *Am J Hum Genet* 62:450.

Sibling: Natural children of the same parents. ▶ λ_s , ▶risk, ▶genetic risk, ▶genotypic risk ratio

Sibling Species: Sibling species are morphologically very similar and frequently share habitat but they are reproductively isolated. ▶species, ▶speciation, ▶fertility

Sibpal: A linkage analysis computer program for sib-pairs. ▶sibling; Fann CS et al 1999 *Genet Epidemiol* 17(Suppl. 1):S151.

Sibship: Natural brothers and sisters. ▶kindred, ▶sibpal

SIC1: Cell cycle S-phase cyclin-dependent kinase (CDK, Cdc28-C1b) inhibitor. ▶CDC34, ▶CDC6,

▶cell cycle [START], ▶mitotic exit, ▶APC; Verma R et al 2001 *Mol Cell* 8:439.

Sickle-Cell Anemia: A human hereditary disease caused by homozygosity of a recessive mutation(s) or deletions in the hemoglobin β chain gene. Heterozygosity causes the sickle cell trait. Under low oxygen supply, the red blood cells lose their plump appearance and partially collapse into sickle or odd shapes because of the aggregation of the abnormal hemoglobin molecules (see Fig. S55).

The disease is not absolutely fatal but crises may occur when the blood vessels are clogged. Complications may arise due to poor blood circulation. In the classical form of the sickle cell disease, in the hemoglobin S a valine residue replaced a glutamine residue of the normal beta chain (hemoglobin A). In the hemoglobin C at the same position, a lysine replacement occurs, and this condition causes less severe clinical symptoms. Other forms, hemoglobin D and E are less common. This disease provided the first molecular evidence that mutation leads to amino acid replacement. Sickle cell anemia affects more than 2 million persons worldwide. About 10% the population of African descent in the USA are carriers (heterozygous) for this mutation and about 1/400 is afflicted with homozygosity at birth. In populations of European (except southern Europeans) descent, the frequency of this mutant gene is about 1/20 of that in Mediterraneans and Africans. The high frequency of the genetic condition in areas of the world with high infestation by malaria is correlated. The individuals without sickle cell anemia gene have about 2–3 times higher chance to be infected by *Plasmodium falciparum*. The mutation is selectively advantageous by protecting heterozygotes against malaria. The globin gene cluster has been located to human chromosome 11p15. The order is 5'— γ G— γ A— δ — β —3'. Correction of the defective allele is possible by transduction of the defective cells with retroviral or adenoviral vectors that can deliver the normal gene to the hematopoietic stem cells. However, these viral vectors may have deleterious consequences for the body. There is a problem of the low expression of the transgene. In a mouse model, embryonic stem cells containing the normal β^A allele, when introduced into β^S embryonic mouse blastocysts produced both types of globins indicating a promise that this approach may help in curing human β -thalassemia (Chang JC et al 2006 *Proc Natl Acad Sci USA* 103:1046).

Another method is to introduce into the lymphoblastoid cells chimeric DNA-RNA oligonucleotides with a correction for the β^S allele mutation, brought about through gene conversion in the target cells. This procedure may eventually be clinically applicable.

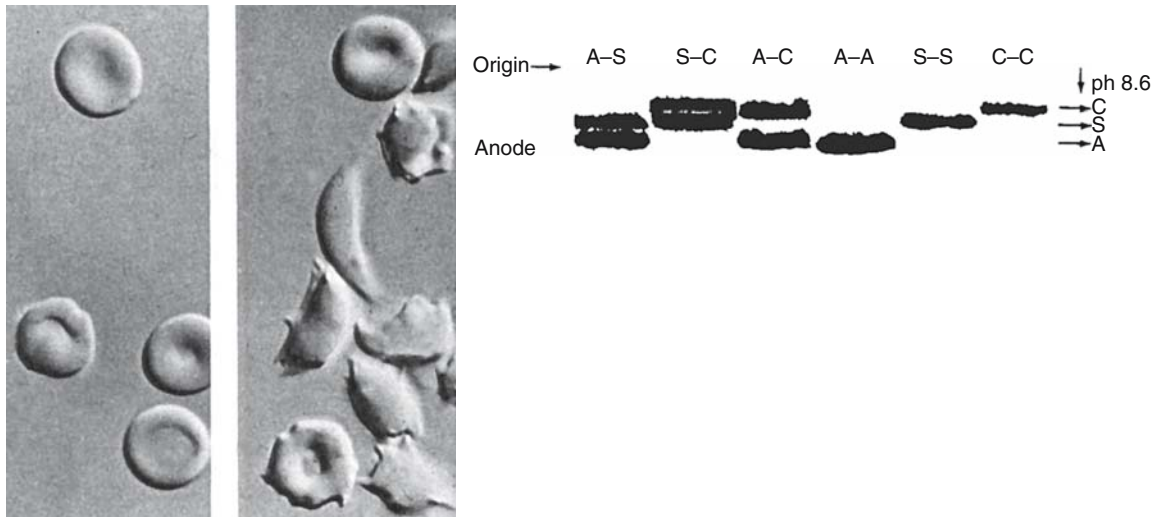


Figure S55. Human red blood cells from a sickle cell anemia patient. Left: In the presence of normal oxygen supply, Right: At low oxygen supply. Normal red blood cells look like biconcave discs very similar to that at left here. The sickling cells are unable to hold oxygen and that condition is responsible for the disease. (Photographs are the courtesy of Cerami A, Manning JM 1971 Proc Natl Acad Sci USA 68:1180). At far right: Carriers or sufferers can be unambiguously identified by electrophoretic separation of the blood proteohomozygotes for the normal blood protein (A-A), sickle cell anemia (S-S), hemoglobin C (C-C). In the heterozygotes (A-S, S-C and A-C)—because of codominance—both types of parental proteins are detected. (From Edington GM, Lehman H 1954 Trans R Soc Trop Med Hyg 48:332)

Another possible therapeutic approach involves correction of the defective β -globin mRNA by the similar (fetal) normal (anti-sickling) protein transcript using a transsplicing ribozyme and the generation of a normally functional transcript. When the hemoglobin α and β genes were knocked out of mouse and mated with animals transgenic for the human sickle cell gene, an animal model was generated for experimentation with this human disease. Attempts are being made to activate the silent fetal hemoglobin genes—by urea compounds—at later developmental stages in order to compensate for the defective adult hemoglobin. ▶malaria, ▶hemoglobin, ▶thalassemia, ▶sickle cell trait, ▶genetic screening, ▶viral vectors, ▶gene therapy, ▶gene conversion, ▶ribozymes, ▶transsplicing, ▶introns, ▶SAD mouse; Pawliuk R et al 2001 Science 294:2368; Vichinsky E 2002 Lancet 360:629.

Sickle Cell Trait: The sickle cell trait is due to heterozygosity of the recessive mutation in the gene controlling the β -chain of hemoglobin. Normally, these heterozygotes do not suffer from this condition but under low oxygen supply, e.g., at high elevations, adverse consequences may arise. ▶sickle cell anemia, ▶hemoglobin

Side-Arm Bridge: An attachment of chromatids resembling chiasma but actually only an anomaly in mitosis or meiosis, usually arising when chemicals or radiation

disturb division (see Fig. S56). ▶bridge, photo is the courtesy of Dr. BR Brinkley & WN Hittelman.

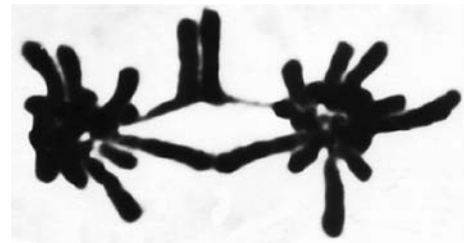


Figure S56. Side-arm bridge

Siderocyte Anemia (sideroblastic anemia): An anemia with erythrocytes containing non-hemoglobin iron; it may be controlled by either autosomal recessive or dominant or X- linked genes and based on defects in erythroid β -aminolevulinatase synthase. ▶anemia

Siderophore: Iron transporter. Transformation into rice plants highly efficient siderophore system genes (for nicotinamine aminotransferase) from barley facilitates iron uptake on alkaline soils and substantially improves growth (Takahashi M et al 2001 Nature Biotechnol 19:466). Mammals sequester excess iron into bacterial siderophores through the mediation of the host protein lipocalin 2. When the Toll receptor

senses infection and the system fights bacteria. This constitutes a novel means of innate immunity (Flo TH et al 2004 Nature [Lond] 432:917). ►immunity innate, ►Toll

Siderosis: Iron overload in the bloodstream.

SIE: STAT-inducible element. ►Jak-Stat pathway

Siemens (SI): A unit of conductance; 1 Ampere/Volt in a tissue of 1 Ohm resistance. ►Ampere, ►Volt, ►Ohm

SIEVE TUBE: A plant food transporting tube-shape, tapered, long cells; they may be connected by sieve plates that hold them together.

SIEVERT (Sv): The name for Sv (unit of absorbed dose equivalent [J/kg]) = 100 rem = 1 Sv. It is commonly used for measuring the occupational radiation hazards. ►rem, ►Gray, ►rad, ►R

SIGLECs (sialic acid recognizing Ig-superfamily lectins, 19q13.3): Immune inhibitory receptors with sialic acid ligands. During evolution, T cell Siglec expression was largely lost from humans while it was retained in apes. This fact explains why human are more at risk by T-cell-mediated diseases, such as AIDS and hepatitis B and C, compared to apes (Nguyen DH et al 2006 Proc Natl Acad Sci USA 103:7765). ►sialic acid, ►AIDS, ►hepatitis

Sigma Factor: A subunit of DNA-dependent bacterial RNA polymerase, required for the initiation of transcription and for promoter selection. It has been reported that in *Bacillus subtilis*, the σ factor alone is sufficient for melting the DNA around site -10 of the promoter (Hsu HH et al 2006 Cell 127:317). The documentation of this finding has been, however, questioned (Xin H 2006 Science 314:1669) and the paper was retracted (2007 Cell 128:211). ►open promoter complex, ►RNA polymerase, ► σ

Sigma Replication: ►rolling circle

Sigma Virus of *Drosophila*: ►CO₂ sensitivity

Sign Mutations: Frameshift mutations because an equal number base addition(s) (+) and deletion(s) (–) at the gene locus may restore the reading frame, although may not always restore normal function. ►frameshift

Signal: A molecular determinant, emitted by an extracellular source, or by an intracellular organizer and is directed either to an adjacent tissue (vertical signal) or to adjacent cells of the same tissue (planar signal). The response to a signal frequently involves change in transcription. ►signal transduction; Camili A, Bassaler BL 2006 Science 311:1113.

Signal End: ►immunoglobulins

Signal Joint: ►signal end

Signal Hypothesis: The signal hypothesis postulated that the signal peptide of the nascent polypeptide chain guides it to the endoplasmic reticulum (and to other) membranes where the signal peptidase cleaves it off, and subsequently the peptide chain is completed within the lumen of the membranes. It has now been validated for transport through bacterial cell membranes, mitochondria, plastids, peroxisomes, etc. ►signal peptides, ►transit peptide, ►protein targeting; Loureiro J et al 2006 Nature [Lond] 441:894.

Signal-Noise Ratio: The signal-noise ratio determines the sensitivity of an instrument or procedure to detect the presence or the function of a molecule in a reliable manner.

Signal Peptidase: ►signal hypothesis

Signal Peptides (signal sequence): 15 to 35-amino acid long sequences generally occurring at the NH₂ terminus of the nascent polypeptide chains of proteins that have a destination for an intra-organellar or transmembrane location. They are made in eukaryotes and prokaryotes but not all the secreted proteins possess signal peptides. At the beginning of the sequence, generally there are one or more positively charged amino acids, followed by a tract of hydrophobic amino acid residues that occupy about three-fourth of the length of the chain. This hydrophobic region may be required to pass into the lipoprotein membrane. The amino acid sequences among the various signal peptides are not conserved, indicating that the secondary structure is critical for recognition by the signal peptide recognition particles and for the function within the membrane. The eukaryotic signal sequences are recognized by the prokaryotic transport systems and the prokaryotic signal peptides can function in eukaryotes. After the passage of the nascent peptide has started the signal, peptides are split off by peptidases on the carboxyl end of (generally) glycine, alanine, and serine. Consequently, the majority of the proteins in the membrane or transported through the membranes, have the nearest downstream neighbor in one of these three amino acids at the amino end. One major characteristic of the signal peptide is the co-transcriptional targeting, whereas the transit peptides are targeted posttranslationally. The signal sequences may show polymorphism that might result in incorrect targeting. ►signal sequence recognition particle, ►transit peptide, ►leader peptide, ►endoplasmic reticulum; von Heijne G et al 1989 Eur J Biochem 180:535; Watanabe N et al 2001 J Biol Chem 276:20474; transmembrane and signal peptide server: <http://phobius.cgb.ki.se/>.

Signal Recognition Particle: ►signal sequence recognition particle, ►SRP

Signal Sequence: The amino terminal of some proteins signals the cellular destination of these proteins, such as the signal peptides. ►[signal peptide](#)

Signal Sequence Recognition Particle (SRP): In mammals, a complex of six proteins and an RNA (7SL RNA) that recognizes the *SRP receptor protein* on the surface of the endoplasmic reticulum and the *signal peptides* of the nascent proteins translated on the ribosomes associated with the endoplasmic reticulum (rough endoplasmic reticulum) and facilitate the transport of these polypeptides into the lumen of the Golgi apparatus and lysosomes (co-translational transport) (see Fig. S57). Signal recognition particle proteins have been located to human chromosomes, 5q21, 15q22, 17q25 and 18.

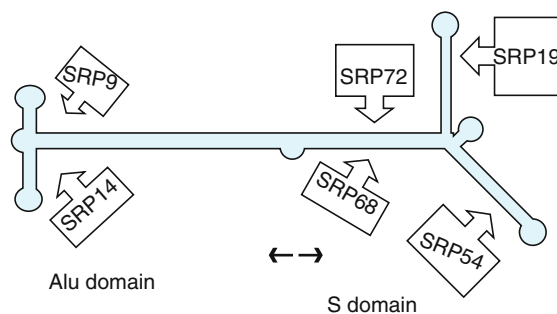


Figure S57. Schematic illustration of a signal recognition particle. The boxes represent the six proteins around the RNA. SRP9—SRP14 and SRP72—SRP68, respectively form dimeric structures. (Modified after Weichenrieder O et al 2000 Nature [Lond] 408:167)

The SRP binds to the signal peptide after a about 70-amino acid chain is completed at the beginning of translation. The polypeptide chain elongation is somewhat relaxed until the SRP attaches to the SRP receptor. Then, the SRP comes off the amino acid chain, elongation resumes its normal rate, and the entry of the chain through the membrane proceeds. In the meantime, a peptidase inside the endoplasmic reticulum cuts off the 15–30 amino acid long signal peptide sequences. ►[lysosomes](#), ►[Golgi](#), ►[signal peptides](#), ►[protein synthesis](#), ►[signal sequence particle](#), ►[RNA 7S](#), ►[protein targeting](#), ►[translocon](#), ►[translocase](#), ►[TRAM](#), ►[protein conducting channel](#); Keenan RJ et al 2001 Annu Rev Biochem 70:755; Fulga TA et al 2001 EMBO J 20:2338; Wild K et al 2001 Science 294:598; Hainzl T et al 2002 Nature [Lond] 417:767; Pool MR et al 2002 Science 297:1345; structure: Egea PF et al 2004 Nature [Lond] 427:215; structure of *E. coli* signal recognition particle bound to ribosome: Schaffitzel C et al 2006 Nature [Lond] 444:503; <http://psyche.uthct.edu/dbs/SRPDB/SRPDB.html>.

Signal Transduction: A system of proteins transforming various stimuli into cellular responses. The process requires four major categories of elements: signals, receptors, adaptors, and effectors.

Signals. The extracellular signals interact with cell membrane receptors (EGFR, FGFR) and subsequently make contacts with intracellular target molecules to stimulate a cascade of events leading to the formation of effector molecules that switch genes on and off and control cellular differentiation in structure and time by regulating transcription. The *signals* are proteins, peptides, nucleotides, steroids, retinoids, fatty acids, hormones, gases (ethylene, nitric oxide, carbon monoxide), inorganic compounds, light, etc. The target cells accept the signals by special sensors, *receptors*. The receptors are generally specific proteins with high binding specificities and positioned on the cell surface or within the plasma membranes and thus readily accept the signal *ligands*. The receptors may be also inside the cells, and the ligands may have to pass the cell membranes to reach them. As a consequence of the binding, a cascade of events is triggered and eventually the instruction reaches the cell nucleus and the relevant genes. The *paracrine signals* are restricted in movement to the proper, a generally nearby, target. The nerve cells are communicating by *synaptic signals*. The *endocrine hormone* signals may affect also distant targets in the entire body. The neurotransmitters are activated through long circuits of the nervous system by electric impulses emitted by neurons in response to the environment. The travel of the electric signals through the neurons is very fast, may pass through meters per second. The neurotransmitters have only a few nanometers to pass and the process takes only a few milliseconds. The local concentration of the endocrine hormones is extremely low. In contrast, the neurotransmitters may be quite concentrated at very small target area. The neurotransmitters also may very rapidly be removed either by re-absorption or by enzymatic hydrolysis. Generally, the hydrophobic signals persist longer in the cells than the hydrophilic ones. The membrane anchored growth factors and cell adhesion molecules are signaled through the *juxtacrine* mediators.

Receptors. The target cells respond by *receptor proteins*. These receptors are endowed with specificities regarding the signal they respond to. Also, the same signal may have different receptors in differently specialized cells. In addition, the interpretation and use of the signal within similar cells may vary. The signals may act also in a combinatorial manner: several signals together may be involved in the cellular decisions and influence the length and quality of the effect of a signal received. The various receptors, despite substantial chemical differences of the signals (e.g., cortisol, estrogen, progesteron,

thyroid hormones, retinoic acid, vitamin D), may bind ligands that control through the signal transduction path closely related and interchangeable upstream DNA consensus elements, involved in the regulation of transcription of different genes. Steroid hormone receptors, after bound to cognate hormones, may activate the transcription of the so-called *primary response genes*. These proteins then repress the further transcription of the primary response genes and turn on the transcription of *secondary response genes* (►regulation of gene activity).

Receptors can be (i) *ion-channel* or (ii) *G-protein* or (iii) *enzyme-linked* types. Group (i), also called transmitter-regulated ion channels, are involved in transmitting neuronal signals (►ion channels). Group (ii) receptors are transmembrane proteins of the so-called seven-membrane type (►seven-membrane proteins) associated with guanosine phosphate-binding G proteins (►G-proteins).

When GTP is bound to the G-protein, a cascade of enzymes or other proteins may be activated or an ion channel may become more permeable. G-protein linked receptors represent a large family of proteins, more than 100 of which, have been already identified in a variety of eukaryotes. The receptors, generally monomeric and evolutionarily related proteins, respond to a variety of signals, such as hormones, mitogens, light, pheromones, etc. Activation of group (iii) receptors may directly or indirectly lead to the activation of enzymes. These three different types of signal transduction may not be entirely distinct because the function of the ion channels may interact with the pathways mediated through G-proteins and various kinases. Some of the receptors are *protein tyrosine phosphatases* (e.g., CD45 protein) and *serine/threonine phosphatases* residing within the membrane or in the cytosolic domain of transmembrane proteins or in the cytosol.

Pathways. Pathways may show a great variation depending on the signals and receptors involved. Ca^{2+} is a general regulator. It may enter nerve cell terminals through voltage-gated Ca^{2+} channels in the cell membranes and stimulates the secretion of neurotransmitters (►ion channels, ►voltage-gated ion channel). Alternatively, Ca^{2+} may play a more general role by binding to G-protein linked receptors in the metabolism of inositol phospholipids, PIP (phospho-inositol phosphate), and PIP_2 (phosphoinositol biphosphate). The specific trimeric G-protein, Gq is involved in the activation of *phospholipase C- β* , that is specific for phosphoinositides, and splits PIP_2 into inositol triphosphates and diacylglycerol. Hydrolysis of PIP_2 yields IP_3 (inositol 1,4,5-triphosphate). The latter sets free calcium from the endoplasmic reticulum through IP_3 -gated channels, ryanodine receptors (►ryanodine). Upon further

phosphorylation, IP_3 may give rise to IP_4 (inositol 1,3,4,5-tetrakisphosphate) that slowly yet steadily replenishes cytosolic calcium. The calcium level in the cytosol rises and subsides in very short bursts according to how phosphatidyl-inositols regulate it (calcium oscillations). These oscillations still may assure increased secretion of second messengers and spare the cell from a constant level of the toxic Ca^{2+} in the cytosol. Besides pumping out Ca^{2+} shielded in the endoplasmic reticulum, diacylglycerol and eicosanoids (arachidonic acid) may be produced.

Diacylglycerol and the latter lipid derivatives may activate the Ca^{2+} -dependent enzymes, serine/threonine kinases, which have key role in activating proteins that mediate signal transduction (►protein kinases). *Protein kinase C* may activate the cytosolic *MAPK* (mitogen activated protein kinase) by phosphorylation and may phosphorylate a cytoplasmic inhibitor complex such as $\text{I}\kappa\text{B} + \text{NF-}\kappa\text{B}$. Thus, *MAPK* may phosphorylate DNA-binding proteins such as *SRF* (serum response factor) and *Elk* (member of the *ETS* oncoprotein family), sitting already at the upstream regulatory regions of a gene(s), such as the serum-response element (*SRE*). The phosphorylation then initiates transcription (►regulation of gene activity). The released protein factor *NF-}\kappa\text{B}* may migrate to the nucleus and, by binding to its cognate DNA site, sets into motion transcription (if other factors are also present). The response of the genes to the transducing signals depends on the number of regulatory proteins responding to the signal. Monomolecular reactions display relatively slow response to the concentration of the signal molecules, whereas if the number of effectors is multiple, the reaction to them may follow 3rd or multiple order kinetics. Similarly, prompt response is expected if the signal activates one reaction (e.g., phosphorylation) and at the same time deactivates an inhibitor or suppressor (e.g., by phosphatase action).

The enzyme-linked signal receptors do not need G-proteins. The transmembrane receptor binds the ligand at the cell surface and the cytosolic domain functions as an enzyme or it associates with an enzyme and the transfer of the signal to the cell nucleus is more direct. An example is the cytokine-activated cell membrane receptor *Jak tyrosine kinases*, which when dimerize, can combine with cytoplasmic *STATs* (signal transducers and activators of transcription) and chromosomal responsive elements. In response of interferon or other cytokine signals, the *JAK* phosphorylates tyrosine of the *SH2* domains in a variety of *STAT* proteins. This may be followed by dimerization and the transfer of these proteins to the nucleus where they may turn on transcription of particular genes (see Fig. S58). It has been estimated that about 1% of the human genes code for protein kinases.

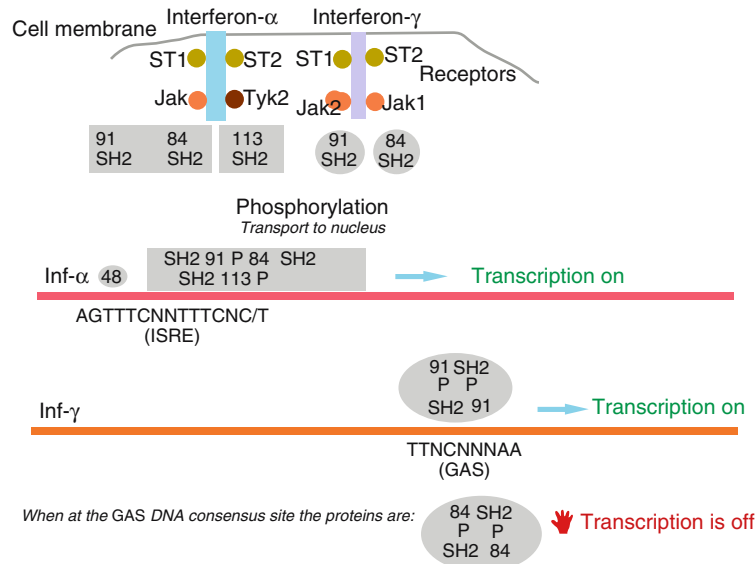


Figure S58. The JAK-STAT signal transduction pathway, based on interferon (IFN)-mediated receptors. *JAK* is a family of the Janus tyrosine protein kinase proteins, and *STAT* stands for signal transducer and activator of transcription. When the ligand binds to the signal-transducing receptors (ST), the receptor-attached *JAK* kinases modify the *STAT* proteins. After dimerization (using SH2 domains), they are transported directly to *ISRE* (interferon- α -response element) or to *GAS* (γ -interferon activation site) in the chromosomal DNA. These two elements vary, yet consensus sequences exist (as shown in the diagram). The 84, 91, 113, and 48 are proteins (in kDa), but additional ones may also be involved, depending on the nature of the signals received. The diagram does not display IFNGR1 and IFNGR2 integral membrane proteins, which are also essential parts of the γ -receptor. (After Darnell JE Jr., et al. 1994. *Science* 264:14125 and Heim MH et al. 1995. *Science* 267:1347.)

In case of autophosphorylation or other reactions involving enzymes, which may bind their own products, the activity of the enzyme may be increased in the course of time with the increase of the number of product molecules, through a positive feedback.

These kinases may be mainly either serine/threonine or tyrosine kinases. Some proteins may phosphorylate all three of these amino acids. The reliance on protein tyrosine kinases for signal transduction is rather general. Epidermal growth factor (EGF), nerve growth factor (NGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin, insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), macrophage colony stimulating factor (M-CSF), etc., function with the assistance of transmembrane *receptor tyrosine kinases*. Upon the arrival of the ligand (signal), the receptor is dimerized either by cross-linking two receptors by the dimeric ligand or by inducing autophosphorylation and linkage of two cytosolic domains of the receptors. The different phosphorylated sites may bind different cytoplasmic proteins. The insulin itself is a tetramer ($\alpha\alpha\beta\beta$) and thus does not need dimerization. After autophosphorylation, it phosphorylates an

insulin receptor (IRS-1) at tyrosine sites and that may bind to other proteins, which also may become phosphorylated and may form different complexes, thus, generating a variety of transcription factors. Alternatively, the *tyrosine kinase-associated receptors* themselves are not tyrosine kinases but associate with proteins of this capability. Some of the enzyme-linked receptors are *serine/threonine kinases* with specificities for these two amino acids. The phosphorylated tyrosine residues are binding sites for proteins with SH2 domains. The *receptor tyrosine phosphatases* may activate or inhibit the signal pathways by the removal of phosphate from tyrosine residues. The receptor guanylate (guanylyl) cyclases operate in the cytosolic domain of the receptors and function by serine/threonine phosphorylation in association with trimeric G-proteins. Within the last decade, discoveries about signal transduction have changed the views about cellular functions and added a new dimension to biology by integrating reversed and classical genetics. The signal transduction mechanisms have a large variety of means to regulate diverse functions of metabolism, differentiation, and development (see Fig. S59). The different signaling molecules are organized into separate pathways. The

different protein components appear to be regulated and coordinated into signaling complexes by SH, pleckstrin-homology, phosphotyrosine, and PDZ (post-synaptic density, dislodge, zo-1) protein domains through protein-protein interactions.

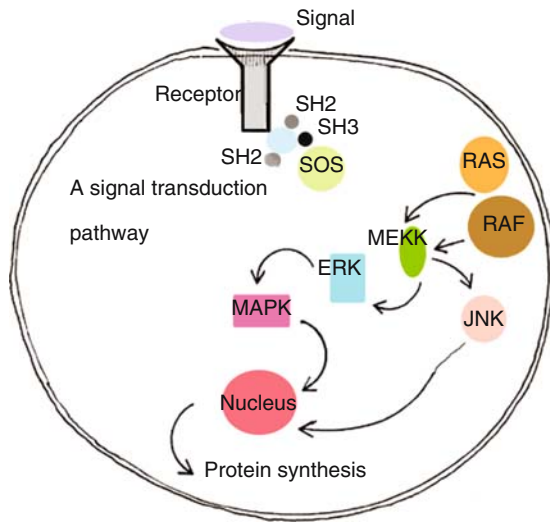
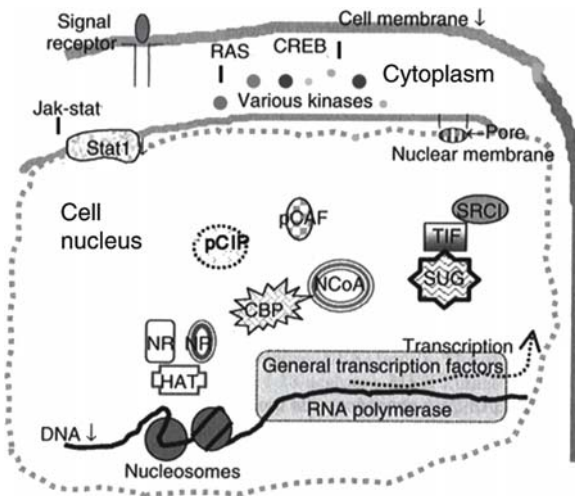


Figure S59. A signal transduction pathway leading through the G-protein RAS. This pathway controls cell division, differentiation, development of cancer, mating type, cell wall biosynthesis, and a variety of other processes. The signal can be a variety of molecules such as epidermal growth factor (EGF), nerve growth factor (NGF) or their homologs in various other animals such as *LET-23* in *Caenorhabditis* or *DER* in *Drosophila* the RAS-mediated pathway operates also in fungi and plants. The process begins with the (mitogen) signal arriving to the double membrane of the cell (see at 12 O'clock). The signal is recognized by a signal receptor protein, which may vary from signal to signal. This is a transmembrane protein with a hydrophobic tract forming generally seven turns within the cell membrane. When the signal arrives, the receptor is activated. The protein tyrosine kinase receptors (e.g., SEV) recruit then the down-stream receptor kinases or adaptor proteins such as GRB (or homologs e.g., SEM-5 in *Caenorhabditis*, DRK in *Drosophila*). The GRB proteins have an SH2 domain, which is a binding site for tyrosine kinase proteins and the SH3 domains are binding sites for proline-rich motif proteins. The SH domains were originally identified in the SRC protein (product of the Rous sarcoma oncoprotein) and both are characteristic for mediators of the signal transduction path. The GRB protein then binds another mediator or adaptor protein, SOS (named after the product of a *Drosophila* gene, called *son of sevenless*). The sevenless gene encodes Rhabdome seven light receptors in the eyes of the flies. In place of SOS, there may also be SHC (an oncoprotein of the pheochromocytoma tumor of the adrenal medulla or in paraganglia and thus causing increased secretion of the hormones epinephrine and norepinephrine). Upon the influence of the GRB-SOS

complex, the membrane-bound RAS G-protein (see at 3 O'clock) becomes activated. The membrane association of RAS is mediated by a carboxy-terminal CAAX box, a signal for farnesylation, proteolysis and carboxymethylation and by the neighboring six lysine residues. RAS (named after rat sarcoma) is also a GTPase. The RAS serves as a turnstile for a series of processes. It is shut down when the situation is RAS*GDP (RAS guanosine diphosphate) and it opens when it becomes RAS*GTP (RAS-guanosine triphosphate). RAS activation may be prevented by another gene, encoding a GTP-ase activating protein (GAP). The RAF protein (its homologs in budding yeast is STE11, and BYR 2 in fission yeast) is also membrane bound by a CAAX box. RAF is a Ser-Thr kinase and it phosphorylates, independently of RAS, also MEK, a protein of the extra-cellular signal regulated kinase (ERK) family. The extracellular regulators can be growth factors (e.g., EGF, NGF), receptor kinases and TPA (12-O-tetradecanoyl-phorbol-13-acetate). MEK kinase (MEKK) is phosphorylated on Thr and Ser residues by RAF. Protein MAPK (mitogen-activated protein kinase) may be capable of autophosphorylation and it may be phosphorylated by the ERK family of kinases at Tyr and Thr residues. MAPK homologs are KSS, HOG-1, FUS3, SLT-2, SPK-1, SAPK (a stress activated kinase), FRS (FOS regulating kinase), etc. MAPK may then activate the FOS and JUN oncogene complex that is also known as the AP-1 heterodimeric transcription factor of mitogen-inducible genes. The RAS to MAPK route may branch downstream through several effector proteins and may control the transcription of several different genes. The specificity of activation depends on combinatorial arrangements of the effectors. (The size, shape or shading of the symbols is not intended to represent their structure.)

Plant Signals. Plant signals are somewhat different from the signals in animals. The plant hormones, similarly to animal hormones, are signaling molecules but most of them—except the brassinosteroids—are very different molecules. In plants, light and temperature signals (photoperiodism, vernalization, phytochrome) are very important for growth and differentiation. Salicylic acid is a signaling molecule for defense genes, etc. In plants, signaling depends a great deal on positional cues.

Several signal transduction pathways may be simultaneously operational within an organism and they may interact at various levels. In addition, the pathways and components may operate differently in different cellular compartments (e.g., plasma membrane, cytosol, nucleus, organelles). The cytoskeleton network may serve in various capacities to direct the flow of reactions through the signaling pathways. The current view is that signaling proteins translocate in the cytoplasm and bind in a reversible manner and dynamic fashion (soft-wired signaling concept). The



JAK-STAT: see more above

RAS: see more above

CREB: cAMP-response element-binding protein

pCIP: p300/CBP/cointegrator-associated protein

CBP: CREB-binding protein

pCAF: chromatin assembly factor

NcoA: nuclear receptor coactivator

SRC1, TIF, SUG: nuclear coactivator proteins

NR: nuclear receptors

HAT: histone acetyltransferase

Besides the molecules shown and named, several other proteins may be involved. Some of the proteins are activated only after binding with their ligands. The size or shape of the structures shown does not reflect the actual nature of these molecules.

Figure S60. Transactions inside the nucleus after the signals arrived

earlier idea was that receptors and other signalling proteins occupy fixed positions in the cell and second messengers mediate the connections with aid diffusion (hard-wired signaling). As opposed to electric circuits, a model signal of transduction is that of a gradient of quantitative information propagated outwards throughout the dense protein network following an input through an individual receptor. A central maximum of information transfer can include the old canonical pathways but the propagation throughout the signaling network may be in part stochastic and influenced by the local network composition. Although, large-scale, global static interaction maps are useful initially, these rarely recapitulate the often-transient connections of known signaling modules. Understanding signal transduction from a network perspective allows an appreciation of how variants of proteins (by mutation or concentration) within the network can lead to quantitatively different outputs. Thus, for diseases linked to disruption of particular signaling networks, comparison of QTLs with functional genomic RNAi screens of those networks synergistically provides a mechanistic insight into disease etiology. Sequencing of a large number of genes from breast and colorectal cancers (Sjöblom T et al 2006 Science 314:268), projected an average of 90 mutated genes per tumor, 11 of which occurred at significant frequency, suggesting that many mutations are needed to attack the robust cell signaling network. It is logical that signal transduction and transcriptional machinery components are extremely common functional categories mutated in these cancers (Friedman A, Perrimon N 2007 Cell 128:225).

The introduction of GFP labeling now facilitates the tracing of the signaling traffic. The interacting

signals are usually expressed in a quantitatively variable manner. Understanding how different cells work under the control of the genetic potentials and the environment will be the most challenging task of the research on growth, differentiation, development, the nervous system, behavior, productivity, pathogenesis, evolution, etc.

►G-proteins, ►diffusion, ►JAK-STAT pathway, ►interferons, ►histidine kinase, ►regulation of gene activity, ►hormones, ►morphogenesis, ►AKAP79, ►T cells, ►integrin, ►ciliary neurotrophic factor, ►adaptor proteins, ►morphogen, ►photomorphogenesis, ►vernalization, ►photoperiodism, ►phytohormones, ►salicylic acid, ►host-pathogen relationship, ►signaling to translation, ►nuclear pore, ►SUG, ►TIF, ►TRIP, ►cell membranes, ►PP2A, ►MPK, ►MPK phosphatase, ►MLK, ►REM, ►GEF, ►CBP, ►GFP, ►cross-talk, ►arrestin, ►desensitization, ►SMAD, ►NF-κB, ►genetic networks, and the other terms mentioned, ►feedback, ►selector genes; <http://www.signaling-gateway.org/>; <http://www.mshri.on.ca/pawson/research.html>; Milligan G (ed) 1999 Signal transduction. A practical approach. Oxford University Press, New York; Morris AJ, Malbon CC 1999 Physiol Revs 79:1373; Hunter T 2000 Cell 100:113; Dohlman HG, Thorner JW 2001 Annu Rev Biochem 70:703; Heldin C-H 2001 Stem Cells 19:295; review articles in 2001 Nature [Lond] 413:186–230; Brivanlou AH, Darnell JE Jr 2002 Science 295:813; for newer reviews: 2002 Science 296:1632 ff; Dorn GWII, Mochly D 2002 Annu Rev Physiol 64:407; Ernstrom GG, Chalfie M 2002 Annu Rev Genet 36:411; Pires-daSilva A, Sommer RJ 2003 Nature Rev Genet 4:39; Pawson T, Nash P 2003 Science 300:445; signal transduction networks: Bhattacharyya RP et al 2006 Annu Rev

Biochem 75:655; signal transduction proteins: <http://www-wit.mcs.anl.gov/sentra>; signaling database: <http://www.signaling-gateway.org/molecule/>; signals: <http://www.grt.kyushu-u.ac.jp/spad/>; <http://www.gene-regulation.com/pub/databases.html>; <http://bibiserv.techfak.uni-bielefeld.de/stcdb/>; prokaryotic signal transduction proteins: <http://compbio.mcs.anl.gov/sentra>; microbial signal transduction database: <http://genomics.ornl.gov/mist>.

Signal Transfer Particle: PDGF associated with phospholipase C- γ , phosphatidylinositol 3-kinase, and the RAF protooncogene product regulates signaling. ►platelet derived growth factor, ►phosphatidylinositol kinase, ►RAF

Signaling: The phosphorylation of enzymes mediated by second messengers leads to their activation through outfolding of the pseudosubstrate domains of the enzymes and thus opens the active sites for the true substrate. ►signal transduction

Signaling Molecule: A signaling molecule alerts cells to the behavior of other cells and environmental factors. ►autoinduction

Signaling to Translation: Signaling transduction is directed toward the 5'-untranslated region (UTR) and involves the translation of ribosomal proteins and elongation factors (eEF1A, eEF2). The target of the signals appears to be the 5'-terminal oligopyrimidine sequences (5'-TOP) and the UTR polypyrimidine tracts. Secondary structure formation with long UTRs may also be regulatory. Growth factors may phosphorylate the eukaryotic initiation factor eIF4E-binding protein, 4E-BP-1, and cause its dissociation from eIF4E. In order that the translation would proceed, the initiation factors eIF4A, -4B, -4G, -4E attach to the methylguanine cap and the secondary structure of the RNA is untwisted by the helicase action of eIF4A. Phosphorylation by the p70^{S6k} kinase activates the S6 protein of the 40S ribosomal subunit, a process subject to enhancement by mitogens. This process is not a general requirement for translation, indicating that it affects only special genes with 5'-TOP and polypyrimidine tracts in their UTRs. Cycloheximide and puromycin are also involved in the phosphorylation of S6. Both of these phosphorylations are inhibited by rapamycin. ►F506, ►P70^{S6k}, ►secondary structure, ►cycloheximide, ►puromycin, ►cap, ►regulation of gene activity, ►regulation of enzyme activity, ►protein synthesis, ►signal transduction; Wilson KF, Cerione RA 2000 Biol Chem 381(5-6):357.

Signalosome: A molecular complex transmitting various cues. ►signal transduction; Lyapina S et al 2001

Science 292:1382; Zhang SQ et al 2000 Immunity 12:301.

Signature, Evolutionary: Within the various genomes (mammalian, mitochondrial, plants, prokaryotes, etc.), there appears to be a characteristic distribution of dinucleotide sequences, which is different from that of the other species. This constitutes an evolutionary signature. (See Campbell A et al 1999 Proc Natl Acad Sci USA 96:9184).

Signature of a Molecule: The characteristic feature(s) convenient for identification. Discriminating sequences of DNA, RNA, or the proteins of organisms may serve as signatures. Molecular signatures can predict the course of diseases (O'Shaughnessy JA 2006 N Engl J Med 355:615).

Signature-Tagged Mutagenesis (STM): The induction of mutation by the insertion of plasmids, transposable elements, or passengers of specially constructed vectors into the genetic material. An insertional mutagenesis system that uses transposons carrying unique DNA sequence tags—flanked by PCR-amplifiable short tracts—was developed for the isolation of bacterial virulence genes. Originally in a murine model of typhoid fever caused by *Salmonella typhimurium*, mutants with attenuated virulence were revealed by use of tags that were present in the inoculum but not in bacteria recovered from infected mice (Hensel M et al 1995 Science 269:400). ►targeting genes, ►vectors, ►insertional mutation; Nelson RT et al 2001 Genetics 157:935; Shea JE et al 2000 Curr Opin Microbiol 3:451; Mazurkiewicz P et al 2006 Nature Rev Genet 7:929.

Significance Level: The significance level indicates the probability of error by rejecting a null hypothesis that is valid (Type I error, α) or accepting one that is not correct (Type II error, β). By convention, 5% (*, significant), 1% (**, highly significant), and 0.1% (***, very highly significant) levels are used most commonly. These are not sacrosanct limits. In field experiments with crops, the 5% level may be a satisfactory measure for comparative yields but even the 0.1% may not be acceptable for pharmaceutical tests because the chance of harming 1/1000 persons is unacceptable. In general experimental practice, levels above 5% and below 0.1% are not considered meaningful although they may have relevance for pharmacology. ►goodness of fit, ►t-test, ►probability, ►power of the test, ►inference

Sign-R1: A lectin, which captures microbial polysaccharides in the spleen and interacts with complement component C1q. ►lectins, ►complement

SIL (short insert library): The SIL is generated by the restriction cleavage of gap-bridging clones (used in

the final stages of physical mapping) into 0.5 kb or smaller fragments to break up secondary structures of the DNA that complicate the determination of continuity in sequencing. ►[chromosome walking](#), ►[physical mapping](#), ►[restriction enzymes](#)

SILAC (stable isotope labeling by amino acid in cell culture): A proteomics technique used for separate identification of similar proteins in high performance liquid chromatography–mass spectrometry (Foster LJ et al 2003 Proc Natl Acad Sci USA 100:5813).

Silencer: A negative regulatory element reducing transcription of the region involving the target genes. Their action bears similarity to the heterochromatic chromosomal regions, which reduce transcription of genes transposed to their vicinity. The Sir proteins may interact with the amino-terminal of histones 3 and 4. Sir2 deacetylates histone H4 lysine¹⁶ tail and mediates the synthesis of 0-acetyl-ADP-ribose. As a consequence, Sir2, Sir3, and Sir4 bind to the histone tail and mediate chromatin silencing (Liou G-G et al 2005 Cell 121:515). Sir2 homotrimer is required for histone deacetylation and rDNA suppression, whereas telomere silencing requires the heterotrimeric complex of Sir2, Sir3, and Sir 4 (Cubizolles F et al 2006 Mol Cell 21:825). Silencing requires combination of a protein(s) and the site where silencing takes place. There is evidence that Sir-generated heterochromatinization interferes with the assembly of the components of the pre-initiation complex (Sekinger EA, Gross DS 2001 Cell 105:403). Some evidence in yeast indicates that TFIIB, RNA polymerase II, and TFIIE occupancy is reduced by a silencer at downstream of the gene activator protein (Chen L, Widom J 2005 Cell 120:37). For example, the *MATa* and *MATα* genes of yeast encode regulatory proteins that permit the expression of *a* and *α* mating types, respectively, of the haploid cells and the non-mating phenotype of the sporulation-deficient *a/a* diploid cells. When these genes are at the *HMLa* and *HMRa* sites, they are silenced until they are transposed to the *MAT* locus. The mating type switch is catalyzed by a cut mediated through HO endonuclease when the mating type alleles are at the *MAT* locus, but not at the *HMLa* and *HMRa* locations. This indicates that the silencing is under the dual control of the repressed domains, which appear to extend to 0.8 kb proximal to the centromere from *HML-E* and a silencer protein and a specific site. Inactivation of *SIR2*, *SIR3*, and *SIR4* derepresses *HML* and *HMR*. These genes affect the telomeric position effect of other genes as well. *SIR2*, *SIR3*, and *SIR4* are also involved in DNA repair and recombination in cooperation with the *HDF1* locus of yeasts (a *Ku* homolog). Mutations at the amino terminus of the *HISTONE 4* gene also have a similar

effect. Over-expression of *SIR2* causes its hypoacetylation, while *SIR3* mutations may alter the conformation of this histone bound to *HMR*. Loci *HML* and *HMR* both are flanked by *HML-E* and *HML-I* silencer elements. These silencers are similar to the autonomously replicating elements of yeast that are involved in DNA synthesis and apparently also in silencing. *HML-E* is capable of repression only in the presence of *HML-I* and is 0.4 kb distal from *HML-I* (based on Loo, Rine 1994 Science 264:1768). *HMR-E* is a very potent silencer endowed with binding sites for ORC (origin recognition complex), Rap1 (a suppressor of RAS-induced replication), and Abf1 (another silencer) suppressors of the S phase of the cell cycle. Recent evidence indicates that transcriptional silencing does not require DNA replication, although it seems to require some cell cycle events. Silencer elements are also present in animal and plant systems. In plants, when multiple copies of a gene are introduced into the genome by transformation, all or most copies of the gene are inactivated (trans-inactivation). The mechanism of this phenomenon is unclear. It has been suggested that when the level of a particular RNA is increased, a degradative process is initiated. This has been attributed to a defense mechanism, since the majority of plant viruses are RNA viruses. Some of the silencing appears, however, post-transcriptional. In fungi, silencing has been attributed to premeiotic methylation when multiple copies are present in cis position. This view is supported by the long-standing knowledge that the repetitive sequences of the heterochromatin are not expressed. Position effect has also been known as a type of silencing. The reversible type of paramutation can also be considered a transinactivation mechanism. Silencing of genes may be accomplished by moving the region of the intact chromosome toward the centromere (position effect). Transposition to the vicinity of heterochromatin may also result in silencing. Sir1 protein is most common in the telomeric region of yeast chromosomes but it may be present also in the nucleolus. Sir3 and Sir4 normally are absent from the nucleolus, but are present in case Sir2 is mutant. The *SIR2* homolog in mammalian cell is *SIRT2*, which controls caloric intake and thereby extends life span. Absence of *SIRT6* in mammals results in genomic instability, autoimmune disease (lymphopenia), metabolic defects, and premature death as a consequence of deficiency in excision repair of DNA (Mostoslavsky R et al 2006 Cell 124:315).

Although silencers have some similarities to insulators, the latter are different because they must be situated in between the enhancer and the target promoter. Unpaired DNA may cause meiotic silencing in *Neurospora*. Hypermethylation of CpXpG nucleotides by chromomethylase 3 in *Arabidopsis*

silences the expression of some genes and its mutation restores wild phenotype to the epigenetically silenced genes and reactivates retrotransposons.

►targeting genes, ►enhancer, ►position effect, ►mating type determination in yeast, ►*Schizosaccharomyces pombe*, ►antisense technologies neuron-restrictive silencer factor, ►CREB, ►co-suppression, ►quelling, ►epigene conversion, ►paramutation, ►heterochromatin, ►dominant-negative mutation, ►methylation of DNA, ►epigenesis, ►histone deacetylase, ►Ku, ►Hst1p, ►Abf, ►ORC, ►RAP1, ►post-transcriptional gene silencing, ►transcriptional gene silencing, ►RNAi, ►micro-RNA, ►HML and HMR, ►nucleosome, ►chromatin remodeling, ►MSUC, ►telomeric silencing, ►looping of DNA, ►insulator, ►methylation of DNA, ►pre-initiation complex, ►sirtuin, ►PIC, ►ascus-dominant, ►DNA repair; Guareente L 1999 Nature Genet 23:281; Kirchmaier AL, Rine J 2001 Science 291:646; Lindroth AM et al 2001 Science 292:2077; Sijen T et al 2001 Curr Biol 11:436; Ogbourne S, Antalis TM 1998 Biochem J 331:1; Moazed D 2001 Mol Cell 8:489; Mlotshwa S et al 2002 Plant Cell 14: S289; Béclin C et al 2002 Curr Biol 12:684; Shiu PKT, Metzberg RL 2002 Genetics 161:1483; Meister G, Tuschl T 2004 Nature [Lond] 431:343; Talbert PB, Henikoff S 2006 Nature Rev Genet 7:793.

Silene: ►*Melandrium*

Silent Information Regulators: Silent information regulators are involved in the assembly of the silent chromatin domains. ►silencer; Moazed D et al 1997 Proc Natl Acad Sci USA 94:2186.

Silent Mutation: Base-pair substitution in DNA that does not involve amino acid replacement in protein and entails no change in function. ►mutation

Silent Sites: Silent sites are where mutations in the DNA base sequence have no consequence for function. ►synonymous codons

Silicon (Si): The second most abundant element (27.6%) in nature. Si occurs in quartz, sand, and sandstone, or as silicate, e.g., in kaolinite. Plants take up 0.1 to 10% of their dry weight as silicic acid (H_2SiO_3) by using genetically determined silicon transporter proteins. It increases firmness of plant tissues and disease resistance (Ma JF et al 2006 Nature [Lond] 440:688). Silicons, organosilicon oxides polymers, are used in the laboratory as lubricants and seals. Silica gels are lustrous granules used for absorption and column chromatography.

Siliconization: In siliconization, glassware used in genetic laboratories is treated in a vacuum by dichlorodimethylsilane in order to prevent DNA molecules sticking to the vessel, and resulting in loss of recovery. ►DNA extraction

Silique: A typical fruit of cruciferous plants; two carpels, dehiscing at the base at maturity, enclose the placenta which sit in one row on each of the opposite sides of the replum. In Figure S61, the carpels were removed before maturity.



Figure S61. Silique

Silk Fibroin: A protein rich in glycine and alanine residues arranged largely in β sheets (β keratin). It is synthesized within the silk gland to protect the pupa. The pupa is called also chrysalis or cocoon. A fibroin gene is transcribed into about 10,000 long-life molecules of mRNA within a few days and they are translated several times into about a billion protein molecules. Each gland manufactures about 10^{15} fibroin molecules (300 μg) in four days. Actually, the gland is a single cell but it contains polytenic chromosomes and thus the fibroin locus is amplified about a million fold ($10^9 \times 10^6 = 10^{15}$ fibroins). In spiders, there is great diversity and also conservation in the silk fibroin genes (Garb JE et al 2006 Science 312:1762). Some of the spiders' silks are tougher than that of silkworm and rival the best man-made fibers. The spider dragline silk, besides its outstanding tensile strength, has unrivalled torsional quality that stop the spider from twisting and swinging and thus makes the animal less conspicuous to predators (Emile O et al 2006 Nature [Lond] 440:621). Spider dragline silk can be synthesized in transgenic tobacco, potato plants, and also in transgenic mammalian cells. ►polytenic chromosomes, ►silk worm, ►resilin; Vollrath F, Knight DP 2001 Nature [Lond] 410:541; Scheller J et al 2001 Nature Biotechnol 19:573; Lazaris A et al 2002 Science 295:472; Jin H-J, Kaplan DL 2003 Nature [Lond] 424:1057.

Silk: The botanical term for the pistils of the maize female inflorescence (see Fig. S62).

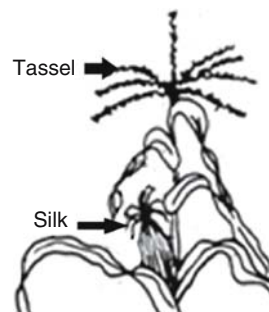


Figure S62. Maize female inflorescence

Silkworm (*Bombyx mori*, $2n = 56$): One of the best-studied insects in genetics (see Fig. S63). There are about 1000 markers in the genetic map spacing at ~ 2 cM. Its RAPD map (~ 2000 cM), includes ~ 1018 markers scattered over all chromosomes.

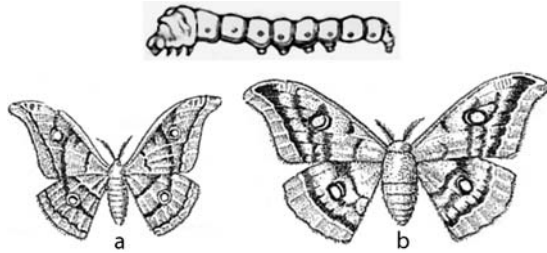


Figure S63. Silkworm larva; at top (a) male (ZZ), at right ZW female (b); wild type Asian imagoes. The pattern varies in the different wild insects and also in the domesticated varieties

About 91% of the genome of the domesticated silkworm has been sequenced and it contains $\sim 18,510$ genes (Xia Q et al 2004 Science 306:1397). Its genome contains a special type of transposable element, R2Bm, that is present also in some other insects. R2Bm has no long terminal repeats. It is inserted in the 28S rRNA genes only and encodes an integrase and a reverse transcriptase function within one protein molecule. The R2 protein nicks one of the DNA strands and uses it also as a primer to transcribe its RNA genome, which is then integrated as DNA-RNA heteroduplex. Subsequently, a host polymerase synthesizes the second DNA strand. [▶transposon](#), [▶complete linkage](#), [▶autosexing](#), [▶tetraploidy](#), [▶polyhedrosis virus](#), [▶silk fibroin](#), [▶RAPD](#), [▶pheromone](#); EST database: Mita K et al 2003 Proc Natl Acad Sci USA 100:14121; silkworm microsatellite database: <http://210.212.212.7:9999/PHP/SILKSAT/index.php>; <http://www.cdfd.org.in/silksatdb>; <http://www.ab.a.u-tokyo.ac.jp/silkbase/>; <http://silkworm.genomics.org.cn>.

Silver Syndrome (Silver spastic paraplegia, SPG17, 11q12-q14): A neurodegenerative disease involving amyotrophy (muscle weakness) in the hands. Hereditary dominant spastic paraplegia is a highly variable disease and it is encoded in several other chromosomes and locations. [▶paraplegia](#), [▶spastic paraplegia](#), [▶Berardinelli-Seip congenital lipodystrophy](#); Patel H et al 2001 Am J Hum Genet 69:209.

Silver-Russel Syndrome: [▶Russel-Silver syndrome](#)

Silverman-Handmaker Syndrome: [▶dyssegmental dwarfism](#)

Silyl-Phosphite Chemistry: Silyl-phosphite chemistry is used in oligoribonucleotide synthesis. (See Agarwal S (Ed.) 1995 Methods in Molecular Biology. Humana, Totowa, New Jersey, p 81).

Simian: Ape or monkey type. [▶primates](#), [▶hominidae](#)

Simian Crease: See [▶Down's syndrome](#) for illustration. It can be rarely observed (1–4%) in normal infants but it is characteristic for human trisomy 21, De Lange, Aarskoog, and other syndromes. [▶Down syndrome](#), [▶Aarskoog syndrome](#), [▶De Lange syndrome](#)

Simian Sarcoma Virus (SSAV): A gibbon/ape leukemia retrovirus with a homologous element in human chromosome 18q21. The long terminal repeat (535 bp) appears to contain transcriptional control and signal sequences. The human chronic lymphatic type leukemia seems to be associated with a break point of chromosome 18. [▶leukemia](#)

Simian Virus 40: A eukaryotic virus of a molecular weight of 3.5×10^6 with double-stranded, supercoiled DNA genetic material of 5243 bp (see Fig. S64). The DNA is organized into a nucleosomal structure that does not have H1 histone. The DNA around the nucleosome cores is 187 ± 11 bp and the cores are separated by 42 ± 39 bp linkers. The viral particles are skewed icosahedral capsids and have 72 protein units.

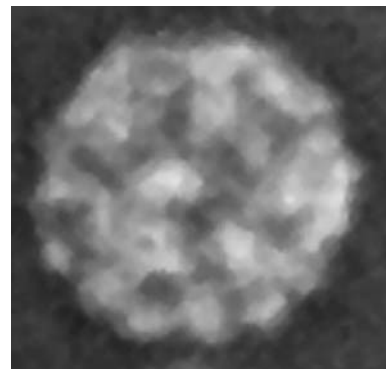


Figure S64. SV40

In primates, the virus generally follows a lytic lifestyle and the virions multiply in the cytoplasm, i.e., primates are *permissive hosts* for replication. SV40 encodes microRNAs that protect to some extent against the host cytotoxic T cells (Sullivan CS et al 2005 Nature [Lond] 435:682).

Occasionally, in humans the viral DNA integrates into the chromosomes. Such an event may lead to cancerous transformation. Rodent cells are *non-permissive hosts* for viral replication and the viral DNA integrates into the chromosomes leading to cancerous tumor formation. The correlation between

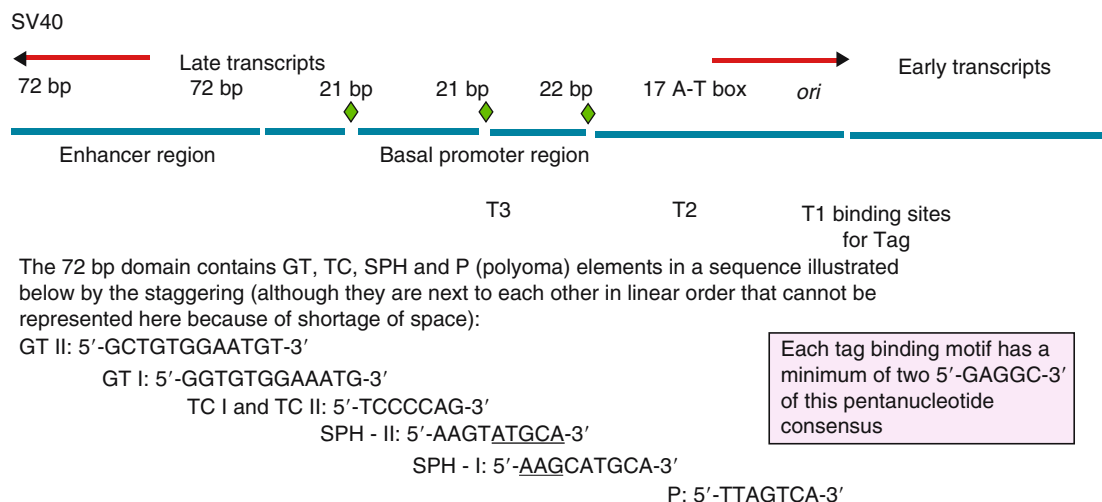


Figure S65. Organization of SV40

SV40 infection and cancer has been questioned (Paulin DL, DeCaprio JA 2006 J Clin Oncol 24:4356). The virus codes for early (t and T antigens) and late (VP1, 2, 3) viral proteins (see Fig. S65).

The viral replication and transcription are bidirectional (see Fig. S66). In the non-permissive host, only the early genes are expressed that are needed for replication of the genetic material before integration, but there is no need for the coat proteins. The integration can take place at different sites, therefore it uses a mechanism of illegitimate recombination. The few integrated copies may be rearranged and may cause continued chromosomal rearrangement in the host. The infectious cycle spans about 70 h. The joint replication and transcriptional origin (*ori*) area extends to about 300 bp and includes a rather sophisticated control system. The replication of the SV40 DNA begins at the 27 bp palindrome of the *ori* site that is adjacent to a region consisting of 17 A-T base pairs. Next to it, on the side of the late genes, there are three other units of 22, 21, and 21 GC-rich repeats that also promote replication, although are not absolutely essential to the process. The SPH elements have an overlapping *octamer* that is present in other eukaryotic genes as well. Several other sequence motifs are similar to those in other promoters. The 72 elements include the 47 bp B and the shorter 29 bp A domains that are parts of the essential enhancer region. The A-T box is essentially a TATA box: 5'-TATTTAT-3'. For the start of replication, the large T has to bind to the Tag binding sites Δ . At the initiation, when low amounts of Tag are available, binding begins at the T1 site located at the pre-mRNA region (right of *ori*). As more Tag will become available, Tag binds to T2 and becomes an ATP-dependent helicase and with the cooperation of

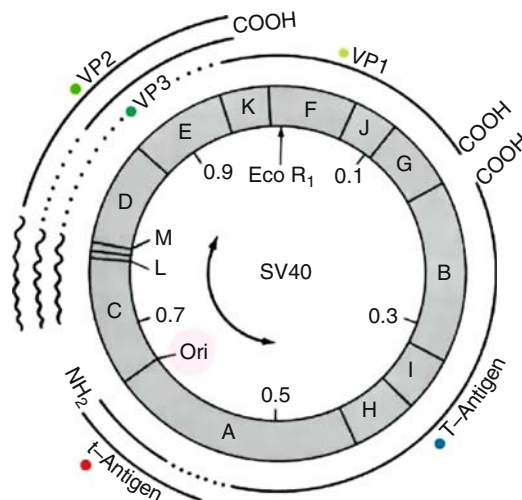


Figure S66. Gene and polypeptide map of SV40

cellular proteins (DNA primase, polymerase, etc.), DNA replication proceeds.

Transcription. For the function of *ori* in transcription the 17 bp A-T sequence is needed, although this TATA box does not affect the rate of transcription. The 21 \diamond 21 \diamond 21 \diamond sequences promote transcription and the two hexamers 5'-GGGCGG-3' within these elements are essential for transcription. Their orientation and inversion does not interfere with transcription. The 72 bp element of SV40 is a capable enhancer also for mammalian, amphibian, plant, and fission yeast genes. The natural host of SV40 is the rhesus monkey (*Macaca mulatta*). In the laboratory, the kidney cell cultures of the African green monkey (*Cercopithecus aethiops*) are used primarily for its

propagation. Single cells, each, may produce 100,000 viral genomes after lysis. The general assumption is that SV40 does not cause human cancer, yet in many tumors its presence was detected by some laboratories, but not by others. ►SV40 vectors, ►COS cell, ►CTL, ►microRNA; Butel JS, Ledniczky JA 1999 J Natl Cancer Inst 91(2):119; see reviews in Semin Cancer Biol 2001 11:5–85; replication initiation complex: Simmons DT et al 2004 Nucleic Acids Res 32:1103; review of virus entry into mammalian cell: Damm EM, Pelkmans L 2006 Cell Microbiol 8:1219.

SimIBD: A computer procedure to assess affected-relative pair calculations.

Similarity Index: ►character index

SIMLINK: A simulation based computer program for estimating linkage information. ►SLINK, ►simulation

Simple Protein: Upon the hydrolysis of a simple protein, only amino acids are produced.

Simple Sequence Length Polymorphism (SSLP): In SSLP, variations in microsatellite sequences can be used for DNA mapping. PCR primers are designed for the unique flanking sequences and their length can thus be determined in the PCR products. ►microsatellite, ►PCR; Cai W-W et al 2001 Nature Genet 29:133.

Simple Sequence Repeats (SSR): SSRs are common in genomes and can be used for mapping genes and for taxonomic studies. (See SSR primer tool: <http://bioinformatics.pcbasc.la.trobe.edu.au/ssrdiscovery.html>).

Simplesiomorphy: The primitive features retained during evolution. It is not very useful to trace evolutionary development. ►synapomorphy, ►homology

Simplex: A polyploid having only a single dominant allele at a particular gene locus; the other alleles are recessive at the locus. ►duplex, ►triplex, ►quadriplex

Simplexvirus: A member of the herpes family of viruses infecting humans and other mammals. ►herpes

Simpson-Golabi-Behmel Syndrome (Simpson Dysmorphia, SGBS): A human Xq26 (500 kilobase stretch) syndrome, encoding the GPC3 gene responsible for the synthesis of glypican (cell surface molecules of heparan sulphate proteoglycans), associated with the insulin-like growth factor (IGF2). Individuals afflicted by this condition are generally very tall, usually have facial anomalies, heart and kidney defects, cryptorchidism, hypospadias, hernias, and bone anomalies and show susceptibility to cancer.

Many of the symptoms involving overgrowth are shared with the Beckwith-Wiedeman syndrome. ►Beckwith-Wiedeman syndrome, ►IGF, see terms at corresponding entries.

SIMS (secondary ions MS): A method for the production of intact molecular ions for mass spectrometry. ►mass spectrometer

Simulation: The representation of a biological system by a mathematical model generated frequently by a computer program. ►modeling; <http://www.nrcam.uchc.edu>; ►Monte Carlo method

Simulon: ►origon

Sin3/RPD: A repressor protein complex probably involved in chromatin remodeling by being recruited to histone deacetylase. It may be associated with SAP18, SAP30, and the retinoblastoma binding protein. ►Mad, ►chromatin remodeling, ►histone deacetylase, ►NuRD; Brubaker K et al 2000 Cell 103:655.

SIN Vector (self-inactivating vector): The SIN vector has a deletion in the U3 element of the 3'-LTR of the retroviral construct, and after replication results in a deletion also in the 5'-LTR promoter and enhancer and prevents the transcription from the cell-specific internal promoter, which may otherwise activate silent cellular oncogenes. This happens because the viral polymerase enzyme uses the 3'-U3 as template for the replication of both 3'- and 5'-U3 sequences. A disadvantage of this construct is the generally slow replication. A high-efficiency heterologous promoter to enhance the expression of the transgene in the retroviral vector may also replace the deleted viral promoter. ►retroviral vector, ►double-copy vector, ►E vector, ►gene therapy; Gatlin J et al 2001 Hum Gene Ther 12:1079.

Sindbis Virus: A single-stranded RNA virus.

sine: The ratio of the side opposite (a) to an acute angle (A) of a right triangle and the hypotenuse (c): a/c, sine of angle A. ►arcsine, ►angular transformation

SINE: Short (≈0.5 kbp) interspersed repetitive DNA sequences that may occur over 100,000 times in the mammalian genomes. The B1 SINE of mice is 130 to 150 bp in length and constitutes nearly 1% of the genome; it is homologous to the human Alu sequences. The B2 SINE (≈190 bp) constitutes about 0.7% of the mouse genome but it apparently has no human homolog or its abundance is very low. In the dog genome, 3 to 5% of the genes have SINE insertions, may differ in the different breeds, and may be a major source of allelic differences (Wang W, Kirkness EF 2005 Genome Res 15:1798). RNA

polymerase III transcribes the B2 SINE elements into short sequences that are not translated. The mouse gene carries an active RNA polymerase II promoter and can support transcription by pol II (Ferrigno O et al 2001 *Nature Genet* 28:77). The SINE elements are retroposons, but lack reverse transcriptase function. SINE type elements occur in all eukaryotes, including birds, fungi, insects, and higher plants. They may be pseudogenes of small RNA genes. The SINE sequences can also be used for fingerprinting and evolutionary studies. These are remnants of ancient retroviral insertions but once they were inserted—because of the loss of the LTR [transposase] function—they remained at the position of insertion. ▶retroposons, ▶transposable elements, ▶LINE, ▶Alu family, ▶DNA fingerprinting, ▶reverse transcriptase; Cantrell MA et al 2001 *Genetics* 158:769; Weiner AM 2002 *Curr Opin Cell Biol* 14:343.

Singing Ability: The ability to sing has genetic determination and some of the “song genes” of birds have been mapped for expression in different parts of the brain. (See Marler P, Doupe AJ 2000 *Proc Natl Acad Sci USA* 97:2965).

Single Burst Experiment: Virus-infected bacterial population diluted and distributed into vessels in such a way that each vessel would contain a single infected bacterial cell. (See Ellis EL, Delbrück M 1939 *J Gen Physiol* 22:365).

Single Cell Analytical Methods (chemical/physical): ▶MALDI/TOF/MS, ▶FISH, ▶immunocytochemistry, ▶immuno-electronmicroscopy, ▶immunoelectrophoresis, ▶immuno-fluorescence, ▶SMART; Cannon DM Jr et al 2000 *Annu Rev Biophys Biomol Struct* 29:239; Slepchenko BM et al 2002 *Annu Rev Biophys Biomol Struct* 31:423; Subkhankulova T, Livesey FJ 2006 *Genome Biol* 7:R18; Xie XS et al 2006 *Science* 312:228.

Single-Chain Fv Fragment: A monoclonal single heavy plus light chain immunoglobulin that can be encoded by a single transgene. Because of its single structure, it is a monovalent antibody in contrast to the common antibodies, which are divalent. It lacks effector function. ▶antibody monovalent, ▶antibody effector function, ▶monoclonal antibody, ▶ScFv, ▶immunostimulatory DNA

Single Copy Plasmids: ▶plasmids

Single Copy Sequence: DNA sequences containing non-redundant, genic portions.

Single Cross: ▶double cross

Single-Feature Polymorphism: ▶allele; Borevitz JO et al 2007 *Proc Natl Acad Sci USA* 104:12057.

Single Gene Trait: A single gene trait is controlled by one gene locus, and shows monogenic inheritance.

Single Nucleotide Polymorphism: ▶SNIPS

Single Strand Assimilation: A single strand displaces another homologous strand and then takes its place during a recombinational event. ▶recombination molecular models

Single Strand Binding Protein: A single strand binding protein binds to both separated single strands of DNA and thus stabilizes the open region to facilitate replication, repair, and recombination. ▶recombination molecular mechanisms, ▶binding proteins; Witte G et al 2005 *Nucleic Acids Res* 33:1662.

Single Strand Conformation Polymorphism (SSCP): In SSCP, when small deletions or even single base substitutions take place in one of the DNA strands of a gene locus, the alteration may be detectable by the electrophoretic mobility of the DNA in denaturing polyacrylamide gels. The two strands, the normal and the affected, may differ. If the individual is heterozygous for the amplified segment of the locus concerned, the electrophoretic analysis may indicate three or more band differences. In some cases, even the homozygotes may show multiple bands. With this method, nearly all of the alterations are detected in fragments of 200–300 bp. ▶gel electrophoresis, ▶polymerase chain reaction, ▶gene isolation, ▶DGGE, ▶mutation detection, ▶dideoxy fingerprinting, ▶MASDA; Orita M et al 1989 *Proc Natl Acad Sci USA* 86:2766.

Single-End Invasion (SEI): A meiotic recombination intermediate during the transition from double-strand breaks to double-Holliday junction. SEIs are formed by strand exchange between one and then the other double strand. The appearance of SEI coincides with that of the synaptonemal complex. SEI is preceded by a nascent double-strand partner intermediate that differentiates into a crossover and a non-crossover type after the synaptonemal complex has formed. Strand exchange occurs relatively late after synapsis and recombination may be avoided between homeologous and structurally rearranged partners. ▶Holliday model, ▶synaptonemal complex, ▶homeologous; Hunter N, Kleckner N 2001 *Cell* 106:59.

Single-Feature Polymorphism (SPF): SPF reveals detailed information about the genomic variations between/among species or different accessions of a species. The genomic DNA is hybridized to an RNA expression platform (gene chip) and single-base differences prevent the hybridization of 25 mer probes. By such a procedure, 4000 SPFs were found

between the Columbia wild type and the Ler genotype *Arabidopsis* plants. On the basis of SPFs, gene map locations, including QTLs, can be readily identified. It can also reveal organizational differences along the chromosomes, e.g., in centromeric or telomeric tracts versus the rest of the yeast chromosomes or various functional regions. (See Borevitz JO et al 2003 *Genome Res* 13:513; Winzeler EA et al *Genetics* 163:79).

Single-Molecule Chemistry: With the currently available optical facilities, it is now possible to observe the dynamic behavior of single biomolecules and to study their kinetics. Within a group of molecules (e.g., in an enzyme), static and dynamic heterogeneity exists among the different molecules; there is also an inherent and ubiquitous fluctuation in the structure and function of these molecules. Classical chemistry could detect only the behavioral average of these molecules. Recent approaches open new vistas in biological chemistry. Conformational change could be detected by fluorescence of an added fluorophore within the T7 DNA polymerase ternary complex, upon binding of a dNTP substrate. This fluorescence change is believed to reflect the closing of the T7 pol fingers domain, which is crucial for polymerase function (Luo G et al 2007 *Proc Natl Acad Sci USA* 104:12610). The single-molecule spectroscopy method directly probes kinetic reversibility and the chaperone role of the nucleocapsid of the HIV-1 immunodeficiency virus strand transfer to cell at various stages along the reaction sequence, giving access to previously inaccessible kinetic processes and rate constants (Zeng Y et al 2007 *Proc Natl Acad Sci USA* 104:12651).

Single-Positive T Cell: The single-positive cell expresses either the CD4 or the CD8 surface proteins. ▶CD4, ▶CD8, ▶T cell

S

Single-Strand Annealing Repair: ▶SSA

Singlet Oxygen ($^1\text{O}_2$): A highly reactive O_2 molecule produced during inflammation, by photosensitization in UV light, chemiexcitation in dark, decomposition of NDPO_2 , etc. $^1\text{O}_2$ may be toxic to molecules in the cell, oxidizes DNA, and produces mutagenic 7-hydro-8-oxodeoxyguanosine. It may affect gene expression and carcinogenesis. ▶ROS, ▶8-oxodeoxyguanosine, ▶photodynamic effect

Singleton: Singly occurring whole-body mutations; the spontaneous frequency in mice for seven standard loci is 6.6×10^{-6} per locus. ▶mutation rate

Singleton-Merten Syndrome: A rare disease involving aortic calcification but defects in bone development.

Singlets: Genes that occur only once in the genome.

Singular Value Decomposition (SVD) of RNA: SVD uncovers in the mRNA data matrix of genes, x arrays, i.e., electrophoretic migration length (Alter O, Golub GH 2006 *Proc Natl Acad Sci USA* 103:11828).

Sink: The storage of metabolites from where they can be mobilized on need.

Sink Habitat: A habitat in which some individuals contribute less to the future generations than the average individual. ▶source habitat, ▶habitat

Sinndakiss: A receptor internalization signal.

Sinorhizobium: ▶nitrogen fixation

Siphonogamy: In siphonogamy, the immotile microgametes of higher plants are delivered to the archegonia through the elongating pollen tube. ▶pollen tube, ▶embryosac, ▶zoidogamy

Sipple Syndrome: ▶phaeochromocytoma

SIR: ▶silencer

Sire: The male mammal; the term used primarily in animal breeding and applied animal genetics. ▶dam

Sirenomelia: A developmental malformation showing fused legs and usually lack of feet.

SIRM: The sterile insect release method. ▶genetic sterilization

siRNA (silencing RNA): A 29-amino-acid peptide specifically binds to the acetylcholine receptor expressed by neuronal cells. To enable siRNA binding, a chimeric peptide was synthesized by adding nine arginine residues at the carboxy terminus of rabies virus glycoprotein (RVG.) This RVG-9R peptide was able to bind and transduce siRNA to neuronal cells in vitro, resulting in efficient gene silencing (Kumar P et al 2007 *Nature [Lond]* 448:39). Low-copy promoter-associated siRNAs transcribed through RNAPII are recognized by the antisense strand of the siRNA and function as a recognition motif to direct epigenetic silencing complexes to the corresponding targeted promoters, in order to mediate transcriptional silencing in human cells (Han J et al 2007 *Proc Natl Acad Sci USA* 104:12422). ▶RNAi, ▶rasiRNA, ▶microRNA, ▶RNA polymerase IV, ▶BBB; Pikaard CS 2006 *Cold Spring Harb Symp Quant Biol* 71:473; human siRNA database: <http://siRNA.cgb.ki.se>; <http://itb.biologie.hu-berlin.de/~nebulus/sirna/v2/>.

Siolimus: ▶rapamycin

SIRPs (signal regulatory proteins, 20p13): Members of the SIRP family inhibit signaling through tyrosine kinase receptors and represent immune inhibitory receptors expressed on macrophages or other blood cells. ▶[tyrosine kinase receptor](#), ▶[macrophage](#); Latour S et al 2001 J Immunol 167:2547.

Sirtuin (Sirt): NAD-dependent histone deacetylase and ADP ribosylase proteins of the Sir2 family. Sirtinol also activates many auxin-inducible plant genes. More than 65% of the 138 sirtinol-induced genes are auxin-inducible. Both auxin- and sirtinol-induction are apparently mediated by ubiquitin-activated protein degradation (Zhao Y et al 2003 Science 301:1107). Resveratrol may activate sirtuins and prolong life (Howitz K et al 2003 Nature [Lond] 425:191). Sirtuin mediates the mobilization of fat by repressing genes controlling the peroxisome proliferator-activator receptor- γ . Overproduction of Sirt reduces adipogenesis, and interference with Sirt RNA enhances fat production. SIRT4 functions in the mitochondria, represses glutamate dehydrogenase by AD2064-ribosylation, downregulates insulin secretion, and opposes the effect of caloric restriction in pancreatic β cells (Haigis MC et al 2006 Cell 126:941). SIRT1 and SIRT3 activate acetyl-CoE synthetase by deacetylation of the cytoplasmic or the mitochondrial enzyme, respectively, by targeting a lysine residue (Hallows WC et al 2006 Proc Natl Acad Sci USA 103:10230). Sirt1 docks with nuclear receptor co-repressor (NcoR) and silencing mediator of retinoid and thyroid hormone receptors (SMRT) leading to PPAR- γ repression. Reduction of fat by lipolysis enhances lifespan (Picard F et al 2004 Nature [Lond] 429:771). Sirtuins regulate aging and age-related diseases such as cancer, diabetes, and neurodegeneration (Longo VD, Kennedy BK 2006 Cell 126:257). In cell-based models of mouse for Alzheimer disease, amyotrophic lateral sclerosis and other tauopathies resveratrol, a SIRT1-activating molecule, promotes neuronal survival (Kim D et al 2007 EMBO J 26:3169). ▶[adipocyte](#), ▶[PPAR](#), ▶[longevity](#), ▶[aging](#), ▶[obesity](#), ▶[ARF](#), ▶[neurodegenerative diseases](#), ▶[silencer](#), ▶[resveratrol](#), ▶[PGC1](#), ▶[acetyl-CoA](#); Grozinger CM et al 2001 J Biol Chem 276:38837; Pandey R et al 2002 Nucleic Acids Res 30:5036; signaling and regulation of protein deacetylation: Sauve AA et al 2006 Annu Rev Biochem 75:435.

SIS: The simian sarcoma virus oncogene is located in human chromosome 22q12.3-q13.1 and mouse chromosome 15. The SIS protein has high homology to the β chain of the platelet derived growth factor (PDGF), KIT oncogene, FOS oncogene, and the colony stimulating factor. ▶[oncogenes](#), ▶[PDGF](#),

▶[colony stimulating factor](#); Liu J et al 2001 Nucleic Acids Res 29:783.

Sis1: The DnaJ structural homolog of budding yeast indispensable protein with multiple chaperone functions, including initiation of translation. ▶[chaperones](#), ▶[DnaJ](#), ▶[DnaK](#)

Sister Chromatid Cohesion: The juxtaposition of the sister chromatids until the end of metaphase in mitosis and until the end of metaphase II in meiosis. The inner centromere proteins (INCENP) and the centromere-linking proteins (CLiP) provide the physical basis of the cohesion. The multiprotein cohesion complex, which binds most tightly to the centromere, was named cohesin. A separation protein (separin, a cysteine protease) mediates sister chromatid cohesion, and the dissociation is achieved when the Scc1/Mcd1/Rad21 subunit of cohesin dissociates from the chromatids upon proteolytic cleavage. Rec8 is also a component of the meiotic cohesin complex. The Esp1 (separin) is tightly bound to the chromosomes by the anaphase inhibitor Pds1 (mammalian homolog Securin). Pds1 is ubiquitinated by the triggering effect of the anaphase-promoting complex (APC) and Cdc20. The sister chromatids are closely juxtapositioned until anaphase, indicating the presence of inter-sister connector structures. Sister chromatid cohesion affects proper disjunction of the mitotic chromatids but it appears important also for meiotic recombination. In mitosis, the separation of the sister chromatids and the splitting of the centromere take place during the single anaphase. In meiosis, at anaphase I, the sister chromatids separate but the centromere does not until anaphase II. This timing is apparently under the control of a specific protein(s). For the orderly segregation together of the sister chromatids during meiosis I, the protein monopolin is required in yeast.

Dominant and recessive mutations have been identified in plants, animals, and yeast that are defective in chromatid cohesion. In yeast, centromeric element III (CDEIII) is essential for sister chromatid cohesion and for kinetochore function. ▶[mitosis](#), ▶[meiosis](#), ▶[synapsis](#), ▶[asynapsis](#), ▶[desynapsis](#), ▶[sister chromatids](#), ▶[sister chromatid exchange](#), ▶[DNA polymerases](#), ▶[chiasma](#), ▶[centromere](#), ▶[cell cycle](#), ▶[cohesin](#), ▶[ORC](#), ▶[condensin](#), ▶[adherin](#), ▶[check-point](#); Nasmyth K et al 2000 Science 288:1379; Tóth A et al 2000 Cell 103:1155; Carson DR, Christman MF 2001 Proc Natl Acad Sci USA 98:8270; Lee JY et al 2001 Annu Rev Cell Dev Biol 17:753.

Sister Chromatid Exchange (SCE): Sister chromatid exchanges are detectable in eukaryotic cells provided with 5-bromo-deoxyuridine for (generally) one

cycle of DNA replication (see Fig. S67). Subsequently, at metaphase the chromosomes are stained with either the fluorescent compound Hoechst 33258 (harlequin staining) or according to a special Giemsa procedure.

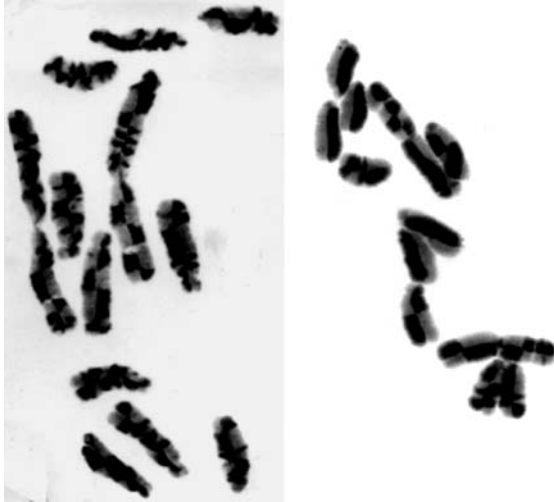


Figure S67. Sister chromatid exchange. Right: Untreated control. Left: Exposed to the alkylating compound thiotepa during DNA synthesis. (Courtesy of Professor BA Kihlman)

If sister chromatids are reciprocally exchanged, sharp bands appear in mirror image-like fashion. The frequency of sister chromatid exchange is boosted by about a third by potential carcinogens and mutagens. This method has been successfully used in various animal and plant cells for identifying genotoxic agents. The data must be evaluated with care in comparison with the concurrent control because BrdU itself may break chromosomes under UV-B light.

In *Saccharomyces cerevisiae*, molecular and genetic evidence are available for meiotic sister chromatid exchange. When one of the bivalents had different number of ribosomal RNA repeats with an embedded LEU2 gene, duplication and deficiency of LEU2 and the repeats were detected. Similar observations were made with other chromosomes and markers. After the DNA double-strand breaks, histone H2AX is phosphorylated at serine 139 and facilitates the homologous recombination of chromosomal double-strand breaks by using the sister chromatids as template (Xie A et al 2004 Mol Cell 16:1017). ▶harlequin staining, ▶Giemsa staining, ▶bioassays in genetic toxicology, ▶ring chromosomes, ▶BrdU, ▶ultraviolet light, ▶genotoxic, ▶sister chromatids, ▶chiasma, ▶crossing over, ▶cohesin, ▶double-strand breaks, ▶DNA repair, ▶histone variants; Shaham J et al 2001 Mutat Res 491:71.

Sister Chromatids: Sister chromatids are attached to the same side of the same centromere but they seem to be coiled in opposite directions (see Fig. S68). Their separation in mitosis requires the activation of a proteolytic enzyme encoded by the *Cut2* gene in *Schizosaccharomyces pombe*. ▶chromatids; Nasmyth K 2001 Annu Rev Genet 35:673.

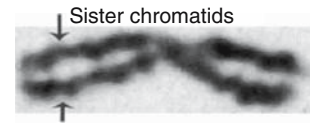


Figure S68. Sister chromatids

Sister-Strand Exchange: Same as sister chromatid exchange.

SIT: A family of protein phosphatases regulating diverse metabolic pathways. ▶PP2A

SIT (sterile insect technique): ▶genetic sterilization, ▶GSM

Site-Directed Immunization: ▶immunization genetic

Site-Directed Mutagenesis: ▶directed mutation, ▶localized mutagenesis, ▶targeting; Storici F et al 2001 Nature Biotechnol 19:773.

Site-Specific Cleavage: The site specific cleavage of nucleic acids is accomplished by restriction endonucleases, some special RNases, and oligonucleotide-phenanthroline conjugates, which may cut both strands of the DNA in the presence of Cu^{2+} and a reducing agent. EDTA-Fe^{2+} may do the same if tethered to triplex molecules, albeit with low efficiency. In the presence of light, ellipticine attached to homopyrimidines may cleave a double helix within a triplex (see Fig. S69). ▶restriction endonucleases, ▶triplex, ▶tethering; Gimble FS 2001 Nucleic Acids Res 29:4215.

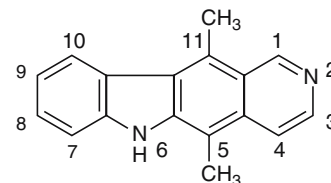


Figure S69. Ellipticine

Site-Specific Mutations: Site-specific mutations occur at particular nucleotides in the DNA and RNA, respectively. ▶base substitution, ▶localized mutagenesis, ▶gene replacement, ▶site-specific recombination, ▶PCR-based mutagenesis, ▶cassette

mutagenesis, ►homolog-scanning mutagenesis, ►alanine-scanning mutagenesis, ►TAB mutagenesis, ►cysteine-scanning mutagenesis, ►Kunkel mutagenesis, ►targeting vector, ►oligonucleotide-directed mutagenesis, ►degenerate oligonucleotide directed mutagenesis, ►look-through mutagenesis

Site-Specific Recombinases: Site-specific recombinases are resolvases that attach at the two-base staggered cut sites. The enzyme is then covalently linked to the 5' ends and the PO₄ of the DNA is covalently linked to the OH group of the recombinase. Subsequently, the broken DNA strand releases the deoxyribose hydroxyl group. The PO₄ is joined to another deoxyribose OH group and the DNA backbone is reconstituted. The members of the integrase group of enzymes attach at sites 6–8-bases apart. The first breakage results in a Holliday juncture, that may lead to branch-migration and after a second strand exchange and rotation isomerization (►Holliday model steps H-J) the strands may be resolved either with an outside marker exchange (classical recombination) or in gene conversion (the constellation of the outside markers retained). It is conceivable that the broken ends are reconstituted without any change, or deletions may also take place, or the position of the broken ends are inverted by 180° resulting in what classical cytology called inversion. Resolvase and integrase reactions can be very specific for the sites and the reaction is secured by the assistance of additional proteins that bring into contact only the appropriate DNA stretches. These two enzymes act only on supercoiled DNA. The integrase family of recombinase enzymes is more liberal in choice, yet affected by various conditions. The Mu phage or the HIV integration does not require covalent association between the DNA and a protein. The phosphodiester bond of the donor DNA is hydrolyzed to generate an OH group. This group and a phosphodiester group of the receiving DNA then join, and thus the strand is integrated. Site-specific recombinase enzymes with new specificities have been engineered using bacterial resolvase domains combined with substrate recognition domains borrowed from a mouse transcription factor (Akopian A et al 2003 Proc Natl Acad Sci USA 100:8688). ►site-specific recombination, ►Holliday juncture, ►resolvase, ►Cre/loxP, ►FLP/FRT, ►integrase, ►phosphodiester linkage, ►transesterification, ►homing endonucleases; Woods KC et al 2001 J Mol Biol 313:49; Dhar G et al 2004 Cell 119:33; structural and biochemical mechanisms of tyrosine and serine types of recombinases: Grindley NDF et al 2006 Annu Rev Biochem 75:567.

Site-Specific Recombination: Site-specific recombination occurs when the recombination is limited to

a specific few nucleotide sequences. Homology may be present at the exchange region in both recombining molecules like at the integration–excision site of the temperate phage. Alternatively, the specificity is limited to only one of the partners like at the 25 bp termini of the T-DNA or the direct and indirect repeats of the transposable elements. In the latter cases, the recombinational target sites may have no or only minimal similarity. The IS30 insertion element can serve as site-specific recombinases when replacing the integration/excision genes of phage λ (Kiss J et al 2003 Proc Natl Acad Sci USA 100:15000). Peptide nucleic acids enhance site-specific recombination and DNA repair. ►lambda phage, ►gene replacement, ►Cre/Lox, ►FLP/FRT, ►switching, ►site-specific recombinase, ►peptide nucleic acids, ►knockout, ►targeting genes, ►chromosomal rearrangement, ►ligand-activated site-specific recombination, ►T-DNA, ►recombination, ►shoufflons, ►integrases, ►DD(35)E; Sauer B, Henderson N 1988 Proc Natl Acad Sci USA 85:5166; Pena CE et al 2000 Proc Natl Acad Sci USA 97:7760; Christ N et al 2002 J Mol Biol 319:305.

Sitosterolemia (phytosterolemia, STSL, 2p21): A rare, recessive hypercholesterolemia resulting in more than 30-fold increase of the level of this plant cholesterol in the plasma. Intestinal absorption of sterols is increased and the excretion of sterols into the bile is impaired. Initially, it causes xanthomatosis and later premature coronary artery disease. Actually, two genes encoding sterolin 1 and sterolin 2 are involved in opposite orientation separated by a short interval. Sterolins apparently regulate sterol transport. ►cholesterol, ►low-density lipoprotein, ►VLDL, ►xanthomatosis, ►familial hypercholesterolemia, ►coronary heart disease; Lee M-H et al 2001 Nature Genet 27:79; Lu K et al 2001 Am J Hum Genet 69:278.

Situs Inversus Ambiguus: Some of the organs situated at the common side of body axis, others are at a misplaced site regarding the axis. ►left-right asymmetry

Situs Inversus Totalis: Complete inversion of left-right body axis. ►left-right asymmetry

Situs Inversus Viscerum (7p21): A malformation of mammals, including humans, where the internal organs such as the heart are shifted to the right side of the chest (thorax). It is frequently accompanied by chronic dilation of the lung passages (bronchi) and inflammation of the sinus; the latter disorder is also called Kartagener syndrome, which is characterized also by the immotility of sperm and cilia. The anomaly may be either autosomal or X-linked recessive. Its incidence in the general population may

be about 1/10,000. In the mouse, the genes *iv* (chromosome 12) and the *inv* (chromosome 4) disturb left-right axis formation and cause 50 and 100% manifestation of situs inversus, respectively. In the chicken, the fibroblast growth factor (FGF8) mediates the determination of the right side and in Sonic hedgehog (SHH), of the left side. In the mouse, FGF8 is instrumental in the left side and SHH in the right side specification. ▶[dynein](#), ▶[heterotaxy](#), ▶[isomerism](#), ▶[Kartagener syndrome](#), ▶[asymmetry of cell division](#), ▶[axis of asymmetry](#), ▶[FGF](#), ▶[sonic hedgehog](#), ▶[left-right asymmetry](#), ▶[ciliary dyskinesia](#); Bartoloni L et al 2002 Proc Natl Acad Sci USA 99:10282; Bisgrove BW et al 2003 Annu Rev Genomics Hum Genet 4:1.

SIV (Simian immunodeficiency virus): a relative of HIV. ▶[acquired immunodeficiency](#), ▶[HIV](#)

Size: Size depends primarily on cell number and cell size and it is developmentally and genetically determined. (See Conton I, Raff M 1999 Cell 96:235). According to Kleiber's rule (1932 Hilgardia 6:315), the size of an organism (body mass) follows the $\sim 3/4$ power of the metabolic/respiratory rate. A morphogen gradient may determine the size of an organ in animals. It is not entirely resolved which way the gradient is controlled. One set of data of *Drosophila* wing size determination indicates that imaginal disk size is determined relative to the fixed morphogen distribution by a certain threshold level of morphogen required for growth. When disk boundary reaches the threshold, the arrest of cell proliferation throughout the disk is induced by mechanical stress in the tissue. Mechanical stress is expected to arise from the non-uniformity of morphogen distribution that drives growth. This stress, through a negative feedback on growth, can compensate for the non-uniformity of morphogen, achieving uniform growth with the rate that vanishes when the disk boundary reaches the threshold (Hufnagel L et al 2007 Proc Natl Acad Sci USA 104:3835).

It seems that plants differ in metabolism from animals extensive data (500 observations on 43 plant species) indicates that respiration (relative to nitrogen content) at a scaling exponent of ~ 1 better represents mass (Reich PB et al 2006 Nature [Lond] 439:457). ▶[body mass](#), ▶[body size](#), ▶[morphogen](#), ▶[imaginal disk](#)

Size-Exclusion Chromatography: In size-exclusion chromatography, molecules are separated by size; large molecules may not enter the surface of the matrix but small molecules may penetrate the core. The penetration depends on size and shape of the analyte and the nature of the matrix.

SJL Mouse: Non-inbred strain.

Sjögren-Larsson Syndrome: ▶[ichthyosis](#)

Sjögren (sicca = dry) **Syndrome** (SS) Autosomal recessive autoimmune disease leading to the destruction of the salivary and lacrimal glands by the production of autoantibody against the SS-A (RoRNA) and SS-B (La Sn RNA) particles. The affected individuals have dry mouth and dry eyes (no tears). The autoantigens have been identified and purified. The Ro autoantigen appears to be encoded in human chromosome 19pter-p13.2. The La autoantigen may be involved with RNA polymerase III. The 120 kDa α -fodrin appears to be the critical autoantigen that elicits the disease. Aberrant T cells with impaired class IA phosphoinositide 3-kinase signaling can lead to organ-specific autoimmunity in mice and resemble human SS (Oak JS et al 2006 Proc Natl Acad Sci USA 103:16882). ▶[autoimmune disease](#), ▶[fodrin](#), ▶[RoRNP](#), ▶[PIK](#), ▶[rosacea](#)

SK: Calcium-activated potassium ion channels. ▶[ion channels](#)

SK Oncogene: The SK oncogene probably regulates tumor progression; it was assigned to human chromosome 1q22-q24.

7SK RNA: A small (330 base) nuclear RNA (snRNA) of ubiquitous presence and involvement in the control of transcription by interfering with the RNA elongation factor P-TEFb. ▶[snRNA](#), ▶[RNA regulatory](#); Yang Z et al 2001 Nature [Lond] 414:317; Michels AA et al 2004 EMBO J 23:2608.

Skeletal Map: The skeletal map uses only microsatellite marker data. ▶[framework map](#), ▶[recombination minimization map](#), ▶[integrated map](#), ▶[genetic map](#), ▶[physical map](#), ▶[radiation mapping](#)

Skewed Distribution: In skewed distribution, the data are not symmetrical around the mean; either one or the other extreme flank is predominant (see Fig. S70). ▶[normal distribution](#), ▶[kurtosis](#)



Figure S70. Skewed distribution

Skewness: Asymmetry in the distribution frequency of the data. ▶[kurtosis](#), ▶[normal distribution](#), ▶[moments](#)

Ski (Sloan Kettering Institute): A protein discovered at the Sloan Kettering Institute, as a viral factor in tumorigenesis. Ski occurs in vertebrates and insects and, along with Sno (Si-related novel gene), regulates the effect of Smad4 and Smad3 proteins that in

response to the phosphorylation signals coming from TGF- β may negatively control gene expression. It interacts with Skip, a transcriptional activator. ▶**Smad**, ▶**TGF**; Prathapam T et al 2001 Nucleic Acids Res 29:3469.

Skin Cancer: Skin cancer constitutes about 40% of all newly diagnosed cancers. The incidence of melanoma is 4%, basal cell carcinoma 80%, and squamous-cell carcinomas 16% of the skin cancers. Sunscreen provides limited protection; conversely, it may even increase the risk because the assumed protection allows more exposure to the sun. The sensitive initial target of carcinogenesis by UV light is mutation in gene p53 and various protooncogenes. The UV-light damage starts with *initiation* in single cells that may be followed by the effects of tumor promoting agents (*expansion*), eventually leading to the *progression* of the tumor cells, resulting in cancer. UVB can enhance these three steps, each, by acting on the signaling molecules, epidermal growth factor (EGF), mitogen-activated protein kinases (MAPK), and phosphatidylinositol 3-kinase (PI3K). EGF activation leads to the production of reactive oxygen species (ROS). ROS effects can be mitigated by antioxidants. UV induces several transcription factors such as AP-1, JUN, FOS, etc., and cyclooxygenase-2. AP-1 activation may be inhibited by salicylate (aspirin) or perillyl alcohol (monoterpene). Several other promising chemical protective agents are under study. (See terms under separate entries; Bowden GT 2004 Nature Rev Cancer 4:23).

Skin Color: ▶**pigmentation of animals**; Sturm RA et al 1998 Bioessays 20(9):712; Barsh G 2003 PLoS Biol 1(1):e7; Lin JY, Fisher DE 2007 Nature [Lond] 445:843.

Skin Diseases: ▶**acne**, ▶**epidermolysis**, ▶**keratosis**, ▶**ichthyosis**, ▶**psoriasis**, ▶**blisters**, ▶**porphyria**, ▶**pemphigus**, ▶**acrodermatitis**, ▶**familial hypercholesterolemia**, ▶**Fabry disease**, ▶**pseudoxanthoma elasticum**, ▶**nevus**, ▶**vitiligo**, ▶**ectodermal dysplasia**, ▶**focal dermal hypoplasia**, ▶**scleroderma**, ▶**lupus erythematosus**, ▶**dermatitis**, ▶**eczema**, ▶**Gardner syndrome**, ▶**Kindler syndrome**, ▶**cutis laxa**, ▶**pigmentation defects**, ▶**light-sensitivity**, ▶**glomerulonephrosis**, ▶**Rothmund-Thompson syndrome**, ▶**Werner syndrome**, ▶**epithelioma**, ▶**dyskeratosis**, ▶**erythrokeratoderma variabilis**, ▶**skin cancer**, ▶**xeroderma pigmentosum**, ▶**connexin**

Skotomorphogenesis: Morphogenesis without dependence on light. ▶**photo-morphogenesis**, ▶**de-etiolation**

SKP (cyclin A-CDK2 associated protein): An intrinsic kinetochore protein (22.3 kDa) widely conserved

among species. It coordinates centromere, centrosomes, and other cell cycle factors. The Skp1p is a proteasome-targeting factor. Mice Skp2^{-/-} is viable, yet has reduced growth rate, has polyploid cells, and accumulates cyclin E and p27^{Kip1} proteins that it cannot efficiently eliminate during the S and G2 phases of the cell cycle (see Fig. S71). For the degradation, SCF^{Skp2} is required. Skp2 is up-regulated in some types of epithelial carcinogenesis. ▶**kinetochore**, ▶**cell cycle**, ▶**CDC4**, ▶**proteasome**, ▶**F-box**, ▶**cyclin A**, ▶**CDK**, ▶**SCF**, ▶**von Hippel-Lindau disease**; Nakayama K et al 2000 EMBO J 19:2069; Latres E et al 2001 Proc Natl Acad Sci USA 68:2515.

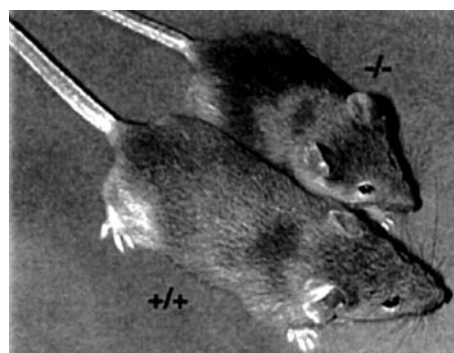


Figure S71. Skp2 disrupted mice is deficient in the F box protein and SCF ubiquitin ligase has enlarged nuclei, multiple centrosomes and reduced growth. They accumulate cyclin E and p27Kip. (From Nakayama K et al 2000 EMBO J 19:2069)

Skunk (*Mephitis mephitis*): 2n = 50; (*Spilogale putorius*), 2n = 64.

Sky: Same as spectral karyotyping. ▶**spectral karyotyping**

Sky: A cellular tyrosine kinase. It regulates B cell development. ▶**B lymphocyte**; Kishi YA et al 2002 Gene 288:29.

SL1, SL2 (spliced leader): SL1 and SL2 are involved in the transsplicing in *Caenorhabditis*. The 100-nucleotide leader donates its 5' end 22 nucleotides to a splice acceptor site on the primary transcript. Trans-splicing is very common (70%) among the nematode's genes. This mechanism is used for the coordinately regulated gene clusters, transcribed in polycistronic RNA. The nematode operons use SL2 whereas other genes use SL1. ▶**transsplicing**, ▶**coordinate regulation**, ▶**operon**

SL1: A transcription factor complex of RNA polymerase I. It is a complex of the TATA-box-binding protein (TBP) and the three TATA box associated

factors (TAF). The TBP protein binds exclusively, either SL1 (RNA pol I) or TFIID (RNA pol II). In the case of RNA pol III, TFIIIB is required for the recruitment of the polymerase to the promoter complex. ►pol I, ►pol II, ►TBP, ►TAF, ►transcription factors

Slicer: A structural homolog of ribonuclease H; it is also a domain of Piw. ►Ribonuclease H, ►piRNA

7SL RNA: An RNA component in the signal recognition protein (SRP) complex. ►signal sequence recognition particle, ►Alu

Slalom Library: The slalom library is based on a combination of the principles of linking and jumping libraries. ►jumping library, ►linking library; Zabarovska VI et al 2002 Nucleic Acids Res 30(2):e6.

SLAM (signaling lymphocyte activation molecule, CDw150): A T cell receptor protein (M_r 70K) of the immunoglobulin family, constitutively and rapidly expressed on activated peripheral blood memory T cells, immature thymocytes, and on some B cells. It is a receptor also for the measles virus. T cells carrying the CD4⁺ antigens produce increased amounts of interferon γ without an increase of interleukins 4 or 5. SLAM function is independent of CD28. ►T cell, ►interferon, ►interleukin, ►CD28, ►Epstein-Barr virus, ►SAP; Bleharski JR et al 2001 J Immunol 167:3174.

SLAM: The gene predictor program for the detection of homologous sequences in different species. ►gene prediction; Alexandersson M et al 2003 Genome Res 13:496.

SLAP (Fyb/Slap): One of the adaptor proteins that regulate TCR-mediated signal transduction. Cbl has an inhibitory effect. SLAP interacts with Sky, ZAP-70 and LAT. ►Fyb, ►TCR, ►signal transduction, ►CBL; Peterson EJ et al 2001 Science 293:2263.

SLD: A yeast chromosomal replication protein acting after phosphorylation during the S phase. ►GINS; Masumoto H et al 2002 Nature [Lond] 415:651.

Sleep: A circadian organization of rest after activity, controlled by several neural genes. Apparently, mutation of the human homolog of *Per2* (2q) may be responsible for the familial advanced sleep phase syndrome. In *Drosophila*, some *Shaker* (1.57.6) null mutants (*Sh*¹⁰², *minisleep*) involved in a voltage-dependent K⁺ channel controlling membrane polarization and transmitter release have reduced requirement for sleep and display apparently normal functions but shorter life span (Cirelli C et al 2005 Nature [Lond] 434:1087). The point mutation

(Ser→Gly) is within the casein kinase I ϵ and alters the circadian clock. Sleep may have a weak role in the consolidation of memory and frequently inspires insight. Insight is a mental restructuring leading to sudden gain of explicit knowledge (Wagner U et al 2004 Nature [Lond] 427:352). Sleep-deprivation seriously affects job-performance and cognitive abilities. The Ampakine (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA) drugs appear promising in non-human primates for alleviating the problems of sleeplessness (Porrino LJ et al 2005 PLoS Biol 3(9):e299). In aging organisms (humans or *Drosophila*) the sleep cycles are generally fragmented and it has been attributed of age-related oxidative damage (Koh K et al 2006 Proc Natl Acad Sci USA 103:13843). ►apnea, ►narcolepsy, ►circadian rhythm, ►memory; Siegel JM 2001 Science 294:1058; Shaw PJ et al 2002 Nature [Lond] 417:287; Pace-Schott EF, Hobson JA 2002 Nature Rev Neurosci 3:591; 2005 Nature [Lond] 437:1253–1289.

Sleeping Beauty (SB): An artificially constructed human mariner transposable element, equipped with a salmon transposase function enabling the otherwise non-mobile element to move in HeLa or other somatic cells by a cut-and-paste mechanism. Another type of transposon vector (pTnori) is outlined here in Figure S72. Another transposon (T2/Onc2), containing a larger fragment of splice acceptor sequence, is flanked by optimized transposons binding sites. It also contains a murine stem cell virus (MSCV) long terminal repeats and a splice donor site to promote gene expression when integrated upstream or within the gene. Low methylation in MSCV promoter and high copy numbers are also an advantage. A more active transposase was constructed to increase transposition frequency and to be expressed in all tissues. This new system generated transposon mutagenesis in many cancer genes and appears promising to shed light on cancer etiology of mammalian cells (Dupuy AJ et al 2005 Nature [Lond] 436:221; Collier LS et al 2005 Nature [Lond] 436:272). Transposition of Sleeping Beauty requires the presence of the Miz-1 transcription factor and the slow-down of the G1 phase of the cell cycle. The slow-down decreases D1/cdk4-specific phosphorylation of the retinoblastoma protein (Walisko O et al 2006 Proc Natl Acad Sci USA

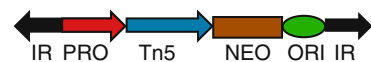


Figure S72. IR: inverted repeats, PRO: promoter, Tn5: bacterial transposon, NEO: selectable marker, ORI: origin of replication (p Tnori)

103:4062). ▶*mariner*, ▶*transposase*, ▶*piggyBac*, ▶*cut-and-paste*, ▶*HeLa*, ▶*cyclin D*, ▶*CDK*, ▶*retinoblastoma*; Horie K et al 2001 Proc Natl Acad Sci USA 98:9191; Izsvák Zs et al 2002 J Biol Chem 277:34581.

Sleeping Sickness: A potentially fatal disease caused by *Trypanosomas*. The tse-tse fly spreads the disease. ▶*Trypanosomas*

SLG: Self-compatibility locus-secreted glycoprotein. ▶*self-incompatibility*

Sliding Clamp: A gp45 gene of phage T4 controls high speed of replication (processivity) by gp43 (DNA polymerase gene); gp44 and gp62 are the clamp loaders for gp45. The clamp hugs the DNA and slides along the duplex DNA. The replication complex is then attached to the clamp. The cellular homologs for p45 are the β units of the DNA polymerase III of prokaryotes and the PCNA of eukaryotes. The transcription may be coupled to replication and regulated by protein-protein and protein site-specific DNA interactions. In eukaryotes, the sliding clamp is PCNA. The τ subunit of DNA polymerase complex switches off the polymerase from the DNA as one Okazaki fragment is finished and then switches on again the β subunit to start a new Okazaki fragment (López de Saro FJ et al 2003 Proc Natl Acad Sci USA 100:14689). ▶*DNA polymerases*, ▶*PCNA*, ▶*replication factor*, ▶*clamp loader*, ▶*Okazaki fragment*; Fishel R 1998 Genes Dev 12:2096; Trakselis MA et al 2001 Proc Natl Acad Sci USA 98:8368; crystal structure: Jeruzalemi D et al 2001 Cell 106:417; Johnson A, O'Donnell M 2005 Annu Rev Biochem 74:283.

SLIK: ▶*SAGA*

Slime Molds: Slime molds are either of plasmodial (*Myxomycetes*) or cellular type (*Acrasiomycetes*) eukaryotes, of which *Dictyostelium discoideum* is perhaps the most important object for research. ▶*plasmodium*, ▶*Dictyostelium*, ▶*Physarum*

SLINK: A computer program for estimating linkage information by a simulation approach. ▶*SIMLINK*

Slippage: Usually, when homopolymeric sequences are embedded in the template DNA strand, the RNA polymerase may synthesize RNA strands that are much longer (by a few to thousands nucleotides) than the template; this is known as slippage. The slippage can be inhibited, however, when nucleotides, representing the next one to the homopolymeric stretch, are added. Frame shift mutations may be interpreted as the result of slippage. Slippage may occur during decoding at translation on the ribosome in case

the codon-anticodon interactions are weak at the ribosomal P site (Hansen TM et al 2003 EMBO Rep 4:499). Slippage during DNA replication may generate trinucleotide repeats, which can lead to neurodegenerative disease. Slippage may be the origin of base mismatches, which generate instabilities (Chi LM, Lam SL 2005 Nucleic Acids Res 33:1604). ▶*slipping*, ▶*attenuator region*, ▶*overlapping genes*, ▶*unequal crossing over*, ▶*microsatellite*, ▶*replication slippage*, ▶*decoding*, ▶*mismatch repair*, ▶*transcript elongation*, ▶*trinucleotide repeat*; Viguera E et al 2001 EMBO J 20:2587.

Slipped-Structure DNA (S-DNA): Incomplete pairing within intrastrand folds (hairpins) in not exactly opposite position to each other. Such a structure may form when there are variable number trinucleotide repeats in the DNA (see Fig. S73). ▶*trinucleotide repeats*, ▶*hairpin*

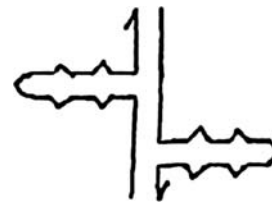


Figure S73. S-DNA

Slipping: A shifting of the translational reading frame. ▶*recoding*, ▶*hopping*, ▶*slippage*

Slip-Strand Mispairing: Slip-strand mispairing may cause replicational error if not corrected by repair; it is frequently the cause of micro- and minisatellite instability. The slippage may cause either additions to or deletions from the repeat sequences. This process is independent from the mechanism(s) of recombination (it is not unequal crossing over), and flanking markers are not exchanged here. In yeast, its frequency is about the same as at mitosis and meiosis. Defects in the genes controlling replication and repair of the DNA may increase the instability and cause more mutations in microsatellites than in other types of DNA sequences. The packaging of the DNA, the temperature, methylation state, base composition, cell cycle stage, etc., may affect its frequency. Its rate may vary among different species because of differences in the replicase and mismatch repair enzymes. CTG repeats in the lagging strands are less stable than in the leading strand. ▶*microsatellite*, ▶*minisatellite*, ▶*MVR*, ▶*unequal crossing over*,

►[slippage](#); Lewis LA et al 1999 Mol Microbiol 32:977.

Slit: An axon-repellent molecule with Robo as its receptor. ►[axon](#), ►[axon guidance](#), ►[Robo](#)

Slithering: A creeping-like motion of the recombination sites towards each other. A recombinase enzyme within a supercoiled DNA molecule may mediate slithering in case of site-specific recombination. ►[site-specific recombination](#); Huang J et al 2001 Proc Natl Acad Sci USA 98:968.

Slot Blot: Binding cDNA or RNA onto slots→ on membrane filters for the analysis of transcripts by hybridization to specific sequences.

Slow Component: During a reassociation reaction of single-stranded DNA, the unique sequences anneal slowly. ►[C₀t value](#), ►[annealing](#)

Slow Stop: In a slow stop, bacterial mutant *dna* may complete slowly the replication underway but cannot start a new cycle at 42 °C. ►[replication](#), ►[strong-stop DNA](#)

SLP-76 (a 76 kDa specific leukocyte protein adaptor): SLP-76 binds to TCR, is phosphorylated at tyrosines near the N-terminus, and provides SH2 binding sites for the VAV protein. SLP also binds the SH3 domain of Grb2. At the C-end, it associates also with SLAP (SLP-76 associated phosphoprotein), resulting in activation of NF-AT. SLP-76 is essential for TCR activity and T cell development in signaling pathways through the activity of phosphotyrosine kinases (PTK), but it is not required for macrophage and natural killer cells. ►[signal transduction](#), ►[TCR genes](#), ►[T cell receptor](#), ►[SH2](#), ►[VAV Grb2](#), ►[NF-AT](#), ►[macrophage](#), ►[killer cell](#), ►[BASH](#), ►[CD3](#), ►[GADS](#); Pivniouk VI et al 1999 J Clin Invest 103:1737.

S

SLS: Sodium lauryl sulfate. ►[SDS](#)

SLT: ►[specific locus mutations assay](#)

SLT-2: A protein kinase of the MAPK family. ►[signal transduction](#), ►[protein kinase](#), ►[MAPK](#)

Slug: Slug, in general usage, means a land mollusk but see also ►[Dictyostelium](#)

Slug: A zinc-finger transcription factor activated by p53. It represses Puma and antagonizes apoptosis (Wu W-S et al 2005 Cell 123:641). ►[apoptosis](#), ►[p53](#), ►[zinc fingers](#), ►[PUMA](#)

Sly Disease: ►[mucopolysaccharidosis type VII](#)

Sma I: A restriction endonuclease; recognition site CCC↓GGG. ►[restriction enzymes](#)

SMAC (supramolecular activation cluster): CD4 T cells with antigen presenting cells, receptors, and intracellular proteins form SMAC. (See terms at separate entries; Potter TA et al 2001 Proc Natl Acad Sci USA 98:12624).

Smac (second mitochondria-derived activator of caspases): Smac inhibits IAPs and facilitates apoptosis by caspase-3. A small, synthetic Smac mimic potentiates the activation of TRAIL and TNFα, inhibits IAP activity, and promotes apoptosis (Li L et al 2004 Science 305:1471). Smac is homologous with Diablo. ►[IAP](#), ►[apoptosis](#), ►[DIABLO](#); Zhang XD et al 2001 Cancer Res 61:7339.

Smad: Signal transducing proteins, which when stimulated by TGF-β can enhance gene transcription and tumor formation (TGF-β signaling). The Smad binding element is GTCTAGAC. The facilitating effects of the bone morphogenetic protein (BMP, acting via the serine/threonine kinase receptor) determine the SMAD protein function and opposing epidermal growth factor (EGF, acting via the receptor tyrosine kinases). Smad2 is essential for the formation of the early embryonic mesoderm of the mouse. Smad3 is normally phosphorylated by the TGF receptor TβRI, and Evi-1 represses its transcriptional activator function. Smad4 controls the mesoderm and visceral endoderm. Other SMADs associated with various ligands of the TGF family control the expression of genes involved in embryonal tissue differentiation. Smad3 and Smad4 cooperate with Jun/Fos (A1) and bind to the TPA-responsive gene promoter elements. SARA (Smad anchor for receptor activation) retains Smad2 and 3 in the cytoplasm. Pancreatic, colon, and other cancers are frequently associated mutation(s) in SMAD2 and SMAD4/DPC4. Smad4 is a tumor suppressor in the gastrointestinal tract of mice (Kim B-G et al 2006 Nature [Lond] 441:1015). SMADs 6 and 7 are modulators/inhibitors of signaling by some SMADs and their mutation may cause hyperplasia of the cardiac valves and other structural anomalies of the heart as well as ossification of the aorta and high blood pressure in mice. The SMAD acronym was derived from the human SPA (spinal muscular atrophy genes, 5q12.2-q13.3) and the *Drosophila* gene *Mad* (*mothers against decapentaplegic*). Smad proteins are classified as R-Smads (receptor regulated), Co-Smads (common Smads), and I-Smads (inhibitory). ►[TGF](#), ►[EGF](#), ►[bone morphogenetic protein](#), ►[serine/threonine kinase](#), ►[receptor tyrosine kinase](#), ►[activin](#), ►[Evi oncogenes](#), ►[TPA](#), ►[API](#), ►[SARA](#), ►[DPC4](#), ►[Mad](#), ►[spinal muscular atrophy](#), ►[Gli](#), ►[Ski](#), ►[osteopontin](#); Wrana JL 2000 Cell 100:189; Zauberman A et al 2001 J Biol Chem 276:24719;

López-Rovira T et al 2002 J Biol Chem 277:3176; Derynck R, Zhang YE 2003 Nature [Lond] 425:577.

Small Cell Lung Carcinoma (SCLC): SCLC is associated with a deletion of the human chromosomal region 3p14.2; the susceptibility is dominant. It accounts for about 1/3 of all lung cancers. Lung cancer genes were located also to 3p21, 3p25, and to several other chromosomes. Smoking may be the major cause of the development of this condition. Surgical remedies are usually not applicable because of the rapid metastasis but it generally responds to radiation and chemotherapy. Deregulation of the MYC oncogene is the suspected cause. Recently, a gene for fragile histidine triad (FHIT) was found to be associated with SCLC and with some of the non-small cell lung carcinomas (NSCLCs). The product of FHIT splits Ap₄A substrates asymmetrically into ATP and AMP. Its metastasis may be inhibited by CC3/TIP30. The heterozygotes (T/C) for the checkpoint kinase gene (CHECK 2/CDS1, human chromosome 22q12.1) was associated with a highly significantly lower incidence of lung cancer than the common T/T genotype [relative risk (RR), T/C versus T/T, 0.44, with 95% confidence interval (CI) 0.31–0.63, $P < 0.00001$] and with a significantly lower incidence of upper aero-digestive cancer (RR 0.44, CI 0.26–0.73, $P = 0.001$; $P = 0.000001$ for lung or upper aero-digestive cancer). The results of this study, involving 4015 smoking patients and 3050 non-smoking individuals in several East-European countries, were surprising because earlier, mutation in the same gene showed an increase in the incidence of the Li-Fraumeni syndrome (Brennan P et al 2007 Hum Mol Genet 16:1794). ▶oncogenes, ▶cancer, ▶MYC, ▶p53, ▶ATP, ▶AMP, ▶semaphorin, ▶metastasis, ▶non-small lung cell carcinoma suppressor, ▶neuroendocrine cancer, ▶Li-Fraumeni syndrome, ▶smoking, ▶checkpoint; Zöchbauer-Müller S et al 2002 Annu Rev Physiol 64:681; Tonon G et al 2005 Proc Natl Acad Sci USA 102:9625.

Small Molecule Microarray: In small molecule microarray, polystyrene beads covered by presumed biologically active ligands are arrayed in micro-well plates. The molecules are released from the beads in a solution and are spread over glass plates and tested for biological function(s) by high-throughput technology. (Uttamchandani M et al 2005 Curr Opin Chem Biol 9:4; MacBeath G et al 1999 J Am Chem Soc 121:7967; Clemons PA et al 2001 Chem Biol 8:1183).

Small Nuclear RNA: ▶snRNA

Smallpox: ▶pox virus, ▶variola

Small RNA (sRNA): sRNA includes microRNA, RNAi, transcripts of small genes, pseudogenes, intergenic regions, and transposons. By the use of massively parallel signature sequencing in *Arabidopsis* plants, a library of a total of 104,800 distinct signatures of these RNAs have been identified. Of these, 77,434 could be matched with the genome (Lu C et al 2005 Science 309:1567). The enormous number of these sequences regulates several ways the expression of the genomes. In *Arabidopsis*, ~2% of the genes may be under the control of microRNAs. Many of these sequences match intergenic regions, indicating that so far, unannotated protein-coding genes, pseudogenes, and transposons are located there. Single miRNAs may regulate on the average five–six times as many genes (Vaughan MW, Martienssen R 2005 Science 309:1525). The small RNAs usually regulate genes by interference (RNAi). Transfection of some dsRNAs into human cell lines was found to cause long-lasting and sequence-specific induction of targeted genes. dsRNA mutation studies reveal that the 5' end of the antisense strand, or “seed” sequence, is critical for activity (Li L-C et al 2006 Proc Natl Acad Sci USA 103:17337). ▶microRNA, ▶RNAi, ▶piRNA, ▶U-RNA, ▶21U-RNA, ▶pseudogene, ▶intergenic region, ▶transposons, ▶RNA non-coding, ▶massively parallel signature sequencing, ▶transitivity; sRNA for cereals: <http://sundarlab.ucdavis.edu/smrnas/>.

Small t Antigen: ▶SV40

Small-Pool PCR: Small-pool PCR amplifies 20–100 molecules of minisatellite DNA from single individuals within a population, and thus reveals a mutation rate that is $>10^{-3}$ in the sperm germline at a number of loci. ▶minisatellite, ▶PCR, ▶MVR; Crawford DC et al 2000 Hum Mol Genet 9:2909.

Small-World Networks: Small-world networks can represent models of many types of self-organizing biological systems, including interaction of gene products. Although the networks can be completely regular or completely random, biological interaction networks are usually connected neither in a completely regular nor in a completely random manner, but in a fashion in between these extremes and thus represent “small-world networks.” Small-world networks display enhanced speed of propagation of signals and coordinated regulation and can be subjected to computational analysis (see Fig. S74). ▶networks, ▶genetic networks, ▶probabilistic graphical models of cellular networks, ▶synthetic genetic array, ▶model; diagram modified after Watts DJ, Strogatz SH 1998 Nature [Lond] 393:440.

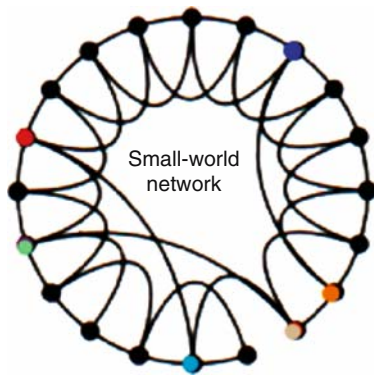


Figure S74. Small-world network

SMART (Simple Modular Architecture Research Tool): SMART facilitates annotation of protein domains. ▶domain, ▶annotation; <http://smart.embl-heidelberg.de/>; <http://smart.embl.de/>.

Smart Ammunition: *Drosophila* P transposable element vectors with selectable markers to produce selectable (e.g., neomycin resistance) insertions. ▶hybrid dysgenesis, ▶insertional mutation; Engels WR 1989, p 437. Mobile DNA. In: Berg DE, Howe MM (Eds.) Am Soc Microbiol, Washington DC.

Smart Cells: A generalized concept that cells (genes) have the ability to sense internal and external cues and respond to them in a purposeful manner, such as shown in signal transduction.

Smart Linkers: Synthetic oligonucleotides with multiple recognition sites for restriction enzymes; they can be ligated to DNA ends to generate the desired types of cohesive ends (see Fig. S75). ▶cloning vectors, ▶cohesive ends, ▶blunt end, ▶blunt end ligation

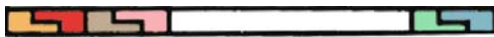


Figure S75. Smart linkers can be cut to different cohesive ends

Smart-PCR: See Villalva C et al 2001 Biotechniques 31:81.

SMC: Proteins involved in the structural maintenance of the chromosomes, including condensation (increasing coiling), cohesion of sister chromatids, and segregation. The top of Figure S76 represents a SMC monomer. The amino and the carboxyl ends are globular and the two long α -helixes and a short hinge domain may facilitate a foldback of the monomer. Two folded monomers may form heterodimers as shown. The DNA single strand may wrap around the termini of the folded dimers and

condensation is facilitated by SMC or the two chromatids may be held together in cooperation with cohesin and the kleisin proteins. SMC proteins are ubiquitous among prokaryotes and eukaryotes. The three Muk gene products of *E. coli* are functionally homologous. ▶sex determination, ▶chromosome coiling, ▶condensin, ▶cohesin, ▶kleisin, ▶achiasmate; Ball AR, Yokomori K 2001 Chromosome Res 9(2):85; Kitajima TS et al 2003 Science 300:1152; Milutinovich M, Koshland DE 2003 Science 300:1101; Nasmyth K, Haering CH 2005 Annu Rev Biochem 74:595.

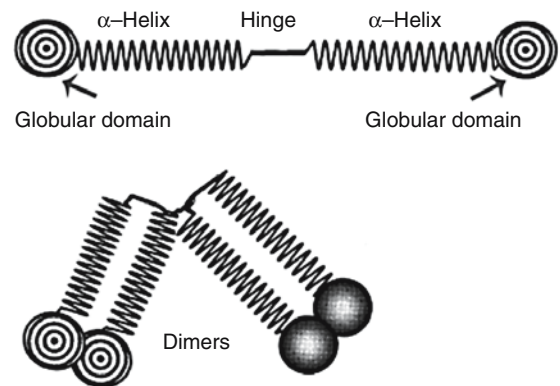


Figure S76. Chromosome structural maintenance proteins

Smear: Preparing a soft specimen for microscopic examination by gentle spreading directly on the microscope slide. ▶squash, ▶sectioning, ▶microscopy

Smg p21: A protein similar to Rap 1. ▶Rap

SMGT (sperm-mediated gene transfer): In SMGT, the sperm internalizes DNA and by artificial insemination, transgenic pigs have been produced that carry the human decay accelerating (hDAF) gene. The efficiency of transformation is high (64%) and the expression is very good (83%). The presence of dDAF is expected to help in overcoming hyperacute rejection of xenotransplanted organs. ▶decay accelerating factor, ▶xenotransplantation, ▶transformation genetic; Lavitrano M et al 2002 Proc Natl Acad Sci USA 99:14230.

Smith-Lemli-Opitz Syndrome (SLOS/RSH): A high prevalence (2×10^{-4}) autosomal recessive anomaly involving microcephalus, mental retardation, abnormal male genitalia, polydactyly, etc., encoded in human chromosomes 11q12-q13 (Type I) and 7q32.1 (Type II). Prevalence in Northern European populations is 1×10^{-4} to 2×10^{-5} . It is caused by Δ^7 -reductase deficiency in the cholesterol pathway and by the accumulation of 7-dehydrocholesterol. Deficiency of the Δ^{24} -reductase results in similar

symptoms. The afflicted individuals show mevalonic aciduria. This condition may also involve holoprosencephaly. Some of the symptoms may overlap with those of the Pallister-Hall syndrome. Prenatal diagnosis in the amniotic fluids after 15 weeks of gestation is feasible. A non-invasive urine analysis may also be practical. ►mental retardation, ►dwarfism, ►head/face/brain defect, ►cholesterol, ►sonic hedgehog, ►holoprosencephaly, ►chondrodysplasia; Wassif CA et al 2001 Hum Mol Genet 10:555.

Smith-Magenis Syndrome (SMS): SMS involves head malformation, short brain, growth retardation, hearing loss, and self-destructive behavior, such as pulling off nails, inserting foreign objects into the ear, etc. The incidence is $>4 \times 10^{-5}$. In 80–90% of the patients, an approximately 4 Mb interstitial deletion heterozygosity is found at the chromosome 17p11.2 region. The locus contains or is flanked by low-copy number repeats, which favor the occurrence of localized recombinations that generate deletions and duplications (Bi W et al 2003 Am J Hum Genet 73:1302). In individuals without cytologically detectable deletions, a 29 nucleotide loss was observed in exon 3 of the RAI1 (retinoic acid induced, 17p11.2) gene. ►mental retardation, ►self-destructive behavior; Slager RE et al 2003 Nature Genet 33:466.

Smith-McCort Dysplasia: ►Dyggve-Melchior-Clausen dysplasia

Smith-Waterman Algorithm: Computer analysis for nucleic acid sequences (Waterman MS 1988 Methods Enzymol 164:765).

SMM: ►stepwise mutation model, ►IAM, ►two-phase model

Smoking: Smoking is responsible for a wide variety of ailments such as heart disease, respiratory problems, cancer, etc., but it may decrease the risk of Parkinson's disease. The inhalation of tobacco smoke by the mother may initiate cancer also in the fetus. Although cancer may be induced by a variety of genotoxic agents in the environment, the smoking induced alteration spectrum in the genetic material is different and thus can be distinguished from the effects of other agents. Tobacco smoke adducts induce a higher proportion of transversion mutations of the p53 gene in the lung and also increases loss of heterozygosity by deleting introns particularly at the fragile site 3 (FRA3B) region including FHIT (fragile histidine triad) in human chromosome 3p14.2. According to one report, 19/31 newborns of smoking mothers had the carcinogen 4-methylnitrosamino-1-(3-pyridyl)-1-butanone in their urine.

The smoking habit is particularly prevalent in affective disorders. In the brain of smokers, the level

of monoamine oxidase B (MAOB) is 40% lower relative to that in non-smokers. MAOB degrades the neurotransmitter dopamine. Subcortical regions, such as the amygdala, the nucleus accumbens, and the mesotelencephalic dopamine system, have been shown in animal models to promote the self-administration of drugs of abuse. Functional imaging studies have shown that exposure to drug-associated cues activates cortical regions such as the anterior cingulate cortex, the orbitofrontal cortex, and the insula. In nicotine addiction, the insula, a narrow island within the brain, seems to play a critical role; persons with disrupted insula are more likely to be able to quit the addiction without relapse (Naqvi NH et al 2007 Science 315:531). The nicotinic acetylcholine receptors play, however, very important roles in the cognitive processes of the brain. Tolerance to smoking seems to be influenced by diet and ethnic background. The carcinogenic effect of smoking tobacco is primarily due to specific N-nitrosamines. Second hand smoking may also stimulate angiogenesis and thus tumor growth (Zhu B et al 2003 Cancer Cell 4:191). ►Parkinson's disease, ►dopamine, ►affective disorders, ►nicotinic acetylcholine receptors, ►nicotine, ►transversion, ►intron, ►fragile site, ►p53, ►chemical mutagens, ►tobacco, ►MAO, ►infertility, ►mortality, ►small cell lung carcinoma; Hecht SS 1999 Mutat Res 424:127; Schuller HM 2002 Nature Rev Cancer 2:455; environmental exposure: Besaterina A et al 2002 Carcinogenesis 23:1171; Allan M Brandt AM 2007 The Cigarette Century. The Rise, Fall, and Deadly Persistence of the Product that Defined America. Basic Books, New York; effect on respiratory tract genes: <http://pulm.bumc.bu.edu/siegeDB>.

Smooth Endoplasmic Reticulum: The smooth endoplasmic reticulum has no ribosomes on its surface. ►SER, ►endoplasmic reticulum

Smooth Muscle: Smooth muscles lacks sarcomeres; they are associated with arteries, intestines, and other internal organs, except the heart. ►sarcomeres, ►striated muscles

SMRT: A silencing-mediator of retinoid and thyroid hormone receptors. It is also corepressor of PPAR δ . ►retinoic acid, ►animal hormones, ►nuclear receptors, ►PPAR; Becker N et al 2001 Endocrinology 142:5321.

Smut: Infection of grasses by *basidiomycete* fungi, causing black carbon-like transformation of the inflorescence (by *Ustilago*, loose smut) or seed tissues (by *Tilletia*, covered smut).

Snail: *Helix pomatia univalens*, 2n = 24.

Snail: A family of zinc-finger transcription factors and a negative regulator of E-cadherin. ▶[cadherin](#); Bettle E et al 2000 *Nature Cell Biol* 2:84; Nieto MA 2002 *Nature Rev Mol Cell Biol* 3:155.

Snakes: Reptiles represented by a large number of cosmopolitan species of diverse sizes up to 30 ft in length. Generally, they do not have legs, except some vestigial remnants in a few species. They use their protruding tongues to smell the environment. Their heat-sensory organs are located between the eyes and the nostrils, are highly sensitive, and are used to detect potential prey. Their teeth (fangs) with grooves conduct their venom to the body of the prey. The venom sacs (in the venomous species) are modified from the salivary gland. Snakes are carnivorous. Their sexual organs are located at the end of the cloaca (alimentary channel). Fertilization is internal but the eggs are laid in the environment, although in some species the eggs hatch within the female body. Snake venom is used primarily for killing the prey. The prey is swallowed when dead, without chewing. Snake protein venoms are very diverse and have evolved from acetylcholinesterase, ADAM, AVIT, complement C3, crotoxin/β-defensin, cystatin, endothelin, factor V, factor X, kallikrein, Kunitz-type proteinase inhibitor, LYNX/SLUR, L-amino oxidase, lectin, natriuretic peptide, β-nerve growth factor, phospholipase A₂, SP1a/Ryanodine, vascular endothelial growth factor, and whey acidic protein/secretory leukoproteinase inhibitor (Fry BG 2005 *Genome Res* 15:403). Knowledge of the physiological/molecular nature of these proteins has evolutionary interest and is important because of its therapeutic relevance.

Snake Venom Phosphodiesterase: Snake venom phosphodiesterase releases 5'-nucleotides from the 3' end of nucleic acids. ▶[phosphodiester bond](#), ▶[phosphodiesterases](#)

S

Snap: ▶[NSF](#), ▶[membrane fusion](#), ▶[SNAREs](#)

Snap-Back: Inverted repeat sequence in nucleic acids. ▶[repeat inverted](#), ▶[lollipop structure](#)

Snapdragon (*Antirrhinum majus*): 2n = 16, a dicotyledonous plant (*Scrophulariaceae*) much employed for the study of mutation (transposable elements) and flower pigments. It is also a popular ornamental. Snapdragon also has many beautiful flower morphology mutants as shown. ▶[TAM](#), ▶[Antirrhinum](#), ▶[peloric](#), flower morphology mutants at ▶[mutation spectrum](#); Schwarz-Sommer Zs et al 2003 *Nature Rev Genet* 4:655; <http://www.antirrhinum.net/>.

SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptor): Binding protein attaching vesicles (v-SNAREs) to target membranes (t-SNAREs) (see Fig. S77).

They mediate, among others, transport through the Golgi compartments. SNAREs also mediate membrane fusions, alongwith plant cell wall penetration resistance to fungal pathogens on normally non-host species. (Collins NC et al 2003 *Nature [Lond]* 425:973). The name has been attributed to surgical wire tools, by which polyps and projections are removed. It could also be linked with bird traps (snare). SNARE seems to be activated by Ypt1p. ▶[NSF](#), ▶[RAB](#), ▶[EEA1](#), ▶[Ypt](#), ▶[snare](#), ▶[synaptobrevin](#), ▶[VAMP](#), ▶[syntaxin](#), ▶[synaptogamin](#), ▶[NSF](#), ▶[Golgi apparatus](#), ▶[membrane fusion](#), ▶[exocytosis](#), ▶[Munc1](#), ▶[Ipk1](#); Bock JB, Scheller RH 1999 *Proc Natl Acad Sci USA* 96:12227; Peters C et al 2001 *Nature [Lond]* 409:581.

SNF: SNF yeast genes are helicases involved in chromatin remodeling (*SNF2*, *SNF5*, *SNF6*, *SNF11*) and *SNF1* is an AMP-activated kinase. SNF1 senses depletion of ATP and increase of AMP in the cell. This is a ubiquitous enzyme family involved in carbohydrate and lipid metabolism, phosphorylation of transcription factors, regulating stress responses in plants, etc. An SNF-6 protein is an acetylcholine transporter in *Caenorhabditis* (▶[muscular dystrophy](#)). ▶[chromatin remodeling](#), ▶[SWI](#), ▶[SUC2](#), ▶[bromodomain](#); Eisen JA et al 1995 *Nucleic Acids Res* 23:2723; Lo W-S et al 2001 *Science* 293:1142.

SNIPs (single nucleotide polymorphism, SNP): SNPs refer to the difference in a single nucleotide at a particular DNA site; these are used as genomic

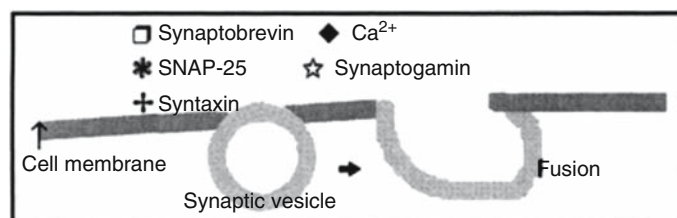


Figure S77. SNARE

markers for human (or other) populations. The most common variation involves C \leftrightarrow T transition in CpG sequences. The analysis uses DNA chips or gel-based sequencing and biotin-labeled probes (VDA, variant detector array). Several different methods exist for the detection of SNPs.

The presence of a single mismatch decreases the electrochemical potential of the DNA. On this basis, transitions and transversions can be detected by the electrochemical response (Inouye M et al 2005 *Proc Natl Acad Sci USA* 102:11606). A survey of 2748 SNPs indicated high degree of polymorphism (4.58×10^{-4}) and mutation rate $\mu \sim 10^{-8}$ to the range of about 10% of the confirmed SNPs. Other estimates for average nucleotide diversity (π) were higher: 9.01×10^{-4} for African-Americans and 6.97×10^{-4} for European-Americans (Crawford DC et al 2005 *Annu Rev Genomics Hum Genet* 6:287). Other studies indicated one SNIP/600 base pairs in the human genome (Kruglyak L, Nickerson DA 2001 *Nature Genet* 27:235). The annotated human chromosome 6 (166,880,988 bp) contains 2761 SNPs in the protein-coding genes (Mungall AJ et al 2003 *Nature [Lond]* 425:805).

SNPs can be mapped to chromosomal location by radiation hybrid cell lines. If the SNP is not within the gene, recombination may lead to false positive identification. SNPs can be generated for the identification of the critical base substitutions responsible for human disease. The majority of SNPs occur in non-coding regions of the genome and are non-informative regarding human disease (Sachidanandam R et al 2001 *Nature [Lond]* 409:928). Some SNPs in non-coding regions may, however, regulate gene expression.

Mapping of SNPs can be carried out by the reduced representation shotgun sequencing (RRS) and by locus-specific polymerase chain reaction amplification (LSA).

Frequently within a gene or within a haplotype, several SNPs exist and several of them may contribute to the disease phenotype. In order to determine their significance for a disease, their location within the haplotype requires mapping (see Fig. S78) (Carlson CS et al 2004 *Am J Hum Genet* 74:106; Livingston RJ et al 2004 *Genome Res* 14:1821). If polony amplification is used from a buccal smear, a single microscope slide permits appropriate genotyping (Mitra RD et al 2003 *Proc Natl Acad Sci USA* 100:5926).

However, when many special cases of the same disease are analyzed, the significance of the base substitutions may be statistically or even causally determined (see Fig. S79). Generally, the number of SNPs is much higher in introns than in exons. For population genetics and linkage studies, the SNPs are frequently classified into types I (involving

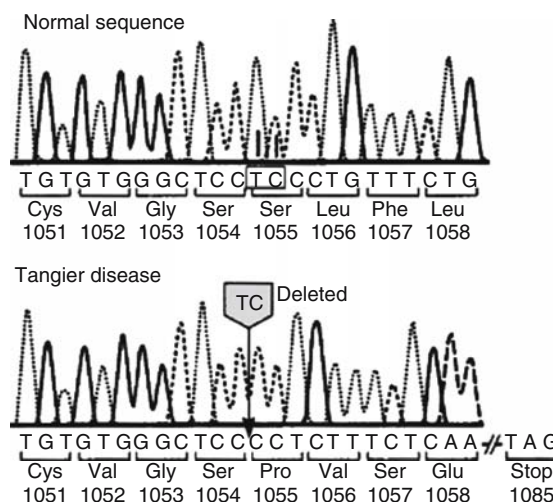


Figure S78. Two-nucleotide deletion in the ABC1 transporter gene results in Tangier disease. Note the frame-shift. (Courtesy of H. Bryan Brewer, Jr. Modified after Remaley AT et al 1999 *Proc Natl Acad Sci USA* 96:12685)

non-synonymous alterations regarding its coding property and being a non-conservative change), II (within coding region and non-synonymous yet conservative), III (in coding sequence but synonymous), IV (within the non-coding 5' sequence), V (within the non-coding 3' sequence), or VI (in other non-coding regions). The type I SNPs are most useful for genetic analyses because they have phenotypic (functional) characteristics. Preliminary information indicates that the majority of the SNIP haplotypes ($\sim 80\%$) occurs in all ethnic groups and only 8% are population-specific (Patil N et al 2001 *Science* 294:1719). MALDI analysis applied to SNPs may facilitate the analysis of QTLs (Mohlke KL et al 2002 *Proc Natl Acad Sci USA* 99:16928). By March 2001, 2.84 million SNPs had been deposited in the public databases and they represented 1.64 million non-redundant mutations (Marth G et al 2001 *Nature Genet* 27:371). The human SNP map includes an ever-increasing number (~ 8 million by 2005; actually 6 million are validated by 2007) of variants of the world population (<http://www.hapmap.org>). Regulatory SNPs were detected in the germline of several breast cancer genes controlling the somatic function, the reactive oxygen species (ROS) pathway (Kristensen VN et al 2006 *Proc Natl Acad Sci USA* 103:7735). ▶allele, ▶DNA chips, ▶MALDI/TOF/MS, ▶genotyping, ▶MRD, ▶radiation hybrid, ▶STS, ▶QTL, ▶RRS, ▶LOS, ▶biotinylation, ▶DASH, ▶DNA repair, ▶padlock probe, ▶linkage disequilibrium, ▶association test, ▶polony, ▶haplotype, ▶giSNP, ▶haplotype block, ▶Tangier disease, ▶breast cancer, ▶ABC transporters, ▶allele-specific

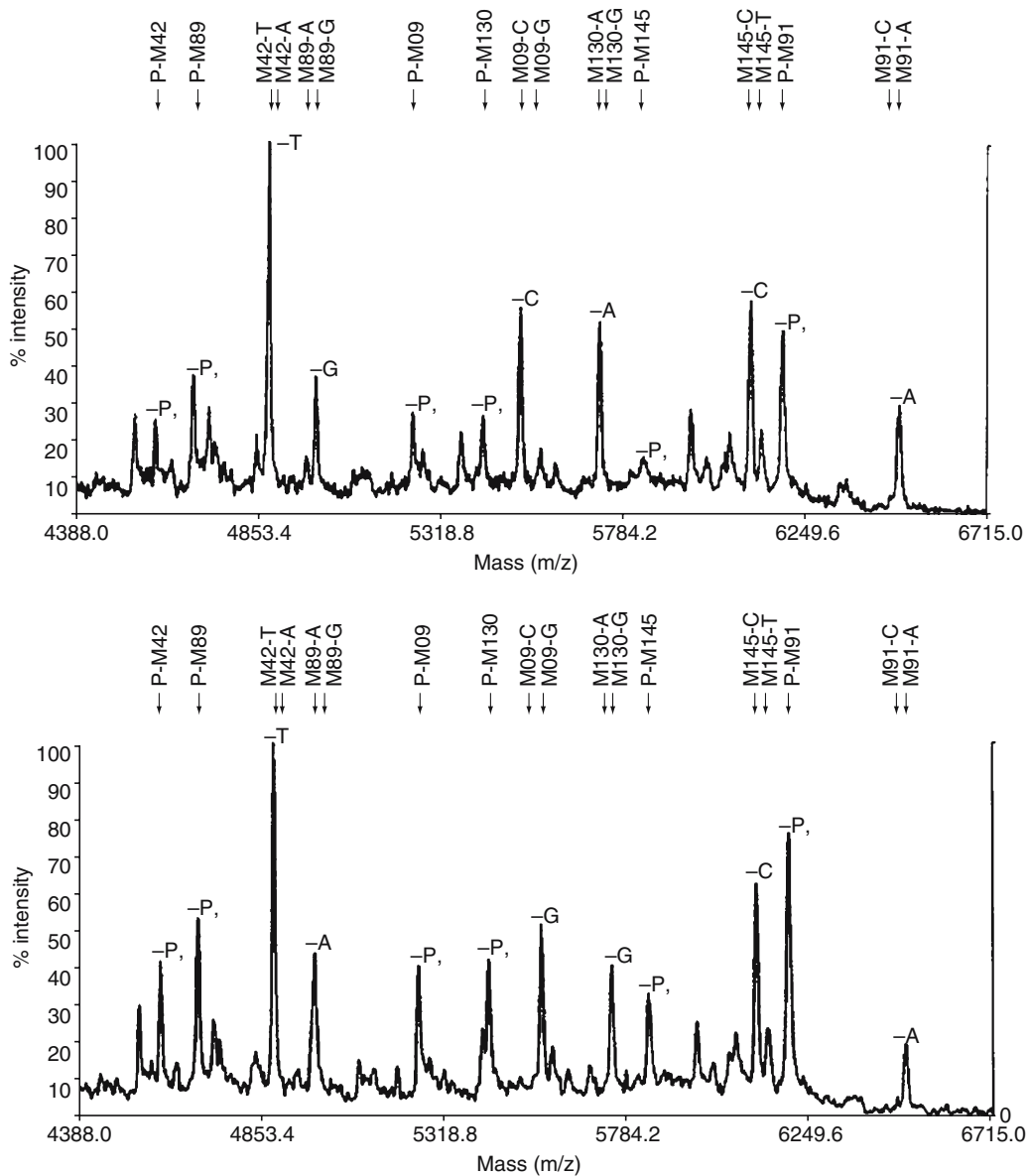


Figure S79. Multiplex primer extension products of the human Y chromosome of two individuals analyzed by MALDI-TOF mass spectrometry displaying allelic differences at the sites indicated at the top. -P indicate the primers and -A, -C, -G, -T stand for the nucleotides. (Courtesy of Silvia Paracchini, Barbara Arredi, Rod Chalk, and Chris Tyler-Smith, 2002.)

probe, ►dynamic allele-specific hybridization, ►genotyping, ►ROS, ►PolyPhred, ►cSNP; Wang DG et al 1998 *Science* 280:1077; Sunyaev S et al 2000 *Trends Genet* 16:198; Mullikin JC et al 2000 *Nature [Lond]* 407:516; Buetow KH et al 2001 *Proc Natl Acad Sci USA* 98:581; Grupe A et al 2001 *Science* 292:1915; Roger A et al 2001 *Genome Res* 11:1100; Miller RD, Kwok P-Y 2001 *Hum Mol Genet* 10:2195; Gut IG 2001 *Hum Mutat* 17:475; Werner M et al 2002 *Hum Mutat* 20:57; Kirk BW et al 2002 *Nucleic Acids Res* 30:3295; Paracchini S et al

2002 *Nucleic Acids Res* 30(6):e27; Coronini R et al 2003 *Nature Biotechnol* 21:21; genotyping SNPs in complex DNA: Kennedy GC et al 2003 *Nature Biotechnol* 21:1233; human genetic variation: <http://www.ncbi.nlm.nih.gov/SNP>; <http://hgbase.interactiva.de>; <http://www.genomic.unimelb.edu.au/mdi/dblist/ccent.html>; tools: <http://bio.chip.org/bio tools>; medical SNP information: <http://snp.cshl.org/>; SNP: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Snp>; SNP effect: <http://snpeffect.vib.be/>; browser tools: <http://genewindow.nci.nih.gov>; SNP

with phenotypic effects: <http://pupasuite.bioinfo.cipf.es/>; medically important SNP search: <http://fastsnp.ibms.sinica.edu.tw/>; SNP associations with disease phenotypes: <http://gmed.bu.edu/>; SNP in protein domains: <http://snpnavigator.net/>; coding SNP tool: <http://www.pantherdb.org/tools/>; detection of human nonsynonymous SNPs: <http://coot.embl.de/PolyPhen/>; sorting intolerant from tolerant amino acid substitutions in proteins: <http://blocks.fhcrc.org/sift/SIFT.html>; <http://www.ncbi.nlm.nih.gov/projects/SNP/>; SNP-short tandem repeat software for human, dog, mouse and chicken: <http://www.imperial.ac.uk/theoreticalgenomics/data-software>; non-synonymous SNPs with relevance to disease: <http://polydoms.cchmc.org/>; SNP annotation platforms: <http://snap.humgen.au.dk/>; <http://snap.genomics.org.cn/>; ethnicity – SNP – disease databases: <http://variome.net>; <http://biportal.net/>; <http://biportal.kobic.re.kr/SNPatETHNIC/>; SNP effect on protein structure: <http://glinka.bio.neu.edu/StSNP/>; markers for genotyping: <http://bioinformoodics.jhmi.edu/quickSNP.pl>.

SNO Oncogenes: Two SKI-related oncogenes. ►SKI, ►oncogene

Snorbozyme: A ribozyme within the nucleolus, processing or degrading nucleolar RNA. (See Samarsky DA et al 1999 Proc Natl Acad Sci USA 96:6609).

snoRNA (small nucleolar RNA): snoRNA is 60–300 nucleotide in length and assists in maturation of ribosomal RNAs in the nucleolus, the folding of RNA, RNA cleavage, base methylation, assembly of pre-ribosomal subunits, export of RNP, etc. A family of snoRNAs of 10–21 nucleotides, complementary to the methylation sites of rRNA, guides the methylation within the nucleolus. Some of the snoRNA genes are situated in introns. The majority of the snoRNAs are either box C/D or H/ACA snoRNA family members. All CD boxes contain fibrillarin and (spliceosomal) Snu13. They are apparently involved in splicing and alternative splicing (Kishore S, Stamm S 2006 Science 311:230). ►RNA maturase, ►pseudouridine, ►introns, ►fibrillarin, ►spliceosome, ►non-coding RNA; Hirose T, Steitz JA 2001 Proc Natl Acad Sci USA 98:12914; Song X, Nazar RN 2002 FEBS Lett 523:182; snoRNA database: <http://www-snoRNA.bio.toul.fr>; snoRNA and Cajal body-specific RNA: <http://gene.fudan.sh.cn/snoRNAbase.nsf>.

Snowdrift Game: One of the theories of evolutionary population dynamics and natural selection. An oversimplified analogy for the principle is that of drivers trapped on either side of a snowdrift. The drivers can either cooperate and both start clearing the road from opposite sides or one of them fails to work (defects). In case of cooperation, they benefit (b) by sharing the

labor (c). The result is $R = b - c/2$. If both defect, the probability to get through is $P = 0$. If only one works, they can both get through, but the defector avoids the cost of labor and gets all the benefits ($b - c$). ►prisoner' dilemma; Hauert C, Doebeli M 2004 Nature [Lond] 428:643; Nowak MA et al ibid. p 646.

SNP: ►SNIPS

snRNA (small nuclear RNA): Low molecular weight RNA in the eukaryotic nucleus, rich in uridylic residues. When associated with protein, sRNA mediates the splicing of primary RNA transcripts and frees them from introns through assistance of the lariat. The spliceosomal snRNP can be exported to the cytoplasm if appropriately capped, i.e., if it possesses the nuclear cap-binding complex, the export receptor CRM1/Xpo1. RanGTP and the phosphorylated adaptor of RNA export (PHAX) are also required for this process. ►hnRNA, ►U1-RNA, ►RNP, ►Ran, ►CRM1/SXPO1, ►export adaptor, ►introns, ►spliceosome, ►lariat, ►Ohno's law, ►7SK RNA; M et al 2000 Cell 101:187; Kiss T 2001 EMBO J 20:3617; 2002 Gene Expr 10(1/2).

snRNP: Small nuclear ribonucleoprotein, (also pronounced as “snurp”). It is involved in the processing of RNA and the assembly of spliceosomes. ►KH domain, ►imprinting, ►spliceosome; Nagengast AA, Salz HK 2001 Nucleic Acids Res 29:3841.

Snurportin: An α importin-like transport protein handling snRNP import to the cell nucleus. ►importin, ►nuclear pore, ►snRNP; Paraskeva E et al 1999 J Cell Biol 145:255.

Snurposomes: A complex of the five snRNP particles (“snurps”) that process RNA transcripts in the Cajal bodies. ►U RNAs, ►Cajal body, ►coiled body; Gall JG et al 1999 Mol Biol Cell 10:4385.

SOAP (Simple Object Access Protocol): <http://www.w3.org/TR/soap/>.

SOB Bacterial Medium: The SOB bacterial medium consists of: H₂O 950 mL, bacto tryptone 20 g, bacto yeast extract 5 g, NaCl 0.5 g plus 10 mL of 250 mM KCl; its pH is adjusted to 7 with 5 N NaOH in a total volume of 1 L. Just before use add 5 mL of 2 M MgCl₂.

SOC (store-operated channel, synonym: TRP transient receptor potential): a group of plasma membrane ion channels controlling the release of ions stored in the lumen of the endoplasmic reticulum. ►ion channels; Ma R et al 2001 J Biol Chem 276:25759.

SOC Bacterial Medium: The same as SOB but contains glucose (20 mM). ►SOB

Social Darwinism: The application of Darwinian views (survival of the fittest) to social order. Many anthropologists, sociologists, and ethicists rejected social darwinism and portend that it is an attempt to justify inequalities, harsh competition without adherence to ethics, aggression, imperialism, racism, and unbridled capitalism as necessities for the survival of the fittest. Social darwinism of the 19th century is no longer accepted in the developed world. ▶[Darwinism](#), ▶[IQ](#), ▶[social engineering](#); Rogers JA 1972 *J Hist Ideas* 33:265.

Social Engineering: The Utopian idea that the genetic determination of an individual is unimportant in defining the abilities and their realization but education, welfare, medical service, etc., may determine how a person will function in a society. Therefore, the state and its institutions must actively control human life from cradle to death. However, even though the importance of compassion, education, caring, and multiple social safety nets are indispensable in a modern society, the significance of individuality cannot be ignored. ▶[social Darwinism](#), ▶[IQ](#); Graebner W 1980 *J Am Hist* 67:612.

Social Insects: Insects like bees, wasps, ants, and termites that live in a colony and generally divide various tasks among different castes, such as workers (soldiers), queen, and drones. The queen (gyne) and the workers and soldiers are diploid. In some species, the workers may produce males. The drones are different because they hatch from unfertilized eggs. The major differences between the queen and the workers is that the queens have predominantly 9-hydroxy-(*E*)2-decanoic acid and 9-keto-(*E*)2-decanoic acid in their mandibular glands. The workers have predominantly 10-hydroxy-(*E*)2-decanoic acid. These pheromones then determine their respective functional roles in the colony. The workers and soldiers have ovaries and under certain circumstances (especially the soldiers) may produce haploid eggs. Cuticular hydrocarbons may regulate sex expression and convert workers into egg-laying females (gamer-gate), although usually smaller in size. Such a change in some groups may take place by physical contact of individuals transmitting the hydrocarbon molecules. Recently, the status of soldiers has been questioned as being genetically equivalent with the workers. The soldiers' (not found in all species of social insects) role is protection of the colony. In the fire ant *Wasmannia auropunctata*, a widely distributed species, sex determination is unique. The queens produce other queens clonally (without sexual reproduction). The diploid sterile workers are the products of sexual reproduction. The males are derived from unfertilized eggs containing only the paternal genome (the maternal genome is eliminated

from the diploid eggs). Therefore, the male and female genomes are completely separated (Fournier D et al 2005 *Nature [Lond]* 435:1230). ▶[sex determination](#), ▶[male-stuffing](#), ▶[ant](#), ▶[honey bee](#), ▶[wasp](#); Bourke AF 2001 *Biologist [Lond]* 48(5):205; Parker JD, Hedrick PW 2000 *Heredity* 85(pt 6):530; Thorne BL, Traniello JFA 2003 *Annu Rev Entomol* 48:283; development of caste differences: Hoffman EA et al 2007 *BMC Biol* 5:23.

Social Selection: Social selection is not based on Darwinian fitness but on the social status of the individual carrying the trait. A particular Y-chromosome is found in a large region from the Pacific to the Caspian Sea where the Mongols of Genghis Khan ruled. It originated about the same time—about 1000 years ago—as the Mongolian Empire. Thus, the rapid spread of this chromosome may be due to the social privileges of the carriers. Preimplantation selection of the sex of human offspring is also called social selection. Its purpose can be the avoidance of defective children caused by chromosomal anomalies and hereditary disease. Family balancing, i.e., having children in a certain proportion of boys and girls is generally an ethically unacceptable goal. In the USA, many institutions object to it and refuse the medical procedure required. ▶[Y chromosome](#), ▶[sex selection](#); Zerjal T et al 2003 *Am J Hum Genet* 72:717.

Sociobiology: The study of the biology and behavior of social insects and other animal communities. ▶[social insects](#); Wilson EO 2000 *Sociobiology: The new synthesis*. Harvard University Press, Cambridge, Massachusetts.

Sociogenomics: Sociogenics studies the genetic and molecular biology of the functions involved in social life. ▶[kin selection](#), ▶[altruism](#), ▶[mutualism](#); Robinson GE et al 2005 *Nature Rev Genet* 6:257.

SOCS-Box (suppressor of cytokine signaling): The SOCS-box contains a protein docking site(s) for protein-protein interaction and seems to be involved in transduction signal attenuation and ubiquitination. SOCS-2^{-/-} mice display greatly increased body weight caused apparently by inappropriate regulation of the Jak/Stat signal transduction and the IGF-I pathways. ▶[cytokine](#), ▶[signal transduction](#), ▶[CIS](#), ▶[JAB](#), ▶[SSI-1](#), ▶[CSAID](#), ▶[ubiquitin](#), ▶[insulin-like growth factors](#); Zhang JG et al 2001 *Proc Natl Acad Sci USA* 98:13261.

SOD (superoxide dismutase): ▶[superoxide dismutase](#), ▶[amyotrophic lateral sclerosis](#)

SODD: ▶[TNFR](#)

Sodium Azide (N_3Na): An inhibitor of respiration that blocks the electron flow between cytochromes and O_2 . It is also a potent mutagen for organisms that can activate it.

Sodium Channel: ► [ion channels](#)

Sodium Dodecyl Sulfate: A synonym for sodium lauryl sulfate; ► [dodecyl sulfate sodium salt](#)

Sodium Pump: A plasma membrane protein that moves Na^+ out and K^+ into the cells with the energy obtained by hydrolyzing ATP; it is also called Na^+/K^+ ATPase. ► [ion channels](#)

Soft Inheritance: Soft inheritance has been a rather controversial notion; its theory claims that environmental influences mold heredity and acquired characters are inherited. ► [acquired characters](#), ► [hard heredity](#) of inheritance of acquired characters, Lamarckism, Neo-Lamarckism, Lysenkoism, and other ideas claiming that environmental factors modify the genetic material at a non-random manner (not including mutation or transformation) but by direct manner shaping adaptive traits. Epigenetics has shown however that some traits are transmitted to the progeny by their acquired status of methylation. (See terms in alphabetical order, ► [hard heredity](#)).

Software: A computer program that tells the hardware (the computer) the applications, i.e., which instructions to carry out and how. ► [databases](#); <http://www.sanger.ac.uk/Software/Pfam/>.

Sog: ► [bone morphogenetic protein](#)

Soil Remediation: Soil remediation involves the removal of environmental pollutants from soil and water. It requires sensitive identification of small amounts of toxic and carcinogenic and mutagenic substances, such as arsenic, heavy metals, polycyclic hydrocarbons, etc. ► [arsenic](#), ► [phytoremediation](#), ► [DNAzyme](#)

Solenoid Structure: A coiling electric conductor used for the generation of a magnetic field; by analogy, the coiled nucleosomal DNA fiber is frequently described as a solenoid, although it has no relation to electricity or magnetism. It merely resembles those coils. The DNA solenoids are about 30 nm in diameter, contain about six nucleosomes per turn, and are packed with a large number of structural and catalytic proteins. Actually two different models have been proposed for the 30 nm solenoid structure of the chromosome sub-fibers although neither of them has been fully and universally confirmed. One has been based on the crystal structure of a four-nucleosome core array lacking the linker histone and the other, far more compact structure, has been derived from the electron microscopic analysis of long nucleosome

arrays containing the linker histone. The first model is of the two-start helix type, the second a one-start helix with interdigitated nucleosomes. Both of these models assume that the fiber is regulated by histones (Robinson PJ, Rhodes D 2006 *Curr Opin Struct Biol* 16:336; Tremethick DJ 2007 *Cell* 128:651). ► [nucleosome](#), ► [nuclear matrix](#), ► [zig-zag model of chromosome fibers](#)

Solid Phase Synthesis: In a solid-phase synthesis, the synthesized molecules are continuously added to a solid support.

Solid State Control: Solid state control is exercised by electric or magnetic means in solids, e.g., in a transistor. ► [semiconductors](#)

Solitary LTR: Long terminal repeats that have lost their internal (transposase) sequences by re-combination and excision. ► [long terminal repeats](#), ► [retrovirus](#), ► [retroposon](#), ► [retrotransposon](#); Domansky AN et al 2000 *FEBS Lett* 472(2–3):191.

Solo Elements: Terminal sequences (LTR) of retroposons that can exist in multiple copies without the coding sequences between the two direct repeats. ► [Ty](#)

Soluble RNA: A somewhat outdated term for transfer RNA. ► [tRNA](#)

Solute: Any substance dissolved in a solvent.

Solution Hybridization: Molecular hybridization in a liquid medium. ► [nucleic acid hybridization](#)

SOM (self-organizing map): A type of mathematical cluster analysis that is particularly well suited for recognizing and classifying features in complex, multidimensional data of microarray hybridization. The method has been implemented in a publicly available computer package, GENECLUSTER, that performs the analytical calculations and provides easy data visualization. ► [microarray hybridization](#), ► [cluster analysis](#); Sinha A, Smith AD 1999 *Microgravity Sci Technol* 12(2):78; Haese K, Goodhill GJ 2001 *Neural Comput* 13:595; Unneberg P et al 2001 *Proteins* 42:460.

Soma: Body cells distinguished from those of sexual reproduction (germinal cells). ► [disposable soma](#)

Somaclonal Variation: Genetic variation occurring at a frequency higher than spontaneous mutation in cultured plant cells (see Fig. [S80](#)). (See Kaeppler SM et al 2000 *Plant Mol Biol* 43(2–3):179).

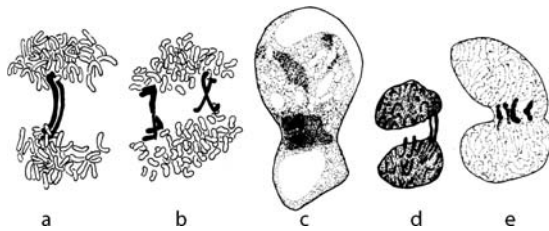


Figure S80. Mitotic anomalies in a clone of tobacco maintained in cell culture. (a), (b) anaphase bridges, (c) telophase bridge, (d) the same as (c) but enlarged nuclei, (e) early interphase with conjoined nuclei. Polyploidy is also of common occurrence. (From Cooper LS et al 1964 Am J Bot 51:284)

The causative mechanism is poorly understood. It is conceivable that the asynchrony between nuclear and cell divisions are accompanied by chromosomal damage. Also, there is evidence that movement

of endogenous transposable elements is involved. The mobility is attributed to the “stress” imposed by the culture (see Fig. S81).

Somatic Cell: The majority of the body cells (reproduced by mitosis), including those of the germline but not the products of meiosis, the sex cells (gametes).
 ▶germline, ▶cell lineages, ▶mitosis, ▶cell genetics, ▶parasexual mechanisms

Somatic Cell Hybrids: Somatic cell hybrids are formed through fusion of different somatic cells of the same or different species. Somatic cell hybrids contain the nucleus of both cells and in addition all cytoplasmic organelles from both parents, in contrast to the generative hybrids where generally mitochondria and plastids are not transmitted through the male.

For the fusion of cultured somatic cells, the use of various special techniques is necessary. Most commonly, protoplasts are used and the fusion medium is:

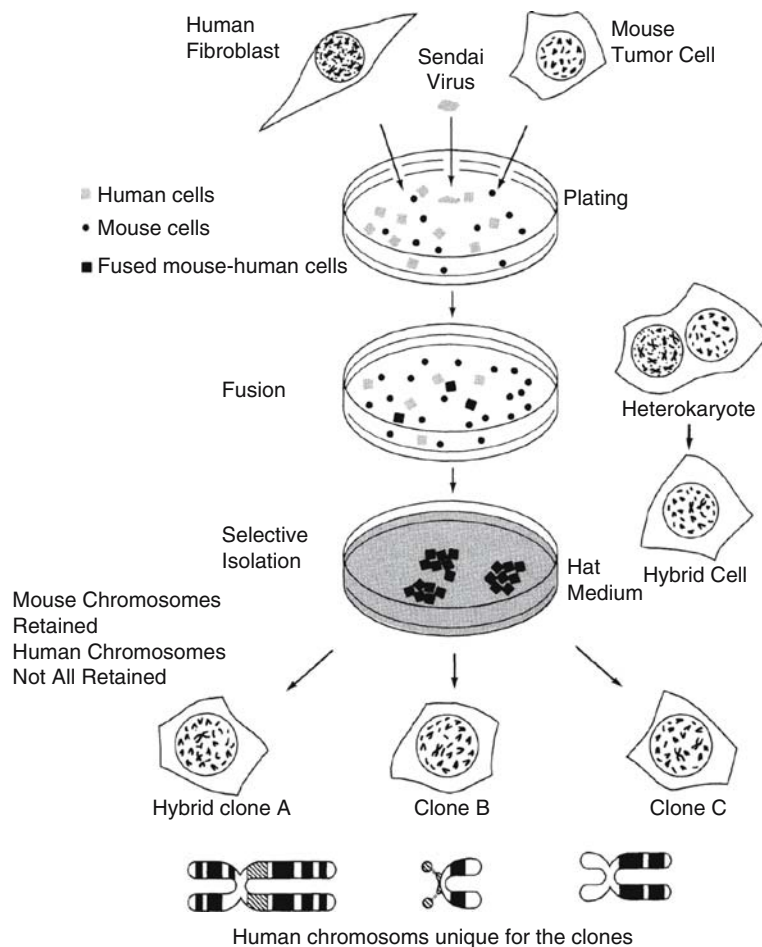


Figure S81. Selective isolation of mouse + human cell hybrids. The fused cell usually retains all mouse chromosomes but the human fibroblast chromosomes may be partially eliminated and in some clones only one or another human chromosome is maintained. (Modified after Ruddle FH, Kucherlapati RS 1974 Sci Am 231(1):36)

polyethylene glycol [MW 1300–1600] 25 g, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 10 mM, KH_2PO_4 0.7 mM, glucose 0.2 M in 100 mL H_2O , pH 5.5 for plants. The best media may vary according to species. The isolation of somatic animal cell hybrids was greatly facilitated by using selective media (see Fig. S82). (►HAT medium).

The fusion of animal cells is promoted by polyethylene glycol, by attenuated Sendai virus, or by calcium salts at higher pH. Immediately after fusion, the somatic cells may become heterokaryotic but eventually the nuclei may also fuse. The availability of fused cells along with loss of one set of chromosomes or partial deletion of chromosomes make possible the localization of many human genes (see Fig. S84). In human genetics, mouse + human cells have been used most commonly. In such cultures, the human chromosomes are gradually eliminated. However, if one of the mouse chromosomes carries a defective gene, the human chromosome carrying a functional wild type

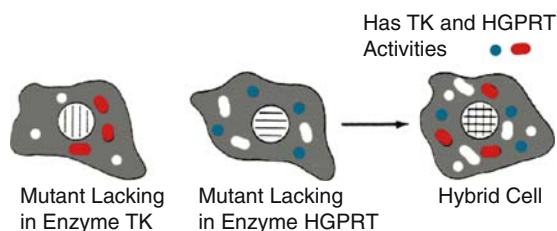


Figure S82. Selective isolation of animal somatic cell hybrids deficient in thymidine kinase and hypoxanthine-guanine phosphoribosyltransferase. On “HAT” medium only the complementary heterokaryons survive. (Modified after Ephrussi B, Weiss MC 1969 Sci Am 220 (4):26)

| | | Human chromosomes | | | | | | | |
|---------------|---|-------------------|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Hybrid clones | A | + | + | + | + | – | – | – | – |
| | B | + | + | – | – | + | + | – | – |
| | C | + | – | + | – | + | – | + | – |

Figure S83. Chromosome assignment of genes on the basis of incomplete clones of mouse + human cell hybrids. A panel of 3 clones, each containing a set of 4 of 8 human chromosomes. If a gene is expressed uniquely in clone (C) but not in (A) or (B), the locus must be in chromosome 7. Because only C carries chromosome 7. Additional panels are needed to test genes in the entire human genome. (After Ruddle FH, Kucherlapati RS 1974 Sci Am 231(1):36)

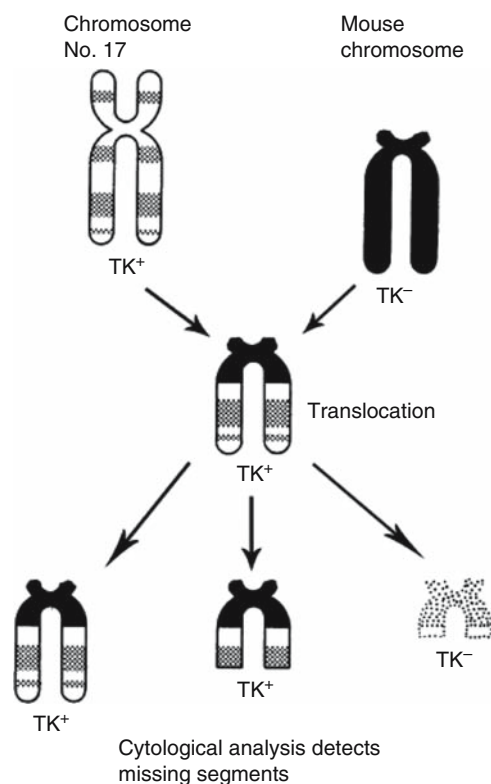


Figure S84. Regional mapping of the thymidine kinase (TK) gene to a segment of human chromosome 17. A translocation was obtained between human chromosome 17 and a mouse chromosome that was deficient for TK. The translocation chromosome was exposed to a chromosome-breaking agent that cleaved off segments of various lengths from the end of the translocation. When the segment containing the gene (TK) was removed, the cells carrying this broken chromosome no longer displayed TK activity and the gene's location was revealed at 17q23.2-q25.3. (►human chromosome map; Modified after F.H. Ruddle and R.S. Kucherlapati)

allele must be retained in order that the culture be viable in the absence of a particular supplement, required for normal function (see Fig. S83). The genetic constitution of the retained human chromosome can be also verified by enzyme assays, electrophoretic analysis of the proteins, or immunological tests. For genetic analysis of higher mammals, and particularly in humans, where controlled mating is not feasible, the availability of somatic hybrids has opened a new and very productive approach. In the somatic hybrid cells, allelism and also synteny or linkage can be shown. If two or more human genes are consistently expressed in a particular chromosome retained, it is a safe conclusion that they are located in the same chromosome. The diagram (see Fig. S83) explains the principle

of gene assignment. Genes can be mapped to particular chromosome bands by deletions. By somatic cell fusion, hybrids can be obtained between taxonomically very distant species.

All kinds of animal cells may be fused with each other, and in addition plant and animal cells can also be fused. Some of these exotic hybrids may have, however, difficulties in continuing cell divisions.

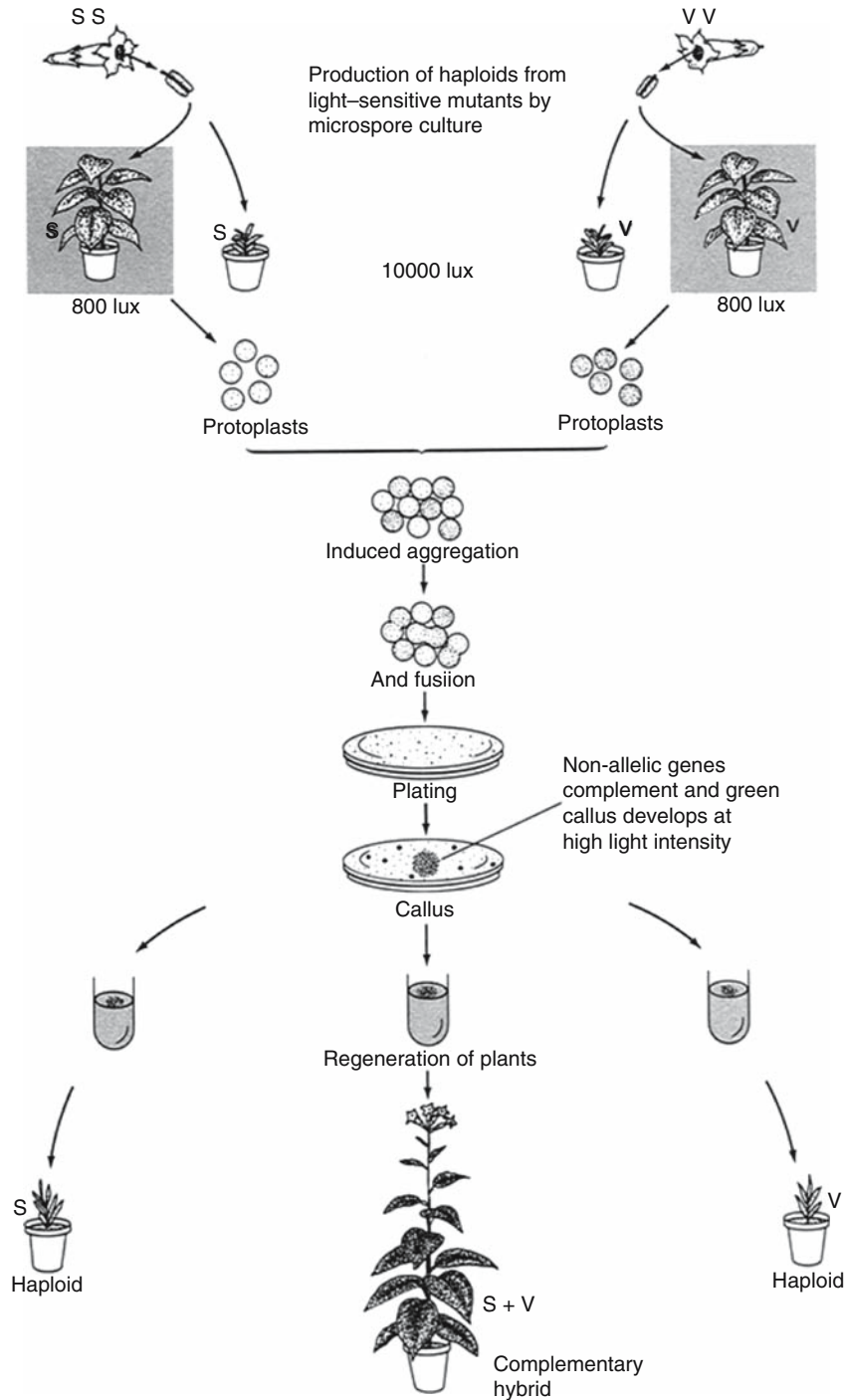


Figure S85. Somatic-cell hybrid production between non-allelic tobacco mutants. (Redrawn by permission after Melchers G & Labib G 1974 Mol. Gen. Genet. 135:277)

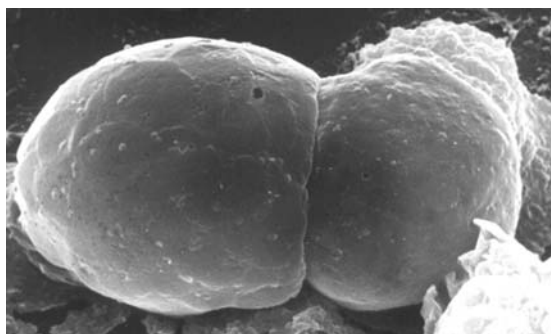


Figure S86. The process of fusion of plant protoplasts. (From Fowke LC et al 1977 *Planta* 135:257)

Somatic cell fusion may also make possible the study of recombination between various mitochondria or chloroplast DNAs in cells. However, in generative hybrids, because of the uniparental (female) transmission of the organelles, such analyses are not feasible. Since plant cells generally retain totipotency in culture, the hybrid cells may be regenerated into intact organisms and can be further studied in favorable cases by the methods of classical progeny analysis.

►HAT medium, ►cell fusion, ►fusion of somatic cells, ►monoclonal antibody, ►human chromosome maps, ►in situ hybridization, ►mapping genetic, ►somatic embryogenesis, ►microfusion, ►radiation hybrids, ►mitochondrial mutation, ►IFGT; Vasil IK (Ed.) 1984 *Cell Culture and Somatic Cell Genetics of Plants*. Academic Press, San Diego, California; Rédei GP 1987 McGraw-Hill *Enc Sci Technol* 6th ed 16:628.

Somatic Cell Nuclear Transfer: After the enucleation of oocytes, the nucleus of somatic cells from the same or different animals is transferred into the oocytes and this way the donor cell or individual is cloned. This procedure was successful initially for sheep; successful procedures for mice, cows, goats, pigs, rabbits, mule, horse, rats, and dogs followed. Eventually, the oocytes with a new donated diploid nucleus is transferred into the oviduct of a female, which carries the embryo to term. Applying such techniques to human cells is restricted or prohibited in many countries. It may be permitted in the UK, Belgium, China, Singapore, South Korea and Australia under regulated conditions. In the USA, such research cannot be supported by federal funds although there are less and variable limitations for private of state-funded activities. ►nuclear transplantation, ►cloning; Lee BC et al 2005 *Nature [Lond.]* 436:641.

Somatic Crossing Over: ►mitotic crossing over

Somatic Embryogenesis: The formation of embryos either directly, or by first passing through a callus stage, from cultured adult plant cells or protoplasts. LEAFY COTYLEDON2 gene controls proteins involved in somatic embryogenesis of *Arabidopsis* (Braybrook SA et al 2006 *Proc Natl Acad Sci USA* 103:3468). In about nine animal phyla, the germline is not separated from the somatic line, therefore gametes develop from the somatic cell lineage. The situation in protists and fungi is essentially similar. A strict germline does not exist in plants either. ►embryogenesis somatic, ►embryo culture, ►apomixis, ►germline; Sata SJ et al 2000 *Methods Cell Sci* 22:299.

Somatic Hybrids: ►somatic cell fusion, ►somatic cell hybrids, ►graft hybrids, ►microfusion

Somatic Hypermutations: Somatic hypermutations generally occur in a region of one to two kilobases around the rearranged V-J regions of the immunoglobulin genes and very rarely extend into the C (constant) sections. These mutations, usually transitions, and predominantly involving guanine, are most common in the complementarity-determining region (CDR) and the events usually take place in the germinal centers. The preferred hot spots are purine-G-pyrimidine-(A/T) sequences, although not all these sequences are hot spots for mutation. The serine codons AGC and AGT can represent a hot spot but the TCA, TCC, TCG and TCT are not. The codon usage in the CDR region appears to be evolutionarily determined to secure the maximum complementarity to antigens. It is not entirely clear what determines the targeting of the hypermutations to the special area but transcriptional enhancers appear to be involved. Hypermutations are limited to the coding strand and occur in a downstream polarity. Deletions and insertions are rare. For somatic hypermutation V(D)J rearrangement is a prerequisite. Activation-induced cytidine deaminase (AID) is apparently targeted by replication protein A to the sites of V(J)D recombination and is one factor of the hypermutations of the immunoglobulin genes (Chaudhuri J et al 2004 *Nature [Lond.]* 430:992). C is deaminated to U by activation-induced deamination (AID) and either mutagenic repair of the mismatch takes place or the broken strand may lead to somatic hypermutation. Error-prone mismatch repair machinery preferentially targets non-template uracils in a way that promotes somatic hypermutation during the antibody response (Unniraman S, Schatz DG 2007 *Science* 317:1227). Somatic hypermutation, along with recombination, is the major source of antibody variation and increases the defense repertoire in mammals. The Rad6/Rad18 protein may recruit error-prone translesion polymerases to the DNA

replication of immunoglobulin G (Ig) genes (Bachl J 2006 Proc Natl Acad Sci USA 103:12081). ▶immunoglobulins, ▶CDR, ▶germinal center, ▶lymphocytes, ▶transition, ▶hot spot, ▶enhancer, ▶hypermutation, ▶mosaic, ▶cytosine deaminase, ▶UNG, ▶replication protein A, ▶translesion pathway; Harris RS et al 1999 Mutat Res 436:157; Meffre E et al 2001 J Exp Med 194:375; Papavasiliou FN, Schatz DG 2002 Cell 109:S35; Di Nola J, Neuberger MS 2002 Nature [Lond] 419:43; Honjo T et al 2005 Nature Immunol 6:655; Di Noia JM, Neuberger MS 2007 Annu Rev Biochem 76:1.

Somatic Mutation: Somatic mutation occurs in the body cells. It is undetectable if recessive, unless the individual is heterozygous. The mutation is manifested by sector formation. This procedure for testing mutability is particularly effective if multiple-marker heterozygotes are treated. It is not inherited to generative progeny unless it occurs or expands also to the germline. It has been successfully used for studies of mutation in the stamen hairs of the plant *Tradescantia*. In fungal cultures mutation in mitotic cells may appear as sectorial colonies. Somatic mutation can be studied in in vitro cell cultures. Recessive mutations are detectable for X-linked genes in hemizygous cells such as those of the male. The procedure is effective if it is directed toward loci with selectable products. If *loxP* is introduced into mammalian cells in a near centromeric region and if *neo* is inserted distal to the selectable marker, after random mutagenesis the *Cre* expressing cells—through recombination—produce homozygotes for some the mutations induced in recessive genes (Koike H et al 2002 EMBO Rep 3:433). Molecular methods (PCR) may permit the identification of the mechanisms involved such point mutations, chromosomal deletions and rearrangement. The frequency of mutation may be affected by age, and various environmental factors and these can be analyzed. ▶pseudodominance, ▶LOH, ▶bioassays in genetic toxicology, ▶*Tradescantia* stamen hairs, ▶somatic hypermutations, ▶paramutation, ▶transposable elements, ▶mosaic, ▶PCR, ▶cancer, ▶SNIP, ▶nucellus, ▶Knudson's two-mutation theory, ▶*Cre/LoxP*, ▶*neo*; Orive ME 2001 Theor Popul Biol 59(3):235; p53 mutation database: <http://www-p53.iarc.fr/>; somatic mutation in cancer: <http://www.sanger.ac.uk/genetics/CGP/cosmic/>.

Somatic Pairing: Generally, only the meiotic chromosomes pair during prophase (possibly late interphase), but in some tissues, such as the salivary glands, the chromosomes are always tightly associated. Also, mitotic association of the chromosomes is a requisite for mitotic (somatic) crossing over in a few organisms

where this phenomenon has been analyzed. (*Drosophila*, some fungi, *Arabidopsis*, etc.). ▶mitotic recombination, ▶parasexual mechanisms, ▶pairing, ▶intimate pairing, ▶polytenic chromosomes; Burgess SM et al 1999 Genes Dev 13:1627.

Somatic Recombination: ▶mitotic crossing over

Somatic Reduction: The reduction of chromosome numbers during mitosis in polyploids.

Somatic Segregation: The unequal distribution of genetic elements during mitoses. ▶mitotic crossing over, ▶somatic mutation, ▶sorting out, ▶chloroplast genetics, ▶mosaic

Somatogamy: The fusion of sexually undifferentiated fungal hypha tips. ▶fungal life cycles

Somatomedin: A second messenger-type polypeptide. In association with other binding proteins, it is involved in the stimulation of several cellular functions. ▶insulin-like growth factor, ▶pituitary dwarfness, ▶second messenger; Deng G et al 2001 J Cell Physiol 189:23.

Somatoplastic Sterility: In certain plant hybrids, the nucellus may show excessive growth, and chokes the embryo to death. The embryo can be rescued if excised early and transferred to in vitro culture media. ▶embryo culture

Somatostatin: A 14–20-amino acid long hypothalamic neuropeptide inhibits the release of several hormones (somatotropin, thyrotropin, corticotropin, glucagon, insulin, gastrin) in contrast to the growth hormone-releasing factor that stimulates the production of the growth hormone. The somatostatin gene has been mapped to human chromosome 3q28 and to mouse chromosome 16. Two somatostatin receptors SSTR1 and 2 (391 and 369 amino acids, respectively) with very substantial homology have been identified. They are sevenpass-transmembrane proteins frequently bound to G-proteins and distributed all over the body, at particularly high levels in the stomach, brain, and kidney. The somatostatin and dopamine receptors may co-oligomerize. ▶animal hormones, ▶G-proteins, ▶seven membrane proteins, ▶signal transduction, ▶GHRH, ▶dopamine, ▶Langerhans islets, ▶pancreas, ▶ovarian cancer; Patel YC 1999 Front Neuroendocrinol 20:157.

Somatotroph: The growth hormone-secreting cell in the adenohypophysis (in the anterior lobe of the pituitary of the brain).

Somatotropin: The mammalian growth hormone (GH, $M_r \approx 21500$), it can correct some dwarfisms when its level is increased; also it stimulates milk production.

Actually, there are three human growth hormones, all coded at chromosome 17q23-q24. Their mRNAs display about 90% homology and their amino acid sequences are shared as well. The placental lactogen protein is an even more effective growth hormone, also located nearby, and it is highly homologous. The human growth hormone gene is transcribed only in the pituitary, whereas the homologs are expressed in the placental tissues. Human and other somatotropin genes have been cloned. Transformation of mice with rat growth hormone genes increased body size substantially. ▶**dwarfism**, ▶**pituitary dwarfism**, ▶**stature in humans**; Yin D et al 2001 J Anim Sci 79:2336.

Somites: Somites are paired mesoderm blocks along the longitudinal axis (notochord) of an embryo that give rise to the vertebral column and other segmented structures. After migration, they may form the skeletal muscles. The development of the somites is controlled mainly by the Notch Wnt family and associated proteins. ▶**Notch**, ▶**wingless**; Pourquié O 2001 Annu Rev Cell Dev Biol 17:311; Pourquié O 2003 Science 301:328.

Somitogenesis: The differentiation of the somites. ▶**somites**

Son of Sevenless: ▶**SOS**

Sonic Hedgehog (Shh, human chromosome 7q36): A vertebrate gene that provides information in the head–tail direction for development; it is a rather general signaling protein of animal differentiation. *Shh* contributes to the specification of the notochord, brain, lung, and foregut. It is homologous to the *Drosophila hedgehog* (*hh*) gene; its receptors are *patched* (*ptc*) and *smoothed* (*smo*), signaling factor genes. A freely diffusible *Shh* is modified by cholesterol and a balance of Patched and the Hedgehog-interacting proteins (Hip) regulates it. Defects in *patched* may cause various carcinomas, medulloblastoma, and rhabdomyosarcoma. These genes have regulatory functions in oncogenic development. Patched activates apoptosis in neuroepithelia if its Sonic Hedgehog ligand is missing (Thibert C et al 2003 Science 301:843). ▶**hedgehog**, ▶**notochord**, ▶**holoprosencephaly**, ▶**GLI**, ▶**medulloblastoma**, ▶**rhabdomyosarcoma**; Villavicencio EH et al 2000 Am J Hum Genet 67:1047; Cohen MM Jr 2003 Am J Med Genet 123A:5; Ingham PW, Placzek M 2006 Nature Rev Genet 7:841.

Sonicator: An ultrasonic (≈20 kHz) equipment used for disrupting cells to extract contents.

Sonography: A method of ultrasonic prenatal analysis of possible structural and other defects in heart, kidney, bone, sex organs, umbilical chord, body

movements, and for verifying pregnancy, etc. Presumably, it entails no appreciable risk. ▶**ultrasonic**, ▶**prenatal diagnosis**, ▶**fetoscopy**

SopE: A guanyl-nucleotide-exchange factor for Rho and Rac GTPase proteins. It participates in the reorganization of the cytoskeleton and mediates bacterial entry into mammalian cells. After entry of the bacteria, SptP (GTPase-activating protein) restores the cytoskeleton. ▶**Rho**, ▶**Rac**, ▶**GTPase**, ▶**cytoskeleton**

Sordaria fimicola (n = 7): An ascomycete with linear spore octads. It has been extensively used for genetic recombination. A large number of mutants is available. In the 1940s, it was suspected that sexuality is relative in this fungus, but now it's been found that the poor maters are just weak mutants.

SORF: The short ORF generally includes not many more than 15 codons. ▶**codon**, ▶**ORF**

Sorghums: Arid, warm region crops. *S. bicolor* (and kaoliang), 2n = 2x = 20. *S. halepense* (Johnson grass) is tetraploid. Their nutritional value compared to other grain crops is lower because of the tannin content and low lysine level of the grain. The folding of its proteins (kafirin) lowers digestibility. Mutant varieties exist, however, that correct these deficiencies (see Fig. S87). (See Oria MP et al 2000 Proc Natl Acad Sci USA 97:5065; Klein PE et al 2000 Genome Res 10:789; molecular cytogenetics: Kim J-S et al 2005 Genetics 179:1963; <http://www.tigr.org/tdb/tgi/>).



Figure S87. Sorghum

Sori: ▶**sorus**

Sorrel: A light chestnut fur color of horses, determined by homozygosity for *d* gene; similar brownish color in other mammals. The sorrel plants *Rumex acetosella*, *R. scutatus* are used as tart vegetables. The sorrel tree is *Oxydendron*. ▶**Rumex**

Sorsby Syndrome: ▶**night blindness**, ▶**Stargardt disease**

Sortase: A bacterial enzyme that anchors surface proteins to the bacterial cell wall. These surface proteins promote interaction between the pathogen and the animal cell. Also, these proteins mediate

escape from the immune defense system of the animal cell. (See Muzmanian SK et al 2001 Mol Microbiol 40:1049).

Sortins: Proteins that inhibit the vacuolar sorting of small molecules. (See Zouhar J et al 2004 Proc Natl Acad Sci USA 101:9497).

Sorting: The mechanism that ensures that molecules (isozymes) are directed into the appropriate cellular compartments (cytosol, nucleus, mitochondria, chloroplasts). The sorted proteins are generally equipped with special NH₂-end signals, generated by differential transcription, and/or translation. This process is assisted by trans-acting transmembrane proteins and glycosylphosphatidylinositol-linked proteins. ▶[transit peptide](#), ▶[chloroplasts](#), ▶[mitochondria](#)

Sorting Out: In sorting-out, genetically different organelles (plastids, mitochondria) segregate into homogeneous groups of cells or during embryogenesis cells of common origin reaggregate in order to form certain cell types and/or structures (see Fig. S88).

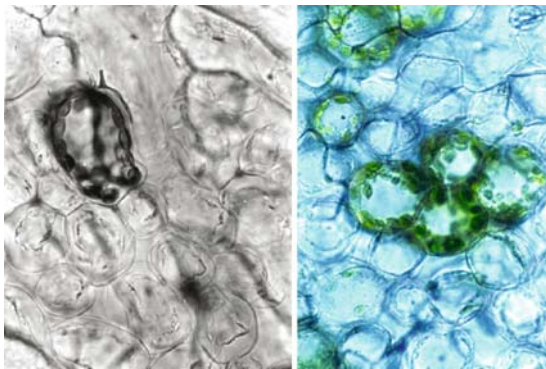


Figure S88. When variegation is caused by a mutation in a nuclear gene all the plastids within a cell are either green or colorless (left). Mutation in the chloroplast genetic material display sorting out at the boundary of sectors, i.e., cells with both green and colorless plastids occur (mixed cells) and in a non-stochastic process cells with all colorless and all green plastids appear in later sectors (right).

The segregation of two different types, A and B, of mitochondria in a heteroplasmic cell line may be characterized by the formula of Solignac, M. et al (Mol Gen Genet 197:183): $V_n = p_0(1 - p_0)(1 - [1 - 1/N]^n)$ where V_n is the variance of p (the fraction of A within a cell) at the n th cell generation and p_0 = the fraction of A in the original cell line, N is the number of sorting out units. In *Schizosaccharomyces*, the distribution of the mitochondria is mediated by microtubules.

In humans, the frequency of mutation in mtDNA is 10 times higher than that in the nuclear DNA, yet heteroplasmy is very rare except in some diseases. Despite the fact that the number of mitochondria in mammalian cell runs to the thousands per cell, usually the replication switches to one type. The number of the founder mtDNAs has been estimated within wide ranges of 1–6 and 20–200 in cattle, and in *Drosophila* 370–740. These founders then undergo a restriction/amplification type of replication, i.e., they pass through a bottleneck and therefore heteroplasmy is very limited. ▶[ctDNA](#), ▶[plasmone mutation](#), ▶[plastid number](#), ▶[mtDNA](#), ▶[mitochondrial genetics](#), ▶[heteroplasmy](#), ▶[Romanovs](#); for mitochondrial sorting, see also Kowald A, Kirkwood TBL 1993 Mutat Res 295:93.

Sorus (plural sori): A group of sporangia, such as found on lower surface of fern leaves.

SOS (son of sevenless, human homolog at 2p22-p21): A *Drosophila* gene that functions downstream from *sevenless*, encoding a receptor tyrosine kinase (RTK) in the light signal transduction pathway. SOS is a guanine nucleotide releasing protein (GNRP/GNRF), it is also called guanine-nucleotide exchange factor, GEF, and it interacts with RTK through the protein Drk receptor kinase, a homolog of the vertebrate Grb2, and SEM-5 in *Caenorhabditis*. These proteins function in a variety of signal transduction pathways involving EGF. SOS is frequently also called a mediator protein. ▶[BOSS](#), ▶[DRK](#), ▶[Grb2](#), ▶[receptor tyrosine kinase \[RTK\]](#), ▶[rhodopsin](#), ▶[signal transduction](#), ▶[GNRP](#), ▶[daughter of sevenless](#), ▶[Noonan syndrome](#); Hall BE et al 2001 J Biol Chem 276:27629; Sondermann H et al 2004 Cell 119:393; crystal structure–function: Freedman TS et al 2006 Proc Natl Acad Sci USA 103:16692.

SOS Recruitment System (SRS): A tool in proteomics. A temperature-sensitive *cdc25–2* allele of yeast permits grows at 25 °C, but not at 36°. Normally this protein, when localized to the plasma membrane, facilitates Ras guanyl nucleotide exchange and via signal transduction events promotes cell growth. The human homolog (hSOS) is complementary for the mutant and secures growth at the otherwise non-permissive regime. The hSOS function requires protein–protein interaction that is secured by fusing a bait to the C-end of the truncated protein. The co-expressed bait and prey are targeted to the membrane. The prey is either an integral membrane protein or a soluble protein, which after myristoylation signaling attaches to the membrane, and then growth is restored. ▶[two-hybrid system](#), ▶[CDC25](#), ▶[proteomics](#); Auerbach D et al 2002 Proteomics 2:611.

SOS Repair: An error-prone repair. ►DNA repair

Sotos Syndrome: ►cerebral gigantism

Source Habitat: In a source habitat, some individuals contribute more to the future generations than do the average individuals. ►sink habitat, ►habitat

Southern Blotting: In Southern blotting, DNA fragments cut by restriction endonucleases are separated on agarose gel by electrophoresis, then transferred to membrane filters by blotting, to hybridize the pieces with radioactively (or fluorescent) labeled DNA or RNA and then identify the physical sites of restriction fragments and genes. The transfer to membranes may be achieved by capillary action of wicks and DNA is sucked through layers of filterpapers on top or by vacuum-driven devices (see Fig. S89). ►restriction enzyme, ►RFLP, ►autoradiography, ►biotinylation, ►fluorochromes, ►nucleic acid hybridization, ►membrane filters

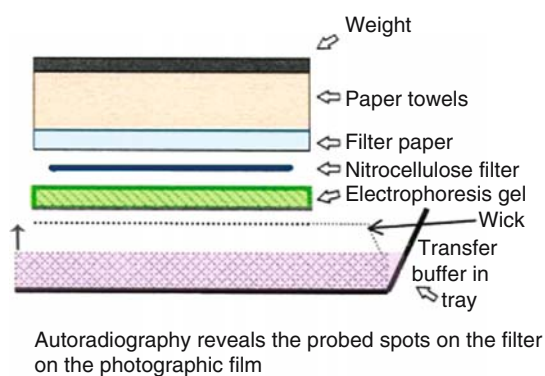


Figure S89. Southern blot

Southern Hybridization: ►Southern blotting

South-Western Method: The simultaneous labeling of cDNA and binding proteins (transcription factors). The screening is carried out by hybridizing labeled probes of DNA to bind to polypeptides immobilized on nitrocellulose filters. ►Southern blot, ►Western blot

Soviet Genetics: The term Soviet Genetics is not meant to define a special genetics because science does not have ideological, political, or ethnic attributes and it transcends all boundaries. A sad exception is “soviet genetics,” a misnomer because it did not involve genetics at all and it collapsed before the implosion of the political system that nurtured and enforced it. Genetics in the Soviet Union had a very remarkable

and successful beginning. In 1944, L.C. Dunn, Professor of Zoology at Columbia University noted: “There are today literally hundreds of trained genetical investigators in the U.S.S.R., certainly more than in any other country outside the U.S.A.” (Science 99:2563). This outstanding research and teaching establishment was destroyed, however, in 1948 and geneticists suffered humiliation, persecution, and almost total physical annihilation for a period of over 20 years by lisenkoism. ►lysenkoism, ►Mitchurin

SOX (SRY type HMG box): Mammalian genes (~30) encoding proteins with over 60% similarity to the HMG box of SRY. The SOX9 gene is critical for the differentiation of the Sertoli cells and chondrocytes. Sox genes apparently encode transcription factors, are capable of transactivation of genes involved in gonadal differentiation, are involved in cartilage formation, and induce testis development in chromosomally XX mice (Vidal VPI et al 2001 Nature Genet 28:216). The bacterial Sox genes are involved in superoxide responses. The mammalian SOXs bind to a 5'-(A/T)(A/T)CAA(A/T)G site in the DNA and regulate the expression of the LINE-1 retrotransposons in human cells. The different SOX genes use different short DNA sequences for binding specific transcription factors. SOX3 transcription factor defects may involve X-linked mental retardation and growth hormone deficiency (Laumonnier F et al 2002 Am J Hum Genet 71:1450). Several human syndromes have mutation in Sox genes. ►SRY, ►HMG, ►campomelic dysplasia, ►Wolffian duct, ►Shah-Waardenburg syndrome, ►Hirschsprung disease, ►LINE, ►anti-Müllerian hormone, ►Sertoli cells, ►lymphedema, ►stem cells; Kamachi Y et al 2000 Trends Genet 16:182; Takash W et al 2001 Nucleic Acids Res 29:4274; Wilson M, Koopman P 2002 Curr Op Genet Dev 12:441.

Soybean: *Glycine max* (2n = 40, ~1100 Mb); the basic chromosome number may be x = 10. Some related species are tetraploid. This crop is of great economic significance because of the high oil (20–23%) and high protein content (39–40%) of the seed. ►legumes; polyploidy in the genome: Walling JG et al 2006 Genetics 172:1893; for gene index: <http://www.soybase.org>; <http://soybeangenome.siu.edu>.

sp: sp as a prefix indicates *Schizosaccharomyces pombe* (fission yeast) DNA, RNA or protein.

Sp1: A mammalian protein, a general transcription factor for many genes recognizing the DNA sequence: $\begin{matrix} \text{GGGCGG} \\ \text{CCCCGC} \end{matrix}$. Sp1 elements also protect CpG islands of housekeeping genes from methylation. Sp1 requires the general transcription factor TFIID and the complex CRSP. Sp3 and Sp4 are very similar; the

latter is expressed in the brain. ▶transcription factors inducible, ▶transcription factors, ▶CRSP, ▶DNA methylation, ▶LCR, ▶MDM2; Nicolás M et al 2001 J Biol Chem 276:22126.

Space Flight: The genetic effects of space flight are not entirely clear. The microgravity in cooperation with space radiation may have adverse stress consequences. (See White RJ, Averner M 2001 Nature [Lond] 409:1115).

Space Search: An experimental study of large-scale protein matrix for detection of interactions. ▶ORF-Eome

Spaced Dyads: Many regulatory sites include a pair of conserved trinucleotides, which are spaced by a non-conserved tract of fixed length. Genes with function(s) coordinated by a common regulatory element are expected to share upstream binding sequences. These elements contain fixed sites for a linker domain and the dimerization domain of transcription factors. Their analysis facilitates the identification of co-regulated genes. (See van Helden J et al 2000 Nucleic Acids Res 28:1808).

Spacer DNA: Non-transcribed nucleotide sequences between genes (IGS) in a cell. In the rDNA, there are spacers within (internal transcribed spacers, ITS) and between gene clusters (external transcribed spacers, ETS). These were thought of earlier as not-transcribed tracts but actually they represented very short transcripts. Animal mtDNA genes generally have very short (few bp) spacers. In fungi, mtDNA spacers are common and variable in length because of recombination and slippage during replication; they may also be mobile. Plastid genes of higher plants are organized into operons without interruptions. Insertions, deletions, and unequal recombinations determine the length of the spacers. ▶ribosomal RNA, ▶rrn; ITS2 database: <http://its2.bioapps.biozentrum.uni-wuerzburg.de/>.

Spanandric Males: Spanandric males occur rarely within hermaphroditic species and are sterile.

Spasmoneme: A rod-like thin bundle of filaments (2 nm each), forming a cytoplasmic organelle of 2–3 mm in extended form. When exposed to calcium, it contracts and serves as an engine for the movement of different structures within the cell of ciliated protozoa. ▶centrin; Maciejewski JJ et al 1999 J Eukaryot Microbiol 45(2):163.

Spasticity: Muscle tone; its increase causes lack of coordination in movement as it occurs in various diseases affecting the brain, such as stroke, spinal cord injuries, etc.

Spastic Paraplegia (Strumpell disease, SPG): A collection of paralytic diseases encoded by at least 14 loci under a variety of genetic control, recessive, dominant autosomal, and Xq28-linked. Genes responsible for the disease have been mapped to 14q (SPG3), 2p21-p22 (SPG4), 15q (SPG6), 12q13, and 8q (SPG8). Currently, 20 genes have been mapped and eight more have been identified. The common denominator of these various genes appears to be aberrant cellular transport (Crosby AH, Proukakis C 2002 Am J Hum Genet 71:1009). The most prevalent form (40–50%) is SPG4, which encodes an AAA protein, spastin, in the microtubules. Atlastin, a Golgi-localized GTPase protein interacts with spastin in axon maintenance (Evans K et al 2006 Proc Natl Acad Sci USA 103:10666). A mitochondrial ATP-dependent protease (m-AAA) defect interferes with ribosome assembly in the mitochondria and with the maturation of the L32 mitochondrial protein (Nolden M et al 2005 Cell 123:277). SPG13 is formed due to a mutation in mitochondrial Hsp60. ▶heatshock proteins, ▶Pelizaeus-Merzbacher disease, ▶Silver syndrome, ▶AAA proteins, ▶ribosomal proteins, ▶mitochondrial diseases in humans; Vazza G et al 2000 Am J Hum Genet 67:504; Svenson IK et al 2001 Am J Hum Genet 68:1077; mutations in the receptor-enhancing protein (2p22) in the mitochondria: Zuchner S et al 2006 Am J Hum Genet 79:365.

Spaying: The neutering of a female. ▶castration

SPB: ▶spindle pole body

Spearman Rank-Correlation Test (SPC): SPC determines the relations between two variables without elaborate calculations (Table S3).

The SR correlation coefficient, $r = 1 - \frac{6 \sum d^2}{n^3 - n}$, for example, $1 - \frac{6 \times 14}{7^3 - 7} = 0.75$

In case of ties, correction can be used, $T = \frac{m^3 - m}{12}$ where m stands for the number of measurements or classifications of identical values. If, for example, there are three measurements of 5, two measurements of 7, and two amounting to 8, the correction for ties among the X trait variables becomes: $\sum Tx = \frac{3^3 - 3}{12} + \frac{2^3 - 2}{12} + \frac{2^3 - 2}{12}$ and in a similar way, the correction for ties can be determined in the Y series. Now we can obtain the terms: $\sum X^2 = \frac{n^3 - n}{12} - \sum Tx$, and $\sum Y^2 = \frac{n^3 - n}{12} - \sum Ty$, and $r = \frac{\sum X^2 + \sum Y^2 - \sum d^2}{2\sqrt{\sum X^2 \sum Y^2}}$

It is a non-parametric test and can also be used for the comparison of traits that cannot be measured but can be classified subjectively (on the basis of their appearance). If the traits are quantified by measures, they are ranked according to their relative magnitude,

Table S3. Example of hypothetical data for the calculation of the Spearman Rank Correlation test

| Pairs | Trait X | Rank | Trait Y | Rank | Difference of Ranks (<i>d</i>) | <i>d</i> ² |
|-------|---------|------|---------|------|----------------------------------|--------------------------------|
| 1 | 8 | 3 | 14 | 2 | 1 | 1 |
| 2 | 10 | 5 | 20 | 7 | -2 | 4 |
| 3 | 12 | 7 | 17 | 5 | 2 | 4 |
| 4 | 9 | 4 | 15 | 3 | 1 | 1 |
| 5 | 6 | 1 | 13 | 1 | 0 | 0 |
| 6 | 11 | 6 | 18 | 6 | 0 | 0 |
| 7 | 7 | 2 | 16 | 4 | -2 | 4 |
| | | | | | Sum <i>d</i> = 0 | Sum <i>d</i> ² = 14 |

i.e., by assigning the highest rank to the largest. If an exact measurement is impractical (e.g., degree of susceptibility), they are simply ranked. In case of ties, an equal rank is assigned to both. The differences of the rank scores are squared and summed. Tables constructed for various degrees of freedom can be used to determine the probabilities. ►correlation, ►non-parametric tests, ►statistics

Specialized Transduction: In specialized transduction, the transducer temperate phage picks up a piece of the host DNA at the immediate vicinity of its established prophage site (and generally leaves behind a comparable length of its own). When this modified phage infects another bacterium, it may integrate into the host genome the gene that it picked up from the previous host. Lambda phage (λgal; meaning a defective lambda that carries *gal*) is a typical specialized transducer with preferred site near 17 min on the map next to the *gal* locus, and it is a specialized transducer of this gene. Another well-known specialized transducer phage is φ80trp that can carry the tryptophan operon (at about 27 and 1/2 min). The specialized transducer phage must be a temperate phages, which transduces (only) the special gene located at its integration site. Gene transfer in eukaryotes by transposable elements, the genetic vectors, is a process similar to prokaryotic transduction. ►transposable elements, ►transformation genetic, flowchart of specialized transduction on Figure S90, ►high-frequency lysate, ►double lyso-genic, ►helper virus, ►bacterial recombination; Morse ML 1954 Genetics 39:984.

Speciation: The process by which a new species diverges from an ancestral species. Evolutionists may distinguish conventional methods of speciation when geographic isolation and accumulated

mutations cause eventually reproductive isolation. According to the *quantum model* of speciation, the divergence begins with spatial isolation followed by the survival of a few new types of individuals that give rise to reproductively isolated new forms as mutations accumulate. *Saltational* speciation comes about by sudden major mutations. *Parapatric* (or stasipatric) speciation occurs without geographic separation and it is initiated from a relatively small number of individuals that produce divergence under continued natural selection. *Sympatric* speciation occurs within the original area of dispersal, due to the emergence of a genetic isolation mechanism or sexual selection. In *homoploid hybrid speciation*, two ancestral taxa give rise to a third by hybridization without a change of chromosome number, and it may occur in the parasitic species of animals (Schwarz D et al 2005 Nature [Lond] 436:546). Reproductive isolation required for speciation may involve hybrid sterility, hybrid inviability, or special mate preference (Ortiz-Barrientos D, Noor MAF 2005 Science 310:1467). Strong assortative mating among the hybrids, favored by the wing pattern of *Heliconius* butterflies, favors hybrid speciation (Mavárez J et al 2006 Nature [Lond] 441:868). The mechanism of speciation in plants and animals differs because in animals, in contrast to plants, behavioral traits may also lead to speciation. In plants, sterility may not necessarily hinder propagation because some species reproduce primarily by vegetative means and they can practice both autogamy and cross-pollination. Chromosomal rearrangements and the action of transposable elements may lead to hybrid sterility, sexual isolation, and eventually speciation. ►evolution, ►sibling species, ►phylogeny, ►co-speciation, ►theory of evolution, ►saltation, ►neo-Darwinism, ►neo-Lamarckism, ►species, ►fertility, ►reproductive isolation, ►Müllerian mimicry, ►hybrid zone,

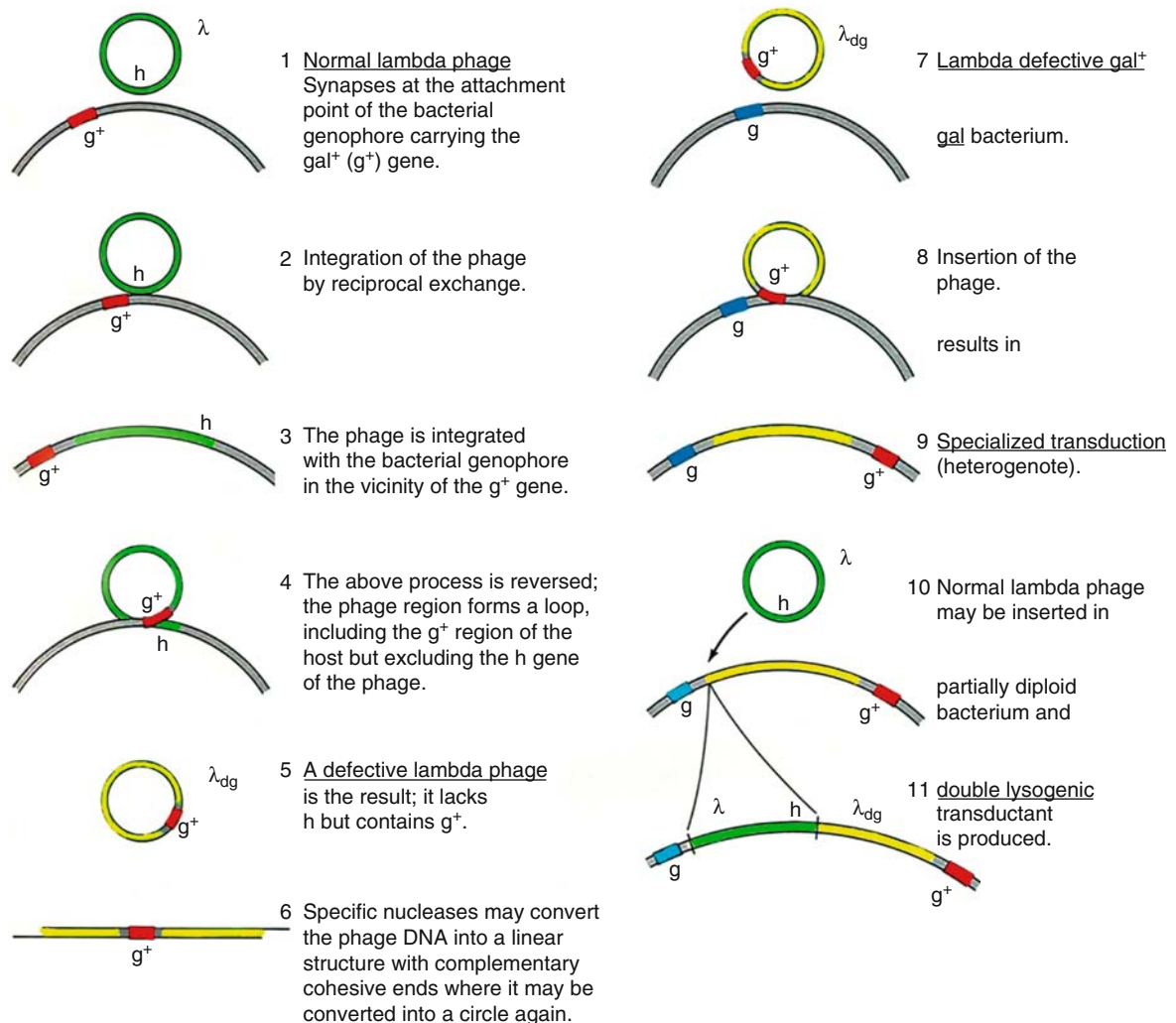


Figure S90. Specialized transduction (Modified after Stent GS 1971 Molecular Genetics. WH Freeman, San Francisco)

► **introgressive hybridization**; Noor MAF, Feder JL 2006 Nature Rev Genet 7:851; plant speciation review: Rieseberg LH, Willis JH 2007 Science 317:910; comprehensive compendium of species: <http://species.wikipedia.org>.

Species: A potentially interbreeding population, which shows reproductive isolation from other species (see discussion of the definition on p 371 and ff in Dobzhansky T 1949 Genetics and the Origin of Species. Columbia University Press, New York). Horizontal transfer of genes among bacteria mediated primarily by phages or direct DNA uptake in natural environment challenge the classical concept of species (Goldenfield N, Woese C 2007 Nature [Lond] 445:369). Also, recombination in mixed populations may be a force of speciation (Fraser C et al 2007 Science 315:476). The transgenic

technology somewhat confuses the classical definition because of the possibility of exchanging genes among totally different taxonomic categories. The number of eukaryotic species is not known but about 10^6 have been described. Expectations are that between 3 to 10 fold more existing have not been discovered yet. By shotgun genome sequencing of mass collection of seawater microbes in the Sargasso Sea, 148 new bacterial phylotypes were discovered representing >1.2 million so far unknown genes (Venter JJ et al 2004 Science 304:66). ► **speciation**, ► **sibling species**, ► **phylotype**, ► **shotgun sequencing**, ► **fertility**, ► **sexual isolation**, ► **species extant**, ► **transgene**, ► **OTU**, ► **endangered species act**, ► **horizontal transmission**; identification by genome profile: Watanabe T et al 2002 Genome Biol 3(2):res.0010; description of ~270,000 species of all types of organisms: <http://www.discoverlife.org/>.

Species Extant: With the increase of agricultural, industrial, and changing land use the currently alive (A), % extinct (E), and % threatened (T) species indicate an alarming reduction of biodiversity: molluscs (A) 10^5 , (E) 0.2, (T) 0.4; crustaceans: (A) $4-10^3$, (E) 0.01, (T) 3; insects (A) 10^6 , (E) 0.005, (T) 0.07; vertebrates total (A) 4.7×10^4 , (E) 0.5, (T) 5; mammals (A) 4.5×10^3 , (E) 1, (T) 11; gymnosperms (A) 758, (E) 0.3, (T) 32; dicots (A) 1.9×10^5 , (E) 0.2, (T) 9; monocots (A) 5.2×10^4 , (E) 0.2, (T) 9. (Data from Smith FDM et al 1993 Nature [Lond] 364:494). Within these larger categories, some species are much more endangered than the figures indicate. These numbers are not exactly valid because new species are being discovered. Between 1980–90 more than 100 new mammals have been identified. The extinction percentages date from the year 1600 A. D. According to Dobson, A.P. et al 1997 (Science 275:550) in the United States of America, the number of endangered species is 503 plants, 84 molluscs, 57 arthropods, 107 fish, 43 herptiles, 72 birds, and 58 mammals. Important factors affecting the survival of the feral species is the annual increase of the human populations (1.7%), urbanization, industrial and livestock production, pollution, and natural disasters.

According to the World Conservation Union 1996 biennial report (<http://www.iucn.org/themes/ssc/index.html>), currently 5205 species are endangered and risk extinction. Actually, the number of species is still unknown and the latest estimates vary from 3.5 to 10.5 million, about a third lower than some earlier estimates. The number of species in an environment has been extrapolated on the basis of the diversity of the 16S RNA of microorganisms. A new complex type of statistical approach is expected to provide better estimates than the most commonly used extrapolation from the lognormal distributions (Hong S-H et al 2006 Proc Natl Acad Sci USA 103:117). Around the world, 595 sites are in danger of imminent extinction. Of these, 203 are within partially protected and 87 in declared protected areas; 27 sites are known to be unprotected, and 48 sites have unknown protection status. In 2005, 794 species were in imminent danger, three times as many as have gone extinct since 1500 (Ricketts TH et al 2005 Proc Natl Acad Sci USA 102:18497). ►species, ►lognormal distribution, ►conservation genetics; 2000 Nature [Lond] 405:207 ff; 2001 Proc Natl Acad Sci USA 98:5389 ff; Alroy J 2002 Proc Natl Acad Sci USA 99:3706; Pitman NCA, Jørgensen PM 2002 Science 298:989; Convention on International Trade of Endangered Species (CITES) 1973 Public law 93–205.

Species, Synthetic: Synthetic species are produced in the laboratory by crossing putative ancestors of amphidiploid forms, which are partially isolated

genetically. Doubling the chromosome number of the hybrids prevents the sterility of the offspring. The synthetic species permit a verification of the putative evolutionary path of existing polyploid species by studying the pairing behavior of chromosomes, the frequency of chiasmata, the number of univalents and multivalents formed, etc. These classical cytogenetic methods may be supplemented with nucleic acid hybridization, in situ hybridization, study of proteins, nucleic acid sequences, etc. Some of the hybrid species if they ever occurred in nature, were not maintained by natural selection (see Fig. S91). ►allopolyploids, ►Triticale, ►Raphanobrassica, ►Mycoplasma, ►synthetic virus, ►speciation, ►evolution



Figure S91. Middle: *Triticale* ($2n = 56$), Left: Wheat ($2n = 42$), Right: Rye ($2n = 14$). (Courtesy of Dr. Árpád Kiss)

S

Specific Activity: The number of molecules of a substrate (μmol) acted on by enzymes (mg protein) per time (minutes) at standard temperature (25°C). Also, it means the relative amount of radioactive molecules in a chemical preparation.

Specific Combining Ability: ►combining ability

Specific Heat: Joules or calories required to raise the temperature of 1 g substance by 1°C .

Specific Locus Mutations Assays (SLT): SLTs have been used to detect X-chromosomal mutations in hemizygous males (mouse), in autosomal heterozygotes for special fur color genes such as the Oak Ridge stock heterozygous for *a*, *b*, *p*, *c^{ch}*, *se*, *d*, *s* or the Harwell tester stock (HT) heterozygous for six loci

(*a*, *bp*, *fz*, *ln*, *pa*, *pe*), or heterozygotes for thymidine kinase or hypoxanthine-guanine phosphoribosyl-transferase genes in different mammalian cell cultures (mouse, Chinese hamster ovary cells). Mutation of the wild type allele is then immediately revealed in the first generation. Similar procedures are applicable also in plants and any other diploid systems. The animal assays are not as simple as the microbial assays, e.g., the Ames test, but they are considered to be more relevant to human studies. ► [bioassays in genetic toxicology](#), ► [mutations in human populations](#), ► [doubling dose](#); Cattanach BM 1971, p 535. In: Chemical Mutagens. Hollaender A (Ed.) Plenum, New York.

Specific Rotation (α): The degrees of the plane of polarized light rotated by an optically active compound of specific concentration at 25°C: (α) = $\frac{r\nu}{nl}$, where the r = rotation in degrees, ν = volume in cubic centimeter of the solution, l = length in centimeters of the light path.

Specificity: A measure of discrimination among compounds. In DNA sequencing, it is the correctly predicted bases divided by the sum of the correctly and incorrectly predicted bases.

Specificity of Mutagen Assays: The percentage of correct identifications by presumably “non-carcinogenic” (“non-mutagenic”) agents. ► [sensitivity](#), ► [accuracy](#), ► [predictivity](#), ► [bioassays in genetic toxicology](#)

Speckles, Intranuclear (IGCs): IGCs are storage areas for primary RNA transcript processing factors; the speckles may not be the compartments of the eukaryotic splicing, which takes place rather in association with transcription. ► [splicing](#), ► [introns](#), ► [paraspeckles](#); Eilbracht J, Schmidt-Zachmann MS 2001 Proc Natl Acad Sci USA 98:3849.

Spect: ► [tomography](#)

Spectinomycin: Spectinomycin inhibits the translocation of charged tRNA from the A site to the P site of the prokaryotic ribosome by interfering with elongation factor G (see Fig. S92).

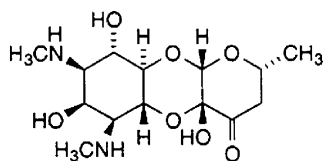


Figure S92. Spectinomycin

Spectral Genotyping: Spectral genotyping uses molecular beacons labeled with different fluorophores.

When the probes for the wild type (green) and for the mutant with one base substitution (red) are fluorophore labeled, the homozygous wild type (green) can be distinguished from the heterozygote's DNA (displaying both green and red) and the homozygous mutant showing only the other color (red). The potential color of the fluorophores can be chosen arbitrarily. This procedure can distinguish genotypes in clinical diagnostic analyses without DNA sequencing. Electrochemical examination of conformational alterations is also detectable at very low concentrations (10 pM). ► [beacons molecular](#), ► [fluorophore](#); Kostrikis LG et al 1998 Science 279:1228; Fan C et al 2003 Proc Natl Acad Sci USA 1009134.

Spectral Karyotyping: In spectral karyotyping, the chromosomes or chromosomal segments are hybridized with probes of fluorescent dyes in a combinatorial manner. Five dyes (Cy2, Spectrum Green, Cy3, Texas Red, and Cy5) provide enough combinatorial possibilities to “paint” each chromosome with a different color or shade. Although the naked human eye cannot distinguish these different hues, by the use of optical filters, Sagnac interferometer, a CCD camera, and Fourier transformation, it was possible to discriminate the special differences in standard classification colors using a computer program. The approach permitted classification of translocations that were not identifiable by other staining techniques. The lowest limit of differentiation by this technology is 500 to 1500 kbp. The procedure is applicable to clinical laboratory testing and evolutionary analyses. (See also Schröck E et al 1996 Science 273:494; ► [chromosome painting](#), ► [FISH](#), ► [GISH](#); <http://www-ermm.cbcu.cam.ac.uk/0000199Xh.htm>).

Spectrins: Filamentous tetrameric proteins (220–240 kDa) present in the red blood cells; they may constitute 30% of the membranes. Spectrins may mediate muscle and neuron organization by facilitating the binding of other proteins. They are also involved in the formation of a network on the cytoplasmic surface in cooperation with actin, dynein, ankyrin, and *band III* protein. The β II-spectrin is the same as fodrin. Several human chromosomes encode spectrins. Spectrin defects may cause auditory and motor neuropathies. ► [ankryn](#), ► [cytoskeleton](#), ► [elliptocytosis](#), ► [spherocytosis](#), ► [poikilocytosis](#), ► [dynein](#), ► [fodrin](#), ► [glycophorin](#), ► [spinocerebellar ataxia](#); Parkinson NJ et al 2001 Nature Genet 29:61.

Spectrophotometry: Spectrophotometry estimates the quality and quantity of a substance in solution on the basis of absorption of monochromatic light passing through it.

Spectrosome: A cytoplasmic organelle anchoring the mitotic spindle, and thus defining the spatial direction

of cell division. It contains spectrins, cyclin A and other regulatory proteins.

Speech and Grammar Disorder (SPCH1): A human FOXP2 ([forkhead box P2]7q31) dominant gene (locus is more than 600 kb) is involved in the lack of coordination of face and mouth muscles (verbal dyspraxia), some cognitive impairment (low IQ), and articulation and expressive language. Heterozygosity for nonsense mutation leads to the truncated protein product affecting neurodevelopment (MacDermot KD et al 2005 Am J Hum Genet 76:1074). ▶language impairment specific, ▶stuttering, ▶human intelligence, ▶dyspraxia, ▶dyslexia, ▶autism, ▶aphasia, ▶MASA syndrome; Lai CSL et al 2000 Am J Hum Genet 67:357; Enard W et al 2002 Nature [Lond] 418:869.

Spemann's Organizer: The embryonic tissue site of signals that mediate the organization of the body. Its signaling center is at the blastopore of the gastrula and releases a variety of polypeptides controlling neural and dorsal or ventral mesodermal differentiation. ▶morphogenesis, ▶organizer, ▶gastrula, ▶blastopore; Niehrs C 2001 EMBO J 20:631; De Robertis EM et al 2000 Nature Rev Genet 1:171.

Sperm: Sperm refers to the animal seminal fluid; geneticists generally understand it as the spermatozoon or plant male generative cells. In the first meaning, the word has no plural, in the other sense both singular and plural are justified. The *Drosophila* spermatozoon far exceeds in length that of any other animal's (up to 58 mm in *D. bifurcata*, although that of *D. melanogaster* is about 1.91 mm; the human spermatozoon is about 0.0045 mm (see Fig. S93), Karr TL, Pitnick S 1996 Nature [Lond] 379:405). In a single normal human ejaculate, the number of spermatozoa is within the range of 20–40 million in the seminal fluid volume of >2 mL. The human spermatozoon count shows a decreasing tendency during the last decades of life. The cause of this appears to be the increase of environmental pollutants with hormone-like effects, such as PCB, (polychlorinated biphenyl) an industrial carcinogen and pesticide, dioxin (a solvent), phthalates (may be present in cosmetics), and bisphenols (used in manufacturing resins and fungicides).

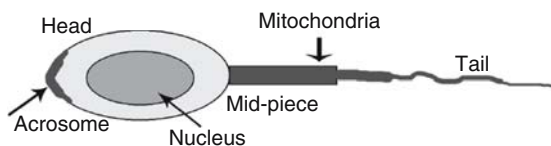


Figure S93. Outline of a human spermatozoon

During fertilization, the animal spermatozoon is attracted to the egg by chemotactic peptides, causing changes in the voltage of the membrane and altering the concentration of cAMP, cGMP, Ca^{2+} , and the activity of K^+ ion channels. In the tail of the spermatozoa, tetrameric proteins (CatSper1) form six transmembrane calcium ion channels, which are hyperactivated during ejaculation to assure appropriate motility and fertilization (Kirichok Y et al 2006 Nature [Lond] 439:73). A sperm chemoattractant protein, a member of the cysteine-rich secretory protein (CRISP) family, allurin has been isolated (Olson JH et al 2001 Proc Natl Acad Sci USA 98:11205). The sperm contains many different RNAs and proteins (Miller D et al 2005 Trends Mol Med 11(4):156), and they have roles in fertilized oocytes. Contrary to earlier views, mammalian spermatozoa can translate proteins but use the mitochondrial ribosomes for the process. These proteins have roles, while the sperm travels through the female reproductive canal and are essential for motility and fertilization (Gur Y, Breitbart M 2006 Genes Dev 20:411). Cytoskeletal proteins of the fertilizing sperm trigger oocyte maturation and ovulation of animals. The number of pollen grains (containing two sperms) released by a plant may vary between a few hundreds to tens of millions. The male poultry reduces the sperm when mating with promiscuous females but allocate more of it in matings with new and attractive females (Pizzari T et al 2003 Nature [Lond] 426:70). ▶oocyte primary, ▶environmental mutagens, ▶fertilization, ▶polyspermic fertilization, ▶gametogenesis, ▶RPTK, ▶DDT, ▶semen, ▶seleno-protein, ▶infertility, ▶acrosomal process, ▶cryopreservation; Wassarman PM et al 2001 Nature Cell Biol 3: E59; Ren D et al 2001 Nature [Lond] 413:603; Swallow JG, Wilkinson GS 2002 Biol Rev 77:153; <http://www.med.unipi.it/agp/siti/siti.htm>.

Sperm Activation: The conversion of the spermatids into moving spermatozoa. In *Caenorhabditis*, four gene loci (*spe-8*, *-12*, *-27*, and *spe-29*) control the process.

Sperm Bank: A (human) sperm depository for the purpose of artificial insemination in case of sterility of the husband or other conditions, which may warrant their use. Thousands of sperm banks (gene banks) exist in the world, most of the deposited samples are anonymous and the genetic constitution of the donors is not known completely. Since the 1930s, HJ Muller advocated the use of the sperm banks for positive eugenics purposes. Accordingly, the donors should be selected on the basis of superior talents, mental ability, and physical constitution. This idea has not been widely accepted, however, because of moral objections and biological shortcomings. Most of the

“superior phenotypes” cannot be evaluated by generally accepted criteria, and the phenotype may not fully represent the heritability of particular traits. Since artificial insemination of domestic animals became routine, sperm banks are exploited for animal breeding programs in order to produce maximal number of progeny of high-performance males. Even for animals, this technology should be used with thorough consideration of population genetics principles in order to avoid narrowing the gene pool and inbreeding. ►[in vitro fertilization](#), ►[ART](#), ►[bioethics](#); Critser JK 1998 Hum Reprod (Suppl. 2):55; Deech R 1998 Hum Reprod 13(Suppl. 2):80.

Sperm Competition: In animals where the females may mate repeatedly during the period of receptivity, the spermatozoa of different genotypes may have selective advantage or disadvantage in fertilization. The success of a particular type of spermatozoa is influenced by a large number of seminal proteins. The accessory gland proteins appear to be more polymorphic than other proteins, yet this may not distinguish between the interpretations of rapid evolution or limited selection. ►[multipaternal litter](#), ►[sperm displacement](#), ►[certation](#), ►[accessory gland](#); Fu P et al 2001 Proc R Soc Lond B Biol Sci 268:1105; Simmons LW 2001 Sperm Competition and its Evolutionary Consequences in the Insects. Princeton University Press.

Sperm Displacement: In animals where the females practice sperm storage, depending on the genetic constitution of the sperm, one or another may interfere with the fertilization of a competing sperm already present in the spermatheca of the female. In this process, the genetic constitution of the female has also a selective role. ►[sperm storage](#), ►[sperm competition](#), ►[sperm precedence](#), ►[spermatheca](#); Gilchrist AS, Partridge L 2000 Evolution Int J Org Evolution 54:534.

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Sperm Morphology Assays in Genetic Toxicology: Sperm morphology assays are based on the expectation that mutagens and carcinogens may interfere with normal spermiogenesis, resulting in abnormal head shape, motility, and viability of the treated or exposed sperm. This expectation is met with some agents but not with all. Thus, sperm alterations may indicate mutagenic and/or carcinogenic properties but not all mutagens/carcinogens seem to affect these sperm parameters within non-lethal doses. ►[bioassays in genetic toxicology](#); Baccetti B et al 2001 Hum Reprod 16:1365.

Sperm Precedence: In multiple copulation of a female with different males within a period of receptivity, one type of sperm (usually the last mating male's) may have selective advantage in producing offspring.

►[sperm competition](#), ►[certation](#), ►[last-male sperm precedence](#); Price CS et al 2000 Evolution Int J Org Evolution 54:2028.

Sperm Receptor: ►[fertilization](#)

Sperm Selection: ►[sex selection](#)

Sperm Storage: Insects commonly store sperm in the spermatheca for two weeks, and fertilization may follow any time within this period. This is why geneticists tend to use virgin females for controlled matings. Sperm can be stored at the temperature of liquid nitrogen (−195.8 °C) and retain its ability of fertilization. The efficiency of storage depends on seminal fluid proteins that the male transmits along with the sperm. Mouse spermatozoa can be stored by freeze-drying and the function is maintained. ►[sperm bank](#), ►[sperm competition](#), ►[sperm displacement](#), ►[sperm precedence](#); Yin HZ, Seibel MM 1999 J Reprod Med 44(2):87; Mortimer D 2000 J Androl 21:357; Corley-Smith GE, Brandhorst BP 1999 Mol Reprod Dev 53:363; Kusakaba H et al 2001 Proc Natl Acad Sci USA 98:13501.

Sperm Typing: Sperm typing permits analysis of recombination in diploids, using the recombinant gametes. The method of analysis requires the analysis of PCR-amplified gamete DNA sequences of known paternal types. This type of analysis can resolve recombination even between single base pairs. The results must be scrupulously studied because the PCR method may have inherent errors. Single sperms can be separated with the aid of fluorescence activated cell sorters. If the sperms are subjected to “primer extension preamplification” (PEP) before analysis, enough material can be obtained to carry out multipoint tests. This procedure is not practical with egg cells. ►[recombination frequency](#), ►[crossing over](#), ►[maximum likelihood applied to recombination](#), ►[polymerase chain reaction](#), ►[cell sorter](#), ►[prenatal diagnosis](#), ►[genetic screening](#); Hubert R et al 1994 Nature Genet 7:420; Shi Q et al 2001 Am J Med Genet 99:34.

Spermatheca: A storage facility of insect females, for sperm to be used at a later fertilization following an initial mating. ►[sperm precedence](#), ►[sperm competition](#), ►[sperm storage](#), ►[sperm displacement](#)

Spermatia: Male sperms produced at the tip of hyphae within the spermatogonia of rust fungi; they are comparable to the microconidia. ►[conidia](#)

Spermatid: A cell formed by the secondary spermatocyte and which differentiates into a spermatozoon. ►[spermatozoon](#), ►[sperm](#), ►[gametogenesis](#), ►[spermiogenesis](#)

Spermatocyte (primary): A diploid cell that by the first division of meiosis gives rise to the haploid secondary spermatocytes. By cell division, these cells form the spermatids, which differentiate into spermatozoa in animals. In plants, the spermatocytes function in a similar manner and thus produce the microspores, which develop into pollen grains and within them the two sperms are formed either before or after the pollen tubes begins to elongate. ►gonads, ►gametogenesis

Spermatocytoma (spermocytoma): The malignancy of the testis or of undifferentiated male gonads. ►seminoma

Spermatogenesis: ►gametogenesis, ►spermiogenesis

Spermatogonia: The primordials of the sperm cells; the secondary spermatogonia, produce the primary spermatocytes. Spermatogonial stem cells can be transformed/transfected by genetic vectors in culture. If introduced into seminiferous tubules of infertile mouse, they undergo spermatogenesis and could produce mutant offspring (Kanatsu-Shinohara M et al 2006 Proc Natl Acad Sci USA 103:8018). ►gametogenesis, ►spermatocyte; in vitro culture: Feng L-Xin et al 2002 Science 297:392; Zhao G-Q, Garbers DL 2002 Dev Cell 2:537.

Spermatophyte: Seed-bearing plant. ►cryptogamic plants

Spermatozoon: The fully developed (differentiated) male germ cell, a sperm. ►sperm, ►spermatid, ►oocyte primary, ►fertilization, see Fig. S94 of a human spermatozoon.



Figure S94. Spermatozoon

Spermidine ($C_7H_{19}N_3$, *N*-[3-aminopropyl]-1,4-butanediamine): A polyamine regulating (+ or -) the binding of proteins to DNA, condensation of DNA, controlling gene expression, etc. Spermidine synthase is encoded by human chromosome 1p36-p22 and 3p14-q21 (see Fig. S95). ►spermine

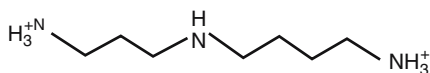


Figure S95. Spermidine

Spermine ($C_{10}H_{26}N_4$, *N,N'*-bis[3-aminopropyl]tetramethylenediamine, a polyamine): The oxidative cleavage product of spermine is spermidine. Spermine

synthase was assigned to human chromosome Xp22.1 (see Fig. S96). Its mouse homolog *Gyro* [*Gy*] is suspected in hypophosphatemia, resulting in rickets, hearing disorders, etc. ►hypophosphatemia, ►hypophosphatasia, ►rickets, ►S-adenosylmethionine decarboxylase, ►polyamine

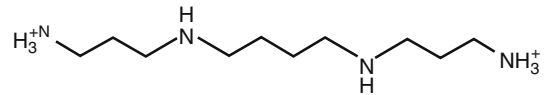


Figure S96. Spermine

Spermiogenesis: A postmeiotic process of differentiation of mature spermatozoa. It is supposed that CREM is involved in the control of genes required for the process because CREM-deficient mouse (obtained by recombination) cannot complete the first step of spermiogenesis and late spermatids are not observed. The defective spermatids are apparently eliminated by apoptosis. Histone 1 (H1) variant H1T2 localizes to the apical chromatin domain at the apical pole and it is required for the reconstruction of chromatin and the replacement of histones by protamines during spermiogenesis (Martianov I et al 2005 Proc Natl Acad Sci USA 102:2808). More than 2000 genes seem to be expressed postmeiotically in the mouse sperm (Schultz N et al 2003 Proc Natl Acad Sci USA 100:12201). ►sperm, ►spermatozoon, ►CREM, ►apoptosis, ►gametogenesis, ►transition protein, ►protamines, ►histones, ►adenovirus; Macho B et al 2002 Science 298:2388.

Spermist: ►preformation

SPF: Cell cycle S phase promoting factor, a kinase. ►cell cycle

SPF Condition: The specific pathogen-free condition of organisms maintained in a quarantine. ►quarantine; Yanabe M et al 2001 Exp Anim 50(4):293.

Spfi-1: An ETS family transcription factor. ►ETS oncogenes

SPH: Protein-binding DNA elements. ►Simian virus 40

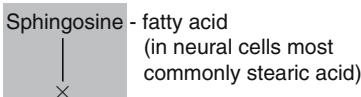
Spherocytosis, Hereditary (HS): The most common hemolytic anemia in Northern Europe. The basic defect involves both recessive and dominant mutations affecting ankyrin-1 (8p11.2) and spectrin. The β -spectrin gene was assigned to human chromosome 14q22-q23. The spectrin α -chain is responsible for elliptocytosis II (1q21). An autosomal dominant form was assigned to human chromosome 15q15. There is also an autosomal recessive type. ►ankyrin, ►spectrin, ►elliptocytosis, ►anemia, ►poikilocytosis

Spheroplast: Spherical bacterial cell after (partial) removal of the cell wall. ▶protoplast

Sphingolipid Activator Protein (SAP, Saposin): A co-factor for the physiological degradation of sphingolipids. The GM2 activators are encoded in different chromosomes and their deficiencies cause metachromatic leukodystrophy-like and Gaucher disease-like symptoms. ▶Gaucher disease, ▶metachromatic leukodystrophy; Matsuda J et al 2001 Hum Mol Genet 10:1191.

Sphingolipidoses: Hereditary diseases involving the metabolism of sphingolipids with the enzyme defects indicated in parenthesis. (See Table S4, diseases under separate entries, ▶sphingolipids).

Sphingolipids: Sphingosine-containing lipids with the following general structure and depending on the particular substitutions at X.



hydrogen (ceramide)
glucose (glucosylceramide), [neutral glycolipid]
glucose and galactose (lactosylceramide), [neutral glycolipid]
complex of sialic acid, glucose, galactose, galactose amine (ganglioside G_{M2})
phosphocholine (sphingomyelin).

If sialic acid (acetyl neuraminic acid (see Fig. S97), glycolylneuraminic acid) is removed, asialogangliosides result. Sphingolipids mediate signal transduction, calcium homeostasis and signaling, traffic of secretory vesicles, cell cycle, etc. They are the lipid moiety of glycosylphosphatidylinositol anchoring proteins. ▶sphingosine, ▶cerebrosides, ▶gangliosides, ▶sphingolipidoses, ▶Sandhoff disease, ▶ceramide; Dickson RC, Lester RL 1999 Biochim Biophys Acta

1438:305; Leipelt M et al 2001 J Biol Chem 276:33621; sphingolipid metabolic map in yeast: Alvarez-Vasquez F et al 2005 Nature [Lond] 433:425.

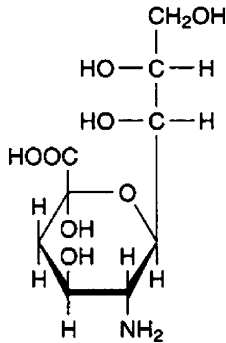


Figure S97. Neuraminic acid

Sphingomyelin: A phospholipid with the sphingosine amino group linked to fatty acids and the terminal OH group of sphingosine esterified to phosphorylcholine. ▶fatty acids, ▶sphingosine, ▶Niemann-Pick disease, ▶osteogenesis imperfecta

Sphingosine: A solid fatty acid-like component of membranes. The principal naturally occurring sphingosine is D(+) erythro-1,3-dihydroxy-2-amino-4-transoctadecene, CH₃(CH₂)₁₂CH=CH(OH)-CH(NH₂)-CH₂OH. In addition to the C₁₇ sphingosines shown, the molecules may have 14, 16, 18, 19, and 20 carbons. The molecules may also be branched or may contain an additional OH group. Sphingosine-1 phosphate is a rather universal signaling molecule for cell proliferation, chemotaxis, differentiation, senescence, and apoptosis. The action of sphingosine kinase is reversed by sphingosine phosphatase. Sphingosine 1-phosphate receptor mediates the egression of lymphocyte from thymus and lymphoid organs. Its activity is increased by two orders of magnitude upon blocking S1P lyase and causes

S

Table S4. Sphingolipidoses

| | |
|---|--|
| Farber's disease (ceramidase) | Lactosyl ceramidosis (β-galactosyl hydrolase) |
| Fabry's disease (α-galactosidase) | Metachromatic leukodystrophy (sulfatase) |
| Gaucher's disease (β-glucosidase) | Niemann-Pick disease (sphingomyelinase) |
| Generalized gangliosidosis (β-galactosidase) | Sandhoff's disease (hexosaminidases A and B) |
| Krabbe's leukodystrophy (galactocerebrosidase) | Tay-Sachs disease (hexosaminidase A) |

See These diseases under separate entries.

lymphopenia in mouse (Schwab SR et al 2005 Science 309:L1735). ►[sphingomyelin](#), ►[lymphopenia](#); Brownlee C 2001 Curr Biol 11:R535; Merrill AH 2002 J Biol Chem 277:25843; Spiegel S, Milstien S 2003 Nature Rev Mol Cell Biol 4:397.

Spi⁺: The wild type λ phage is sensitive to phage P2 inhibition. Phage λ lacking the functions of *red* and *gam* can grow in P2 carrying-lysogens if it has *chi* (recombination sites for the RecBC system). ►[lambda phage](#)

Spi1 Oncogene: The spleen focus forming retrovirus homolog; it is located in human chromosome 11p11.22. Spi1 is an ETS family transcription factor. ►[oncogenes](#), ►[ETS](#), ►[PU.1](#)

Spiders (Aranae): An extremely large group of ancient genera of animals. ►[silk](#); <http://research.amnh.org/entomology/spiders/catalog/index.html>.

Spidey: A mRNA-to-genomic DNA alignment program that can be used for draft sequences, finished sequences, and inter-species comparisons. ►[mRNA](#); <http://www.ncbi.nlm.nih.gov/spidey/>.

Spielmeyer-Sjögren-Vogt Disease: ►[ceroid](#) ►[lipo-fuscinosis](#)

Spike: An inflorescence, which is alternatively called head or ear; a typical example is the spike of wheat or some other grasses. The spikelets or flowers are sessile on opposite sides of the axis that is called rachis. Also, spike refers to short duration electrical variations along the nerve axon, a peak in electric potential.

Spike: The claw-like structures on the base plate of bacteriophages. ►[development](#)

Spikelet: A group of florets sitting on a common base in a spike (see Fig. S98). ►[spike](#)



Figure S98. Wheat spikelet

Spiked Oligos: Phosphoramidates are incorporated into deoxyribonucleotides and when these are used as primers for PCR-based mutagenesis random mutations may be selected that slow down the activity of the mutant gene products (proteins) and opens a chance to screen for extragenic suppressors that

restore better full function. ►[phosphoramidate](#), ►[PCR-based mutagenesis](#), ►[suppressor gene](#); Hermes JD et al 1989 Gene 84:143.

Spiking: Information transfer by neurons.

Spin Infection: In spin infection, adherent cells are exposed to transformation vector mix by centrifuging.

Spina Bifida: A developmental disability in various mammals, including humans, determined by autosomal dominant inheritance and reduced penetrance. The spinal column is incompletely closed and in some instances this involves no serious problem and is detectable only by X-ray examination (spina bifida occulta). The more serious case is the spina bifida aperta when the spinal cord, the membranes (meninges), spinal cord, and nerve ends are protruding (*myelomeningocele*). Hydrocephalus, incontinence, etc., frequently accompany this condition. The *meningocele* form involves only membrane extrusion and consequently it is a less severe defect. Defects in cadherins may be responsible for the anomalous differentiation. The overall frequency of these anomalies may be 0.2–0.3% in the general population. The anomaly may be the consequence of folic acid deficiency (Lucock M 2004 Br Med J 328:211). ►[neural tube defects](#), ►[prenatal diagnosis](#), ►[genetic screening](#), ►[MSAPF](#), ►[mental retardation](#), ►[hydrocephalus](#), ►[cadherins](#)

Spinach (Spinacia oleracea): A dioecious plant, $2n = 12$ (XX or XY, included). Many of the trisomics can be identified without cytological examinations. All six pairs of the chromosomes have distinct morphology.

Spinal and Bulbar Muscular Atrophy (SBMA): ►[Kennedy disease](#)

Spinal Muscular Atrophy (SMA): A degeneration of the spinal muscles; it occurs in different forms and under different genetic controls. The adult type, proximal, is autosomal dominant and may be associated with different chromosomes. The juvenile (Kugelberg-Welander syndrome) affects primarily the proximal limb muscles and frequently involves twitching. This form was assigned to human chromosome 5q11.2-q13.3. The prevalence of this type is about 1/6000 in newborns. The literature also distinguishes the Werdnig-Hoffmann disease type, however, the various juvenile forms map to the same chromosomal segment, although the expressions may differ. Deletions of this area are frequently the basis of the disease. The combined, estimated gene frequency is about 0.014. The spinal muscular dystrophy with microcephaly and mental retardation, the spinal muscular dystrophy distal (11q12-q14), SMA proximal adult type, and other variations of it appear autosomal recessive. SMA expression is positively

associated with the activity of the *survival motor neurons* controlled by the centromeric SMN2 gene (human chromosome 5q12.2-q13.3.) SMN proteins (38 kDa) are part of spliceosomal small ribonuclear simplex. The highly homologous SMN1 gene has telomeric location. The transcript of SMN2 is frequently deficient in exon 7 due to a single nucleotide substitution; otherwise it is identical with SMN1. The two proteins function in association and the truncated protein can be compensated for by higher amounts and can ameliorate the phenotype (Le TT et al 2005 Hum Mol Genet 14:865). Mutation in SMA may affect the U snRNA nuclear import system. Spinal muscular atrophy with respiratory distress (SMARD) is caused by mutation, if an immunoglobulin (IgG) binding protein (IGHMBP2) is encoded at 11q13.2-q13.4. ▶muscular atrophy, ▶Kennedy disease, ▶dystrophy, ▶atrophy, ▶lipodystrophy familial, ▶muscular dystrophy, ▶neuromuscular diseases, ▶dynein, ▶Kugelberg-Welander syndrome, ▶Silver syndrome, ▶Werdnig-Hoffmann disease, ▶URNA, ▶SMAD, ▶gemini of coiled bodies, ▶NAIP; Jablonka S et al 2001 Hum Mol Genet 10:497; Grohmann K et al 2001 Nature Genet 29:75; Feldkötter M et al 2002 Am J Hum Genet 70:358; Frugier T et al 2002 Curr Opin Genet Dev 12:294; Paushkin S et al 2002 Curr Opin Cell Biol 14:305; review of SMN1: Monani UR 2005 Neuron 48:885.

Spindle: A system of microtubules ($\approx 20\text{--}30$ nm) emanating from the poles (centrioles of the centrosomes in animals) during mitosis and meiosis, attaching to the kinetochores within the centromeres, and pulling the chromosomes toward the poles. In plants and also in some animal oocytes, there are no centrosomes and the chromosomes assume some of the centrosome functions. In yeast, the spindle forms within the nucleus. Some of the microtubules reach from one pole to the other without attaching to the kinetochore. In *Drosophila* meiosis, the spindle originates from each of the chromosomes and as the prophase progresses, a bipolar spindle emerges. This stage uses a kinesin-like protein (NCD). The arrangement of the microtubules also requires the motor protein dynein. The meiotic pole is different from the mitotic centrosomes (DMAP60, DNAP190 and γ -tubulin are apparently absent). According to a model, for the capture of microtubules and development of the spindle apparatus, the chromosomes distribute a gradient of RAN guanosine triphosphate and importin- β toward the cytoplasm, in the direction of the microtubules emanating from the centrosomes. This eventually leads to self-organization of the bipolar spindle (Caudron M et al 2005 Science 309:1373). About 200 genes determine the spindle assembly in *Drosophila* (Goshoma G et al 2007 Science 316:417).

The orientation of the spindle may be controlled in yeast by myosin V. In case of univalents, only monopolar spindle is formed. In some species, the spindle origination from the chromosome is apparently suppressed by the centrosome. In some other species, the chromosomes and the centrosomes cooperate in developing the meiotic spindle. The mitotic spindle may also need both chromosomes and the centrosomes (echinoderms) (see Fig. S99). Microtubule assembly is not an exclusive property of the kinetochores as holocentric chromosomes indicate. Anaphase and cytokinesis, however, can take place in cells after the chromosomes have been removed. On the oocyte chromosomes of several species, surface proteins (NOD, Xklp1) are found that stabilize prometaphase chromosomes, and in achiasmatic meiosis, substitute for the chiasmata. According to recent views, the information for meiotic disjunction resides within the chromosomes and not in spindle apparatus. The kinetochore determines the transition from metaphase to anaphase. The spindle checkpoint ensures the fidelity of chromosome segregation by preventing cell-cycle progression until all the chromosomes make proper bipolar attachments to the mitotic spindle and are subjected to tension. Some experiments indicate that the checkpoint recognizes the lack of microtubule attachment to the kinetochore, others indicate that the checkpoint senses the absence of tension generated on the kinetochore by microtubules. Both of these alternative explanations may be true (Pinsky BA, Biggins S 2005 Trends Cell Biol 19:486). Tension of the kinetochore generates a checkpoint signal (Cdc20, fizzy, Cdc55), and it is supposed that a phosphorylated kinetochore protein attracts proteins. At least six known genes seem to be involved in kinetochore functions. The X-chromosomes in XO cases of sex determination do not involve such a pause. The cytoskeleton is also involved in the correct organization of the spindle. The mRNA export protein Rae1 is a microtubule-associated protein that binds directly to importin β .

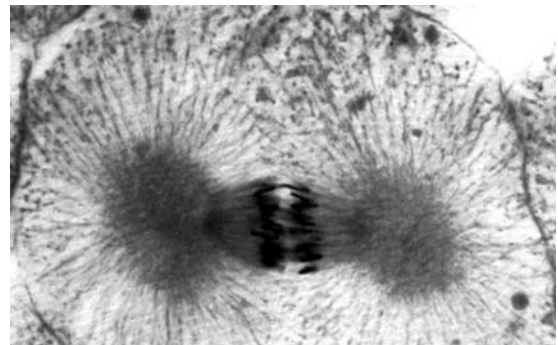


Figure S99. Spindle with chromosomes in the middle

and in egg extract it stabilizes microtubules by RanGTP/importin. Rae 1 is located in a large RNA-containing complex and thus indicates that RNA also has a role in spindle formation (Blower MD et al 2005 Cell 121:223). In some large cells, such as oocytes, the spindle fibers are not long enough to reach and capture the centromeres. In such cases, a contractile nuclear actin network is formed that facilitates the attachment of the centromeres to the spindle fibers (Lénárt P et al 2005 Nature [Lond] 436:812). Spindle assembly requires the presence of lamin B, which is activated by RanGTP (Tsai M-Y et al 2006 Science 311:1887). ▶nucleus, ▶centromere, ▶centromere proteins, ▶chromokinesins, ▶spindle fibers, ▶cytoskeleton, ▶tubulins, ▶myosin, ▶kinetochore, ▶chromatid, ▶mitosis, ▶meiosis, ▶BTB, ▶securin, ▶NuMA, ▶dynactin, ▶kinesin, ▶Bim, ▶univalent, ▶holocentric chromosome, ▶achiasmate, ▶Swi6p, ▶microtubule, ▶PARP, ▶RMSA-1, ▶CENP, ▶Stathmin, ▶APC, ▶multipolar spindle, ▶acenaphthene, ▶Cdc2, ▶Cdc20, ▶Cdc55, ▶Mad2, ▶RAN, ▶ASAP; Sharp DJ et al 2000 Nature [Lond] 407:41; Shah JV et al 2000 Cell 103:997; Compton DA 2000 Annu Rev Biochem 69:95; Karsenti E, Vernos I 2001 Science 294:543; Musachio A, Hardwick KG 2002 Nature Rev Mol Cell Biol 3:731; Lew DJ, Burke DJ 2003 Annu Rev Genet 37:251; Kline-Smith SL, Walczak CE 2004 Mol Cell 15:317; Gadde S, Herald R 2004 Curr Biol 14:R797; orientation of the mitotic spindle: Théry M et al 2007 Nature [Lond] 447:493; Illustration by courtesy of Dr. P.C. Koller.

Spindle Fibers: Microtubules clearly visible (by appropriate techniques) during mitotic and meiotic nuclear divisions. The microtubules originate at the spindle poles, the asters in animals. Three classes of fibers emanate from the poles: the astral microtubules that radiate from the centrioles, the polar microtubules that meet at the divisional plane and appear to stabilize the spindle, and the kinetochore microtubules that are anchored at the centromere of the chromosomes and at anaphase pull them toward the opposite poles. The eukaryotic spindle fibers are made largely of tubulin. The analogous prokaryotic system is built mainly of actin filaments. ▶spindle, ▶mitosis, ▶meiosis, ▶aster, ▶centrioles, ▶centromere, ▶kinetochore, ▶centrosome, ▶tubulins, ▶Pac-Man model

Spindle Poison: Spindle poisons block the formation of spindle fibers and as a consequence polyploidy may result. ▶polyploidy, ▶colchicine, ▶acenaphthene, ▶Stathmin

Spindle Pole Body (SPB): The fungal equivalent of the centrosome. Cyclins and cyclin-dependent kinases promote and regulate their duplication. SPBs assist

in the assembly of membrane proteins in the meiotic pro-spores of yeast. Their defect results in genetic instability, aneuploidy. SPBs affect also mRNA metabolism. ▶centrosome, ▶mitochondrial genetics; Haase SB et al 2001 Nature Cell Biol 3:38; Bajgier BK et al 2001 Mol Biol Cell 12:1611; Lang BD et al 2001 Nucleic Acids Res 29:2567.

Spinobulbar Muscular Atrophy: ▶Kennedy disease

Spinocerebellar Ataxia (SCA): Autosomal dominant defects involving CAG repeats (polyglutamine) in the coding region of the ataxin genes (SCA1, SCA2, SCA3, SCA7) and causing nerve degeneration and loss of Purkinje cell and neurons in the brain. As a consequence, motor functions deteriorate. SCA5 is due to mutation in spectrin B, which destabilizes glutamate transporter EAAT4 on the surface of the plasma membrane (Ikeda Y et al 2006 Nature Genet 38:184). SCA6 affects a calcium ion channel. In a normal state, the number of repeats is 6–44, while in the diseases state it is 40–93. The ataxin gene (SCA1) encoded at 6p23 is transcribed into 792–869 amino acids, depending on the number of CAG repeats. The mouse homolog is *Math1*. Ataxin-1 binds to RNA and controls the expansion of the polyglutamine sequences. The insect transcription factors Sens and the mammalian homolog Gfi-1 interact with the AXH domain of ataxin and mediate neurodegeneration (Tsuda H et al 2005 Cell 122:633). The SCA8 involves CTG repeats. SCA10 (22q13-qter) displays ATTCT repeats in variable numbers in intron 9. SCA12 (5q31-q33) is caused by CAG repeats in the regulatory subunit of protein phosphatase PP2A. SCA13 childhood ataxia with mental retardation and delayed motor functions is encoded at 19q13.3-q13.4. The SCA13 area contains the KCNC3 voltage-gated ion channel, and its mutation leads to neurodegeneration (Waters MF et al 2006 Nature Genet 38:447). SCAN11 (spinocerebellar ataxia with axonal neuropathy, 14q31-q32) is caused by a defect in tyrosyl-DNA phosphodiesterase (TDP1), involved in normally transient single-strand DNA break and repair generated by topoisomerase function (El-Khamisy SF et al 2005 Nature [Lond] 434:108). ▶trinucleotide repeats, ▶topoisomerases, ▶spectrin, ▶GLAST, ▶GLT, ▶Huntington chorea, ▶Kennedy disease, ▶Machado-Joseph disease, ▶myotonic dystrophy, ▶ataxia, ▶migraine, ▶CACNA1A, ▶RNAi; Stevanin G et al 2000 Eur J Hum Genet 8:4; Yue S et al 2001 Hum Mol Genet 10:25; Libby RT et al 2003 Hum Mol Genet 12:41.

Spiracle: The breathing hole on the insect body.

Spiralization: A pattern of winding of molecules or chromosomes. ▶coiling

Spirochetes (Spirochaeta): Filiform bacteria (5–6 μm) that cause sex ratio distortion in *Drosophila* by the fatal effect of their toxin on the male flies. For the killing of the male flies by *Spiroplasma poulsoni*, the normal function of the *Msl* genes of *Drosophila* (involved in dosage compensation) is required (Veneti Z et al 2005 Science 307:1461). Leptospirosis, a flu-like disease with frequent hepatic hemorrhage and jaundice, is caused *Leptospira interrogans* (see Fig. S100). Its sequenced genome consists of two chromosomes of 4,322,241 and 358,943 bp and encoding 4360 and 367 proteins, respectively. Its physiological characteristics are quite different from *Treponema* or *Borrelia*. Some lower animals (e.g., *Schistosoma*) are also called spirochetes. ▶*Schistosoma*, ▶*Treponema*, ▶*Borrelia*, ▶dosage compensation, ▶killer genes, ▶segregation distorter, ▶endosymbiont, ▶symbionts hereditary; Ren S-X et al 2003 Nature [Lond] 422:888.

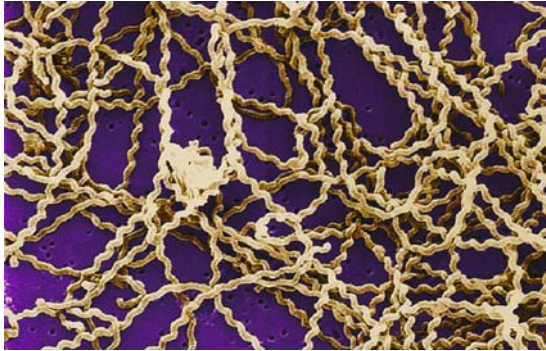


Figure S100. *Leptospira* bacteria. (Courtesy of CDC Rob Weyant and Janice Carr)

Spirochete (hydantocytin): A herbicidal growth regulator of *Streptomyces hygroscopicus*. ▶herbicide

Spiroplasma: ▶symbionts hereditary, ▶sex ratio, ▶spirochetes

S

Spite: An inimical action toward other individuals without benefit to the actor.

spitz (*Drosophila* chromosome 2–54): The 2–54 locus encodes the Spitz protein, a ligand of DER. ▶DER

SPK-1: A protein kinase of the MAPK family. ▶signal transduction

Spleen: An upper left abdominal, oblong (ca. 125 mm) ductless gland. At the embryonal stage, it participates in erythrocyte formation, in adults it also manufactures lymphocytes. By decomposing the erythrocytes, it provides to the liver, the hemoglobin to form bile. The red pulp contains red blood cells and macrophages, the white pulp carries the lymphocytes. It has a role in the defense mechanism of the body. It is

generally very enlarged in some lysosomal storage diseases, e.g., Gaucher's disease. ▶asplenia, ▶lysosomal storage diseases, ▶hemophilias, ▶Gaucher's disease

Splice: The resolution of a recombination intermediate (Holliday junction), resulting in an exchange of the flanking markers. ▶Holliday model, ▶introns, ▶spliceosome

Spliceosomal Intron: Spliceosomal introns utilize spliceosomes in eukaryotes for the removal of introns in contrast to the prokaryotic group I and II introns, which do so themselves. ▶introns, ▶spliceosome, ▶splicing; origins and evolution: Rodríguez-Trelles F et al 2006 Annu Rev Genet 40:47.

Spliceosome: A protein-U snRNA (there are five main uridine-rich oligonucleotides) complex required for the folding of pre-mRNA into the proper conformation for removal of introns and splicing the transcripts of exons. The spliceosome contains about 300 proteins (Rappsilber J et al 2002 Genome Res 12:1231). The majority of eukaryotic primary transcripts contain introns with 5' GU and AG 3' splice sites, and the mammalian consensus is: (A/C) AG↓GUA/GAGU. In yeast, the consensus is: (A/G)↓GUAUGU. Less than 1% of the mammalian splice junctures are GC–AG. In the excision, the spliceosome complex U1, U2, U4–U6, and U5 snRNAs and non-snRNAs work together. Initially, the U1 and U2 snRNA attaches by base pairing to the splice and to the branch sites, respectively. The U4–U6•U5 tri-snRNP complex joins in pre-splicing complexes. This is followed by snRNP–snRNP and mRNA–snRNP interactions. U6 base-pairs with U4. During spliceosome assembly, U1 and U4 are displaced and U6 pairs with the 5' splice site and with U2 snRNA. Through the coordination of a divalent metal ion (Mg^{2+}), the U6 snRNA contributes to the splicing of the RNA transcript. The 5' splice site and the branch nucleotide then move toward each other and the 2'-OH group of the latter serves as an electron donor for the first step of splicing. The excised 5'-exon and the lariat intron-3'-exon are the reaction intermediates. This first step is followed by a reaction between the electron donor nucleophile and the electron-deficient electrophile at the 3' splice junction by the 3'-OH of the freed 5'-exon, resulting in the ligation of the exons, and the removal of the intron.

A minority (0.1%) of the introns, the AT-AC introns, occurs in some animal genes such as encoding PCNA. The 5' splice site of such introns has the consensus AT↓ACCTT and their branch site is TCCTTAAC. Their splicing complex includes U11 and U12 snRNP and one or more U5 snRNP variants (Russell AG et al 2006 Nature [Lond] 443:863). The

PCNA branch site pairs with U12 and a loop of U5 aligns the exons of PCNA for ligation. U4 and U6 snRNAs are not used, but the highly divergent U4atac and U6atac take over their role. The reaction at the 5' splice site is mediated by a metalloenzyme but not at the 3' site. The spliceosome is a huge and variable complex of proteins. For the recognition of the 3' AG splice site, U2AF³⁵ (the 35K subunit of the heterodimeric [M_r 65K] U2AF⁶⁵ protein) is required in vivo, it is needed for viability and it is present in different organisms. U2AF was considered to be only an auxiliary factor (because in vitro it was not indispensable) to recognize the 5'-polypyrimidine sequences. For splicing, the U2AF protein must be in the close vicinity of the polypyrimidine tract that is recognized by its 35K subunits. The *Drosophila* protein Sex-lethal (SXL) controls dosage compensation by inhibiting splicing of the *male-specific-lethal-2* transcripts. When the large subunit of U2AF is displaced from the polypyrimidine tract—3'AG interval by SXL, the 35K subunit can mediate the removal of the intron. In the neurons the Nova proteins regulate alternative splicing. Nova binding the YCAY nucleotide sequences (Y stands for either pyrimidine) in exons blocked U1 snRNP binding and thereby exon inclusion, whereas intronic YCAY clusters promoted spliceosome assembly and exon inclusion. Thus, mapping Nova binding sites predicts mRNA regulation in neurons (Ule J et al 2006 Nature [Lond] 444:580). ▶introns, ▶exons, ▶splicing, ▶PCNA, ▶snRNA, ▶dosage compensation; Hastings ML, Krainer AR 2001 Curr Opin Cell Biol 13:302; Nagai K et al 2001 Biochem Soc Trans 29:15; Valadkhan S, Manley JL 2001 Nature [Lond] 413:701; Sträßer K, Hurt E 2001 Nature [Lond] 413:648; Nilsen TW 1998, p 279. In: RNA Structure and Function. Simons RW, Grunberg-Manago (eds). Cold Spring Harbor Laboratory Press; Villa T et al 2002 Cell 109:149; Zhu Z et al 2002 Nature [Lond] 419:182; Brow DA 2002 Annu Rev Genet 36:333; Patel AA, Steiz JA 2003 Nature Rev Mol Cell Biol 4:960; Shukla GC, Padgett RA 2004 Proc Natl Acad Sci USA 101:93; structure: Azubel M et al 2004 Mol Cell 15:833; core crystal structure:

Schellenberg M et al 2006 Proc Natl Acad Sci USA 103:1266; Xue S et al 2006 Science 312:906; spliceosome components: Stark H, Lührmann R 2006 Annu Rev Biophys Biomol Struct 35:435; supra-spliceosomes: Chen Y-IG et al 2007 Nucleic Acids Res 35:3928.

Splicing: Joining of RNA with RNA or DNA with DNA at the sites of previous cuts. Constitutive splicing indicates that the exons are spliced in the same order as they occur in the primary RNA transcript, in contrast to alternative splicing when the exons may be joined in alternative manners, thus providing mRNAs for different proteins transcribed from the same gene. The general scheme of pre-mRNA splicing is shown in Figure S101. The *Dscam* axon guidance gene of *Drosophila* has more than 38,000 alternative splice variants and dozens of different forms may be present within single cells (Neves G et al 2004 Nature Genet 36:240). About 74% of the human genes are alternatively spliced and about 15% of the human hereditary diseases are caused by mutation in the splicing mechanism (Johnson JM et al 2003 Science 302:2141).

The splicing factor family SR (named so because they are rich in serine [S] and arginine [R]), contain an RNA recognition motif (RRM/RNP) and Ψ-RRM domain Ser-Trp-Gln-Asp-Leu-Lys-Asp, separated by a Gly rich tract. The Ser-Arg domains are well phosphorylated by the serine kinase SRPK1. The 3' splice site is recognized by the U2AF⁶⁵/U2AF³⁵ heterodimer. The former binds to the polypyrimidine sequence in the RNA, whereas the latter associates with the RS domain of other RS-containing factors or the U4/U6.U5 small ribonuclear complexes at the 5' splice site. These proteins select the splice sites and are active parts of the spliceosome complex (▶spliceosome). The ASF/SF2 family recruits the U1 snRNP to the RNA transcript. SR proteins communicate also between introns across exons, and affect alternative splicing. The SR proteins are subject to regulation. Dephosphorylation of the splicing factor SRp38 represses splicing (Shinj C et al 2004 Nature [Lond] 427:553). Between the branch site and AG, there are located polypyrimidine sequences, which

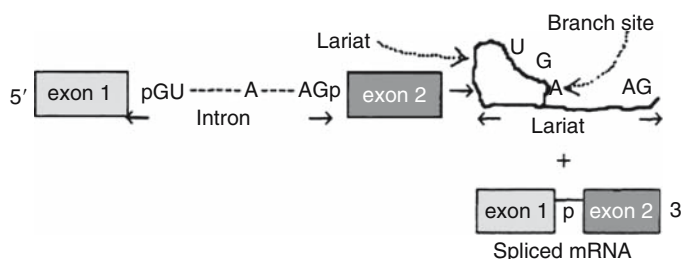


Figure S101. Pre-mRNA splicing

assist with the aid of various proteins to define the 3' splice site. Inactivation of ASF/SF2 results in genetic instability due to the formation of an R loop between RNA and the non-template strand of DNA (Li X, Manley JL 2005 Cell 122:365). Some of the many relevant proteins are PTB (polypyrimidine tract-binding protein) and PSF (PTB-associated splicing factor). The splicing reaction is driven by various nucleotidetriphosphatases. Genome-wide analysis revealed 285 human (ESR) exonic splicing regulatory sequences (Goren A et al 2006 Mol Cell 22:769). Plants also have splicing factors but these are more variable than those of animals and this is the cause why animal introns are not spliced out in plants. Splicing precedes the export of the RNA to the cytoplasm and requires the association of the mRNA with the splicing factor Aly. ▶restriction enzyme, ▶exon junction complex, ▶vectors, ▶introns, ▶speckles intranuclear, ▶lariat, ▶spliceosome, ▶alternative splicing, ▶U1 RNA, ▶snRNA, ▶alternative splicing; Madhani HD, Guthrie C 1994 Annu Rev Genet 28:1; Kramer A 1996 Annu Rev Biochem 65:367; Kim N et al 2001 EMBO J 20:2062; Thanaraj TA, Clark F 2001 Nucleic Acids Res 29:2581; Luo M-J et al 2001 Nature [Lond] 413:644; Clark TA et al 2002 Science 296:907; splicing factors: Sanford JR et al 2005 Proc Natl Acad Sci USA 102:15043; splice site prediction: <http://spliceport.cs.umd.edu:2000/SplicingAnalyser.html>.

Splicing Enhancer, Exonic (ESE): The repetitive GAA sequences associated with proteins; they facilitate the joining of exons. Pre-messenger RNA, containing introns, is retained within the nucleus. Intronless mRNAs containing ESEs were found to be poorly exported from the nucleus; spliced mRNAs produced from ESE-containing pre-mRNAs were found to be efficiently exported to the cytoplasm (Taniguchi I et al 2007 Proc Natl Acad Sci USA 104:13684). ▶pre-mRNA; Fairbrother WG et al 2002 Science 297:1007.

Splicing Inhibition: Splicing inhibition may be brought about by (phosphorothioate) 2'-O-methyl-oligoribonucleotides or morpholino oligonucleotides that are resistant RNase H (see Fig. S102).

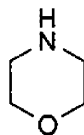


Figure S102. Morpholine

However, sometimes these analogs activate cryptic splice sites within exons. (See Wang Z et al 2004 Cell 119:831).

Splicing Junction (splice junction): Sequences at the exon-intron boundaries. They are needed for the selective export of mature mRNAs from the nucleus. In addition, they assist in RNA surveillance that leads to degradation of mRNAs with premature transcription termination. Mutations at splice junctions may cause the removal or the ordering of some exons. ▶introns, ▶exons, ▶spliceosome, ▶RNA surveillance, ▶nonsense-mediated decay; Lykke-Andersen J et al 2001 Science 293:1836.

Splicing of Proteins: Protein splicing involves post-translational excision by an endopeptidase of polypeptides and ligation the resulting carboxy- and amino-terminal sequences. Such a mechanism may occur in prokaryotes, plants, and animals. The shorter peptide can be then sliced up by a proteasome, further processed, and short pieces may be delivered with the aid of a transporter of MHC class I molecules to the cell surface where cytotoxic T lymphocytes (CTL) may destroy them. Such a mechanism can get rid of the FGF-5 fibroblast growth factor fragment responsible for renal cancer. ▶splicing, ▶inteins, ▶CTL, ▶proteasome, ▶MHC; Hanada K-i et al 2004 Nature [Lond] 427:252.

Splign: A tool for computing cDNA-to genomic or spliced alignments. (See <http://eu-transcoder.usablenet.com/tt/www.ncbi.nlm.nih.gov/sutis/splign/>; <http://www.ncbi.nlm.nih.gov/sutis/splign/splign.cgi?textpage=downloads>).

Splinkerette: A modified vectorette for PCR walking. In a PCR reaction, the free 3' end of the bottom strand flips back on itself forming a hairpin and begins elongation further along the bottom strand. The resulting double-stranded structure is stable and it is functionally removed from further reaction (see Fig. S103). (Diagram redrawn after Devon RS et al 1995 Nucleic Acids Res 23:1644). The system is well-suited for large-scale identification of mouse gene trap events (Horn C et al 2007 Nature Genet 39:933). ▶vectorette, ▶trapping promoters

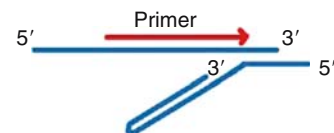


Figure S103. Splinkerette

Split Gene: The split gene is discontinuous because introns are intercalated between exons; the majority of the eukaryotic genes contains introns. ▶introns, ▶exons, ▶splicing, ▶spliceosome

Split-Hybrid System: The split-hybrid system provides means for positive selection for molecules that disrupt protein-protein interactions. The genetically engineered construct is shown in Figure S104.

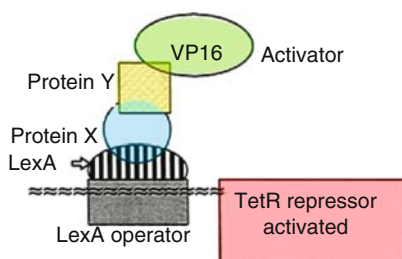


Figure S104. Split-hybrid method. If binding of X and Y is prevented the VP16 transactivator cannot turn on the TetR repressor and thus permitting the expression of *HIS3* gene and can be seen by the growth of the yeast cells in histidine-free medium

►two-hybrid method, ►VP16, ►one-hybrid binding assays, ►split-hybrid system, ►three-hybrid system, ►tTA, ►rtTA; Goldman PS et al 2001 *Methods Mol Biol* 177:261.

SPM (scanning probe microscope): SPM images biological macromolecules under a thin layer of aqueous solution. ►scanning electronmicroscopy

Spm (suppressor mutator): A transposable element system of maize of an autonomous *Spm* and a non-autonomous (originally unnamed) element. The non-autonomous element cannot insert or excise by its own power because it is defective in the transposase enzyme. This system is the same as the *En* (*Enhancer*)-*I* (*Inhibitor*) system. The non-autonomous component has also been called *dSpm* (*defective Spm*). The original name represents the fact that insertional mutations caused by the non-autonomous *dSpm* (*I*) element revert at high frequency only when *Spm* (*En*) is introduced into the genome because the latter has a functional transposase gene. The insertion does not always eliminate the function of the target gene and both a recessive mutation and the *Spm* element may be expressed. Such a case at the *A* (anthocyan) locus of maize (chromosome 3L-149) was designated as *a-m2* (*a* mutable) because of its frequent reversion to the dominant allele and displaying sectors in the presence of *Spm* (see Fig. S105). The *Spm*-dependent alleles harbor a non-autonomous (*dSpm* or *I*) insertion element that may jump out (and cause reversion), only when the functional *Spm* is introduced. The *Spm* suppressible alleles indicate the presence of a non-autonomous element that may or may not permit the expression of the gene, but the presence of the active *Spm* allows the insert's removal. The terms *Spm-w* and *Spm-s* indicate

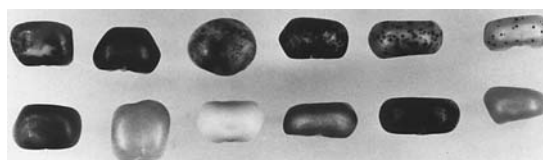


Figure S105. The dominant alleles of maize normally form dark color but the *a^{m-1}* allele possessing the *Spm* element may display alternative states. In the absence of an inactive *Spm* any shade of solid color may appear (bottom row) but in the presence of an active *Spm* a variety of sectors are displayed (top row). (Courtesy of Barbara McClintock)

weak and strong *Spm* transposase elements, respectively. *Inactivated Spm* has been called *Spm-i*, and elements that have alternating active and inactive phases were called *cycling Spm* (*Spm-c*), whereas very stable inactive forms were named *cryptic Spm* (*Spm-cr*). In addition, a *Modifier* factor has been named that enhances the activity of *Spm*. The various forms of the *Spm* alleles were found to alter their activity with time, according to developmental stage and extraneous factors, which cause chromosome breakage (radiation, tissue culture, etc.). The term *presetting* was applied to the phenomenon, in which *Spm* determined the expression of a gene even after its removal from the genome; but this effect later may fade away. Presetting is supposed to occur during meiosis and it is attributed to methylation. Indeed, the first exon of *Spm* is rich in cytidylic residues, the most commonly methylated base in DNA. Methylation may be instrumental in the variations and the inactivation of the various *Spm* elements named. A *Regulator* element is credited with the control of the extent of methylation. Although, the various *Spm* alleles display some heritable qualities, they appear to represent labile “changes in states” of the element, except the *dSpm* or other deletional forms. Transposition of the *Spm* elements is not tied to DNA replication and the transposition favors new insertion sites within the same chromosome, although it may move to any other part of the genome. Integration of *Spm* results in a 3 bp duplication at the target site. The frequency of insertion and excision is influenced also by the base sequences flanking the target site. The *Spm* appears to be modified by the process of excision and involves various lengths of terminal deletions, but the subterminal repetitious sequences may also be involved. Deletion of the terminal repeats abolishes transposition of the element. The abilities of *Spm* to transpose and to affect gene expression are inseparable.

The *Spm* element is transcribed into a 2.4 kb RNA with 11 exons; it includes two close open reading frames. The transcript may be alternatively spliced

into four different open reading frames, called *tnpA*, *tnpB*, *tnpC* and *tnpD*, the latter being the longest.

Transcripts *tnpA* and *tnpD* are necessary for transposition. The sequences downstream from the transcription initiation site are rich in GC base pairs and are susceptible to methylation. The active *Spm* elements, located at about 0.6 kb around the transcription start site, are not methylated. The methylated elements are, however, inactive. The entire element (8.4 kb) is flanked by 13 bp inverted repeats (CACTACAAGAAAA and TTTTCTTG TAGTG). In a region 180 bp from the 5'-end and 299 bp from its 3'-end, several copies of a receptive consensus CCGACATCTTA occur. The defective elements, *dSpm* have various lengths of internal deletions covering the entire length or part of the two open reading frames. Some partially deleted elements may still function as a weak *Spm-w* element. The function of an *Spm* element is regulated by sequences within the element and the location of the transposable element within the target genes. The function of the target genes depends on when, where, and how the *Spm* element and the target gene's transcripts are spliced. ▶transposable elements, ▶hybrid dysgenesis, ▶insertional mutation, ▶*Ac-Ds*; Fedoroff N 1989, p 375. In: Mobile DNA. Berg DE, Howe MM (Eds.) Am Soc Microbiol, Washington DC.

SPN (single nucleotide polymorphism): SPN indicates single nucleotide difference between two nucleic acids. ▶SNIP

SPO: A group of sporulation mediating proteins in yeast. (See Kee K, Keeney S 2002 Genetics 160:111).

Spondylocostal Dysostosis (SD): Non-syndromal short stature and vertebral and rib defects encoded at 19q13.1-q13.3 (see Fig. S106). The defect in the homolog of *Drosophila* gene *Delta* (*Dll3*) is involved. ▶Alagille syndrome, ▶Simpson-Golabi-Behmel syndrome



Figure S106. Spondylocostal dysostosis may involve increased size abdomen and deformed vertebral column. (Modified after Turnpenny PD, Kusumi K 2004)

Spondyloepimetaphyseal Dysplasia (SEMD): The heterogeneous group of hereditary skeletal bone and

cartilage diseases involving defects in protein sulfation. A recessive type was assigned to chromosome 10q23-q24.

Spondyloepiphyseal Dysplasia (SED): The *autosomal dominant* phenotype of SED includes flattened vertebrae, short limbs and trunk, barrel-shaped chest, cleft palate, myopia (near-sightedness), muscle weakness, hernia, and mental retardation. Collagen defects are incriminated in many cases. *Autosomal recessive* forms mimic arthritis-like symptoms (arthropathy), besides the short stature. The autosomal recessive forms may not involve flat vertebrae and the defect was attributed to a deficiency of phosphoadenosine-5'-phosphosulfate and thus to undersulfated chondroitin. An *X-linked* SED (Xp22.2-p22.1) was also described. SED type diseases were located to human chromosomes 5q13-q14.1, 12q13.11-13.2, and 19p13.1. The prevalence of the X-linked form is about 2×10^{-6} . ▶achondroplasia, ▶dwarfness, ▶arthropathy-campylodactyly, ▶chondroitin sulfate, ▶collagen, ▶Schimke immuno-osseous dysplasia; Gedeon AK et al 2001 Am J Hum Genet 68:1386.

Spontaneous Generation, Current: Until Louis Pasteur (1859–61), it was assumed by many scientists that microorganisms were formed from abiotic material even during the present geological period. However, Pasteur demonstrated that the organisms found in broth and other rich nutrients grew only when the solutions were not heated to sufficiently high temperature, were maintained for a certain duration of time, and exposed to unfiltered air. His discovery has been fundamental to modern microbiology and medicine and proved that spontaneous generation is not responsible for the current variations in microbial cultures. ▶spontaneous generation unique or recurrent, ▶lysenkoism, ▶pleomorphism, ▶biogenesis; Farley J 1972 J Hist Biol 5:285, *ibid.* 95.

Spontaneous Generation, Unique or Repeated: An explanation for the abiotic origin of life. It is assumed that after the earth was formed, simple molecules, such as water, carbon dioxide, ammonia, and methane were first formed. Subsequently, in a reducing atmosphere or at deep oceanic vents containing reducing minerals (iron and nickel sulfides) and high temperature (300–800°C), molecular nitrogen could have been reduced to ammonia. When energy sources became available at the surface (ultraviolet light), simple organic acids (acetic acid, formic acid) arose. In the presence of ammonia, methane, hydrogen, hydrogen cyanide, and lightning energy amino acids could be formed. In following steps, nucleotides could arise. Actually, under simulated early earth conditions chemists could synthesize amino acids, polypeptides,

carbohydrates, and nucleic acids. These simple organic molecules might have aggregated into some sorts of micellae (bubbles), and after self-replicating mechanisms came about the possibility for the generation of an ancestral cell with a primitive RNA as the genetic material. It is not entirely clear when, where, how, and how many times these events took place. Life is estimated to have begun 3–4 billion years ago. It is not known whether on other planets, under similar conditions to that of the earth, living cells evolved. ▶biopoiesis, ▶exobiology, ▶spontaneous generation current, ▶evolution prebiotic, ▶origin of life, ▶abiogenesis; Lennox J 1981 J Hist Philos 19:19; Harris H 2002 Things Come to Life: Spontaneous Generation Revisited. Oxford University Press, New York.

Spontaneous Mutation: Spontaneous mutation occurs at a relatively low frequency when no known mutagenic agent is or was present in the environment of the cell or organism; the cause of the mutation is thus unknown. The spontaneous frequency of mutation in mice for seven standard loci is 6.6×10^{-6} per locus. The frequency in man is in the range of 10^{-5} to 10^{-6} , in *Drosophila* 10^{-4} to 10^{-5} , in yeast *Neurospora* 10^{-5} to 10^{-9} , in bacteria 10^{-4} to 10^{-9} , and in bacteriophages, 10^{-4} to lower to 10^{-11} range has been reported. In maize, the frequency is comparable to that in other eukaryotes. At some other loci and in other organisms, it may be substantially higher or lower. In higher eukaryotes, the frequencies appear lower than in microorganisms but this does not seem to be due to intrinsic biological differences; rather it reflects the limitations of the size of the populations, which were amenable to screening. The extent of DNA repair may have profound influence on the mutations recovered. ▶mutation rate, ▶mutation spontaneous, ▶diversity; Wloch DM et al 2001 Genetics 159:441.

Spooling: Spooling assumes that the triple- or quadruple-stranded naked DNA molecules are wound into the RecA protein filament for pairing and exchange. After the formation of heteroduplexes, the DNAs are released. ▶recombination molecular mechanism

Sporadic: Sporadic refers to the rare occurrence of an off type, which does not show a clear familial pattern, and the etiology (cause or origin) is unknown. ▶epidemiology

Sporangiophore: A sporangium-bearing branch. ▶sporangium

Sporangium (plural sporangia): The spore-producing and -containing structure in lower organisms (fungi, protozoa) (see Fig. S107).

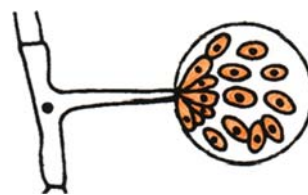


Figure S107. Sporangiphore and sporangium

Spore: A reproductive cell; generally the product of the eukaryotic *meiosis*, or it may arise *mitotically* as fungal conidiospores (conidia). The *bacterial spores* are metabolically dormant cells, surrounded by a heavy wall for protection under very unfavorable conditions.

Spore Mother Cell: ▶sporocyte

Sporidium: The “sexual” spore of basidiomycetes fungi. ▶basidium

Sporocyte: A diploid cell that produces haploid spores as a result of *meiosis*. ▶gametogenesis

Sporogenesis: The mechanism or process of spore formation. ▶meiosis, ▶conidia

Sporophore: The fruiting body capable of producing spores in fungi. ▶spore

Sporophyte: The generation of the plant life cycle that produces by *meiosis* the (1n) gametophytes. The common form of plants (displaying leaves and flowers, etc.) is the (2n) sporophytic generation. ▶gametophyte

Sporopollenin: Sporopollenins are mainly polymerized carotenoids forming the exine of the pollen grains, facilitating its adhesion to the stigma of the female reproductive structure of plants.

Sporozoite: The infective stage of protozoan life cycle; in malaria, they are formed within the mosquito. ▶malaria, ▶*Plasmodium*, ▶*Anopheles*

Sporulation: In bacteria, the process of formation of morphologically altered cells that can survive adverse conditions and assure the survival of the sporulating bacteria. *Bacillus subtilis* is a typical spore-forming bacterium. Within its cell, a new cell is pinched off to create the spore that can eventually develop into a new regular cell (see Fig. S108). Also, ascospore formation through *meiosis* in fungi is sporulation. In budding yeast, 334 sporulation-essential genes have been identified. ▶meiosis; Enyenihi AH, Saunders WS 2003 Genetics 163:47; Fujita M, Losick R 2003 Genes Dev 17:1166; <http://cmgm.stanford.edu/pbrown/sporulation/>.

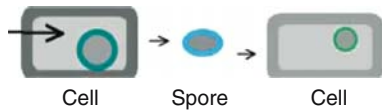


Figure S108. Sporulation

Spot Test: A variation of the mutagen/carcinogen bioassays when the compound to be tested by bacterial reversions is added to the surface as a crystal or a drop after the Petri plates have been seeded by the bacterial suspension and the S9 microsomal fraction added. If the substance to be tested is mutagenic, a ring of revertant cells should appear around the spot where it was added (see Fig. S109). This type of mutagenic assay is no longer much in use. ▶Ames test, ▶plate incorporation test, ▶reversion assays of *Salmonella*; Ames BN 1971, p 267. In: Chemical Mutagens I. Hollaender A (Ed.) Plenum, New York.

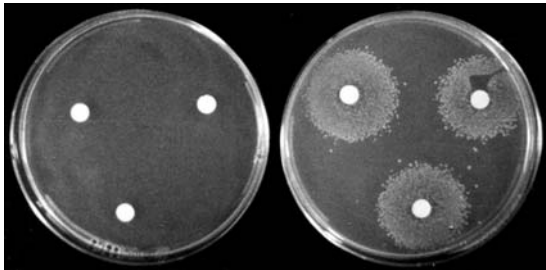


Figure S109. Reversion assay of *Salmonella* bacterium by the spot test. (Courtesy of Dr. G. Ficsor)

Spotting: Spotting at specific body parts is frequently found in various species (see Fig. S110). The basic colors (melanin or melanin precursors) are generally uniformly distributed at various intensities. Mutations in regulatory cis elements create novel opportunities for transcription factors for association with the mutant sequences and determine the intensity of the local deposition of the pigment. Genes in trans



Figure S110. *Drosophila* wing spotting

locations in the genome encode the transcription factors. (Gompel N et al 2005 Nature [Lond] 433:481). ▶cis-acting element, ▶transacting element, ▶piebaldism, ▶transcription factors, ▶KIT oncogene, ▶variegation

spp: The abbreviated plural of the word species.

Spreader: A simple instrument for distributing micro-organisms on the surface of agar plates (see Fig. S111).



Figure S111. Spreader

Spreading: Moving silencing proteins along the chromosome. ▶silencer

Sprekella formosissima (Amaryllidaceae): Subtropical plant, $n = \text{ca. } 60$; genome size 1.8×10^{11} bp.

spretus: *Mus spretus*, a species of mouse, commonly used for genetic analyses.

Springer: ▶copia

Spruce (*Picea* spp): Timber tree species with $2n = 2x = 24$. ▶pine, ▶douglas fir

Sprue: A tropical intestinal disease, apparently due to infection(s).

SP-Score: ▶MP-score

SPT: A suppressor of transposition (e.g., of a Ty element) and a regulator in SAGA function in yeast. The *Drosophila* homologs are *Dspt4* and *Dspt6*. This family of genes encodes histones H2A and H2B and TATA-binding proteins. There is evidence for their regulation of transcription, replication, recombination, and some developmental processes. ▶SAGA, ▶histones, ▶transcription, ▶TBP; Yamaguchi Y et al 2001 J Biochem 129:185.

Spt Proteins: Spt proteins are involved in the elongation of RNA transcripts on DNA. ▶RNA polymerase; Winston F 2001 Genome Biol 2(reviews):1006.

SptP: ▶SopE

Squalene: ▶prenylation

Squamous: Squamous denotes scaly, e.g., as in squamous cell carcinoma, a form of epithelial cancer. Sunscreen provides some protection against it. C57BL/6 strain of mice is resistant to skin squamous carcinomas (SCCs) induced by an activated Ras oncogene, whereas FVB/N mice are highly susceptible. Susceptibility is under

the control of a carboxy-terminal polymorphism in the mouse *Ptch* gene. F1 hybrids between C57BL/6 and FVB/N strains are resistant to Ras-induced SCCs, but resistance can be overcome either by elimination of the C57BL/6 *Ptch* allele (*Ptch*B6) or by overexpression of the FVB/N *Ptch* allele (*Ptch*FVB) in the epidermis of *K5Hras*-transgenic F1 hybrid mice. The human Patched (PTCH1, 9p22.3) gene is a classical tumor suppressor gene for basal cell carcinomas and medulloblastomas. Apparently, *Ptch* is critical for determining both basal or squamous cell lineage, and both tumor types can arise from the same target cell depending on carcinogen exposure and host genetic background (Wakabayashi Y et al 2007 Nature [Lond] 445:761). ▶[epidermolysis](#), ▶[nevroid basal cell carcinoma](#), ▶[medulloblastoma](#); Lin JY, Fisher DE 2007 Nature [Lond] 445:843.

Squash: *Cucurbita maxima* (winter squash) 2n = 24, 40; *C. pepo* (summer squash) 2n = 40; *C. moschata* (pumpkin), 2n = 24, 40, 48.

Squash Preparation: For microscopic analysis of chromosomes in soft (softened) tissues, there may be no need for sectioning but the fixed and stained material can be examined after smearing it directly on the microscope slide. In some cases, the fixation is done by gentle heating on the slide followed by adding a small drop of aceto-carmin or aceto orceine stain or even just placing the specimen into a drop of acetic stain and heating. These rapid procedures may permit an estimation of the stage of meiosis or mitosis. ▶[microscopy](#), ▶[stains](#); Belling J 1921 Am Nature 55:573.

Squelching: The suppression or silencing of adverse effects.

Squirrel: *Tamiasciurus hudsonicus streator*, 2n = 46; *Callospermophilus lateralis*, 2n = 42; *Ammodontomys*, 2n = 32; *Citellus citellus*, 2n = 40.

SR1: A cytoplasmic mutant of tobacco resistant to streptomycin. ▶[Nicotiana](#), ▶[streptomycin](#)

SR Motif: Serine/arginine-rich domains in RNA-binding proteins, involved in splicing pre-mRNA transcripts. They are required in the early steps of spliceosome assembly. One SR protein (SC35) alone is sufficient to form a committed complex with human β-globin pre-mRNA. Different single SR proteins commit different pre-mRNAs to splicing and different sets of SR proteins may determine the alternative and tissue-specific splicing within an organism. The SR proteins are regulated by phosphorylation/dephosphorylation. The ASF/SF2 SR-binding protein is required for genomic stability (Li X, Manley JL 2005 Cell 122:365). ▶[splicing](#), ▶[spliceosome](#), ▶[processing](#),

▶[primary transcript](#), ▶[introns](#), ▶[tissue specificity](#), ▶[DEAD-box proteins](#), ▶[DEAH box proteins](#), ▶[ESE](#); Tian H, Kole R 2001 J Biol Chem 276:33833; Shopland LS et al 2003 J Cell Biol 162:981.

SR Proteins: ▶[SR motif](#)

SRA (steroid-receptor RNA activator): An RNA coactivator of steroid hormone receptors. ▶[nuclear receptors](#), ▶[RNA regulatory](#); Lanz RB et al 2002 Proc Natl Acad Sci USA 99:16081.

SRB: Protein stabilizing RNA polymerase II binding to general transcription factors and it phosphorylates pol II RNA polymerase. SRBs occur in eukaryotes from yeast to humans and have the forms, SRB 2, 4, 5, 6, 7, 10, and 11. The CDK-like *SRB* genes involve mutation control and promotion/suppression of transcription by phosphorylating the carboxyl-terminal of RNA pol II. ▶[transcription factors](#), ▶[transcription complex](#), ▶[kinase](#), ▶[CDK](#), ▶[RNA polymerase holoenzyme](#), ▶[open promoter complex](#), ▶[regulation of gene activity](#), ▶[TUP](#), ▶[mediator complex](#); Hampsey M, Reinberg D 1999 Curr Opin Genet Dev 9:132; Carlson M 1997 Annu Rev Cell Dev Biol 13:1.

SR-BI (scavenger receptor class B1): A high-density lipoprotein receptor mediating cholesterol uptake and secretion into the bile. PDZK1 protein regulates its expression and controls HDL level. ▶[high-density lipoprotein](#), ▶[cholesterol](#); Nakamura T et al 2005 Proc Natl Acad Sci USA 102:13404.

SRBC: Sheep red blood cell.

SRC: Rous sarcoma virus oncogene of chicken. Its product is a protein-tyrosine kinase, a cellular signal transducer. Its homology domains SH2 and SH3 are present in several cytoplasmic mediator and adaptor proteins in the signal transduction pathways in different organisms. These domains bind phosphotyrosine or proline-rich residues. Phosphorylation, dephosphorylation and proteolysis regulate SRC. In humans, SRC is in chromosome 20q12-q13. SRC may be involved in both RAS-dependent and RAS-independent signaling pathways and may lead through either FOS or MYC to transcription factors. This family of non-receptor kinases includes Src, Yes, Fgr, Fyn, Lck, Hck, Blk, Zap70, Tec, Csk. Cells display increased Src, Fyn and Lyn activity. The Src proteins may also have autoinhibitory function. The Cbl oncogene acting downstream of Src is responsible for bone resorption in osteoporosis. c-SRC has been implicated in various types of cancers. Src enzyme with mutation Arg-388 to alanine with about 5% enzyme activity can be rescued to about half of normal activity by the use of the tautomerism-inducing small

molecule of imidazole under in vivo conditions (Qiao Y et al 2006 Science 311:1293). ▶**oncogenes**, ▶**SH2**, ▶**SH3**, ▶**signal transduction**, ▶**Tec**, ▶**Zap-70**, ▶**Yes**, ▶**Fgr**, ▶**Fyn**, ▶**Lck**, ▶**Hck**, ▶**Blk**, ▶**Csk**, ▶**Cbl**, ▶**osteoporosis**, ▶**imidazole**, ▶**tautomeric shift**, ▶**TCR**; Schlessinger J 2000 Cell 100:293.

SRC-1 (steroid receptor coactivator-1): Enhances the stability of the transcription complex controlled by the progesteron receptor. It is actually a co-activator of histone acetyltransferase and mediates the access of the transcription complex within the nucleosome. ▶**transcription**, ▶**progesteron**, ▶**histone acetyltransferase**, ▶**N-CoR**, ▶**TGF**; Liu Z et al 2001 Proc Natl Acad Sci USA 98:12426; Auboef D et al 2002 Science 298:616.

SRE: A cis-acting enhancer element responding to serum induction: CC(AT)₆GG (CarG box) is present in all serum response factor regulated genes. ▶**MADS box**, ▶**TCF**, ▶**serum response element**, ▶**serum response factor**

SREBP (sterol regulatory element binding proteins): Hairpin shaped it is found in the membrane of the endoplasmic reticulum (ER). The N-terminal domain is in the cytosol and acts as a basic helix-loop-helix transcription factor. The C-terminus is also in the cytosol and it is complexed with the cleavage activating protein SREBP-SCAP, which has 8 membrane-spanning regions. When the ER is low on sterols the complex is transferred to the cleavage compartment. In case of sterol overload the complex is sequestered into the ER and there is no cleavage. SREBP controls cholesterol and lipid homeostasis (Yang F et al 2006 Nature [Lond] 442:700). Cholesterol and oxysterol bind to a hexapeptide (MELADL) of the SREBP-escort protein Scap, and causes Scap to bind to Insig anchor proteins. Oxysterols bind to Insigs, causing Insigs to bind to Scap. Mutational analysis of the six transmembrane helices of Insigs reveals that the third and fourth are important for binding Insigs to oxysterols and to Scap. Thus Insigs are oxysterol-binding proteins, explaining the long-known ability of oxysterols to inhibit cholesterol synthesis in animal cells (Radhakishnan A et al 2007 Proc Natl Acad Sci USA 104:6511). S1P and S2P process SREBP. SREBP may suppress the insulin regulator IRS-2 and has a potential therapeutic role as a drug target in some diabetes (Ide T et al 2004 Nature Cell Biol 6:351; Sun L-P et al 2007 Proc Natl Acad Sci USA 104:6519). ▶**sterols**, ▶**cholesterol**, ▶**oxysterol**, ▶**statins**, ▶**Insig**, ▶**Rip**, ▶**SCAP**, ▶**lipodystrophy**, ▶**diabetes**, ▶**ATF2**; Shimano H 2001 Progr Lipid Res 40:539; Dobrosotskaya IY et al 2002 Science 296:879.

SRF (serum response factor): A transacting regulatory protein binding to SRE and regulating serum-induced gene expression. ▶**trans-acting element**, ▶**serum response element**; Kim SW et al 2001 Oncogene 20:6638.

SRK: Self-compatibility protein receptor kinase. An Srk1 kinase associated with Cdc25 phosphatase controls mitotic checkpoints (López-Avilés S et al 2005 Mol Cell 17:49). ▶**self-incompatibility**, ▶**Cdc25**, ▶**checkpoint**; Takayama S et al Nature [Lond] 413:534.

sRNA: ▶**suppressor RNA**

sRNA: ▶**RNAi**

S-RNase: A ribonuclease responsible for pollen rejection (with factor HT) in self-incompatible plants, ▶**self-incompatibility**; Luu DT et al 2001 Genetics 159:329.

SRP (signal recognition particle): An element of polypeptide transport systems through the membranes of the endoplasmic reticulum in eukaryotes and to the plasma membranes in prokaryotes. Some of the polypeptides are inserted in the endoplasmic reticulum and others are destined toward the cell membrane for secretion. The subunit (Ffh), which recognizes the signal sequence as well as the α subunit (FtsY) of its receptor (SR) are GTPases. The SRP has a variable length RNA component (4.5 S in prokaryotes and 7SL in eukaryotes). The Ffh subunit has an N domain where the signal peptide binds and the G domain of the GTPases. Adjacent to the signal-binding pocket the methionine-rich M domain forms a small globular structure, which folds into helix-turn-helix type motif for binding the RNA component. ▶**7SL RNA**, ▶**endoplasmic reticulum**, ▶**signal sequence recognition particle**, ▶**signal peptide**, ▶**Fts**; Batey RT et al 2000 Science 287:1232; Oubridge C et al 2002 Mol Cell 9:1251.

SRS2: A helicase protein; displays single-strand Dna-dependent ATPase activity. When mutant, it increases sensitivity to genotoxic agents and may cause chromosome loss. Normally, it suppresses RAD51-dependent recombination by dislodging RAD51 protein but when it is defective, it increases recombination. ▶**RAD51**, ▶**PCNA**; Krejci L et al 2003 Nature [Lond] 423:305; Veaute X et al 2003 Nature [Lond] 423:309.

SRY (sex-determining region Y, called earlier TDF [testis determining factor]): A mammalian gene in the short arm of the Y chromosome (Yp11.3) responsible for testis determination and for the development of pro-B lymphocytes. The protein (223 amino acids) is a member of the high-mobility group proteins. In mice

this HMG protein includes a large CAG trinucleotide repeat tract, which functions as a transcriptional trans-activator and it is required for male sex expression. The expression of SRY initiates the formation of the Müllerian inhibiting substance (MIS) and the synthesis of testosterone. For normal function of SRY three insulin or insulin-like receptor tyrosine kinases are required in mouse (Nef S et al 2003 Nature [Lond] 426:291). SRY contains the DNA minor groove-binding domain, the HMG box that is conserved among mammals. Mutations affecting human sex-reversal are generally within the HMG box. Sex reversal may be the result of defect in the nuclear localization signals of SRY and the N-terminal signal is not recognized by the nuclear receptor protein β -importin (Harley VR et al 2003 Proc Natl Acad Sci USA 100:7045). A human chromosome 17q24.3-q225.1-located gene SRA-1 (sex reversal autosomal) may also be controlled by SRY. Another sex-reversal gene was identified in human chromosome 9p24. In rodents, several *tda* (testis-determining autosomal) alleles exist. In the short arm of the human X-chromosome (Xp21) there is the DSS (dosage-sensitive sex reversal) locus that may be involved in sex reversal (male→female) in case of its duplication or in case the SRY alleles are weak. Deletion in the 160 kb DSS region (DAX) does not affect male development but may cause adrenal hypoplasia. Apparently the DAX gene encodes nuclear hormone receptors. DAX1 (Nr0b1) expression ceases early in testis development but persists through the development of the ovaries. There is/are the SRYIF inhibitory factor(s) involved in gonadal differentiation. The voles (rodents) *Ellobius lutescens* 2n = 17, XO constitution in males, and females and *E. tancrei* 2n = 32–54, XX in both males and females, as a normal condition do not have SRY, whereas SRY is present in other rodents as well as in other eutherian and marsupial species. The *Sry* gene is specifically expressed in the substantia nigra of the brain of rodent males in tyrosine hydroxylase-expressing neurons and it controls specific motor behavior. This condition is not the consequence of gonadal hormone action yet it contributes to the sexual differentiation of the brain (Dewing P et al 2006 Curr Biol 16:415). ▶high mobility group proteins, ▶SOX, ▶TDF, ▶Müllerian ducts, ▶ZFY, ▶animal hormones, ▶Wolffian ducts, ▶campomelic dysplasia, ▶eutherian, ▶adrenal hypoplasia, ▶Swyer syndrome, ▶trinucleotide repeat, ▶LINE; Murphy EC et al 2001 J Mol Biol 312:481; Yuan X et al 2001 J Biol Chem 276:46647.

σ^S (RpoS): Required for the expression of many growth phase and osmotically regulated prokaryotic genes.
▶ σ subunit of RNA polymerase.

SS Blood Group: ▶MN blood group

SSA (single-strand annealing): A repair mechanism apparently employed by prokaryotes and eukaryotes when one or more units of tandem repeats are eliminated by bacterial RecBCD-mediated degradation or by other nucleases (see Fig. S112). ▶DNA repair; Van Dyck E et al 2001 EMBO Rep 2:905; Paques F, Haber JE 1999 Microbiol Mol Biol Rev 63:349, Diagram redrawn after Sugawara N et al 2000 Mol Cell Biol 20:5300.

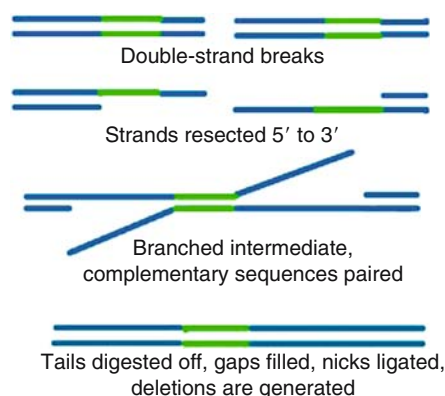


Figure S112. SSA repair

SSA: ▶Hsp70

Ssb: ▶Hsp70

SSB: A single-strand (DNA) binding protein; in yeast it is encoded by gene *RPA1*. ▶recombination molecular mechanism, ▶replication protein A, ▶DNA repair (SOS repair); Reddy MS et al 2001 J Biol Chem 276:45959.

SSC: Somatic stem cell. ▶ESC, ▶stem cell

SSC: 1 × SSC is a solution of 0.15 M NaCl + 0.015 M sodium citrate, frequently used as a solvent for nucleic acids. ▶DNA extraction

Ssc: ▶Hsp70

SSCA (single-strand conformation analysis): ▶single-strand conformation polymorphism

SSCP: ▶single-strand conformation polymorphism

ssDNA: A single-strand DNA.

SSE: same as HSP, ▶HSP

SSEA (stage-specific embryonic antigen): Can be used as surface markers for undifferentiated embryonic stem cells.

Ssh: ▶Hsp70

Ssi: ▶Hsp70

SSI-1 (STAT-induced STAT inhibitor): ►STAT

SSLP: ►simple sequence length polymorphism

SSM (slipped-strand mispairing): ►unequal crossing over

SSN6: The yeast factor abolishing glucose repression of SUC2 invertase and regulator of nucleosome positioning in the chromatin. Other *SSN* genes are components of the RNA polymerase II complex and are negative regulators of transcription. ►SUC2, ►SNF, ►catabolite repression; Li B, Reese JJ 2001 J Biol Chem 276:33788.

SSNC (second-site non-complementation): Two heterozygous recessive mutations at different chromosomal sites exhibit mutant phenotype by some sort of interaction in contrast to expectation that non-allelic recessive mutations would be complementary. ►cis-trans test, ►allelic complementation; Halsell SR, Kiehart DP 1998 Genetics 148:1845.

SSPA (significant segment pair alignment): Each sequence is used to align with a standard other sequences. It accommodates indels and other gaps. The information obtained can be used for searches for similarities in databases. ►indel, ►BLOSUM, ►ITERALIGN; Brocchieri L, Karlin S 1998 J Mol Biol 276:249.

SSR (small segment repeat or simple sequence repeat, microsatellite): These clusters of single to multiple nucleotides within the genome occurring per ~6 to ~30 to ~80 kb in plants and per ~6 kb in mammals have been used as chromosomal markers in various types of genetic studies. They may show high degree of mutability. In bacteria, only very short repeats occur (contingency loci) and they facilitate bacterial adaptation. ►microsatellite, ►phase variation; Qi X et al 2001 Biotechniques 31:358; Bacon AL et al 2001 Nucleic Acids Res 29:4405; Moxon R et al 2006 Annu Rev Genet 40:307.

SsrA (tmRNA, 10Sa RNA): ►protein repair

SSRP1 (structure-specific recognition protein): A high-mobility group protein probably targets FACT to the nucleosomes and facilitates gene transcription by RNA polymerase II. ►FACT, ►high-mobility proteins, ►transcription factors, ►nucleosome remodeling; Bruhn SL et al 1993 Nucleic Acids Res 21:1643.

SSV: A simple sequence variation in DNA.

ST-1: A single-stranded DNA phage, related to ϕ X174 and G4. ►map, ► ϕ X174 and, ►G4, Figure S113 is by courtesy of D. N. Godson.

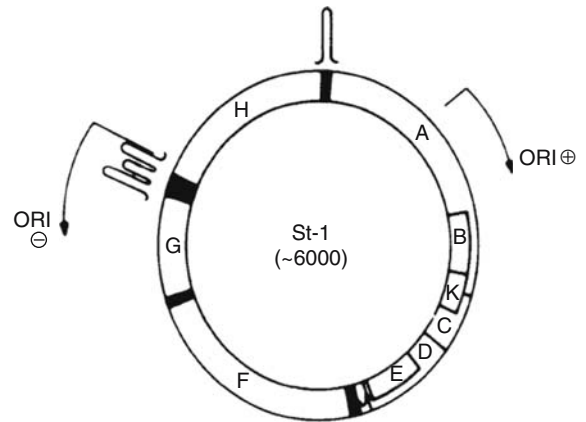


Figure S113. St-1 single-stranded DNA phage

Stab Culture: The microbial inoculum is introduced into agar medium by a stabbing motion of the inoculation needle or loop for the purpose of propagation.

Stabilizing Selection: ►selection types

Stable RNA: Ribosomal and tRNA that persists long in the cell in comparison to mRNA that may be degraded in minutes. ►rRNA, ►tRNA, ►mRNA

Stack: Sequence Tag Alignment and Consensus Knowledgebase: <http://ziggy.sanbi.ac.za/stack/stacksearch.htm>. ►gene indexing

Stacking Gel: A porous gel on top of the SDS polyacrylamide electrophoresis running gel. It concentrates large volumes into a thin, sharp band at the beginning of the run and thus permits sharper separation of proteins. ►electrophoresis, ►SDS

STAGE (sequence tag analysis of genomic enrichment): A method similar to ChIP-chip for detecting protein factor binding regions but use extensive short sequence determination rather than genomic tiling arrays. ►ChIP, ►ChIP-chip, ►tiling, ►STAT; mapping chromosomal STAT: Bhing AA et al 2007 Genome Res 17:910.

Staggered Cuts: After a double-stranded DNA is cut, the length of the two polynucleotides is unequal.



Staggered Extension Process (StEP): A method for in vitro mutagenesis and recombination of polynucleotides. By using it, mutant proteins can be generated in vitro. The template sequences are primed, then

repeated cycles of denaturation and very short annealing and extension follows. In each cycle, the extended fragments anneal to different templates depending on complementarity, and the extension continues until full length is formed. The template switching generates recombined sequences from different parental sequences. ▶molecular evolution, ▶directed mutation, ▶RNA-peptide fusions; Zhao H et al 1998 Nature Biotechnol 16:258; Xia G et al 2002 Proc Natl Acad Sci USA 99:6597.

Stains: For light microscopic examination of chromosomal specimens aceto-carmin, aceto-orcin or Feulgen stains are commonly used. Preparation: 0.5–1 g dry carmin powder is boiled for about half an hour under reflux in 100 mL 45% acetic or propionic acid. Orcin 1.1 g is dissolved in 45 mL glacial acetic acid or propionic acid and filled up to 100 mL by H₂O. Filter and store stoppered at about 5°C. Feulgen: 1 g leuco-basic fuchsin is dissolved by pouring over 200 mL boiling H₂O, shake, cool to 50°C, filter, add 30 mL 1/N HCl, then 3 g K₂S₂O₅, allow to bleach in dark for 24 h stoppered. Decolorize by 0.5 g carbon, shake 1 min then filter and store stoppered in refrigerator. For carmin or orcin staining, fix specimens in Carnoy and stain. For Feulgen, fix in Farmer's solution for a day, rinse with water, hydrolyze at 60 °C for 4–10 min. (The duration of hydrolyzation is critical and may need adjustment for each species). Rinse with stain for 1–3 h. Tease out tissue in 45% acetic acid, remove debris, flatten by coverslip and examine. May need overstaining with carmin if Feulgen staining is poor. For histological staining a variety of other stains may be used such as haematoxylin, methylene blue, ruthenium red, malachite green, sudan black, coomassie blue, fluorochromes, etc. may be employed. ▶fixatives, ▶sectioning, ▶light microscopy, ▶C-banding, ▶G-banding, ▶Q-banding, ▶chromosome painting, ▶harlequin stain, ▶FISH, ▶fluorochromes, ▶aequorin

Stamen: The male reproductive organs of plants composed of the anther, which contains the pollen and the filament (see Fig. S114). ▶anther, ▶pollen

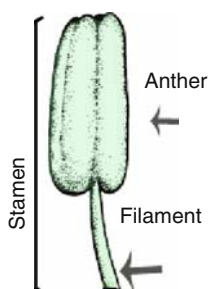


Figure S114. Stamen

Stamen Hair Assay: ▶*Tradescantia*

Stamina: The capacity to endure, vigor.

Staminode(s): Infertile stamen(s).

Staminate Flower: The male flower of monoecious or dioecious plants.

Stammering: A most serious form of speech defects, *stuttering*. The sufferers usually cannot talk fluently and after involuntary stops repeat syllables or entire words. The frequency of stammering is very frequent among Japanese and very unusual among American Indians. Autosomal dominant inheritance seems to be involved. Apparent linkage to chromosomes 1, 5 and 7 was detected and to chromosome 12 the linkage displayed lod scores 4.61 to 3.51 (Riaz N et al 2005 Am J Hum Genet 76:647). ▶lod score, ▶stuttering

Standard: An accepted point of reference, e.g., standard wild type. ▶control

Standard Deviation (parametric symbol σ): A measure of the variability of members of the populations $s = \sqrt{\text{variance}}$. ▶variance, ▶standard error, ▶normal deviate

Standard Error: Measures the variation of the means of various samples of a population $s\sqrt{m}$ (by some authors standard error and standard deviation are used as synonyms); standard error of proportions or fractions or frequencies is shown by the boxed formula where p = proportion or frequency and n is the population size (or number of measurements).

$$\sqrt{\frac{p(1-p)}{n}}$$

Standard Type: Generally means the wild type used as a genetic reference. ▶wild type

Standardized Fitness: ▶selection coefficient

Stanford–Binet Test: A modified Binet intelligence test. ▶Binet test, ▶human intelligence

Stanniocalcin: The protein hormone inhibiting Ca²⁺ uptake and stimulating phosphate adsorption in fishes and mammals. (See Varghese R et al 1998 Endocrinology 139:4714).

Staphylococcus aureus: A bacterium responsible for toxic shock, scarlet fever and hospital-acquired infections and various inflammations. In some strains a conjugative plasmid has been detected that harbors trimethoprim, β -lactam, aminoglycoside as well the Tn1546 transposon carrying also vancomycin resistance. The genome sequence and partial annotations of 27 bacteria phages of *S. aureus* are available (Kwan T et al 2005 Proc Natl Acad Sci USA 102:5174). ▶toxic shock syndrome, ▶aminoglycosides, ▶ β -lactamase, ▶trimethoprim, ▶vancomycin,

►**inflammasome**; Kuroda M et al 2001 Lancet 357:1225; Weigel LM et al 2003 Science 302:1569.

STAR (signal transduction and activation of RNA): Generally, a 200 amino acid protein domain associated with the cell and RNA splicing. The tripartite domain has a single RNA-binding site, a KH module of different length (2–14) and flanked by QUA1 (80) and QUA2 (30) amino acid sequences. These complexes have been detected in a wide range of eukaryotic organisms and they appear to be regulators of translation. STAR family proteins may repress *tra-2* and cause masculinization in females. ►**Sam 68**, ►**sex determination**; Stoss O et al 2001 J Biol Chem 276:8665.

STAR (signature-tagged allele replacement): May facilitate genetic analysis in cases where mutational studies are impractical due to the essentiality of the gene for viability. ►**signature of a molecule**, ►**targeting genes**; Yu Y et al 2001 Microbiology 147:431.

STAR (subtelomeric antisilencing region): An insulator type sequence that protects a gene from the action of a silencer if it lies in between the silencer and the gene. ►**silencers**, ►**insulator**

StAR (steroidogenic acute regulatory protein, 8p11.2): Enhances mitochondrial conversion of cholesterol into pregnenolone, an intermediate in steroid biosynthesis. Mutation in the coding gene results in deficiency of adrenal and gonadal steroidogenesis, and leads to congenital lipoid adrenal hyperplasia, an autosomal recessive disorder. ►**cholesterol**, ►**steroid**, ►**pregnenolone**, ►**hormones**, ►**adrenal hyperplasia**; Petrescu AD et al 2001 J Biol Chem 276:36970.

Starch: ►**amylopectin**

Starfish: *Asterias forbesi*, 2n = 36 (see Fig. S115).



Figure S115. Starfish

Stargardt Disease: A complex recessive degenerative disease of the retina evoked by environmental factors such as smoking and high cholesterol. In both, the early onset form (macular dystrophy with flecks) and the age-related macular degeneration (AMD),

mutations in the ATP-binding cassette transporter of the retina (ABCR) gene are involved. ABCR contains 51 exons in chromosome 1p13-p21. Physically the product is located in the outer segment of the retinal rods (called also rim protein). The autosomal dominant form is caused by mutation in the ELOVL4 gene, involved in fatty acid chain elongation. In mice, so affected undigested phagosomes and lipofuscin and other fluorophores accumulate and that is followed degeneration of the retinal pigment epithelium (Karan G et al 2005 Proc Natl Acad Sci USA 102:4164). In many cases, the disease is responsible for blindness. The Sorsby fundus dystrophy, an autosomal dominant disease, appears somewhat similar but it is caused by a malfunction of the tissue inhibitor metalloproteinase-3 gene (TIMP3). ►**ABC transporters**, ►**macular degeneration**, ►**eye diseases**, ►**macular dystrophy**, ►**retinal dystrophy**, ►**retinitis pigmentosa**, ►**lipofuscin**, ►**phagosome**, ►**fluorophore**

Start: ►**cell cycle**

Start Codon: AUG in RNA that specifies either formylmethionine (in prokaryotes) or methionine (in eukaryotic cells). Note that the Met codon in mitochondria varies in different organisms. In some organisms other triplets may also initiate translation. ►**genetic code**

Start Point: The position in the transcribed DNA where the first RNA nucleotide is incorporated. ►**transcription**

Stasis: An equilibrium state without change.

STATs (signal transducers and activators of transcription): Cytoplasmic proteins, which become activated by SRC (SH2, SH3) mediated phosphorylation of tyrosine at around residue 700 and serine residues at the C-terminus through the action of Jak kinases, which are receptors for cytokine signals and enzymes at the cytosolic termini. PDGF, EGF and CSF catalyze phosphorylation also. The latter process requires the action of the 42 kDa MAPK or ERK2. Stat 1 mediates reactions to microbial and viral infections. Stat4 protein is essential for interleukin-12 mediated functions such as the induction of interferon- γ , mitogenesis and T lymphocyte killing and helper T lymphocyte differentiation. Disruption of STAT 2 & 3 cause embryonic lethality. Synthetic Sta3-inhibitory peptide (corresponding of the Tyr⁷⁰⁵ phosphorylation site of immunoglobulin G) reduced embryo transplantation by 70%. Normally phosphorylation of the luminal epithelium of the uterus by LIF (leukemia inhibitory factor) is required for implantation (Catalano RD et al 2005 Proc Natl Acad Sci USA 102:8585). STAT 5A & B are required for breast development in mice, and for the stimulation of T cell proliferation. Stat5 tetramerization is associated with

leukemogenesis (Moriggi R et al 2005 Cell Metab 1:87). Stats 1, 3, 4 recognize and activate different genes by binding to the TTCC(C/G)GGAA(TTN5AA) sequences. Rac1 GTPase may regulate STAT 3 activation through phosphorylation. Stat6 prefers TTN6AA. Cooperative binding of Stats makes possible the recognition of variations at the different binding sites. The sequence-selective recognition resides in their amino terminal domains. In humans, there are at least seven STAT genes encoding proteins of 750 to 850 amino acids. The 130-amino-terminal residues bind to multiple sites in the DNA. Residues 600–700 are homologous to SH2 domains and mediate dimerization. Disruption of Stat activity leads to the loss of interferon-controlled immunity to pathogens. STAT genes can be found in mouse (m) and human (h) chromosomes: STAT1, STAT4: m 1, h 2q12-q33, STAT 3, STAT 5A & B m 11, h 12q13-q14-1, STAT 2 & 6: m 10, h 17q11.1-q22. Stat genes occur also in *Drosophila* and *Dictyostelium*.

The PIAS family of proteins includes negative regulators of STATs. Stat3 is active in many tumors, including breast cancer. It probably activates Bcl2 protein and is thus anti-apoptotic. Sta-21 protein inhibits breast cancer cells by reducing Stat3 binding to DNA (see Fig. S116) (Song H et al 2005 Proc Natl Acad Sci USA 102:4700). ▶signal transduction, ▶Jak-STAT pathway, ▶signal transduction, ▶SRC, ▶lymphocytes, ▶leptin, ▶PDGF, ▶EGF, ▶CSF, ▶SH2, ▶SH3, ▶SSI-1, ▶interferon, ▶RAC, ▶Bcl2, ▶apoptosis, ▶STAGE; Davey HW et al 1999 Am J Hum Genet 65:959; Naka T et al 1999 Trends Biol Sci 24:394; Levy DE, Darnell JE 2002 Nature Rev Mol Cell Biol 3:651; Dupuis S et al 2003 Nature Genet 33:388.

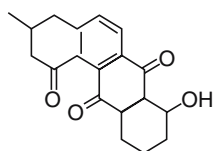


Figure S116. STA-21

Stathmin (op18): Regulates microtubule polymerization by affecting tubulins. The activity of Stathmin is controlled through phosphorylation by chromatin. Stathmin expressed in the amygdala of the brain modulates the psychological responses of innate and learned fear in mice (Shumyatsky GP et al 2005 Cell 123:697). ▶spindle; Gavet O et al 1998 J Cell Sci 111:3333; Charbaut E et al 2001 J Biol Chem 276:16146; Niethammer P et al 2004 Science 303:1862.

Stathmokinesis: Mitotic arrest. ▶spindle poison

Statins: Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, an important enzyme of

cholesterol biosynthesis. Cholesterol-lowering drugs reduce the incidence of Alzheimer disease too. Statins are useful also for the treatment of hypertension and autoimmune diseases by inhibiting MHC class II molecules and by shifting from T_h1-type pro-inflammatory cytokines to T_h2-type cytokines. ▶cholesterol, ▶lovastatin, ▶SREBP, ▶Alzheimer disease, ▶autoimmune disease, ▶MHC, ▶T_h, ▶cytokine; Fassbender K et al 2001 Proc Natl Acad Sci USA 98:5856.

Stationary Phase: The population size is maintained without increase or decrease. At this stage the genetic material may not replicate and the mutations occurring in bacteria are expected to be due to recombination. Mutation (chromosome breakage) in the stationary phase cells of higher eukaryotes may be one of the causes of cancer. ▶growth curve; Bull HJ et al 2001 Proc Natl Acad Sci USA 98:8334.

Stationary Renewal Process: An assumption—based on a paper of R.A. Fisher (1947 Phil Trans Roy Soc B 233:55)—that crossing over is formed as a regular sequence starting from the centromere and the length between two adjacent crossovers always following the same distribution. The idea that crossing overs begin at the centromere and proceed toward the telomere turned out to be incorrect yet the stationary renewal process gained entry into several later models of recombination, interference and mapping functions. ▶mapping function; Zhao H, Speed TP 1996 Genetics 142:1369.

Statistic: An estimate of a property of an observed set of data (e.g., mean) that bears the same relation to the data as the parameter does to the population. ▶statistics

Statistics: A mathematical discipline that assists in collecting and analyzing data; guides to make conclusions and predictions based on the analysis and reveals their trustworthiness by determining probability or likelihood. Authors with inadequate training in this discipline might have incorrectly used statistical procedures in some published papers (Giles J 2006 Nature [Lond] 443:379; ▶fluctuation test). Classical genetic analyses usually require statistical methods. Statistics is used for collections of facts on demography, industrial productivity, trade, etc., such as in statistical yearbooks. Statistics cannot replace the need for sound biological data (Spence MA et al 2003 Am J Hum Genet 72:1084). *Sufficient statistics* reduces the information to that needed for the parameter of interest and avoids nuisance parameters. ▶probability, ▶Bayes' theorem, ▶likelihood, ▶maximum likelihood, ▶non-parametric tests, ▶inference statistical, ▶nuisance parameter; Robbins LG 2000 Genetics

154:13; assistance for the use of the most frequently needed statistical procedures: <http://faculty.vassar.edu/~lowry/VassarStats.html>; <http://www.ruf.rice.edu/~lane/rvls.html>.

Statistical Mechanics: Extrapolates from the microscopic structure to macroscopic features.

Statolith: Granules that are believed to sense gravity in cells. ► [gravitropism](#)

Stature in Humans: Influenced by environmental causes such as nutrition, disease, and injuries, by the use of various medications and by simple or complex genetic factors. Heritability of human height commonly exceeds 80%. Prenatal anomalies of bone length may be determined by prenatal diagnosis. QTL analysis (Hirschorn JN et al 2001 Am J Hum Genet 69:106) of Scandinavian and Canadian populations involving 2327 individuals revealed linkage of height to 6q24-q25 (lod score 3.85), 7q31.3-q36 (lod score 3.40), 12p11.2-q14 (lod score 3.35), 13q32-q33 (lod score 3.56) and 3.26 (lod score 3.17, Wiltshire S et al 2002 Am J Hum Genet 70:543). The most common types of genetically determined human dwarfism and other defects involving reduced stature are: achondroplasia, hypochondroplasia, achondrogenesis, osteochondromatosis, dyschondrosteosis, Russel-Silver syndrome, Smith-Lemli-Opitz syndrome, Opitz-Kaveggia syndrome, dwarfism, SHORT, Aarskog syndrome, Noonan syndrome, Hirschsprung disease, Turner syndrome, Trisomy, Mulibrey nanism, hairy elbows, Pygmy. ► [growth hormone](#), ► [growth retardation](#), ► [limb defects](#), ► [exostosis](#), ► [regression](#), ► [lod score QTL](#)

STC (sequence-tagged connector): ► [genome project](#)

STCH: ► [Hsp70](#)

STE (sterile): Proteins are pheromone receptors and scaffolding proteins, and coordinate and organize the signal transduction paths in budding yeast. Ste3 and Ste2 are receptors of the α and a mating type factors, respectively. Ste7 is MAPKK, Ste4 is the β subunit, Ste18 is the γ subunit of the G trimeric proteins, Ste5 is a member of the MAPK cascade, Ste11 is MAPKKK, Ste 20 is a PAK/MEKKK protein and it is required for the MAPK activation of G $\beta\gamma$. A Ste20-like protein kinase Mst regulates chromatin structure and apoptosis. Ste12 is a transcription factor. In fission yeast, the homologs *Byr* are extra-cellular signal regulated kinase homologs of MEK and ERK. (The *Ste* [*Stellate*, 1–45.7] locus of *Drosophila* encodes protein crystals in the primary oocytes). ► [signal transduction](#), ► [G proteins](#), ► [pheromones](#), ► [MAPK](#), ► [MEK](#), ► [MEKK](#), ► [MP1](#), ► [FUS3](#), ► [KSS1](#), ► [PAK](#), ► [mating type determination in yeast](#); Graves JD et al 2001 J Biol Chem

276:14909; Ura S et al 2001 Proc Natl Acad Sci USA 98:10148; Ge B et al 2002 Science 295:1291.

Steady State: In a reaction enzyme-substrate concentration and other intermediates appear constant over time but input and output are in a flow.

Steel Factor (stem cell factor): A 40–50 kDa dimeric protein produced by the bone marrow and other cells and migrates to the hematopoietic stem cells. Its receptor is a transmembrane protein tyrosine kinase. ► [cell migration](#), ► [hematopoiesis](#), ► [tyrosine kinase](#), ► [microphthalmos](#), ► [Kit oncogene](#), ► [stem cell factor](#)

Steer: An emasculated bovine male animal. ► [emasculation](#)

Steinernema carpocapsae: A nematode. ► [Caenorhabditis](#), ► [Xenorhabdus](#)

Steinert Disease (dystrophia myotonica 1, 19q13.2-q13.3): Dominantly inherited diseases affecting different tissues and it is caused by duplication of the CTG triplet in the DNA. ► [myotonic dystrophy](#)

Stele: The core cylinder of vascular tissues in plant stems and roots. ► [root](#)

Stem Cell Factor (SCF/M-CSF, 5q33.2-q33.3): Required for the normal development of B lymphocytes. The Kit oncogene product is its receptor. ► [lymphocytes](#), ► [B cells](#), ► [Kit oncogene](#), ► [M-CSF](#); Broudy VC 1997 Blood 90:1345; Smith MA et al 2001 Acta Haematol 105:143.

Stem Cells: Stem cells of animals are not terminally differentiated, can divide without limit and when they divide the daughter cells, can remain stem cells or terminally differentiate in one or more ways (Hock H, Orkin SH 2005 Nature 435:573), or they may have a restricted potential for differentiation (*transit amplifying cell*) and with time only produce differentiated cells. When human embryonic stem cells (hESC) were encapsulated in (3D HA) hyaluronic hydrogels (but not within other hydrogels or in monolayer cultures on HA), hESCs maintained their undifferentiated state, preserved their normal karyotype, and maintained their full differentiation capacity (Gerecht S et al 2007 Proc Natl Acad Sci USA 104:11298). Among the 300–500 stem cell lines (existing in 2007), 59 human embryonic stem cell lines from 17 laboratories worldwide were characterized. The lines were not identical, however, and differences in expression of several lineage markers were evident, and several imprinted genes showed similar allele-specific expression patterns, but some gene-dependent variation was observed. Some female lines expressed readily detectable levels of XIST, whereas others did not. No significant contamination of the lines with mycoplasma, bacteria

or cytopathic viruses was detected. Despite diverse genotypes and different techniques used for derivation and maintenance, all lines exhibited similar expression patterns for several markers of human embryonic stem cells (International Stem Cell Initiative 2007 Nature Biotechnol 25:803). Differentiation could be induced within the same hydrogel by simply altering soluble factors. Mammalian embryonic stem cells, derived from the inner cell mass of the blastocyst, are considered *pluripotent*, i.e., endowed with the potential to develop any type of cells under appropriate conditions. Pluripotency of embryonic stem cells is mediated by transcription factors Oct4, Sox2 and NANOG, which co-occupy substantial portion of their target genes, encoding mainly other transcription factors and by transcriptional regulatory circuits maintain the cell's self-renewal (Boyer LA et al 2005 Cell 122:947; Wang J et al 2006 Nature [Lond] 444:364). Nanog expression in mouse is upregulated in embryonic stem cells by binding brachyury (T) and STAST3 to its enhancer element. Nanog then blocks bone morphogenetic protein-induced differentiation of mesoderm by interacting with Smad1 and interfering with the recruitment of co-activators to the Smad transcriptional complexes (Suzuki A et al 2006 Proc Natl Acad Sci USA 103:10294). Under conditions of culture suitable for embryonic stem cells, adult mouse fibroblasts required Oct3/4, Sox2, c-Myc and Klf4 for the formation of pluripotent stem cells but Nanog was not necessary. These induced pluripotent stem cells (iPS) caused tumors in nude mice containing tissues from all three germ layers. When iPS was injected into blastocysts, mouse embryonic development ensued (Takahashi K, Yamanaka S 2006 Cell 126:663). Laser-assisted injection of ES cells into eight-cell-stage embryos efficiently generates viable and healthy mice that contain no more than 0.1% host cell contamination. These mice, derived from either heterozygous or homozygous mutant ES cells, can be used directly in phenotypic analyses. The mutant phenotypes in these mice are indistinguishable from those observed in mice derived by conventional breeding (Poueymirou WT et al 2007 Nature Biotechnol 25:91).

An important development in stem cell research is the simultaneous and independent discovery of new methods for the production of pluripotent stem cells from adult somatic cells. These methods apparently obviate the need for using human embryos to which moral, ethical and legal objections exist. Furthermore the technology required for harvesting and processing human eggs has several impediments. The new methods reprogram somatic cell nuclei to an undifferentiated state by the introduction of four transcription factors Oct4, Sox2, Nanog and Lin28 (Yu J et al 2007 Science 318:1917) or Oct3/4, Sox2, Klf4 and

c-Myc (Takahashi K et al 2007 Cell 131:861). In both sets of experiments the results were comparable to that obtainable by embryonic stem cells in cell morphology, proliferation, surface antigens gene expression, epigenetic status of pluripotent cell-specific genes and telomerase activity. The reprogrammed cells have the ability to differentiate into all three primary germ layers or form teratomas and appear suitable for all the uses embryonic stem cells. One cautionary note: the somatic cells (skin fibroblasts) were transformed by a retroviral vector containing a mouse viral receptor (Sic7a1). The vector integrated into more 20 sites of the human chromosomes and increased the risk of tumorigenesis by more than 20% in mice. The c-Myc reactivation might have been the major cause of the problem. c-Myc may not be absolutely necessary and other constructs can be used; the report in Science actually does not use it. The technical problems will certainly be ironed out in the future.

Identification of stem cells requires appropriate cell autonomous markers that distinguish them from other cells in a tissue. Only a few of such markers have been found and they seem to suppress translation as a means of preventing their differentiation (Siddall NA et al 2006 Proc Natl Acad Sci USA 103:8402).

It appears that in *Drosophila*, the double-stranded RNA processing enzyme (Dicer) controls stem cell development in as much as microRNAs are required for the germline stem cells to bypass the G1/S checkpoints and maintain ability for continuous cell division (Hatfield SD et al 2005 Nature [Lond] 435:974). They occur in various tissues. *Drosophila* ovarian germ cells may dedifferentiate into stem cells (Kai T, Spradling A 2004 Nature [Lond] 428:564). In *Drosophila* ovaries ISWI chromatin remodeling protein controls germline stem cell status maintenance whereas in the ovarian somatic stem cells the DOM chromatin remodeling factor is critical (Xi R, Xie T 2005 Science 310:1487). Adult mouse ovaries can rapidly generate hundreds of oocytes despite the small number of germ cells. Spermatogonial stem cells of adult mouse testis also display pluripotency in 27% and acquire embryonic stem cell properties (Guan K et al 2006 Nature [Lond] 440:1199). Bone marrow transplantation restores oocytes production in chemosterilized or ataxia telangiectasia mutated gene-deficient sterile animals. Also, oocytes carrying donor-derived genetic markers were detected after peripheral blood transplantation (Johnson J et al 2005 Cell 122:303). The conclusions of the Johnson et al 2005 paper have been questioned (Powell K 2006 Nature [Lond] 441:795, ► [oocyte primary](#)). Although some studies indicate karyotypic stability in stem cell cultures (Amit M et al 2000 Dev Biol 227:271), more recently aneuploidy (gain of human chromosomes 17q and 12) has been observed (Draper JS et al 2004

Nature Biotechnol 22:63). Spontaneous mutation rate/nucleotides in embryonic stem cell cultures after repeated passage is $\sim 10^{-9}$ and the alterations may involve also genomic copy number (45%), mtDNA sequence (22%) and promoter methylation (90%). These mutations may or may not have serious consequences depending on their selective value (Maitra A et al 2005 Nature Genet 37:1103).

Stem cells, by definition, are expected to multiply in an undifferentiated state, besides giving rise to specialized cells, in practice, after a period of time they undergo aging and decline (see Fig. S117). In mouse embryonic stem cells both X chromosomes are demethylated or have reduced methylation and this indicates that both X chromosomes are active although one is frequently lost (Zvetkova I et al 2005 Nature Genet 37:1274). A chromosome 2 (odd ratio 4.4) factor of mouse controls aging of hematopoietic stem cells. Apparently, inadequate DNA repair is responsible for the process (Geiger H et al 2005 Proc Natl Acad Sci USA 102:5102).

The gene expression profile in embryonic, neural and hematopoietic stem cells displays some overlaps yet distinct specificities are also evident (Ramalho-Santos M et al 2002 Science 298:597; Ivanova NB et al 2002 Science 298:601). More recent data indicate that embryonic stem cells obtained by fertilization or nuclear transfer are functionally equivalent (Brambrink T et al 2006 Proc Natl Acad Sci USA 103:933). The favorable environment (niche) of hematopoietic stem cells was located to the surface of the bone marrow at the surface of the cancellous (spongy) material of the trabeculae ossis (anastomosing spicules of the bones). At this location, the number of spindle-shaped, N-cadherin⁺-CD45⁻ osteoblasts positively correlates with the number of hematopoietic stem cells (Zhang J et al 2003 Nature [Lond] 425:836). Notch activation is required for the increase

of osteoblast number (Calvi LM et al 2003 Nature [Lond] 425:841). The frequency of hematopoietic and epidermal stem cells within these tissues is $\sim 1 \times 10^{-4}$ (Schneider TE et al 2003 Proc Natl Acad Sci USA 100:11412). Cryopreserved hematopoietic cord blood stem cells may remain functional after 15 years of storage (Broxmeyer HE et al 2003 Proc Natl Acad Sci USA 100:645). Umbilical cord blood is rich in hematopoietic and other stem cells are gaining increasing attention especially for HLA-mismatched recipients (Newcomb JD et al 2007 Cell Transplant 16:150). Human umbilical cord blood hematopoietic stem/progenitor cells transplanted in utero into mouse may differentiate into human hepatocyte-like cells with evidence of the expression of human hepatocyte-specific proteins as well as partially repair or protect liver damage induced by CCl₄ (Qian H et al 2006 Int J Mol Med 18:633). Pre-immune fetus develops a no injury human-rat xenograft in which the in utero transplantation of low-density mononuclear cells (MNCs) from human umbilical cord blood (hUCB) into fetal rats at 9–11 days of gestation led to the formation of human hepatocyte-like cells (hHLCs) with different cellular phenotypes (Sun Y et al 2007 Biochem Biophys Res Commun 357:1160).

Several investigators reported that the bromodeoxyuridine or other nucleoside (analog)-labeled bone marrow cells transplanted into mouse brains transformed into new neurons and supporting glial cells (e.g., Kopen GC et al 1999 Proc Natl Acad Sci USA 96:10711). These findings may be flawed (Burns TC et al 2006 Stem Cells 24:1121), however, because the original bone marrow cells so labeled may decay and other cells can pick up the label or even cell markers and the observations may be misleading (Kuan C-Y et al 2004 J Neurosci 24:10763).

Embryonic mouse stem cells differentiate into T lymphocytes in vitro if co-cultured with OP9 cells with the Notch receptors engaged by Delta-like 1 ligand. The T cells are functional in immunodeficient mice (Schmitt TM et al 2004 Nature Immunol 5:410). Also, human embryonic stem cells, transferred into human thymic tissue growing in immunodeficient mouse, resulted in the differentiation of T lymphoid cells that appeared functional by being able to express appropriate markers (Galic Z et al 2006 Proc Natl Acad Sci USA 103:11742). Adult neural stem cells may differentiate into cells of diverse germ layers with broad developmental potentials. The balance between self-renewal of stem cells and differentiation seems to be determined by the signal receptors or their phosphorylation in the neighboring cells. In the ovaries of mammals, the initial stem cells are arrested after a finite number of divisions and then enter into meiotic prophase. Functionally they resemble the meristem in plants. The *embryonic germ cells* (EG)



Figure S117. Blastocyst

have been used for transfer into mouse blastocysts and are capable to differentiate into most types of fetal tissues, including the germline.

Oocyte differentiation takes place in vitro in mouse embryonic stem cell medium in the presence of Oct4 transcription factor. Follicular structures are formed and blastocyst-like structures were observed. After 16 days, the oocytes were ready for meiosis but did not proceed beyond prophase (Hübner K et al 2003 Science 300:1251). Mouse embryonic stem cells, however, differentiated into primordial germ cells, erased methylation, characteristic for *Igf-2* and *H19* gene methylation in imprinting, and developed into haploid male gametes and were capable of—apparently normal—fertilization of eggs (Geijsen N et al 2004 Nature [Lond] 427:148). From embryonic stem cells the regeneration of viable, fertile adults, using tetraploid embryo complementation, has been reported (Eggan K, Jaenisch R 2003 Methods Enzymol 365:25).

The synthetic heterocyclic compound, SC1, permits the propagation of murine embryonic stem cells in an undifferentiated, pluripotent state under chemically defined conditions in the absence of feeder cells, serum, and leukemia inhibitory factor. Long-term SC1-expanded murine ES cells can be differentiated into cells of the three primary germ layers in vitro and can generate chimeric mice and contribute to the germ line in vivo. Biochemical and cellular experiments suggest that SC1 works through dual inhibition of RasGAP and ERK1 (Chen S et al 2006 Proc Natl Acad Sci USA 103:17266).

Sterile, hermaphrodite male mouse could produce fertile offspring when nuclear transfer cells were injected into normal, diploid blastocysts. Many of the offspring were chimeric but one was found, which transmitted genes from the sterile hermaphrodite to fertile daughters and thus overcame the problem of the “father,” which originally lacked germ cells (Wakayama S et al 2005 Proc Natl Acad Sci USA 102:29). The feasibility of culturing pluripotent (endoderm, mesoderm, ectoderm) human embryonic stem cells (ES) opens new potential for the generation of tissues (Smith AG 2001 Annu Rev Cell Dev Biol 17:435). They may be used for the purpose of transplantation and study and treat neurodegenerative diseases (Jakel RJ et al 2004 Nature Rev Genet 5:136), spinal cord injuries, liver diseases, diabetes, immunological diseases, cancer and find means for the repopulating of hematopoietic cells, etc. (Krause DS et al 2001 Cell 105:369). Human central nervous system cells grown as neurospheres survive, migrate and express differentiation markers for neurons and oligodendrocytes after long-term engraftment in mice with spinal cord injuries. Locomotor activity was also restored (Cummings BJ et al 2005 Proc Natl Acad Sci USA 102:14069).

Stem cells derived from another individual may lead to adverse immune reaction. Neural stem cells repeatedly provided protection against inflammation of the central nervous system of mouse with an immune-like mechanism (Pluchino S et al 2005 Nature 436:266). Allogeneic, hematopoietic bone marrow cell transplantation into host cells treated by ionizing radiation or other immunosuppressive techniques, however, may become permanently tolerant of the foreign stem cells. The intolerance to a third-party donor, however, is not entirely solved (Sykes M, Nikolic B 2005 Nature [Lond] 435:620).

The immunological intolerance can be prevented when blastocysts formed from donated human oocytes (preferably by less than 30 years old donors) are used into which the nucleus of potential female or male recipient's own skin cells is transferred. The blastocysts were generated by this nuclear transfer by an average of ~24% success. The immunological identity of the stem cells to that of the donor was confirmed. In addition, this newer procedure solved another problem, i.e., rather than using mouse feeder cells it employed human feeders (Hwang WS et al 2005 Science 308:1777). These developments may assure progress toward medical use of embryonic stem cells. Some of the results, unfortunately, have been questioned and there is evidence on faking and fabricating some or much of the data. Authors have withdrawn the paper after an international uproar (Kennedy D 2006 Science 311:36) and on 20 January 2006, the Editor withdrew the invalid papers of this research group (Kennedy D 2006 Science 311:335).

The production of embryonic stem cells by somatic nuclear transfer into oocytes remained unsuccessful for primates. The failure has been attributed to an effect of the nuclear spindle in the oocyte due to maturation factor deficiency that prevented proper reprogramming of the introduced nucleus. Complete removal of the meiotic spindle from the karyoplasts was a key factor for reprogramming. Then the donor fibroblast nuclei were introduced into cytoplasts by electrofusion, incubated for 2 h to allow nuclear remodeling to occur, and subsequently activated and cultured to the blastocyst stage and 16% (35 out of 213) blastocyst formation took place. This new protocol prevented premature cytoplasm activation and maturation promoting. The rate of successful development of stem cells was relatively low but their quality appeared identical to that of embryonic stem cells. Factor decline resulted in robust nuclear envelope breakdown and premature chromosome condensation and in significantly increased blastocyst development in *Macaca mulatta* monkeys.

The earlier failures were attributed to the detrimental effect of fluorochrome bisbenzimidazole (Hoechst

33342) and ultraviolet on the relatively transparent primate oocyte. The dye and the UV light were used for the removal of the spindle. These factors apparently reduced cytoplasmic mitochondrial DNA function. The rate of successful development of stem cells was relatively low, 0.2–3.4% per oocyte and 4–10% per blastocyst but their quality appeared identical to that of embryonic stem cells (Byrne JA et al 2007 *Nature [Lond]* 450:497).

In mouse pluripotent embryonic stem cells were generated from blastocysts, which were deficient in the *Cdx2* transcription factor. Such blastocysts—generated by nuclear transfer—were unable to form functional trophoblast, necessary for the development of the implanted embryo but formed normal internal cell mass, a suitable source for pluripotent embryonic stem cells. This procedure was named ANT (for altered nuclear transfer). The mouse model thus excluded the development of embryos from the blastocysts yet provided good source of pluripotent stem cells overcoming the ethical objections—in case of humans—to destroying and manipulating embryos (Meissner A, Jaenisch R 2006 *Nature [Lond]* 439:212). Withdrawing single cells from mouse blastomeres or using trophoblast cells permits the normal development of the embryo and the isolated cells form embryonic stem cell lines with pluripotent capabilities (Chung Y et al 2006 *Nature [Lond]* 439:216). Arrested human embryos can express pluripotency marker genes such *OCT4*, *NANOG* and *REX1* and others, and can differentiate under in vitro and in vivo conditions into three germ layers. All the new lines derived from late arrested embryo have normal karyotype. Such stem cells may obviate the need for using normal embryonic stem cell lines (Zhang X et al 2006 *Stem Cells* 24:2669). Undifferentiated amniotic fluid stem cells (AFS) cells expand extensively without feeders, double in 36 h and are not tumorigenic. Lines maintained for over 250 population doublings retained long telomeres and a normal karyotype. AFS cells are broadly multipotent. Clonal human lines verified by retroviral marking were induced to differentiate into cell types representing each embryonic germ layer, including cells of adipogenic, osteogenic, myogenic, endothelial, neuronal and hepatic lineages (De Coppi P et al 2007 *Nature Biotechnol* 25:100).

Cells derived from single human blastomeres display the characteristics of embryonic stem cells and the biopsies show normal differentiation (Klimanskaya I et al 2006 *Nature [Lond]* 444:481). Adult bone marrow co-purifying with mesenchymal stem cells when injected into early blastocysts can develop into most types of cells (Jiang Y et al 2002 *Nature [Lond]* 418:41). (The results of this paper by Catherine Verfaillie laboratory was difficult to replicate by

other laboratories because of the complicated technique used [*Nature* 442:344] and there are some errors in details but the main conclusions seem valid) (Check E 2007 *Nature [Lond]* 447:763). Bone-marrow-derived stem cells regenerate into liver cells primarily after fusion with hepatocytes (Vassilopoulos G et al 2003 *Nature [Lond]* 422:901). There is evidence that bone marrow-derived stem cells develop into neurons, cardiomyocytes (heart muscle cell) and liver cells by fusion rather than by a transdetermination type mechanism (Alvarez-Dolado M et al 2003 *Nature* 425:968). Recent studies could not confirm the transdifferentiation of hematopoietic stem cell into cardiac myocytes (Murry CE et al 2004 *Nature [Lond]* 428:664; Balsam L et al *ibid.* p 668). Bone marrow-derived mesenchymal stem cells—despite their allogeneic origin—successfully repaired damage inflicted by myocardial infarction when administered through a catheter intra-myocardially in pigs, closely following the time (three days after) of the infarction. The procedure provided good healing without rejection (Amado LC et al 2005 *Proc Natl Acad Sci USA* 102:11474). Steel factor positive bone marrow-derived stem cells can repair the heart muscles by neovascularization and myogenesis after myocardial infarction in mice (Ayach BB et al 2006 *Proc Natl Acad Sci USA* 103:2304). Pluripotent murine stem cells can be converted to adipocyte lineage by bone morphogenetic protein (BMP-4) if methylation is prevented (Bowers RR et al 2006 *Proc Natl Acad Sci USA* 103:13022). A complex differentiation process converts human embryonic stem cells to endocrine cells capable of synthesizing the pancreatic hormones insulin, glucagon, somatostatin, pancreatic polypeptide and ghrelin. This process mimics, in vivo, pancreatic organogenesis by directing cells through stages resembling definitive endoderm, gut-tube endoderm, pancreatic endoderm and endocrine precursors to cells that express endocrine hormones (D'Amour KA et al 2006 *Nature Biotechnol* 24:1392).

Normal embryonic stem cells, however, can rescue mouse embryos with cardiac defects because of being deficient in the *Id* proteins, which are dominant antagonists of basic helix-loop-helix transcription factors (Fraidenraich D et al 2004 *Science* 306:247). Some postnatal rodent cardioblasts can develop into fully differentiated cardiomyocyte lines (Laugwitz K-L et al 2005 *Nature [Lond]* 433:647). Cardiac stem cells ameliorated myocardial infarction when delivered by intravascular injection in rats (Dawn B et al 2005 *Proc Natl Acad Sci USA* 102:3766) and similar observations were made in dogs (Linke A et al 2005 *Proc Natl Acad Sci USA* 102:8966). Using adenoviral virus-derived vectors and homologous recombination, defects in hypoxanthine phosphoribosyl transferase mutations could

be corrected at high efficiency in mouse embryonic stem cells by random integration within and between genes (Obhayashi F et al 2005 *Proc Natl Acad Sci USA* 102:13628).

On polymer scaffolds the development of three-dimensional structures may be facilitated (Levenberg S et al 2003 *Proc Natl Acad Sci USA* 100:12741). It is conceivable that co-transplantation of hematopoietic stem cells and stem cell for other tissues using the same donor may become feasible. In order to maintain stem cells in culture in the pluripotent state, transcription factor Oct4 and the leukemia inhibitory factor (Lif), both must be expressed. When Lif is withdrawn various types of differentiation may begin. TCF and LEF may also be important. Actually this may be regarded as a teratocarcinoma type of growth. Hypoxia (ca. 5% oxygen)—rather than normal atmospheric conditions (21% O₂)—favors the maintenance of the embryonic, pluripotent stem cell state (Ezashi T et al 2005 *Proc Natl Acad Sci USA* 102:4783).

In order to force the cells into a specific type of differentiation appropriate and special culture conditions must be established. In bone marrow-derived stem cells the presence of mesenchymal stem cells, sonic hedgehog and retinoic acid signals synergistically promote the differentiation glutamatergic sensory neuron markers (Kondo T et al 2005 *Proc Natl Acad Sci USA* 102:4789). Retinoic acid, insulin (triiodothyronine) passage may lead to the differentiation of adipocytes. Employing c-Kit (a transmembrane tyrosine kinase) + Erythropoietin may lead to the development of erythrocytes. Macrophage colony stimulating factor + IL-3, IL-1 lead to the differentiation of macrophages. Fibroblast growth factor and epidermal growth factor combinations coax the ES culture to form astrocytes and oligodendrocytes. There will be a potential for genetically engineering embryonic stem cells (ES) for special medical purposes. Undifferentiated mouse ES cells may become tumorigenic, developing into teratomas or teratocarcinomas when introduced into an animal. A rich source of embryonic stem cells is the umbilical cord at birth. Epithelial cells, hair follicles, intestinal epithelium, multipotent brain cells, hematopoietic cell may be employed as potential ES. The full clinical exploitation of stem cell technology requires technical improvements (Humpherys D et al 2001 *Science* 293:95).

On 19 December 2000, the British Parliament approved greater freedom in embryonic stem-cell research (Ramsay S 2000 *Lancet* 356:2162). On 15 June 2006, the parliament of the European Union voted for lifting the ban on funding for human embryonic stem cells (Vogel G 2006 *Science* 312:1732). In the U.S., human embryonic stem cell research can be funded by government agencies only

on the existing ca. 60 cell lines (9 August 2001). Many research workers are dissatisfied with this restriction. Although embryonic stem cells are supposed to have the potential to develop into any kind of differentiated cells—in fact, there are differences among embryonic stem cells because practically no two human beings are genetically identical—therefore, there is a need for the development of additional embryonic cell lines. (Monozygotic twins may not remain entirely identical genetically because of epigenetic changes during development). Stem cell research, thus, face great promises and great challenges; some of the problems are biological, others are ethical and regulatory. It is unfortunate that ethicists and public policy makers are not fully aware of the biology and some of the research workers are inclined to take political stands. The objection against the use of human embryonic stem cells (and destroying human embryos) could be eliminated if appropriate and effective means would be available for reprogramming somatic cells to embryonic state. One recent investigation fused human fibroblasts (2n = 46) with pluripotent embryo cells (2n = 46) into 92-chromosome cells, successfully securing their proliferation as reprogrammed somatic hybrid cells. Both component cells were appropriately marked and their fusion was verified. Similarly the embryonic state of the fusion product was established. This procedure of reprogramming would be of great significance if the chromosome number could be reduced to the normal level (2n = 46). Unfortunately, this is still a formidable obstacle to overcome (Cowan CA et al 2005 *Science* 309:1369).

There are many technical problems with human embryonic stem cell cultures because they—unlike mouse embryonic stem cells—require mouse fibroblast feeder cells and a lipid-rich bovine serum (ALBUMAX) for maintenance of stem cell condition. It appears that human cells take up from the animal products *N*-glycosyl neuraminic acid, which may cause rejection in humans if transplanted. In addition, the animal medium may transmit viruses of potential health hazard.

The mouse cells also require LIF (leukemia inhibitory factor). LIF binds a LIF receptor and glycoprotein 130, which activate the Jak/Stat3 signaling pathway sustaining the cells in undifferentiated state. These factors, however, are not sufficient for human embryonic stem cells. Human stem cells need FGF2 (fibroblast growth factor) and noggin (an inhibitor of bone morphogenetic protein, BMP) in addition to serum, to keep the human stem cells in undifferentiated state. This new medium is, however, a substantial progress in developing useful human stem cell cultures (Xu R-H et al 2005 *Nature Methods* 2:185).

No human embryos are supposed to be generated for the purpose of extracting stem cells or no fertilized and unused eggs generated by the process of in vitro artificial fertilization should be used for stem cell research. The objection to stem cell research originates from the belief that life begins at fertilization and extracting embryonic stem cells from 4–5 days old blastomeres amounts to violation of the sanctity of life (►ensoulment). The ethical problems may be dispelled if somatic stem cells occurring in placental, umbilical or fat tissues are used. Another, albeit tenuous, possibility is to generate blastomeres by inserting diploid somatic nuclei into enucleated human eggs and cloning them. Transplantation of nuclei harboring human disease genes into oocytes may make it possible to generate large quantities of embryonic tissues for laboratory studies of the mechanism and potentially the treatment of the disease. Not all cells originate from stem cells as some terminally differentiated animal cells may retain significant proliferative capacity (Dor Y et al 2004 *Nature [Lond]* 429:41). Stem cell antigen (Sca-1) is expressed in a small fraction of various cells such as of hematopoietic tissue, cardiac tissue, mammary gland, skin, muscle, testis, murine prostatic duct and the anti-apoptotic protein Bcl-2 may protect them to survive. The expression of Sca-1 and Bcl-2 may help in isolation and enriching the stem cell populations for therapeutic purposes (Burger PE et al 2005 *Proc Natl Acad Sci USA* 102:7180). Post-natal muscle-derived stem cells maintained proliferating ability for 300 doublings and displayed regenerating ability after transplantation into a mouse model of Duchenne muscular dystrophy even after 200 doublings. After that lower muscle regeneration occurred and loss of CD34 expression and loss of myogenic activity were observed. Nevertheless, this appeared a remarkable long-term self-renewal for non-embryonic stem cells (Deasy BM et al 2005 *Mol Biol Cell* 16:3323).

The exact mechanisms of the differentiation from stem cells into specific somatic cells are not entirely clear, yet compelling evidence is available for some cases of effectiveness in clinical applications. Therefore, continued research is indispensable (Quesenberry PJ et al 2005 *Science* 308:1121). In 2007, three laboratories succeeded to some extent in producing pluripotent stem cells without the use of eggs or embryos by applying specific transcription factors in culture introduced into cells by viral vectors (Okita K et al 2007 *Nature [Lond]* 448:313; Wernig M et al 2007 *Nature [Lond]* 448:318; Maherali M et al 2007 *Cell Stem Cell* 1:55). Unlike interphase zygotes, mouse zygotes temporarily arrested in mitosis can support somatic cell reprogramming, the production of embryonic stem cell lines and the

full-term development of cloned animals. Thus, human zygotes and perhaps human embryonic blastomeres may become useful for stem cell research (Egli D et al 2007 *Nature [Lond]* 447:679). Earlier researchers concluded (McGrawth J, Solter D 1984 *Science* 226:1317) that nuclei transferred to enucleated zygote cannot support development in vitro.

There are various ethical and moral problems in transplantation of human neural stem cells into animals, particularly into non-human primates. These brain cells may alter the cognitive development of animals, particularly if the implantation takes place at early embryonal or post-natal periods (Greene M et al 2005 *Science* 309:385). To overcome the objections against the use of human embryonic stem cells and avoid the adverse immunological reactions to foreign cells, in 2007, pluripotent human embryonic stem cell (hESC) lines were obtained from blastocysts of parthenogenetic origin. Parthenogenesis was chemically induced. The parthenogenetic human embryonic stem cells (phESC) demonstrate typical hESC morphology, express appropriate markers, and possess high levels of alkaline phosphatase and telomerase activity. The phESC lines had a normal 46, XX karyotype and had been cultured from between 21 to 35 passages. The phESC lines form embryoid bodies in suspension culture and teratomas after injection to immunodeficient animals and give differentiated derivatives of all three embryonic germ layers (Revazova ES et al 2007 *Cloning Stem Cells* 9:432).

►meristem, ►microRNA, ►regeneration in animals, ►activin, ►nuclear transplantation, ►cryopreservation, ►niche, ►embryo research, ►oocyte, ►transplantation, ►grafting in medicine, ►graft rejection, ►transplantation of nuclei, ►pluripotent, ►Polycomb, ►therapeutic cloning, ►GSK3 β , ►teratoma, ►hematopoiesis, ►hematopoietic stem cells, ►diabetes, ►Krabbe's leukodystrophy, ►mesenchyma, ►reprogramming, ►transcriptional priming, ►hepatocyte, ►bone marrow, ►genetic engineering, ►tissue engineering, ►leukemia inhibitory factor, ►Oct, ►Sox, ►NANOG, ►Smad, ►Stat, ►brachyury, ►bone morphogenetic protein, ►KIT, ►LIF, ►TCF, ►LEF, ►erythropoietin, ►PTEN, ►retinoic acid, ►adipocyte, ►insulin, ►macrophage colony stimulating factor, ►IL-1, ►IL-3, ►fibroblast growth factor, ►epidermal growth factor, ►metaplasia, ►public opinion, ►transdetermination, ►MAPCs, ►plasticity, ►cancer stem cell, ►EC, ►Parkinson disease, ►neurogenesis, ►helix-loop-helix, ►transcription factors, ►adoptive cellular therapy, ►satellite cells, ►trophoblast, ►transformation genetic, ►sickle cell anemia; patents: Loring JF, Campbell C 2006 *Science* 311:1716; Fuchs E, Segre JA 2000 *Cell* 100:143; Weissman IL 2000 *Science* 287:1442; Mezey É et al 2000 *Science* 290:1779; Edwards

BEBA et al 2000 Fertil Steril 74:1; Lennard AL, Jackson GH 2001 West J Med 175:42; Wakayama T et al 2001 Science 292:740; Odorico JS et al 2001 Stem Cells 19:193; Blau HM et al 2001 Cell 105:829; Nichols J 2001 Curr Biol 11:R503; Toma JG et al 2001 Nature Cell Biol 3:778; Edwards RG 2001 Nature [Lond] 413:349; Nature [Lond] 2001 414:87–131; Hochedlinger K, Jaenisch R 2002 Nature [Lond] 415:1035; 2002 J Cell Biochem 85: S38; Board of Life Sciences, National Research Council and Board on Neuroscience and Behavioral Health, Institute of Medicine 2002 Stem Cells and the Future of Regenerative Medicine. National Academic Press, Washington DC; 2003 Proc Natl Acad Sci USA 100(Suppl. 1); germline stem cell regulation: Wong MD et al 2005 Annu Rev Genet 39:173; historical background of stem cell research: Solter D 2006 Nature Rev Genet 7:319; stem cell niches: Moore KA, Lemischka IR 2006 Science 311:1880; review and evaluation of major methods: Yamanaka S 2007 Cell Stem Cell 1:38; International Society for Stem Cell Research: <http://www.isscr.org/>; intestinal stem cells: Crosnier C et al 2006 Nature Rev Genet 7:349; stem cells for neurological disorders: Lindvall O, Kokaia Z 2006 Nature [Lond] 441:1094; stem cell therapy for heart: Srivastava D, Ivey KN 2006 Nature [Lond] 441:1097; USA stem cell registry: <http://stemcells.nih.gov/research/registry>; Guidelines for Human Embryonic Stem Cell Research 2005 (National Academies Press; free online): <http://newton.nap.edu/books/0309096537/html/>; database of embryonic stem cell lines: <http://www.stemcellcommunity.org>; mutant mouse stem cell lines: <http://www.genetrap.org/>.

Stem-Loop Structure: Any DNA or RNA that may have non-paired single strand loops associated with a double-strand stem similar to a lollipop (see Fig. S118). In the stem, the Watson-Crick pairing may not be perfect along its length. ▶palindrome, ▶repeat inverted



Figure S118. Stem-loop structure

Stem Rust: Caused by infection of the basidiomycete fungus *Puccinia graminis* on cereal plants. The haploid spores produced on the wheat plant germinate on the leaves on barberry shrubs and form pycnia (pycnidium). The pycniospores of different mating types undergo plasmogamy and form dikaryotic aecia (aecidia) on the lower surface of the barberry leaves. The aeciospores infect the wheat leaves and form the

dark brown rust pustules, called uredia. The dikaryotic uredospores reproduce then asexually and spread the disease. At the end of the growing season karyogamy takes place and the diploid teliospores are formed. The teliospores overwinter and eventually undergo meiosis and liberate the haploid basidiospores that germinate on barberry and restart the cycle. Stem rust may cause very substantial crop loss in wheat and other Gramineae. The newer varieties are genetically more or less resistant to the fungus. *P. spp* have chromosome numbers 3–6. ▶host-pathogen relationship, ▶rust

Stenosis: The narrowing of a body canal or valve such as in the aorta, heart valve, pulmonary artery, vertebral canal, etc. ▶restenosis

Stenospermocarpy: Genetically determined abortion of the embryo soon after fertilization resulting in seedless normal size berries, a desirable trait of table grapes. ▶seedless fruits

Stenting: Medical use of some device that keeps a graft or a structure in place.

Step: Single-target expression profile.

Step Allelomorphism: A historically important concept that paved the way to allelic complementation and to the study of gene structure. In the late 1920s, Russian geneticists discovered that partial complementation among allelic genes may occur in a pattern and that was inconsistent with the then prevailing idea that the gene locus is the ultimate unit of function, mutation and recombination and that alleles are stereochemical modifications of an indivisible molecule. ▶allelic complementation, ▶Offermann hypothesis; Carlson EA 1966 The gene: A Critical History. W.B. Saunders, Philadelphia, Pennsylvania.

Step Gradient Centrifugation: In the centrifuge tube usually three different concentrations of CsCl or sugar are layered without allowing mixing. The highest concentration is at the bottom of the tube. The different components of the mix, layered at the top, accumulate at the boundaries, which have higher density than the separated component.

Stepwise Mutation Model (SMM): In this model, microsatellites may change by repeated gain or loss of small number of nucleotide repeats. Electrophoretic variations of enzymes may be also fitted to such a model. ▶microsatellite, ▶infinite allele mutation model, ▶trinucleotide repeats; Moran PAP 1975 Theor Popul Biol 8:318; Ohta T, Kimura M 1973 Genet Res 22:201.

Stereocilia: Protoplasmic thin filaments like the ones in the inner ear. Whirlin, a PDZ domain protein of the

stereocilia interacts with a membrane-associated protein kinase (Ca^{2+} -calmodulin serine kinase) and erythrocyte protein p55 (4.1 R) and plays similar roles (actin cytoskeletal assembly) in erythrocytes as well as in stereocilia (Mboru P et al 2006 Proc Natl Acad Sci USA 103:10973). ▶deafness, ▶PDZ domain; Frolenkov GI et al 2004 Nature Rev Genet 5:489.

Stereoisomers: Molecules of identical composition but with different spatial arrangement.

Stereomicroscopy (dissecting microscopy): Used for visual analysis under relatively low magnification of natural specimens without sectioning. It has special advantage for dissecting structural elements with binocular viewing and top or side illumination without fixation and/or staining. ▶confocal microscopy, ▶scanning electronmicroscopy, ▶microscopy

Stereotactic: An action precisely positioned in space such as irradiation of a small spot in the body, surgical introduction of cells, a genetic vector at a defined location of the brain, etc.

Steric-Exclusion Model: This model of DNA replication states that the Watson-Crick hydrogen pairing is not an absolute necessity for the faithful replication of DNA but it is essential that the building block (not necessarily a purine or pyrimidine) would fit into the frame of the DNA double helix. A pyrene nucleoside triphosphate, with the size close to a nucleotide pair, has sufficient steric complementarity to fit into an abasic site and permits DNA replication (see Fig. S119). ▶Watson and Crick model, ▶DNA replication, ▶hydrogen pairing, ▶abasic sites; Matray TJ, Kool ET 1999 Nature (Lond) 399:704.

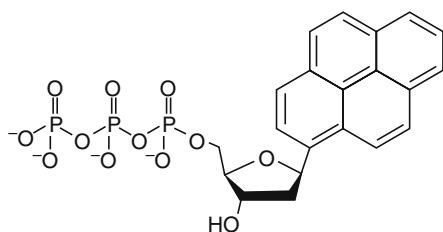


Figure S119. Pyrene nucleoside triphosphate

Sterigma: A small stalk at the tip of a fungal basidium where spores come off. ▶basidium

Sterile Insect Technology (SIT): ▶genetic sterilization

Sterile RNA: ▶germline transcript

Sterility: Either the male, the female, or both types of gametes (haplontic), or the zygotes (diplontic) have

reduced or no viability caused by lethal or semilethal genes, chromosomal defects, differences in chromosome numbers or incompatible cytoplasmic organelles. ▶infertility, ▶semisterility, ▶somatoplastic sterility, ▶cytoplasmic male sterility, ▶incompatibility, ▶self-incompatibility, ▶hybrid sterility, ▶azoo-spermia, ▶infertility, ▶deletion, ▶inversion, ▶translocation

Sterilization: ▶autoclaving, ▶filter sterilization, ▶pasteurization, ▶aseptic, ▶axenic, ▶radiation effects, ▶ethanol, ▶hypochlorate, ▶ethylene oxide, ▶genetic sterilization, ▶*Cochliomya hominivorax*, ▶sterilization humans, ▶birth control

Sterilization, Genetic: ▶genetic sterilization

Sterilization, Humans: Practiced by various societies for different reasons. The eunuchs of the Chinese imperial courts and of the Osmanic harems served as guardians of the privileges of tyrannical social structures. The castration of male Italian opera artistes were performed for singing in female roles, in an era when women were banned from the performing arts. In the 1880s, by the publications of Sir Francis Galton sought scientific justifications for negative eugenics in order “to produce a highly gifted race of men by judicious marriages during consecutive generations.” 1890s initiated sporadic sterilization of institutionalized, mentally retarded persons. Starting in 1907, in about 14 states (USA), laws were enacted for systematic sterilization of mentally retarded, blind, deaf, crippled or afflicted by tuberculosis, leprosy, syphilis, and chronic alcoholism. This “practical, merciful and inevitable solution” eventually degenerated into legal suggestions to eliminate criminal behavior, disease, insanity, weaklings and other defectives and “ultimately to worthless race types.” By the time strong moral objections gained noticeable ground in the year 1956, nearly 60,000 human individuals were legally sterilized. Interestingly, the Oklahoma law exempted from mandatory sterilization offenses against prohibition, tax evasion, embezzlement and political crimes. Several state laws advocated mandatory sterilization also as a guard against illegitimacy, particularly by unwed recipients of the Aid to Families with Dependent Children (AFDC). Until 1965, judicial approval could be obtained for a “good cause” for forced sterilization of mentally retarded individuals whose family had hardship in supporting the offspring of promiscuous children. Although not all states rescinded yet the old laws, sterilization of humans is now practiced only voluntarily by ligation of the vas deferens (vasectomy), tubal constriction, ovariectomy or by the use of various types of mechanical and hormonal contraceptives. Mandatory sterilization was practiced

for eugenic and social reasons in several enlightened countries (e.g., Sweden) until the 1970s. Compulsory sterilization is objectionable on moral ground because reproduction is a basic human right although the society cannot support irresponsible reproductive behavior in cases of certain genetic defects. Reproductive rights must be balanced with the right of born and unborn children with potential severe genetic load (►[wrongful birth](#))

Sterilization is particularly reprehensible when advocated as a selective measure against certain human races. The Third Reich annihilated millions and sterilized thousands for eugenic and other evil reasons. From genetic perspective it is controversial since 83% of the mentally retarded children are born to non-retarded parents. In addition, selection against the majority of human defects is quite inefficient, since the vast majority of the defective genes are in heterozygotes and many of the conditions are under polygenic control or are non-hereditary. Furthermore, there are no objective scientific or practical measures for the evaluation of most of the human traits. ►[selection](#), ►[selective abortion](#), ►[eugenics](#), ►[polygenic](#), ►[salpingectomy](#), ►[vasectomy](#), ►[ovariectomy](#); Reilly P 1977 Genetics, Law, Social Policy. Harvard University Press, Cambridge, Massachusetts.

Sternites: The ventral epidermal structures of the abdomen. ►[Drosophila](#)

Steroid 5-Beta Reductase (SRD5B1, 7q32-q33): Catalyzes reduction of bile acid intermediates and steroid hormones.

Steroid Dehydrogenase-Like Protein (NSDHL, XDq28): The mutations affect cholesterol biosynthesis and may cause male lethality. Hydroxysteroid dehydrogenase (HSD3B1, 1p13.1) deficiency may involve adrenal hyperplasia, hypospadias and gynecomastia. ►[cholesterol](#), ►[hypospadias](#)

Steroid Doping: Used by athletes to boost performance. Amphetamines increase alertness and may reduce onset of fatigue. Side effects are insomnia, exhaustion, violence and potential heart disease. The health hazards are increased if anabolic steroids, insulin, insulin-like growth hormone, etc., are used simultaneously. Even non-steroid anti-inflammatory drugs

may be risky because they mask pain and may aggravate injuries. ►[anabolic steroids](#)

Steroid Hormones: Derived by the pathway shown in Figure S120. [3] is the principal hormone of the endocrine gland, corpus luteum, in the ovarian follicle after the release of the ovum.

They regulate the expression of the secondary sexual characters of females. [4] is the main male sex hormone that is produced in 6–10 mg quantities daily in men and ca. 0.4 mg in women. It is responsible for the production of facial hair and baldness and the regulation of growth [5] is formed by oxidative removal of C-129 from its precursor; primarily a female hormone occurring in the ovaries and placenta and it is responsible for regulating, among other functions, bone growth, increased fat content and smoother skin of females compared to men. This hormone is present also in the testes. In cooperation with progesterone it regulates also the menstrual cycles. [6] and [7] are synthesized in the kidney cortex and regulate, among others, mineral (Na^+Cl^- , HCO_3^-) reabsorption and are frequently called as mineralcorticoid hormones. [8] is a glucocorticoid affecting protein, carbohydrate metabolism regulates the immune system, allergic reactions, inflammations, etc. [9] is also an anti-inflammatory glucocorticoid with a role in activating the glucocorticoid receptors. The number of steroid hormones is about 50 and they are present in practically every cell of the body, besides those mentioned, and they, along with thyroid hormones, have important roles in activation of genes. Up to 1966, the general assumption was that plants do not use steroid hormones. It has been demonstrated that brassinolids (related to cholesterol, ecdysone) mediate several developmental processes in plants, such as elongation, light responses, etc. The steroid receptor superfamily includes receptors for estrogen, progesterone, glucocorticoid, mineralcorticoid, androgen, thyroid hormone, vitamin D, retinoic acid, 9-cis retinoic acid and ecdyson. The steroid hormone receptors stimulate the formation and then stabilize the pre-initiation complex of transcription. Most commonly the condition of their binding to the hormone response element is the binding to their appropriate ligands.

Some, such as the thyroid hormone receptor, can bind to DNA in the absence of a ligand. In the

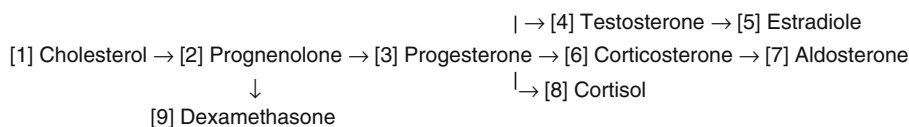


Figure S120. Steroid hormone biosynthetic pathway

absence of the ligand, they function as silencers through interaction with the TFIIB transcription factor. ▶hormone-response elements, ▶silencer, ▶PIC, ▶transcription factors, ▶transcriptional activator, ▶coactivator, ▶regulation of gene activity, ▶animal hormones, ▶estradiol, ▶aromatase, ▶plant hormones, ▶brassinosteroids, ▶anabolic steroids, ▶prenylation, ▶steroids, ▶SRC-1; Lösel R, Wehling M 2003 Nature Rev Mol Cell Biol 4:46.

Steroid Receptor: ▶hormone receptors

Steroid Sulfatase Deficiency: ▶ichthyosis

Steroidogenic Factor-1: ▶SF-1

Steroids: Contain a four-ring nucleus consisting of three six-membered rings and one five-membered ring. (See structural formula in Figure S121, ▶steroid hormones, ▶brassinosteroids).

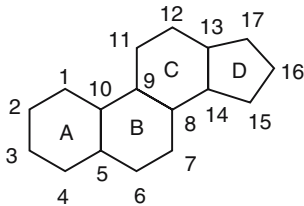


Figure S121. General structural formula of steroids

Sterols: Lipids with a steroid nucleus. The concentration of free sterols determines the fluidity of the eukaryotic cell membranes. Esterification of sterols prevents their participation in membrane assembly. The process is mediated the ACAT complex (acyl-CoA:cholesterol acyltransferase). Increase of ACAT activity may lead to hyperlipidemia and atherosclerosis. Sterol esterification may modify the LDL receptors and potentiates atherogenic processes. The ACAT inhibitor, CP-113-818 reduces amyloid plaques in mice (Hutter-Paier B et al 2004 Neuron 44:227). It may limit intestinal sterol absorption. ▶hyperlipidemia, ▶amyloids, ▶atherosclerosis, ▶LDL, ▶membranes, ▶cholesterol, ▶SREBP, ▶phytoestrogen, ▶oxysterol; Kelley RI, Herman GE 2001 Annu Rev Genomics Hum Genet 2:299; Xu F et al 2005 Proc Natl Acad Sci USA 102:14551.

Stevens-Johnson Syndrome (toxic epidermal necrolysis susceptibility, 6p21.3): The drugs carbamazepine, phenobarbital and allopurinol may evoke cutaneous blistering, epidermal detachment, fever and potentially death. Han Chinese people are more likely to show this reaction than Caucasians. The major histocompatibility complex Class I B5801 allele may be responsible for it. ▶allopurinol, ▶gout, ▶HLA; Hung S-I et al 2005 Proc Natl Acad Sci USA 102:4134.

stg (string, map position 3-99): *Drosophila* gene locus controlling the first ten embryonic divisions (similarly to gene *Cdc28* in *Schizosaccharomyces pombe*); it is a cyclin gene. ▶cell cycle

Stick-and-Ball Model: A representation of chemical structure (see Fig. S122).



Figure S122. Stick- and ball model

Stickiness of Chromosomes: Observed as some sort of adhesion between any chromosomes within a cell. ▶side-arm bridge

Stickleback (*Gasterosteus aculeatus*, $2n = 42$ visible chromosomes, XXIII linkage groups): Small, common fresh and seawater fish (see Fig. S123). (See <http://cegs.stanford.edu/index.jsp>).



Figure S123. Stickleback

Stickler Syndrome (arthroophthalmopathy, AOM): An early and strong progressive myopia (nearsightedness) and hearing deficit. Retinal detachment may result in blindness, caused probably by a dominant mutation in the collagen (COL11A1) gene (human chromosome 1p21). Overlapping mutations are responsible for the Marshall syndrome at 1p21. Stickler syndrome 3 is located at 6p21.3. The collagen type II (COL2A1, 12q13.11-q13.2) defects of the Stickler syndrome involve achondroplasia, skeletal dysplasia, eye and hearing defects. ▶collagen, ▶eye disease, ▶connective tissue disorders, ▶skin diseases; Annunen S et al 1999 Am J Hum Genet 65:974; Richards AJ et al 2000 Am J Hum Genet 67:1083.

Sticky Ends: Double-stranded DNA with a single-stranded overhang to what complementary sequences

are available and so they can stick by base pairing (see Fig. S124).

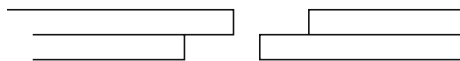


Figure S124. Sticky ends

Stigma: The tip of the style that is normally receptive to the pollen of plants. In zoology, it means spot, such as a hemorrhagic small area on the body. ▶gametophyte female, ▶gametophyte male, ▶protogyny, ▶protandry

Stigmasterol: A plant lipid derivative formed by methylation of ergosterol. For guinea pigs, it is a vitamin necessary to avoid stiffness of the joints. ▶ergosterol, ▶cholesterol

Stilbene: ▶resveratrol

Still-Birth: The birth of a dead offspring. It is caused by chromosomal defects in ca. 7% of the stillborn or by other pathological conditions. ▶chromosomal breakage

Stipule: A leaf like bract at the base of a leaf (see Fig. S125).

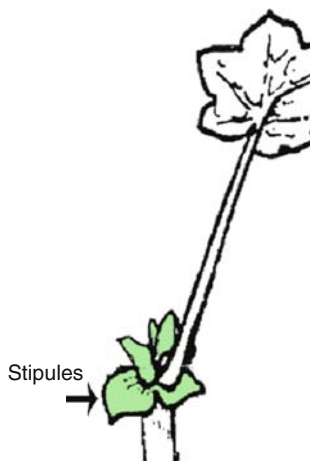


Figure S125. Stipules

Stk: A macrophage-stimulating factor receptor. ▶macrophage

STM: ▶scanning tunneling microscope

Stn1: A telomere length determining protein factor of yeast working in concert with Cdc13. ▶Cdc13; Grandin N et al 1997 Genes Dev 11:512.

Stochastic: Corresponds to a random process; a process of joint distribution of random variables. In a population—in contrast to a deterministic model—random

drift and other chance events may determine the gene frequencies. Mutations are assumed to occur at random, and selective forces acting upon these random alterations shape evolution. Generally, deterministic and stochastic processes run parallel and simultaneously. ▶deterministic model

Stochastic Detriment of Radiation: The combined risk of cancer, genetic damage and life shortening due to radiation exposure. The figures may vary according to tissues: for gonads it may be 1.33, for bone marrow 1.04, for breast 0.24, for liver 0.16 (in 10^{-2} Sv^{-1}), etc. ▶radiation hazards

Stock: A genetically defined strain of organisms; also a root stock on what a scion is grafted.

Stock, Garden (*Matthiola incana*): ▶*Matthiola*

Stoke: A unit of kinematic viscosity (the ratio of viscosity to density). ▶viscosity

Stolon: A horizontal underground stem such as the tuber-bearing structures of potatoes.

Stoma (plural stomata): A small pore on the leaf surface surrounded by two guard cells, which control opening and closing. Basic helix-loop-helix proteins under the control of three genes (Plitteri LJ et al 2007 Nature [Lond] 445:501) control stoma differentiation, although several other factors also have regulatory role. The stoma permits gas exchange (CO_2 uptake), and release of water vapors (transpiration). The opening of the stomata requires an increase in the turgor of the guard cells (see Fig. S126). It had been suggested that the process could be promoted by opening of K^+ and Cl^- channels and the subsequent influx of K^+ and Cl^- . A light controlled proton pump activates the opening of the K^+ channel. The closure of the stomata is controlled by the hormone ABA and the influx of Ca^{2+} and the efflux of K^+ and Cl^- .



Figure S126. Open stoma

The calcium level is sensed by a cyclin-dependent protein kinase (CDPK). Blue light photoreceptors *CRY1* and *CRY2* and phototropin genes *PHOT1* and *PHOT2* receptors regulate blue light response but the quadruple mutants *cry1*, *cry2*, *phot1*, *phot2* mutants barely responded. Mutation in COP1 (constitutive photomorphogenesis) permitted opening of the stomata in darkness and in blue light the triple

recessive mutants displayed open stomata (Mao J et al 2005 Proc Natl Acad Sci USA 102:12270). Pattern of stoma development is controlled by a MAPKK kinase (Bergmann D et al 2004 Science 304:1494).

Erecta mutants (*er*, *erl1*, *erl2*) defective in the regulation in leucine-rich repeat receptor kinases cause clustering of the guard cells of the leaves (see Fig. S127) (Shpak ED et al 2005 Science 309:290). Besides stoma density in the *erecta* mutants, epidermal cell expansion, mesophyll cell proliferation and cell-cell contacts regulate transpiration and photosynthesis in plants and determine the efficiency of carbon fixation (Masle J et al 2005 Nature [Lond] 436:866). (For the phenotype of *er/er* see ▶*Arabidopsis thaliana* entry.)

In the regulation of stomata, Ca^{2+} -dependent ATPases and GTPases have major role. The processes involve changes in the electric potentials (depolarization). In the control of the ABA response, syntaxin-like proteins play a role. Sphingosine-1-phosphate level signals to calcium mobilization. Phospholipase D α 1-produced phosphatidic acid signals to abscisic acid-promoted stomatal closure. Phospholipase D α 1 and phosphatidic acid interact with the G α subunit of the heterotrimeric G protein to mediate abscisic acid inhibition of stoma opening (Mishra G et al 2006 Science 312:264). Open stomata provide passive entry for bacterial infection of plants. Stomatal guard cells—as an innate immune reaction—perceive bacterial surface molecules by the FLS2 receptor, production of nitric oxide and guard cell-specific OST1 kinase and respond with stomatal closure. Some plant pathogenic bacteria have developed, however, a virulence mechanism for reopening the entry port (Melotto M et al 2006 Cell 126:969). ▶ion channels, ▶cell cycle, ▶aequorin, ▶calmodulin, ▶cyclin, ▶ATPase, ▶MAP kinase, ▶GTPase, ▶proton pump, ▶ABA, ▶abscisic acid, ▶phospholipase,

▶syntaxin, ▶sphingolipids, ▶G protein, ▶abscisic acid, ▶phosphatidate, ▶host-pathogen relation; Blatt MR 2000 Annu Rev Cell Dev Biol 16:221; Schroeder JI et al 2001 Nature [Lond] 410:327; Wang X-Q et al 2001 Science 292:2070; Schroeder JI et al 2001 Annu Rev Plant Physiol Plant Mol Biol 52:627; Hetherington AM 2001 Cell 107:711; Nadeau JA, Sack FD 2002 Science 296:1697; Hosy E et al 2003 Proc Natl Acad Sci USA 100:5549; Hetherington AM, Woodward FJ 2003 Nature [Lond] 424:901.

Stomatin: A cation conductance protein in the cell membrane. ▶anesthetics

Stone: ▶scaffolds in genome sequencing

Stop Codon: ▶nonsense codon, ▶genetic code

Stop Signal: ▶transcription termination in eukaryotes, ▶transcription termination in prokaryotes, ▶stop codon, ▶release factor [RF]

Stoppers: Mitochondrial mutations in *Neurospora* displaying stop-start growth. ▶poky

STP: ▶signal transfer particle

STP β (second strand transfer protein): ▶recombination mechanisms eukaryotes, ▶Sep 1

STR: Short/single tandem repeats, such as found in micro- and minisatellites. Using the profiles of only 13 STRs it is possible to provide a rapid test for crime scenes; STR are used for forensic analysis and for population studies. ▶microsatellite, ▶minisatellite, ▶forensic genetics, ▶DNA fingerprinting

Strabismus: An anomaly of the eyes; they may be either divergent or convergent or one directed up, the other down because of the lack of coordination of the muscles concerned. Some persons display this anomaly only periodically. The pattern of inheritance is not entirely clear; most likely dominant factor(s) are involved. The recurrence among the offspring of convergent probands is higher than that among children of the divergent type. Its incidence in the general population is ~ 0.002 . ▶eye diseases, ▶Duane retraction syndrome, see Fig. S128.



Figure S128. Strabismus

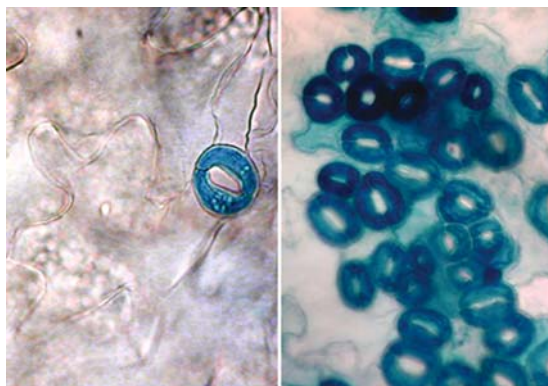


Figure S127. Rosette leaf epidermis wild type (left) and *erecta* triple mutant (right). Stomata express GUS activity. (Courtesy of Drs. Jessica McAbee and Keiko Tori)

Strain: An isolate of an organism with some identifiable difference from other similar groups. This term does not imply any stringent other criteria.

Strain Distribution Pattern (SDR): The distribution of two alleles of a diploid among the progeny where linkage is studied either by a backcross or by recombinant inbred procedure. ▶backcross, ▶linkage, ▶recombinant inbred

Strand Assimilation: The *exo* gene of lambda phage codes for a 5'-exonuclease (M_r 24,000) that can convert a branched DNA structure to an unbranched nicked duplex by the process called strand assimilation during recombination. A progressive incorporation of one DNA strand into another during recombination (•••••) (see Fig. S129). ▶recombination, ▶lambda phage

Strand Bias: ▶gene distribution

Strand Displacement: A type of viral replication involving the removal of the old strand before the new strand is completed. Similar mechanism is used by mtDNA, ▶D loop

Stratification: Layering; in statistical analysis studying the population by, for e.g., age groups, ethnicity or other suitable attributes besides some other criteria of comparison, such as onset of a disease. Stratification may lead to false positive association; comparison of gene frequencies among population mandates appropriate case controls. Principal component analysis and stratification is used by the method of Eigenstrat for minimizing spurious associations in disease studies (Price AL et al 2006 Nature Genet 38:904). Lactase persistence and tall stature was strongly associated in Americans of European descent (Campbell CD et al 2005 Nature Genet 37:868). ▶lactose intolerance, ▶case control, ▶descent; Hoggart CJ et al 2003 Am J Hum Genet 72:1492; Reich DE, Goldstein DB 2001 Genet Epidemiol 20:4.

Stratification Artefact: The disease and control alleles dealt with are from different (ethnic) populations in case-control studies. Sib, parent or other family comparisons may correct the problems. Lower gene frequencies favor reliable result. ▶case—control method

Stratified Random Sample: Represents the entire population (including subpopulations) in a reliable manner.

Stratocladistics: The study of evolution on the basis of fossil records. It minimizes the significance of homoplasy and lack of preservation of lineages that would preserve other lineages under examination. ▶cladistic

Strauss Family: Viennese composers and conductors of three generations. Johann Strauss the Elder (1804–1849) became celebrated for his light waltzes and other dance music. His son Johann Strauss the Younger (1825–1899) is the author of the Blue Danube and many other waltzes was the most celebrated composer (see Fig. S130). His brothers Josef Strauss (1827–1870) and Eduard Strauss (1835–1916) were also famous conductors and composers. Son of Eduard, Johann (1866–1939) was also a renowned conductor. ▶musical talent



Figure S130. Johann Strauss Jr.

Strawberry (*Fragaria ananassa*): About 46 *Fragaria* species with $x = 7$; the wild European *F. vesca* is diploid ($2n = 14$), *F. moschata* ($2n = 42$), some east Asian species are tetraploid, the American strawberries as well as the garden strawberries are $2n = 56$. (See <http://bioinformatics.pcbasc.latrobe.edu.au/index.htm>).

Streak (primitive streak): A sign on the early embryonal disc indicating the movement of cells and the beginning of the formation of the mesoderm and an embryonal axis. ▶organizer

Streking: Spreading microbial cells on the surface on a nutrient agar medium to observe growth or lack of it. (See Fig. S131).



Figure S129. DNA strand assimilation

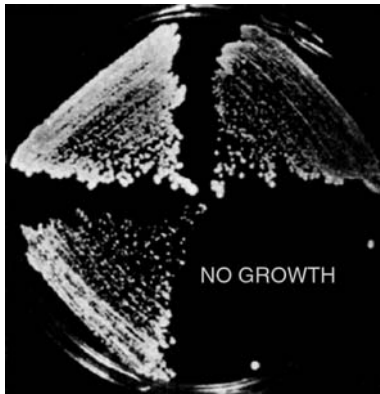


Figure S131. Streaking of wild type (left top) and mutant strains of yeast

Streptavidin: Conjugated with rhodamine, it specifically binds to biotin (biotinylated nucleic acids, immunoglobulins) and permits their detection by fluorescence. The binding constant for biotin is $k_a = 10^{15} \text{ M}^{-1}$.
 ►avidin

Streptavidin-Peroxidase: Identifies biotinylated antibodies in ELISA, in immunochemistry in general and in protein blots. ►genomic subtraction, ►ELISA, ►biotinylation

***Streptococcus pneumoniae* A (*Diplococcus pneumoniae*):** The common pathogenic bacterium causing pharyngitis (sore throat) (see Fig. S132). About 5–10% of the infections may involve necrotic lesion of various severities. In rare extreme cases, it may cause death. Some strains secrete substantial amount of a pyrogenic (fever-producing) exotoxin A, which stimulates the immune system as a superantigen. The excessive stimulation results in the overproduction of cytokines that may damage the lining of the blood vessels and thus cause fluid leakage, reduced blood flow and necrosis of the tissues because of the lack of oxygen. As a further consequence, fasciitis (inflammation of the fibrous tissues) and myositis

(inflammation of the voluntary muscles) may follow. Immunity to *S. pneumoniae* may be independent of the capsular antigens and protection requires the presence of CD4^+ T cells at the time of infection (Malley R et al 2005 Proc Natl Acad Sci USA 102:4848).

The destruction of the tissues may result in death within a very short period after infection by the extremely virulent strain of “flesh-eating bacteria.” *Streptococcus* (B) *agalactiae* is a serious threat to diabetic, cancerous or elderly people; it may be responsible for neonatal sepsis occurring during vaginal delivery. *Streptococcus pneumoniae* (*Pneumococcus*) provided the first information on genetic transformation in 1928. Its sequenced genome (in 2001) of 2,160,837 bp contains 2236 ORFs (see Fig. S133). Approximately 5% of its genome is insertion sequences. The completely sequenced genome of *S. pyogenes* M1 has 1,852,442 bp and encodes ~1752 proteins. *Streptococcus mutans* UA159, the major cause of tooth decay contains 2,030,936 bp and 1963 ORF; its genome has several insertion elements and transposons. Group B *Streptococcus* pathogens display multiple serotypes and they are life threatening to newborns in the first week after birth. The infection comes generally from the healthy mothers who (in 25–40%) harbor the bacteria in anogenital area. This bacterium as many other pathogens are resistant to several antibiotics. Vaccine production has problems because of the serotype variation. However, four proteins provide rather general type of protective antibodies against the various types of *Streptococcus* B bacteria. The protective antibody (immunoglobulin G, IgG) is transmitted to the baby through the placenta (Maione D et al 2005 Science 309:148). ►transformation genetic, ►necrosis, ►superantigen, ►toxic shock syndrome, ►streptolysin, ►fratricide, ►host-resistance genes; Tettelin H et al 2001 Science 293:498; Ferretti JJ et al 2001 Proc Natl Acad Sci USA 98:4658; Hoskins J et al 2001 J Bacteriol 183:5709; Tettelin H et al 2002 Proc Natl Acad Sci USA 99:12391; Ajdic D et al 2002 Proc Natl Acad Sci USA 99:14434.

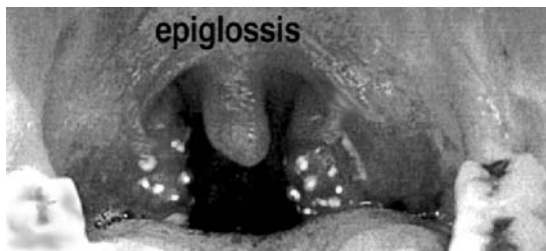


Figure S132. *Streptococcus* exudates on tonsils appear as white spots in severe sore throat. (Modified after Nimishikavi S & Stead L 2005 New England J. Med. 352: p e10)

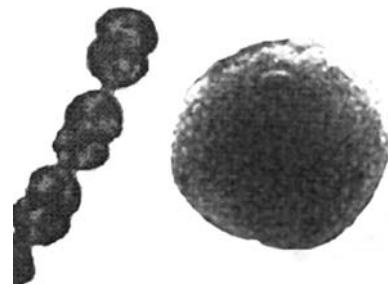


Figure S133. *Streptococcus* colonies; Single cell at high magnification

Streptokinase: An activator of plasminogen. ►[plasminogen activator](#), ►[plasmin](#)

Streptolygidin: An antibiotic that blocks the action of prokaryotic RNA polymerase.

Streptolysin: A cholesterol-binding bacterial exotoxin, which forms large holes through the mammalian plasma membrane. At low concentration, it is suitable for introducing proteins through living cell membranes without irreversible damage to the cell. Streptolysin O prevented *Streptococcus* internalization into lysosomes, killing the extracellular pathogen (Håkansson A et al 2005 Proc Natl Acad Sci USA 102:5192). ►[cytolysin](#); Walev I et al 2001 Proc Natl Acad Sci USA 98:3185.

Streptomyces: A group of Gram-negative bacteria of the actinomycete group, characterized by mycelia-like septate colonies. On these mycelial colonies spore-bearing organs develop. These bacteria somewhat simulate a multicellular type of development. Their genetic material, unlike the majority of prokaryotes, is a linear DNA. The sequenced genome of *S. coelicolor* A3(2) is 8,667,507 bp, containing an estimated 7825 genes (Bentley SD et al 2002 Nature [Lond] 417:141). *S. avermitilis* has linear chromosome built of 9,025,608 bp encoding at least 7574 open reading frames (Ikeda H et al 2003 Nature Biotechnol 21:526; chromosome: Hopwood D 2006 Annu Rev Genet 40:1).

Streptomycin: An antibiotic compound, precipitates nucleic acids, inhibits protein synthesis and interferes with proofreading, and thus causes translational errors (see Fig. S134). Mutation in its S12 ribosomal protein binding sites leads improved translational precision. Some mutations may lead to streptomycin-dependence. Streptomycin resistant mutations in the

ctDNA are maternally inherited; such mitochondrial DNA mutations may lead to hearing loss in humans. ►[antibiotics](#), ►[mitochondrial diseases in humans](#), ►[mtDNA](#)

Streptozotocin (a nitrosamide, 2-deoxy-2-[3-methyl-3-nitrosoureide]-D-glucopyranose): A methylating, carcinogenic, antibiotic agent (effective even against fungi). Induces diabetes and poisons B lymphocytes.

Stress: A condition when living beings must cope with difficult mental or physiological conditions. A major gene duplication for panic and phobic disorders appeared to be at human chromosome 15q24-q26 but another study failed to confirm this finding (Taberner M et al 2003 Am J Hum Genet 72:535). Stress or anxiety activates the corticotropin releasing factor (CRF/CRH) synthesis in the hypothalamus. CRF then stimulates the CRF receptors (CRHR) in the pituitary and this turns on the adrenocorticotropin hormone (ACTH) in the kidneys leading to the production of glucocorticoids, which hinder by feedback to the brain the stress reaction. In case of a failure to respond successfully with some type of a homeostatic mechanism, death or substantial harm may result. Phosphoinositide 3-kinase (PIK) related kinases mediate a variety of cellular stress responses (Bakkenist CJ, Kastan MB 2004 Cell 118:9). Stress activates sphingomyelinase to generate ceramide and the latter initiates apoptosis. Disruption of the glucocorticoid receptor gene may lead to reduced anxiety. Stress also activates heatshock proteins and glucose-regulated proteins (GRP). The GRP proteins are highly active during tumor progression. Their suppression may lead to apoptosis and rejection of the tumor cells. The stress signals may mediate the activation of genetic repair systems or, in animals, may proceed through three main pathways, the c-Abl or the JNK or the p53 routes. The first two are specific to different types of genotoxic agents, the p53 protein responds rather generally to various chemical stresses. The signal transducers eventually reach the DNA by the activation of transcription factors. Ionizing or excitatory (UV) radiations may directly cause chromosome breakage resulting in either repair or apoptosis. In plants, stress stimulates the formation of elicitors and pathogenesis-related proteins. *Arabidopsis* plants exposed to ultraviolet radiation (UV-C), to stress caused by infection by pathogens, or to flagellin, displayed increased level of homologous somatic recombination; the genomic instability persisted in following generations and the condition was transmitted as a dominant trait by both female and male gametes to progeny (Molinier J et al 2006 Nature [Lond] 442:1046). ►[homeostasis](#), ►[p38](#), ►[GADD153](#), ►[CAP](#), ►[ceramides](#), ►[sphingolipids](#), ►[sphingolipidoses](#), ►[SAP](#), ►[SAPK](#), ►[apoptosis](#),

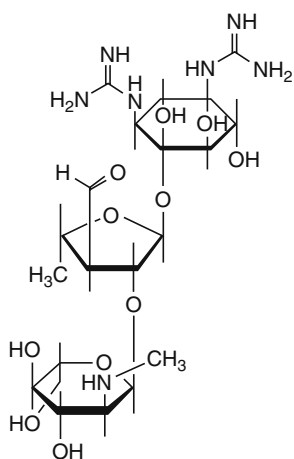


Figure S134. Streptomycin

►JNK, ►cAbl, ►p53, ►pathogenesis-related proteins, ►heat-shock proteins, ►adrenocorticotrophic hormone, ►human brain, ►glucocorticoid, ►drought resistance, ►salt tolerance, ►host-pathogen relations, ►flagellin, ►ultraviolet light, ►instability genetic, ►Pik; Smith MA et al 1995 Proc Natl Acad Sci USA 92:8788; Gratacòs M et al 2001 Cell 106:L367; Dolan RJ 2002 Science 298:1191.

Stress Granules: May accumulate in mammalian and other cells under physical or chemical stress and regulate metabolism (Andreson P, Kedersha N 2006 J Cell Biol 172:803).

Stress Proteins: Most commonly mean heat shock proteins. ►heat-shock protein

Stretching Chromosomes: For more precise localization of FISH labels the chromosome can be extended 5–20 times their highly coiled length using hypotonically treated, unfixed metaphase chromosomes and centrifugation. ►FISH; Bennink ML et al 2001 Nature Struct Biol 8:606.

Striated Muscles: The heart and skeletal muscles are made of sarcomeres and thus striated transversely. ►smooth muscles

Striatum: A layered tissue region, e.g., in the subcortical area of the brain where cognitive and movement regulation functions are mediated. ►brain human

STRING (search tool for the retrieval of interacting genes/proteins): ►genetic network; <http://string.embl.de/>.

String Edit Distance: Determined upon addition, deletion or replacement one base symbol in order to transform a DNA sequence (a string) into another. ►tree edit distance

Stringent: Rigidly controlled.

S

Stringent Control: In amino-acid-starved bacteria (auxotrophs), the product of the *relA*⁺ gene shuts off ribosomal RNA synthesis as an economical device. In the presence of *relA* amino acid synthesis is promoted (relaxed control) because ppGpp regulates the discriminator regions of the promoters. ►fusidic acid, ►relaxed control, ►discriminator region, ►ribosomes; Chatterji D et al 1998 Genes Cells 3:279; Chatterji D, Ojha AK 2001 Curr Opin Microbiol 4:160; Barker MM et al 2001 J Mol Biol 305:673.

Stringent Genomes: These are the nuclear ones because each chromosome is normally replicated once during the cell cycle and normally during mitosis, each member of a diploid (or other euploid) chromosome set is partitioned equally between the daughter cells. ►relaxed genomes

Stringent Plasmid: The low copy number of it is genetically controlled.

Stringent Replication: Limited replication of the low copy number plasmid DNA.

Stringent Response: Under poor growth condition prokaryotic cells may shut down protein synthesis by limiting tRNA and ribosome formation. The synthesis of the *rrn* genes is mediated by binding ppGpp or pppGpp sequences to the *rrn* promoters. Proteins DksA or GreA and Mdf are also regulators (Trautinger BW et al 2005 Mol Cell 19:247). ►stringent control, ►magic spot, ►rrn, ►ribosomes, ►transfer RNA, ►guanosine tetraphosphate, ►Rel oncogene; Chatterji D Ojha AK 2001 Curr Opin Microbiol 4(2):160; van Delden C et al 2001 J Bacteriol 183:5376.

STRL: Co-receptor of HIV and SIV. ►acquired immunodeficiency syndrome

stRNA: ►RNAi, ►microRNA

Stroke: see <http://www.stroke-statement.org/>; ►HuGENet, ►risk

Stroke: Causes 150,000 death/year and afflicts three times as many in the USA. Stroke results from occlusion of a cerebral artery. A mouse model indicates that newborn neurons can migrate to the ischemic regions and may affect recovery in some cases (Jin K et al 2006 Proc Natl Acad Sci USA 103:13198). The major genetic factors involved are telangiectasia, the Osler-Weber-Rendu syndrome, CADASIL, Ehlers-Danlos syndrome, polycystic kidney disease, Marfan syndrome, cardiovascular diseases, hypertension, MELAS syndrome. Gretarsdottir, S. et al (2002 Am J Hum Genet 70:593) reported a susceptibility locus at 5q12 encoding phosphodiesterase 4D acting probably through atherosclerosis in ischemic stroke (Gretarsdottir S et al 2003 Nature Genet 35:135). The genetic association of stroke with the *PDE4* marker or SNP45 could not be generally replicated not due to entirely clear bases, but because of the complexity of the major types of stroke (ischemic [blockage of vessels by blood clots], hemorrhagic [rupture of blood vessels] or other subtypes [cardiogenic or large vessels]) may account for the discrepancies (Rosand J et al 2006 Nature Genet 38:1091; Gulcher JR et al 2006 Nature Genet 38:1092). Protein kinase PRKCH appears to be liable for the pathogenesis of cerebral infarction in Japanese populations (Kubo M et al 2007 Nature Genet 39:212). (See terms mentioned under separate entries).

Stroma: The aqueous solutes within an organelle. A pseudoparenchymatous association of fungal mycelia is also so named. The supportive tissue of an organ;

stroma cells in the bone marrow may produce collagen and extracellular matrix. ► **parenchyma**

Stroma Cell-Derived Factor-1 α : A chemoattractant for hematopoietic stem cells and has role in cell migration within or to the bone marrow. It may affect cell proliferation and cell migration in cancer metastasis.

Stromelysin: ► **metalloproteinases**, ► **transin**

Strong-Stop DNA: When reverse transcriptase initiates transcription of the first strand DNA—from the RNA—then a second strand is made on the first strand DNA template. The transcriptase pauses after the transcription of the R U5 segments (first strand). The U5 R, U3 (second strand) “strong stop” DNA species accumulate (in the latter case including small portions of the RNA primer) before transcription continues to completion of the first, and then of the second strand, respectively. ► **retroviruses**, ► **reverse transcriptase**; Driscoll MD et al 2001 J Virol 75:672.

Strontium: An earth metal with several isotopic forms, the ^{90}Sr , a β -emitter radioactive component of nuclear fallout is readily substituted for calcium and, thus, may be concentrated in the milk if the cows grazed on contaminated pastures. Its half-life is 28 years. After the bomb testings in the 1950s, it became especially threatening to children whose bones accumulated 2.6 μCi in contrast to adults (0.4 μCi). ► **radiation hazards**, ► **Ci**, ► **isotopes**

STRP: Short tandem repeat polymorphism. ► **microsatellite**

Structural Classification of Proteins: ► **SCOP**, ► **ASTRAL**

Structural Gene: A primarily non-regulatory DNA sequence that codes for the amino acid sequence in a protein or for rRNA and tRNA.

Structural Genomics: Develops high-resolution models of protein structure in order to understand catalytic and other functional mechanisms, ligands, domains, reveal critical targets for site-directed mutagenesis, and develop means for therapeutic interventions. The main tools are x-ray crystallography and nuclear magnetic resonance analysis. (See Baker D, Sali A 2001 Science 294:93; <http://www.nysgrc.org/>).

Structural Heterozygosity: Involves normal and rearranged homologous chromosomes within cells. ► **inversion**, ► **translocation**, ► **aberration chromosomal**

Structural Variants of Chromosomes: involve deletions, duplications, inversions, transpositions, translocation, complex rearrangements and copy number variations. The Database of Structural Variants of the human genome in 2007 includes a total of 29,289

entries. Among those 11,784 were copy number variants of 4357 loci, 182 inversions, and 17,323 indels (<http://projects.tcag.ca/variation/>). These variants are more numerous than initially expected and seriously affect the function of many loci. Paired-end mapping (PEM) is an effective means for their identification. PEM involves the preparation and isolation of paired ends of 3 kb fragments and their massive sequencing with 454 technologies and computationally. In two individuals 1300 structural variants (SVs) were identified suggesting that humans may differ to a greater extent in SVs than in single nucleotide polymorphism (Korbel JO et al 2007 Science 318:420). ► **paired-end sequence method**; 454 sequencing: <http://www.454.com/products-and-reagents/genome-sequencer.asp>.

Structure-Directed Combinatorial Mutagenesis: PCR-based mutagenesis.

Strumpell Disease: ► **spastic paraplegia**

STS: ► **sequenced tagged sites**

STS-Content Mapping: In physical mapping, the large sequences used (YAC clones) contain STS tracts and thus their position can be mapped. ► **sequenced tagged sites**, ► **YAC**; Chen YZ et al 2001 Genomics 74:55.

Stuart Factor Deficiency: ► **prothrombin deficiency**, ► **antihemophilic factors**

Student's *t* Distribution: A statistical test for assessing a hypothesis about the means of two populations. This distribution enables the statisticians to compute confidence limits for μ (the true mean of a population) when σ (the standard deviation of the true mean) is not known, and only the standard deviation of the sample s is available.

The quantity of t is determined by the equation:

$$t = \frac{\bar{X} - \mu}{s/\sqrt{n}}$$

where \bar{X} is the experimental mean and n is the population size. The critical t values are generally read from statistical tables after it had been quantified by the calculated t value,

$$t = \frac{d}{\sqrt{V}}$$

where d is the difference between means and V is variance. Under practical conditions the significance of the difference between two means is calculated by

the formula $t = (\bar{x}_1 - \bar{x}_2) / \sqrt{[s_1]^2 + [s_2]^2}$ where the x values stand for the two means and s^2 values are the variances of the two populations. ► **arithmetic mean**, ► **standard deviation**, ► **variance**, ► **paired *t* test**, see Table S5.

Table S5. The calculated value at the determined degrees of freedom (*df*) must be identical or greater than the closest value found on the pertinent *df* line in order to qualify for the probability shown at the top of the columns. E.g., for *df* = 10, and *t* = 3.169 *P* = 0.01 but if the *t* would be only 3.168 *P* would be only 0.05 according to table and statistical conventions. The use of *t* charts or linear interpolation using the logarithms of the two-tailed probability values (Simaika 1942 Biometrika 32:263) can obtain more precise *P* values. Remember that the *t* test indicates the probability of the null hypothesis that the two means would be identical

| <i>df</i> | <i>P</i> → 0.900 | 0.500 | 0.400 | 0.300 | 0.200 | 0.100 | 0.050 | 0.010 | 0.001 |
|-----------|------------------|-------|-------|-------|-------|-------|--------|---------|---------|
| 1 | 0158 | 1.000 | 1.376 | 1.963 | 3.078 | 6.314 | 12.706 | 63.654 | 636.620 |
| 2 | 0.142 | 0.816 | 1.061 | 1.386 | 1.886 | 2.920 | 4.303 | 9.925 | 31.599 |
| 3 | 0.137 | 0.765 | 0.978 | 1.250 | 1.638 | 2.353 | 3.182 | 5.841 | 12.924 |
| 4 | 0.134 | 0.741 | 0.941 | 1.190 | 1.533 | 2.132 | 2.776 | 4.604 | 8.610 |
| 5 | 0.132 | 0.727 | 0.920 | 1.156 | 1.476 | 2.015 | 2.571 | 4.032 | 6.869 |
| 6 | 0.131 | 0.718 | 0.906 | 1.134 | 1.440 | 1.943 | 2.447 | 3.707 | 5.959 |
| 7 | 0.130 | 0.711 | 0.896 | 1.119 | 1.415 | 1.895 | 2.365 | 3.500 | 5.408 |
| 8 | 0.130 | 0.706 | 0.889 | 1.108 | 1.397 | 1.860 | 2.306 | 3.355 | 5.041 |
| 9 | 0.129 | 0.703 | 0.883 | 1.100 | 1.383 | 1.833 | 2.262 | 3.250 | 4.781 |
| 10 | 0.129 | 0.700 | 0.879 | 1.093 | 1.372 | 1.812 | 2.228 | → 3.169 | 4.587 |
| 11 | 0.129 | 0.697 | 0.876 | 1.088 | 1.363 | 1.796 | 2.201 | 3.106 | 4.437 |
| 12 | 0.128 | 0.696 | 0.873 | 1.083 | 1.356 | 1.782 | 2.179 | 3.054 | 4.318 |
| 13 | 0.128 | 0.694 | 0.870 | 1.080 | 1.350 | 1.771 | 2.160 | 3.012 | 4.221 |
| 14 | 0.128 | 0.690 | 0.868 | 1.076 | 1.345 | 1.761 | 2.145 | 2.977 | 4.140 |
| 15 | 0.128 | 0.691 | 0.866 | 1.074 | 1.341 | 1.753 | 2.131 | 2.947 | 4.073 |
| 16 | 0.128 | 0.690 | 0.865 | 1.071 | 1.337 | 1.746 | 2.120 | 2.921 | 4.015 |
| 17 | 0.128 | 0.689 | 0.863 | 1.069 | 1.333 | 1.740 | 2.110 | 2.898 | 3.965 |
| 18 | 0.127 | 0.688 | 0.862 | 1.067 | 1.330 | 1.734 | 2.101 | 2.878 | 3.922 |
| 19 | 0.127 | 0.688 | 0.861 | 1.066 | 1.328 | 1.729 | 2.093 | 2.861 | 3.883 |
| 20 | 0.127 | 0.687 | 0.860 | 1.064 | 1.325 | 1.725 | 2.086 | 2.845 | 3.850 |
| 21 | 0.127 | 0.688 | 0.859 | 1.063 | 1.323 | 1.721 | 2.080 | 2.831 | 3.819 |
| 22 | 0.127 | 0.686 | 0.858 | 1.061 | 1.321 | 1.717 | 2.074 | 2.819 | 3.792 |
| 23 | 0.127 | 0.685 | 0.858 | 1.060 | 1.320 | 1.714 | 2.069 | 2.807 | 3.768 |
| 24 | 0.127 | 0.685 | 0.857 | 1.059 | 1.318 | 1.711 | 2.064 | 2.797 | 3.745 |
| 25 | 0.127 | 0.684 | 0.856 | 1.058 | 1.316 | 1.708 | 2.060 | 2.787 | 3.725 |
| 26 | 0.127 | 0.684 | 0.856 | 1.058 | 1.315 | 1.706 | 2.056 | 2.779 | 3.707 |
| 27 | 0.127 | 0.684 | 0.855 | 1.057 | 1.314 | 1.703 | 2.052 | 2.771 | 3.690 |
| 28 | 0.127 | 0.683 | 0.855 | 1.056 | 1.312 | 1.701 | 2.048 | 2.763 | 3.674 |
| 29 | 0.127 | 0.683 | 0.854 | 1.055 | 1.311 | 1.699 | 2.045 | 2.756 | 3.659 |
| 30 | 0.127 | 0.683 | 0.854 | 1.055 | 1.310 | 1.697 | 2.042 | 2.750 | 3.646 |
| 40 | 0.126 | 0.681 | 0.851 | 1.050 | 1.303 | 1.684 | 2.021 | 2.704 | 3.551 |
| 60 | 0.126 | 0.679 | 0.848 | 1.046 | 1.296 | 1.671 | 2.000 | 2.660 | 3.460 |
| 120 | 0.126 | 0.678 | 0.845 | 1.041 | 1.289 | 1.658 | 1.980 | 2.617 | 3.373 |
| ∞ | 0.126 | 0.674 | 0.842 | 1.036 | 1.282 | 1.645 | 1.960 | 2.576 | 3.290 |

Study Bias: A difference in being studied because of a certain property of the entity attracted more interest for research workers.

Stuffer DNA: Part of the phage λ genome is not entirely essential for normal functions of the phage. Sequences between gene *J* and *att* representing about one-fourth of the genome can be removed and replaced (stuffed in) by genetic engineering without destroying viability of the phage. ► [lambda phage](#), ► [vectors](#); Parks RJ et al 2001 J Virol 73:8027.

Sturge-Weber Syndrome (phakomas): Ektodermal hamartomas, angiomas of the meninges. ► [hamartoma](#), ► [angioma](#), ► [meninges](#), ► [von Hippel-Lindau disease](#), ► [tuberous sclerosis](#)

sturt: The unit of fate mapping; named after Alfred Sturtevant who first used fate mapping. ► [fate maps](#)

Stutter Bands: DNA slippage may occur during PCR replication, (especially of long dinucleotide repeats) and may create shorter sequences than expected, making the identification of the heterozygotes for microsatellite sequences difficult. ► [microsatellite](#), ► [PCR](#); Miller MJ, Yuan BZ 1997 Anal Biochem 251:50; Walsh PS et al 1996 Nucleic Acids Res 24:2807.

Stuttering: A transcription termination phenomenon; poly U may easily break U-A associations. ► [stammering](#)

Stylopodium: The bones of the humerus and femur.

Stylus (style): The slender structure leading from the stigma to the ovary of plants through which the pollen tube grows to the embryosac. ► [gametophyte female](#), ► [gametophyte male](#)

su1 = supD, su2 = supE, su3 = supF, su4 = supC, su5 = supG and su7 = supU: ► [su⁻](#)

su⁻: The wild type allele of a suppressor mutation; the suppressor allele is *su⁺*.

su⁺: The suppressor allele at a locus in contrast to the wild type that is designated *su⁻*.

Su Blood Type: Occurs in pigs and resembles the Rh blood type in humans. ► [Rh blood type](#), ► [erythroblastosis fetalis](#)

Subcellular: An organelle or other structure or site within a cell. (See subcellular localization of mouse proteins: <http://locate.imb.uq.edu.au/>; proteins of several organisms: <http://bioinformatics.albany.edu/~ptarget>; <http://gpcr.biocomp.unibo.it/esldb/>; Arabidopsis subcellular proteins: <http://www.suba.bcs.uwa.edu.au>).

Subcellular Localization: The expression levels of many genes are correlated with their subcellular site(s). Gene expression level is generally high in the cytoplasm, low in the nuclear membrane, and intermediate level in the secretory pathways (endoplasmic reticulum and Golgi). In each group fluctuations occur. It has been estimated that in yeast, 47% of the proteins are located in the cytoplasm, 13% in the mitochondria, 27% in the nucleus and nucleolus, and 13% in the endoplasmic reticulum and secretory vesicles (Kumar A et al 2002 Genes Dev 16:707). ► [mitochondria](#), ► [mitochondrial diseases in humans](#), ► [chloroplast genetics](#), ► [FL-REX](#), ► [gene ontology](#), ► [organelle](#), ► [tissue-specificity](#); Drawid A et al 2000 Trends Genet 16:426; Feng Z-P, Zhang C-T 2002 Int J Biochem Cell Biol 34:298; protein targeting signals: Schneider G, Fechner U 2004 Proteomics 4:1571; Gene Ontology Molecular Function and Subcellular Localization: <http://www.cs.ualberta.ca/~bioinfo/PA/GOSUB/>; subcellular localization of mammalian proteins: <http://locate.imb.uq.edu.au/>.

Subcloning: Recloning a piece of DNA. ► [cloning molecular](#), ► [cloning vectors](#)

Subculturing: Transferring of a culture into a fresh medium.

Subcutaneous: Beneath/under the skin.

Suberin: A corky, complex polymeric material (of fatty acids but no glycerol associated with it) on the surface and within plant cells. In many plants, there is a subepidermal layer of suberin in air-filled cells and in various scar tissues. Suberin is frequently associated with cellulose, tannic acid, dark pigments (phlobaphenes) and inorganics. The commercial cork produced by the oak, *Quercus suber*, is suberin. ► [host-pathogen relation](#)

Subfunctionalization: Gene duplication involving somewhat different function of the duplicated copy, e.g., expression at a different location of the body. In *Arabidopsis* and *Antirrhinum*, the *AGAMOUS* and the *PLENA* genes, respectively, descended in a non-orthologous manner from the *SHATTERPROOF* and *FARINELLI* genes, respectively (Causier B et al 2005 Curr Biol 15:1508). Subfunctionalization model assumes that the paralogous genes are selectively neutral and thus permitted to mutate and explore new adaptive functionalities without extinction. Eventually, one of the copies may be converted to the status of pseudogenes or is entirely lost. The duplicated genes may have lost one of the function, therefore, both copies became necessary and favored by evolution or they might be preserved by drift.

►duplication, ►paralogous, ►pseudogene, ►neofunctionalization; Force A et al 1999 *Genetics* 151:1531; Tochini-Valentini GD et al 2005 *Proc Natl Acad Sci USA* 102:8933.

Sublethal: Only about 50% of the affected my live until sexual maturity.

Sublimon: Sub-stoichiometric molecules of mtDNA that are supposed to be the products of recombination within short repeated sequences in this organelle. ►mtDNA; Kajander OA et al 2000 *Hum Mol Genet* 9:2821.

Subline: New colony of rodents set up in a new laboratory. ►substrain, ►inbred

Submetacentric: Chromosome with two arms clearly unequal in length (see Fig. S135). ►chromosome morphology



Figure S135. Submetacentric

Submission: ►data submission standards

Submission Signal: In the majority of vertebrates, aggressive behavior generally ends when the weaker partner in the conflict displays the submission signal, e.g., dogs lie on their back. The human race does not employ such definite signals and thus, the conflicts frequently end in violence. ►aggression, ►behavior genetics, ►human behavior, ►ethology

Subspecies: A group of organisms within a species distinguishable by gene frequencies, chromosomal morphology and/or rearrangement(s), and may show some signs of reproductive isolation from the rest of the species. ►species

Substance Abuse: The proclivity is genetically controlled. Morphine preference has at least three known QTLs; alcoholism has also several QTLs. Some of these conditions may be associated with variations in the serotonin transporter. A genetic factor for the latter is linked to the human ALPC2 locus, controlling vulnerability to alcohol. The conditions leading to depression may generally affect substance abuse, some of the quantitative trait loci mentioned, however, do not appear to act globally. ►alcoholism, ►serotonin, ►QTL, ►steroid doping; Uhl GR et al 2001 *Am J Hum Genet* 69:1290.

Substantia Nigra: A site in the middle part of the brain (mesencephalon) with dark pigment deposits. The pigments are the products of the dopaminergic

neurons that control movement and coordination; dopamines are essential neurotransmitters. In Parkinson disease, the cells degenerate and cannot make sufficient amounts of the dopamine pigment. Somatic mutations (deletions) in the mitochondrial DNA are associated with respiratory deficiency and selective loss of neurons that are observed in aging and Parkinson disease (Bender A et al 2006 *Nature Genet* 38:515; Kraytsberg Y et al 2006 *Nature Genet* 38:518). ►Parkinson disease, ►neurotransmitter, ►aging, see Fig. S136.

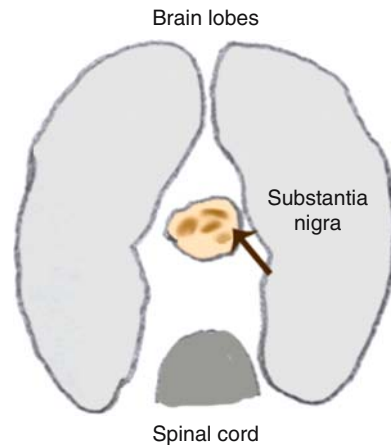


Figure S136. Substantia nigra location in the brain

Substitution, Disomic: Two homologous chromosomes replaced by two others. ►alien substitution, ►inter-varietal substitution

Substitution Line: One of its chromosomes (or pair) is derived from a donor variety or species. ►alien substitution, ►intervarietal substitution

Substitution, Monosomic: One entire chromosome is substituted for another. ►substitution line

Substitution Mutation: When a base pair is replaced by another. The evolutionary mutation rate in the human X chromosome is lower than in the Y chromosome and the ratio is about 1.7 at the 95% confidence level according to one study based on molecular analysis (see Fig. S137). ►transition and transversion, ►base substitution, ►point mutation, ►Li-Fraumeni syndrome, ►SNIP, ►base sequences

Substoichiometric Shift: The mtDNA of some species undergoes rounds of unequal recombinations and, thus, generates mutations in this organelle and possibly also in the plastids. The organelle mutations are then maternally inherited. ►mutator genes, ►mitochondrial genetics

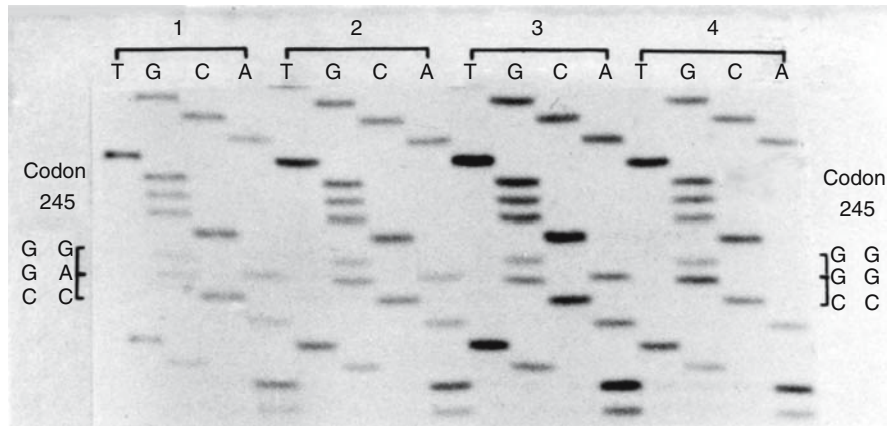


Figure S137. Base substitution mutations in the p53 gene in the noncancerous fibroblast cells in a family with the Li-Fraumeni syndrome. (1) Proband, (2) his brother, (3) their father and (4) a normal control. In codon 245 GGC→GAC mutations are evident in the two generations investigated. (Courtesy of Professor Esther H. Chang; see also Nature [Lond] 348: 747)

Substrate: The compound an enzyme can act on, or the culture medium for an organism, or a particular surface. ▶ [pseudosubstrate](#)

Substrate Adhesion Molecules (SAM): Bind as extracellular molecules to independent receptors on adhering cells.

Substrate Cycle: ▶ [futile cycle](#)

Substrate Induction: Enzyme synthesis is stimulated by the presence of the substrate of the enzyme. ▶ [lac operon](#), ▶ [substrate](#)

Substrate Ordering: The order of degradation—by multiubiquitination—of the cell cycle regulators by the anaphase-promoting complex (APC). (See Rape M et al 2006 Cell 124:89; ▶ [cell cycle](#), ▶ [APC](#), ▶ [ubiquitin](#)).

Subtelomeric Duplications: ▶ [telomeres](#)

Subtiligase: An enzyme capable of ligating esterified peptides in aqueous solutions.

Subtilisin: A protease enzyme that cuts at serine in the context Gly-Thr-Ser-Met-Ala-Ser; chymotrypsin also cuts at serine but within a different sequence. Subtilisin is translated as a pre-pro-polypeptide containing the IMC (intramolecular chaperon) sequence between the signal peptide and the mature enzyme. IMC is responsible for the folding of the final enzyme without being present in the functional subtilisin, which is a general scavenger molecule. ▶ [chymotrypsin](#), ▶ [scavenger molecules](#), ▶ [signal peptide](#)

Subtraction Genomic: ▶ [genomic subtraction](#)

Subtractive Cloning (driver excess hybridization): Provides information of genes selectively expressed in different tissues. A single-stranded RNA (or DNA,

the so-called tracer) is hybridized to another nucleic acid (the driver), which is present in the reaction mixture at least 10-fold in excess. Usually, from the tester RNA a cDNA is generated by the use of poly (dT) primers. Then from the single strand cDNA, double-strand DNA is generated with the aid of poly (dT) primer. The tester cDNA is mixed with an excess of driver cDNA and the cDNAs are allowed to reanneal after denaturation. The double-strand DNA is removed by adsorption to a hydroxyapatite column. The hybrids and the unhybridized driver are selectively removed (subtraction) and the remaining single-stranded, unhybridized tracer is further enriched by hydroxyapatite, biotinylation and selection by streptavidin, chemical cross-linking, RNase H and PCR. The process may be repeated until pure tracer-specific nucleic acid becomes available. This can then be used to screen a library for tracer-specificity. The procedure bears much similarity to c_0t or r_0t analysis. Hyperchromicity or digestibility by S1 nuclease can monitor the single-stranded molecules. The technique may provide information on the number or kind of genes expressed in specific tissues. ▶ [hydroxyapatite](#), ▶ [streptavidin](#), ▶ [genomic subtraction](#), ▶ [RFLP subtraction](#), ▶ [positive selection](#), ▶ c_0t , ▶ r_0t analysis, ▶ [S1 nuclease](#), ▶ [hyperchromicity](#), ▶ [tissue-specificity](#), ▶ [nucleic acid hybridization](#), ▶ [cascade hybridization](#), ▶ [subtractive hybridization](#), ▶ [normalization](#); Sagerström CG et al 1997 Annu Rev Biochem 66:751.

Subtractive Hybridization: ▶ [subtractive cloning](#)

Subtractive Suppression Hybridization (SSH): First subtracted cDNA libraries are generated. Then selective and/or suppressive cycles of PCR is combined with normalization and subtraction in

a single procedure. The normalization equalizes the abundance of cDNAs within the samples and the subtraction excludes the sequences common to the target and driver populations. The procedure is well suited for identification of disease, developmental or other differentially expressed genes. ▶PCR, ▶subtractive cloning; Diatchenko L et al 1999 Methods Enzymol 303:349; den Hollander AI et al 1999 Genomics 58:240; Nishizuka S et al 2001 Cancer Res 61:4536; selective transcriptome extraction: Li L et al 2005 Nucleic Acids Res 33:(16):e136.

Substrain: A line separated from another after 8–19 cycle of inbreeding or when a single colony is different from the rest of the strain of rodents. ▶subline, ▶inbred

Subunit Vaccine: Contains only a fragment of the antigenic protein, sufficient to stimulate an immune response. ▶vaccines, ▶antigen

Subunits of Enzymes (protomers): The polypeptides that make up the oligomeric proteins.

Subvital: Has reduced viability, yet has 50% chance to survive up to the reproductive period of the species. ▶sublethal

SUC2: Yeast invertase gene; it mediates glucose effect and may be suppressed by *ssn* (suppressor of *snf*). ▶SSN6, ▶SNF, ▶glucose effect

Succinate Dehydrogenase: A non-heme iron, inner mitochondrial dehydrogenase enzyme (subunits encoded at human chromosomes 11q23 and 1q21). It converts succinate to fumarate while flavin adenine dinucleotide serves as a H_2 acceptor. ▶phaeochromocytoma, ▶mitochondrial diseases in humans

Sucrose Gradient Centrifugation: ▶density gradient centrifugation

Sucrose Intolerance: ▶disaccharide intolerance

Sucrose Transporters: Deliver the photosynthetically produced sucrose within the plant body. ▶photosynthesis; Truernit E 2001 Curr Biol 11:R169.

Sudan Black: In microscopic use, it stains fatty tissues, wax, resins, cutins, etc., red.

Sudden Infant Death Syndrome (SID): Unexpected death of healthy, normal infants within the first year of life during sleep. It appears to be associated with a deficiency in the binding of the muscarinic cholinergic receptors of the brain resulting in accumulation of carbon dioxide or lack of oxygen in the blood. ▶muscarinic acetylcholine receptors

Sufficiency, Statistical: Indicates that all necessary information about a parameter has been obtained.

SUG1: An ATPase and activator of transcription; it can substitute in yeast for Trip1 and can interact with the transcriptional activation domain of GAL4 and herpes virus protein VP16. ▶ATPase, ▶transcriptional activator, ▶Trip1, ▶GAL4, ▶signal transduction

Sugar Beet (*Beta vulgaris*): $2n = 18$ (see Fig. S138). One of the greatest success stories of plant breeding. In the middle of the eighteenth century, the average sugar content of the plant was about 2%. This increased by the twentieth century to about 20%, and the sugar yield per hectare increased to about 4 metric tons. Some of the modern varieties have numerous agronomically important features (disease resistance, monogerm), and this is a rare plant where triploid varieties (besides bananas) are grown commercially. ▶banana, ▶monogerm seed



Figure S138. Sugar beet

Sugar Code: Hypothesized to involve proteoglycan modifications on the basis that heparan sulfate and chondroitin sulfate proteoglycans would control axon guidance. ▶heparan sulfate, ▶chondroitin sulfate, ▶axon guidance; Holt CE, Dickson BJ 2005 Neuron 46:169.

Sugarcane: (*Saccharum*, $x = 10$); its diploid forms are unknown and the cultivated varieties have high and variable number of chromosomes (*S. spontaneum* $2n = 36-128$, *S. robustum* $2n = 60-170$, *S. officinarum* $2n = 70-140$), including polyploids and aneuploids. The modern cultivated forms are natural hybrids of *S. spontaneum* \times *S. officinarum* (this hybrid is also called *S. barberi* in India and *S. sinense* in China). Genetic mapping requires DNA markers, which—unlike the gene markers—can be studied despite the complex chromosomal situations. It is the most important source of saccharose or common sugar. ▶sugar beet

Sugars: Mono- and oligosaccharides, components of polysaccharides and have important role in nutrition, and in complexes of critical significance in immunology, cancer, other diseases, several pigments, etc. Database for chemistry, classification, structure,

physiological role: <http://www.glycosciences.de/sweetdb/index.php>.

Suicidal Antibody: The antibody is equipped with a targeting signal that can direct it to a degradative cellular compartment (e.g., lysosome, proteasome) where the bound antigen is destroyed. ►[lysosome](#), ►[proteasome](#); Larbig D et al 1979 Pharmacology 18:1; Hsu KF et al 2001 Gene Ther 8(5):376.

Suicidal Behavior: Appears to have a familial component. The suspected association between tryptophan hydroxylase and suicidal behavior is not supported by recent analysis (Lalovic A, Turecki G 2002 Am J Med Genet 114:533).

Suicide Inhibitor: A molecule that inhibits enzyme action after the enzyme acted upon it. In the original form, it is only a weak inhibitor but after reacting with the enzyme it binds to it irreversibly and becomes a very potent inhibitor. Allopurinol, fluorouracil are such molecules. ►[allopurinol](#), ►[regulation of enzyme activity](#)

Suicide Mutagen: Uses a ^{32}P -labeled or other radioactive nucleotide that is incorporated into the genetic material and causes mutation by localized radiation. ►[magic bullet](#)

Suicide Vector: Delivers a transposon into the host cells in which the vector itself cannot replicate but the transposon can be maintained and used for transposon mutagenesis. Additional use involves the delivery of Herpes simplex virus thymidine kinase gene (HSV-TK) and administering ganciclovir or acyclovir. The HSV-TK is about three orders of magnitude more effective than the cellular TK in phosphorylating these DNA base analogs and thus blocking DNA synthesis. The phosphorylated ganciclovir is also impaired in moving through cell membranes and has longer-lasting local effects. Eventually some ganciclovir resistance may develop. The delivery of the gene for cytosine deaminase (CD) and the compound 5-fluorocytosine may produce within the target 5-fluorouracil, a DNA inhibitor. Xanthine-guanine phosphoribosyltransferase (XGPRT) may make the tumor cells more sensitive to 6-thioxanthene. P450-2B1 gene encoding a cytochrome, converts cyclophosphamide into the toxic phosphoramidate mustard. The *deoD* bacterial gene (purine-nucleoside phosphorylase) converts 6-methylpurine deoxyribonucleoside into the deleterious 6-methylpurine. The bacterial nitroreductases convert the relatively non-toxic monofunctional N-chloroethylamine-derivative, C1954, into 10^4 times more active bifunctional alkylating agent. Employing HSV-TK, CD and XGPRT to the same tumor, three different

transgenic cell populations, a mosaic may result. Theoretically, this could be used in a preventive program in putative cancer-prone cases. If the HSV-TK cells would become cancerous, ganciclovir would eliminate that cell subpopulation and the healthy tissues carrying the CD and XGPRT can take over as a prophylactic measure. Unfortunately, this mosaic approach has serious limitations at this time. Targeting a foreign antigen (e.g., HLA-B7 protein) to the cancer cells may stimulate the immune system of the host and kill the tumor cells. The immune system may be stimulated by transformation with cytokine genes. ►[transposon mutagenesis](#), ►[ganciclovir](#), ►[gene therapy](#), ►[cancer gene therapy](#), ►[immunotherapy adoptive](#), ►[cytokines](#), ►[HLA](#), ►[bystander effect](#), ►[cytosine deaminase](#), ►[thymidine kinase](#); Takamatsu D et al 2001 Plasmid 46:140.

Sulfatase Deficiency: ►[mucosulfatidosis](#)

Sulfhydryl Group: —SH, and when two are joined the linkage is a disulfide bond. Sulfhydryl compounds, such as cysteine and cysteamine are protectors against ionizing radiation. ►[thiol](#), ►[cysteine](#), ►[cysteamine](#)

Sulfocysteinuria: A deficiency of sulfite oxidase. Restricted intake of sulfur amino acids in the diet greatly reduces sulfocysteine and thiosulfate in the urine and improves conditions.

Sulfolobus (Archaea): genomes database: <http://www.sulfolobus.org>.

Sulfonylurea: A group of compounds that stimulate insulin production by regulating insulin secretion and lower blood sugar level; it is used to treat patients with non-insulin dependent diabetes. These drugs interact with the sulfonylurea receptor of pancreatic β cells and inhibit the conductance of ATP-dependent K^+ ion channels. Reduction of potassium exit activates the inward rectifying Ca^{2+} channels and promotes exocytosis. Sulfonylureas are inhibitors of the acetolactate synthase enzyme and there are also sulfonylurea herbicides. ►[ion channels](#), ►[diabetes](#), ►[herbicides](#)

Sulfur Mustard: See Fig. S139 where Al is an alkyl group. If the two alkyl groups are chlorinated (Cl) the compound is called bifunctional. If only one alkyl group is chlorinated, the compound is monofunctional. ►[nitrogen mustard](#), ►[alkylating agents](#); Michaelson S 2000 Chem Biol Interact 125:1.

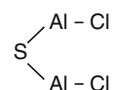


Figure S139. Sulfur mustard

Sulfurylase: Catalyzes the reaction $\text{ATP}^{3-} + \text{SO}_4^{2-} \rightarrow$ adenylyl sulfate (adenosine-5'-phosphosulfate, $\text{C}_{10}\text{H}_{14}\text{N}_5\text{O}_{10}\text{PS}$).

Sulston Score: Used for comparative microsynteny analysis. It displays matching status of fingerprints of a chosen genomic clone and its matching sequences in others by a given probability of coincidence and a given tolerance. The analysis permits physical mapping of genomes. The scores may vary from 04 to 38 and the lower is more stringent. (See Sulston J et al 1988 Comput Appl Biosci 4:125).

Summary Statistic: Defines characteristics of a diverse population by the mean and variances. ▶mean, ▶variance

Sum of Squares: The sum of the squared deviations from their mean of the observations; it is used in statistical procedures to estimate differences. ▶analysis of variance, ▶intraclass correlation

SUMO (small ubiquitin-like modifier, 2q32.2-q33): Ubiquitin-like carrier proteins (11 kDa). Sumos are conjugated to a variety of proteins (RanGAP1-Ubc9-Nup358) and seem to be involved in multiple functions such as cell cycle progression, DNA repair, spontaneous mutation, heterochromatin stabilization and counteract recombination events at damaged replication forks, etc. Histone sumoylation may repress transcription. ▶UBL, ▶monoubiquitin, ▶sentrin, ▶PIC, ▶IκB, ▶IKK, ▶RAN, ▶Ubc9, ▶nuclear pores, ▶Huntington's chorea, ▶NF-κB; Melchior F 2000 Annu Rev Cell Dev Biol 16:591; Müller S et al 2001 Nature Rev Mol Cell Biol 2:202; Shiio Y, Eisenman RN 2003 Proc Natl Acad Sci USA 100:13225; Reverter D, Lima CD 2005 Nature [Lond] 435:687; crystal structure of thymine DNA glycosylase-SUMO: Baba D et al 2005 Nature [Lond] 435:979; heterochromatin: Shin JA et al 2005 Mol Cell 19:817; sumoylation site server: <http://bioinformatics.lcd-ustc.org/sumosp/>.

Sunburn: Sunburn (UV) causes keratoses in about 60% of the cases. The p53 gene may suffer mutation(s), mainly C→T transitions. These p53 mutant cells, after clonal propagation, may develop into squamous cell skin cancer (SCC). In over 90% of the SCC cells, the p53 gene is mutant. The increased melanin production involved with ultraviolet light exposure may be correlated with the DNA repair system. ▶p53, ▶keratoses, ▶DNA repair, ▶ultraviolet light, ▶pigmentation in animals, ▶melanoma

Sunds: ▶Brugada syndrome

Sunflower (*Helianthus*): An oil crop with about 70 xenogamous species, $2n = 2x = 34$. (See Burke JM et al 2002 Genetics 161:1257).

Sun-Red Maize: Develops anthocyanin pigment when the tissues are exposed to sunshine (e.g., through a stencil) (see Fig. S140).



Figure S140. Sun-red maize ear

SUP35: ▶prion

supB: Ochre/amber suppressor; it inserts glutamine.

supC: A suppressor mutation for amber (5'-UAG-3') and ochre (5'-U3') chain-terminator codons. The mutation causes a base substitution in the anticodon of tyrosine tRNA (5'-GUA-3') and it changes to 5'-UUA-3' that can recognize both the ochre and amber codons as if they were tyrosine codons. Note: pairing is 5'-3' and 3'-5'. For the recognition of the former, wobbling is required. ▶suppressor, ▶wobbling, ▶anticodon, ▶ochre, ▶amber

supD: An amber suppressor mutation that reads the amber (5'-UAG-3') chain termination codon as if it would be a serine (5'-UCG-3') codon because the normal serine tRNA anticodon (5'-CGA-3') mutates to (5'-CUA-3'), therefore, instead of terminating translation, a serine is inserted into the amino acid chain. (Remember, the pairing is antiparallel). ▶suppressor, ▶anticodon

supE: An amber-suppressor mutation that reads the chain-termination codon 5'-UAG-3' (amber codon) in the mRNA as if it would be a glutamine codon (5'-CAG-3') because the glutamine tRNA anticodon mutates to 5'-CUA-3' from the 5'-CUG-3'. As a consequence, the translation proceeds and a glutamine is inserted at the site where in the presence of an amber codon in the mRNA the translation would have terminated. (Note: the pairing is antiparallel).

supF: Amber suppressor; it inserts tyrosine.

Superantigen: Native bacterial and viral proteins that can bind directly (without breaking up into smaller peptides) to MHC class II molecules on antigen-presenting cells. The variable regions of T cell receptor β chains thus activate more T cells against, e.g., enterotoxins of *Staphylococci*—causing toxic shock syndrome or food poisoning—than normal antigens. Cellular superantigens are likely to be responsible for such diseases as diabetes mellitus. ▶MHC, ▶TCR, ▶enterotoxin, ▶toxic shock

syndrome, ►diabetes mellitus, ►antigen, ►endogenous virus; Muller-Alouf H et al 2001 Toxicon 39:1691; Alam SM, Gascoigne NR 2003 Methods Mol Biol 214:65.

Superchiasmatic Nucleus: A region near the optical center of the hypothalamus in the brain controlling circadian signals. ►brain, ►circadian rhythm

Supercoiled DNA: May assume the *positive supercoiled* structure by twists in the same direction as the original, generally (right handed) coiling of the double helix, or it may be twisted in the opposite direction, *negative supercoiling*. Negative supercoiling (Z DNA) may be required for replication and transcription (see Fig. S141).

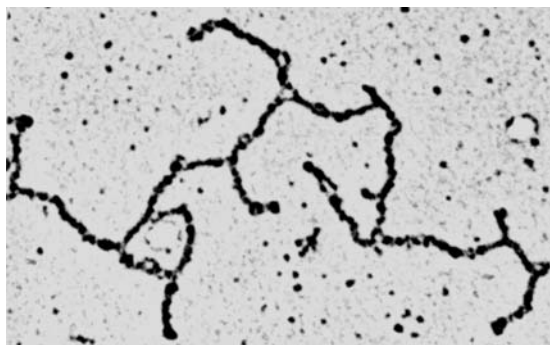


Figure S141. Supercoiled DNA plasmid of *Streptococcus lactis*. (Courtesy of Dr. Claude F. Garon)

The superhelical density expresses the superhelical turns per 10 bp and it is about 0.06 in cells as well as in virions. Loss of positive supercoiling may be lethal. Localized negative supercoiling may be lethal. Localized negative supercoiling is essential for gene expression, replication and many other functions of the DNA. ►DNA replication prokaryotes, ►transcription, ►Z DNA, ►packing ratio, ►linking number; Holmes VF, Cozarelli NR 2000 Proc Natl Acad Sci 97:1322.

Superdominance: Same as overdominance or monogenic heterosis. ►hybrid vigor, ►overdominance

Superfamily of Genes: A group of genes that are structurally related and may have descended from common ancestors although their present function may be different. (See <http://supfam.mrc-lmb.cam.ac.uk/SUPERFAMILY/index.html>).

Superfamily of Proteins: Evolutionarily related proteins. (See <http://cathwww.biochem.ucl.ac.uk/latest/index.html>).

Superfemale (metafemale): *Drosophila*, trisomic for the X-chromosome (XXX) but disomic for the autosomes; she is sterile. ►aneuploidy, ►supermale *Drosophila*

Superfetation: Due to an apparently rare autosomal dominant gene ovulation may continue after implantation of the fertilized egg and an unusual type of twinning results. In animals, when a female may mate repeatedly with several males, the same litter may become multipaternal. Human dizygotic twins may also be of different paternity when during the receptive period the female had intercourse with two different males. ►twinning, ►multipaternal litter; Fontana J, Monif GR 1970 Obstet Gynecol 35:585.

Supergenes: Linked clusters of genes that are usually inherited as a block because inversion(s) prevent(s) the survival of the recombinants for the clusters and thus have evolutionary and applied significance in plant and animal breeding. Supergenes may be adaptively linked polymorphic loci.

Superinfection: A bacterium is infected by another phage. This is generally not possible in a lysogenic bacterium because of immunity, i.e., the superinfecting phage cannot enter a vegetative cycle within the lysogen. Infection by two T even phages may fail in such an attempt by “superinfection breakdown.” Some higher organisms may be infected by parasites of different genotypes. The number of clones of the parasites may not increase with the progression of the disease indicating competition among the superinfecting strains (e.g., *Plasmodium*) ►immunity, ►phage, ►Plasmodium; Hayes W 1965 The Genetics of Bacteria and their Viruses. Wiley, New York; Vogt B et al 2001 Hum Gene Ther 12(4):359.

Supermale Asparagus: Can be obtained by regenerating and diploidizing plants obtained from Y chromosomal microspores or pollen by the techniques of cell culture. Thus, their chromosomal constitution is 18 autosomes + YY. These plants are commercially advantageous because of the higher yield of the edible spears. ►YY Asparagus

Supermale Drosophila: Has 1 X and 3 sets of autosomes, i.e., the fly is monosomic for X but he is trisomic for all the autosomes; he is sterile. ►superfemale, ►sex determination

Superman: A homeotic mutation in *Arabidopsis* resulting in excessive development of the androecium at the expense of other flower parts. The DNA base sequences are the same as in the wild type but the mutation evokes methylation. ►flower differentiation, ►androecium; Koshimoto N et al 2001 Plant Mol Biol

46:171; Cao X, Jacobsen SE 2002 *Curr Biol* 12:1138; Dathan N et al 2002 *Nucleic Acids Res* 30:4945.

Super-Mendelian Inheritance: The transmission of one of the alleles in a diploid is preferential because of the advantage of a gene at meiosis or post-meiotic steps of gametogenesis. This advantage may not be due an intrinsic superiority of the allele. Homing endonuclease genes (HEG) may be preferentially transmitted horizontally, but may or may not be propagated at a selective advantage. ▶homing endonuclease, ▶segregation distorter, ▶meiotic drive, ▶preferential segregation; Goddard MR, Burt A 1999 *Proc Natl Acad Sci USA* 96:13880.

Supermutagen: An efficient mutagen that causes primarily point mutations without inducing frequent chromosomal defects. ▶point mutation, ▶ethyl-methane sulfonate, ▶nitrosoguanidine

Supermutation: ▶hypermutation, ▶somatic hypermutation, ▶antibody gene switching

Supernatant: The non-sedimented fraction after centrifugation of a suspension or in general, any floating fraction derived of a mixture.

Supernatural: ▶paranormal

Supernumerary Chromosome: ▶B chromosome, ▶cat eye syndrome

Supernumerary Marker Chromosome: Rare ($\sim 3 \times 10^{-4}$) abnormal chromosomes with internal duplications and deletions. The majority ($\sim 60\%$) involves two inverted copies of the short arm, centromere and the proximal segment of the long arm of human chromosome 15 (SMC[15]). The majority of the latter are dicentric but one of the centromeres is inactive (pseudocentromeric 15). ▶chromosomal rearrangements; Roberts SE et al 2003 *Am J Hum Genet* 73:1061.

S

Superoperon: A regulatory complex tied together, e.g., photoreceptor pigment synthesis and photosynthesis. ▶operon, ▶überoperon, ▶supraoperon

Superovulation: By injection of gonadotropic hormones (into mice), the number of eggs produced may increase several fold. Fertilization follows after about 13 h and the eggs can be surgically collected to study, in vitro, the preimplantation development. Hormonal treatment may cause superovulation also in usually monoparous animals too. ▶twinning

Superoxide ($O_2^{\bullet-}$): A highly reactive species of oxygen. In the hypersensitivity reaction defense mechanism, it appears to play an important role along with nitric oxide. ▶nitric oxide, ▶hypersensitivity reaction,

▶SOD, ▶hydrogen peroxide, ▶ROS, ▶Fenton reaction, ▶peroxynitrite, ▶peroxides

Superoxide Dismutase (SOD): Catalyzes the reaction $2O_2 + 2H^+ \rightarrow O_2 + H_2O_2$ and thus participates in the detoxification of the highly reactive (mutagenic) superoxide radical $O_2^{\bullet-}$. These enzymes are the main detoxificants of the free radicals. SOD overexpression confers resistance to ionizing radiation under aerobic conditions. There are three isozymes of SOD: the cytosolic SOD-1 (human chromosome 21q22.1, the mitochondrial SOD-2 [6q25.3] and the extracellular SOD-3 [4pter-q21]). In SOD deficiency, cardiomyopathy, brain damage, mitochondrial defects, Lou Gehrig's disease and precocious aging may result. A non-peptidyl manganese complex with bis (cyclohexylpyridine)-substituted macrocyclic ligand may mimic SOD activity. Inhibition of SOD enzymes may trigger suicide of leukemia cells, which have a higher rate of oxidative metabolism. Cell suicide may also occur when the level of hydrogen peroxide is high or when the latter is converted to hydroxyl radicals in a Fe^{2+} dependent process. Using the cytosolic SOD gene in an adenoviral vector may provide protection against ROS injury. ▶amyotrophic lateral sclerosis, ▶granulomatous disease, ▶cardiomyopathies, ▶aging, ▶ROS, ▶host-pathogen relationship, ▶oxidative stress, ▶AMPA; Fridovich I 1975 *Annu Rev Biochem* 44:147; Danel C et al 1998 *Hum Gene Ther* 9:1487.

Superparamagnetic Scale Particles: ▶magnetic relaxation switches, ▶magnetic targeting

Super-Repressed: Bacterial operon cannot respond to inducer. ▶repression, ▶inducer

Supershift: ▶gel retardation assays

Supersuppressor: A dominant suppressor acting on more than one allele or even on different gene loci. ▶suppressor; Gerlach WL 1976 *Mol Gen Genet* 144:213.

Supervillin: ▶androgen receptor

Supervised Learning: Finding shared patterns or motifs common to all "positive" sequences and absent from all "negative" ones in a curated way. ▶motif, ▶unsupervised learning, ▶curated; Moler EJ et al 2000 *Physiol Genomics* 2(2):109.

Supervital: Fitness exceeds that of the standard (wild) type.

supF: An amber-suppressor mutation in $tRNA^{Tyr}$ that recognizes the chain-termination codon (5'-UAG-3') as if it would be a tyrosine codon (5'-UAC-3' or

5'-UAU-3') because a mutation at the anticodon sequence in the tyrosine tRNA changes the 5'-GUA-3' into a 5'-CUA-3' and thus the tyrosine tRNA inserts a tyrosine into the growing peptide chain where translation would have been terminated. ►[suppressor tRNA](#), ►[πVX](#).

supG: Suppressor mutation for both amber (5'-UAG-3') and ochre (5'-UAA-3') chain termination codons, by a base substitution mutation in the anticodon of lysine tRNA from (5'-UUU-3') to 5'-UUA-3' that can recognize the amber and ochre codons in the mRNA, as if they would be lysine (5'-AAA-3' or 5'-AAG-3') codons and thus inserting in the peptide chain a lysine rather than discontinuing translation. (Note: the pairing is antiparallel).

Support: A statistical concept it is synonymous with log likelihood. ►[likelihood](#)

Support Vector Machine (SVM): A computer program based on the principle of supervised learning techniques. It uses a training set to determine which data should be clustered a priori. The operations start with a set of genes that are already known to have common function, e.g., genes that encode ribosomal proteins. It picks another set of genes that are not members of the functional group specified. These two sets form the training examples and the genes are marked positive in case they fall in the specified functional class or negative if they are not. The SVM thus learns from the two groups how to discriminate and classify any “unknown” on the basis of function. This procedure can classify genes based on microarray hybridization data and identify functional clusters genome-wide. ►[microarray hybridization](#), ►[machine learning](#), ►[supervised learning](#), ►[cluster analysis](#); Brown MPS et al 2000 Proc Natl Acad Sci USA 97:262; Hua S, Sun Z 2001 Bioinformatics 17(8):721; Cristianini N, Shawe-Taylor J 2000 An Introduction to Support Vector Machines and Other Kernel-Based Learning Methods. Cambridge University Press, New York.

Supportive Counseling: To alleviate the psychological problems involved with the discovery of hereditary disorders and birth defects in families. ►[counseling genetic](#)

Suprachiasmatic Nucleus: A small site in the hypothalamus above the optic region controlling rhythmic function of the body and memory of all vertebrates. ►[brain human](#)

Supramolecular/Supermolecular: Literally means beyond molecular, but it is also used for structures assembled from molecules held together by bonds weaker than those within molecules are. The number

of molecules, how they are connected, and the way they are oriented relative to each other, characterizes the system structurally. Supermolecular structure is important for understanding how cells function. (See Turro NJ 2005 Proc Natl Acad Sci USA 102:10765).

Supraoperon: A region of the prokaryotic genome where operons of similar function are located, e.g., in the aromatic (*aro*) amino acid pathway including tryptophan (*trp*) and histidine (*his*): ►[operon](#), ►[überoperon](#), ►[superoperon](#); Berka RM et al 2003 Proc Natl Acad Sci USA 100:5682.

Supravalvar Aortic Stenosis (SVAS): A human chromosome 7q11 dominant mutation in an elastin gene with a prevalence of about 5×10^{-5} causing obstruction of the aortic blood vessels. The basic defect is due to a deficiency of elastin. It is pleiotropic and part of the Williams syndrome. ►[coarctation of the aorta](#), ►[cardiovascular diseases](#), ►[William's syndrome](#), ►[elastin](#)

Suppressor, Bacterial: Protein product of the bacterial regulator gene (e.g., *i* in the *Lac* operon) that when associated with the operator prevents transcription. ►[Lac operon](#), ►[ara operon](#)

Suppressor, Extragenic: The suppressor mutation is outside the boundary of the suppressed gene. ►[suppressor tRNA](#), ►[second-site suppressor](#), ►[second site reversion](#)

Suppressor Gene: Restores function lost by a mutation without causing a mutation at the site suppressed. The suppressor can be intragenic (within the cistron but also at another site) or at any other locus, e.g., in the signal transduction pathway. The suppressor may act by reducing and also by overexpression of a gene product. ►[suppressor extragenic](#), ►[suppressor intragenic](#), ►[suppressor informational](#), ►[frameshift](#), ►[mutation in organelle DNA](#)

Suppressor, Haplo: Dominant suppressor that can act in a single dose.

Suppressor, Informational: Interferes with the expression of another gene at the level of translation by affecting either tRNAs or ribosomes or peptide elongation factors.

Suppressor, Intragenic: The suppressor site is within the gene where suppression takes place. ►[frameshift suppressor](#)

Suppressor Mutation: ►[suppressor gene](#), ►[sup](#), ►[suppressor tRNA](#), ►[suppressor RNA](#), ►[frameshift suppressor](#), ►[mitochondrial suppressor](#)

Suppressor RNA (sRNA): Prevents translation of a mRNA by partial base pairing with a specific

sequence of the target. Two 22 and 40 nucleotide long tracts of the *lin-4* transcripts control the translation of gene *lin-14*. The latter is an early expressed nuclear protein in *Caenorhabditis* but its expression is blocked during later stages by the *lin-4* RNA that itself is not operating through a protein. Several other genes are subject to RNA suppressors in other organisms. The mechanism of this suppression seems to be different from that of the suppressor tRNA. ▶**suppressor tRNA**, ▶**suppressor gene**, ▶**antisense RNA**, ▶**antisense DNA**, ▶**RNAi**, ▶**repressor**; Olsthoorn RC et al 2004 RNA 10:1702.

Suppressor, Second Site: A suppressor outside the boundary of the locus but usually within the same chromosome. ▶**suppressor gene**, ▶**second site reversion**

Suppressor Selection Gene Fusion Vector: Carries nonsense codon(s) in the structural gene and can be expressed only if the target genome carries nonsense suppressors. ▶**vectors gene fusion**, ▶**transcriptional gene fusion vector**

Suppressor T Cell: Can suppress antigen-specific and allospecific T cell proliferation by competing for the surface of antigen-presenting cells. ▶**T cell**, ▶**allospecific**; Maloy KJ, Powrie F 2001 Nature Immunol 2:816.

Suppressor tRNA: Makes the translation of nonsense or of missense codons in the original, normal sense possible because a mutation in the anticodon of the tRNA recognizes the complementary sequence in the codon but its specificity resides in the tRNA molecule (see Fig. S142). Exceptions are possible, however. In the anticodon 5'-CCA-3' of the tryptophan codon (5'-UGG-3') is not mutant yet it may deliver to the opal position a tryptophan if at position 24 of the D loop of the tryptophan tRNA a guanine is replaced by an adenine. Similarly, if in the GGG codon of glycine another G base is inserted by a frameshift mutagen but subsequently, in its anticodon (CCC) an extra C is inserted then the tRNA may read the four bases normally as a glycine codon rather than nonsense. Beyond the codon-anticodon binding, mutation elsewhere in tRNA^{Trp} can effect the correct decoding (Cochella L, Green R 2005 Science 308:1178). ▶**tRNA**, ▶**Hirsh suppressor**, ▶**code genetic**, ▶**mutation in organelle DNA**, ▶**phenotypic reversion**, ▶**translation in vitro**; Smith JD et al 1966 Cold Spring Harb Symp Quant Biol 31:479; Murgola EJ 1985 Annu Rev Genet 19:57; Beier H, Grimm M 2001 Nucleic Acids Res 29:4767.

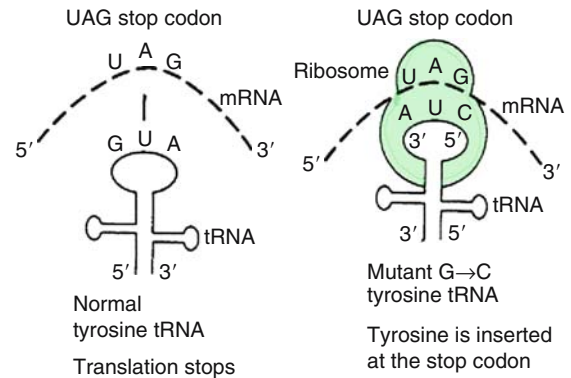


Figure S142. Suppressor tRNA

supU: A suppressor of the opal (5'-UGA-3') chain terminator codon with an anticodon sequence of 5'-UCA-3'. The mutation changes the anticodon of the tryptophan tRNA from 5'-UCA-3' to 5'-CCA-3' and that permits the insertion of a tryptophan residue into the polypeptide chain where it would have been terminated without the suppressor mutation (codon-anticodon recognition is antiparallel). This suppressor mutation is unusual because it recognizes both the tryptophan codon (5'-UGG-3') and the opal suppressor codon, i.e., its action is ambivalent.

SurA: Periplasmic parvulin type peptidyl-prolyl isomerase involved in chaperoning outer membrane proteins. ▶**peptidyl-prolyl isomerase**, ▶**parvulin**, ▶**periplasma**

Surface Antigen: Generally, glycoprotein molecules on the cell surface that determine the identity of the cells for immunological recognition. The display of surface antigens is regulated at the level of transcription. ▶**VSA**, ▶**antigen**, ▶**Trypanosomas**, ▶**Borrelia**

Surface Plasmon Resonance (SPR): Incoming light, in a certain angle, hits a hydrophilic dextran layer covered gold surface. The interacting molecule is immobilized on this surface. As the molecule injected binds to this surface the refractive index of the medium is increased and the change in the angle at which the intensity change occurs is measured in resonance units. The size of the macromolecule is positively correlated with the response. This analysis has numerous biological applications for the determination of protein-protein interactions such as antibody affinities, epitope, growth factor, signal transducing molecule, receptor, ligand binding, etc. ▶**biosensors**, ▶**microcalorimetry**, ▶**immunoprecipitation**; Heaton RJ et al 2001 Proc Natl Acad Sci USA 98:3701.

Surfactant: Common surfactants are soaps and detergents. In gene therapy, different surfactants such as perfluorochemical liquids, phospholipids may facilitate gene delivery to pulmonary tissues.

Surfection: A procedure to transfer genes to cells layered of the surface of polyethylenimine/collagen-coated wells. It can deliver multiple plasmids into cells at large-scale arrays. The procedure can assay RNAi-mediated silencing, live-cell imaging and cell-based drug screening. ▶RNAi; Chang F-H et al 2004 *Nucleic Acids Res* 32(3):e33.

Surrogate Chains (ΨL, ΨH): Of immunoglobulins are found in the progenitor (pro-) B lymphocytes. In the human and mouse fetal liver and adult bone marrow an 18 kDa protein with (~45%) homology to the variable regions of the κ, λ and heavy chains and a 22 kDa protein with ~70% homology to the constant region of the λ chain have been found. The synthesis of these proteins (ΨL) ceases after the IgM chains appear on the lymphocyte surface. They participate in the formation of the B cell receptor with other immunoglobulins and a short μ chain containing only the N-terminal D(J)C sequences. The ΨL light chains are associated with a complex of 130 kDa/35–65 kDa glycoproteins (ΨH) and together make the surrogate receptors. ▶immunoglobulins, ▶B lymphocytes, ▶immune system; Meffre E et al 2001 *J Immunol* 167:2151.

Surrogate Genetics: ▶reversed genetics

Surrogate Mother: A female who carries to term a baby for another couple. She may actually contribute the egg or may just be a gestational carrier of a fertilized egg and has no genetic share in the offspring. In either case, moral, ethical, psychological and legal problems must be pondered before this method of child bearing is chosen. Civil law generally keeps the maternal right of the gestational mother despite any contractual agreement contrary to natural parenthood. In case, however, the gestational mother is not the donor of the ovum, the maternal right pertains to the biological ovum donor. Obviously, there are serious ethical problems here beyond the principles of genetics. The society must protect the best interest of the child. ▶oocyte donation, ▶ART, ▶paternity testing

Surveillance, mRNA: A mechanism of quality control for the elimination of defective proteins. (See Hilleren P et al 1999 *Annu Rev Genet* 33:229; ▶immunological surveillance).

Survey Sequencing: Covers only 1x-2x of the genome, providing information on 60–80% of the sequences in a fragmented form, compared with complete sequencing that employs 6x-8x coverage. It is

a temporary compromise mandated by monetary, physical and manpower limitations. It still provides substantial information because several other genomes with homologies supplement and complement the missing information. (See Hitte C et al 2005 *Nature Rev Genet* 6:643).

Survival: The total survival probability per genetic damage is expressed by the equation:

$$S(\rho, \partial) = \sum_{h=0}^{h=\partial} P(\rho, h, \partial!)$$

where ρ = hit probability, ∂ = VD, V = total cell volume, D = density of the active events [dose], P = likelihood of survival. (See more in Alpen EL 1998 *Radiation Biophysics*. Academic Press; ▶target theory, ▶neutral mutation, ▶beneficial mutation, ▶cost of evolution, ▶genetic load, ▶fitness)

Survival Factors: Interfere with apoptosis. The balance between survival and apoptosis is very complex and a large number of proteins and ligands are involved through different pathways. (See Fig. S143, ▶apoptosis, ▶BAD, ▶survivin)

Survival Estimator: ▶Kaplan-Meier estimator

Survival of the Fittest: ▶fitness, ▶neo-Darwinism, ▶social engineering, ▶social Darwinism

Survival Phenotype: Under poor nutritional condition the fetus develops a lean body, undersized visceral organs, fewer muscle cells, undersized nephrons and liver. Because of the maternal nutritional deficiency, the promoters of many genes remain unmethylated in the early embryo, resulting in altered phenotype persisting into adulthood. After birth, they may gain more weight when food becomes available and may become diabetic. ▶nephron, ▶diabetes; Gluckman P, Hanson M 2005 *The fetal matrix: Evolution, development and disease*. Cambridge University Press.

Survivin: An inhibitory protein (16.5 K) of caspases that are activated by cytochrome c. It is antiapoptotic. Survivin is expressed as a passenger protein at the G2—mitosis phases of the cell cycle and it is associated with the microtubules of the mitotic spindle. Apoptosis may be caused by the disruption of this association. Overexpression of survivin may lead to cancer. Disruption of survivin action may reduce melanoma growth. Survivin is essential for the development of erythroid cells; but overexpression of survivin interfered with megakaryocyte development but did not affected erythroid cells (Gurbuxani S et al 2005 *Proc Natl Acad Sci USA* 102:11480). The *survivin* gene promoter contains several Sp1 canonical, Sp1-like, and p53-binding elements, suggesting participation of the Sp1

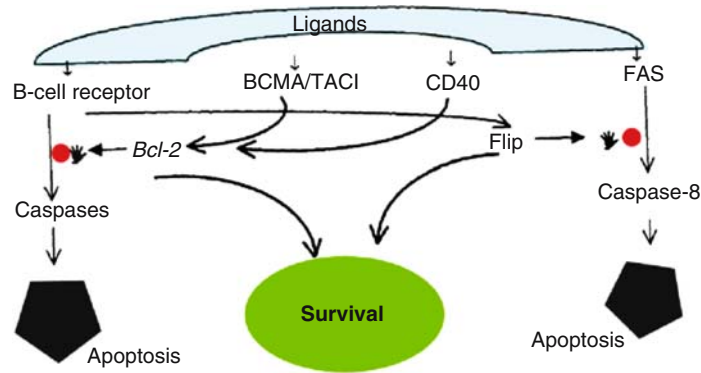


Figure S143. Survival factors

transcription factor and/or p53 in gene regulation. Furthermore, *survivin* transcription is down-regulated by the DNA-damaging agent doxorubicin, which mediates p53 induction in acute lymphoblastic leukemia (Estève P-O et al 2007 J Biol Chem 282:2615). ▶apoptosis, ▶cell cycle, ▶spindle, ▶survival factor, ▶passenger protein, ▶Stat, ▶megakaryocyte, ▶erythrocyte, ▶p53, ▶doxorubicin, ▶leukemia; Wheatley SP et al 2001 Curr Biol 11:886; Hoffman WH et al 2002 J Biol Chem 277:3247; Altieri D 2003 Nature Rev Cancer 3:46.

Suspension Culture: The cells are grown in liquid nutrient medium.

Suspensor: A line of cells through which the plant embryo is nourished by the maternal tissues. In general, anatomy ligaments may be called suspensors.

Sutent: ▶Gleevec

Suture: A junction of various solid animal and plant tissues.

Su(var): Suppressor of variegation. ▶heterochromatin; Rudolph T et al 2007 Mol Cell 26:103; Haynes KA et al 2007 Genetics 175:1539.

SUV39H1 (Clr): ▶histone methyltransferases

Sv: ▶Sievert

SV2s: Glycosylated transmembrane proteins, homologous to prokaryotic and eukaryotic transporters. ▶transporters

SV40 Tag: Simian virus 40 large T antigen. ▶Simian virus 40

SV40 Vectors: SV40 plasmids (vectors) can be packaged only if their DNA is within the range of 3900 to 5300 bp. Since these small genomes do not have much dispensable DNA, it is almost impossible to construct a functional vector with any added genes

to it. Fortunately, functions provided by helper DNA molecules might help to overcome these problems. Simian Virus 40 cannot replicate autonomously if the replicational origin (*ori*) is defective, yet it can integrate into chromosomal locations of green monkey cells and can then be replicated along the chromosomal DNA (such a cell is COS [cell origin simian virus]). Also, since the early genic region is normal (▶Simian Virus 40 for structure), it may produce the T antigen within the cell. If such a cell is transformed by another SV40 vector in what the viral early gene region was replaced by a foreign piece of DNA, the COS cell may act as a helper and replicate multiple copies of the second, the engineered SV40 DNA. Since the late gene region of this plasmid is normal, the viral coat proteins can be synthesized within the cell. The availability of the coat proteins permits the packaging of the engineered SV40 DNA into capsids.

The virions so obtained can be used to infect other mammalian cells where the passenger DNA can be transcribed and translated and the foreign protein can be processed. The transformed cell thus can acquire a new function. Also, an SV40 plasmid can be constructed with insertion into the late gene cluster, a foreign gene with a desired function. This plasmid can then use inactivated (deleted) early genes but with a good *ori* site. Upon coinfection of a mammalian cell with these two plasmids, the SV40 plasmids can replicate to multiple copies and the inserted foreign gene can be expressed. Also, it is feasible to insert into a prokaryotic pBR322 plasmid the *ori* region of SV40 and another piece of DNA including all the necessary parts of a foreign gene. When this plasmid is transfected into a COS cell, the passenger gene can be transcribed, translated and processed thanks to the multiple copies replicated within this mammalian cell. With the assistance of SV40 based constructs, mammalian and other genes can be shuttled between mammalian and bacterial cells.

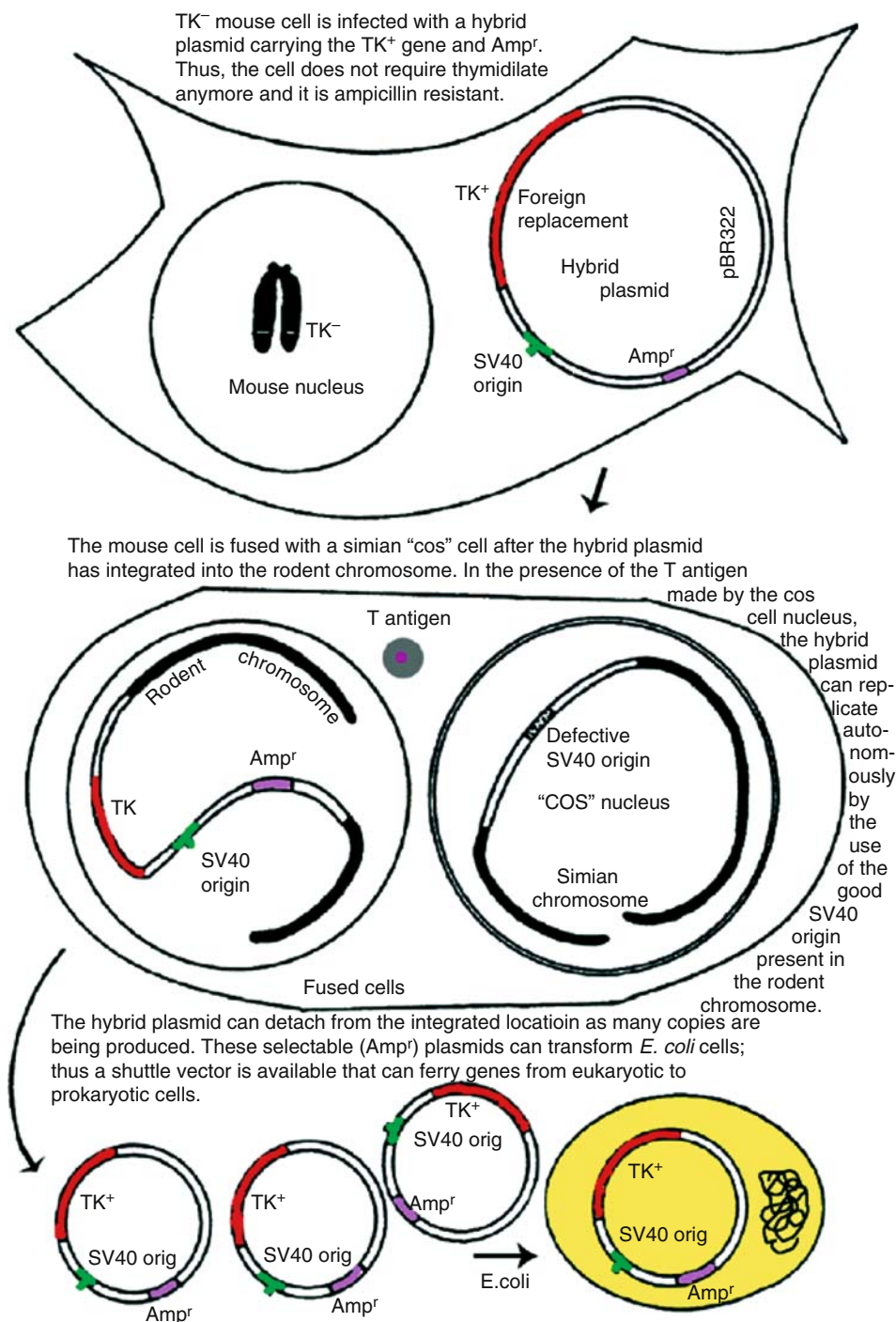


Figure S144. SV40 shuttle vectors can ferry genes from mammals to prokaryotes

The procedure: a thymidine kinase-deficient (*tk*⁻) rodent cell is transformed by pBR322 bacterial plasmid carrying the *ori* of SV40 and the TK⁺ (functional thymidine kinase), and an ampicillin resistance gene (*amp*^R) for bacterial selectability. Within the rodent cell the bacterial plasmid is integrated into a chromosome of the rodent cell and

this cell is then fused with a COS cell. The integrated pBR322 plasmid is replicated into many copies thanks to the presence of the COS nucleus. The hybrid plasmid carrying a bacterial replicon, an SV40 *ori*, the TK⁺ and *amp*^R can infect *E. coli* cells and can be selectively propagated there. Thus, the shuttle function is achieved. Another SV40 and pBR322

based vector is the pSV plasmid. This contains, in a Pvu II and HinD III restriction enzymes generated fragment, the promoter signals and the mRNA initiation site. When any open reading frame is attached to it, transcription can proceed. In addition, an intron of the early region provides splicing sites for other genes. The region also contains the transcription termination and polyadenylation signals. Some other pBR322 parts may be equipped with additional specific, selectable markers. ▶[Simian virus 40](#), ▶[vectors](#), ▶[viral vectors](#), ▶[shuttle vector](#); Jayan GC et al 2001 Gene Ther 8:1033; see Fig. [S144](#).

SVA: Non-autonomous transposable elements in the human genome that are mobilized by L1. ▶[transposable element](#), ▶[LINE](#); Ostertag EM et al 2003 Am J Hum Genet 73:1444.

SVC: ▶[carbon dioxide \(CO₂\) sensitivity](#)

SVD (singular value decomposition): A comparative mathematical procedure for genome-scale study of expression of two data sets, containing “genelets,” shared by both sets. (Alter O et al 2003 Proc Natl Acad Sci USA 100:3351).

Svedberg Units: ▶[sedimentation](#)

SVF-2: A member of the tumor necrosis factor receptor family. ▶[Fas](#), ▶[TNF](#)

Swapping Genes: exchanging genes by horizontal transfer via plasmids. ▶[transmission](#), ▶[site-specific recombination](#), ▶[targeting genes](#); Nebert DW et al 2000 Ann N Y Acad Sci 919:148.

Swede (*Brassica napus*): A leafy fodder crop in Northern climates and it also an edible human vegetable; 2n = 38, AABB genomes. ▶[rape](#)

Sweet Clover (*Melilotus officinalis*): A fragrant leguminous plant because of its coumarin content. The coumarin-free forms (*M. albus*) are used as hay, 2n = 16. ▶[coumarin](#)

Sweet Pea (*Lathyrus odoratus*, 2n = 14): An ornamental that had been exploited for studies on the genetic determination of flower pigments (see Fig. [S145](#)). Another peculiarity is that the “long”/“disc” pollen shape (*L/l*) is determined by the genotype of the sporophytic (anther) tissue rather than by the gametophyte. Therefore, delayed inheritance is observed. ▶[delayed inheritance](#)



Figure S145. Sweet pea

Sweet Potato (*Ipomoea batatas*): Primarily a warm climate vegetable with about 25 species with basic chromosome number x = 15 and a single genome; the most common cultivated form is hexaploid, although related species may be diploid or tetraploid.

Swept Radius: ▶[linkage](#)

SWI, SWI2/SNF2, SWI3: Yeast genes encoding transcriptional activators by chromatin remodeling. The homologous protein in *Drosophila* is BRAHMA. SWI2/SNF2 is a DNA-dependent ATPase. A heterodimer of Swi4 and Swi5 is SBF. A heterodimer of Swi6 and Mbp1 is MBF. ▶[activator genes](#), ▶[co-activator](#), ▶[transcriptional activator](#), ▶[Polycomb](#), ▶[chromatin remodeling](#), ▶[NURF](#), ▶[CHRAC](#), ▶[ACF](#), ▶[nucleosome](#), ▶[nuclease-sensitive sites](#), ▶[Mbp1](#), ▶[SBF](#); Muchardt C, Yaniv M 1999 J Mol Biol 293:187; Sengupta SM et al 2001 J Biol Chem 276:12636.

Swi6: A centromeric repressor chromodomain protein in *Schizosaccharomyces pombe*, essential for centromere function. ▶[centromere](#)

Swimming in Bacteria: Movement by counterclockwise rotation of the flagella.

Swine: Most commonly used name for the female animals of the *Sus* species (hogs). ▶[pig](#)

SWI/SNF: ▶[nucleosome](#), ▶[chromatin remodeling](#), ▶[SWI](#)

SwissProt Database: protein information: <http://www.expasy.org/>; <http://www.ebi.ac.uk/swissprot/>.

Switch, Genetic: An individual cell may initially express immunoglobulin gene C_μ but in its clonal progeny it may change to the expression of C_α as a result of somatic DNA rearrangement. Similar DNA switch may occur in the variable region of the light-chain genes. Switching occurs during the mating type determination of yeast and phase variation in prokaryotes. The operation of genetic switch was first thoroughly studied in phage lambda. ▶[immunoglobulins](#), ▶[antibody gene switching](#), ▶[epigenesis](#),

► *Trypanosomas*, ► *Borrelia*, ► lambda phage, ► site-specific recombination, ► mating type determination in *Saccharomyces*, ► phase variation, ► Gene-Switch; Ptashne PM 2004 Genetic Switch, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; ► riboswitch

Switching, Phenotypic: May occur without any change in the genetic material and involves only altered regulation of transcription resulting in different phenotypes.

Swivelase (topoisomerase type I): After a single nick in a supercoiled DNA, it permits the cut strand to make a turn around the intact one to relieve tension. ► DNA replication, ► prokaryotes, ► topoisomerase; Zhu Q et al 2001 Proc Natl Acad Sci USA 98:9766.

SWR: ► chromatin remodeling

SWR Mouse: Prone to cancer and autoimmunity.

Swyer Syndrome (gonadal dysgenesis XY type, Xp22.1-p21.2): Apparently mutation or loss in the SRY gene is responsible for the anomaly. The afflicted individuals appear normal females until puberty but display only deficient (“streak”) gonads and fail to menstruate. ► gonadal dysgenesis, ► testicular feminization, ► SRY, ► sex determination, ► Denys-Drash syndrome

Sxl (sex lethal): (chromosomal location 1-19.2) Controls sexual dimorphism in *Drosophila*; it is required for female development. ► sex determination

SXR (steroid xenobiotic receptor in humans): Its mouse homolog is Pxr. This protein is an inducer of the cytochrome P450 detoxifying enzyme CYP3A4 (7p22.1). Mice transgenic for SXR displayed enhanced protection against environmental and drug carcinogens. This system also has important role in the oxidative activation of procarcinogens such as aflatoxin B and many different drugs. Apparently, the herb St. John’s wort, which may lower the effectiveness of the antiseizure phenobarbital, breast cancer drug tamoxifen, the contraceptive ethinyl estradiol, etc., activates SXR/Pxr. ► cytochromes; Synold TW et al 2001 Nature Med 7:536.

Sybase: A computer program that links various databases for macromolecules such as GeneBank, EMBL. ► data management system, ► databases; <https://login.sybase.com/login/userLogin.do>.

Sycamore (*Platanus* spp): Large attractive monoecious trees, 2n = 42.

SYK (M_r 72 K): A signal protein for the interleukin-2, granulocyte colony-stimulating factor and for other agonists. It is a protein tyrosine kinase of the SRC

family and indispensable for B lymphocyte development. Syk is downregulated by the Cbl protein. Syk seems to modulate epithelial cell growth and may suppress human breast carcinomas. ► B cell, ► ZAP-70, ► agonist, ► B lymphocyte receptor, ► Cbl, ► BTK; Sada K et al 2001 J Biochem 130:177.

Syllogism: A form of deductive reasoning using a *major premise*, e.g., mice show graft rejection, the rejection of transplants is based on the presence of the MHC system (*minor premise*), and therefore mice must have a major histocompatibility system (*conclusion*). ► logic

Symbionts: Mutually interdependent cohabiting organisms, such as the *Rhizobium* bacteria within the root nodules of leguminous plants, or algae within green hydra animals. The boundary between pathogenesis and mutualistically advantageous situation is not always clear. Many symbionts are essential for nutrition, digestion, development, and defense against other pathogens whereas others are definitely harmful for the health or reproduction of the host.

The leaf-cutting ants rear and feed only a single species of fungus through millions of years and develop mutualistic relations with it (Poulsen M, Boomsma JJ 2005 Science 307:741). Some wasps (*Philanthus triangulum*) cultivate *Streptomyces* bacteria in their antennal glands and apply them to the blood and this protects the cocoon from fungal infestation (Kaltenpoth M et al 2005 Curr Biol 15:475). Symbiosis may lead to loss or inactivation of genes that are no longer necessary in a cohabiting situation. The marine worm *Olavius algarvensis* lack mouth, gut and nephridia (excretory organs) and the nutritional functions are supplied by the cohabiting sulphur-oxidizing and sulphate reducing bacteria (Woyke T et al 2006 Nature [Lond] 443:950). On the other hand, new functions may be acquired or pre-existing gene functions may be enhanced that are mutually beneficial. Symbiosis may be interpreted either as mere cohabitation or a mutually meaningful association (advantageous or parasitic). Bacterial nitrogen fixation and mycorrhizal symbiosis is controlled by a ligand-gated cation (Ca²⁺, calmodulin) channel (Lévy J et al 2004 Science 303:1361). Calcium spiking is one of the initial steps in the symbiotic process. The proteins for establishing the symbiotic relationship for both fungi and bacteria reside in the plastids of the plant roots (Imaizumi-Anraku H et al 2005 Nature [Lond] 433:527). The plant pathogenic fungus *Rhizopus* harbors intracellular *Burkholderia* bacteria, which are responsible for the production of a polyketide, rhizoxin toxin. The toxin poisons β-tubulin and has strong antimitotic effect and, thus, can have medical use as an anticancer

agent (Partida-Martinez LP, Hertweck C 2005 Nature [Lond] 437:884). ►mycorrhiza, ►nitrogen fixation, ►mutualism, ►*Piriformospora indica*; Bermudes D, Margulis L 1987 Symbiosis 4:185; Currie CR 2001 Annu Rev Microbiol 55:357; mutualistic symbiosis among insects, bacteria and viruses: Moran NA et al 2005 Proc Natl Acad Sci USA 102:16919.

Symbionts, Hereditary: Occur in a wide range of eukaryotic organisms and their maternal transmission simulates extranuclear inheritance. They may be more wide spread than recognized. The temperate viruses of prokaryotes and the retroviruses may also be classified along these groups. In some strains of the unicellular protozoa, *Paramecium aurelia*, carrying the *K* gene, bacteria (e.g., *Caedobacter taeniospiralis*) live in the cytoplasm and is transmitted to the progeny. The first such infectious particles were named kappa (κ) particles before their bacterial nature was recognized, and were supposed to be normal extranuclear, hereditary elements. Many of these kappa particles contain R (refractive) bodies that are bacteriophages. The κ particles with R bodies appear "bright" under the phase-contrast microscope. The non-bright cells may give rise to bright, indicating that the phages are in the free and infectious stage and the brights are in the integrated, proviral stage. The virus directs the synthesis of toxic protein ribbons that are responsible for killing kappa-free paramecia ($\kappa\kappa$). The strains carrying the dominant *K* gene are immune to the toxin. Other strains have been discovered carrying different infectious particles lambda, sigma, mu that also make toxins. The mu particles do not liberate free toxin and kill only the cells with which they mate (mate killer). Other symbionts delta, nu and alpha are not killer symbionts.

In *Drosophila* strains Rhabdovirus σ may be in the cytoplasm and responsible for CO₂-sensitivity. Normal flies can be anesthetized with the gas for shorter periods without any harm. Those, which carry the virus may be paralyzed and killed by the same gas treatment. This virus is similar to the vesicular stomatitis virus of horses that cause fever, eruptions and inflammation in the mouth of horses, and to the fish rhabdovirus. In the non-stabilized strains, only the females transmit the virus to part of the progeny (depending on whether a particular egg does or does not contain the virus). Some of the non-stabilized may become stabilized. Stabilized strains transmit it through nearly 100% of the eggs and even some of the males transmit σ with some of the sperm yet the offspring of the male will not become stabilized. The *ref* mutants in chromosomes 1, 2 and 3 are refractory to infection. In some strains, there are mutants of the virus that are either temperature-sensitive or constitutively unable to cause CO₂ sensitivity although

they are transmissible. Different ribosomal picorna-viruses can be harbored in *Drosophila* that may reduce the life and fertility of the infected females. Females with the sex ratio (SR) condition produce no viable sons and the transmission is only maternal. In their hemolymph (internal nutrient fluids) the females carry spiroplasmas, bacteria without cell wall. If the infection is limited to the XX sector of gynanders, they may survive but not if the infection is in the XO sector. Triploid intersexes or females, phenotypically sterile males because of the genes *tra* (*transformer*, chromosome 3-45), *ix* (*intersex* gene located at 2-60.5) or *dsx* (*double-sex*, intersexes, chromosome 3-48.1) are not killed. Their special viruses may destroy the spiroplasmas. In plants (petunia, sugar beet), cytoplasmically inherited male sterility can also be transmitted by grafting. Some of the variegated tulips (broken tulips) are infected by viruses and had special ornamental value. During the seventeenth and eighteenth century "tulip mania," some rich Europeans paid the mainly Turkish and Persian merchants for the bulbs of the most attractive varieties, in equal weights in gold. ►lysogeny, ►cytoplasmic male sterility, ►extranuclear inheritance, ►*Drosophila*, ►aphids, ►meiotic drive, ►segregation distorter, ►broken tulips, ►sex determination, ►*Wolbachia*, ►*Spirochetes*, ►*Paramecia*, ►endosymbiont theory, ►pathogenicity island; Preer JR 1975 Symp Soc Exp Biol 29:125; Ehrman L, Daniels S 1975 Aust J Biol Sci 28:133; review of bacterial symbionts: Dale C, Moran NA 2006 Cell 126:453.

Symbiosis: ►symbiont

Symbiosome: In legume root nodules 2 to 5 μ m structures enclosing (by peribacteroid membrane) 2 to 10 bacteroids. The fixed nitrogen is released through this membrane to the plant and reduced carbon is received by the bacteroids from the plant. ►nitrogen fixation

Symbols: ►gene symbols, ►*Drosophila*, ►pedigree analysis

Symmetric Heteroduplex DNA: ►Meselson-Radding model of recombination

Symmetry: ►axis of asymmetry, ►asymmetric cell division, ►bilateral symmetry, ►left-right asymmetry, ►retinoic acid

Sympathetic Nervous System: Communicates with the central nervous system (CNS, brain) through the thoracic and lumbar parts of the spinal cord, controls the blood vessels in the various organs, and the involuntary movements (reflexes) of the body.

Sympatric: Populations have overlapping habitats; it may be a beginning of speciation. ► [speciation](#)

Sympatric Speciation: Species that live in the same, shared area, for some reason become sexually isolated. This is a relatively rare phenomenon because most commonly geographical isolation is the major factor in speciation. ► [allopatric](#), ► [parapatric](#); palm trees: Savolainen V et al 2006 Nature [Lond] 441:210; cichlid fish: Barluenga M et al 2006 Nature [Lond] 439:719.

Sympetaly: Fused petals in a flower, see e.g., ► [snapdragon](#)

Symphalangism, Proximal: Fusion of the carpal and tarsal bones (SYM1, 17q22) caused by a defect in the noggin protein. ► [noggin](#), ► [bone diseases](#)

Symphlast: Multinucleate giant cell.

Symplastic Domain: A regulatory (supracellular) unit of several cells within the body.

Symplekin: A CPEB and CPSF binding protein scaffold, essential for cytoplasmic polyadenylation of mRNA in connection with xGLD-2 poly(A) polymerase. ► [polyadenylation signal](#); Barnard DC et al 2004 Cell 119:641.

Symplesiomorphic: Two or more species sharing a primitive evolutionary trait. ► [plesiomorphic](#), ► [apomorphic](#), ► [synapomorphic](#)

Symport: Co-transportation of different molecules through membranes in the same direction.

SYN: A prefix indicating union of tissues named after.

SYN: ► [ANTI](#)

Synaesthesia: Involuntary physical experience of a cross-modal linkage, e.g., hearing a tone (an inductive stimulus) and seeing a color or perception of smell or taste (Beeli G et al 2005 Nature [Lond] 434:38).

Synapomorphic: Species sharing an apomorphic trait. ► [apomorphic](#), ► [plesiomorphic](#), ► [symplesiomorphic](#)

Synapomorphy: Shared derived characters that can be used to advance phylogenetic hypotheses. ► [simple-siomorphy](#); Venkatesh B et al 2001 Proc Natl Acad Sci USA 98:11382.

Synaps (synapse): The site of connection between neural termini at which either a chemical or an electric signal is transmitted from one neuron to another (or to another type of cell) (see Fig. S146). Neurotransmitter release occurs at the presynaptic active zones and at postsynaptic densities. There is now evidence that extrasynaptic (ectopic) transmission also occurs (Coggan JS et al 2005 Science 309:446).

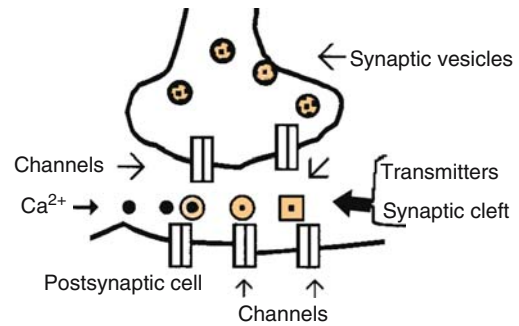


Figure S146. Synaps

The neurotransmitter may diffuse across the synaps or the electric signal may be relayed from one cytoplasm to the other through a gap junction. The neurons must interpret the postsynaptic potentials (PSP) and integrate the excitatory (EPSP) and inhibitory (IPSP) paired pulse potentials. The leukocyte common antigen related (LAR) protein, liprin (encoded by gene *syd-2* in *Caenorhabditis*), regulates the differentiation of the presynaptic vessels. This protein has tyrosine phosphatase activity. Mitochondria normally accumulate close to the site of synaps and their movement is controlled by Miro mitochondrial GTPase (Verstreken P et al 2005 Neuron 47:365; Guo X et al 2005 Neuron 47:379). ► [neurotransmitters](#), ► [tyrosine phosphatase](#), ► [gap junction](#), ► [memory](#), ► [ionotropic receptor](#), ► [metabotropic receptor](#), ► [neuregulin](#), ► [heregulin](#), ► [synaptic scaling](#), ► [Dscam](#), ► [NMDA](#); Ziv NE 2001 Neuroscientist 7(5):365; 2002 Science 298:770–791; Yamada S, Nelson WJ 2007 Annu Rev Biochem 76:267; <http://syndb.cbi.pku.edu.cn>.

Synapse, Immunological: The adhesion (gap) between the T lymphocyte receptor and the antigen presenting cell carrying the MHC—antigen complex or the killer cell inhibitory molecules and the special T cell receptor. Cytotoxic killer cells destroy virus-infected and tumorigenic cells by delivering secretory lysosome granules to the synaptic targets. The delivery is mediated by transient contact of the centrosome and plasma membrane and it is driven by the reorganization of the actin cytoskeleton (Stinchcombe JC et al 2006 Nature [Lond] 443:462). ► [T cell](#), ► [MHC](#), ► [killer cell](#); Khan AA et al 2001 Science 292:1681; Bromley SF et al 2001 Annu Rev Immunol 19:375.

Synapse, Informational: A specialized cell-cell junction mediating chemical or electric communication and displays a supramolecular structure to mediate information transfer between cells. (See Dustin ML et al 2001 Annu Rev Cell Dev Biol 17:133).

Synapsins: Bind to actin filaments, microtubules, annexing, SH3 domains, calmodulins and important regulators of synaptic vesicles. ▶[actin](#), ▶[annexin](#), ▶[SH3](#), ▶[calmodulin](#), ▶[synaptic vesicles](#), ▶[synaps](#)

Synapsis: Intimate chromosome pairing during meiosis between homologous chromosomes that may lead to crossing over and recombination (see Fig. S147). In some instances, non-homologous chromosomes or chromosomal regions may also associate. Protein-mediated synapsis involves recombination facilitated by integrases. Unpaired DNA causes meiotic silencing in *Neurospora* (Shiu PK et al 2001 Cell 107:905). Similarly in mouse in unsynapsed chromosomes the tumor suppressor BRCA1 and the kinase ATR co-localize to meiotic nodules (recombination nodules) and apparently because of the lack of phosphorylation of H2AX histone associated with the X and Y chromosomes asynapsis, sterility and apoptosis results (Turner JMA et al 2005 Nature Genet 37: 41). ▶[pairing](#), ▶[illegitimate pairing](#), ▶[meiosis](#), ▶[crossing over](#), ▶[synaptonemal complex](#), ▶[res](#), ▶[topological filter](#), ▶[tracking](#), ▶[integrase](#), ▶[asynapsis](#), ▶[histone variants](#), ▶[breast cancer](#), ▶[recombination nodule](#), ▶[ATR](#); McClintock B 1930 Proc Natl Acad Sci USA 16:791; Romanienko PJ, Camerini-Otero RD 2000 Mol Cell 6:975; Baudat F et al 2000 Mol Cell 6:989; minireview: McKim KS 2005 Cell 123:989.

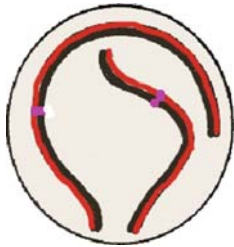


Figure S147. Synapsed homologous chromosomes (2 pairs)

S

Synapsis, Bimolecular: Occurs between complementary ends of different/separate transposable elements. ▶[transposable elements](#)

Synaptic Adjustment: The degree of synapsis may change during meiosis in certain chromosomal regions. ▶[synapsis](#)

Synaptic Cleft: Electric neuronal signals are transmitted from the presynaptic cell to the postsynaptic cell by the gap called the synaptic cleft. ▶[neuron](#), ▶[synaptosome](#)

Synaptic Scaling: A bidirectional phenomenon in which excitatory synapses scale up in response to activity

reduction but scale down in response to increases in activity of neurons. Synaptic scaling is mediated by the pro-inflammatory cytokine, tumor-necrosis factor- α (TNF- α) of the glia. ▶[neuron](#), ▶[glia](#), ▶[synaps](#), ▶[TNF](#); Stellwagen D, Malenka RC 2006 Nature [Lond] 440:1054.

Synaptic Vesicles: Originate from endosomes, and store and release the neurotransmitters and other molecules required for signal transmission between nerve and target cells. Ca^{2+} regulates their function. ▶[neurotransmitters](#), ▶[syntaxin](#), ▶[RAB](#), ▶[synaptotagmins](#), ▶[synaptophysin](#), ▶[NSF](#), ▶[neuromodulin](#), ▶[neurogenesis](#); Cousin MA, Robinson PJ 2001 Trends Neurosci 24:659.

Synaptnemal Complex: ▶[synaptonemal complex](#)

Synaptobrevins (VAMP): ▶[syntaxin](#), ▶[SNARE](#)

Synaptogamins: Integral membrane proteins, binding calcium and interacting with other membrane proteins in the synaptic vessels of the nerves. Synaptogamins may interact with the different types of PtdIns and Ca^{2+} . ▶[neurexin](#), ▶[botulin](#), ▶[synaptic vesicles](#), ▶[SNARE](#), ▶[phosphoinositides](#), ▶[clathrin](#), ▶[Ipk1](#); Li C et al 1995 Nature [Lond] 375:594; Südhof TC 2002 J Biol Chem 277:7629.

Synaptogyrin: Membrane proteins; may be phosphorylated on tyrosine. (See Zhao H, Nonet ML 2001 Mol Biol Cell 12:2275).

Synaptojanin: A neuron-specific phosphatase (M_r 145,000) working on phosphatidylinositol and inositols and its putative role is in the recycling of synaptic vesicles. Its defect is responsible for Lowe's oculocerebrorenal syndrome. It binds to the SH3 domain of Grb2. ▶[synaptotagmin](#), ▶[syntaxin](#), ▶[Lowe's oculocerebrorenal syndrome](#), ▶[Grb2](#), ▶[dynamin](#); Khvotchev M, Südhof TC 1998 J Biol Chem 273:2306; Ha SA et al 2001 Mol Biol Cell 12:3175.

Synapton: same as synaptonemal complex.

Synaptonemal Complex: Proteinaceous element between paired chromosomes in meiosis. In yeast—analyzed by green fluorescent protein labeling—the complex is initiated at zygotene and by pachytene it forms a ribbon-like structure. At diplotene the complex falls apart yet the association of the homologs continues because of the mature chiasmata (White E et al 2004 Genetics 167:51). They consist of two lateral and a central element (see Fig. S148). Denser spots within it are called recombination nodules and were supposed to have a role in genetic recombination. It is supposed that the complex holds in place the recombination intermediates rather than actively promoting the process. Actually, in some

fungi (*Saccharomyces*, *Aspergillus*) no synaptonemal complex is observed and concomitantly chromosome interference is absent. These observations led to the assumption that the complex is responsible for interference rather than recombination.

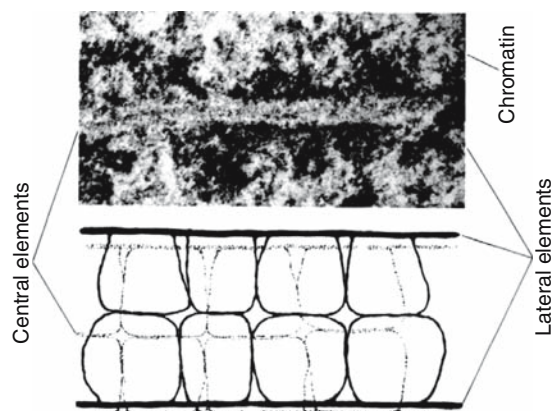


Figure S148. The tripartite structure may be visible from interphase through diplotene. (Electronmicrograph by the courtesy of Dr. H.A. McQuade. Interpretative drawing after Comings DE, Okada TA 1970 Nature [Lond] 227:451)

Actually, recombination may precede the formation of the synaptonemal complex, thus, the role of the complex in interference may be questionable. In *Drosophila*, synaptonemal complex may be formed in the absence of meiotic recombination (crossing over or gene conversion), however, in the male flies both the synaptonemal complex and meiotic recombination are absent yet mitotic recombination may be observed.

►synapsis, ►meiosis, ►interference, ►recombination mechanism eukaryotes, ►association site, ►recombination nodule, ►single-end invasion, ►crossing over, ►mitotic crossing over, ►male recombination; Westergaard M, von Wettstein D 1972 Annu Rev Genet 6:71; Schmekel K et al 1993 Chromosoma 102:669; Solari AJ 1998 Methods Cell Biol 53:235; Heng HH et al 2001 Genome 44:293; Page SL, Hawley RS 2004 Annu Rev Dev Biol 20:525; Lynn A et al 2002 Science 296:2222.

Synaptophysin: Membrane-spanning proteins in the synaptic vessel involved in neurotransmitter release. ►synaptic vessel, ►neurotransmitter, ►ceroid lipofuscinosis

Synaptosome: The protein complex mediating interactions among neurotransmitters and receptors across the synaptic cleft. ►neurotransmitter; Husi H, Grant SG 2001 Trends Neurosci 24:259.

Synaptotagmins: Proteins in the synaptic vesicles and have a role in Ca^{2+} -involved release of neurotransmitters, and in general in exo- and endocytosis. Exocytosis of synaptic vesicles is controlled by complexin and synaptotagmin (Tang J et al 2006 Cell 126:1175). ►synaptotagmin, ►syntaxin, ►complexin, ►synapse, ►SNARE; Fernandez-Chacon R et al 2001 Nature [Lond] 410:41; Hui E et al 2005 Proc Natl Acad Sci USA 102:5210.

Synchronous Divisions: The cells are at the same stage of the cell cycle.

Synchrotron: Radiation emitted by high-energy, high-speed electrons accelerated in magnetic fields. The range varies from infrared to hard X-rays. Their high energy permits to study their effects also in monochromatic forms. ►ionizing radiation; <http://www.srs.ac.uk/srs/>.

Synclinal: ►anticlinal

Syncytial Blastoderm: An early stage of embryogenesis when the single layer of nucleated cytoplasmic aggregates do not yet have a cell membrane. ►blastoderm

Syncytium: A collection of nuclei surrounded by cytoplasm without the formation of separate membranes around each, such as in early embryogenesis or among the progeny of a single spermatogonium or abnormal multinucleate cells or the plasmodia of slime molds. ►imaginal discs, ►blastoderm, ►Dictyostelium

Syndactyly: Webbing or fusion between fingers and toes (see Fig. S149). In polysyndactyly, mutation in the polyalanine extension of the amino terminal of human homeotic gene (HOX13) is the responsible factor. Syndactyly 1 was located to 2q34-q36. ►Poland syndrome, ►limb defects, ►Rubinstein-Taybi syndrome, ►Greig's cephalopolysyndactyly, ►GLI3 oncogene, ►homeotic genes, ►polysyndactyly, ►Pallister-Hall syndrome, ►Guttacher syndrome; Bosse K et al 2000 Am J Hum Genet 67:492.



Figure S149. Syndactyly

Syndecans: Heparan sulfate proteoglycans, membrane-spanning cell adhesion molecules and co-factor receptors bearing heparan sulphate proteoglycans distal from the plasma membrane. Syndecan promotes over-eating and obesity in mice. Syndecan-1 opposes the effect of the melanocyte-stimulating

hormone. Syndecan-1, -2, -3, -4 are encoded in human chromosome 2p23-p24, 8q23, 1p32-p36 and 20q12-q13, respectively. ►CAM, ►selectin, ►heparan sulphate, ►glypican, ►obesity, ►melanocyte-stimulating hormone; Reizes O et al 2001 Cell 106:105; Couchman JR 2003 Nature Rev Mol Cell Biol 4:926.

Syndrome: A collection of symptoms, traits caused by a particular genetic constitution. In humans, there are about 2000 syndromes determined mainly by single genes. The individual symptoms of different syndromes, however, may overlap among a large number of genetic and non-genetic disorders. Therefore, the precise identification is often an extremely difficult task. More accurate identification will probably be possible when the genome projects will provide structural and topological evidence for all the loci concerned. The *unknown genesis syndromes* usually occur sporadically yet they may have genetic bases. ►genome projects, ►association, ►non-syndromic, ►physical mapping, ►microarray, ►epistasis; Brunner HG et al 2004 Nature Rev Genet 5:545; human medical databases: <http://www.lmdatabases.com/>.

Synergids: Two haploid cells in the embryosac of plants flanking the egg. The pollen tube first penetrates one of the synergids, after the rupture of that synergid and rupture of the pollen tube the tube elongation is arrested, and the vegetative and the sperm nuclei fertilize the polar nuclei and the egg nucleus, respectively. The *FER* gene of *Arabidopsis thaliana* encodes a synergid-expressed, plasma membrane-localized, receptor-like kinase. The FER protein accumulates asymmetrically in the synergid membrane at the filiform apparatus. Interspecific crosses using pollen from *Arabidopsis lyrata* and *Cardamine flexuosa* on *A. thaliana* stigmas resulted in a *fer*-like phenotype that correlates with sequence divergence in the extracellular domain of FER. Our findings show that the female control of pollen tube reception is based on a *FER*-dependent signaling pathway, which may play a role in reproductive isolation barriers (Escobar-Restrepo J-M et al 2007 Science 317:656). ►gametogenesis, ►gametophyte, ►pollen tube; Higashiyama T et al 2001 Science 293:1480.

Synergistic Action: The participating elements enhance the reaction above the sum of the separate strength of their separate actions. ►interaction variance, ►epistasis

Synexpression Groups: Genes that are expressed together either spatially, temporally or developmentally. Their identification is facilitated by microarray hybridization. These groups do not need to be genetically linked and therefore are different from gene clusters or operons of prokaryotes that are linked. ►macroarray analysis, ►microarray hybridization,

►operon, ►clustering of genes; Nirehrs C, Pollet N 1999 Nature [Lond] 402:483.

Syngamy: The union of two gametes in fertilization leading potentially to the fusion of the two nuclei in the cell. ►plasmogamy, ►karyogamy, ►synkaryon, ►semigamy

Syngen: A reproductively isolated group of ciliates.

Syngeneic: Antigenically similar type cells (in a chimera). ►antigen, ►immunoglobulins

Synkaryon: A cell (zygote, fused conidia or spores) with a nucleus originated by the union of two nuclei. ►karyogamy, ►heterokaryon, ►dikaryon

Synonymous Codons: These have different bases in the triplet yet they specify the same amino acids. The 61 sense codons stand for 20 common amino acids. Some amino acids have up to 6 codons. Thus, mutation may not have any genetic consequence, except when exon splice site is involved. A synonymous single nucleotide polymorphism (SNP) in the *Multidrug Resistance 1 (MDR1)* gene, leads to altered function of the *MDR1* gene product P-glycoprotein (P-gp) and results in altered drug and inhibitor interactions. Although the mRNA and protein levels are similar, conformation was altered. Supposedly, the presence of a rare codon affects the timing of cotranslational folding and insertion of P-gp into the membrane, thereby altering the structure of substrate and inhibitor interaction sites (Kimchy-Sarfaty C et al 2007 Science 315:525). Some bases may affect the intensity of translation. In functional areas of the genome, synonymous substitutions are more common than non-synonymous ones. Purifying selection usually eliminates the deleterious non-synonymous mutations. Slightly deleterious non-synonymous substitutions can be maintained in bacterial populations with high effective population size (Hughes AL 2005 Genetics 169:533). ►genetic code, ►splicing, ►exon, ►intron, ►non-synonymous codon, ►radical amino acid substitution, ►effective population size, ►Grantham's rule

Synostosis: Bone fusion. ►noggin

Synovial Sarcoma: ►SYT

Synpolydactyly: ►polydactyly, ►polysyndactyly, ►syndactyly

Syntax: Sentence structure; organization of groups of words, phrases and clauses in the correct manner. The term is also used by computerized information retrieval.

Syntaxin: A synaptic membrane protein forming part of the nerve synaptic core complex along with the synaptosome associated protein and synaptobrevin (VAMP), a vesicle associated membrane protein. Omega-3 and omega-6 fatty acids act on syntaxin and stimulate membrane expansion (Darios F, Davletov B

2006 Nature [Lond] 440:813). Syntaxins are involved in vesicular transport between the endoplasmic reticulum and the Golgi apparatus as target membrane receptors. Syntaxin-5 is an integral part of the endoplasmic reticulum-derived transport vesicles. A synaptobrevin-like gene (SYBL1) was located to the pseudoautosomal region of the human X chromosome. It recombines with Y-chromosomal homolog, displays lyonization in the X chromosome, and is inactivated in the Y chromosome. A score of syntaxins have been identified in humans encoded at chromosomes 7q11.2, 17p12, 16p11.2, etc. ▶[synaptotagmin](#), ▶[SNARE](#), ▶[synaps](#), ▶[endoplasmic reticulum](#), ▶[Golgi apparatus](#), ▶[pseudoautosomal region](#), ▶[lyonization](#), ▶[Munc](#), ▶[cystic fibrosis](#), ▶[stoma](#), ▶[omega-3 fatty acids](#); Bennett MK et al 1992 Science 257:255; Mullock BM et al 2000 Mol Biol Cell 11:3137.

Syntelic Distribution: The kinetochores of the two sister chromatids are attached to spindle fibers that pull them to the same pole during mitotic anaphase.

Syntenic Genes: Within the same chromosome; they may, however, freely recombine if they are 50 or more map units apart. Gene blocks may display synteny among related taxonomic entities even when their chromosome number varies. Syntenic gene sets may provide information on phylogeny of the species. ▶[linkage](#), ▶[crossing over](#)

Syntenin: 32 kDa adaptor protein with two PDZ domains involved in cytoskeleton-membrane organization. ▶[PDZ](#), ▶[IL-5](#); Zimmermann P et al 2001 Mol Biol Cell 12:339; Cierpicki T et al 2005 Structure 13:319.

Synthases: Mediate condensation reactions of molecules without ATP. ▶[synthetases](#)

Synthetases: Mediate condensation reactions that require nucleoside triphosphates as energy source. ▶[synthases](#)

Synthetic Biology: A new area of science aiming either to introduce new (synthetic) molecules into existing organisms, or interchange existing molecules between organisms or chemically synthesizes new systems from known compounds, e.g., create synthetic viruses on the basis of the genetic code. This field includes from de novo organic synthesis, to genetic engineering, stem cell research, etc. Networks have been designed from natural transcription factors and binding sites. Its aims include creation of toggle switches, cellular oscillators, new forms of cell-to-cell communications and cell pattern formation. A beautiful paper reports the duplication and parallel modifications of the 16S prokaryotic ribosomal RNA (the anti-Shine-Dalgarno sequence, CCUCC) and the Shine-Dalgarno sequence (GGAGG) of the mRNA. The new ribosome may or may not function anymore

as the original one; the modified ribosome however can translate the modified mRNA. Through mutations in both the ribosomes and in the mRNA, various combinations of enormous variety of potential functions can be established and tried (Rackham O, Chin JW 2005 Nature Chem Biol 1:159).

Although this type of research can generate altered or new organisms that may pose unknown hazards, the potential advantages for agriculture and medicine outweigh the risks. ▶[genetic engineering](#), ▶[stem cells](#), ▶[synthetic genes](#), ▶[gene circuits](#), ▶[synthetic virus](#), ▶[influenza virus](#), ▶[protein engineering](#), ▶[oscillators](#); Benner SA, Sismour AM 2005 Nature Rev Genet 6:533; <http://syntheticbiology.org>.

Synthetic DNA Probes: If the amino acid sequence in the protein is known but the gene was not yet isolated, a family of synthetic probes may be generated to tag the desired gene. This probe is generally no longer than 20 base because of the difficulties involved in their synthesis. The genetic code dictionary reveals which triplets spell the amino acids. An amino acid sequence that uses few synonymous codons is selected. A computer match generally chooses the possible combinations. E.g., a probe for the His-Thr-Met peptide sequence would require the following 8 polynucleotide sequences to consider all possible sequences for a probe (see Fig. S150). The inclusion of **Methionine** (having a single codon) is simplifying the task. **Histidine** is relatively advantageous because it has only two synonymous codons. **Threonine** with four codons make the work more difficult; leucine, serine and arginine containing parts of the proteins should be avoided (because they have six codons) but tryptophan, also with a single codon would be highly desired. Insertion of ambiguous deoxyinosine nucleotides at some positions may facilitate the design of probes. ▶[probe](#), ▶[functional cloning](#), ▶[gene isolation](#); Ohtsuka E et al 1985 J Biol Chem 260:2605; Lichtenstein AV et al 2001 Nucleic Acids Res 29(17):E90.

| | His | Thr | Met |
|----|-----|-----|-----|
| 5' | CAC | ACA | UAG |
| | CAC | ACC | AUG |
| | CAC | ACG | AUG |
| | CAC | ACU | AUG |
| | CAU | ACA | AUG |
| | CAU | ACC | AUG |
| | CAU | ACG | AUG |
| | CAU | ACU | AUG |
| 3' | | | |

Figure S150. Synthetic probe

Synthetic Enhancement: Basically an epistatic process by increasing or reducing interaction between gene products by using crossing, knockouts, transformation, etc.

Synthetic Genetic Networks: Constructs to simplify the understanding of regulated gene complexes. It is based on tools of nonlinear dynamics, statistical physics and molecular biology. ▶[genetic networks](#); McMillen D et al 2002 Proc Natl Acad Sci USA 99:679.

Synthetic Genomes: ▶[synthetic virus](#), ▶*Mycoplasma genitalium*, ▶[potentials of functional](#); synthetic microbial genomes: Holt RA et al 2007 BioAssays 29:580.

Synthetic Lethal (synthetic enhancement): Gene is inviable only in certain genetic constitutions. Thus, two single mutations have no or insignificant phenotypic consequence separately but the double mutant may be lethal. In yeast, only ~1000 of the genes are essential and 5000 are viable even when deleted. The synthetic lethals cells include more than one defective gene. Partners in synthetic lethal systems can be essential as well as non-essential genes. In gene networks, at least one of the genes must be essential although most of the non-essential genes can compensate for each other. Synthetic lethals may be involved in inbreeding depression and may be the cause of some hybrid inviabilities and sterility. A synthetic lethal test may be used in anticancer drug design by combining two different mutations that in combination, seriously impair cells to gain information on how to kill cancer cells. ▶[inbreeding](#), ▶[synthetic genetic array](#), ▶[synthetic genetic networks](#), ▶*Saccharomyces cerevisiae*; Jacobson MD et al 2001 Genetics 159:17; Davierwala AP 2005 Nature Genet 37:1147.

Synthetic Organisms: ▶[synthetic biology](#)

Synthetic Polynucleotides: Nucleic acid oligomers or polymers generated in the laboratory by enzymatic or other synthetic methods. Nucleic acid synthesizer machines produce some of them. (See Benner SA et al 1998 Pure Appl Chem 70:263).

Synthetic Seed: Somatic embryos encapsulated into a protective capsule (e.g., calcium alginate) and used for propagation in cases when regular seed is not available or homozygotes are difficult to obtain. ▶[artificial seed](#)

Synthetic Species: Amphidiploids of presumed progenitors of existing species obtained by crossing and diploidization. Some synthetic species have never existed in nature before as the *Raphanobrassica*, $2n = 36$, an amphidiploid of radish (*Raphanus sativus*, $n = 9$) and cabbage (*Brassica oleracea*, $n = 9$) (see Fig. S153). *Triticale*s are similarly new amphidiploids either $2n = 48$ or $2n = 56$, obtained by crossing tetraploid ($2n = 28$) or hexaploid ($2n = 42$) wheat (*Triticum*) with diploid rye (*Secale cereale*, $2n = 14$). Some synthetic species are only

reconstructions of the evolutionary form, e.g., *Nicotiana tabacum*, *Hylandra suecica*, *Primula kewensis*, etc. The entire *Mycoplasma* genome of one species has been transferred intact to another and entirely replaced that of the recipient, creating a new species. ▶[alien substitution](#), ▶[amphiploid](#), ▶*Mycoplasma*, ▶*Triticale*; *Raphanobrassica*: Karpetchenko GD 1928 Z Indukt Abstammungs Vererbungs 48:1.

Cabbage
Brassica oleracea, $2n = 18$



Raphanobrassica, $2n = 36$



Radish
Raphanus sativus, $2n = 18$



Figure S153. Synthetic *Raphanobrassica*

Synthetic Variety: Composed of several selected lines, which may reproduce by out-crossing within the group. ▶[polycross](#)

Synthetic Vector: ▶[liposome](#)

Synthetic Virus: The functional RNA poliovirus and the single-stranded DNA virus ϕ X174 have been assembled from synthetic oligonucleotides and the technology is already available to generate cellular genomes within the laboratory. ▶[polio virus](#), ▶ ϕ X174, ▶[influenza virus](#); Smith HO et al 2003 Proc Natl Acad Sci USA 100:15440.

Synthon: A synthetically produced molecule, in the laboratory.

Syntrophic: Can be maintained (only) by cross-feeding. Based on cross-feeding metabolic pathways of microorganisms could be identified on culture media. In a metabolic pathway $A \rightarrow B \rightarrow C \rightarrow D$ mutation blocked before D may cross-feed mutants blocked before C and B. Mutation blocked before C may facilitate the growth of mutants inactive in step B, and so on. A syntrophic hypothesis is that the mitochondria of eukaryotes evolved by the fusion of an achaeon, a δ -proteobacterium and an α -proteobacterium. ▶[cross-feeding](#), ▶[channeling](#)

Synuclein (α -synuclein, 4q21): A 140-amino acid protein in the presynaptic neurons, a major constituent of the Lewy bodies. All synucleins display imperfect KTKEGV amino acid motifs and a variable C-terminus. Synucleins are phosphorylated at Ser and

Tyr tail residues and this reduces aggregation. Hydrophobic residues 71-82 promote aggregation. α -synuclein promotes the fibrillization of tau in neurodegenerative diseases (Giasson BI et al 2003 Science 300:636). A truncated α -synuclein accumulates in the neuronal cells and promotes Parkinson disease (Li W et al 2005 Proc Natl Acad Sci USA 102:2162). It interacts with synphilin-1 for normal function. In the oxidized or nitrated forms synuclein aggregates and may cause the synucleinopathies such as Parkinson disease, Alzheimer disease, amyotrophic lateral sclerosis and Huntington disease. In the majority of cases of sporadic Parkinson disease (PD) several mutant genes have been identified. The principal genes that cause (PD) are alpha-synuclein, parkin, leucine-rich repeat kinase 2 and PTEN-induced putative kinase 1 (Wood-Kaczmar A et al 2006 Trends Mol Med 12:521). Beta synuclein gene, also expressed in the brain in Alzheimer disease, was assigned to 5q35, gamma synuclein/persyn (in breast cancer) to 10q23.2-q23.3. ▶[Lewy body](#), ▶[neurodegenerative diseases](#), ▶[Parkinson disease](#), ▶[alcoholism](#), ▶[PTEN](#); Touchman JW et al 2001 Genome Res 11:78; Shimura H et al 2001 Science 293:263; Cuervo AM et al 2004 Science 305:1292.

SYP: A tyrosine phosphatase.

Syphilis: ▶[Treponema pallidum](#)

Sypro Ruby: A sensitive protein stain used in 2-dimensional gel electrophoresis.

Syringa: ▶[lilac](#)

Syringe Filter: A syringe equipped with a commercially available sterilizing filter block (0.45 or 0.20 μ m pores) and removes microbial contaminations instantly without heating (see Fig. [S154](#)).



Figure S154. Syringe filter

Syringomyelia: A rare autosomal dominant or autosomal recessive cavitations (formation of cavities) in the spinal cord. It may be also due non-hereditary causes.

System Biology: Biological phenomena can be fully understood only by learning their complex interacting networks. (Kitano H 2002 Curr Genet 41:1).

Systematic Error: The same bias affects all measurements or observations.

Systematics: A method of classification such as taxonomy. Carl Linné (Linnaeus) Swedish botanist (1707–1778) initiated the classification and binomial nomenclature of organisms.

Systemic: Affects the entire cell or the entire body of an organism.

Systemic Acquired Resistance: ▶[SAR](#)

Systemic Amyloidosis, Inherited: An extracellular deposition of fibrous proteins in the connective tissues under autosomal dominant control. ▶[amyloidosis](#)

Systemic Genes: Cell autonomous versus genes, regulated by intercellular communication.

Systemin: An 18-amino acid signaling peptide for plant defense mechanisms. ▶[plant defense](#), ▶[host-pathogen relation](#)

Systemoid: Similar to a system, alternatively it is used to denote tumors that include different types of tissues. ▶[teratoma](#)

Systems Biology: Studies biological mechanisms by monitoring gene, genome, protein, proteome and informational pathways systematically using all possible, suitable means. The genes control metabolic functions and are associated with regulatory elements. The proteins may function in complexes and networks and through systems of interacting networks. The simplest controls of the genes are exercised through cis elements such as general and specific transcription factors. The genes are also subject to external signals (signal transduction). The different elements of these systems may change dynamically and thus physiological and developmental modifications arise such as in the healthy or pathologically affected conditions (Hood L et al 2004 Science 306:640). Systems biology separates the effects of noise, and permits the development of rational models and offers new approaches for controlling complex system of the cells, tissues and organisms using bioinformatics, biological and molecular methods. It permits prediction regarding emergent complex phenomena involving, and may enable preventive, predictive and personalized medicine. The components of the system may respond dynamically to different stimuli in time and space and follow different trajectories before steady state is reached (Barbano PE et al 2005 Proc Natl Acad Sci USA 102:6245). A new method has been developed for integration of multiple datasets by using a free software (POINTILLIST) package (Hwang D et al 2005 Proc Natl Acad Sci USA 102:17296). The method was successfully applied to 18 datasets of galactose utilization of yeast involving mRNS, protein

abundance, genome-wide protein interaction data, etc. (Hwang D et al 2005 Proc Natl Acad Sci USA 02:17302). Because of the rapid progress in experimental research and the increasing number of databases containing important relevant information, new bioinformatic tools are indispensable for integration of the knowledge. The databases must be found and the data must be converted into forms suitable for integration by electronic means. Modern database management system must be expanded and appropriate interfaces must be used. The Trace Ensemble Server only on Unix system (<http://trace.ensembl.org/>) already contains more than one billion information about 759 species. ►genetic networks, ►networks, ►drug development, ►ONDEX, ►databases; Recon H-InvDB Hood L, Galas D 2003 Nature [Lond] 421:444; Ideker T et al 2001 Annu Rev Genomics Hum Genet 2:343; Shogren-Knaak MA et al 2001 Annu Rev Cell Dev Biol 17:405; Philippi S Köhler 2006 Nature Rev Genet 7:482; software standardization: Swertz MA, Jansen RC 2007 Nature Rev Genet 8:235; <http://bind.ca/>; <http://www.cytoscape.org>; network tool: <http://biologicalnetworks.net/>; system biology tool: <http://babelomics.bioinfo.cipf.es/>.

Systems of Breeding: Sexual reproduction may be allogamous, autogamous, inbreeding, assortative mating, hermaphroditic, monoecious and dioecious but reproduction may also be asexual. ►breeding system

Systole: Contraction of the heart and the forcing of the blood into the arteries. ►hypertension

SYT (synovial sarcoma): Oncogene in human chromosome 18q11.2. Translocations t(X;18) (p11;q11) are common. Gains of 8q and 12q as well as losses of 13q and 3p are frequent.

SZI: ►micromanipulation of the oocyte

Szostak Model of Recombination (Szostak JW et al 1983 Cell 33:25): A double break and repair model. It is applicable to transformational insertion of DNA molecules as well, as it can account for gene conversion and/or conventional recombination by outside marker exchange. The version of the model shown in Figure S155 does not explain why in yeast 5:3 gene conversion does not occur. (*Saccharomyces cerevisiae* has 4 spores per ascus but *Schizosaccharomyces pombe* has 8 unordered ascospores.)

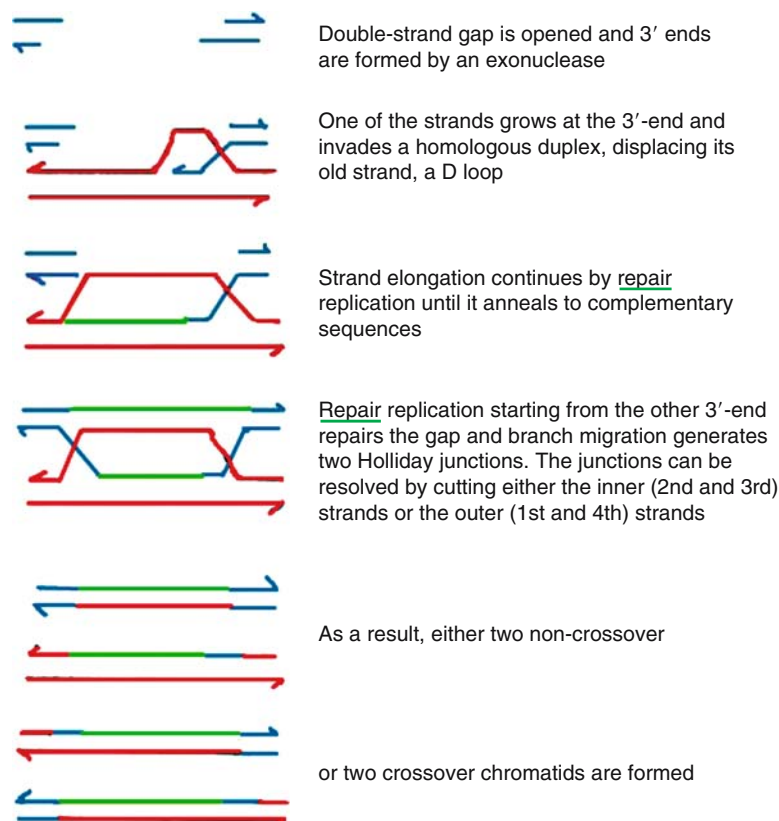


Figure S155. The Szostak et al model of recombination is based on double-strand breaks in contrast to the Holliday or the Meselson—Radding models that suggest single-strand breaks in the DNA

Other modified models of Szostak can account for these types of experimental data. Genetic recombination in eukaryotes generally occurs by double-strand break. Radiation and various chemicals can increase the frequency of double-strand breaks.

Double-strand breaks can also be increased in plant cells by transformation of a restriction endonuclease into the cell. ►[recombination molecular models](#); Szostak JW et al 1983 Cell 33:25; Smith GR 2000 Annu Rev Genet 34:243, see Fig. [S155](#).

Historical vignettes

Wilson EB 1896 The Cell in Development and Heredity. Macmillan, New York.

“Now, chromatin is known to be closely similar to, if not identical with, a substance known as nuclein—which analysis shows to be a tolerably definite compound composed of nucleic acid (a complex organic acid rich in phosphorous) and albumin [protein]. And thus we reach the remarkable conclusion that the inheritance may, perhaps, be effected by the physical transmission of a particular chemical compound from parent to offspring.”

Linus Pauling’s letter to S Leonard Wadler on August 15 1966. (Cited after the Oregon State University Manuscript Collection). Pauling received Nobel Prize in 1954 for the nature of the chemical bond and again in 1962 for peace.

“I have suggested that the time may come in the future when information about heterozygosity in such serious genes as the sickle cell anemia gene would be tattooed on the forehead of the carriers, so that young men and women would at once be warned not fall in love with each other.”

Kingman JFC 2000 in Genetics 156, p 1463
“Those who analyze stochastic models always lift their eyes from their equations to ask what they actually mean.”

T

T: ▶ [thymine](#) (see Fig. T1).

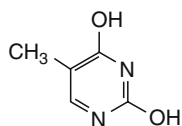


Figure T1. Thymine

t: Time.

τ: Yeast retroelement. ▶ [Ty](#)

θ (population mutation parameter): θ is characterized by the number of segregating alleles in the population (Watterson GA 1975 Theor Popul Biol 7:256).

θ: The symbol of recombination (and some other) fractions. ▶ [w](#)

T2: A virulent bacteriophage. ▶ [bacteriophages](#), ▶ [T4](#)

T4: A virulent (lytic) bacteriophage of *E. coli*. It has double-stranded DNA genetic material of 1.08×10^6 Da (about 166 kbp) with a total length of about 55 μm. Its cytosine exists in hydroxymethylated and glycosylated forms. The linear DNA is terminally redundant and cyclically permuted. The redundancy occupies more than 1% of the total DNA. It was an unexpected discovery that its thymidylate synthetase gene contains an intron. Introns are common in eukaryotes but exceptional in prokaryotes. The phage has over 80 genes involved in metabolism but only about a fourth of them are indispensable. The metabolic genes control replication, transcription, and lysis. Other metabolic genes have functions overlapping those of the host. After infection, the phage turns off or modifies bacterial genes, degrades host macromolecules, dictates the transcription of its own genes, and utilizes the host machinery for its own benefit. For the synthesis of its own DNA, it relies on the nucleotides coming from the degradation of the host DNA. The bacterial RNA polymerase transcribes the phage genes. The viral protein Alc interacts with the β subunit of the host and terminates transcription on templates with cytosine residues. The viral DNA contains hydroxymethyl cytosine, which can serve as a template. The cytidylic acid residues of the host are prevented from being incorporated into the phage DNA by phosphatases. A deaminase converts them to thymidylic acid or a methylase enzyme converts them to hydroxymethyl cytosine through a few steps. The hydroxymethylcytidylate is

then glucosylated by a glucosyl transferase enzyme. The molar proportion of thymidylate is higher in T4 than in *E. coli*, presumably because of the conversion of cytidylate into thymidylate. A series of more than 50 genes are involved in morphogenesis. At least 40% of the genome is required for the synthesis and assembly of the viral particle. 24 genes mediate head assembly, while the baseplate and tail require at least 31 genes. ▶ [development](#), ▶ [one-step growth](#), ▶ [bacteriophages](#), ▶ [sliding clamp](#); Calendar R (Ed.) 1988 The Bacteriophages, Plenum, New York; Knipe DM, Howley PM (Eds.) 2001 Fundamental Virology, Lippincott Williams & Wilkins, Philadelphia, Pennsylvania.

T7: A virulent bacteriophage with DNA genome size 39,937 bp, which encodes 59 proteins. ▶ [bacteriophages](#)

T18: A transcriptional activator protein.

2,4,5-T: ▶ [agent orange](#)

T Alleles: ▶ [Brachyury](#)

T Antigen: The T antigen of SV40 virus is a 708-amino acid multifunctional protein and an effector of DNA polymerase α function. It assists in separating the DNA strands for replication and generates the replication bubble as the polymerase moves on. It has a special role in SV-induced tumors after tumor-suppressor proteins are eliminated or weakened. The T antigen and sequentially similar proteins are also factors in nuclear localization. ▶ [Simian virus 40](#), ▶ [SV40](#), ▶ [nuclear localization sequences](#); Li D et al 2003 Nature [Lond] 423:512; Sullivan CS, Pipas JM 2002 Microbiol Mol Biol Rev 66:179.

t Antigen: The t antigen shares the same N-terminal sequences with the T antigen but the carboxyl end is different. The t antigen has homology to the G_t protein, an α subunit of the trimeric G-proteins involved in the activation of cGMP phosphodiesterase involved in photoreception and other processes. ▶ [Simian virus 40](#), ▶ [G-proteins](#)

T Band: ▶ [T-band](#)

T Box (Tbx): A conserved ~14-nucleotide DNA domain upstream of the transcription terminator of Gram-positive bacteria in about 250 genes encoding aminoacyl-tRNA synthetases, and amino acid biosynthetic and transport enzymes. Uncharged tRNAs appear to interact with the leader sequence of these genes by their amino acid-accepting termini at the middle of the T box (UGGN') to stabilize antitermination at the expense of the terminator. T box genes (although named differently) occur in all species. In humans sequencing, the genome identified at

least 18. These are generally transcription factors and are specific to diverse downstream genes. T box proteins interact with each other (through heterodimerization) and with many other proteins. They are involved in Wnt (winged), TGF- β (transforming growth factor), hedgehog, FGF (fibroblast growth factor), Notch, and receptor guanylate phosphate signaling. Several developmental disorders and human diseases are due to T box genes, which show both positive and negative effects on development. ▶*antitermination*, ▶*MAR*, ▶*Brachyury*, ▶*eomesodermin*, ▶*Holt-Oram syndrome*, ▶*DeGeorge syndrome*, ▶*Scheinzel syndrome*, ▶*T-bet*; Papaioannou VE, Silver LM 1998 *Bioessays* 20:9; Smith J 1999 *Trends Genet* 15:154; Putzer H et al 2002 *Nucleic Acids Res.* 30:3026; Showell C et al 2004 *Dev Dyn* 229:201; Naiche LA et al 2005 *Annu Rev Genet* 39:219.

T Cell Receptor (TCR): T cell surface glycoproteins recognize antibodies. The differentiation of the T cells begins with the differentiation of their receptors. At the beginning, the TCR is double negative, i.e., it is CD4⁻ CD8⁻. The disulphide-linked heterodimers have α and β or γ and δ chains, containing variable and constant regions and are homologous to the corresponding antibodies. First, the TCR β is rearranged, followed by the rearrangement of the α chain. At this stage, the β chain may signal allelic exclusion and this means the end of rearrangements. After this, the double positive (DP) stage follows, i.e., CD4⁺ CD8⁺ TCR appears. A selection process ensues, resulting in an array of self MHC-restricted and self-tolerant TCRs. The TCR α chain is a transmembrane protein and the cytoplasmic (carboxyl) end has two potential phosphorylation sites and a Src homology 3 (SH3) domain (see Fig. T2). The TCR β chain regulates the development of the T cells in the absence of the α chain. The $\alpha\beta$ TCR generally recognizes antigens bound to the major histocompatibility (MHC) molecules. The TCR complex also

includes the CD3 protein, required for signal transduction. It is made of the γ , δ , ϵ , and ζ chains. The ζ chain plays a role in thymocyte development but it is not indispensable for signal transduction. The chromosomal site of the human α (14q11), β (6q35), γ (7p15-p14), δ (14q11.2), and ζ (1p22.1-q21.1) chains are shown in parenthesis. Marsupials also have TCR μ that does not have a known homolog in eutherian mammals but has features analogous to a TCR isoform in sharks (Parra ZE et al 2007 *Proc Natl Acad Sci USA* 104:9774).

Activation is triggered when the T cell receptor binds the MHC associated ligand on the antigen presenting cell (Choudhuri K et al 2005 *Nature [Lond]* 436:578). Co-stimulating signals may help. The CD3 component of the TCR may be altered, and protein tyrosine kinases (PTK) are activated. The PTKs may turn on the calcium-calcineurin, the RAS-MAP, and the protein kinase signaling pathways (see Fig. T3).

These pathways then may activate the transcription factors NFAT, NF- κ B, JUN, FOS (AP1), and ETS. They, in turn, activate new genes, some of which are specific transcription factors that facilitate the release of cytokines that further activate the clonal expansion of T cells. This is followed by the production of antibodies by B cell or T cell cytotoxicity. Immune memory, immune tolerance, anergy, and apoptosis are alternative functions that follow. Regulation of the development of TCR requires the cooperation of the protein tyrosine kinases (Src family), phospholipase C (PLC γ), CD5, CD28, CD48, CD80, VCP, ezrin, VAV, SHC, PtdIns, PIP2, PIP3. TCR may also regulate apoptosis of T cells. For the TCRs, there are 42 variable (V) and 61 joining (J) segments at the α chain immunoglobulin locus, and 47 V, 2 diversity (D), and 13 J segments for the β chain genes. During rearrangements, V α —J α and V β —D β —J β deletions and additions of nucleotides and dimerization may increase the variations. In blood, there appears to be $\sim 10^6$ different β chains that may combine on the average with ~ 25 different α chains. In the memory subsets, the diversity appears about 1/3 less. The number of estimated distinct TCR receptors may be 10^{12} . ▶*TCR genes*, ▶*ICAM*, ▶*LFA*, ▶*T cells*, ▶*lymphocytes*, ▶*immunoglobulins*, ▶*RAG*, ▶*Src*, ▶*Yes*, ▶*Fgr*, ▶*Fyn*, ▶*Lck*, ▶*Hck*, ▶*Blk*, ▶*Zap70*, ▶*Tec*, ▶*antibody*, ▶*MHC*, ▶*CD3*, ▶*LCK*, ▶*ITAM*, ▶*B lymphocytes*, ▶*phosphoinositides*, ▶*PIP*, ▶ $\gamma\delta$ T cells, ▶*immune system*, ▶*immunological synaps*, ▶*integrin*, ▶*signal transduction*, ▶*thymus*, and the other factors under separate entries, ▶*SLP-76*, ▶ *α -CPM*, ▶*caveolae*, ▶*ICOS*, ▶*CTLA-4*; Hennecke J, Wiley DC 2001 *Cell* 104:1; Germain RN 2001 *J Biol Chem* 276:35223; Isakov N, Altman A 2002 *Annu Rev Immunol* 20:761; Natarajan K et al 2002

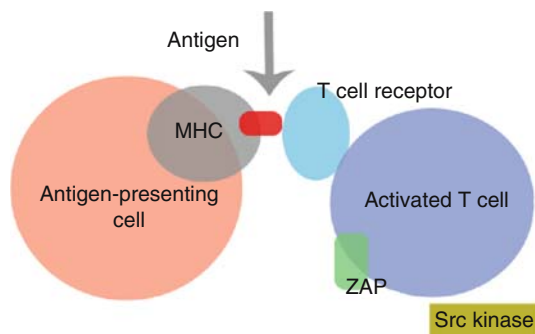


Figure T2. T cell receptor in T cell function

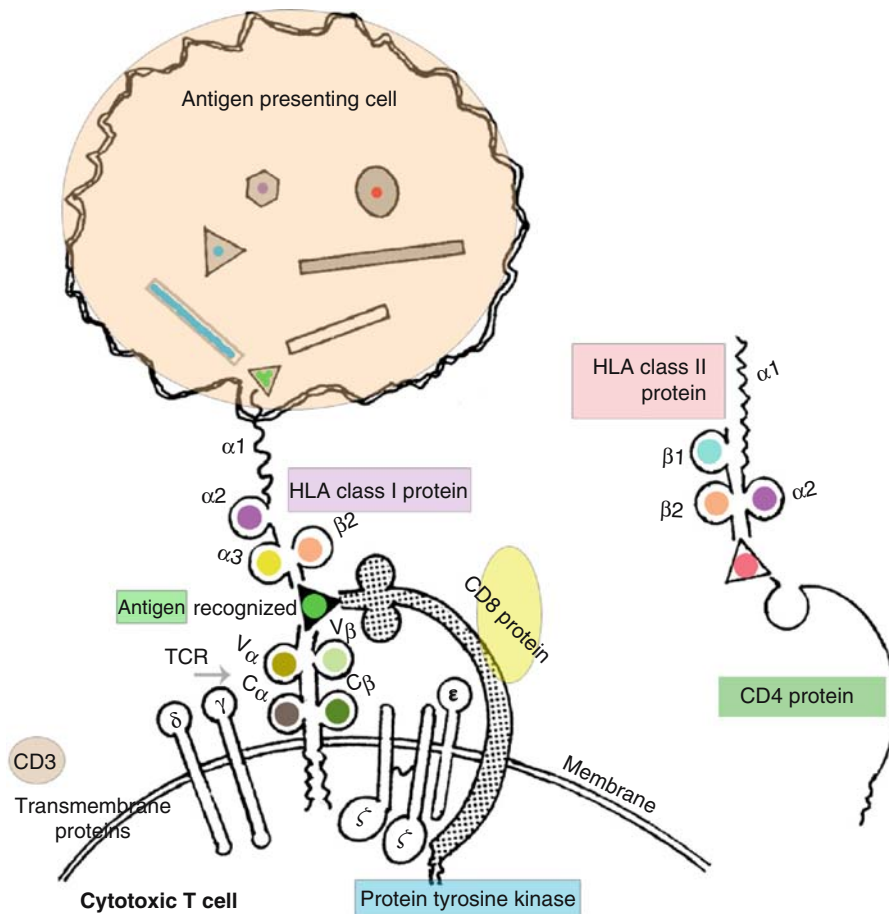


Figure T3. A general outline of the functions of the T cell receptor (TCR) complex. Although diagrams always generalize beyond reality, they may be helpful to obtain a broad understanding. The foreign antigens are presented to the T lymphocytes either by the antigen-presenting cells or by macrophages. The macrophages are capable of partially degrading the large molecules or the invading cells. These cells associate then with either class II or class I MHC proteins, which are encoded by the HLA genes. The MHC molecules recognize the foreign antigens and bring them to the TCR and to the CD protein complex associated with the T cell surface. The class I gene products use the CD4 transmembrane proteins, whereas the class II molecules rely on CD8. The COOH ends of the TCR chains are inside the T cell's double membrane and the NH₂ end is involved in the recognition of the antigen in association with the MHC and CD elements. The TCR complex includes also the CD3 transmembrane proteins. The ζ subunit serves also as an effector in signal transduction. Protein tyrosine kinase is an important element in several signal transduction pathways. ICAM-1 on the antigen-presenting cell and LFA-1 on the CD8⁺ also cooperate in mediating the adhesion of the MHC complex. The right side of the incomplete diagram shows the association of the class II and CD4 proteins with an antigen. The other elements of this system are very similar to that shown at the left main part of the outline

Annu Rev Immunol 20:853; Werlen G et al 2003 Science 299:1859; Call ME et al 2006 Cell 127:355; <http://imgt.cines.fr/>.

T Cell, Regulatory (Treg/Tr): Regulatory T cells may disarm non-tolerant (self-reactive) naive lymphocytes (*dominant tolerance*) and bring about *infectious tolerance* of tissue grafts. These T cells occur in CD4⁺ CD25⁺ and CD4⁺ CD25⁻ cells. FOXP3 controls Treg by cooperation with NFAT. Ca²⁺ regulate NFAT

transcription factors. In activated T cells, NFAT forms co-operative complexes with AP-1. Structural mutation in FOXP3 progressively disrupts its interaction with NFAT. FOXP3 has the reduced ability to repress T cell growth factor IL-2; Treg markers CTLA4 and CD25 are upregulated. Thus, murine autoimmune diabetes is suppressed (Wu Y et al 2006 Cell 126:375). FOXP3 (Forkhead box P3; Xp11.23-q13.3) mutations involve aggressive autoimmunity mediated by regulatory T cells. Interaction of FOXP3

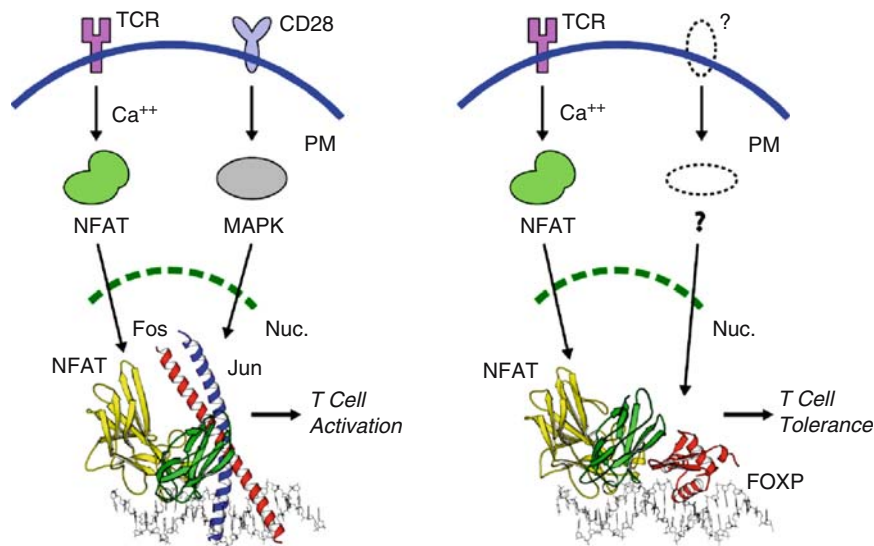


Figure T4. Left: Schematic representation of the T cell activation program mediated in part by the assembly of the NFAT/Fos-Jun/DNA complex on specific promoters. Right: schematic representation of the T cell tolerance program mediated in part by the assembly of the NFAT/FOXP3/DNA complex on specific promoters. Signals involved in the regulation of FOXP3 are currently unknown and indicated by ? mark. (Courtesy of Lin Chen and James stroud)

with AML1/Runx1 (acute myeloid leukemia 1/Runt-related transcription factor 1) controls Treg (Ono M et al Nature [Lond] 446:685). Mast cells are recruited by IL-9 to immune-tolerant tissues through activation by Treg and are essential for immune tolerance of allografts (Lu L-F et al 2006 Nature [Lond] 442:997). Autoimmune disease susceptibility and resistance alleles on mouse chromosome 3 (*Idd3*) correlate with differential expression of the key immunoregulatory cytokine interleukin-2 (IL-2). Reduced IL-2 production correlates with reduced function of CD4⁺ CD25⁺ regulatory T cells (see Fig. T4) (Yamanouchi J et al 2007 Nature Genet 39:329). ▶T cells, ▶autoimmune disease, ▶immune tolerance, ▶Mast cell, ▶IL-2, ▶IL-9, ▶forkhead, ▶NFAT, ▶MAP kinase [MPK], ▶AP1, ▶fos, ▶CD28, ▶T cell receptor [TCR], ▶T cells, ▶Cd25, ▶CTLA-4, ▶IL-2, ▶IL-9, ▶leukemia, ▶Runx; Graca L et al 2002 J Exp Med 195:1641; Rudensky AY et al 2006 Cell 126:253; Wan YY, Flavell R 2007 Nature [Lond] 445:766; Gavin MA et al 2007 Nature [Lond] 445:771.

T Cell Replacing Factor: A lymphokine. ▶lymphokines

T Cell Vaccination: Immunization with irradiated autologous T cells. This type of vaccination is expected to deplete circulating autoreactive T cells and has therapeutic significance for autoimmune diseases.

▶autologous, ▶autoimmune disease; Hong J et al 2006 Proc Natl Acad Sci USA 103:5024.

T Cells: Thymic lymphocytes control cell-mediated immune response (the foreign antigens are attached to them). The T lymphocytes originate in the bone marrow, differentiate in the thymus, and later migrate to the peripheral lymph nodes. While the early T cells are located in the thymus, a *negative selection* eliminates those T cells that react with self-antigens. At about the same stage of T cell development, a positive selection takes place under the influence of the MHC complex, securing the survival of those T cells that can interact with antigens associated with these cells. These encounters lead to the differentiation and activation of T cells. Cytotoxic T cells (CTL) are the major elements of the immune system; they cooperate with the natural killer cells (NK) and degrade foreign antigens with immunoproteasomes. The heterodimeric PA28a and PA28b (proteasome activating protein) activate the immunoproteasomes.

The helper T_H (CD4⁺ T cells) and the T suppressor (T_S) cells mediate the humoral (secreted) immune responses. On the surface of the T cells are the T cell surface receptors (TCR). The T_H cells stimulate the proliferation of the B (bursa) cells when they recognize their cognate antigens. The joint action of T_H cell surface receptors (TCR) and the B cell's

antigens bring about in the B cells the formation, growth, and differentiation of the proteins named lymphokines, which stimulate the propagation of B cells and the secretion of the humoral antibody. The T cell surface receptors recognize foreign antigens only if they become associated with major histocompatibility (MHC) molecules carried to the TCR by the antigen presenting cells (APC) or macrophages. The TCR links to the various intracellular signaling pathways. The activation of the T cells requires phosphorylation by SRC tyrosine kinase of the CD3 immunoglobulin chains. The activation involves co-stimulatory molecules CD28, ICAM-1, and LFA-1. For full activation, ZAP-70 protein-tyrosine kinase is also needed. The T cells are presented with a variety of antigens, including self-antigens that are carried by the APCs without discrimination. T cells distinguish self/foreign antigens. This ability begins to develop while the T cells are still in the thymus. Discrimination is a difficult task to achieve and complex phosphorylations are required for surveying the very large array of ligands of varying degree of specificity (affinity). Alternatively, it is conceivable that one peptide-MHC complex interacts first with one TCR. Then, in a contact cap this TCR detaches from the ligand, thus making possible for the ligand to bind another TCR. The process is repeated in a serial manner and assembles sufficient number of TCRs in the contact cap for productive signaling.

Chemokines enhance immunity by guiding naïve CD8⁺ T cells to sites of CD4⁺ T cell and antigen presenting dendritic cell interaction (Castellino F et al 2006 Nature [Lond] 440:890). The activation of the T cell may be only partial in case there is a subtle change (e.g., one amino acid replacement) in the peptide-MHC. The subtle variants may also inhibit the CD4⁺ helper T cells from responding to the real antigen. Altered ligands or lack of co-stimulatory signals may cause anergy of the T cell, and cannot be stimulated by the TCR but may or may not proliferate under the influence of interleukin 2 (IL2). The ligands thus can be *agonists* that fully or partially activate the T cells, or altered ligands may be weakened agonists or even *antagonists* and reduce activation. The *null ligands* provoke no response. The weak agonists may not activate ZAP-70 and may have a different pattern of phosphorylation of the CD3 ζ chain. For the fully active immune reaction, all the elements of the complex T cell activation must be in place. Some viral infections (HIV-1, hepatitis B, etc.) may lead to the production of antagonist ligands and then the cytotoxic T cells (CTL) cannot protect the body against the invader. Some aspects of the T cell activation and regulation are outlined.

On the cell membrane is the *T cell receptor* associated with CD3 and CD4 immunoglobulins. This receptor TCR mediates phosphorylation with the aid of a *protein tyrosine kinase* (PTK), *phospholipase C- γ 1*. The so activated PLC- γ 1 cleaves phosphatidylinositol-4,5 bis-phosphate (PIP2) and generates *inositol trisphosphate* (IP3) and *diacylglycerol* (DAG), which are second messengers. These second messengers activate *protein kinase C* and make available cytoplasmic Ca²⁺ for *calcineurin* (also called protein phosphatase IIB). As a consequence, the transcription factor NFAT (*nuclear factor activated T cell*) promotes the transcription of the *interleukin-2 gene*. Calcineurin also contributes to the activation of *ERK* (member of the mitogen-activated protein kinase family, MAPK). Co-stimulation is provided through the CD28 immunoglobulin system, which activates protein tyrosine kinase C that, in collaboration with the RAS G protein, stimulates the *Jun NH₂-terminal kinase* (JNK). It is also known that the *FOS* and *JUN* oncogenes contribute to the formation of the *AP* group of transcription factors, probably by acting on protein kinase C (PKC). *Phorbol myristyl acetate* (PMA) is an adjuvant for the stimulation of the *IL-2 gene*. These processes of development of effector T cells may be down-regulated when the *2E1 antibody* attaches to the *effector cell protease receptor-1*. Immunosuppressive agents such as FK506, cyclosporine, and OKT3 may cause further down-regulation.

Another important player in the T cell response is CTLA (cytotoxic T lymphocyte antigen), a molecule with about 75% homology to CD28. While CD28 is a co-stimulator of T cell activation, CTLA-4 is a negative regulator and protects against rampant lymphoproliferative disorders. The recognition of the role of CTLA offers an opportunity to neutralize its effect by specific antibodies and thereby accelerate the action of the antitumor interleukin production without serious side effects. T cell differentiation is accompanied by the appearance of surface markers in an order: CD4, CD25, CD44, CD8, and CD3. The commitment of T cell differentiation requires tumor necrosis factor- α (TNF- α) and interleukin-1 α [IL-1 α]. About 5–10% of the T cells are regulatory (T_R) and may express the CD25 activation marker. The CD4⁺ T_R cells may prevent autoimmune disease, transplant rejection, and inflammatory bowel disease (Hori S et al 2003 Science 299:1057). The understanding of these circuits may lead to designing better drugs against infections and the suppression of the rejection of tissue grafts and cancer. (See Fig. T5, ►TCR, ►T cell regulatory, ►SLAM TIL, ►HLA, ►MHC, ►killer cells, ►proteasomes, ►TAP, ►vacines, ►antibody, ►ZAP-70, ►CD3, ►CD4, ►CD8,

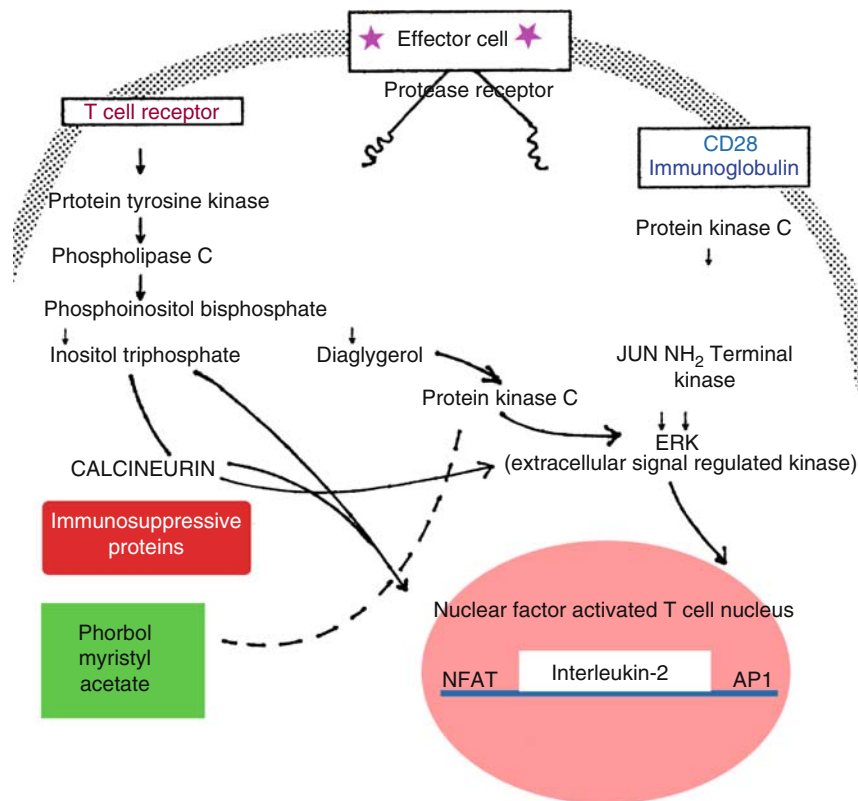


Figure T5. T cell signaling pathways. (Modified after Trucco M, Stassi G 1996 Nature (Lond.) 380:284)

►CD28, ►CTLA-4, ►ICOS, ►GATA, ►Cd117, ►SRC, ►HIV, ►immune system, ►immunoglobulins, ►protein tyrosine kinase, ►phospholipase C, ►PIP, ►IP₃, ►EPR, ►calcineurin, ►NFAT, ►interleukin, ►ERK, ►MAPK, ►RAS, ►AP, ►phorbol esters, ►FK506, ►cyclosporin, ►OKT, ►LCK, ►RANTES, ►immunophilins, ►signal transduction, ►ICAM, ►AKAP79, ►TAP, ►RAD25, ►NF-AT, ►NF-κB, ►Fas, ►autoantigen, ►αβ T cells, ►γδ T cells, ►T_H, ►thymus, ►ICAM, ►LFA; Dustin ML, Chan AC 2000 Cell 103:283; Staal FJT et al 2001 Stem Cells 19:165; Barry M, Bleackley RC 2002 Nature Rev Immunol 2:401; Sadelain M et al 2003 Nature Rev Cancer 3:35).

T Complex: The products of the virD2 and virE2 agrobacterial virulence genes associated with the 5'-end of the transferred strand of agrobacteria. ►agrobacterial virulence genes, ►T-DNA

t Complex: ►brachyury

T Cytoplasm: Texas male sterile cytoplasm of maize; almost 100% of the pollen is incapable of fertilization (sporophytic control of male sterility). ►cytoplasmic male sterility

t Distribution: ►Student's t distribution, ►t value

t Haplotype: ►brachyury

T Helper Cell: ►T_H

t Loop: ►telomeres

T Lymphocytes: ►T cells

T1 Phage: A double-stranded DNA (48.5 kbp) virulent phage, a general transducer. Only 0.2% of its cytosines and 1.7% of the adenines are methylated. The terminal redundancy is about 2.8 kb. It infects *E. coli* and *Shigella* strains. ►bacteriophages

T2, T4, and T6 Phages: T-even virulent phages that are closely related. The 166 kbp linear genome of T4 contains glycosylated and hydroxymethylated cytosine and 1–5% of its DNA is terminal redundancy; it encodes about 130 genes with known function, and about 100 additional open reading frames have been revealed. ►bacteriophages, ►development

T5 Phage (relatives BF23, PB, BG3, 29-α): The genetic material of T5 phages is linear double-stranded DNA (≈121.3 kbp) with terminal repeats (≈10.1 kbp) but without methylated bases. Three internal tracts can be deleted without loss of viability. They

are virulent phages with long tails. ▶bacteriophages, ▶development

T7 Phage (T3 is related): A virulent phage; it does not tolerate superinfection (would be required for recombination). Its 39.9 kbp genetic material is enclosed in an icosahedral head with a very short tail. It codes for about 55 genes. The T7 promoter is used in genetic vectors for in vitro transcription. Its replication requires DNA and RNA polymerase, helicase-primase complex, single-strand-binding protein, and endo- and exonuclease activities. ▶bacteriophages

θ Type Replication: θ type replication generally occurs in small circular DNA molecules starting at a single origin and following a bidirectional course (see Fig. T6). ▶replication, ▶bidirectional replication



Figure T6. Bidirectional (theta) replication

t Value (t test): The ratio of the observed deviation to its estimate of standard error: $t = \frac{d}{\sqrt{V}}$. It is used as a statistical device to estimate the probability of difference between two means. In its most commonly used form, the t is calculated as,

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{[s\bar{x}_1]^2 + [s\bar{x}_2]^2}}$$

where \bar{x} indicates the mean of the two sets of data and s stands for the standard deviation. ▶standard deviation, ▶Student's t distribution, ▶paired t test

Ta: A copia-like element (5.2 kbp) in *Arabidopsis*, flanked by 5 bp repeats but without transposase function. ▶copia, ▶retroposon, ▶TatI

Tα: A non-viral retrotransposable element. ▶retroposon, ▶retrotransposon

TAB1: A human TAK1 kinase-binding protein. Overproduction of TAB1 enhances the activity of the promoter of the inhibitor of the plasminogen activator gene, which regulates TGF-β and increases the activity of TAK1 human kinase. ▶TAK1, ▶plasmin [plasminogen], ▶TGF-β

TAB Mutagenesis: (two amino acid Barany): In TAB mutagenesis, a DNA segment containing two sense codons is introduced at a certain position into a gene in vitro; thus, probing the effect of the two amino acid modification regarding the function of the protein product. A brief outline of the essence of the procedure is shown in Figure T7. ▶directed mutagenesis, ▶cassette mutagenesis, ▶localized, ▶site-specific mutagenesis; Barany F 1985 Proc Natl Acad Sci USA 82:4202.

Tabatznik Syndrome: Heart and hand disease II. ▶Holt-Oram syndrome

TAC: Transcriptionally active complex. ▶open promoter complex, ▶transcription complex, ▶transcription factors, ▶transcription factors inducible

TAC: Transformation-competent bacterial artificial chromosome. ▶BAC

TACC: A centrosomal protein that in combination with other factors regulates spindle formation. ▶centrosome, ▶spindle; Gergely F et al 2000 Proc Natl Acad Sci USA 97:14352.

TACE (tumor necrosis factor α converting enzyme): A member of the ADAM metalloproteinase family of proteins involved in inflammatory responses. It removes ectodomains from cell surface TNF-α receptors and ligands, selectins, etc., and cleaves amyloid precursor proteins. It proteolytically makes available soluble growth factors synthesized on the cell surface. ▶metalloproteinases, ▶ADAM, ▶TNF, ▶selectins, ▶secretase, ▶β-amyloid, ▶FAS, ▶TACI; Skovronsky DM et al 2001 J Neurobiol 49:40; Black RA 2002 Int J Biochem & Cell Biol 34:1.

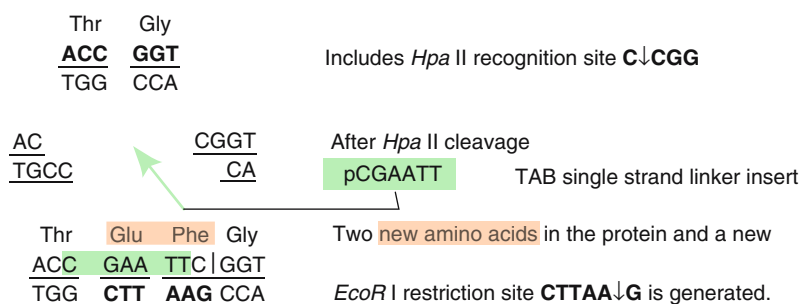


Figure T7. TAB mutagenesis

Tachykinins: Peptides mediating secretion, muscle contraction, and dilation of veins. ▶[angiotensin](#); Labrou NE et al 2001 J Biol Chem Oct 12 Online.

Tachytelic Evolution: ▶[bradytelic evolution](#)

TACI (transmembrane activator and calcium modulator and cyclophilin ligand [CAML]): One of the TNF receptors, which regulate the expression of transcription factors NF-AT, NF- κ B, and AP-1. ▶[TNF](#), ▶[TNFR](#), ▶[TACE](#); Wang H et al 2001 Nature Immunol 2:632; Pan-Hamarström Q et al 2007 Nature Genet 39:429.

TACTAAC Box: A highly conserved consensus in mRNA introns of *Saccharomyces* yeast.

Tadpole: Amphibian (frog/toad) larva at an early developmental stage. As the tadpole matures, it loses its gills, a more pronounced tail appears, and legs develop. Subsequently, the tail is lost before the frog/toad emerges from the free-swimming larva (see Fig. T8).

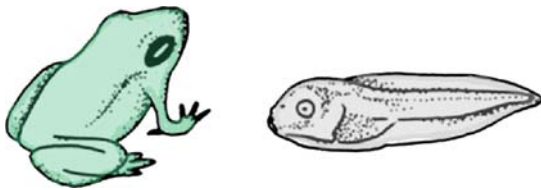


Figure T8. Left: frog; right: tadpole

TAE (Tris-acetate-EDTA): ▶[electrophoresis buffers](#)

TAF: TATA box-associated factors TAF250, TAF150, TAF110, TAF60, TAF40, TAF30 α , and TAF30 β . In yeast there are promoters that require TATA box binding protein (TBP) and TAFs (i.e., they are TAF-dependent). TAFs may require TIC for efficient function. Alternatively, other promoters are independent of TAFs and require only TBP. ▶[TBP](#), ▶[TIC](#), ▶[core promoter](#), ▶[fermentation](#); Wassarman DA, Sauer F 2001 J Cell Sci 114:2895; Green MR 2000 Trends Biochem Sci 25:59.

TAF1: TAF1 subunit, TFIID carboxy-terminal kinase, activates transcription by phosphorylation of Ser³³ residue in histone H2B (Maile T et al 2004 Science 304:1010). ▶[transcription factors](#)

TAF_{II} (transcription activating factors): TAF_{II} serve as coactivators of enhancer-binding proteins. TAF_{II} appear to have sufficient homology to transcription factor TFIID that in the absence of TAF_{II} transcription

can still proceed in yeast. TFIID is actually a complex of TBP and TAFs. TAF causes a conformational change in transcription factor TFIIB. The TAF_{II}250 subunit apparently modifies the H1 histone protein to facilitate the access of the RNA polymerase to the DNA in the chromatin. The acidic activator disrupts the amino and carboxy-terminal interactions within this molecule and this results in an exposure of the binding sites for the general transcription factors to enter into a preinitiation complex with TFIIB. TFIIB initiates the formation of an open promoter complex. ▶[regulation of gene expression](#), ▶[TF](#), ▶[open promoter complex](#), ▶[transactivator](#), ▶[co-activator](#), ▶[transcription factors](#), ▶[histones](#), ▶[SAGA](#); Frontini M et al 2002 J Biol Chem 277:5841.

TAF_{II} 230/250: TAF_{II} 230/250 has histone H3, H4 acetyltransferase and protein kinase domains. The two bromodomains of the protein apparently accommodate acetyl lysines and support the activity of TFIID. The TFIID transcription complex regulates gene expression and several critical developmental processes. ▶[histone acetyltransferase](#), ▶[bromodomain](#)

TAFE (transverse alternating field electrophoresis): TAFE is used for pulsed field gel electrophoresis, when a current is pulsed across the thickness of the gel. ▶[pulsed field gel electrophoresis](#)

Taffazzin: A fibroelastin group of proteins in the muscles. ▶[Barth syndrome](#)

Tag: Large T antigen, an early-transcribed gene of SV40. It functions as an ATP-dependent helicase in the replication of the DNA. The two Tag binding sites, each, include two consensus sequences 5'-GAGCC-3', separated by six or seven A = T base pairs. In order to start replication, Tag must bind to the replicational origin, *ori*, and to neighboring sequences of the virus. ▶[Simian virus 40](#)

tag: The small t antigen of SV40, an early-transcribed gene product.

Tag1: An autonomous transposable element (3.3 kb with 22 bp inverted repeats) of (Le-) *Arabidopsis*. It is a member of the Ac (maize), Tam3 (*Antirrhinum*), and hobo (*Drosophila*) family of elements (see Fig. T9). ▶[Arabidopsis](#), ▶[retrotransposons](#), ▶[Ac-Ds](#), ▶[Tam](#), ▶[hybrid dysgenesis](#), ▶[GUS](#), ▶[gametophyte](#); Galli M et al 2003 Genetics 165:2093.

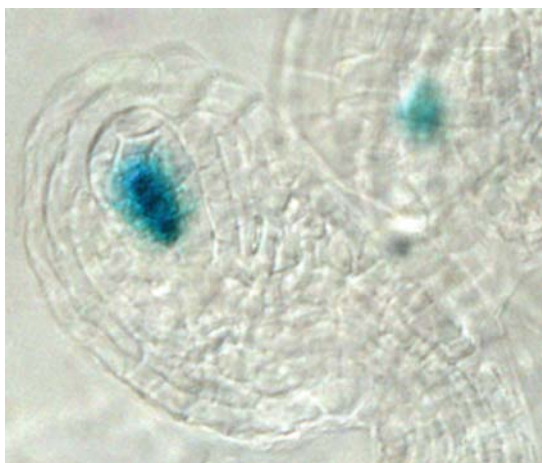


Figure T9. The *Tag1* element displays late excision during vegetative and reproductive development. When its transposase is fused to the GUS gene and transformed by such a construct, the expression (detected by the blue color) is limited to the male and female gametophytes. The illustration shows its expression in the megagametophyte. Similar is its behavior in the pollen. If however an enhancer is in its vicinity, its expression in the vegetative parts of the plants is restored. (Courtesy of Mary Galli and Nigel M. Crawford)

TAG SNP (tagSNP): A single-nucleotide(s) polymorphism characteristic for a haplotype. ▶[SNIPs](#), ▶[haplotype](#); Mueller JC et al 2005 *Am J Hum Genet* 76:387.

Tagging: Identifying a gene by the insertion of a transposon, an insertion element, a transformation vector, or by annealing with a DNA probe. These tags have known DNA sequences and can be detected on the basis of homology. When they are inserted within a structural gene or a promoter or other regulatory element of a gene, the expression of the gene may be modified or abolished. Therefore, their location may be detected by alteration in a specific function and may also assist in the isolation and cloning of the target DNA sequence. ▶[transposon tagging](#), ▶[transformation genetic](#), ▶[insertional mutation](#), ▶[probe](#), ▶[chromosome painting](#), ▶[FISH](#)

Tagmosis: The segmental organization of the insect body. ▶[homeotic genes](#); Angelini DR, Kaufman TC 2005 *Annu Rev Genet* 39:95.

Tail Bud: The tail bud gives rise to the tail of the animal from epithelial cells of the mesenchymal tailbud. Its differentiation is usually completed after the basic organization pattern of the embryo has been realized.

Tailing Homo-A: The eukaryotic mRNA generally contains a post-transcriptionally added polyA tail. Poly-A or other homopolynucleotide sequences may be added to DNAs by terminal transferases. ▶[mRNA](#), ▶[terminal transferase](#)

Tail-Less: ▶[Brachyury](#), ▶[Manx](#)

Tail-PCR (thermal asymmetric interlaced-PCR): A polymerase chain reaction resembling inverse PCR. A non-specific primer is paired with specific primers to obviate the need for circular genomic fragments. ▶[polymerase chain reaction](#), ▶[inverse PCR](#); Liu YG, Whittier RF 1995 *Genomics* 25:674.

Tailpiece, Secretory: Immunoglobulins IgM and IgA possess an 18-amino acid heavy chain C-terminal extension, and 11 of these amino residues are identical between them. This tailpiece interacts with the J chain. ▶[immunoglobulins](#), ▶[membrane segment](#); Olafsen T et al 1998 *Immunotechnology* 4(2):141.

Tajima's Method: Tajima's method statistically tests the neutral mutation theory on the basis of DNA polymorphism. D is the normalized difference of the two estimates shown.

$$D_t = \frac{\pi - \theta_s}{\sqrt{\text{Var}(\pi - \theta_s)}}$$
, where θ_s is the expected number of polymorphic sites and π is the average number nucleotide differences. ▶[mutation neutral](#); Tajima F 1989 *Genetics* 123:585.

TAK1: A human homolog of the kinase MAPKKK, an activator of the TGF- β signal. ▶[TGF- \$\beta\$](#) , ▶[TAB](#), ▶[MAP](#); Wang C et al 2001 *Nature [Lond]* 412:285.

Talin: A cytoskeletal protein binding integrin, vinculin, and phospholipids. ▶[adhesion](#), ▶[integrin](#); Xing B et al 2001 *J Biol Chem* 276:44373; Wegener KL et al 2007 *Cell* 128:171.

Talipes: ▶[clubfoot](#)

TAM (transcription associated mutation): In TAM, the rapid rate of transcription may involve increase of mutation, apparently because translesion, nucleotide excision, or recombination may not repair the DNA damage. ▶[translesion](#), ▶[DNA repair](#), ▶[Cockayne syndrome](#)

TAM (transposable element *Antirrhinum majus*): TAM are responsible for the high mutability of genes controlling the synthesis of flower pigments, known in this plant since pre-Mendelian times. There are several TAM elements. The termini of the TAM1 and TAM2 are homologous and their insertion results in a 3 bp target site duplication. Their termini are almost identical to those of the *Spm/En* transposons of maize and somewhat homologous to the termini of the *Tgm1*

transposon of soybean. The *TAM3* transposon is different from *TAM1* and *TAM2* and 7/11 bps of its terminal repeats are homologous to the *Ac* element of maize. Both *TAM3* and *Ac* may generate 8 bp target site duplications, although *TAM3* may be flanked also by 5 bp repeats. *TAM* elements, similarly to the maize transposons, seem to move by excision and relocation. The excision is usually imprecise. The insertion within genes results in mutation and the resulting mutant phenotype depends on the site of the insertion. The excision results in more or less faithful restoration of the non-mutant phenotype depending on the extent of alteration left behind at the insertion site (see Fig. T10). ▶transposable elements plants, ▶transposons; Coen ES et al 1989 Mobile DNA. In: Berg DE, Howe MM (Eds.) Amer Soc Microbiol Washington, DC, pp 413 photograph is by courtesy of BJ Harrison and Rosemary Carpenter.



Figure T10. TAM

Tamarins: New world monkeys. ▶*Callithricidae*

TAMERE (trans-allelic meiotic recombination): TAMERE is mediated by a targeted mechanism involving *loxP* sites in between two markers situated in trans, i.e., in homologues pairs of chromosomes. The recombinations may result in deletions and duplications. ▶*Cre/LoxP*; Herault Y et al 1998 Nature Genet 20:381.

Tamoxifen (2-[4-{1,2-diphenyl-1-butenyl}phenoxy]-*N,N* dimethyl-ethanamine): A selective estrogen modulator drug used for the treatment of breast cancer; it may cause endometrial cancer although the benefits may outweigh the risk (Michalides R et al 2004 Cancer Cell 5:597). Tamoxifen binds to AP1 and to other estrogen response elements in

the uterus. Tamoxifen and estrogen both activate PAX2 by hypomethylation of the PAX2 promoter (see Fig. T11). This may be the cause of endometrial cancer (Wu H et al 2005 Nature [Lond] 438:981). A multigene assay has predictive value for cancer recurrence in tamoxifen-treated node-negative breast cancer (Paik S et al 2004 New Engl J Med 351:2817). ▶breast cancer, ▶raloxifene, ▶AP1, ▶estrogen receptor, ▶estrogen response element, ▶antiestrogens, ▶estradiol; Brewster A, Helzlsouer K 2001 Curr Opin Oncol 13:420.

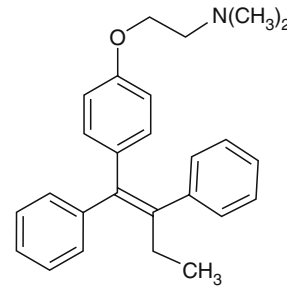


Figure T11. Tamoxifen

TAN (translocation-7-9-associated *Notch* homolog): TAN is located in human chromosome 9q34. It is involved in T cell acute leukemia. ▶morphogenesis in *Drosophila* [*Notch*], ▶*Notch*, ▶leukemia, ▶T cell; Suzuki T et al 2000 Int J Oncol 17:1131.

Tandem Duplications: ▶tandem repeats

Tandem Fusion: In tandem fusion, elements are associated head-to-tail, following each other in the same direction.

Tandem Mass Spectrometry: The tandem mass spectrometry procedure selects one kind of peptide in a mixture by collision with argon or nitrogen gas. The fragments are then processed in the tandem mass spectrometer, thus obtaining the MS/MS spectrum. This analytical method has been very useful for the detection of inborn metabolic errors in small complex blood samples. ▶electrospray, ▶MALDI, ▶MS/MS, ▶proteomics; Kinter M, Sherman NE 2000 Protein Sequencing and Identification Using Tandem Mass Spectrometry, Wiley-Interscience, New York; Chace DH et al 2002 Annu Rev Genomics Hum Genet 3:17.

Tandem Repeat: Adjacent direct repeats (such as ATG ATG ATG) of any size and number. In *Caenorhabditis elegans*, 2.7% of the genome involves tandem repeats and these occur on the average once per 3.6 kb. Comparative genomic analysis of breeds of dogs and other species indicate that increase or

decrease of tandem repeats affect the apparently rapid evolution of morphological traits, particularly in the *Alx-4* (aristaless-like 4) and *Runx-2* (runt-related transcription factor) involved in skull and limb morphology, respectively (Fondon JW Garner HR 2004 Proc Natl Acad Sci USA 101:18058). ▶repeat inverted, ▶*Drosophila*, ▶runt; <https://tandem.bu.edu/cgi-bin/trdb/trdb.exe>.

Tangier Disease (HDL deficiency): Tangier disease has a human chromosome 9q22-q31 recessive phenotype caused by a deficiency of the α -I component of apolipoproteins. The afflicted individuals have enlarged orange tonsils, liver, spleen, and lymph nodes and deficiency of the beneficial high-density lipoproteins. They accumulate cholesterol in their cells because of a defect in the ABC transporter (cholesterol-efflux regulatory protein [CERP]) that normally pumps out excessive amounts of cholesterol into the low-density lipoprotein fraction. Therefore, these patients are prone to develop coronary heart disease. ▶apolipoprotein, ▶high-density lipoprotein, ▶cardiovascular disease, ▶ABC transporters, ▶HDL, ▶cholesterol, ▶SNIPS; Brooks-Wilson A et al 1999 Nature Genet 22:336; McManus DC et al 2001 J Biol Chem 276:21292.

Tankyrase (TRF1-interacting ankyrin-related ADP-ribose polymerase, 8q13): A telomere associated protein binding a negative regulator of telomere length (TRF1) through the 24 ankyrin repeats of 33 amino acids involved in binding to TRF1; at its C terminal domain it exhibits homology to poly (ADP-ribose) polymerase. TRF2 is located at 10q23.2. Tankyrase1 inhibition in human cancer cells enhances telomere shortening by a telomerase inhibitor, hastens cell death, and offers a therapeutic potential (Seimiya H et al 2005 Cell Metabolism 1:25). Upon DNA damage in humans, TRF2 is transiently phosphorylated by ataxia telangiectasia mutated locus (ATM) and in the phosphorylated state it does not bind the telomere (Tanaka H et al 2005 Proc Natl Acad Sci USA 102:15539). ▶telomere, ▶cohesin, ▶ankyrin, ▶shelterin, ▶TRF, ▶PARP, ▶ATM; Lyons RJ et al 2001 J Biol Chem 276:17172.

Tanning: The ability to produce darker skin color depends largely on the activity of the melanocyte stimulating hormone (MSH) and its receptor (MC1R). Red-haired individuals—low in these activities—do not tan easily and are susceptible to UV damage (skin cancer). ▶pigmentation in animals, ▶albinism, ▶UV, ▶melanoma, ▶melanin, ▶hair color melanocortin

TAP: (transporter associated with antigen processing, encoded by loci TAP1 [6p21.3] and TAP2 [6p21.3]

within the HLA complex): TAP delivers major histocompatibility class I molecule-bound peptides with the cooperation of β_2 microglobulin to the endoplasmic reticulum. When these peptides exit from the endoplasmic reticulum, they are carried to the T cell receptors (TCR). Mutation in TAP may prevent antigen presentation. One member of the TAP proteins is the retroviral constitutive transport element (CTE), which may mediate RNA (hnRNP, tRNA, mRNA) export from the nucleus. Efficient export, however, requires that RNA transcript would be processed within the nucleus, i.e., introns would be removed. Some retroviruses, using CTE can transport RNA. The TAP gene contains a functional CTE element in alternatively spliced intron 10 and if this is present, mammalian mRNAs can also be exported to the polyribosomes (Li Y et al 2006 Nature [Lond] 443:234). ▶HLA, ▶major histo-compatibility antigen, ▶microglobulin, ▶immune system, ▶TCR, ▶proteasomes, ▶endoplasmic reticulum, ▶RNA export, ▶hnRNP, ▶DriP, ▶REF, ▶introns; Karttunen JT et al 2001 Proc Natl Acad Sci USA 98:7431.

TAP (tandem affinity purification): A method for rapid purification of protein complexes under native conditions. A tag is affixed to either the N or C end of one of the target proteins to facilitate the process. Proteins interacting with the tags can be purified as complexes. ▶proteomics, ▶affinity purification; Puig O et al 2001 Methods 24:218; Ghammaghami S et al 2003 Nature [Lond] 425:737.

Tap: A bacterial transducer protein responding to dipeptides.

TAPA-1: A membrane-associated protein that in association with CD19 protein and the complement receptor 2 (CR2) mediates early immune reaction by the B-lymphocytes. ▶CD19, ▶CD81, ▶complement, ▶B lymphocyte, ▶immunity; Dijkstra S et al 2000 J Comp Neurol 428:266.

Tapasin: A transmembrane glycoprotein, encoded by an HLA-linked gene. Tapasin is involved with the endoplasmic reticulum chaperone, calreticulin, in processing the MHC class I restricted antigens, and in oncogenesis. ▶MHC, ▶HLA, ▶major histocompatibility complex, ▶antigen processing and presentation, ▶TAP, ▶chaperone, ▶calnexin, ▶calreticulin; Turnquist HR et al 2001 J Immunol 167:4443; Vertegaal ACO et al 2003 J Biol Chem 278:139.

Tapetum: The lining, nutritive tissue of the anther, sporangia, or other plant or animal organs (see Fig. T12). During meiosis, they may become bi- or even multinucleate cells. The presence of B chromosomes may increase these irregularities.

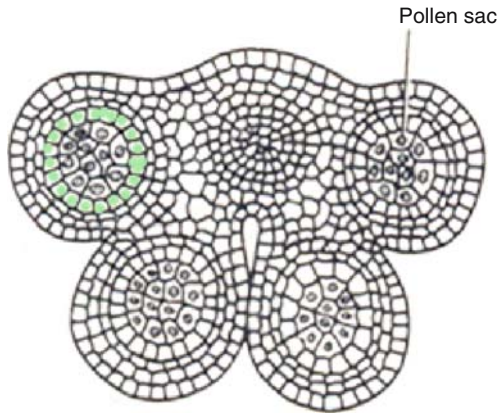


Figure T12. Anther cross section with tapetum colored green at left

Taphonomy: Taphonomy considers the processes of organisms becoming part of the fossil record. ► [fossil record](#)

Tapir: *Tapirus terrestris*, $2n = 80$.

Taq DNA Polymerase: A single polypeptide chain, 94 kDa enzyme that extends DNA strands 5'→3'; it has also shows a 5'→3' exonuclease activity. The enzyme is obtained from the bacterium *Thermus aquaticus*. The commercially available, genetically engineered enzyme AmpliTaq has temperature optima of 75 to 80°C. The enzyme is used for DNA sequencing by the Sanger method, for cloning, and for PCR procedures of DNA amplification. For the latter applications, it is particularly useful because during the heat denaturation cycles it is not inactivated and it is not necessary to add a new enzyme after each cycle. Phosphate buffers and EDTA are inhibitory to polymerization. ► [DNA sequencing](#), ► [polymerase chain reaction](#); Kainz P 2000 Biochim Biophys Acta 1494:23.

TaqMan (RT-PCR, real time PCR): A fluorogenic 5'-nuclease assay using a FRET probe, generally consisting of a green fluorescent dye at the 5'-end and an orange quencher dye at the 3'-end of a DNA. In a PCR process when the probe anneals to the complementary strand, the Taq polymerase cleaves the probe and the dye molecules are separated. Thus, the quencher can no longer suppress the reporter (e.g., the green dye) and a fluorescence detector can quantitate the green emission and the green fluorescence directly correlates with the yield of the PCR product. In seven minutes, sufficient quantities of DNA can be produced for the identification of pathogenic microbes. This technique may be used also for the molecular definition of deletions and SNIPs. ► [Taq DNA polymerase](#), ► [FRET](#), ► [PCR](#), ► [quenching](#), ► [SNIPs](#); Medhurst AD et al 2001 Brain

Res Mol Brain Res 90(2):125; Ranade K et al 2001 Genome Res 11:1262.

TAR (trans-activation responsive element): ► [transcription factors](#), ► [hormone response elements](#), ► [regulation of gene activity](#), ► [DNA binding proteins](#), ► [acquired immunodeficiency](#)

TAR: ► [transformation-activated recombination](#)

Tar: Bacterial chemotaxis transducer protein with aspartate and maltose being attractants and cobalt and nickel, repellents.

TAR Syndrome: ► [Robert's syndrome](#)

TARDP (TDP43, Transcription of RNA activating protein/TAR DNA binding protein, human chromosome 1p36.2): TARDP activates the long terminal repeat of the HIV-1 virus and regulates transcription of some other viruses. ► [amyotrophic lateral sclerosis](#)

Target: Anything that is the site for an action, e.g., target cell, target organ, target for DNA insertion. The target of an X-ray machine is the surface hit by the electrons, following which electromagnetic radiation is emitted in the cathode tube. ► [insertion element](#), ► [transposons](#), ► [probe](#), ► [x-rays](#)

Target Immunity (transposition immunity): As per target immunity, transposable elements usually do not insert within themselves or not even within close vicinity of an existing element. ► [insertional mutation](#)

Target Site Duplications: The insertion, transposable, and other mobile genetic elements generally make staggered cuts in the DNA where they move; on completion of the process the gaps are filled by complementary nucleotides, creating duplications at the flank (see Fig. T13).



Figure T13. Target site duplication after insertion (grey) and filling gaps

Target Theory: The target theory interprets the effect of radiations by direct *hits* on sensitive cellular targets. Physicists recognized that the amount of radiation energy delivered to living cells and causing biological (genetic) effects is extremely low and a comparable dose of heat energy would have no effect at all. Therefore, there must be certain special sensitive targets in the cells that respond highly to ionizing radiations. Studies with irradiated sperm and cytoplasm of *Drosophila* indicated that the targets are the chromosomes and the genes. These experiments in the period between 1920s and 1940s paved the way to physical inquiries into the nature of genetic material.

At this early period, it was hoped that the different radiation sensitivities among genes would permit the estimation of the size of these genes. It turned out, however, that radiation-sensitivity of the same genes varied according to the physiological stage of the tissues (higher in imbibed seeds than in dry, dormant ones) and it was higher in spermatozoa than in spermatogonia. Furthermore, temperature, genetic background, and irradiation of only the culture media of microorganisms affected radiation-sensitivity, indicating that radiation sensitivity is a more complex phenomenon and it does not precisely reveal the molecular nature of the gene. The direct action of radiation is proportional to the molecular weight of the target molecule = $(7.28 \times 10^{11})/D_{37}$, where D_{37} is the dose required to reduce the number of undamaged molecules to 37% of the initial total at a radiation dose of Gy^{-1} . DNA ($\times 10^8 \text{ mol s}^{-1}$) interacts with radiolytic products of water: $\text{OH}\cdot$ 3, $\text{H}\cdot$: 8×10^7 , e_{aq}^- (hydrated electrons): 1.4×10^8 . ▶radiation effects, ▶physical mutagens, ▶radiation indirect effects, ▶survival; Dessauer F 1954 Quantenbiologie, Springer, Heidelberg, Germany; Timofeëff-Ressovsky NW et al 1935 Nachr Ges Wiss Göttingen Math Phys Kl Biol 1:189; Lea DDA, Catchside DG 1945 J Genet 47:41.

Targeted Gene Transfer: Targeted gene transfer is used for “knockouts” ▶targeting genes, ▶knockout

Targeted Gene Trap: As per targeted gene transfer, the targeted gene flanks in the vector assures precise local insertion by homologous recombination into the gene (intron). The target promoter should be avoided. The targeting cassette contains selectable marker(s). The selectable/selected cells contain inactivated copies of the target and display the selected marker. Apparently, the efficiency of the procedure is very high, ~50% (Friedel RH et al 2005 Proc Natl Acad Sci USA 102:13188). ▶trapping promoters, ▶translational gene fusion

Targeted Mutation Recovery: In targeted mutation recovery, mutations are induced by chemical or physical mutagens. The genetic alterations are then determined by polymerase chain reaction combined with denaturing high performance liquid chromatography to distinguish between homo- and heteroduplex DNA sequences. If homozygotes were mutagenized, the presence of heteroduplexes indicates mutation at the selected locus. ▶PCR, ▶HPLC; Bentley A et al 2000 Genetics 156:1169.

Targeted Nucleotide Exchange (TNE): In TNE, a oligonucleotide sequence homologous to a gene and carrying a nucleotide that is critically different from

a single nucleotide within the gene is aligned by homology with the gene after transformation. At a low frequency, recombination may take place and the (mutant) nucleotide within the gene is replaced by the one delivered by the oligonucleotide sequence. ▶targeting genes; Liu L et al 2002 Nucleic Acids Res 30:2742.

Targeted Recombination: ▶Cre/loxP, ▶FLP/FRT, ▶targeting genes

Targeting: Aiming at or transporting to a site of some molecules. The homing of free cancer cells recognizes endothelial surfaces by their peptide markers and permits organ selectivity. ▶lymphocytes, ▶metastasis, ▶transit peptide, ▶transit signal, ▶site-specific mutagenesis, ▶mRNA targeting

Targeting Frequency: The number of insertions formed at homologous or quasi homologous site in a genome by a transforming vector.

Targeting Genes: Gene targeting can be accomplished either by insertional mutagenesis or gene replacement. *Inducible gene targeting* can be carried out by first introducing into an embryonic stem cell of a mouse by homologous recombination the gene *loxP*, to a flanking position of the desired target gene; *lox* facilitates the recognition of the sites for the *Cre* recombinase of phage P1 (see Fig. T14). Then the

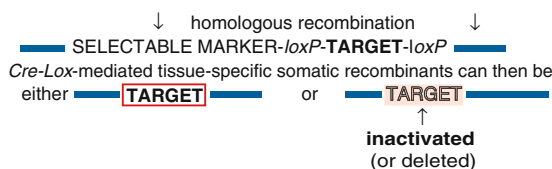


Figure T14. Targeting genes

mouse is crossed with a transgenic line expressing the *Cre* recombinase under the control of an interferon-responsive cell type-specific promoter. The tissue-specific recombinase (fused to a tissue-specific promoter), thus can remove from a particular type cell the targeted gene (“floxing”). The same procedure is applicable to other eukaryotic organisms using either the phage *Cre/loxP* or the yeast *FLP/FRT* system. Since the introduction of this site-specific alteration procedure, thousands of genes have been targeted, and in mouse alone several thousand targeted stocks have been generated. Lately gene targeting became one of the most powerful tools in genetic analysis of eukaryotes. The general principles of the procedures are illustrated. By gene targeting through double crossover within the flanking chromosomal region, different copies of the gene can be inserted (replaced) or the gene can be placed under

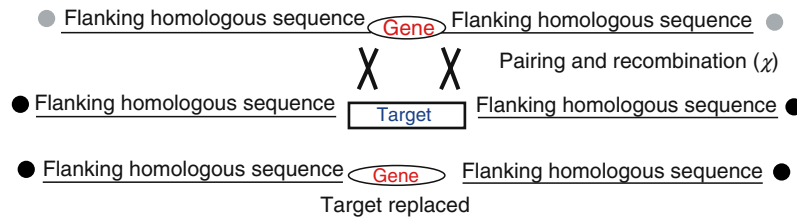


Figure T15. Target replacement by homologous recombination

the control of a specific endogenous or foreign promoter (see Fig. T15).

Targeting mammalian genes is feasible but the efficiency is fairly low (10^{-2} to 10^{-5}) compared to embryonic chicken stem cells (ES). In the transfection of avian leukosis virus (ALV)-induced chicken pre-B cells, the efficiency of recombination between the exogenous DNA and target locus may be as high as 10 to 100%. When a single mammalian chromosome is transferred to chicken cells by microcell fusion, in the somatic hybrid cell the recombination proficiency of the mammalian chromosome at the selected locus may increase up to 10–15%. The recombined chromosome can then be shuttled back to mammalian cells for analysis.

Another targeting procedure takes advantage of the bacterial tetracycline repressor gene that attaches to the promoter of some genes and keeps them silent unless tetracycline is applied that binds to the repressor; by inactivating it the genes are turned on. When this prokaryotic tetracycline repressor gene is inserted into a murine activator gene by transformation, the activator is incapacitated and the gene silenced. Alternatively, by inserting the tetracycline suppressor into a viral activator gene, all the genes of the transgenic mice that recognize the tetracycline suppressor—activator construct are turned on in the absence of tetracycline. On adding tetracycline to such a system, the antibiotic combines with the repressor—activator in the hybrid construct and the genes are now shut off because the suppressor—activator construct is removed from the activation position. Such a targeting construct can thus be used for on/off switching of particular genes. The success of targeting may be increased if the vector is an RNA-DNA hybrid molecule that pairs more efficiently with the target. By the PCR targeting procedure, a 20 bp DNA sequence tag may be generated using the photolithography procedure and DNA chips. The tag sequences are as different as possible, yet possess hybridization properties to be identified simultaneously on high-density oligonucleotide arrays. Genomic DNA is isolated from a pool of deletions tagged and used as templates for amplification. For

selectability, a resistance gene (aminoglycoside phosphotransferase) may be used. The targeting sequence is amplified by PCR that have primers at the 3'-end homologous to the marker and at the 5'-end homologous to the target. This system is introduced into the cells by transformation. After homologous recombination at two flanks of the targeted open reading frame, the target is replaced by a construct including the 20-base tag, the selectable marker, and the deletion mutation sequence (see Fig. T16).

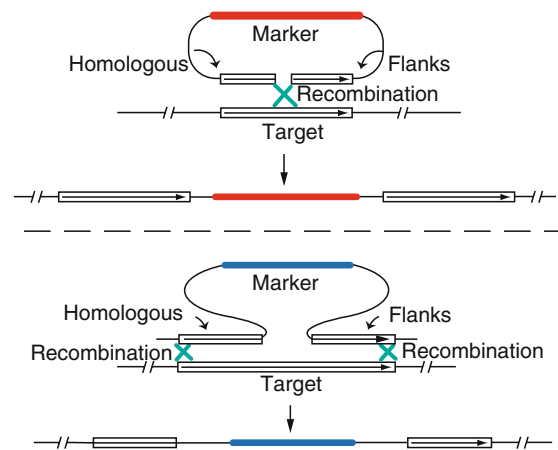


Figure T16. In *Drosophila* gene targeting can be achieved by “ends-in” (upper part of the diagram) and by “ends-out” (lower part of the diagram) procedures. The lower diagram indicates that parts of the 3' and 5' sequences of the target are deleted by the recombination. The requisites are (i) expressing a site-specific recombinase transgene, (ii) a transgene expressing a site-specific endonuclease, and (iii) a transgenic donor construct carrying recognition sites for both enzymes and the DNA of the locus targeted. This gene targeting mutates genes, which are not known by function but only by sequence. (Modified after Rong YS, Golic KG 2000 Science 288:2013)

The large number of tagged deletion strains can then be pooled and tested under a variety of conditions to test how deletion affects the function of the gene. The molecular tags are amplified and

hybridized to a high-density array of known oligonucleotides, complementary to the tags. The relative intensity of hybridization reveals the relative proportion of the individual deletion strains in the pool and their fitness. Phenotypic methodological and other relevant information is contained in the TBASE <http://www.jax.org/>. Chimeric, site-specific nucleases when used with appropriate nuclear localization signals, greatly enhance targeting by the generation of double-strand breaks in the human somatic cells (Porteus MH, Baltimore D 2003 Science 300:763; Bibikov M et al 2003 Science 300:764). A precisely placed double-strand break induced by engineered zinc finger nucleases (ZFNs) can stimulate integration of long DNA stretches into a predetermined genomic location, resulting in high-efficiency site-specific gene addition. Using an extrachromosomal DNA donor carrying a 12 bp tag, a 900 bp ORF, or a 1.5 kb promoter-transcription unit flanked by locus-specific homology arms, we find targeted integration frequencies of 15%, 6%, and 5%, respectively, within 72 h of treatment, and with no selection for the desired event. Importantly, we find that the integration event occurs in a homology-directed manner and leads to the accurate reconstruction of the donor-specified genotype at the endogenous chromosomal locus, and hence presumably results from synthesis-dependent strand annealing repair of the break using the donor DNA as a template. This site-specific gene addition occurs with no measurable increase in the rate of random integration. Remarkably, we also find that ZFNs can drive the addition of an 8 kb sequence carrying three distinct promoter-transcription units into an endogenous locus at a frequency of 6%, also in the absence of any selection (Moehle EA et al 2007 Proc Natl Acad Sci USA 104:3055). Gene targeting should be extended to any animal in which embryonic stem cells can be successfully managed. Unfortunately, this has not been realized with the majority of mammals, with the exception of mice and sheep. An alternative approach by nuclear transplantation appears more practical (Kubota C et al 2000 Proc Natl Acad Sci USA 97:990). Initially, the success of gene targeting in plants was generally in the 10^{-4} – 10^{-3} range but this has been greatly improved recently. Locus-specific deletions (52 to 1 bp), which were meiotically transmissible, could be obtained in *Arabidopsis* plants by generating double-strand breaks with the aid of zinc-finger nucleases (Lloyd A et al 2005 Proc Natl Acad Sci USA 102:2232). When the promoterless GFP (green fluorescent protein) gene was inserted into the *CRUCIFERIN* seed protein gene of *Arabidopsis* and it acquired the functional promoter, the expression of the green fluorescence could be easily detected in the large seed-output of the plants. In plants transgenic for the yeast chromatin-remodeling

and recombination-promoting protein gene, RAD54, the success of targeting increased from 10^{-2} to 10^{-1} and could be readily detected by capturing the promoter in the Cruciferin-GFP fusion protein (Shaked H et al 2005 Proc Natl Acad Sci USA 102:12265).

Actually, the INO80 protein encoded in *Arabidopsis* also displays an effect similar to Rad54 (see Fig. T17) (Fritsch O et al 2004 Mol Cell 16:479). ▶insertional mutation, ▶GAMBIT, ▶local mutagenesis, ▶gene replacement, ▶RMCE, ▶knock-out, ▶homologous recombination, ▶site-specific recombination, ▶ends-in ends-out recombination, ▶adeno-associated virus, ▶gene therapy, ▶chromosomal rearrangement, ▶homing endonucleases, ▶chromosome uptake, ▶IRES, ▶photolithography, ▶DNA chips, ▶RNA double-stranded, ▶RNAi, ▶Cre/loxP, ▶Flp/FRT, ▶GMO, ▶nuclear transplantation, ▶conditional targeting, ▶RID, ▶TFO, ▶targeted nucleotide exchange, ▶MICER, ▶gene targeting, ▶trapping promoters; Thomas KR et al 1986 Cell 44:419; Sauer B 1998 Methods 14:381; Vasquez KM et al 2001 Proc Natl Acad Sci USA 98:8403; Rong YS et al 2002 Genes Dev 16:1568; a historical account of targeting complex disease genes: Smithies O 2005 Nature Rev Genet 6:419.

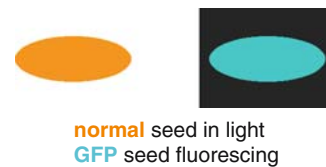


Figure T17. GFP-labeled cruciferin in *Arabidopsis* seed

Targeting Physiological: Physiological targeting locates regulatory factors to the appropriate intracellular site. Protein domains may control these functions and may be hampered by chromosomal translocation and gene fusion.

Targeting Proteins: ▶two-hybrid system, ▶one-hybrid binding assay, ▶three-hybrid system, ▶microcalorimetry, ▶surface plasmon resonance, ▶gel retardation, ▶gel filtration, ▶immunoprobe, ▶immunolabeling, ▶prenylation, ▶myristic acid; Fischer W et al 2001 Infect Immun 69:6769.

Targeting Signal: ▶signal peptide, ▶signal sequence, ▶signal sequence recognition particle

Targeting, Transcriptional: Transcriptional targeting is generally directed to the enhancer/promoter area of a specific gene. The goal is to avoid non-specific genes that may have deleterious consequences. (See Sadeghi H, Hitt MM 2005 Curr Gene Ther 5:411; Izumo T et al 2007 Int J Oncol 31:379).

Targeting Vector: In a viral vector, a section of the envelope protein gene is replaced by the coding sequences of, e.g., 150-amino acids of erythropoietin (EPO) and thus, the replacement improves its ability to recognize the EPO receptor. Other approaches involve pseudotyping or attaching special ligands to the envelope (Müller OJ et al 2003 Nature Biotechnol 21:1040). Liposomal vehicles may be conjugated with special antibodies for target recognition. Bifunctional antibodies that recognize both viral epitopes and target cell antigens have been constructed. Another approach was found to covalently link biotin to recombinant adenovirus. The Kit receptor and the stem cell factor (SCF) were then linked through an avidin bridge to the target to assure the proper tropism. It is highly desirable that ligand–receptor pairs be limited to specific functions rather than cross over to members of regulatory networks. Such a goal can be reached by stepwise, individual, site-specific saturation mutagenesis followed by phenotypic screening based on the yeast two-hybrid system. The nuclear hormone estrogen receptor so modified can favor a synthetic 4,4'-dihydroxybenzil by more than a million-fold over the natural ligand 17 β -estradiol. Such a technique can specifically target human endometrial cancer (Chockalingam K et al 2005 Proc Natl Acad Sci USA 102:5691). ▶liposome, ▶vectors, ▶pseudotyping, ▶magic bullet, ▶gene therapy, ▶KIT oncogene, ▶stem cell factor, ▶biotin, ▶avidin, ▶epitope, ▶dihydroxybenzil, ▶nuclear receptor, ▶estradiol, ▶estrogen receptor, ▶targeting transcriptional; Peng KW et al 2001 Gene Ther 8:1456; Yu D et al 2001 Cancer Gene Ther 8:628; therapeutic applications: Waehler R et al 2007 Nature Rev Genet 8:573.

Target-Primed Reverse Transcription: Retrotransposons without long terminal repeat sequences are inserted into eukaryotic genomes by a process in which cleaved DNA targets are used to prime reverse transcription of the RNA transcript of the element. ▶LINE, ▶reverse transcription

TART: A telomere-specific retroposon of *Drosophila* with an about 5.1-kb 3'-non-coding tract, which is homologous to HeT-A; it also encodes a reverse transcriptase. ▶telomere, ▶Het-A, ▶LINE, ▶retroposon, ▶reverse transcription; Haoudi A, Mason JM 2000 Genome 43:949.

Tarui Disease: ▶glycogen storage diseases (Type VII)

TAS (termination associated sequences): Signals for ending transcription. Also, telomere-associated sequences involved in the silencing of genetic functions. ▶transcription, ▶telomere, ▶silencing

tasiRNA: Transacting siRNA produced by Dicer4. ▶Dicer, ▶RNAi, ▶siRNA

Tasmanian Devil (*Sarcophilus harrisii*, $2n = 12 + XY$): Australian, large, black, white-spotted, carnivorous marsupial frequently with large tumors on its face (⇒) that generally become fatal because the animals cannot feed (see Fig. T18). Tissue fragments acquired during fighting with infected individuals probably transmit the tumors. In the tumor cells in each of the 11 animals examined, the sex chromosomes, a pair of chromosome 2, one chromosome 6, and one arm of chromosome 1 were missing, but four chromosomes of unidentified origin were added so the tumor cells had 13, rather than the normal 14 chromosomes (Pearese A-M, Swift K 2006 Nature [Lond] 439:549; Owen D, Pemberton D 2006 Tasmanian Devil: A Unique and Threatened Animal. Natural History Museum, Allen & Unwin. London, UK; McCallum H, Jones M 2006 PLoS Biol 4(10): e342). ▶canine transmissible venereal tumor



Figure T18. Tasmanian devil

Tassel-seed: Mutations (*ts*) in maize result in kernels on the normally male inflorescence (tassel) as a result of the effemination. ▶sex determination

Taste: Taste is controlled by a signal transducing G protein, gustducin. Both bitter sweet and unamintasting is mediated by gustducin. Ionic stimuli of salts and acids interact directly with ion channels and depolarize taste-receptors. Sugars, amino acids, and most bitter stuff bind to specific receptors outside the cell membrane and these are then connected to G proteins. It is assumed that gustducin is involved with a phosphodiesterase. Phospholipase C also appears to play a role in the taste circuits. Gustducin receptors are present in the tongue and also in the stomach and the intestines. Taste buds are only a few

thousand in number, with 3 to 5×10^4 taste receptors. The TRPM cation channel family greatly enhances sweet perception at temperatures between 15°C and 35°C (Talavera K et al 2005 Nature [Lond] 438:1022). A locus in human chromosome 5p15 was associated with sensing the bitter taste of 6-n-propyl-2-thiouracil. The phenylthiocarbamide taste locus (PTC/PROP) is a receptor, TAS2R, located in human chromosome 7q. There is great variation among the TASR genes. Some individuals, however, fail to identify its bitter taste. Seven transmembrane domain taste receptor sequences were attributed to clusters also in human chromosomes 7q31-q32 and 12p13. The T1R-1/TAS1R taste receptor gene (1p36) family is apparently specific for sweetness, whereas T1R2 for bitter taste. The latter may include 50–80 genes. Mammals can taste sour, salty, sweet, bitter, and umami (monosodium glutamate). Genes for different taste receptors have been isolated. A distinct and separate sour taste receptor is PKD2L1 (polycystic kidney disease-like ion channel; Huang AL et al 2006 Nature [Lond] 442:934). ▶ion channels, ▶degenerin, ▶signal transduction, ▶olfactogenetics, ▶fragrances, ▶phenylthiocarbamide; Dulac C 2000 Cell 100:607; Nelson G et al 2001 Cell 106:381; Lindemann B 2001 Nature [Lond] 413:219; Margolske RF 2002 J Biol Chem 277:1; Bufe B et al 2002 Nature Genet 32:397; brain circuits of bitter and sweet: Sugita M, Shiba Y 2005 Science 309:781; Drayna D 2005 Annu Rev Genomics Hum Genet 6:217; mammalian taste receptors: Chandrashekar J et al 2006 Nature [Lond] 444:288.

TAT (twin-arginine translocase): A ~600 kDa protein complex that moves proteins through thylakoid and prokaryotic membranes. ▶thylakoid; Robinson C, Bolhuis A 2001 Nature Rev Mol Cell Biol 2:350.

Tat: 14 kDa primary regulator of the HIV virus. ▶acquired immunodeficiency

Tat1: A transposon-like element (431 bp) in *Arabidopsis*, flanked by 13 bp inverted repeats and 5 bp target-site duplications, but without any open reading frame and thus incapable of movement by its own power. There is also a Tat1 human sulfate transporter and TAT 1 and TAT2 yeast amino acid permeases. ▶Arabidopsis, ▶transposons, ▶open reading frame; Peleman J et al 1991 Proc Natl Acad Sci USA 88:3618; Toure A et al 2001 J Biol Chem 276:20309; Schmidt A et al 1994 Mol Cell Biol 14:697.

TAT-GARAT: The TAATGARAT enhancer motif of Herpes simplex virus. ▶cigar

TATA Box: Thymine (T) and adenine (A) containing binding sites for transcription factors and the RNA polymerase complex. The bases, their numbers, and

the exact base sequences in the TATA boxes vary. In yeast, the TATA box is 40–120 bp, in the majority of other eukaryotes 25–30 bp ahead of the transcription initiation site (Struhl K 1989 Annu Rev Biochem 58:1051). Many housekeeping genes and the RAS oncogene do not have this sequence (Suzuki Y et al 2001 Genome Res 11:677). In case of the absence of TATA, some other A and T nucleotides may associate with the TATA-box-binding proteins (TBP). A downstream promoter element (DPE) has also been identified. DPE may bind TFIID. In *Drosophila*, some core promoters have both TATA box and DPE or only one of the two (Kutach AK, Kadonaga JT 2000 Mol Cell Biol 20:4754). ▶Pribnow box, ▶Hogness (Goldberg) box, ▶transcription factors, ▶transcription complex, ▶open promoter complex, ▶asparagine synthetase, ▶core promoter, ▶promoter, ▶TBP, ▶PWM, ▶DPE; Smale ST, Kadonaga JT 2003 Annu Rev Biochem 72:449.

TATA Box Binding Protein: ▶TBP

TATA Factor (TF): ▶transcription factors, ▶TATA box

TATA Inr: Core promoters may or may not contain these pyrimidine-rich transcription initiator elements. ▶TATA box, ▶open promoter complex, ▶transcription factors, ▶core promoter

Tatsumi Factor: A blood-clotting factor required for the activation of Christmas factor by activated PTA. It is controlled by an autosomal locus. ▶antihemophilic factors, ▶blood clotting pathways, ▶PTA deficiency disease, ▶hemostasis

TAU (MAPT, 17q21.1): The size of the tau gene can vary from ~352 to 441 amino acids in the isoforms of the microtubule-associated proteins by alternative splicing of the mRNA (Margittai M, Langen R 2004 Proc Natl Acad Sci USA 101:10278).

By reducing motor reattachment rates, tau affects cargo travel distance, motive force, and cargo dispersal. Different isoforms of tau, at concentrations similar to those in cells, have dramatically different potency.

These defined mechanism show how altered tau isoform levels could impair transport and thereby lead to neurodegeneration without the need of any other pathway (Vershinin M et al 2007 Proc Natl Acad Sci USA 104:87). It seems to form tangles by virtue of the $^{306}\text{Val-Gln-Ile-Val-Tyr-Lys}^{311}$ motif in the 6 tau monomers in several types of nerve degenerative diseases (e.g., Pick disease, Alzheimer disease, progressive supranuclear palsy, corticobasal degeneration).

A pseudogene exists at 6q21. Base substitution and splice site mutations may lead to Pick disease, parkinsonism and Alzheimer's disease. In the tangle

of the paired helical filaments, tau is hyperphosphorylated causing defects in microtubule assembly and mitotic arrest. The use of a kinase inhibitor (at lysine 252) can prevent hyperphosphorylation of tau and the aggregation of tau without reducing the tangles; such a treatment reduces severe motor function impairment in transgenic mice indicating that aggregation rather than tangling is the cause of the development of tau pathology (Le Corre S et al 2006 Proc Natl Acad Sci USA 103:9673).

The adverse effect of hyperphosphorylation may be prevented by trimethylamine N-oxide (TMAO) because this natural compound lowers the concentration of tubulin needed for assembly. The hyperphosphorylated tau may self-assemble and the causes the fibrillary tangle observed in the degenerated brain of Alzheimer's patients. Cyclic-AMP-dependent protein kinase (PKA), glycogen synthase kinase 3 β (GSK-3 β), or Cdk5 may carry out the phosphorylation.

Phosphorylation of a Ser or a Thr amino acid preceding a Pro creates a binding site for the prolyl-isomerase Pin1. When Pin1 binds to this site in tau, it may deplete it in the brain leading to some of the problems related with Alzheimer's disease. Amyloid- β immunotherapy can clear the fibrillar tangle with the aid of proteasomes, if applied before the hyperphosphorylation of tau (Oddo S et al 2004 Neuron 43:321). In human Parkinsonism, mutation can affect aberrant splicing of exon 10. Using a spliceosome-mediated trans-splicing, the mRNA can be reprogrammed. Thus, creating a new exon 9–exon 10 junction indicates the feasibility of therapeutic trans-splicing (Rogriguez-Martin T et al 2005 Proc Natl Acad Sci USA 102:15659). Neurofibrillary degeneration is increased when both A β and tau are expressed the same time. In a mouse model of Alzheimer's disease, the chronic supply of nicotine exacerbates tau tangles (Oddo S et al 2005 Proc Natl Acad Sci USA 102:3046). In mouse transgenic for a suppressible tau, memory was recovered and neuron numbers were stabilized after suppression of tau, yet neurofibrillary tangles continued to grow, indicating that the tangles are not sufficient to account for the degenerative phenomena (see Fig. T19) (SantaCruz K et al 2005 Science 309:476). Fragments of the repeat domain of tau, containing mutations of FTDP17 (frontotemporal dementia with Parkinsonism linked to chromosome 17 also called Pick disease), produced by endogenous proteases, can induce the aggregation of full-length tau. Fragments are generated by successive cleavages, first N-terminally between lysine257 and serine258, then C-terminally around residues 353–364; conversely, when the N-terminal cleavage is inhibited, no fragmentation and aggregation takes place. The C-terminal truncation and the

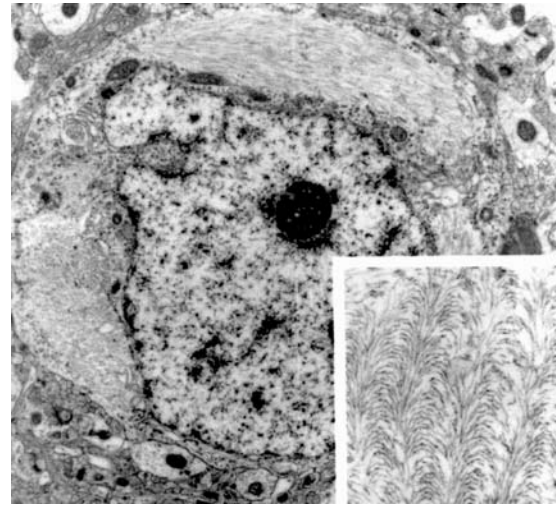


Figure T19. Transgenic mouse brain expressing neurofibrillary tangle (enlarged in insert) and A β plaques similar that occurs in humans afflicted by Alzheimer disease. (Courtesy of Drs. Dennis W. Dickson and Wen-lang Lin, Mayo Clinic, Jacksonville, Florida; I am indebted also to Mike Hampton, Maryland)

coaggregation of fragments with full-length tau depend on the propensity for β -structure. The aggregation is modulated by phosphorylation but does not depend on it. Aggregation but not fragmentation is toxic to cells; conversely, inhibiting either aggregation or proteolysis can prevent toxicity (Wang YP et al 2007 Proc Natl Acad Sci USA 104:10252). In a *Drosophila* model of tauopathy, neurodegenerative symptoms appeared without the fibrillary tangle. ▶FTDP-17, ▶prion, ▶amyloids, ▶secretase, ▶sirtuin, ▶Pick disease, ▶Alzheimer disease, ▶p35, ▶parkinsonism, ▶microtubule, ▶CDK, ▶palsy, ▶corticobasal degeneration, ▶synuclein, ▶RNAi, ▶trans-splicing; von Bergen M et al 2000 Proc Natl Acad Sci USA 97:5129; Wittmann CW et al 2001 Science 293:711; Lewis J et al 2001 Science 293:1487; Liou Y-C et al 2003 Nature [Lond] 424:556.

Taurine ($\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{SO}_3\text{H}$): An amino acid absent from muscle proteins but present in several body fluids (it was first isolated from the bile of cattle [*Bos taurus*]; hence the name). It is important for membrane transport and as an antioxidant and is thus an essential nutrient. In its absence from the tRNA, Leu^{UUR} (5-taurinomethyluridine) may cause mitochondrially-determined disease. ▶mitochondrial disease

Tautomeric Shift: The reversible change in the position of a proton in a molecule, affecting its chemical properties; it may trigger base substitution and thus

mutation in DNA. ▶hydrogen pairing, ▶enol form, ▶substitution mutation; Watson JD, Crick FHC 1953 Cold Spring Harbor Symp Quant Biol 19:123.

TAX1: A human T-cell leukemia virus (40 kDa) protein gene (1q32.1) with three 21 bp CRE-like sites; it increases DNA binding of transcription factors containing a basic leucine zipper domain. ▶leucine zipper, ▶leukemia, ▶CRE, ▶CREB, ▶HTLV; Soda Y et al 2000 Leukemia 14:1467.

Taxol (Paclitaxel): A spindle fiber blocking natural substance isolated from the yew *Taxus brevifolia*; it is a carcinostatic and radio-sensitizing drug. It induces apoptosis. ▶spindle, ▶carcinostasis, ▶epothilone, ▶microtubule, ▶apoptosis, ▶Herceptin, ▶Abraxane; Okano J-i, Rustgti AK 2001 J Biol Chem 276:19555; Jennewein S et al 2001 Proc Natl Acad Sci USA 98:13595; Ganesh T et al 2004 Proc Natl Acad Sci USA 101:10006; 19 proteins involved in taxol synthesis: Jennewein S et al 2004 Proc Natl Acad Sci USA 101:914.

Taxon (plural taxa): The collective name of taxonomic categories.

Taxonomy: (biological) classification with a number of different systems. The bases of this classification are morphology, anatomy, genetics, biochemistry, physiology, cytology and macromolecular structure (DNA, RNA and proteins). Generally, five broad categories are recognized: prokaryotes and viruses, protists, fungi, plants, and animals. The taxonomic categories of eukaryotes include Phylum, Class, Order, Family, Genus, Species, and Subspecies (such as varieties, cultivars, breeds). In the past, the classification was more rigid because the species was considered the mark of genetic isolation. Today, with somatic cell hybridization and transformation (transfection) there is no limit to genetic exchange between various categories. There are over 300,000 plant and over 1,000,000 animal species named and classified by rules of nomenclature. For naming, binomial nomenclature is used. The capitalized first letter of the first name identifies the genus and the species is designated by the second name in lower case letters. This is sometimes followed by the name of the first taxonomists who classified the organisms, e.g., *Arabidopsis thaliana* (L.) Heynh., indicating *Arabidopsis* as the genus, *thaliana* as the species, L. stands for Linnaeus and Heynh. is the abbreviation for Heynhold who suggested the current name. Plant taxonomy: <http://www.itis.gov/>; virus taxonomy: <http://www.ncbi.nlm.nih.gov/ICTVdb>; NCBI taxonomy database: <http://0-www.ncbi.nlm.nih.gov.library.vu.edu.au/Taxonomy/>. For sequence-based taxonomy: <http://www.ncbi.nlm.nih.gov/Taxonomy/>

taxonomyhome.html; sequence database: <http://www.ebi.ac.uk/seqdb/Projects.html>.

Tay-Sachs Disease: One of the most thoroughly studied biochemical diseases in human populations; it is controlled by an autosomal recessive gene (see Fig. T20). This defect occurs in all ethnic groups, but it is particularly common among Ashkenazi (eastern European) Jews where the

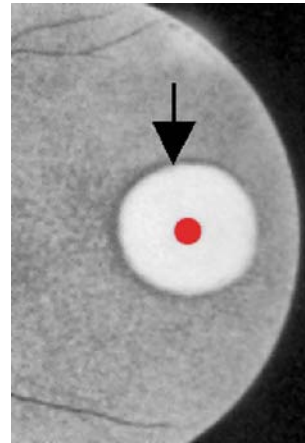


Figure T20. Cherry-red spot on the macula in Tay-Sachs disease

frequency of the gene is approximately 0.02 and the frequency of heterozygotes may be over 3%. The prevalence is about 1/2,500 to 1/5,000 per birth. Among the Sephardim Jews and other ethnic groups, the frequency is about 1/1,000,000. Since the afflicted individuals generally die by age three to four, the high frequency indicates that some heterozygote advantage must have existed for this gene. The effective genetic screening for heterozygotes in the USA has greatly reduced the prevalence of this disease (Kaback MM 2001 Adv Genet 44:253). The onset is at six months when general weakness, extension of the arms in response to sounds, a scared look, and muscular stiffness and retardation appear in an earlier apparently normal child. Then in rapid succession, paralysis, reduction of mental abilities, and vision problems leading to blindness become evident. One characteristic symptom is a cherry-red spot (↓) on the macula (gray opaque part of the cornea [eye]), caused by cell lesions. All these symptoms are the results of a deficiency of β -hexosaminidase enzyme α subunit that controls the conversion of ganglioside G_{M2} into G_{M3} . As a consequence, G_{M2} ganglioside accumulates leading to degeneration of the myelin of the nervous system. Hexosaminidase A is composed of the α subunits (human chromosome 15q23-q24) and hexosaminidase B is a multimer of

the β subunits (human chromosome 5q13). Sandhoff's disease involves both hexosaminidase A and B deficiencies or only hexosaminidase B deficiency, and has somewhat similar symptoms with more rapid progression. Another (Type 3), milder form of GM₂ gangliosidosis (5q31.3-q33.1) with some hexosaminidase A activity may permit survival up to age ~15. In a mouse model, *N*-butyldeoxynojirimycin prevents the accumulation of GM₂. In Sandhoff's disease model mouse, stereotactic (precisely positioned) brain injection by adeno-associated virus vector containing the α and β subunits of the human β -hexosaminidase gene, including also the tat sequence of the HIV virus (for enhancing protein expression and distribution), resulted in the transgene being expressed and consequently GM₂ ganglioside storage and inflammation being reduced. The survival of the animals expanded to more than twice as long, to over a year, and motor function was restored, indicating that this type of gene therapy may be eventually applicable for this incurable human disease (Cachón-Gonzalez MB et al 2006 Proc Natl Acad Sci USA 103:10373).

The older common name of these gangliosidoses was amaurotic familial idiocy. ▶Sandhoff's disease, ▶hexosaminidase, ▶gangliosidoses, ▶gangliosides, ▶sphingolipids, ▶lysosomal storage disease, ▶genetic screening, ▶Jews and genetic disease, ▶gene therapy; Mahuran DJ 1999 Biochim Biophys Acta 1455:105; Myerowitz R et al 2002 Hum Mol Genet 11:1343.

Tay Syndrome: ▶trichothiodystrophy

T-Bam: Same as CD40 ligand.

T-Band: The telomeric regions of chromosomes with the highest concentrations of genes and G + C in the genome. ▶band, ▶chromosome banding, ▶isochores

T-bet (T-box expressed in T cells): A 530-amino acid transcription factor that promotes the differentiation and activity of T_H1 cells and represses the formation of T_H2 lymphocytes. The repression of T_H2 is brought about by tyrosine kinase-mediated interference of GATA-3 binding to its target DNA (Hwang ES et al 2005 Science 307:430). T-bet deficiency reduces atherosclerosis in mice (Buono C et al 2005 Proc Natl Acad Sci USA 102:1596). T-bet is aided by CpG DNA oligonucleotides in innate immunity (Lugo-Villarino G et al 2005 Proc Natl Acad Sci USA 102:13248). ▶T_H, ▶T box, ▶GATA, ▶omesodermin, ▶innate immunity, ▶memory immunological; Mullen AC et al 2001 Science 292:1907; Lovett-Racke AE et al 2004 Immunity 21:719.

TBL1: transducin-beta-like protein. ▶transducin; Tomita A et al 2004 Mol Cell Biol 24:3337.

TBP (TFII τ): TATA box binding protein is a subunit of the general transcription factors, TFIID, SL1, and TFIIB proteins that bind to DNA like a saddle in a two-fold symmetry (see Fig. T21) (Burley SK, Roeder RG 1996 Annu Rev Biochem 65:769). The TFIIB complex shares amino-terminal homology with TFIIB. TFIIB has anti-parallel β sheets at the concave area where it forms a reaction with the special A and T rich sequence of the DNA. TFIIB-related factor (Bref1) at the carboxy-terminal mediates the binding of TBP to the DNA. The convex surface provides opportunities for interaction with other proteins. The TBP is highly conserved among different organisms from yeast to the plant *Arabidopsis* to mammals. TBP may form a complex with several TAF proteins. It apparently nucleates the pre-initiation complex of all three DNA-dependent RNA polymerases—pol I, II, and III—but in a somewhat different manner (Fan X et al 2005 Nucleic Acids Res 33:838). The TBF-like factors (TLFs) variously denoted as

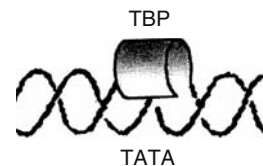


Figure T21. TBP—TATA box schematic representation. TBP of *Arabidopsis* recognizes the minor groove of TATAAAAG

TRF2 or TRP are orthologs of TFL and appear functionally different from TBP. TLF appears to be required for differentiation and is needed for the transcription of some special sets of genes. The TBP may also bind SL1 transcription factor of pol I but this binding is exclusively either with TFIID or SL1. The pol III TBP complex is called TFIIB. The Dr1 repressor binds to TBP and selectively inhibits pol II and pol III action but pol I is not affected, however, because when pol II and III are repressed the relative output of pol I appears higher. The TFIID complex activity is restricted by the nucleosomal organization of the chromatin. The C-terminus of TBP is highly conserved, whereas the N region displays great variations. In TBP^{-/-} mouse cells, DNA-dependent RNA polymerase II seems functional but pol I and pol III are arrested. ▶transcription factors, ▶pol, ▶TAF; Berk AJ 2000 Cell 103:5; Magill CP et al 2001 J Biol Chem 276:46693; Zhao X, Herr W 2002 Cell 108:615; Martianov I et al 2002 Science 298:1036.

TB-parse: A program for the identification of protein-coding sequences. (See Nucleic Acids Res 22:4768).

TBR: Transforming growth factor receptors. ►TGF

Tc: A family of transposons in *Caenorhabditis*. *Tc1* is silenced in the germline by a natural RNAi (Sijen T, Plasterk RHA 2003 Nature [Lond] 426:310). ►transposon, ►*Caenorhabditis elegans*

TC4: A small nuclear G protein with CD28 being its primary ligand. It is involved in the regulation of T lymphocytes. ►G proteins, ►RAN; Nieland JD 1998 Cancer Gene Ther 5:259.

TC Motif: ►AP1, ►AP2, ►transcription factors

TCC (terminal complement complex): TCC includes C5b-9, C5b-8, and C5b-7 complement components involved in the complement-mediated killing of foreign cells. ►complement, ►immune system

TCC (transitional cell carcinoma): See Dal Cin P et al 1999 Cancer Genet Cytogenet 114(2):117.

TCCR (T cell cytokine receptor): TCCR mediates adaptive immune response of T_H1 lymphocytes. (See Chen Q et al 2000 Nature [Lond] 407:916).

TCF (ternary complex factors): TCF are co-activators of transcription such as Elk, Sap-1a, Sap-1b, ERP-1, and other members of the ETS family of transcription factors and oncoproteins. Some are members of the high mobility group proteins. TCF usually binds to the AACAAAG sequences of the promoter. In case of defect in the tumor suppressor APC gene (adenomatous polyposis) and/or in the β -catenin gene, Tcf-4 (responsible for crypt stem cells) is activated and malignancy may result. TCF4 when interacting with phosphorylated Jun regulates intestinal cancer (Nateri AS et al 2005 Nature [Lond] 437:281). CBP seems to be a repressor of TCF. ►high mobility group proteins, ►ETS, ►CBP, ►Gardner syndrome, ►melanoma, ►LEF, ►catenins, ►mtTAF, ►CBP, ►Wingless; Morin S et al 2001 Mol Cell Biol 21:1036.

TCGF: ►interleukin 2, ►IL-2

TCID₅₀: Tissue culture infective dose causing (viral) infection to 50% of the cells.

Tcl: ►hybrid dysgenesis

TCL1: An oncogene (14q32.1). It is normally expressed in fetal thymocytes, in pre-B, and immature B cells and weakly in CD19⁺ peripheral blood lymphocytes. Chromosomal translocations or inversions near the enhancer element of TCR may cause leukemia or lymphoma. It enhances the Akt kinase activity and promotes nuclear transport. ►B lymphocyte, ►CD19, ►TCR, ►leukemia, ►lymphoma, ►Akt; Pekarsky Y et al 2001 Oncogene 20:5638.

TCLo: Toxic concentration low; the lowest concentration of a substance in air that produces toxic, neoplastic, and carcinogenic effects in mammals.

t-Complex: The t-complex of mouse consists of six complementation groups in chromosome 17, affecting tail development and viability. Homozygous mutants, of the same complementation group, are generally lethal. ►brachyury

TCP-1 (CCT): The cytoplasmic α subunit chaperonin coded for by the t-complex in mouse chromosome 17. Its homolog occurs also in the pea leaf cytosol. A TCP protein has been suggested to mediate the curvature of the leaf surface of crinkly mutations (Nath U et al 2003 Science 299:1404). ►chaperonins, ►chaperone, ►brachyury

Tcp20: Synonymous with CCT ζ and Cct6. ►chaperonins; Li WZ et al 1994 J Biol Chem 269:18616.

TCR Genes: The T cell receptors are glycoproteins and are similar to the antibody molecules. The TCR α chain has variable (V), diversity (D), junction (J), and constant (C) regions in the polypeptides, which are generated with rearrangements of the gene clusters in human chromosome 14, in the proximity of the immunoglobulin heavy chain genes (IgH). These recombinations take place in the switching regions and the TCR genes also have the same hepta- and nanomeric sequences as the Ig genes. In the mouse, TCRA (α) genes are in mouse chromosome 14 whereas the Ig heavy chains of the mouse are in chromosome 12. The TCR δ chain locus is situated within the human α gene between the V_α and J_α regions. When the δ gene is excised, an excision circle is generated which includes also the excision signal joints (TREC). The human β chain of TCR is encoded in chromosome 7q22-7qter. (In mouse, its homolog is in chromosome 6). The expression of the β genes also requires rearrangement of the VDJ genes next to the C genes. The $\gamma 1$ and $\gamma 2$ chain genes are located in the human chromosome 7p15-p14 area, whereas their homologs are in mouse chromosome 6. The early lymphocytes carry TCR built of γ and δ polypeptides, whereas in the later, about 95% of the TCRs are built of α and β chains. The size of the $\alpha\beta$ TCR is about 80-kDa, built of four subunits. After the $\alpha\beta$ TCRs are formed, the $\gamma\delta$ TCRs are eliminated. The $\alpha\beta$ TCR is part of the protein complex CD3 γ , δ , ϵ , and ζ . These chains also contain 1 ITAM motif except ζ which has 3. Phosphorylation of the ITAM motif facilitates signal transduction from TCR. Subunit ζ determines largely the specificity by specific series of phosphorylations. In contrast to the $\alpha\beta$ antigen receptors, which recognize only peptides (fragments) bound to MHC molecules, the $\gamma\delta$ TCRs recognize the polypeptides without the

MHC molecules and also the MHC molecules without bound peptides. Also the $\gamma\delta$ TCRs may use non-peptide ligands such as phosphate-containing molecules. The TCR molecules are of a great variety, and are determined by rearrangements, just like in immunoglobulins. It appears that the TCR does not mutate somatically, in contrast to the Ig genes. The association of TCR either with Class I and Class II HLA gene products (MHC) augments the specificity of the TCR. The Class I HLA antigens are associated with the cytotoxic (killer) cells, whereas the helper lymphocytes attach to the Class II antigens. In the function of the TCRs, an important role is played by the CD4 (in Class I) and CD8 (in Class II associations). Both types of TCRs also require the CD3 transmembrane proteins complex involved in signal transduction. The CD peptides also activate some protein tyrosine kinases, important elements of several signal transduction pathways. Many forms of cancer are associated with chromosome breakage in the regions where the TCR proteins are coded. The human TCR β locus, consisting of 685 kb, has been sequenced. This large family includes, besides the TCR elements, other genes too, such as a dopamine-hydroxylase-like gene and eight trypsinogen genes. The large locus involves, besides the 46 functional genes, 19 pseudogenes and 22 relics (genes with major lesions in one or more components). A portion of the locus is translocated from chromosome 7q22–7qter to 9. The V β segments include promoters, the first exon as a signal peptide, with RNA splicing signals, the second exon is the V element and DNA rearrangement signal sequence. In some V β families a conserved decamer interacts with binding proteins.

►T cell receptor, ►immunoglobulins, ►immune response, ►antibody, ►HLA, ►lymphocytes, ►CD4, ►CD8, ►SLAM, ►antigen-presenting cell, ►MHC, ►ITAM; Mak TW et al 1987 J Infect Dis 155:418; Weiss A 1990 J Clin Invest 86:1015; Moffatt MF et al 2000 Hum Mol Genet 9:1011; Willemsen RA et al 2003 Hum Immunol 64:56.

T

TCV: ►Turnip crinkle virus

TD₅₀ (toxic dose): A dose causing toxic (carcinogen) effects in 50% of the experimental organisms. Frequently identified as mmol/kg/day. ►CASE

TDF (testis determining factor): ►sex determination, ►SRY, ►H-Y antigen

TDM: Tissue-specific differentially methylated regions in the genome (Song F et al 2005 Proc Natl Acad Sci USA 102:3336). ►methylation of DNA

T-DNA (transferred DNA): The T-DNA of the Ti plasmid is bordered by 24–25 bp incomplete direct repeats: TGGCAGGATATATT \overline{C}_A X \overline{A}_G TTGTAAA for the left and

TGGCAGGATATATT \overline{C}_A X \overline{A}_G TTGTAAA for the right in the octopine plasmids of *Agrobacterium*. The border sequences of the nopaline plasmids are somewhat different. The left part of the sequences within the borders, T_L (14 kb) and right, T_R (7 kb) are distinguished. The left segment carries, among others, genes for plant oncogenicity (coding for the plant hormones indole acetic acid and the cytokinin, isopentenyl adenine) and either octopine or nopaline, the right segment contains genes for other opines and others with unknown functions. The integration of the T-DNA into plant chromosomes is mediated by the virulence genes (VirA/G) of the Ti plasmid and some chromosomal loci rather than by the T-DNA sequences. In the plant tissues, phenolic compounds such as acetosyringone, cell wall sugars, and pH5.5 favor the transfer of the T-DNA. The transferred DNA of about 20 kb encodes the enzymes for the synthesis of indoleacetic acid and for cytokinin, required for tumorous growth in the plant. In addition, opine genes, which provide carbon and nitrogen nutrition for the growing tumor are transferred. In monocots (maize), 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3(4H)-one (DIMBOA) inhibits *vir* genes as well as growth. The related compound 2-hydroxyl-4,7-dimethoxy-benzoxazin-3-one inhibits *vir* genes but not the growth of the tumor. These compounds may be the reason why it is so difficult to transform maize by *Agrobacterium*. After transformation is completed in dicots, the no longer needed *vir* genes are shut down by indoleacetic acid (Piu P, Nester EW 2006 Proc Natl Acad Sci USA 103:4658).

The T-DNA can integrate into the chromosome of plants by a process of illegitimate recombination at practically random locations. The integration involves most likely only one of the strands, called T-strand. The Ku80 protein of the plants appears to be involved in the recombination between an intermediate double-stranded DNA and the plant DNA (Li J et al 2005 Proc Natl Acad Sci USA 102:19231). Because of the transfer feature, the T-DNA can be utilized as the most efficient plant transformation vector. The oncogenes or other sequences can be deleted and replaced by any desired DNA sequences (genes) and they are still inserted into the plant chromosome as long as the border sequences are retained. In *Agrobacterium*, besides the T-DNA, multi-subunit protein complexes are also transmitted to the eukaryotic cell. ►*Agrobacterium*, ►Ti plasmid, ►transformation plants, ►virulence genes of *Agrobacterium*, ►binary vectors, ►cointegrate vectors, ►overdrive, ►opines, ►Ku; Koncz C et al 1992 Methods in Arabidopsis Research. In: Koncz C et al (Eds.) World Scientific, Singapore, pp 224; Szabados L et al 2002 Plant J 32:233; T-DNA *Arabidopsis*: <http://www.GABI-Kat.de>.

TDT: ▶ [transmission disequilibrium test](#)

TE: *Drosophila* transposable elements cytologically localized in chromosomes 1, 2, and 3.

TE Buffer: TE buffer contains Tris-EDTA, the pH range is 7.2–9.1. ▶ [Tris-HCl buffer](#), ▶ [EDTA](#)

TEC: A family of non-receptor tyrosine kinases required for signaling through the T cell receptor. ▶ [TCR genes](#), ▶ [T cell receptor](#), ▶ [Zap-70](#), ▶ [Src](#), ▶ [MAPK](#); Mao J et al 1998 EMBO J 17:5638.

Technology Transfer: Converting basic or laboratory research results into industrial, agricultural, medical, pharmaceutical, or other applications.

Tectorin: A protein encoded at human chromosome 11q and mouse chromosome 9, and defective in a non-syndromic deafness. ▶ [deafness](#)

Tectum: The dorsal part of the midbrain, controlling visual reflexes and hearing stimuli. ▶ [brain](#)

TEFb: A positive transcript elongation protein factor (P-TEFb). The *Drosophila* dimer has one ~43 and one ~120 kDA subunits. The small subunit is homologous to PITALRE and the large subunit is called also cyclin T. Protein TEFb phosphorylates the carboxyl-terminal domain of the largest subunit of DNA-dependent RNA polymerase II and thereby assures that the transcript elongation proceeds with few or no pauses. ▶ [TFIIS](#), ▶ [DRB](#), ▶ [DSIF](#), ▶ [NELF](#), ▶ [NusG](#), ▶ [transcript elongation](#), ▶ [PITALRE](#), ▶ [cyclins](#); Lee DK et al 2001 J Biol Chem 276:9978.

Tegument: A protein layer between the viral capsid and envelope (see Fig. T22).

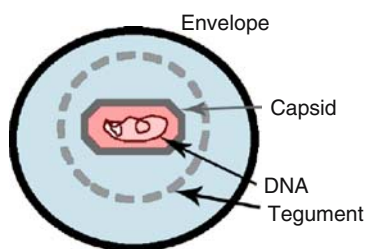


Figure T22. Tegument

Teichoic Acid: A constituent of the cell membrane and cell of some bacteria. The membrane teichoic acid contains polyglycerol phosphate, linking glycerol units through phosphodiester, and there are glycosyl substitutions and alanine residues at some positions. The cell teichoic acids are more variable polymers of 6 to 20 units and include polyribitol phosphate chains. ▶ [gram-negative/positive](#)

TEL: The phosphatidylinositol kinase of yeast. ▶ [PIK](#)

Telangiectasia, Hereditary Hemorrhagic (Osler-Rendu-Weber syndrome): A generally non-lethal bleeding disease (except when cerebral or pulmonary complications arise) caused by lesions of the capillaries due to weakness of the connective tissues. The gene ORW1 in human chromosome 9q13 encodes a receptor (endoglin) for the transforming growth factor β , expressed on vascular endothelium. ORW2 was mapped to chromosome 12, and it encodes an activin receptor-like kinase 1, a member of an endothelial serine/threonine kinase family. The prevalence of ORW syndrome in the USA is about 2×10^{-5} . ▶ [hemostasis](#), ▶ [Rothmund-Thompson syndrome](#), ▶ [transforming growth factor \$\beta\$](#) , ▶ [endoglin](#), ▶ [activin](#), ▶ [ataxia telangiectasia](#), ▶ [lymphedema](#)

Telangiectasis (telangiectasia): Defective veins causing red spots of various sizes. ▶ [poikiloderma telangiectasia](#), ▶ [glomerulonephrosis](#)

Telemicroscopy: In telemicroscopy, a microscope linked to a computer transmits JPEG compressed images through the Internet network to distant viewers.

Teleology: A dogma attributing a special vital force and ultimate purpose to natural processes beyond the material scientific evidence. (See Lennox J 1981 J Hist Philos 19:219).

Telethonin: A Z-disc protein in the sarcomeres. It mediates the assembly of titin molecules. ▶ [sarcomere](#); Faulkner G et al 2000 J Biol Chem 275:41234.

Teliospores: Fungal spores protected by a thick wall; these are either dikaryotic or diploid (see Fig. T23). ▶ [stem rust](#), ▶ [telium](#)

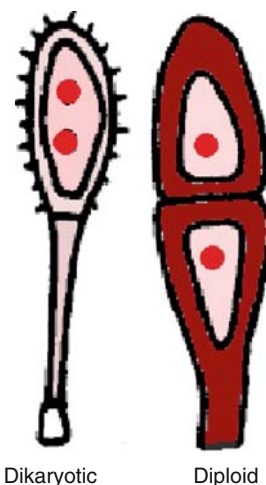


Figure T23. Teliospores

Telium: A fruiting structure (sorus) of fungi producing dikaryotic teliospores.

Telocentric Chromosome: A telocentric chromosome has terminal centromere (has one arm) (see Fig. T24). Telochromosomes can be used to determine which genes are located in that particular single chromosome arm if a telotrisomic female is used according to the scheme represented in Figure T25.



Figure T24. Telochromosome

The segregation of $B:b$ in both the $2n$ and $2n + \text{telo}$ progeny is expected to be 1:1 (testcross). Among the $2n$ offspring, none or very few are expected to be A by phenotype because the telocentric egg cannot remain functional because of dosage effect of the essential genes in the missing chromosome arm. The A phenotype is usually due to recombination between the telo and the biarmed chromosomes. The $2n + \text{telo}$ offspring should be all A by a because of the dominant phenotype and none a because the dominant A allele is in the trisomic arm (see Fig. T25).

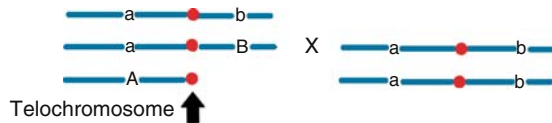


Figure T25. Gene localization with the aid of telochromosome

In allopolyploids, telochromosomes can be used to assign genes to the telochromosome and to determine recombination frequency between genes and the centromere. ▶centromere mapping in higher eukaryotes, ▶misdivision of the centromere [see Fig. T26], ▶Robertsonian translocation, ▶tetrad analysis, photo is the courtesy of Dr. ER Sears.

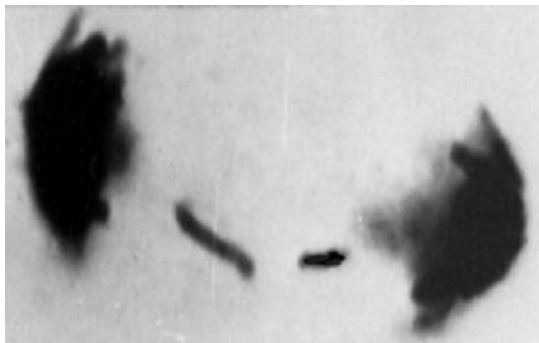


Figure T26. Misdivision generates telocentrics

Telochromosome: Telocentric chromosome.

Teloisodisomic: In wheat, $20'' + ti''$, $2n = 42$, [$''$ = disomic, t = telosomic, i = isosomic].

Teloisotrisomic: In wheat, $20'' + (ti)1''$, $2n = 43$, [$''$ = disomic, $'''$ = trisomic, t = telosomic, i = isosomic].

Telomerase (TERT [telomere reverse transcriptase]):

The enzyme synthesizing telomeric DNA. This enzyme is different from other replicases inasmuch as a RNA template (TERC) that is a part of the telomerase (ribozyme) specifies the telomeric DNA. An RNA polymerase II enzyme transcribes this RNA and it has a 5'-2,2,7-trimethyl guanosine cap. It has a binding site for Sm proteins that are characteristics for snRNPs. TERT (telomere reverse transcriptase) is the enzyme synthesizing telomeric DNA. The transcription of the human TERT (*hTERT*) is activated by the joint action of Sp1 and cMyc. It seems that the occupancy of the E box by either Myc or Mad1 determines the acetylation/deacetylation of the chromatin in HeLa cells and thus the regulation of human hTERT. This enzyme is different from other replicases inasmuch as a RNA template (TERC) that is a part of the telomerase (ribozyme), which specifies the telomeric DNA. The RNA has A and C repeats and therefore T and G repeats characterize the shortening of the telomeres that leads to p53-dependent senescence of the cells in vivo and limits tumor progression (Feldser DM, Greider GW 2007 Cancer Cell 11:461). The human telomerase template has 11 nucleotides: 5'-CUAACCCUAAC and the telomere has (5'-TTAGGG-3')_n repeats. In *Oxytricha*, the telomere consists of 36 nucleotides of which 16 form a single strand of 3'-G₄T₄G₄T₄ overhang protruding from the double-stranded remainder. The telomere-end-binding protein (TEBP) binds to the 3'-G₄T₄ tract and protects it from degradation. During replication this TEBP is displaced for the replication to proceed. By rejoining the end it displaces the telomerase and thus regulates telomere length. In murine embryonic stem cells but not in other types of cells, sister chromatid exchange at the telomeres may contribute to shortening of telomeres (Wang Y et al 2005 Proc Natl Acad Sci USA 102:10256). In budding yeast, the *TLC1* gene is responsible for telomerase activity and gene *EST1* is also needed for the maintenance of the telomeres. The *TLC1* (telomerase component) gene is also required for the preservation of the RNA template and normal telomerase function. The telomeres are made mainly of double-stranded DNA repeats, however the far end has only single strand G repeats. When the telomerase stays at the end of the chromosomes (capped state) the cells—even when the telomeres are short—remain viable. When the telomeres become uncapped the

cells exit from cycling and senesce. An automated highthroughput quantitative telomere FISH platform allows the quantification of telomere length as well as percentage of short telomeres in large human sample sets. This technique provides the accuracy and sensitivity to uncover associations between telomere length and human disease (Canela A et al 2007 Proc Natl Acad Sci USA 104:5300). Stronger and positive correlation and association seems to occur between telomere length (TL) in the offspring and paternal TL ($r = 0.46$), than offspring and maternal TL ($r = 0.18$) (Njajou T et al 2007 Proc Natl Acad Sci USA 104:12135).

The replication of the telomere takes place near the end of the cell cycle. Telomerase elongates only the G-rich strand and the C-rich strand is filled in later. In budding yeast, p23 molecular chaperone Sba1p controls telomere length maintenance and that Sba1p can modulate telomerase DNA binding and extension activities in vitro (Toogun OE et al 2007 Proc Natl Acad Sci USA 104:5765). Protein RCF binds also to the telomeric DNA and it is required for the replication of the leading strand by pol δ . The Pif1 helicase inhibits yeast telomerase by removing it from the DNA and may suppress healing of double-strand breaks by telomerase (Boulé J-B et al 2005 Nature [Lond] 438:57). Yeast cells recognize telomere replication as double-strand breaks and recruit to the telomeres the MRX complex of Mre11, Rad 50, and Xrs proteins. At late S phase, Mec1 is recruited to the telomeres where it assembles the Cdc13 and Est telomerase regulators (Takata H et al 2005 Mol Cell 17:573). Telomere-binding proteins (TEBP) bind either to the single-strand terminal repeats (*Oxytricha* proteins) or to the double strand sequences (Rap1). The telomeres of the ciliate *Oxytricha fallax* terminate in duplex DNA loops. The TEBP heterodimer α subunit (M_r 56K) binds to the 3'-T₄G₄ single-stranded end whereas the β subunit (M_r 41 K) attaches to other proteins. The heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) is also required for the maintenance of the normal length of the telomeres. The E6 protein of the Human Papilloma Virus-16 (HPV16) activates telomerase but does not immortalize the cells, although it expands their life span. The newly replicated telomeres are processed to size by proteins. Telomerase activity in tumor tissues is high but it is low in somatic cells or in benign neoplasias (Artandi SE, De Pinho RA 2000 Curr Opin Genet Dev 10:39). Intact telomere length and telomerase activity are required for the maintenance of function of epidermal stem cells (Flores I et al 2005 Science 309:1253). Targeting the telomerase by antisense technologies may be an approach to anticancer therapy. The telomerase RNAs of *Tetrahymena*, *Euplotes*, and *Oxytricha* seem to be transcribed by

polymerase III and the human telomerase RNA may be the product of pol II because it is sensitive to α -amanitin. The telomere end of *Tetrahymena* where it was originally discovered is somewhat different. In the RNA template, 5'-CAACCC-3', and in the telomere 5'-GGGTG-3' repeats occur. The Cdc13 protein of yeast mediates the access of the telomerase to the telomere. In the catalytic subunit of a telomerase of yeast (*EST2*, *ever-shorter telomeres*), reverse transcriptase-like motifs were identified. The telomeres are usually shortened as nuclear division proceeds and aging has been attributed to reduced telomerase activity. Lack of telomerase does not prevent tumorigenesis, however telomerase-deficient mice are resistant to skin tumorigenesis. Maintenance of normal telomere function is critical for the prevention of carcinogenesis. Usually in normal cells telomerase activity is barely detectable but it is well-expressed in tumor cells. The catalytic subunits bear structural similarities to reverse transcriptases. In mammals reduction in telomerase activity is harmful to the reproductive and blood-generating systems. On introduction into mammalian cells, an active telomerase may substantially extend the life of the cell. Telomerase defects increase the susceptibility to damage by ionizing radiation. Nevertheless, sustained telomerase activity does not result in malignancy. The ubiquitous c-MYC protein normally activates telomerase. The promoter of the TERT catalytic subunit has several c-MYC binding sites. Sheep produced by nuclear transplantation displayed apparently shorter telomeres than normally generated animals yet in the small-scale experiments no premature aging was observed. Mutations in the telomerase genes may result in senescence and late-onset sterility. Further, when the telomeres are substantially lost the chromosomes may fuse end-to-end. One class of *Caenorhabditis* telomerase mutants (*mrt*, *mortal germline*) is pleiotropic because in addition to the symptoms displayed by the other mutants in yeast and mice, it involves chromosomal loss and sensitivity to DNA-damaging agents. Mutation *mrt-2* was identified to have a defect in checkpoint function that is apparently repaired when the telomerase is normal. Loss of the telomerase function leads to swift progressive deterioration in animals but *Arabidopsis* plants may survive up to ten generations without telomerase function. However, eventually due to chromosomal aberrations both vegetative and reproductive fatal damage ensues. The human TERT expression is necessary for repairing chromosome breaks (Masutomi K et al 2005 Proc Natl Acad Sci USA 102:8222). In the presence of manganese, both human and yeast TERT can switch to RNA- and template-independent mode of DNA synthesis and act as a terminal transferase (Lue NF et al 2005 Proc Natl Acad Sci

USA 102:9778). TERT induction can also cause the proliferation of hair follicles—without a need for TERC, the RNA component of telomerase—and as a result abnormal heavy hair growth is observed in mice (Sarin KY et al 2005 *Nature [Lond]* 436:1048). Damaged telomeres can be repaired even in the absence of telomerase by relying on a break-induced recombination process (BIR). The pathways and mechanisms of BIR have been reviewed (McEachern MJ, Haber JE 2006 *Annu Rev Biochem* 75:111). ▶telomeres, ▶ribozyme, ▶RAP, ▶tankyrase, ▶pol II, ▶pol III, ▶α-amanitin, ▶*Tetrahymena*, ▶aging, ▶p16^{INK}, ▶ribozyme, ▶tumorigenesis, ▶antisense technologies, ▶hTERT, ▶malignant growth, ▶MYC, ▶Mad2/Mad1, ▶E box, ▶RNP, ▶cap, ▶SP1, ▶Myc, ▶nuclear transplantation, ▶MRX, ▶Mre11, ▶RAD50, ▶Xrs, ▶Cdc13, ▶Est, ▶pseudoknot, ▶p23; Collins K 1999 *Annu Rev Biochem* 68:187; Herbert B-S et al 1999 *Proc Natl Acad Sci USA* 96:14276; Tzfati Y et al 2000 *Science* 288:863; Cooper JP 2000 *Curr Opin Genet Dev* 10:169; Betts DH et al 2001 *Proc Natl Acad Sci USA* 98:1077; Wenz C et al 2001 *EMBO J* 20:3526; Antal M et al 2002 *Nucleic Acids Res* 30:912; Arai K et al 2002 *J Biol Chem* 277:8538; Neidle S, Parkinson G 2002 *Nature Rev Drug Discovery* 1:383; structure and function: Autexier C, Lue NF 2006 *Annu Rev Biochem* 75:493; history of discovery of telomerase: de Lange T 2006 *Cell* 126:1017; telomere replication review: Verdun RE, Karlseder J 2007 *Nature [Lond]* 447:924.

Telomere Crisis: The demise of the telomerase reverse transcriptase and the loss of telomere replication. The chromosome becomes unstable. ▶telomerase; Chin K et al 2004 *Nature Genet* 36:984.

Telomere Mapping: The eukaryotic chromosome has characteristic telomeric repeats and can be used for mapping RFLPs relative to the telomeres. ▶telomeres, ▶RFLP

Telomere Position Effect: ▶telomeric silencing

Telomere Switching: In *Trypanosoma*, the variable surface antigens (VSG) are encoded at the telomeres and frequent recombination of the chromosome ends can generate new variations and may affect the expression of the VSG glycoproteins. ▶telomeres, ▶*Trypanosoma*; Rudenko G et al 1998 *Trends Microbiol* 6:113.

Telomere Terminal Transferase: The ribozyme involved in replication telomeric DNA. ▶telomerase

Telomeres: Special terminal structural elements of eukaryotic chromosomes rich in T and G bases.

Electronmicroscopic observations indicate that in mice and humans the end of the telomeres bend

backward and form a D loop/t-loop as the telomeric single-strands pair with the double-stranded telomeric DNA (Figure T28). T loops normally prevent (NHEJ) non-homologous end joining recombination and the loss of the T loops may cause loss of telomere integrity (Wang RC et al 2004 *Cell* 119:355). In human chromosomes and all vertebrates, *Trypanosomas*, and fungi the many times repeated telomeric box is CCTAA/TTAGGG (ca. 300 bp). The telomeric region is highly conserved among diverse eukaryotes; in some species, however variations exist. In *Drosophilas* (and other insects), the telomeres are unusual inasmuch as rather than having the common repeats, they have transposable elements, e.g., *HeT-A* and *TART* in *Drosophila* (Casacuberta E, Pardue M-L 2003 *Proc Natl Acad Sci USA* 100:3363). This transposable element may assist the replication of the telomeric DNA. In most organisms proximal to the telomere, middle-repetitive DNA is found (telomere-associated DNA, TA), which may display some similarity to the *Drosophila* transposable sequences (Levis RW et al 1993 *Cell* 75:1083). The subtelomeric regions are repetitive and yet highly variable. Ectopic recombination in this tract may lead to restoring defective ends but it may be the cause also of undesirable rearrangements (Heather C et al 2002 *Nature Rev Genet* 3:91; Linardopoulou EV et al 2005 *Nature [Lond]* 437:94). The length of the telomeric sequences may vary among the organisms but variations exist during the life of the cells, according to developmental stage. By aging the telomeres usually become shorter in cultured cells although in mice telomere length may not be correlated with lifespan (Hemann MT, Greider CW 2000 *Nucleic Acids Res* 28:4474). The *Rtel* helicase-like gene (chromosome 2q) controls telomere length in mice and it essential for survival beyond days 10–11.5 of gestation (Ding H et al 2004 *Cell* 117:873). In maize, telomere-mediated truncation of chromosome ends appeared (Yu W et al 2006 *Proc Natl Acad Sci USA* 103:17331).

Mutants of shorter telomeres may function reasonably well, although a transient pause may occur in the cell division. The length of the human telomeres may be different between homologous chromosomes (Londoño-Vallejo JA et al 2001 *Nucleic Acids Res* 29:3164). Telomere length in humans is apparently linked to the X chromosome and the transmission occurs from father to son or father to daughter but no correlation was found between mother and son or mother and daughter (Nordfjäll K et al 2005 *Proc Natl Acad Sci USA* 102:16374). Various techniques are available for measuring the length of the telomeres. (Baird DM et al 2003 *Nature Genet* 33:203).

The non-nucleosomal special chromatin, including the repeats of yeast, is called telosome, which

contains six core proteins: TRF1, TRF2, RAP1, TIN2, POT1, and TPP1 (O'Connor MS et al 2006 Proc Natl Acad Sci USA 103:11874). TPP1 (telomere binding human homolog of TEBP) and POT1 (protection of telomere) form a complex with telomeric DNA that increases the activity and processivity of the human telomerase core enzyme. POT1–TPP1 seems to switch from inhibiting telomerase access to the telomere, as a component of *shelterin*, to serving as a processivity factor for telomerase during telomere extension (Wang F et al 2007 Nature [Lond] 445:506). However, in mammals the large telomeric DNA is nucleosomal. The major structural protein associated with the yeast telomeres is Rap1. TPP1 and TIN2 (TRF-interacting factor) are critical for the assembly of the telomeric complex. The same protein may also be present at other locations of the chromosomes and acts either as a repressor or activator of transcription. Telomeres are required for the proper replication of the linear eukaryotic chromosomes. This is probably the reason why among the diverse types of chromosomal aberrations cytologists failed to find attachments of internal chromosomal pieces to the telomeres or telomere to telomere fusions although chromosomes with broken ends may fuse into dicentric chromosomes after replication. Shortened telomeres may fuse and involve elevated frequencies of different types of chromosomal aberrations (Mieczkowski PA et al 2003 Proc Natl Acad Sci USA 100:10854). Normally, the telomeric repeat binding factor, TRF2, or DNA-dependent protein kinase (DNA-PK) prevents telomeric fusions. In ciliates, a cap is built at the telomere by binding TEBP α and β to 16-nucleotide single-strand DNA overhang. In fission yeast, the Taz1 protein protects the telomeric ends of the chromosomes from fusion, which otherwise might be mediated by the Ku proteins recognizing double-strand breaks (ends) of the DNA. In *taz⁻* cells *rad22* may also promote telomere fusion (Godinho Ferreira M, Promisel Cooper J 2001 Molecular Cell 7:55). In the budding yeast, telomere capping is mediated by Cdc13 protein that recruits other proteins (Ten1/Stn1) to build a protective cap. DNA-dependent protein kinase may play a critical role in capping (Gilley D et al 2001 Proc Natl Acad Sci USA 98:15084). In *Drosophila*, the HP1 protein interacts with histone methyltransferases and histone H3 methylated lysine 9 and participates in telomere capping, elongation, and silencing (Perrini B et al 2004 Mol Cell 15:467). In fission yeast, Pli1p is a SUMO E3 ligase and mutants are impaired for global sumoylation, yet they are viable, but exhibit deregulated homologous recombination, marked defects in chromosome segregation, and centromeric silencing, as well as a consistent increase in

telomere length. Telomere lengthening induced by lack of sumoylation is not due to unscheduled telomere–telomere recombination. Instead, sumoylation increases telomerase activity, suggesting that this modification controls the activity of a positive or negative regulator of telomerase (Xhemalce B et al 2007 Proc Natl Acad Sci USA 104:893).

In mammals, the TRF2 protein has an end-protective role. It may also remodel the chromosome ends by forming the so-called *t loop*. The *t loop* of mammals is double-stranded DNA. In both fission yeast and mammals, the *POT1* (protection of telomere) wild type allele encodes a telomere-capping protein, which binds to the G-rich telomeric single-strand tail and also to the *t loop*. POT1 in humans has some role in elongating the telomeres and may disrupt the G-quadruplexes to allow proper elongation (Zaug AJ et al 2005 Proc Natl Acad Sci USA 102:10864). Mice have two POT proteins (POT1 and POT2) whereas humans have only one (Hockermeyer D et al 2006 Cell 126:63). In budding yeast, the evolutionarily conserved KEOPS complex, including Cdc13, protein kinase and peptidase, is a telomere regulator (Downey M et al 2006 Cell 124:1155). In *Drosophila*, a zinc-finger protein, a putative transcription factor, encoded by gene *Woc*, prevents telomeric fusion (Raffa GD et al 2005 Mol Cell 20:821). The mammalian single-strand DNA with 3'-end may encompass 300 nucleotides and is located where the loop folds onto the main double-strand DNA (Baumann P, Cech TR 2001 Science 292:1171).

The structure of the telomere may bear some similarity to the centromere and in some instances (e.g., rye) it may function as a neocentromere. It may be somewhat of a puzzle how the normally fragmented somatic chromosomes of *Ascaris* are still able to produce their telomeres and how the germline chromosomes control the apparently multiple intercalary telomeres. In the polyploid ciliate macronucleus, millions of centromeres may exist in some species. HIV-infected individuals appear to have shorter telomeres than healthy individuals of comparable age. Telomere loss or inactivation may play a role in senescence and telomerase activation may be a mechanism of cellular immortalization. The replication of the telomeric DNA is carried out by the ribozyme, telomerase. A specific telomere-binding human protein hTRF (60 kDa), recognizing the TTAGGG (and mammalian) sequences, has been isolated. TRF1 (8q13) is regulated by TIN2 (TRF1-interacting nuclear protein). The corresponding repeat in *Tetrahymena* is TTGGGG and in yeast, TG_{1–3}. One of its domains is similar to the Myb oncogene product. Telomeric sequences may be shortened in several types of cancer cells, although

in about 90% of the malignant cell types the activity of the telomerase enzyme is higher than in normal cells. The enzyme poly(ADP-ribose) polymerase (PARP) that recognizes DNA interruptions, adds ADP-ribose units to the DNA ends. Defects in the encoding gene (ADPRP) and the protein PARP results in chromosomal instability and shortening of the telomeres. In *Caenorhabditis*, all chromosomes are capped by the same 4–9 kb tandem repeats of TTAGGC, but the sequences next to it differ among the chromosomes. Double-strand break repair proteins mediate the capping of the chromosomes. Intact telomeres cannot fuse but a repair pathway may generate non-homologous end-joining (NHEJ). When, however NHEJ fuses two telomeres, unstable dicentric chromosomes are produced. Chromosomes lacking telomeres can perform most functions but lack stability and undergo fusion, degradation, and loss at a high rate and the chromatids may not be able to separate normally. If yeasts lose the *TRT-1* telomerase subunit gene, the cells may survive either by circularizing the chromosome or by restoring the function through recombination controlled by *RAD50* or *RAD51* genes. In the majority of tumors, the telomeres are not shortened during consecutive divisions, whereas normal somatic human cells may lose 100 bp by each cell division and that may lead to discontinuation of cell divisions and cellular aging. In ciliates, telomeres may arise de novo but in yeast this rarely occurs. In humans, telomerase may rarely replace lost telomeres. Genes that would be normally transcribed by either pol I, pol II, or pol III are frequently repressed at the telomeric location (see Figs. T27 and T28). ▶telomerase, ▶breakage-fusion-bridge cycle, ▶neocentromere, ▶chromosome diminution, ▶immortalization, ▶senescence, ▶Myb, ▶RAP, ▶telomeric probe, ▶HeT-A, ▶TART, ▶plasmid telomere, ▶pol, ▶Ku, ▶non-homologous end-joining [NHEJ], ▶tankyrase, ▶dyskeratosis, ▶aging, ▶Werner syndrome, ▶TRF, ▶UbcD1, ▶ALT, ▶G-quadruplex, ▶Cdc13; Griffith JD et al 1999 Cell 97:503; Pardue M-L, DeBaryshe PG 1999 Chromosoma 108:73; Varley H et al 2000 Am J Hum Genet 67:610; Knight SJL et al 2000 Am J Hum Genet 67:320; McEachern MJ et al 2000 Annu Rev Genet 34:331; Hodes R 2001 Proc Natl Acad Sci USA



Figure T27. Glowing telomeres probed by a fluorescent sequence

98:7649; Shay JW et al 2001 Hum Mol Genet 10:677; Blackburn EH 2001 Cell 106:661; McEachern MJ et al 2002 Genetics 160:63; Ren J et al 2002 Nucleic Acids Res 30:2307; Phan AT, Mergny J-L 2002 Nucleic Acids Res 30:4618; Pardue M-L, DeBaryshe PG 2003 Annu Rev Genet 37:485; telomeres in disease, cancer and aging: Blasco MA 2005 Nature Rev Genet 6:611; human disease: Artandi SE 2006 New England J Med 355:1195.



Figure T28. D- or t-loop formation of mammalian telomeres

Telomeric Fusion: As per telomeric fusion, end-to-end fusion of chromosomes does not take place between intact, telomere-capped chromosomes. However, it may take place in double-strand repair deficient cells. ▶non-homologous end-joining

Telomeric Probe: Telomeric probes are fluorochrome-labeled DNA sequences, complementary to the telomeric repeats TTAGGG; they can be used for the cytological identification of short (cryptic) translocations. ▶chromosome painting, ▶telomere

Telomeric Silencing (telomeric position effect): As per telomeric silencing, telomeres frequently reduce transcription of associated genes. This effect is similar to the silencing or position effect exercised by heterochromatin, although it may occur in this region even in the absence of heterochromatin. It may be due to higher order chromatin arrangement. Rap1 (repressor and activator protein) recruits the Sir3 and Sir4 (silent information regulators) and Rif1 (Rap1-interacting factor). Histones 3 and 4 and the Ku proteins are among the best known regulators. Mec1 (mitotic entry checkpoint) protein controls S-phase arrest of the cell cycle in reaction to DNA damage and regulates telomere length; some forms may also affect telomeric silencing. These genes/proteins are highly conserved but may have different names in the various organisms. In yeast, *DOT1* (disruptor of telomeric silencing) encodes a methyltransferase specific for histone 3 in the nucleosome globular domain and trimethylates lysine 79. The *Rmt1* methyltransferase dimethylates arginine at position 3 in histone-4 termini. ▶heterochromatin, ▶position effect, ▶telomeres, ▶RAP1A, ▶Ku, ▶silencers, ▶checkpoint, ▶MEC1; de Bruin D et al 2001 Nature 409:109; Lacoste N et al 2002 J Biol Chem 277:30421.

Telomutation: A (dominant) premutation occurring in and transmitted through both sexes but expressed

only in the offspring of the heterozygous female. ► [premutation](#), ► [delayed inheritance](#); Aleck KA, Hadro TA 1989 Am J Med Genet 33:155.

Telophase: The final major step of the nuclear divisions. The chromosomes have been pulled by the spindle fibers all the way to the poles. The microtubules attached to the kinetochores fade from view and the nuclear envelope reappears. The chromosomes relax and the nucleoli become visible again. ► [mitosis](#), ► [meiosis](#)

Telosome: A telocentric chromosome; the non-nucleosomal, six-protein chromatin complex at the end of the yeast, ciliate, and mammalian chromosomes is also called telosome or *shelterin*. ► [telomeres](#), ► [telochromosome](#); Liu D et al 2004 J Biol Chem 279:51338; de Lange T 2005 Genes Dev 19:2100.

Telotrisomic: A trisomic having two bi-armed and one telochromosome. ► [trisomy](#)

Telson: The most posterior part (opposite to the head) of the arthropod body. ► [Drosophila](#)

TEM (transmission electronmicroscopy): ► [electronmicroscopy](#)

TEM (triethylenemelamine): An alkylating clastogen. ► [alkylating agent](#), ► [alkylation](#), ► [clastogen](#)

TEM1: A GTPase. ► [GTPase](#)

TEMED: ► [acrylamide](#)

Temperate Phage: A temperate phage has both lysogenic and lytic life-styles. The temperate phages may be of different types: (i) those that insert their DNA into one or few preferred sites like λ phage, (ii) those that insert their DNA into the host bacterial chromosome with the aid of a transposase at different sites like Mu-1, (iii) those, e.g., P1, that do not insert their DNA into the host chromosome but are maintained as a plasmid and (iv) those, e.g., P4, which can be either plasmids or prophages. ► [bacteriophage](#), ► [lysogen](#), ► [lysogeny](#), ► [prophage](#), ► [plasmid](#), ► [lambda phage](#), ► [specialized transduction](#)

Temperature Conversion: $0.556^{\circ}\text{F} - 17.8 \rightarrow ^{\circ}\text{C}$, $1.8^{\circ}\text{C} + 32 \rightarrow ^{\circ}\text{F}$, $\text{K} - 273.15 \rightarrow ^{\circ}\text{C}$

Temperature-Sensitive Mutation (ts): The ts mutation causes such an alteration in the primary structure of the polypeptide chain that its conformation varies according to temperature, and it is functional at either high or low temperature but is non-functional at the other (non-permissive temperature). Temperature-sensitive conditional lethal mutants are very useful for various analyses because the biochemical/molecular basis of the genetic defect can be analyzed at the

permissive temperature range, within which, the cells or organisms grow (normally). ts condition is correlated with the buried hydrophobic residues in the protein. The majority of organisms (mesophiles) normally thrive best at temperatures $<40^{\circ}\text{C}$; hyperthermophiles may exist at temperatures around 100°C . Temperature variations are sensed by the transient receptor potential activation channels (Voets T et al 2004 Nature [Lond] 430:748). Inflammation and elevated temperature caused pain is controlled by the calcitonin gene-related neuropeptide and it is correlated with the differences in heat/pain response variations in mouse strains (Mogil JS et al 2005 Proc Natl Acad Sci USA 102:12938). ► [hyperthermia](#), ► [cold hypersensitivity](#), ► [pain-sensitivity](#), ► [trichothiodystrophy](#)

Template: A template determines the shape or structure of a molecule because it serves as a “mold” for it (in some way similar to the mold to cast iron). Old DNA strands serve as templates for the new, or one of the DNA strands may be a template for the mRNA and the other for another sense or nonsense RNA. Molecular biologists frequently call template (or antisense) the strand of the DNA that serves for the synthesis of mRNA by complementary base pairing. T7 RNA polymerase can bypass up to 24-nucleotide gaps in the template strand by copying a faithful sequence of the deletion using the non-template strand. ► [semiconservative replication](#), ► [replication fork](#), ► [sense strand](#), ► [coding strand](#)

Template Switch: As per the template switch, during replication the polymerase enzyme may jump to another DNA sequence and copy elements, which were not present in the original DNA tract. Such a switch may occur when plasmid DNA (T-DNA) is inserted into a chromosomal target site. As a consequence, deletions and rearrangements may follow. During primer extension, the strand displaced may reanneal onto the template and the extended strand may be partially dissociated. A single-stranded sequence, attached to the 5' end of the displaced strand and complementary to the dissociated segment of the extending strand, can thus serve as an alternative template ► [switch](#), ► [copy choice](#), ► [T-DNA](#), ► [primer extension](#); Negroni M, Buc H 2000 Proc Natl Acad Sci USA 97:6385.

Tenascin: A large glycoprotein complex with disulfide-linked peptide chains. It either promotes or interferes with cell adhesion, depending upon the type of cell and the different protein domains. It also controls cell migration, axon guidance embryogenesis, and oncogenic pathways. ► [cell migration](#), ► [cell adhesion](#); Hicke BJ et al 2001 J Biol Chem 276:48644; Daniels DA et al 2003 Proc Natl Acad Sci USA 100:15416.

Tendril: A plant organ that coils around objects and provides support (see Fig. T29). ►circumnutation



Figure T29. Tendril

Tensin: A cytoskeletal protein binding vinculin and actin; it contains an SH2 domain. ►actin, ►vinculin, ►multiple hamartomas, ►PTEN; Chen H et al 2002 Proc Natl Acad Sci USA 99:733.

Tension: The force(s) generated by pulling the mitotic/meiotic chromosomes to the opposite poles, opposed by the attachment between the homologs. ►spindle, ►kinetochore, ►pole

Teosinte: ►maize

TEP1 (TGFB β -regulated and epithelial cell-enriched phosphatase): A tumor suppressor function of PTEN. TEP1 is also an RNA-binding protein, which interacts with the mammalian and other telomerases. ►PTEN, ►vaults; Sharrard RM, Maitland NJ 2000 Biochim Biophys Acta 1494:282.

ter Sites: ►DNA replication prokaryotes

tera-: 10^{12}

Terahertz Radiation (T-rays): Electromagnetic radiation between microwaves and infrared. Semiconductor crystals of alternating layers of gallium arsenide and aluminum gallium arsenide emit light when electrons are boosted to higher level of energy by exposure to laser. Terahertz devices are expected to detect hidden objects of industrial and biological importance, such as anthrax pores within an envelope beyond what is detectable by other technologies. Apparently the T-rays are not harmful to living material. ►electromagnetic radiation

Teratocarcinoma: Malignant tumor containing cells of embryonal nature; common in testes. The teratocarcinoma cells may differentiate into various types of tissues in vitro and have been used for studies of differentiation. ►cancer, ►teratoma, ►stem cells;

Silver LM et al (Eds.) 1983 Teratocarcinoma Stem Cells, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Teratogen: Teratogens are agents causing malformation during differentiation and development.

Teratogenesis: Malformation during differentiation and development. The inducing agents may be genetic defects, physical factors and injuries, infections, drugs and chemicals. In frogs, limb developmental anomalies have been traced to trematode (*Planorbella campanulata* and *Ribeiroira* sp.) infection stimulated by agricultural pesticides. (See Kiesecker JM 2002 Proc Natl Acad Sci USA 99:9900).

Teratoma: A mixed tissue group with cells of different potentials for development. It may be formed in various early or late animal tissues and may eventually become a malignant tumor. Teratomas are most common in the germinal tissues. In plants amorph, undifferentiated tumor tissue may be interspersed with differentiated elements giving rise to either shoots or roots. Teratomas may be formed in the tumors induced by *Agrobacterium rhizogenes*. ►Agrobacterium

Tergite: The dorsal epidermis developed from histoblasts not from imaginal disks. ►histoblast

Terminal Deoxynucleotidyl Transferase (TdT): An enzyme that can elongate DNA strands—at the 3-OH end—with any base that is present in the reaction mixture. It is used in genetic vector construction to generate homopolymeric cohesive tails for the purpose of splicing a passenger DNA to a plasmid. The passenger and the plasmid are equipped with complementary bases, such as polyA and polyT, respectively, and can readily anneal and be ligated. Terminal nucleotidyl transferase is also expressed in the adult bone marrow and generates immunoglobulin diversity. The enzyme occurs primarily as a 58 kDa protein but much smaller molecules were also found. Its N-terminus is homologous to the C-terminus of the breast cancer gene, BRCA1. The N-terminus of TdT interacts with the heterodimeric Ku autoantigen, which is the DNA-binding component of a 460 kDa DNA-dependent protein kinase complex. This complex apparently plays a role (besides RAGs) in the generation of immunoglobulin diversity and DNA double-strand break repair. ►vectors, ►cloning vectors, ►immunoglobulins, ►T cell, ►breast cancer, ►Ku, ►RAG, ►immunoglobulins, ►double-strand break; Delarue M et al 2002 EMBO J 21:427.

Terminal Differentiation: Terminal differentiation is usually irreversible; in plants, however, under culture of high levels of phytohormones, dedifferentiation may be possible. ►dedifferentiation, ►differentiation

Terminal Nucleotidyl Transferase: The enzyme that can add homopolymeric ends to DNA. It is useful in generating cohesive termini (in genetic plasmid vectors), if one of the reaction mixtures contains adenylic acids and the other (e.g., passenger DNA), thymidylic acid (or G and C, respectively). ▶ [terminal deoxynucleotidyl transferase](#), ▶ [cloning vectors](#)

Terminal Protein (TP): Serine, threonine, or tyrosine residues of the terminal proteins provide OH groups for the initiation of replication, instead of 3' OH group of a nucleotide in a linear double-stranded viral DNA.

Terminal Redundancy: Repeated DNA sequences at the ends of phage DNA. (See permuted and non-permuted terminal redundancy.)

Terminalization of Chromosomes: During meiosis, the bivalents may display one or more chiasma(ta), which eventually (during anaphase) move toward the telomeric region in the process called terminalization (see Fig. T30). ▶ [meiosis](#)



Figure T30. Terminalization of chromosomes

Terminase: The terminase phage enzyme binds to specific nucleotide sequences and cuts in the vicinity of the binding at cohesive sites (*pac* or *cos*). ▶ [lambdaphage](#); de Beer T et al 2002 Mol Cell 9:981.

Termination Codons: ▶ [nonsense mutation](#), ▶ [genetic code](#), ▶ [terminator codons](#)

Termination Factors: The proteins that release the polypeptide chains from the ribosomes.

Termination of Replication in Bacteria: The termination of replication in bacteria is mediated by the homodimeric replication terminator protein (RTP). Two dimers bind to the two *Ter* inverted repeat sites in the DNA. The binding site has a strong core and an auxiliary site. First one dimer binds to the core and the binding of the second dimer follows this to the auxiliary site. When the replication fork encounters the RTP-*Ter* site, it is blocked, but not when it encounters it from the auxiliary site. The terminator prevents the unwinding of the DNA by the helicase. There are several *Ter* sites. (See Lemon K et al 2001 Proc Natl Acad Sci USA 98:212).

Terminator: The sequence at the end of a gene that signals for the termination of replication or transcription. The RNA polymerase recognizes this signal

directly or indirectly by various proteins. The intrinsic terminator of *E. coli* (*rho*) uses two sequence motifs for the release of RNA from the DNA template: (i) a stem-loop hairpin and (ii) a tract of 8–10 nucleotides immediately downstream at the end of the released RNA. Before termination, there is generally a pause, mediated by U-rich transcribing DNA segment. ▶ [transcription termination](#), ▶ [antitermination](#), ▶ [protein synthesis](#), ▶ [release factor](#), ▶ [rho factor](#), ▶ [pausing transcriptional](#), ▶ [RNA polymerase](#)

Terminator Codons: UAA, UAG, and UGA in RNA (same as nonsense codons).

Terminator Technology: Terminator technology uses three different transgenes in plants to control their ability to bear seed, to protect the interest of seed companies by preventing unauthorized use of their genetic stocks. One of the genes is a repressor of a recombinase, the other is a recombinase that is capable of deleting internal spacers, and the third is a toxin gene. The seed company can grow seed-bearing plants because the toxin gene is inactivated by a spacer sequence between the promoter and the structural toxin gene as long as the recombinase is suppressed. Treating the commercially sold seed by the antibiotic tetracycline, the synthesis of the suppressor is prevented, the recombinase then deletes the spacer, and the toxin gene becomes activated to cause seed failure. This trick of biotechnology may become a safeguard for the property of the company but may hurt the poor potential consumer who cannot afford buying the seeds annually. Similar, although simpler, technology has been practiced by the seed industry for decades in the commercially available double-flowered garden stocks. Although social activists condemn the terminator technology, its principles may offer promises for shutting off undesirable genes or activating useful ones, and serve beneficial roles in improving agricultural productivity ▶ [T-Gurt](#), ▶ [suppressor](#), ▶ [recombinase](#), ▶ [tetracycline](#), ▶ [promoter](#), ▶ [structural gene](#), ▶ [Mat-thiola](#); Kuvshinov VV et al 2001 Plant Sci 160:517.

Termisome: Nucleic acid terminal protein complexed with other proteins and DNA. ▶ [terminator](#), ▶ [protein synthesis](#)

Ternary: Ternary has two meanings; either that it is made up of three elements, or it is third in order.

Ternary Complex Factors: ▶ [TCF](#)

Terpenes: Hydrocarbons or derivatives (>30,000) with isoprene repeats; occur as animal pheromones and diverse types of plant fragrances. ▶ [pheromones](#), ▶ [fragrances](#), ▶ [prenylation](#), ▶ [Gossypium](#); Trapp SC, Croteau RB 2001 Genetics 158:811.

Terrestrial Radiation: Terrestrial radiation is emitted from the unstable isotopes in the soil, such as uranium-containing rocks. ▶cosmic radiation, ▶radiation hazard assessment, ▶radiation effects, ▶ionizing radiation, ▶isotopes

Terrific Broth (TB): Bacterial nutrient medium containing bacto-tryptone 12 g, bacto-yeast extract 24 g, glycerol 4 mL, H₂O 900 mL, and buffered by 100 mL phosphate buffer.

Tertiary Structure: The three-dimensional arrangement of the secondary structure of the polypeptide chain into layers, fibers, or globular shapea. It is also a third order of complexity, folding or coiling the secondary structure once more. ▶protein structure

Test Statistics: The specific procedure used to test a parameter or a null hypothesis.

Testa (seed coat): Maternal tissue in hybrids, therefore seed coat characters display delayed expression of recessive markers by one generation (e.g., to F₃) rather than in F₂.

Testcross: A cross between a heterozygote and a homozygote for the recessive genes concerned, e.g., (*AB/ab*) × (*ab/ab*); segregation is 1:1. ▶recombination frequency; *Arabidopsis* testcross photo (see Fig. T31); Rédei unpublished)

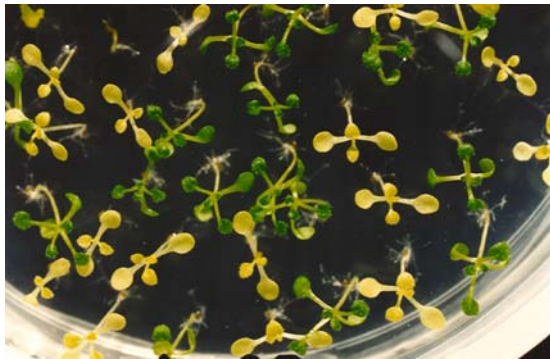


Figure T31. Segregation of a test cross progeny

T

Tester: A tester in a genetic cross is intended to reveal either the qualitative or quantitative gene content of the individual(s) tested. ▶testcross, ▶hybrid vigor, ▶combining ability

Testes (sing. testis): The male gonads of animals, producing the male gametes. ▶gonad, ▶gamete, ▶sex determination; Raymond CS et al 2000 Genes Dev 14:2587.

Testicles: Same as testes.

Testicular Feminization: Is a developmental anomaly, which occurs in humans and other mammals. The

chromosomally XY individuals display female phenotype including the formation of a blind vagina (no uterus), female breasts, and generally the absence of pubic hairs (see Fig. T32). Usually, the individuals affected by this recessive disorder (human chromosome Xq11.1-q12) appear very feminine but sterile. Generally, they develop abdominal or somewhat herniated small testes. About 1.5×10^{-5} of the chromosomally males have this disorder. The condition is the result of a complete or partial deficiency or instability of the androsterone receptor protein (917 amino acids). The function of this androgen receptor protein may be either totally missing or only partial (Reifenstein syndrome). This receptor appears to be highly conserved among mammals. The gene extends to about 90 kb DNA. The protein binds to DNA by two domains encoded by exons 2 and 3, five exons code for androgen binding, while exon 1 has a regulatory function. ▶chromosomal sex determination, ▶hermaphrodite, ▶hormone receptors, ▶pseudoherma-phroditism, ▶dihydrotestosterone, ▶Swyer syndrome, ▶sex reversal, ▶SF-1; Boehmer AL et al 2001 J Clin Endocrinol Metab 86:4151.

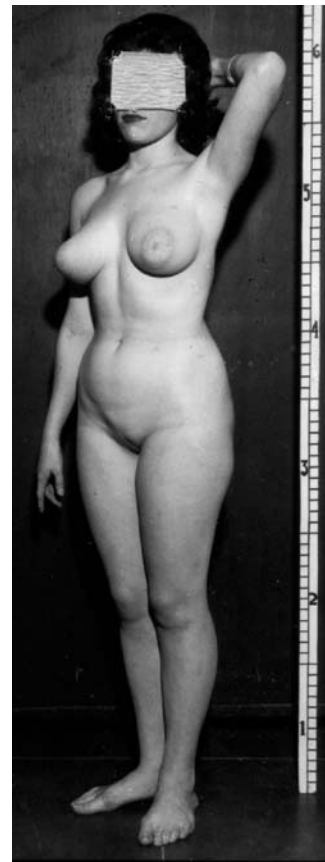


Figure T32. Testicular feminization. (Courtesy of Dr. McL. Morris)

Testicular Germ-Cell Tumor: The TGCT gene at Xq27 conveys susceptibility to this cancer affecting about 2×10^{-3} of men of Western European descent between ages 15–40.

Testin (TES, human chromosome 7q31-q31.2): A tumor suppressor in humans and mice. The protein contains three LIM motifs and is localized along actin fibers of the cytoskeleton. ►LIM domain; Drusco A et al 2005 Proc Natl Acad Sci USA 102:10947.

Testing, Genetic: ►genetic screening

Testosterone: The most important androsterone. Testosterone increases the risk of coronary heart disease and atherosclerosis. If testosterone is converted to estrogen by aromatase, the risk is reduced (see Fig. T33). ►animal hormones, ►hormonal effects on sex expression, ►progesterone

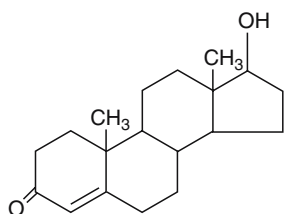


Figure T33. Testosterone

Testtube Baby: ►in vitro fertilization, ►intrauterine insemination, ►intra-fallopian transfer, ►ART

Testweight: The mass of 1,000 seeds or kernels randomly withdrawn from a sample. ►absolute weight

TET: Tetracycline antibiotic, inhibits protein synthesis, genetic (selectable) marker in the pBR plasmids. ►pBR322, ►tetracycline

TET (tubal embryo transfer): Essentially, the same as intrafallopian transfer of zygotes. ►intra-fallopian transfer, ►ART

Tet A: The tetracycline resistance protein that controls the efflux of the antibiotic from the cells. ►tetracycline, ►TetR

Tetanus: Tetanus toxin, ►tetany

Tetany: A highly stimulated condition of the nervous and muscular system caused by low levels of calcium due to various diseases and to infection by *Clostridium tetani*. Vaccines are available. The anaerobic, spore-forming soil bacterium with a genome size of 2,799,250 bp includes 2,368 open reading frames; it also has a low G + C content plasmid of 74,082 bp. ►biological weapons, ►*Clostridium perfringens*;

Brüggemann H et al 2003 Proc Natl Acad Sci USA 100:1316.

Tethering: Bringing together two distantly located nucleic acid sequences either by DNA looping, or catenanes or RNA lariats. ►introns, ►lariat RNA

Tet-OFF: ►tetracycline

Tet-ON: ►tetracycline, ►targeting genes

TetR: The tetracycline repressor (homodimer) regulates its own expression as well as that of the antiporter (TetA, which exports the drug from the cells) at the level of transcription and it is activated by $[Mg - Tc]^+$ complex. The tetracycline repressor binds to the dual operators of the TetR (repressor) and the TetA genes and blocks their transcription. Tetracycline alters the conformation of the repressor protein, which then is not capable of blocking transcription by the RNA polymerase at the operators even in some eukaryotes. This system is thus suitable for exogenous regulation—by tetracycline—of a gene promoter fused by genetic engineering to the TetR system. The failure of the system in eukaryotes is determined by the toxicity of tetracycline to a particular organism. ►tetracycline, ►antiport; Scholz O et al 2001 J Mol Biol 310:979.

Tetracycline (Tet): An antibiotic that prevents the binding of amino acid-charged tRNAs to the A site of the ribosomes (see Fig. T34). The tetracycline repressor gene (TetR) interferes with the expression of tetracycline resistance. Tetracycline in the medium prevents the binding of TetR to the DNA and relieves repression. Tetracycline is widely used as a tool in turning genes ON and OFF, respectively. When the TetR gene is fused to the activation domain of the Herpes simplex virus protein VP16, it becomes a very effective Tet-responsive transactivator (tTA) of other genes. In the absence of Tet or Tet analogs, the tTA binds the Tet operator (TetO) and initiates transcription. When Tet is present in the culture medium, the transactivator (TA) binds the antibiotic, the DNA binding is disrupted, and transcription is prevented. A mutant form of TetR protein binds to the TetO only in the presence of the antibiotic doxycycline, a Tet

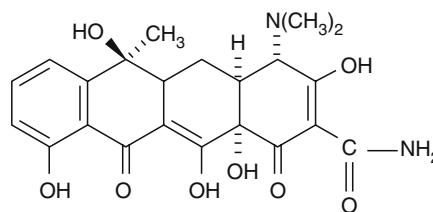


Figure T34. Tetracycline

analog, and when fused to VP16 (rtTA) transcription is activated. Modification of the D ring yielded highly effective new enantiomorphs against some antibiotic resistant pathogens (Charest MG et al 2005 Science 308:395). ▶doxycycline, ▶pBR322, ▶ribosomes, ▶protein synthesis, ▶targeting genes, ▶tTA, ▶rtTA, ▶transactivator, ▶Gene-Switch, ▶antibiotic resistance; Chopra I, Roberts M 2001 Microbiol Mol Biol Revs 65:232; Stebbins MJ et al 2001 Proc Natl Acad Sci USA 98:10775.

Tetrad, Aberrant: The allelic proportions deviate from 2:2 because of polysomy, gene conversion, non-disjunction, suppression, etc. ▶polysomy, ▶gene conversion, ▶non-disjunction, ▶suppression

Tetrad Analysis: The meiotic products of ascomycetes (occasionally some other organisms) stay together as the four products of single meiosis, as a *tetrad*. In some organisms, tetrad formation is followed by a post-meiotic mitosis within the ascus, resulting in spore *octads*. If the four spores are situated in the same linear order as produced by the two divisions of meiosis it is an *ordered tetrad*.

In the ordered tetrad, considering two genes *A* and *B*, three arrangements of the spores (parental ditype [PD], tetratype [TT], non-parental ditype [NPD]) can be distinguished as seen in the Figure T35. The parental ditype (PD) indicates no crossing over; tetratype (TT) reveals one recombination between the two genes and the second division segregation of the B/b alleles reveals recombination between the B/b gene and the centromere (see Fig. T36).

The nonparental ditype (NPD) is an indication of double crossing over between the two gene loci. The PD, TT, and NPD may appear even if the genes are in separate chromosomes. An excess of PD over NPD is

an indication of linkage. If the deviation from the 1:1 ratio between PD and NPD is small, a *chi square test* may be used to test the probability of linkage by the formula: $\chi^2 = (PD - NPD)^2 / (PD + NPD)$.

By counting the number of tetrads of the above three types, *recombination frequency between the two loci* can be calculated as $\frac{[1/2]TT + \text{all NPD}}{\text{all tetrads}}$, and recombination frequency between the B/b gene and the centromere can be calculated as $\frac{TT[1/2]}{\text{all tetrads}}$. (Dr. Fred Sherman recommended to me to use for the gene-gene map distance the formula of Dr. David Perkins [Genetics 34:607], i.e. $100\{[0.5(TT) + 6NPD]/[PD + TT + NPD]\}$.)

The recombination frequencies (if they are under 0.15) multiplied by 100 provide the map distances in centiMorgans. If the recombination frequencies are larger, mapping functions should be used. From the genetic constitution of the tetrads, a great deal of information can be revealed about recombination. When the four meiotic products are not in the order brought about by meiosis, the tetrad is *unordered*. For the estimation of gene-centromere distances from unordered tetrad data, one must rely on three markers, from which no more than two are linked, and algebraic solutions are required (e.g., Whitehouse 1950 Nature 165:893, see unordered tetrads). Tetrad analysis is most commonly used in ascomycetes (*Neurospora*, *Aspergillus*, *Ascobolus*, *Saccharomyces*, etc.) (see Fig. T37) yet it can be applied to higher plants where the four products of male meiosis stick together (*Elodea*, *Salpiglossis*, orchids, *Arabidopsis* mutants). Using transgene constructs encoding pollen-expressed fluorescent proteins of three different colors in the *qrt1* mutant, which retains pollen in the tetrad stage, segregation of the fluorescent alleles in 92,489 pollen tetrads could be

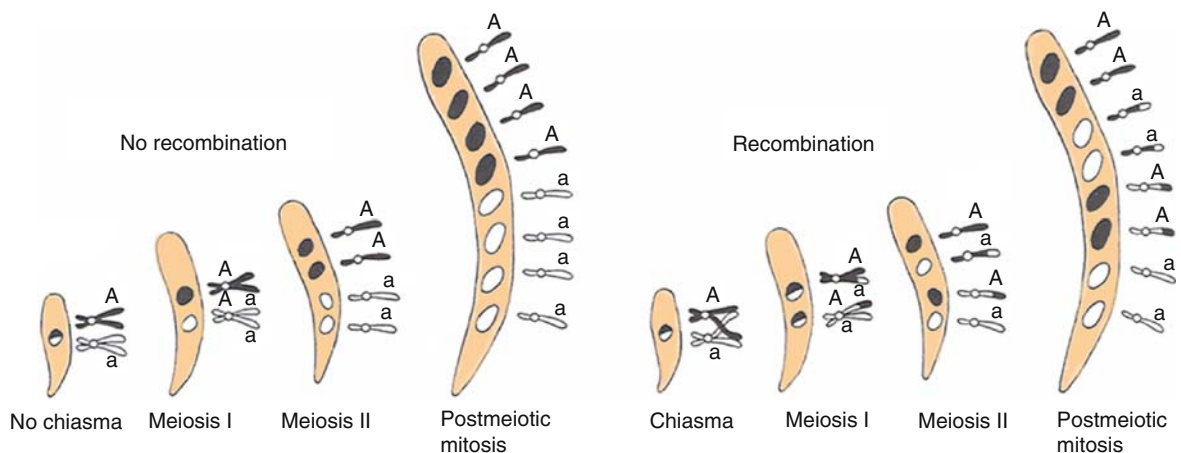


Figure T35. Spore tetrads and octads without and with recombination

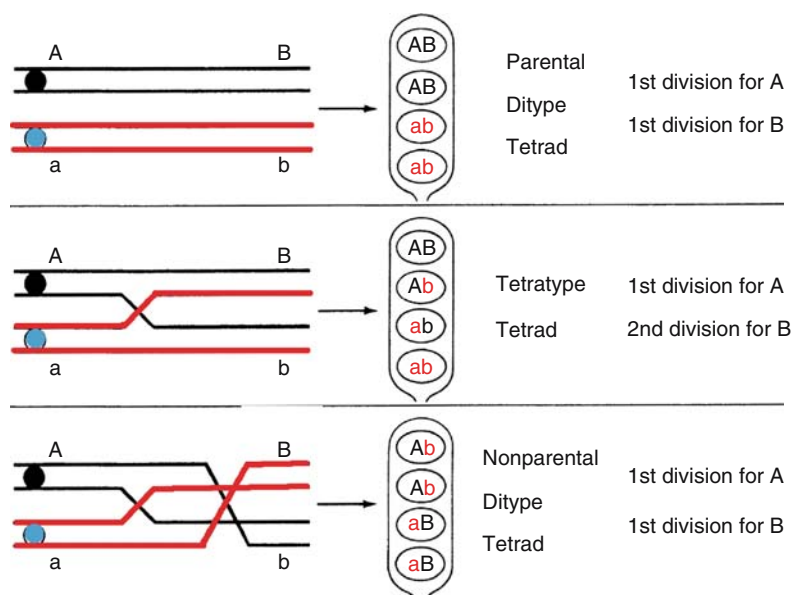


Figure T36. Transactions and results exemplified by two gene loci in an ordered tetrad. Gene A is so close to the centromere that practically no recombination occurs between them. (Diagram after Barratt RW et al 1954 Adv Genet 6:1)



Figure T37. *Neurospora* octads. (Courtesy of Dr. David Stadler)

observed (see Fig. T38). Correlation between developmental position and crossover frequency, temperature dependence for crossingover frequency, meiotic gene conversion, as well as interference were detectable (Francis KE et al 2007 Proc Natl Acad Sci USA 104:3913). In *Drosophila* with attached X-chromosomes half-tetrad analysis is feasible. Since several genomes of higher eukaryotes have been sequenced, molecular markers are available for tetrad analysis for the cases when the products of individual meioses can be identified. ▶unordered tetrads, ▶half-tetrad analysis, ▶meiosis, ▶mapping, ▶linkage, ▶mapping function, ▶four-point analysis of tetrads

Tetrahydrofolate (THF): The active (reduced) form of the vitamin folate, a carrier of one-carbon units in oxidation reactions, and a pteridine derivative. ▶hyper-homocysteinemia

Tetrahymena pyriformis: ($2n = 10$) is a ciliated protozoan with linear mtDNA. Its rRNA transcripts are self-spliced. ▶splicing, ▶mtDNA, ▶telomerase, ▶micronucleus, ▶macronucleus, ▶chromosome breakage programmed; Turkewitz AP et al 2002 Trends Genet 18:35; <http://www.lifesci.ucsb.edu/~genome/Tetrahymena/>; <http://www.ciliate.org/>.

Tetralogs: Paralogous gene groups originated by duplications (polyploidy), e.g., the families of multiple kinases or other genes. Some of these genes can be deleted without serious phenotypic consequence, yet their point mutations (dominant negative) may be quite deleterious, especially if they have multiple interactive domains and function in protein complexes. Some of the evolutionarily redundant genes can further evolve by selectable mutations. ▶polyploidy, ▶paralogous loci, ▶point mutation, ▶dominant negative, ▶duplication, ▶co-ortholog, ▶semi-ortholog; Spring J 1957 FEBS Lett 200:2.

Tetralogy of Fallot: ▶Fallot's tetralogy

TetraLoop: In structured RNAs, duplex runs are connected by loops of 5'GNRA (or UNCG or CUYG) tetranucleotides (N = any nucleotide, R = purine, Y = pyrimidine). They are involved in long-range molecular interactions, such as in hammerhead ribozymes and introns. ▶ribozymes, ▶introns,

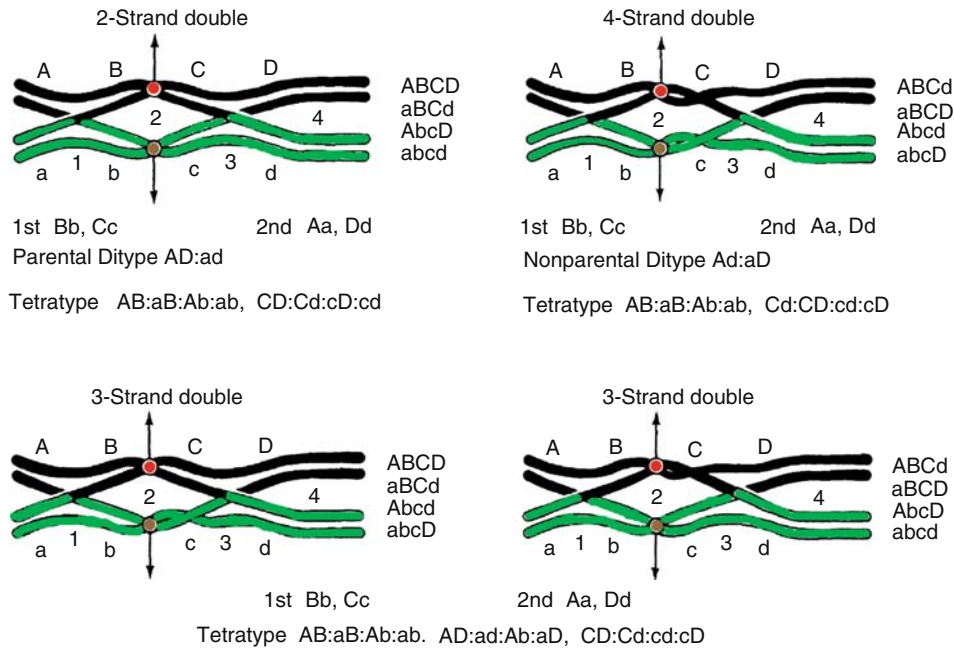


Figure T38. Four-point cross with genes in both arms of the chromosomes. It is a five-point cross if we consider the centromere as a genetic marker. From the spore order we can determine even if the chromatids rotated 180° after the exchange. (After Emerson S 1963 p 167. In: *Methodology in Basic Genetics*. Burdette WJ (Ed.) Holden-Day, San Francisco)

►[stem-loop](#), ►[ribose zipper](#), for illustration of a tetraloop see ►[ribonuclease III](#); Baumrook V et al 2001 *Nucleic Acids Res* 29:4089; Koplin J et al 2005 *Structure* 13:1255.

Tetranucleotide Hypothesis: A historical assumption that nucleic acids are made of repeated units of equal numbers of the four bases (A, T/U, G and C), and because of this monotonous structure could not qualify for being the genetic material. It was probably first proposed around the turn of the twentieth century by the great German chemist, Albrecht Kossel, but became a rather widely accepted view during 1909 to 1940 through the brilliant yet erroneous work of Phoebus Levine. (See Levine PA 1909 *Biochem Zeit* 17:120; Levine PA 1917 *J Biol Chem* 31:591).

Tetraodon: ►[pufferfish](#)

Tetraparental Offspring: Tetraparental offspring results if in vivo fused blastulas of different matings are implanted together into the uterus. ►[allophenic](#), ►[multiparental hybrids](#), ►[chimera](#)

Tetraplegia (quadriplegia): Paralysis of the four limbs, caused by brain injury. Various mechanical devices have been designed to alleviate the incapacitation. Recent experiments inserting small neuromotor prostheses into the brain seem promising in

restoring control of movement (Hochberg LR et al 2006 *Nature [Lond]* 442:164). Brain-computer interfaces can provide means to operate computer cursors (Santhanam G et al 2006 *Nature* 442:195).

Tetraplex (quadruplex): Consecutive guanine sequences may take four-stranded parallel or antiparallel conformations in the DNA or RNA in several different configurations (see Fig. T39). The tetraplex structure may have biological significance for the telomeres, specific recombination of the immunoglobulin genes, dimerization of the HIV genome, etc. ►[telomere](#), ►[G-quadruplex](#), ►[immunoglobulins](#), ►[HIV](#); Simonsson T 2001 *Biol Chem* 382:621; Weisman-Shomer P et al 2002 *Nucleic Acids Res* 30:3672; Saccà B et al 2005 *Nucleic Acids Res* 33:1182; ►[tetrasomic](#)

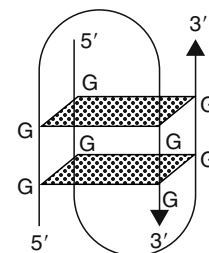


Figure T39. Guanine (G) tetraplex

Tetraploid: Tetraploids have four sets of genomes (4x) per nucleus. Tetraploid plants have broader leaves and petals, and larger seeds (see Fig. T40). ▶[autopolyploidy](#), ▶[tetrasomic](#)



Figure T40. *Cardaminopsis petraea* tetraploid (4x) and diploid (2x); Rédei, unpublished

Tetraploid Embryo ComplEmentation: Embryonic stem cells have a unique ability to complete embryonic development after nuclear transplantation or after injection into tetraploid host blastocysts. Tetraploid mouse blastocysts cannot autonomously develop into embryos normally, but they can do so when complemented by diploid embryonic stem cells. The success is substantially better if the nuclei are not derived from inbred cells. Tetraploid embryo complementation assay has shown that mouse embryonic stem cells (ES) cells alone are capable of supporting embryonic development and adult life of mice. Newly established F1 hybrid ES cells allow the production of ES cell-derived animals at a high enough efficiency to directly make ES cell-based genetics feasible (George SHL et al 2007 Proc Natl Acad Sci USA 104:4455). ▶[stem cells](#), ▶[nuclear transplantation](#), ▶[embryo culture](#); Ewggan K et al 2001 Proc Natl Acad Sci USA 98:6209.

Tetrapod: The collective evolutionary designation of four-limbed vertebrate animals in contrast to lobe-finned fishes (sarcopterygians). ▶[missing link](#), Long JA et al 2006 Nature [Lond] 444:199.

Tetrasomic: In tetrasomics, one chromosome is present in four doses in the nuclei. Tetrasomy exists in tetraploids for all chromosomes and may not involve any serious anomaly although generally the fertility is reduced. Tetrasomy for individual chromosomes may have more serious consequences because of genic imbalance. Tetrasomy is usually not tolerated by animals. Tetrasomic mosaicism for human chromosome 12p leads to developmental anomalies, mental retardation, defects in the central nervous system and speech, etc. ▶[polyploidy](#), ▶[autopolyploid](#), ▶[trisomy](#), ▶[sex-chromosomal anomalies in humans](#), ▶[cat-eye syndrome](#)

Tetrasomic-Nullisomic Compensation: In allotetraploids, the homoeologous chromosomes may compensate for each other, and thus if two chromosomes are missing (nullisomy), and one type or their homoeologues is present in four copies (tetrasomy), the individuals may function rather well, depending on the particular chromosomes involved. When, however, in the presence of nullisomy a non-homoeologous chromosome is substituted, the condition is worsened. ▶[chromosome substitution](#), ▶[nullisomic compensation](#); Morris R, Sears ER 1967 p 19. In: Wheat and Wheat Improvement. Quisenberry KS, Reitz LP (Eds.) Am Soc Agron Madison, Wisconsin.

Tetraspanins: Cell membrane molecules functioning in cell adhesion, motility, proliferation, differentiation signal transduction, and fertilization. The TM4SF2 protein encoded at Xp11.4 and involved in determining a non-syndromic mental retardation also belongs to the tetraspanin family of proteins. ▶[CD9](#), ▶[CD63](#), ▶[CD82](#), ▶[mental retardation](#); Cannon KS, Cresswell P 2001 EMBO J 20:2443.

Tetratrico Sequences (TPR): Amphipathic α -helical amino acid tracts punctuated by proline-induced turns. CDC16, CDC23, and CDC27 of yeast and their homologs in other eukaryotes all contain tandem repeated ~ 34 -residues. Such motifs exist in more than 100 proteins and may control mitosis and RNA synthesis in the cells. ▶[APC](#), ▶[CDCs](#); Wendt KS et al 2001 Nature Struct Biol 8:784; Cortajarena AL, Regan L 2006 Protein Sci 15:1193.

Tetratype: The meiotic products concerned with two genes show four types of combinations (e.g., *AB Ab aB ab*). ▶[tetrad analysis](#)

Tetrazolium Blue: Tetrazolium blue detects oxidation-reduction enzyme activity and thus identifies living cells and cancerous metabolism.

Tetrodotoxin: ▶[toxins](#)

T-Even Phages: The designation has even numbers such as T2, T4, etc. ▶[bacteriophages](#)

Texas Red: A fluorochrome with excitation at 580 nm and emission peak at 615 nm. ▶[fluorochromes](#)

Text-Mining: The search for specific (overlooked) connections in the literature for the purpose of revealing specific trends/rules in multiple papers. ▶[literature mining](#)

Textpresso: The information retrieval and extraction system for *Caenorhabditis*. (See <http://www.textpresso.org/>).

TF: Transcription factors such as TF I, TF II, or TF III, involved in the control of transcription by pol I, pol II, or pol III, respectively; TFs assist transcription by

cooperation with other binding proteins. ▶transcription factors, ▶TFIIS, ▶open transcription complex

TF: ▶transferrin

Tfam: ▶mtFAM

TFD (transcription factor decoy): A double-stranded nucleotide sequence (e.g., $\begin{smallmatrix} \text{GGG} & \text{ACTTT} & \text{CC} \\ \text{CCC} & \text{TGAAAGG} \end{smallmatrix}$) that may sequester a transcription factor, e.g., NF-κB, within the cytoplasm by virtue of the attachment of the TF to a sequence homologous to its recognition site in the upstream region of the gene(s) in the nucleus. As a consequence, the nuclear gene may be (partially) silenced. Such an approach may be exploited for the control of oncogenes. ▶NF-κB, ▶antisense technologies; Mann MJ, Dzau VJ 2000 J Clin Invest 106:1071.

TFE: Helix-loop-helix leucine zipper transcription factor. ▶DNA binding protein domains

TFG: ▶transforming growth factor

TFII: ▶transcription factors, ▶TBP, ▶PIC

TFIIS: The eukaryotic transcript elongation stimulatory factor. It makes yeasts hypersensitive to 6-azauracil, which reduces the intracellular UTP and GTP pool. In *Drosophila*, the transcripts of two protein factors, N-TEF (negative transcript elongation) and P-TEF, regulate elongation. The positive effect is mediated by ATP-dependent phosphorylation of the RNA polymerase. ▶backtracking, ▶elongation factors, ▶transcription factors, ▶azauracil, ▶DSIF, ▶NELF, ▶TEF, ▶DRB, ▶PITSRE, ▶transcript elongation; Lindstrom DL, Hertzog GA 2001 Genetics 159:487; Ubukata T et al 2003 J Biol Chem 278:8580.

TFII: Synonymous with TBP.

TFM: ▶testicular feminization

TFO (triple-helix-forming oligonucleotide): TFO may be used to interfere with the activity of genes.

The effective TFO needs to recognize 10 to 17 bases in order to be gene specific. Some problems arise in vivo by the fact that genes in the chromosomes are organized as chromatin. TFO seems to mediate mutation, nucleotide excision repair, and transcription-coupled repair and consequently enhances mutation rate induced by UV-A in the presence of psoralen dye sensitization at 365 nm. Psoralen is a bifunctional photoreagent. TFO may also stimulate targeted gene conversion using nucleotide excision repair and may be antiviral. The triplex-directed, site-specific mutagenesis is much improved when cationic phosphoramidate linkages replace the phosphodiester backbone, particularly by employing *N,N*-diethyl-ethylenediamine to target short polypurine tracts (see Fig. T41). ▶antisense

RNA, ▶antisense DNA, ▶triple helix formation, ▶triplex, ▶inhibition of transcription, ▶peptide nucleic acid, ▶targeting genes, ▶directed mutation, ▶DNA repair, ▶ultraviolet light, ▶gene conversion, ▶psoralen, ▶pseudoknot; Vasquez KM et al 2000 Science 290:530; Vasquez KM et al 2001 J Biol Chem 276:38536; Besch R et al 2002 J Biol Chem 277:32473.

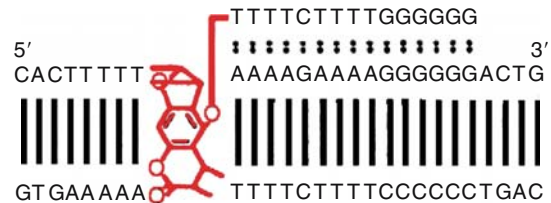


Figure T41. TFO. Modified after Barre FX et al 2000 Proc Natl Acad Sci USA 97:3084

TFR: Transferrin receptor. ▶transferrin

TFTC (TBP-free TAF_{II}-containing complex): ▶transcription factors, ▶TAF; Walker AK et al 2001 EMBO J 20:5269.

TGF: The transforming growth factors are cell proliferation inhibitors and their loss may be involved in cancerous growth. In humans, the TGFA gene is in chromosome 2p13, TGFB1 in 19q13.1-q13.3, TGFB2 in 1q41, and TGFB3 in 14q24. A member of the family, Vg1, a factor localized to the vegetal pole of the animal embryo, may be involved in the induction of mesoderm formation in the embryo. The TGF-β family cytokines activate the receptors of the heterodimeric serine-threonine kinases. TGF-β binds directly to TGF receptor II, a kinase. The bound TGF-β then, binds by the TGF receptor I and becomes phosphorylated (P) by it. Type I receptor contains a repeated GS (Gly.Ser) domain and a binding site for FKBP12. TGFR I then transmits the cytokine signal along the signaling cascade and the target genes may be turned on. In humans, about 30 members of the TGFβ protein family exist and various homologs—although in smaller numbers—occur in other species. TGFβ acts on cytotoxic T lymphocytes (CTL) and specifically inhibits perforin, granzyme A and B, Fas ligand, and interferon (Thomas DA, Massagué J 2005 Cancer Cell 8:369).

Ligand induced phosphorylation of receptor-activated Smads (R-Smads) is catalyzed by TGFβ type I receptor kinase. The PPM1A/PP2Cα phosphatase dephosphorylates and promotes nuclear export of Smad2/3. Ectopic expression of PPM1A abolishes TGFβ-induced antiproliferative and transcriptional responses but depletion of this phosphatase boosts

TGF β signaling in mammalian cells (Lin X et al 2006 Cell 125:915). The SMAD3 protein affecting the pathway outlined in the diagram is also a co-activator of the vitamin D receptor by forming a complex with the steroid receptor co-activator-1 protein (SRC-1) in the cell nucleus (see Fig. T42).

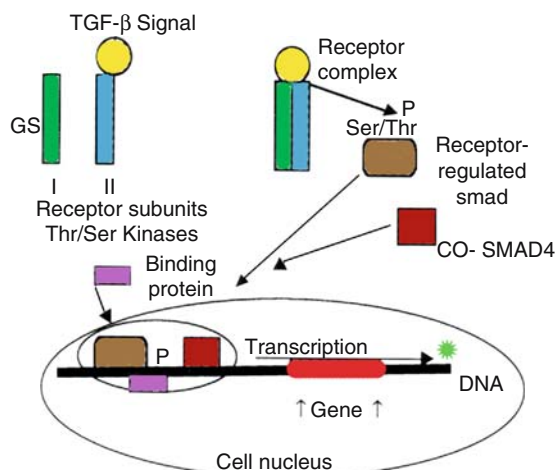


Figure T42. TGF signaling

TGF- α is an epidermal growth factor-like molecule. Mutations leading to chondrodysplasia involve members of the TGF family (CDMP1). Beta-glycan and endoglin cell surface proteins are also involved somehow with TGF. Endoglin and ALK1 (a type I receptor) mutations are found in hereditary hemorrhagic telangiectasia. TGF β receptor I mutations were found in different types of cancers and TGF β mutations may be responsible for heart disease, hypertension, osteoporosis, and fibrosis. TGF β mutations upregulate the transforming growth factor in the arterial wall in Loeys-Dietz syndrome and in aortic aneurism cause arterial tortuosity. The human genome includes 42 TGF β genes compared with nine in *Drosophila* and six in *Caenorhabditis*. ▶activin, ▶bone morphogenetic protein, ▶leukemia inhibitory factor, ▶ectoderm, ▶serine/threonine kinase, ▶signal transduction, ▶SMAD, ▶immunophilins, ▶SRC-1, ▶cytokines, ▶EGF, ▶MDM2, ▶FK506, ▶PP2A, ▶telangiectasia hereditary hemorrhagic, ▶Müllerian ducts, ▶Loey-Dietz syndrome; Massagué J 1998 Annu Rev Biochem 67:753; Massagué J, Chen Y-G 2000 Genes & Development 14:627; Massagué J et al 2000 Cell 103:295; Zwaagstra JC et al 2001 J Biol Chem 276:27237; Wakefield LM, Roberts AB 2002 Current Opin Genet Dev 12:22; Waite KA, Eng C 2003 Nature Rev Genet 4:763.

T-GURT (trait-specific genetic use restriction technology): T-GURT is applied to products of plant breeding with the aid of biotechnology and makes the plants express special traits such as salt or drought tolerance on condition that a special (chemical) treatment is applied. The plants will grow without the special treatment but do not express the agronomically advantageous special trait to the same extent. Such seed stocks protect the proprietary interests of the seed companies, which developed them. ▶terminator technology, ▶GMO, ▶RBF

T_H (or Th): T helper cell. They can be T_H1 type activating macrophages and T_H2 type, which activate primarily B cells. T-bet transcription factor regulates the activity of T_H1 cells. T_H1 cells produce IL-2, interferon- γ (IFN- γ), and tumor necrosis factor- β (TNF- β) and offer defense against intracellular pathogens by aiding cellular immunity. T_H2 cells make interleukin-4, -5, -6, -10, and -13 (IL-4, IL-5, IL-13) against extracellular pathogens and allergens, promote antibody formation, and have direct cytolytic activity. Interleukin-12 (IL-12) favors the development and maintenance of T_H1, whereas IL-4 promotes the differentiation of T_H2. IL-18 may both promote and hinder T_H2 activity by its effect on IL-13. T_H3 cells may express transforming growth factors. A new type of T helper cells T_H17 provides protection against extracellular bacteria and is involved in autoimmune diseases. T_H17 cells produce IL-17. Its development is linked to IL-23 and IL-12 and transforming growth factor TGF β , which is antagonized by interferon γ and IL-4 (Mangan PR et al 2006 Nature [Lond] 441:231). The differentiation factor for T_H17 is not IL-23 but IL-6 and TGF- β together. There is a different path for the development of the regulatory T_H17 cells that inhibit autoimmune tissues and T_H17 cells, which induce autoimmunity (Betteli E et al 2006 Nature [Lond] 441:235). ▶T cells, ▶B cell, ▶T-bet, ▶dendritic cell, ▶macrophage, ▶IL-4, ▶IL-5, ▶IL-6, ▶IL-10, ▶IL-12, ▶IL-13, ▶IFN- γ , ▶TNF, ▶TCCR; O'Garra A, Arai N 2000 Trends Cell Biol 10:542; Mullen AC et al 2001 Science 292:1907; Helmby H et al 2001 J Exp Med 194:355; Ho I-C, Glimcher LH 2002 Cell 109: S109; minireview: Reiner SL 2007 Cell 129:33.

Thalamus: A double-egg-shaped area deep within the basal part of the brain, involved in transmission of sensory impulses. ▶fatal familial insomnia, ▶brain human

Thalassemia: Hereditary defects of the regulation (or deletions) of hemoglobin genes, causing anemia. In the thalassemias, generally the relative amounts of the various globins is affected because of deletions of the hemoglobin genes. *Thalassemia major* is the most

severe form of the disease in patients homozygous for a defect in the two β -chains and who have an excessive amount of the F hemoglobin (HPFH: *hereditary persistence of fetal hemoglobin*). *Cooley's anemia* is also caused by β chain defects. *Thalassemia minor* is a relatively milder form with some hemoglobin A₂ present; usually, slight elevation of the F hemoglobin is characteristic for the heterozygotes. In the β -thalassemias, different sections of the β globin gene family from human chromosome 11p15.5 (5'- ϵ G γ $\psi\beta$ δ β - 3') are missing. The deletions may involve only 600 bp from the 3' end as in β^0 or about 50 kbp, eliminating most of the family beginning from the 5' end and retaining only the β gene at the 3' end in human chromosome 11p. In the β chain gene, about 100 point mutations and various deletions have been analyzed. In severe cases, the symptoms of the β thalassemias are anemia, susceptibility to infections, bone deformations, enlargement of the liver and spleen, iron deposits, delayed sexual development, etc. These may appear within a few months after birth. In the α -thalassemias (in human chromosome 16p13), various members of the α chain gene cluster (5'- ζ $\psi\zeta$ $\psi\alpha$ $\psi\alpha$ $\alpha 2$ $\alpha 1$ δ - 3') or even all four α chains are defective; the latter case results in the lethal hereditary disease, hydrops fetalis (Bart's hydrops), entailing accumulation of fluids in the body of the fetus and severe anemia, resulting in prenatal death. In α -thalassemia-1, both the $\alpha 1$ and the $\alpha 2$ genes are deleted, in thalassemia α -thal-2 only either the left (α *thal* 2L) or right end (α *thal* 2R) of the α -gene(s) is lost. The *Hb Lepore hemoglobin* is the consequence of unequal crossing over within the α gene cluster, resulting in N-terminal- $\delta\beta$ -C protein fusion. The N- $\beta\delta$ -C reciprocal protein fusion is called *Hb anti-Lepore* or *F thalassemia*. One of these types of hemoglobins was first reported in 1958 in the Lepore Italian family. Since then, a large number a Lepore type hemoglobins were discovered in various parts of the world and named Greece, Washington, Hollandia, etc., hemoglobin. The Xq13.1-q21.1 locus (ATRX) is a regulator of α -thalassemia and it usually involves mental retardation and a variety of developmental abnormalities. Thalassemias have much higher incidence worldwide in areas where malaria is a common disease. Homozygotes for thalassemias rarely contribute to the gene pool, thus the heterozygotes appear to have selective advantage in the maintenance of this condition. Some recent studies, however, indicate that α thalassemia homozygotes have a higher incidence of uncomplicated childhood thalassemia and splenomegaly (enlargement of the spleen an indication of infection by *Plasmodium*). This increase of susceptibility to the relatively benign *P. vivax* may provide some degree of immunization in the later stages of life against the more severe disease

caused by *P. falciparum* infection. This relatively high incidence of thalassemias in tropical and subtropical areas and the well-known molecular genetics mechanism makes this disease a candidate for somatic gene therapy by either bone marrow transplantation or transformation. The prevalence of thalassemias varies from about 10 to 5×10^{-4} . However, in some geographically isolated areas in the Mediterranean region, the frequency of the thalassemias may be much higher. Thalassemias are frequently associated with sickle cell anemias that are β globin defects and comorbidity aggravates the conditions (see Fig. T43). Prenatal diagnosis is possible by the use of protein or DNA technologies. Fetal mutation may be identified after PCR amplification of chorionic samples (9–12 weeks) or in directly withdrawn cells from the amniotic fluid after the third month of pregnancy. Hydrops can be identified by ultrasonic techniques during the second trimester. Transformation by a functional β -globin gene may ameliorate the condition in a mouse model. Erythroid specific expression of the transduced human α -globin gene and relatively high levels of expression of the human α -globin gene were observed in mice receiving the lentiviral vector by yolk sac vessel injection at midgestation. However, the expression decreased to low levels on long-term follow up (Han X-D et al 2007 Proc Natl Acad Sci USA 104:9007). ▶hemoglobin, ▶methemoglobin, ▶sickle cell anemia, ▶plasma proteins, ▶hemoglobin evolution, ▶unequal crossing over, ▶genetic screening, ▶PCR, ▶trimester, ▶*Plasmodium*, ▶antisense RNA, ▶Juberg-Marsidi syndrome, ▶ATRX, ▶hydrops fetalis; Weatherall DJ 2001 Nature Rev Genet 2:245; β -thalassemia review: Rund D, Rachmilewitz E 2005 New England J Med 353:1135.

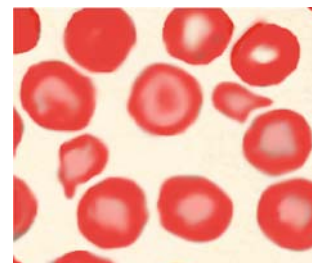


Figure T43. Thalassemia blood smear. Irregular cells are characteristic

Thalidomide (*N*-phtaloyl

glutamide): A sedative and hypnotic agent of several trade names. It had been used experimentally also as an immunosuppressive and antiinflammatory drug. Its medical use as a tranquilizer during pregnancy caused one of the most tragic disasters in

medical history, resulting in severe malformations of primate embryos and newborns. It does not appear to be mutagenic and it is not teratogenic for other mammals. It is effective against multiple myeloma and possibly some other cancers. ▶[teratogen](#), ▶[phocomelia](#), ▶[amelia](#); Ashby J et al 1996 Mutation Res 396:45; Meierhofer C et al 2001 BioDrugs 15 (10):681; Richardson P et al 2002 Annu Rev Med 53:629.

Thallophyte: A plant, fungus, or algal body, a thallus. ▶[thallus](#)

Thallus: A relatively undifferentiated colony of plant cells without true roots, stem or leaves.

Thanatophoric Dysplasia: A dominant lethal human (4p16.3) dwarfism caused by deficiency of the fibroblast growth factor receptor 3, FGFR3. FGFR3 has constitutive tyrosine kinase activity, which activates the STAT1 transcription and nuclear translocation. This system also controls the p21^{WAF1/CIP1} protein involved in cell cycle suppression. Its prevalence is about 2×10^{-4} . ▶[dwarfism](#), ▶[fibroblast growth factor](#), ▶[STAT](#), ▶[p21](#), ▶[receptor tyrosine kinase](#), ▶[achondroplasia](#), ▶[Schneckenbecken dysplasia](#)

Thea (*Camellia sinensis*): 82 species, $2n = 2x = 30$. The epigallocatechin-3 component of green tea appears to be an angiogenesis inhibitor and thus can have anticancer effect. ▶[angiogenesis](#), ▶[angiostatin](#), ▶[endostatin](#), ▶[polyphenols](#); Kuroda Y, Hara Y 1999 Mutation Res 436:69.

Theileriosis: An African or East Cost Fever parasitic *Theileria* infection of the cattle's immune system, causing disease and death to the infected animals. In the T lymphocytes casein kinase II, a serine/threonine protein kinase is markedly higher. This protein is not identical with the common casein kinase found in lactating animals. *Theileria annulata* and *T. parva* are tick-borne protozoa ($n = 4$, genome size 8,351,610 and 8,308,027 bp, respectively). (See Pipano E, Shkap V 2000 Ann NY Acad Sci 916:484; Pain A et al 2005 Science 309:131; Gardner MJ et al 2005 Science 309:134).

Thelytoky: Parthenogenesis from eggs resulting in maternal females. ▶[ant](#), ▶[arrhenotoky](#), ▶[deuterotoky](#), ▶[sex determination](#), ▶[chromosomal sex determination](#); Normark BB 2003 Annu Rev Entomol 48:397.

Theobromine: The principal alkaloid in cacao bean, containing 1.5 to 3% of the base. It is also present in tea and cola nuts. The TDLo orally for humans is 125 mg/kg. It is a diuretic, smooth muscle relaxant, cardiac stimulant, and a vasodilator (expands vein passages). ▶[TDLo](#), ▶[caffeine](#)

Therapeutic Cloning: The generation of (human) stem cells that induces them to differentiate into a certain type of tissue which can be used to replace damaged tissues without the risk of rejection. The transfer stem cells are prepared by dislodging the nucleus of an oocyte and replacing it by the nucleus of an adult cell of the individual who is supposed to be treated by the stem cells. Such a modified oocyte (any type, possibly even from a different species) is then grown in culture until the blastocyst stage. The inner cell mass is then excised and cultivated in vitro until differentiated cells (either muscle, or neural, or hematopoietic cells) develop under the direction of the experimental conditions applied. Subsequently, the cells can be transplanted into the body of an individual. Nuclear transfer is possible between different species but the few experiments carried out so far could not maintain steady normal development. An alternative to the use of oocytes is to fuse an embryonic cytoplasm with an appropriate karyoplast. The ES cells do not develop into an embryo even it is transplanted into a uterus because the extra-embryonic membranes required would not be formed. If such a stem cell is introduced into a blastocyst, chimeric embryos (host + ES) may form in the mouse. These cells may form different types of tissues (pluripotent) but are apparently not totipotent. The therapeutic cloning is thus similar in some respects to reproductive cloning but current laws prohibit the latter in the majority of countries. Some of the cloned embryos suffered from (lethal) developmental anomalies. Although the majority of the implanted stem cells develop rather normally, some may become teratogenic and carcinogenic when transferred into mice. ▶[stem cell](#), ▶[nuclear transplantation](#), ▶[graft rejection](#), ▶[grafting in medicine](#), ▶[cytoplasm](#), ▶[karyoplast](#), ▶[blastocyst](#), ▶[totipotency](#), ▶[cloning animals and humans](#); Mitalipov SM 2000 Ann Med 32:462; Illmensee K 2002 Differentiation 69:167; Rideout WM III et al 2002 Cell 109:17.

Therapeutic Index: The therapeutic index reveals the dose of a drug with optimal, threshold, maximal tolerated or lethal, etc., effect in a particular organism or tissue. At high therapeutic index, a low dose gives the desirable effect without the possible toxic effects possible at higher doses.

Therapeutic Radiation: ▶[radiation hazard assessment](#)

Therapeutic Vaccine: vaccination may force down the level of an infective agent (e.g., HIV) and then eventually the natural immune system may overpower the infection. ▶[vaccines](#)

Thermal Asymmetric Interlaced-PCR: ▶[tail-PCR](#)

Thermal Cycler: An automatic, programmable incubator use for the polymerase chain reaction. ▶[PCR](#)

Thermal Neutrons: ►physical mutagens

Thermal Tolerance: Thermal tolerance is genetically determined and in plants may be affected by fatty acid biosynthesis and abscisic acid deficiency, etc. Heatshock proteins have also been credited with it. In *Tetrahymena thermophila*, a small cytoplasmic RNA (G8 RNA) is responsible specifically for thermotolerance independently from a heat shock response. ►temperature-sensitive mutation, ►heat-shock proteins, ►RNA G8, ►antifreeze protein

Thermatoga maritima: A thermophil (80° C optimum) bacterium; it has a completely sequenced circular DNA genome of 1,860,725 bp with 46% G + C content; 24% of its genes appear homologous to archaea bacteria. (Nelson KE et al 1999 Nature 399:323).

Thermodynamic Values: The thermodynamic values of chemicals are measured in calories; 1 calorie = 4.1840 absolute joule. ►joule

Thermodynamics, laws of: 1). When a mechanical work is transformed into heat, or the reverse, the amount of work is equivalent to the quantity of heat. 2). It is impossible to continuously transfer heat from a colder to a hotter body.

Thermoluminiscent Detectors: Thermoluminiscent detectors are used for personnel monitoring. In a small crystalline detector (lithium fluoride, lithium borate, calcium fluoride or calcium sulfate, and metal ion traces as activators), radiation is absorbed in the crystalline body and upon heating, is released in the form of light. The useful range is 0.003–10,000 rem. Radiophotoluminiscent (RPL) and thermally stimulated exoelectron emission (TSEE) detectors may be used instead of film badges in radiation areas. ►radiation measurements

Thermoplasma acidophilum: An archaea bacterium with a completely sequenced genome of $\sim 1.5 \times 10^6$ bp. Its temperature optimum is 59 °C, pH opt. 2. Its cells are without cell wall. ►Archaea; Ruepp A et al 2000 Nature [Lond] 407:508.

Thermosome: ►chaperonins

Thermotolerance: Some mutants of plants display increased growth relatively to the wild type at higher temperature. Some kinds of temperature-sensitivity are associated with differences in fatty acid biosynthesis. Thermosensation neurons in mammals are located in the keratinocytes of the skin (Moqrich A et al 2005 Science 307:1468). The tolerance of higher temperature in plants is correlated with reduced level in trienoic fatty acids. Trienoic acid synthesis is controlled by omega-3 fatty acid desaturase in the chloroplast membrane. If this desaturase is

silenced, photosynthesis is improved at higher temperature. ►cold-regulated genes, ►temperature-sensitive mutation, ►antifreeze protein, ►fatty acids; Mirkes PE 1997 Mutation Res 396:163.

THF: ►tetrahydrofolate

Theta Replication: θ is a stage of bidirectional form of replication in a circular DNA molecule (see Fig. T44). When the two replication forks reach about half way toward the termination sites, the molecule resembles the Greek letter θ . ►DNA replication, ► θ replication, ►bidirectional replication, ►replication, ►prokaryotes



Figure T44. Theta replication

"5,0,1,0,105pt,105pt,0,0>Thiamin (vitamin B₁): The absence of thiamin from the diet causes the disease beri-beri, alcoholic neuritis, and the Wernicke-Korsakoff syndrome. Its deficiency was the first auxotrophic mutation in *Neurospora*, and it is the most readily inducible auxotrophic mutation at several loci in lower and higher green plants, such as algae and *Arabidopsis* (see Fig. T45). The vitamin is made of two moieties: 2-methyl-4-amino-5-aminomethyl pyrimidine and 4-methyl-5- β -hydroxyethyl thiazole. The pyrimidine requirement of the thiamin mutants cannot be met by the precursors of nucleic acids. In *Arabidopsis*, more than 200 absolute auxotrophic mutations for thiamin have been isolated at five loci. This is remarkable because absolute auxotrophs in other metabolic pathways still need to be found in higher plants. ►thiamin pyrophosphate, ►Wernicke-Korsakoff syndrome, ►megaloblastic anemia, ►vitamins; Rédei GP, Koncz C 1992

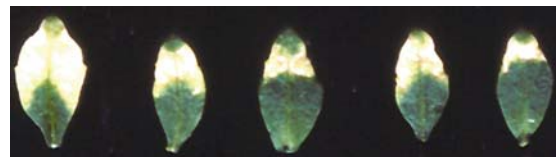


Figure T45. Thiamin deficiency symptoms on *Arabidopsis* leaves, appearing after the vitamin supplementation ceased. A bleached band appears at about the upper third-fourth part of the leaf blade where the metabolism is most active (From Rédei, G.P., unpublished)

Methods in Arabidopsis research, pp 16–82. In: Koncz C et al (Eds.) World Scientific; Miranda-Ríos J et al 2001 Proc Natl Acad Sci USA 98:9736.

Thiamin Pyrophosphate: The coenzyme of vitamin B₁. It is an essential cofactor for pyruvate decarboxylase (alcoholic fermentation), pyruvate dehydrogenase (synthesis of acetyl Co-A), α -ketoglutarate dehydrogenase (citric acid cycle), transketolase (photosynthetic carbon fixation), and acatolactate synthetase (branched chain amino acid biosynthesis). ▶[thiamin](#); Frank RAW et al 2004 Science 306:872.

Thiazolidinediones: Antidiabetic (Type 2) drugs enhancing sensitivity to insulin. They are agonists and ligands to PPAR- γ receptors of adipocytes. They may have modest beneficial effects on the level of the desirable high-density lipoprotein (see Fig. T46). ▶[diabetes](#), ▶[PPAR](#), ▶[high-density lipoprotein](#), ▶[adipocytes](#), ▶[insulin](#); Yki-Järvinen H 2004 New England J Med 351:1106.

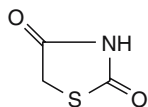


Figure T46. Thiazolidinedione

Thin-Layer Chromatography (TLC): The separation of (organic) mixtures within a very thin layer of cellulose or silica gel layer applied uniformly onto the surface of a glass plate or firm plastic sheet and used in a manner similar to paperchromatography. The material is applied at about 2 cm from the bottom and the plate is then dipped into an appropriate solvent (mixture). Generally, the substances are separated rapidly and with excellent resolution. Identification is made generally on the basis of natural color or with the aid of special color reagents. ▶[Rf](#)

Thioester: Acyl groups covalently linked to reactive thiol (see Fig. T47); they are high-energy acyl carriers in coenzyme A; also thioester may assist the formation of oligopeptide without any cooperation by ribosomes). There are suggestions that thioethers are the relics of prebiotic conditions when sulfurous (volcanic) environment existed on the Earth and might have played a role in the origin of living cells by being energy carriers. ▶[sulfhydryl](#), ▶[disulfide](#)

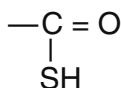


Figure T47. Thioester

Thioguanine (2-amino-1,7-dihydro-6H-purine-6-thione): An antineoplastic/neoplastic agent. Its delayed cytotoxicity is attributed to postreplicative mismatch repair. After incorporation into the DNA, it is methylated and pairs with either thymine or cytosine. The immuno-suppressant, azathioprine (6-[1-methyl-4-nitroimidazol-5-yl]-thiopurine), used in organ transplantation, can be converted to thioguanine and may be the cause of the increased incidence of cancer after transplantation. ▶[DNA repair](#), ▶[mismatch](#), ▶[base analogs](#), ▶[hydrogen pairing](#); Nelson JA et al 1975 Cancer Res 35:2872.

Thiol (SH⁻): Thiol compounds may reduce DNA breakage by scavenging radiation induced hydroxyl radicals and may repair the radicals chemically on the DNA by hydrogen atom transfer. Thiols have various regulatory roles in oxidative metabolism and nitrosative stress. ▶[sulfhydryl](#); Paget MSB, Buttner MJ 2003 Annu Rev Genet 37:91.

Thiopurine-S-Methyltransferase (TPMT): An enzyme, which can inactivate mercaptopurine and azathiopurine drugs, and is used for controlling cancerous growth. If the gene encoding TPMT is deficient for two of the same alleles (homozygous), excessive amounts of the drugs may accumulate and lead to potentially lethal hematopoietic toxicity unless much reduced (5–10% of the usual) doses are administered to the affected individuals. ▶[azathiopurine](#), ▶[mercaptopurine](#); Evans WE 2002 Pharmacogenetics 12:421.

Thioredoxins (TRX): ~12 kDa dithiol proteins that mediate the reduction of disulfide bonds in proteins. Also, light regulates photosynthesis through reduced thioredoxin, linked to the electron transfer chain by ferredoxin. Light also modulates translation in the chloroplast by redox potential. In insects it may substitute for glutathione reductase. Histone deacetylase inhibitors (suberoylanilide hydroxamic acid, and a benzamide) cause an accumulation of reactive oxygen species (ROS) and activation of caspases in cancer cells but not in normal cells. In normal cells, thioredoxin, a reducing agent, accumulates due to histone deacetylase inhibition but this does not happen in transformed cells. Thus, a selective apoptosis results, indicating therapeutic potentials (Ungerstedt JS et al 2005 Proc Natl Acad Sci USA 102:673). The thioredoxin domain of *E. coli* processivity factor represents a molecular switch, which regulates interaction of T7 DNA polymerase with other proteins of the replisome (Hamdan SM et al 2005 Proc Natl Acad Sci USA 102:5096). ▶[photosynthesis](#), ▶[photosystems](#), ▶[glutaredoxin](#), ▶[lysosomes](#), ▶[pullulanase](#), ▶[oxidative stress](#),

►processivity, ►replisome; Yano H et al 2001 Proc Natl Acad Sci USA 98:4794.

Thiostrepton ($C_{72}H_{85}N_{19}O_{18}S_5$): An antibiotic, binding to *E. coli* rRNA and 10 folds less effectively to yeast ribosomes. (See Porse DT et al 1998 J Mol Biol 276:391).

Thiotepa: An alkylating agent, formerly also used as an antineoplastic drug. It induces a very high frequency of sister-chromatid exchange. ►alkylating agent, ►sister chromatid exchange

Thiouracil: RNA base analog, carcinogen (?). Thiouracil—just as uracil—can base-pair with both adenine and guanine, while the analog-containing nucleic acids show enhanced resistance to nucleases and display increased thermostability. 2-Thiouridine regularly occurs at the first anticodon position (s^2 -U34) in place of uridine in the glutamate, lysine, and glutamine tRNAs. Thiouridine assures appropriate wobble for precise translation on the ribosome. The modified s^2 -U is also required for the proper assembly of the HIV-1 viral genome and for the viral reverse transcriptase primer. 4-Thiouridine (s^4 -U8) can be found at the junction of the acceptor stem and D stem of the tRNA (see Fig. T48).

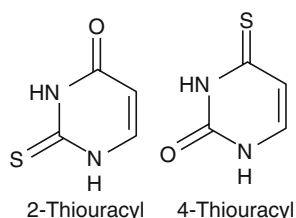


Figure T48. Left: 2-thiouracil; right: 4-thiouracil

In *E. coli*, the MnmAS thiouridylase synthesizes s^2 -U with the aid of IscS desulphurase, which eliminates sulphur from L-cysteine. S is then transferred to MnmA via the Tus relay and it is incorporated in a precise manner into the correct tRNA site. The structural bases of the complex process was revealed by Numata T et al 2006 (Nature [Lond] 442:419). ►antisense technology, ►anticodon, ►tRNA, ►wobble, ►Tus, ►acquired immunodeficiency syndrome; Diop-Frimpong B et al 2005 Nucleic Acids Res 33:5297.

Third Messengers: Third messengers propagate signals of the second messenger and thus activate or deactivate a series of genes. ►second messenger

Thomsen Disease: ►myotonia

Thorax: The chest of mammals, the segment behind (posterior) the head in *Drosophila*.

Threading: A combinatorial alignment of amino acid sequences and DNA base sequences. On this basis a quantitative measure of protein-DNA binding can be derived statistically using, e.g., the Z score. The process permits a conclusion with regard to macromolecular structure. ►Z, ►binding protein; Papaleo E et al 2005 J Mol Model 21:1.

Three-Hybrid System: A construct that detects the role of RNA-protein interactions (see Fig. T49). ►two-hybrid system, ►one-hybrid binding assay, ►split-hybrid system; Koloteva-Levine N et al 2002 FEBS Lett 523:73.

Three M Syndrome (6p21.1): An intrauterine and postnatal growth retardation anomaly caused by impaired endovascular trophoblast invasion and reduced placental perfusion. It is caused by mutations in gene CUL7, which assembles the E3 ubiquitin

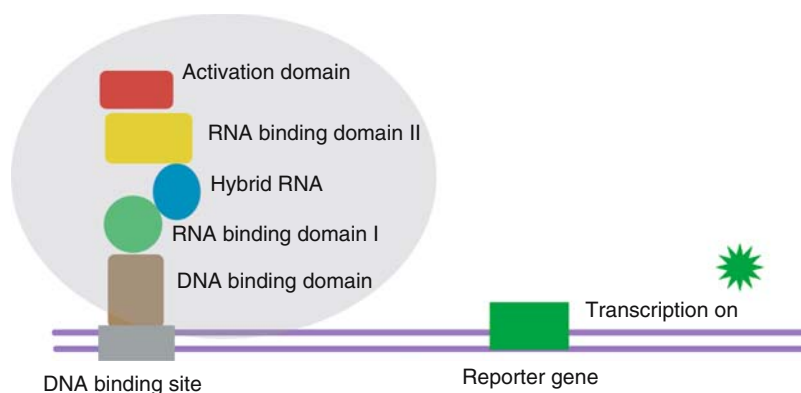


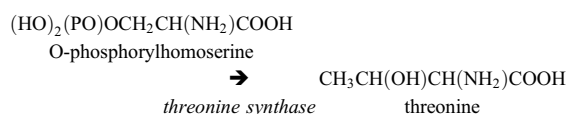
Figure T49. Three-hybrid system. The DNA-binding domain (e.g., LexA bacterial protein), the RNA-binding domain (e.g., MS2 phage coat protein), the top-binding proteins contain an RNA binding domain (e.g., IRP1[iron-response element]), and an activation domain (e.g., Gal4). The hybrid RNA (two MS2 phage RNAs) links the proteins together and in case of function the reporter gene (e.g., *LacZ*) is turned on. (Modified after Gupta DJS et al 1996 Proc Natl Acad Sci USA 93:8496)

ligase complex (Skp1, Fbx29 and ROC). ►ubiquitin; Huber C et al 2005 Nature Genet 37:1119.

Three-Point Testcross: The three-point testcross uses three genetic markers and thus permits the mapping of these genes in a linear order. ►mapping genetic, ►testcross

Three-Way Cross: A three-way cross is one in which a single-cross (the F₁ hybrid of two inbred lines) is crossed with another inbred. The purpose is to test the performance of the single-cross. ►combining ability

Threonine: This amino acid is derived from oxaloacetate via aspartate and immediately from:



Threonine dehydratase degrades threonine into α -ketobutyrate and NH_4^+ ; and then, after another five steps, isoleucine is produced from α -ketobutyrate. The first of these steps is mediated by threonine deaminase. ►isoleucine-valine biosynthetic steps, ►threoninemia

Threonyl tRNA Synthetase (TARS): TARS charges tRNA^{Thr} by threonine. It is encoded in human chromosome 5 in the vicinity of leucyl tRNA synthetase gene. ►aminoacyl-tRNA synthetase

Threose: A D-aldose sugar synthesized from D-glyceraldehyde (see Fig. T50).

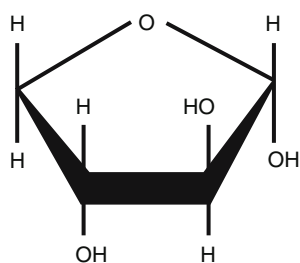


Figure T50. Threose

Threose DNA: A synthetic molecule containing threose in place of deoxyribose (see Fig. T51).

Threose DNA and RNA are capable of base pairing despite the presence of the sugar analog.

Threshold Traits: Threshold traits are expressed conditionally when the liability reaches a certain level. These characters are frequently under polygenic control and yet they may fall into two recognizable classes—irrespective of whether they exhibit it or

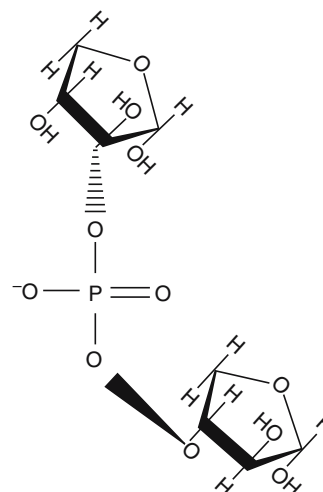


Figure T51. Threose DNA

not—although with special techniques more classes may be revealed. Many pathological syndromes may fall into this category thereby making it very difficult to determine the genetic control mechanisms. ►syndrome, ►liability

Thrombasthenia: Autosomal dominant and autosomal recessive forms involving a platelet defect causing anemia and bleeding after injuries. The recessive form was assigned to human chromosome 17q21.32. ►platelet, ►anemia, ►thrombophilia

Thrombin (fibrinogenase): A serine protease enzyme that converts fibrinogen to fibrin and causes hemostasis (blood clotting). Thrombin also plays another role of an anticoagulant by the proteolytic activation of protein C in the presence of Ca^{2+} . These seemingly conflicting functions are modulated by allosteric alteration brought about by Na^+ and the thrombomodulin protein, changing the substrate-specificity of thrombin. The level of the activated protein C is further increased by a compound named LY254603. The protease-activated G protein-coupled receptor of thrombin (PAR1) is vitally important for embryonic development of mice. ►fibrin, ►fibrin-stabilizing factor deficiency, ►hemostasis, ►antihemophilic factors, ►plasmin, ►protein C, ►PAR, ►anticoagulation; Coughlin SR 2000 Nature [Lond] 407:258; Griffin CT et al 2001 Science 293:1666; carcinogenesis regulation by thrombin: Nierodzik ML, Karparkin S 2006 Cancer Cell 10:355.

Thrombocytes: The same as platelets.

Thrombocytopenia (TAR syndrome): An autosomal dominant bleeding disease (10p11.2-p12) caused by low platelet counts. Autosomal recessive (11q23.3-qter deletion and 21q22.1-q22.2) forms are associated with heart and kidney anomalies and absence of the

radius (the thumb side arm bone), phocomelia, etc. Another thrombocytopenia is linked in human chromosome Xp11. It is allelic to the Wiskott-Aldrich gene, WAS. Mutation in GATA1 may also cause the disease. The May-Hegglin anomaly, Fechtner syndrome, and the Sebastian syndrome involve macrothrombocytopenia (giant platelets) and leukocyte inclusions besides some specific symptoms. All three of these diseases show mutations in non-muscle myosin heavy chain 9. In some instances, the Epstein syndrome and the Alport syndrome display macrothrombocytopenia. ▶[Holt-Oram syndrome](#), ▶[Roberts syndrome](#), ▶[phocomelia](#), ▶[Wiskott-Aldrich syndrome](#), ▶[thrombopathic purpura](#), ▶[May-Hegglin anomaly](#), ▶[Alport disease](#), ▶[Kassabach-Merritt syndrome](#), ▶[GATA](#), ▶[dyserythropoietic anemia](#), ▶[platelets](#), ▶[giant platelet syndrome](#), ▶[radioulnar synostosis](#); Heath KE et al 2001 *Am J Hum Genet* 69:1033.

Thrombomodulin: ▶[thrombin](#), ▶[anticoagulation](#)

Thrombopathia (essential athrombia): A collection of blood clotting anomalies caused by problems in aggregation of the platelets. ▶[platelet abnormalities](#), ▶[hemophilias](#), ▶[hemostasis](#)

Thrombopathic/Thrombocytopenic Purpura (TTP, called also von Willebrand-Jürgen's syndrome, 9q34): TTP is caused by an autosomal recessive condition with symptoms resembling the bleeding and platelet abnormalities present in the Glanzmann's disease. The primary defect may involve the platelet membrane. Other symptoms may vary from case to case. Blood transfusion may shorten the time of bleeding. The basic defect is in the ADAMS13 zinc metalloproteinase genes. ▶[platelet abnormalities](#), ▶[hemophilias](#), ▶[hemostasis](#), ▶[thrombocytopenia](#), ▶[Glanzmann's disease](#); Levy GG et al 2001 *Nature [Lond]* 413:488.

Thrombophilia: A complex blood clotting disease that may occur as a consequence of mutation in any of the genes of antithrombin III, protein C, protein S, antihemophilic factor V, plasminogen, plasminogen activator inhibitor, fibrinogens, heparin cofactor, thrombomodulin, etc. Mutation at the 3'-untranslated region of the prothrombin gene may result in increased mRNA levels and protein synthesis due to this gain-of-function and to the disease. See separate entries, ▶[giant platelet syndrome](#), ▶[prothrombin deficiency](#); Gehring NH et al 2001 *Nature Genet* 28:389.

Thromboplastin: ▶[antihemophilic factors](#)

Thrombopoietin: Thrombopoietin regulates blood platelet formation and megakaryocytopoiesis. It is member of a cytokine receptor superfamily and it is similar to erythropoietin and granulocyte colony-stimulating factor receptors. In the brain, it is pro-apoptotic

(Ehrenreich H et al 2005 *Proc Natl Acad Sci USA* 102:862). ▶[megakaryocytes](#), ▶[platelet](#), ▶[erythropoietin](#), ▶[thrombocytopenia](#), ▶[G-CSF](#), ▶[apoptosis](#); Kato T et al 1998 *Stem Cells* 16:322; structure of receptor-binding domain: Feese MD et al 2004 *Proc Natl Acad Sci USA* 101:1816.

Thrombosis: A type of obstruction in blood flow caused by the aggregation of platelets, fibrin, and blood cells. Thrombosis may be caused by mutation in serpin. Antihemophilic factors V, VII, VIII, IX, XI, XII, the von Willebrand disease, tissue plasminogen activator, homocysteine and the activated protein C ratio display a genetic correlation with the incidence of thrombosis. ▶[antihemophilic factors](#), ▶[serpin](#), ▶[protein C](#), ▶[protein C deficiency](#), ▶[thrombocyclins](#), ▶[protein C](#), ▶[protein S](#), ▶[APC](#), ▶[cyclooxygenase](#), ▶[serpin](#), ▶[plasminogen activator](#); Souto JC et al 2000 *Am J Hum Genet* 67:1452.

Thrombospondin (THBS): Thrombospondin are glycoprotein inhibitors of angiogenesis. THBS1 (15q15) is a 180-K MW platelet membrane protein occurring on the endothelium, fibroblasts, and smooth muscles. THBS2 (6q27) binds thrombin, fibrinogen, heparin, plasminogen, etc. THBS2 functions as a tumor inhibitor by curtailing angiogenesis. Immature astrocytes express THBS and thereby promote synaptogenesis in the central nervous system (Christopherson KS et al 2005 *Cell* 120:421). ▶[angiogenesis](#), ▶[apoptosis](#), ▶[COMP](#); Hawighorst T et al 2001 *EMBO J* 20:2631; Rodríguez-Manzanique CC et al 2001 *Proc Natl Acad Sci USA* 98:12485; Adams JC 2001 *Annu Rev Cell Dev Biol* 17:25.

Thrombotic Disease: ▶[protein C deficiency](#)

Thromboxanes: Thromboxanes induce the aggregation of platelets and act as vasoconstrictors. They are antagonists of prostacyclin G₂ and may mediate intrauterine growth retardation. ▶[cyclooxygenase](#), ▶[prostaglandins](#)

Thumb: ▶[DNA polymerase](#)

Thy-1: A 19–25 kDa, single-chain glycoprotein expressed on mouse thymocytes but not on mature T cells of humans or rats.

Thylakoid: Thylakoids are flat, sac-like internal chloroplast membranes; when stacked they look like grana. Diacylglycerol galactolipids are common in these membranes but are absent from others. An estimated 80 proteins constitute the intra-thylakoid lumen. ▶[grana](#), ▶[chloroplast](#), ▶[girdle bands](#), (see Fig. T52); Dalbey RE, Kuhn A 2000 *Annu Rev Cell Dev Biol* 16:51; Schubert M et al 2002 *J Biol Chem* 277:8354; Kóta Z et al 2002 *Proc Natl Acad Sci USA* 99:12149.

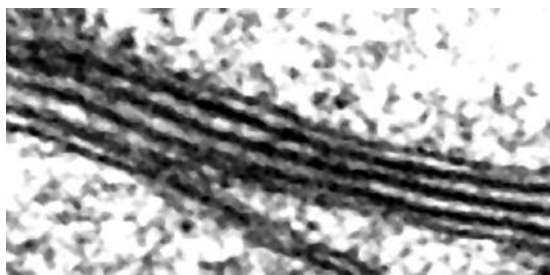


Figure T52. Thylakoids

Thymidine: A nucleoside of thymine; thymine plus pentose (deoxyribose or ribose). (See formula of thymine at T).

Thymidine Kinase (thymidine phosphorylase): ▶TK

Thymidylate Synthetase: Thymidylate synthetase mediates the synthesis of thymidylic acid (dTMP) from deoxyuridine monophosphate (dUMP). Its gene is assigned to human chromosome 18p11.32. Its inhibition may lead to apoptosis. A number of nonsymbiotic archaea and bacteria lack this enzyme and use another protein, dependent on reduced flavin nucleotides rather than tetrahydrofolate as the source for reduction, as is the case in the majority of organisms. This is not a part of the salvage pathway. Thymidylate synthase may play an indirect role in carcinogenesis. ▶apoptosis, ▶salvage pathway, ▶synthase; Myllykallio H et al 2002 Science 297:105.

Thymidylic Acid (nucleotide of thymine): Thymine + pentose + phosphate.

Thymine: A pyrimidine base occurring almost exclusively in DNA. An exception is the T-arm of tRNA. ▶tRNA, ▶pyrimidines, formula at T.

Thymine Dimer: UV light-induced damage in DNA, covalently cross-linking adjacent thymine residues through their 5 and 6 C atoms. This cyclobutane structure interferes with the replication and other functions of the DNA. Cytidine and uridine can also form similar dimers. The dimers can be eliminated by enzymatic excision and replacement replication (excision or dark repair). Alternatively, the dimers can be split by DNA photolyase, an enzyme that is activated by visible light maximally at 380-nm wavelength (light repair). ▶DNA repair, ▶cyclobutane dimer, ▶pyrimidine-pyrimidinone photoproduct, ▶cys-syn dimer, ▶DNA polymerases; Medvedev D, Stuchebrukhov AA 2001 J Theor Biol 210:237.

Thymocytes: Thymocytes are precursors of T lymphocytes. Bone marrow stem cells migrate into the thymus and, in response to antigens, develop from

naïve $CD4^-CD8^-$ cells with the cooperation of the T cell receptors into double positive $CD4^+CD8^+$ cells that undergo clonal selection with the assistance of MHC molecules and eventually become specific T cells. ▶T cell, ▶T cell receptor, ▶MHC, ▶antigen presenting cells, ▶immune system, ▶memory immunological, ▶thymus

Thymoma: A cancer of the thymus. ▶AKT oncogene

Thymosins: A group of about 40 different proteins with an apparent immune-boosting ability. Thymosin $\alpha 1$ consists of 28 amino acids and thymosin $\beta 4$ contains 43. They may have therapeutic values. $\beta 4$ binds monomeric actin and prevents its polymerization into filaments. Its expression increases when cancer cells metastase. ▶actin, ▶metastasis; Hall NR, O'Grady MP 1989 Bioessays 11:141; Goldstein AL, Garaci E (Eds.) 2007 Thymosins in Health and Disease Ann NY Acad Sci 1112.

Thymus: A bilobal organ with three functionally important compartments—the subcapsular zone, the cortex and the medulla. The immature lymphoid cells coming from the bone marrow invade it. The subcapsular space contains most of the immature $CD4^-$ and $CD8^-$ lymphoid stem cells. When they enter the cortex they begin to express the CD molecules and they rearrange the T cell receptors and form the different TCR $\alpha\beta$ heterodimers. Defects in the genes of *Foxn1* and *Aire* of mouse cause immunodeficiency and autoimmunity, respectively. The epithelial cells in the cortex express MHC I and MHC II molecules. The fate of the T cell will be determined here in response to the MHC molecules carried by the antigen-presenting cells (thymic selection). The $CD4^+CD8^-$ cells with TCR recognizing the MHC II complex, or the $CD4^-CD8^+$ with TCR specific for MHC I will leave the thymus and populate the secondary lymphoid tissue. Those cells that do not acquire self-peptide-MHC specificity are eliminated. Those with strong avidity for self-peptide MHC die by apoptosis because they would be autoreactive (non-autoimmune). Aging (involution) reduces the thymic tissues and it was thought that this lead to a loss in their activity too. In the thymus, developing, autoreactive T cells undergo negative selection. Vascularized thymic lobe grafts from juvenile donors were capable of inducing tolerance in thymectomized juvenile hosts. Also, the aged, involuted thymus, transplanted as a vascularized graft into juvenile recipients, leads to rejuvenation of both thymic structure and function, suggesting that factors extrinsic to the thymus are capable of restoring juvenile thymic function to aged recipients. A rejuvenated aged thymus has the ability to induce transplant tolerance across class I MHC barriers

indicating that it may be possible to manipulate thymic function in adults to induce transplantation tolerance after the age of thymic involution (Nabori S et al 2006 Proc Natl Acad Sci USA 103:19081).

Newer evidence indicates the thymus can generate new peripheral T cells after antiviral treatment of HIV patients. In mice, a second lymphoid thymic structure may be present in the neck (cervical thymus) and its function is very similar to the thoracic thymus although its number of thymocytes is $\sim 1.6 \times 10^5$ whereas in the thoracic organ it is $\sim 10^8$ (Terszowski G et al 2006 Science 312:284). In the C57BL/6 strain, cervical thymus occurs in about 50% whereas in BALB/c mice its occurrence is in over 90%. ▶ **T cells**, ▶ **T cell receptor**, ▶ **TCR genes**, ▶ **MHC**, ▶ **autoimmune**, ▶ **spleen**, ▶ **HIV**, ▶ **nude mice**

Thyroglobulin: An iodine containing protein in the thyroid gland and has a hormone-like action upon the influence of the pituitary hormone. ▶ **animal hormones**

Thyroid Carcinoma: The transforming sequence was localized to human chromosome 10q11-q12, and a tumor suppressor gene in human chromosome 3p may be involved. Susceptibility loci to nonmedullary thyroid carcinoma have been revealed at 2q21, 19p13.2 and 1q21 (McKay JD et al 2001 Am J Hum Genet 69:440).

Thyroid Hormone Resistance: Dominant hyperthyroxinemia mutations (ERBA2) due to defects in the thyroid hormone receptor (3p24.3). (See Tsai MJ, O'Malley BW 1994 Annu Rev Biochem 63:451).

Thyroid Hormone Responsive Element: ▶ **TRE**, ▶ **hormones**, ▶ **hormone response elements**, ▶ **regulation of gene activity**, ▶ **goiter**

Thyroid hormone unresponsiveness: Autosomal recessive in humans. ▶ **hyperthyroidism**

Thyroid Peroxidase Deficiency (TPO): A group of recessive human chromosome 2p13 defects involving the incorporation of iodine into organic molecules.

Thyroid Stimulating Hormone (TSHB, 1p13): The β -chain and its deficiency leads to hypothyroidism, goiter, and cretinism. It also regulates both bone formation and bone resorption. ▶ **goiter**, ▶ **osteoporosis**

Thyroid Transcription Factor: The TTF-2 defect is responsible for thyroid agenesis and cleft palate in mice and the human homologue, FKHL1 (9q22), also controls the same functions and also choanal atresia (closure of the nasal passageways).

Thyronine (3p-[p(p-hydroxyphenoxy)-phenyl]-L-alanine): A component of the thyroglobulin of the

thyroid hormone. It generally occurs as 3,5,3'-triiodothyrosine. ▶ **VDR**

Thyrotropic: Affecting (targeting) the thyroid gland.

Thyrotropin: A thyrotropin deficiency is apparently due to a defect in the thyroid stimulating hormone β -chain defect at 1p13. Deficiency of the thyrotropin-releasing hormone (TRH, 3q13.3-q21) results in hypothyroidism and various malformations including defects in the development of the central nervous system. Hyperthyroidism may involve fast pulsation of the heart and goiter and adenoma. Hyperthyroidism may be transient during pregnancy. ▶ **goiter**, ▶ **adenoma**

Thyroxine: ▶ **goiter** (see Fig. T53)

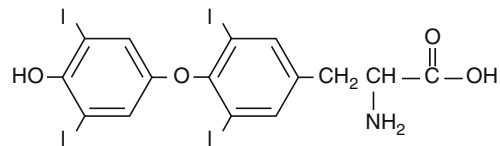


Figure T53. Thyroxine

Thyroxine-Binding Globulin (TBG, Xq22.2): A deficiency of the thyroxine-binding globulin generally does not lead to disease although in Graves disease it may be more common. ▶ **goiter**, ▶ **Graves disease**

TI Antigens: TI antigens stimulate antibody production independently of T cells and in the absence of MHC II molecules. The TI type 2 (TI-2) has polysaccharide antigens, which are usually large molecules with repeating epitopes that activate the complement and are rather stable. The TI-1 type is mitogenic for mature and neonatal B cells. ▶ **antigen**, ▶ **antibody**, ▶ **T cell**, ▶ **MHC**; Vinuesa CG et al 2001 Eur J Immunol 31:1340.

Ti Plasmid: A large (about 200 kbp) tumor-inducing plasmid of *Agrobacterium tumefaciens*.

It is responsible for the crown gall disease of dicotyledonous plants. There are a few particularly important regions in this plasmid. The T-DNA of the octopine plasmid shown is divided into the left (T_L) and right (T_R) segments and is flanked by the two border sequences (B_L and B_R); in-between are several genes. The nopaline-type Ti plasmid (pTiC58) has only a single 20 kb T-DNA. The virulence gene cascade, and its function, is described under virulence genes of *Agrobacterium*. The origin of vegetative replication (*oriV*) is functioning during proliferation of the cells; the nearby Inc (incompatibility) site determines host-specificity. The *oriT* is the origin of replication operated on during conjugation. The latter is often called bom (base of mobilization) or CON

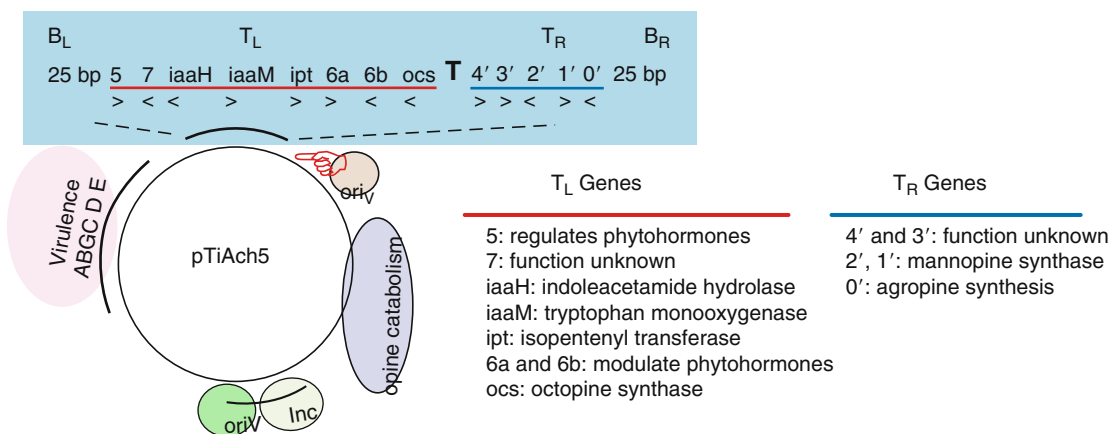


Figure T54. Major landmarks of the Ti octopine plasmid, pTiACH5. Arrowheads indicate the direction of transcription. T marks the T_L-T_R boundary

(conjugation) because the synthesis of the transferred DNA begins there. The actual transfer starts when the mob site encoded protein (Mob, synonym Tra) attaches to a specific nick site, a single-strand cut, and one of the strands (the T-strand) is transported to the recipient bacterial cell through the cooperation of some pore proteins. The oriT and Mob complex includes proteins TraI, TraJ, and TraH. TraJ attaches to a 19 bp sequence in the vicinity of the nick and binds also TraI, which is a topoisomerase. TraH promotes these bindings. The process is a rolling circle type replication and transfer. The integrity of virulence genes *virD* and *virB* are absolutely required for productive conjugation (see Fig. T54). ▶*Agrobacterium*, ▶T-DNA, ▶virulence genes of *Agrobacterium*, ▶transformation, ▶rolling circle, ▶conjugation; Hellens R et al 2000 Trends Plant Sci 5:446; Suzuki K et al 2000 Gene 242:331.

TIBO (O-TIBO and CI-TIBO): The non-nucleoside (benzothiadiazepin-derivatives) inhibitors of HIV-1 reverse transcriptase. ▶Nevirapine, ▶acquired immunodeficiency syndrome, ▶AZT

TIC (translation initiator-dependent cofactor): ▶TAF

TID50: A 56 kDa mitochondrial protein of *Drosophila*, encoded at 2–104 in the nucleus by the *l(2)Tid* tumor suppressor gene. It is homologous to the DnaJ chaperone. ▶chaperones, ▶DnaK, ▶tumor suppressor factors

Tie1, Tie2: Receptor tyrosine kinases, expressed during endothelial cell growth and differentiation of the blood vessels. ▶vascular endothelial growth factor, ▶Flk-1, ▶Flt-1, ▶tyrosine kinase, ▶transmembrane proteins, ▶signal transduction; Lin TN et al 2001 J Cereb Blood Flow Metab 21:690.

Tier: An ordered arrangement by increasing stringency of a series of tests, e.g., the first tier provides an overview of potential mutagens but subsequent tiers (using different techniques) may be necessary for clearance even when the first test might have been negative. Each tier may provide a different weight of evidence.

TIF1-α: Interacts with the steroid hormone receptor. ▶steroid hormones, ▶hormone receptors

TIF1-β: A transcription initiation factor of mouse binding to the core promoter of rRNA genes and controlling RNA polymerase I function. TIF1β is a component of the histone deacetylase complex. ▶transcription factors

TIF1-γ (TRIM33/RFG7/PTC7/Ectodermin): A Transcriptional Intermediary Factor, a protein that selectively binds receptor-activated Smad 2 and Smad 3. It mediates erythroid differentiation in response to TGFβ (He W et al 2006 Cell 125:929). ▶Smad, ▶TGF, ▶erythrocyte

Tight Junction (zonula occludens): A tight junction forms a seal between adjacent plasma membranes and provides a barrier to paracellular leakage of membrane lipids and proteins and thus guards cellular polarity (see Fig. T55). Tight junctions are apical domains of polarized epithelial and endothelial cells. The family of PDZ genes includes CLAUDIN 1, encoding a senescence-associated membrane protein; CLAUDIN 3, a *Clostridium perfringens* receptor [7q11]; CLAUDIN 4, a *C. p.* enterotoxin receptor; CLAUDIN 5, a velocardiofacial syndrome protein [22q11.2]; CLAUDIN 11, which mediates sperm and nerve functions [3q26.2-q26.3]; CLAUDIN 14, a deficiency responsible for deafness [21q22.3]; and CLAUDIN 16, which encodes paracellin, a paracellular

conductance protein associated with hypo-magnesia [3q27]; and others that are distributed over the genome. ZO-1 and ZO-2 proteins determine where the claudins are polymerized (Umeda K et al 2006 Cell 126:741). ▶deafness, ▶velocardio facial syndrome, ▶infertility, ▶PDZ; Tsukamoto T, Nigam SK 1999 Am J Physiol 276:F737; Tsukita A et al 2001 Nature Rev Mol Cell Biol 2:285; Gonzalez-Mariscal L et al 2003 Progr Biophys Mol Biol 81:1.

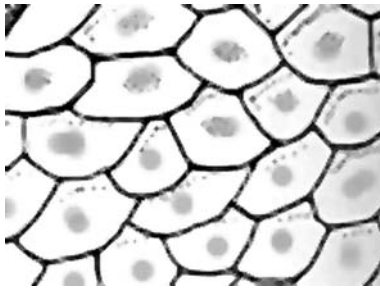


Figure T55. Tight junction of epithelial cells

Tiger (*Panthera tigris*): $2n = 38$. The tiger cat (*Leopardus tigrina*): $2n = 36$.

Tiglic Acid: A methyl-2-butenic acid. It is present with geranyl in the ornamental geranium and as an ester in the oil of chamomile (*Matricaria chamomilla*), a herbal medicine used as a tea or disinfectant.

Tiglicacidemia: A defect in the degradation of isoleucine to propionic acid leading to large amounts of tiglic acid accumulating in the urine.

TIGR: The Institute for Genomic Research in Rockville, MD, USA. ▶databases

TIL: ▶tumor infiltrating lymphocytes

Tiling: Generating a longer (minimally overlapping) DNA fragment map spanning the overall length of the genome or chromosome. By tiling, the transcribed sequences of the nucleus, chloroplast and mitochondria have been identified in *Arabidopsis* (Stolc V et al 2005 Proc Natl Acad Sci USA 102:4453). ▶physical map, ▶contig, ▶DNA crystals, ▶sequence-tagged connectors, ▶genome project, ▶scaffold in genome sequencing, ▶TUF, ▶noncoding RNA; Siegel AF et al 1999 Genome Res 9:297; Bertone P et al 2004 Science 306:2242; transcript maps: Cheng J et al 2005 Science 308:1149; Emanuelsson O et al 2007 Genome Res 17:886.

Tiling Microarrays: In microarray hybridization overlapping nucleotide sequences are used. ▶microarray hybridization

Tiling Path Array: A tiling path array includes a set of minimally overlapping clones.

Tiller: A lateral shoot of grasses arising at the base of the plant. (See Li X et al 2003 Nature [Lond] 422:618).

Tilling (targeting induced local lesions in genomes): Attempts to induce mutations by chemical mutagens (e.g., ethylmethane sulfonate) and use of denaturing high-performance liquid chromatography (DHPLC) to detect base alterations by heteroduplex analysis. By such a procedure 246 *waxy* alleles were identified in wheat. This holds promise of useful modifications without transgenic methods (Slade AJ et al 2004 Nature Biotechnol 23:75). ▶ethylmethanesulfonate, ▶HPLC, ▶*wx* gene, ▶heteroduplex; McCallum CM et al 2000 Nature Biotechnol 18:455; Till BJ et al 2003 Genome Res 13:524; <http://tilling.fhcrc.org:9366/>.

TIM (transfer inner membrane): A protein complex that regulates the import of proteins into mitochondria. ▶mitochondria, ▶TOM; Meinecke M et al 2006 Science 312:1523.

Time of Crossing Over: The time of crossing over appears to coincide with the meiotic prophase (late leptotene and early diplotene, probably at zygotene). Some experimental data indicate that treatments at S phase have an effect on the outcome. It is difficult to assess, however, whether these effects are direct or indirect. Meiosis is under the control of a long series of genes acting sequentially and cooperatively and any of these may affect crossing over. ▶crossing over, ▶recombination, ▶recombination mechanisms; Allers T, Lichten M 2001 Cell 106:45.

Time-Lapse Photography: Time-lapse photography records events continuously as they take place in time.

Timeless (Tim): A protein of *Drosophila* involved in the circadian clock. ▶circadian clock

Timothy Syndrome (long QT syndrome, 12p13.3): A calcium ion channel defect leading to Ca^{2+} accumulation in the cells. It causes a variety of abnormalities such as heart arrhythmia, webbed fingers and toes, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism (Splawski I et al 2004 Cell 119:19; Splawski I et al 2005 Proc Natl Acad Sci USA 102:8089). ▶QTL

TIMP (tissue inhibitor metalloproteinase): ▶metalloproteinases, ▶night blindness [Sorsby], Brew K et al 2000 Biochim Biophys Acta 477:267.

Tinkering in Evolution: The idea that evolution does not precede on the basis of purposeful plans; rather, it uses the means at hand at a particular stage. ▶evolution; Jacob F 2001 Ann NY Acad Sci 929:71.

TIP: Also known as tumor-inducing principle. ▶ *Agrobacterium*

TIP (tail-interacting protein): TIP47 (47 kDa) recognizes the cytoplasmic domains of mannose-6-phosphate and binds to Rab9. It facilitates the endosome to Golgi transport and recruits effector proteins for appropriate membrane targeting. ▶ *RAB*, ▶ *mannose-6-phosphate receptor*, ▶ *Golgi*, ▶ *endosome*; Carroll KS et al 2001 Science 292:1373.

TIP (T cell immunomodulatory protein): The T cell immunomodulatory protein causes secretion of IFN- γ , TNF- α and IL-10 in vitro; in vivo it protects against the host-versus-graft disease. ▶ *IFN*, ▶ *TNF*, ▶ *IL-10*, ▶ *host-versus-graft disease*; Fiscella M et al 2003 Nature Biotechnol 21:302.

TIP60 (HIV-1 Tat-interacting protein, 11q13): The 60 kDa regulator of HIV gene expression is a product of TIP60 (Kamine J et al 1996 Virology 216:357). The *Drosophila* TIP60 phosphorylates histone variant H2AX in case of DNA damage and remodels the chromatin by acetylation and replacement of H2A by an H2A variant (Kusch T et al 2004 Science 306:2084). ▶ *acquired immunodeficiency*, ▶ *prostate cancer*

Tipping Point: An epidemiological concept when treatment reaches a critical level resulting in a qualitative change, a turning of the tide of infections or inflammation (immune reaction) or the spread of the disease. It is a critical physiological stage in between health and disease.

TIR: Terminal inverted repeats as occurring in transposons ABCD—DCBA. It appears that hobo, Ac, TAM transposable elements have similar amino acid sequences although they occur in fungi, animals, and plants (Calvi BR et al 1991 Cell 66:465).

TIRAP (Mal): A PIP2 domain-containing adaptor controlling Toll-like receptor (TLR) signaling. It recruits MyD88 to TLR (Kagan JC, Medzhitov R 2006 Cell 125:943). Heterozygosity for leucine substitution at Ser180 in TIRAP attenuates Toll-like receptor signaling and increases resistance to infectious disease conveyed by *Plasmodium*, pneumococcal disease, bacteremia, and tuberculosis in diverse populations (Khor CC et al 2007 Nature Genet 39:523). ▶ *Toll*, ▶ *Toll-like*, ▶ *Plasmodium*, ▶ *Diplococcus/Pneumococcus*, ▶ *mycobacteria*, ▶ *PIP2*, ▶ *MyD88*

TIS1: ▶ *nur77* and ▶ *NGFI-B*

TIS-8: A mitogen-induced transcription factor. ▶ *NGFI-A*, ▶ *egr-1*

TIS11: A transcription factor, inducible by various hormones (similar to Nup475). ▶ *Nup475*

TIS11b: A murine homolog of cMG1. ▶ *cMG1*

TIS11d: A transcription factor with 94% identity to 367 amino acids in TIS11b. ▶ *TIS11b*

Tiselius Apparatus: An early model of electrophoretic separation equipment.

Tissue Culture: The in vitro culture of isolated cells of animals and plants. ▶ *cell culture*, ▶ *cell genetics*, ▶ *organ culture*, ▶ *cell fusion*, ▶ *somatic cell fusion*, ▶ *embryogenesis somatic*, ▶ *axenic*, ▶ *aseptic*

Tissue Engineering: The purposeful culture of stem cells for producing tissues and organs. For example, long-lasting blood vessels can be formed in mice by co-implantation of vascular endothelial cells and mesenchymal precursor cells. Submillimeter size collagen rods, seeded with endothelial cells, could be assembled into a man-made vascular system that permits percolation of blood through it. Such a construct is expected to be suitable for supplying blood into tissue without thrombosis, would delayed clotting time and inhibit loss of platelets (McGuigan AP, Sefton MV 2006 Proc Natl Acad Sci USA 103:11466).

Another approach is to deliver signaling molecules and cells on a three-dimensional scaffold that supports cell infiltration and tissue organization. Artery bypass experiments have shown that nanofibrous scaffolds allowed efficient infiltration of vascular cells and matrix remodeling. Acellular grafts without mesenchymal stem cells (MSCs) resulted in significant intimal thickening, whereas cellular grafts (with MSCs) had excellent long-term patency and exhibited well-organized layers of endothelial cells (ECs) and smooth muscle cells (SMCs), as in native arteries. Short-term experiments showed that nanofibrous scaffolds alone induced platelet adhesion and thrombus formation, which was suppressed by MSC seeding. Cell-seeded scaffolds provide proper environment for native tissue-like environment and can be well aerated at a small scale (Hashi CK et al 2007 Proc Natl Acad Sci USA 104:11915). Soft lithography permits the control of surface topography and spatial distribution of molecules on scaffold surfaces.

Replica molding of biocompatible polymers from patterned silicon wafers constructed from poly(dimethylsiloxane) (PDMS) or poly(DL-lactide coglycolide) (PLGA) or poly(glycerol sebacate) (PGS) are used. Hydrogels with gradients of signaling or adhesive molecules or various cross-linking densities can provide means for migration, adhesion, and

differentiation. Microfluidic technology can be employed on PLGA surfaces for the generation of two-dimensional patterns. A microtextured and nanotextured substrate may facilitate the generation of topographical features favoring cell adhesion, gene expression, and migration. For engineering bone tissues, porous ceramic or demineralized bone matrix support with bone marrow-derived mesenchymal cells and/or bone morphogenetic protein have been used with appropriate growth factors. Alternatively, in a space (called bioreactor) between the surface of a long bone and the membrane-rich periosteum (a connective tissue around the bone with the potentials of forming bone tissue) there is a niche for the injection of biocompatible calcium-alginate gel cross-linked in situ and it facilitates reconstitution of the functional living bone. The new microbioreactors provide a suitable niche, proper nutrients, and aeration for tissue fabrication. The engineered bone or liver tissue can then be transplanted to an area where bone tissue replacement is required. By inhibiting angiogenesis and promoting hypoxic conditions cartilage formation occurs (Stevens MM et al 2005 Proc Natl Acad Sci USA 102:11450). The availability of various types of stem cells and regulated culture conditions opens new approaches for the fabrication of special tissues. Experiments are in progress for the use of high throughput technology for tissue engineering. The goal is to replace defective human tissues with man-made tissues of high quality and without the danger of immune rejection. One product, Carticel, has been licensed for therapeutic use. Since 1997 more than 10,000 patients with injured knee cartilage have been treated with this autologous chondrocyte procedure (Parson A 2006 Cell 125:9). This is a very rapidly expanding field and by early 2006 more than 6,600 papers were published worldwide. By 2007, this number exceeded 8,500 although clinical applications are in infancy. ▶**stem cells**, ▶**progenitor**, ▶**anchorage dependence**, ▶**microfluidics**, ▶**lithography**, ▶**biotechnology**, ▶**wound healing**; Shin H et al 2003 Biomaterials 24:4353; Koike N et al 2004 Nature [Lond] 428:138; Nature Mater 3:249; Jakab K et al 2004 Proc Natl Acad Sci USA 101:2864; review: Khademhosseini A et al 2006 Proc Natl Acad Sci USA 103:2480; osteoblast formation: Datta N et al 2006 Proc Natl Acad Sci USA 103:2488; muscle degeneration after in vivo delivery of myoblasts on a scaffold: Hill E et al 2006 Proc Natl Acad Sci USA 103:2494; smooth muscle regeneration was greatly improved by ectopic expression of human telomerase reverse transcriptase transfection: Klinger RY et al 2006 Proc Natl Acad Sci USA 103:2500; review: Atala A 2006 Current Opin Pediatr 18(2):167; review: MacNeil S 2007 Nature [Lond] 445:874.

Tissue Factor (TF): A cell surface glycoprotein mediating blood clotting after injuries by its interaction with the clotting factor VIIa. It is also important for hemostasis, inflammation, angiogenesis, atherosclerosis, and cancer. Protein S has an inhibitory effect. ▶**antihemophilic factors**, ▶**blood clotting pathways**, ▶**Protein S**; Hackeng TM et al 2006 Proc Natl Acad Sci USA 103:3106.

Tissue Microarray (TMA): An adaptation of the microarray hybridization to tissue samples in order to reveal the cellular location of gene activity at the DNA, RNA or protein level. Cylindrical core specimens (biopsies) are acquired from formalin-fixed paraffin-embedded tissues and arrayed into high-density TMA blocks. Archival specimens are also suited for this analysis. Then, up to 300 5 µm sections are prepared for probing with DNA, RNA or protein using in situ hybridization (or FISH) or immunostaining. A single TMA allows the simultaneous study of the targets in thousands of specimens on microscopic slides. By TMA on a single slide the activity of one gene can be analyzed in 1000 tissue specimens. By microarray hybridization thousands of genes can be probed from a single tissue. TMA can be used to study cancerous tissue but it is not suitable for clinical diagnostics. This technique permitted the identification of some common transcriptional mechanisms in various types of cancer (Rhodes DR et al 2004 Proc Natl Acad Sci USA 101:9309) ▶**microarray hybridization**, ▶**FISH**, ▶**immunostaining**; Kallioniemi O-P et al 2001 Hum Mol Genet 10:657; ONCOMINE: <http://www.oncomine.org/meta>.

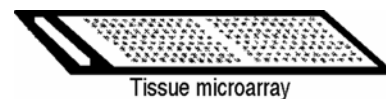


Figure T56. Tissue microarray

Tissue Plasminogen Activator (tissue plas): A tissue plasminogen activator cleaves plasminogen to plasmin and enhances fibrinolysis; it controls blood coagulation. ▶**blood clotting pathways**, ▶**PARs**

Tissue Remodeling: A coordinated series of events regulated by a balance between tissue proliferation and anti-proliferation factors such as cyclins, cyclin inhibitors and other metabolic regulators. Morphogenesis and various diseases involve alterations/anomalies in these processes. (See Nabel EG 2002 Nature Rev Drug Discovery 1:587).

Tissue-Specific Promoter: A tissue-specific promoter facilitates gene expression limited to certain tissues or organs. ▶**promoter**

Tissue-Specificity: The expression of a gene is limited to certain tissue(s). Tissue-specificity may be controlled at many levels (transcription initiation, differential recruitment of repressors or activators to the gene targets, promoter clearance, attenuator, transcription termination, etc.). The macrophage colony stimulating factor receptor gene is constitutively expressed in many cell types but only in the macrophages is the elongation of the transcripts permitted (see Fig. T57).

The evolutionarily determined size of a gene may have something to do with tissue-specificity. In the extremely fast dividing embryonic tissues the very large genes may not have enough time to be fully transcribed. The proportion of tissue-specific genes has been estimated by transformation of *Arabidopsis* with transcriptional and translational gene fusion vectors. Of the 200 transgenic plants about 10% displayed some degree of tissue-specific expression of the reporter gene (aph[3']). A large number of genes are expressed only in the central nervous system but repressed in other tissues. The REST/NRSF (repressor element silencing transcription factor/neuronal restricted silencing factor) along with the CoREST corepressor recruit histone deacetylase to chromosomal regions in the non-neuronal tissues to accomplish the task (Lunyak VV et al 2002 Science 298:1774). A computational model for the identification of cell-specific genes from the EST database is available (Nelander S et al 2003 Genome Res 13:1838). The identification of cis-regulatory elements and cognate transcription factors, expressed or inhibited in 45/56 different human and mouse tissues, permits a statistically significant predictions for tissue-specificity (Smith AD et al 2006 Proc Natl Acad Sci USA 103:6275). A global survey of specificity of 3,274 mouse proteins in six organs (brain, heart, kidney, liver, lung, and placenta) provides a searchable store for proteomics (see Fig. T58) (Kislinger T et al 2006 Cell 125:173; http://genome.dkfz-heidelberg.de/menu/tissue_db/faq.html). ▶transcription illegitimate, ▶housekeeping genes, ▶macrophage colony stimulating factor, ▶constitutive mutation, ▶aph, ▶subtractive cloning, ▶cascade

hybridization, ▶chromatin remodeling, ▶SATB1, ▶microarray hybridization, ▶isoenzymes, ▶EST, ▶organelle, Appendix II-10; Su AI et al 2002 Proc Natl Acad Sci USA 99:4465.

Tissue Typing: Determining the genetic constitution of a potential graft before transplantation. Blood typing is used. Even better, it can be done by DNA analysis (RFLP) or by polymerase chain reaction. ▶blood typing, ▶DNA fingerprinting, ▶polymerase chain reaction

Titer: The amount of a reagent in titration required for a certain reaction. The number of phage particles per volume determines phage titer by counting the pfu number on a bacterial lawn after a series of dilution. The vector titer is assessed by the expression of a reporter gene (e.g., GFP, galactosidase, luciferase) in the target cells on a plate. Alternatively, special RNA or DNA can be quantitated by PCR. ▶pfu, ▶reporter gene, ▶GFP, ▶galactosidase, ▶luciferase, ▶PCR

Titin (connectin): One of the largest protein molecules (3×10^6 M_r) along with nebulin; it forms a network of fibers around actin and myosin filaments in the skeletal muscles, and may also be involved in the condensation of the chromosomes. The human titin gene contains 178/234 exons. Titin keeps myosin within the sarcomeres by being anchored to the Z discs (membrane bands in the striated muscles) and assures that the stretched muscles spring back. Titin is made up mainly of repeated modules but at its C-end it also has threonine/serine kinase domain specifically phosphorylating myosin. Calmodulin is required for its activation. The titin kinase domain itself is activated by phosphorylation at a tyrosine residue. Mutation in titin at 2q31 may cause dilated cardiomyopathy and tibial muscular dystrophy. The titin N2B region is dispensable for cardiac development and systolic properties but is important to integrate trophic and elastic functions of the heart (Radke MH et al 2007 Proc Natl Acad Sci USA 104:3444). ▶nebulin, ▶glutenin, ▶sarcomere, ▶dystrophin, ▶calmodulin, ▶cardiomyopathy, ▶CaMK, ▶exon; Labeit S, Kolmerer B 1995

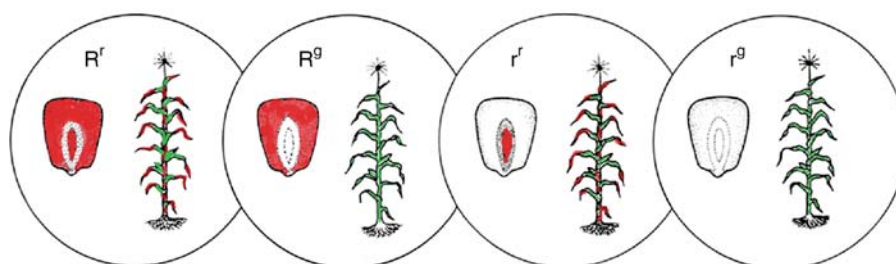


Figure T57. Tissue-specificity of expression (anthocyanin formation) of four different *R* alleles of maize in the aleurone, embryo, stalk, tassel and leaf tips

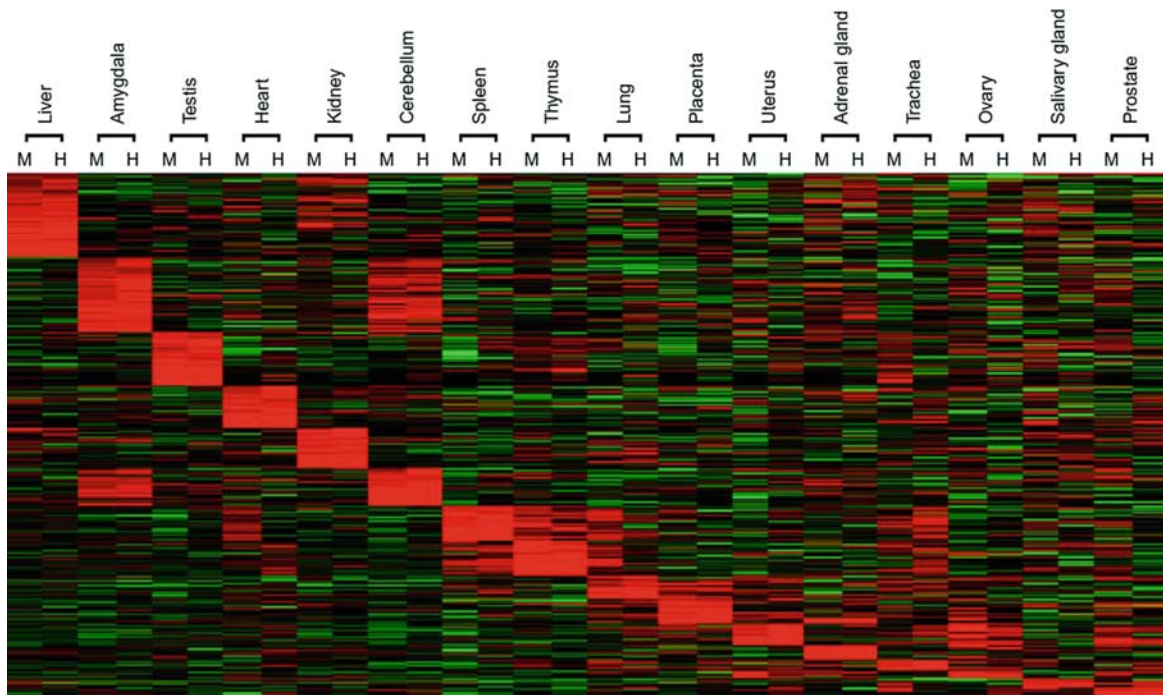


Figure T58. Transcriptome of 427 human and mouse gene pairs. Gene expression profile in 16 different types of tissues detected by Affymetrix GENECHIPS. Individual tissues express about 30 to 40% of the genes. Statistical analysis indicated that 78 to 82% of the genes were expressed differently in the mouse (M) and humans (H). The expression of the genes may be strictly tissue-specific. In this particular study, 85 human genes were expressed in the testis alone. (From Su AI et al 2002 Proc Nat Acad Sci USA 99:4465–4470; Copyright 2002 National Academy of Sciences, USA Courtesy of Dr. JB Hogenesch The Genomics Institute of the Novartis Research Foundation, San Diego, California)

Science 270:293; Machado C, Andrew DJ 2000 J Cell Biol 151:639; Gerull B et al 2002 Nature Genet 30:201; Hackman P et al 2002 Am J Hum Genet 71:492; Lange S et al 2005 Science 308:1599.

Titration: The addition of a measured amount of a solution of known concentration to a sample of another solution for the purpose of determining the concentration of the target solution on the basis of the appearance of a color or agglutination, etc. Also, by using this method, the number of cells or phage particles in a series of dilutions can be determined. ▶titer, ▶gene titration

TK: Thymidine kinase, which phosphorylates thymidine. Its gene in humans encodes the cytosolic enzyme that contains 7 exons in the short arm of human chromosome 17q25-q25.3; but the mitochondrial TK gene is in chromosome 22q13.32-qter. The latter enzyme defect may be responsible for myoneurogastrointestinal encephalopathy. The TK sequences are apparently highly conserved in different species. The herpes virus TK gene activates acyclovir and ganciclovir drugs and is used in gene therapy. ▶HAT medium, ▶gene therapy, ▶ganciclovir, ▶myoneurogastrointestinal encephalopathy

T_L: The left border of the T-DNA. ▶T-DNA, ▶Ti plasmid

TLC: ▶thin layer chromatography, ▶telomerase

TLE: ▶groucho, ▶Tup

TLF: ▶TBP

TLR: Toll-like receptor. ▶Toll

TLV (threshold limit value): The upper limit or time-weighted average concentration (TWA) of a substance that people can be exposed to without adverse consequences.

T_m: ▶melting temperature

TM1, TM2: Transmembrane amino acid domains of *E. coli* transducers, spanning the membrane layer inner space. TM1 is well conserved among the various transducers; TM2 is variable. ▶transducer proteins

TMF: TATA box modulatory factor. ▶TATA box, ▶promoter, ▶transcription

TMHMM2: A program for the detection of transmembrane topology helices.

TMP: Thymidine monophosphate (see Fig. T59). (See formula at right)

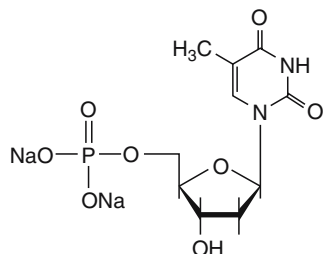


Figure T59. Thymidine monophosphate

TMRCA (time back to the most recent common ancestor): The concept for the study of the evolutionary descent of species or other taxonomic entities. It is estimated on the basis of the frequency of microsatellite variations associated with a particular mutation. If the mutation is recent the microsatellite variation linked to it is none and as time goes by the variation in microsatellites increases. The estimate may be biased by several factors, e.g., some variations may be lost by genetic drift, the generation time may be variable, etc.

tmRNA (10Sa RNA, SsrA): tmRNA basically is a tRNA and an mRNA hybrid molecule. It is used in bacteria to protect against the detrimental effects of mRNAs that lack stop codons and then stall translation. The SmpB (small protein B) protein binds to tmRNA and promotes its stable association with the 70S ribosome. The tmRNA is first charged with alanine and then it associates with EF-Tu. It binds to the A site of the ribosome and the alanine is incorporated into the growing peptide chain. Simultaneously, the mRNA-like domain of tmRNA substitutes for the defective mRNA on the ribosome. The tmRNA facilitates the inclusion of an additional 10 amino acids into the growing chain and then when the translation is stopped, the polypeptide is released. Proteins so formed are recognized by proteases because of the tmRNA tag and destroyed. This thus protects against defective proteins in the cell. This RNA is generated by RNase E cleavage. ▶aminoacylation, ▶regulation of gene activity, ▶eEF, ▶EF, ▶EF-Tu, ▶GTP, ▶proteasomes, ▶ribonuclease E, ▶protein repair, ▶ARAGORN, ▶ribosome recycling; Zwieb C et al 1999 Nucleic Acids Res 27:2063; Lee S et al 2001 RNA 7:999; Moore SD et al 2003 Science 300:72; structure and ribosome binding: Gutmann S et al 2003 Nature [Lond] 424:699; Asano K et al 2005 Nucleic Acids Res 33:5544; Moore SD, Sauer RT 2007 Annu Rev Biochem 76:101; <http://www.indiana.edu/~tmrna>; <http://www.ag.auburn.edu/mirror/tmRDB/>; <http://psyche.uthct.edu/dbs/tmRDB/tmRDB.html>.

TMS (tandem mass spectrometry): A method used to detect defects in fatty acid metabolism, organic acidemias and other human anomalies. ▶mass spectrum, ▶MALDI-TOF

TMV (tobacco mosaic virus): A single-stranded RNA virus of about 63,900 bases. Its cylindrical envelope contains 2,130 molecules of a 158-amino acid protein. Its rod-shape particles are about 3,000 Å long and 180 Å in diameter (see Fig. T60). The historical reconstitution experiments from coat protein and RNA demonstrated that RNA could be genetic material. Its mutagenesis by nitrous acid contributed substantially to the genetic confirmation of RNA codons. Its genome encodes four open reading frames. Foreign genes attached to the regulatory tract of the coat protein or to the coat protein itself can be expressed in tobacco plants. Thus, tobacco plants may be eventually used to manufacture proteins, e.g., α-glycosidase that is deficient in Fabry disease patients or the antigen of Hodgkin's lymphoma. ▶genetic code, ▶Fabry disease, ▶Hodgkin's disease, ▶plant vaccines; Goelet P et al 1982 Proc Natl Acad Sci USA 79:5818; Culver JN 2002 Annu Rev Phytopathol 40:287.

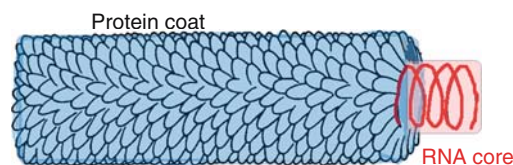


Figure T60. TMV

Tn3 Family of Transposons: Genetic elements that can move within a DNA molecule and from one DNA molecule to another and carry genes besides those required for transposition. The best-known representative is the Tn3 element carrying ampicillin resistance *Ap^r*. Tn3 is 4,957 bp long with 38 bp inverted terminal repeats and leaving behind—after moving at the transposition target site—5 bp direct duplication. Although the terminal repeats of the various Tn elements vary, some sequences are well conserved. The GGGG sequence is generally present outside the repeats and ACGPyTAAG is common inside of one or both terminal repeats. In the Tn3 group an internal ACGAAAA is common. Normally transposition requires the presence of both terminal repeats; the presence of only one of them may still allow a lower frequency transposition. The sites of integration may vary and yet AT-rich sequences are preferred and some homology between the terminal repeats and the insertional target may be needed. Some proteins of the host cell (IHF = integration host factor and FIS = factor for inversion stimulation) may

facilitate the expression of the transposase. Other members of the family are Tn1, Tn2, Tn401, Tn801, Tn802, Tn901, Tn902, Tn1701, Tn2601, Tn2602, and Tn2660. All are about 5 kb length with 39 bp terminal repeats and are found in various Gram-negative bacteria. Related to these is the $\gamma\delta$ (Tn1000) element in the F plasmid of 5.8 kb and with 36/37 bp terminal repeats and IS101 (insertion element 101), a cryptic element. Tn501 (8.2 kb) was the source of mercury resistance (*Hg^r*), Tn1721, Tn1771 (11.4 kb) for tetracycline resistance (*Tc^r*), Tn2603 (22 kb) for resistance to oxacillin (*Ox^r*), and hygromycin (*Hg^r*), streptomycin (*Sm^r*), and sulfonamide (*Su^r*). Tn21 (19.6 kb) carried resistance to *Su^r*, *Hg^r*, *Ap^r*, *Sm^r*, and *Su^r*. Tn4 (23.5 kb) was endowed with genes for *Ap^r*, *Sm^r*, and *Su^r*. Tn2501 (6.3 kb) was cryptic (i.e., expressed no genes besides the transposase). Tn551 and Tn917 (both 5.3 kb) from *Staphylococcus aureus* and *Streptococcus fecalis*, respectively, carried the erythromycin resistance (*Ery^r*) gene. The cryptic Tn4430 (4.1-kb) was isolated from *Bacillus thuringiensis*, R46 from enterobacteria, and pIP404 from *Clostridium perfringens* plasmids coded for the resolvase protein. The terminal repeats are generally within the range of 35–48 bp. The transposition is usually replicative and its frequency is about 10^{-5} to 10^{-7} per generation. The integration of the element requires the presence of a specific target site, called *res* site or IRS (internal resolution site), and genes *tpnA* (a transposase of about 110 MDa) and *tpnR*, encoding a resolvase protein (ca. 185 amino acids). The *res* site (about 120 bp) is where the resolvase binds and mediates site-specific recombination and protects the DNA against DNase I. Within the *res* site are located the promoters of *tpnR* and *tpnA* genes, functioning either in the same or in opposite direction, depending on the nature of the *Tn* element. The recombination between two DNA molecules requires the presence of at least two *res* sites in a negatively supercoiled DNA. The resolvase apparently has type I DNA topoisomerase function too. After synapses, mediated by resolvase and multiple *res* sites, strand exchange and integration may result. The recipient molecule thus acquires the donor transposon. The transposition event requires replication of the transposon DNA and then a fusion of the donor and the recipient replicons. This must be followed by a resolution of the cointegrate into a transposition product. ►transposable elements,

►gram-positive bacteria, ►transposon, ►cointegration, ►topoisomerase, ►antibiotics, ►resolvases; Sherratt D 1989, p 163. In: Mobile DNA. Berg DE, Howe MM (Eds.) Amer Soc Microbiol, Washington, DC.

Tn5: A bacterial transposon of 5.8 kb of the structure shown on Fig. T61.

The inverted termini represent the IS50 insertion element that includes the *tnp* (58 kDa protein) and *inh* genes (product 54 kDa). The left (L) and right (R) IS50 elements are almost identical except that the L sequences contain an ochre stop codon in the *tnp* gene, rendering it non-functional, save when the bacteria carry an ochre suppressor (see Fig. T61). At the I (inside ends) site binds the IHF (integration host factor) protein. O is the outside end of the IS sequence. Within the repeat beginning at nucleotide 8 is the bacterial DnaA protein-binding site TTATCA₈CA₈A. The DnaA product controls the initiation of DNA synthesis. Within the 2,750 bp central region are the genes for resistance to kanamycin (*kan*) and G418, bleomycin [phleomycin] (*ble*), and streptomycin (*str*) antibiotics; they are transcribed from the *p* promoter located within the IS L element at about 100 bp from the I end. These antibiotic resistance genes may not convey resistance in some cells, e.g., *str* may be cryptic in *E. coli*. The activation of this antibiotic resistance operon is contingent on the ochre mutation in the *tnp* gene. The inhibitor protein (product of *inh*) apparently interacts with the terminal repeats rather than with the transcription or translation of the *tnp* gene.

Tn5 can insert one copy at many potential target sites within a genome. The IS terminal repeats are capable of transposition themselves without the internal 2.8 kb element. In *direct transposition* the complete Tn5 will occur in the same sequence as shown in the diagram. In *inverse transposition*, mediated by the I ends, the 2.8 kb central element is left behind, away from the termini. Inverse transposition occurs 2–3 orders of magnitude less frequently than the direct one. In5 can form cointegrates with plasmids or bacteriophages and in these the IS elements and the entire Tn5 may occur and the orientation of the termini may be either direct or indirect as shown in the diagram. The transposon may be present as a monomer or as a dimer. Transposition may not require special homologous target sequences yet some targets represent “hot spots” (displaying

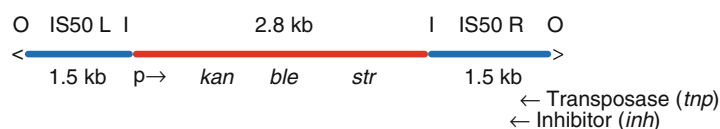


Figure T61. Structure of transposon Tn5

G•C or or C•G pairs next to the 9 bp target duplications) because they are preferred for insertion. The less frequently used targets generally show G•C and A•T pairs at the ends. Tn5 insertions, in general, are almost random and yet it appears that transcriptionally active promoters may present favorable targets. Insertion of the transposon into active genes usually results in inactivation because of the interruption of the coding sequences. Excision of the transposon may revert the gene to the original active state. This may occur at frequencies of 10^{-8} to 10^{-4} per cell divisions. The transposase gene alone does not mediate excision. It is independent from the bacterial *recA* gene but it depends on the structure of the inverted terminal repeats. Replicational errors involving slippage of pairing between the new and template DNA strands may occur. The presence of some sequences in the target may also promote Tn excision. The excision may also involve flanking DNA sequences and in this case the wild type function of the target gene is not restored. Several mutations in *E. coli* (*recB*, *recC*, *dam*, *mutH*, *mutS*, *mutD*, *ssb*) may promote excision, and mutation to *drp* reduces excision. Tn5, unlike Tn3, does not have a resolvase function. DNA gyrase, DNA polymerase I, DnaA protein, IHF and Lon (a protease cleaving effectively the Sula protein, a cell division inhibitor), may affect transposition. Transposition of Tn5 is substantially increased in *dam* mutant strains that are deficient in methylating GATC sequences. The *I* ends contain GATC sequence and can thus be affected by methylation. The *O* ends do not have a methylation substrate yet they are also affected by methylation in the *I* sequences (19 bp) (see Fig. T62). ▶transposon, ▶Tn3, ▶Tn7, ▶Tn10, ▶transposable elements bacteria, ▶transposable elements, ▶cut-and-paste, ▶resolvase; Berg DE 1989 Mobile DNA. In: Berg DE Howe MM (Eds.) Amer Soc Microbiol, Washington, DC, pp 185; Naumann TA, Reznikoff WS 2002 J Biol Chem 277:17623; Peterson G, Reznikoff W 2003 J Biol Chem 278:1904.

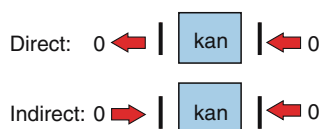


Figure T62. Tn5 termini can be reverse oriented

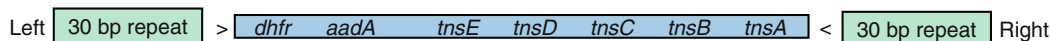


Figure T63. Tn7. *dhfr* = dehydrofolate reductase gene with much reduced sensitivity to trimethoprim, an inhibitor of the enzyme involved in the biosynthesis of both purines and pyrimidines and thus nucleic acids. *aadA* = adenylyl transferase gene, encoding an enzyme, which inactivates aminoglycoside antibiotics, streptomycin and spectinomycin, and thus conveys resistance to the cells. The *tns* genes are responsible for transposition

Tn7: A 14 kb bacterial transposon of the following general structure. The Tn7 element has a high capacity to insert into the specific *att* Tn7 site of *E. coli* (25 kb counterclockwise from the origin of replication at map position 83). The target DNA required for Tn7 transposition is within the C-terminus of the glucosamine synthetase (*glmS*) gene in bacteria and it has similar specificity for the human homolog of *glmS*, GFPT-1 and GFPT-2, at chromosomal location 2p13 (Kuduvalli P et al 2005 Nucleic Acids Res 33:857). When this site is not available it may transpose—at about two orders of magnitude lower frequency—to a *pseudo-att* Tn7 or to some other unrelated sites (see Fig. T63). At the *att* Tn7 the right end is situated proximal to the bacterial *o* gene. Genes *tnsABC* mediate all transpositions but through different pathways; for transposition to *att* Tn7 and *pseudo-att* Tn7, the function of gene *D* is also required, whereas for transposition to all other sites the expression of the *ABC + E* genes are needed. (The name *tns* abbreviates transposon seven.) The insertion at *att* Tn7 is also in a consistent orientation and it is within an intergenic region and thus does not harm the host. Insertion of the Tn7 element protects the cell from an additional Tn7 insertion (immunity). Yet under some conditions the immunity may not work. Integration results in 5 bp target site duplication; these duplications are different at *att* Tn7 and other sites. Several bacterial species besides *E. coli* have specific *att* Tn7 sites in their genomes. For transposition both *L* and *R* terminal repeats are required. Elements with two *L* repeats do not move whereas two complete *R* termini can assure insertion to *att* Tn7 sites. Tn7, because of the site specificity, is not very useful for insertional mutagenesis, but it has an advantage of inserting genes at the standard map position. Tn7 inserts preferentially in the vicinity of triple-helical sites. The Tn7 family of transposons includes Tn73, Tn1824, and Tn1527 with substantial similarity or even identity. Tn1825 is a clearly distinct member. ▶transposons bacterial, ▶transposable elements, ▶triplex; Craig N 1989, p 211. In: Mobile DNA. Berg DE, Howe MM (Eds.) Amer Soc Microbiol, Washington, DC.

Tn10: A bacterial (*E. coli*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*, *Pseudomonas*, etc.) transposable element of 9.3 kb. It may move within a bacterial

genome, from the bacterial chromosome to a temperate phage or plasmid and among different bacterial species. Its overall structure can be represented as in Figure T64.

The boxed left insertion element *IS10* (L) is a defective transposase. The boxed right *IS10* element (R) is a functional transposase (see Fig. T64). Thus *Tn10* is a composite transposable element. The *tetR*, *A*, *C* and *D* genes are involved in resistance against tetracycline. The *tetR* is a negative regulator and *tetA* encodes a membrane protein. The arrows indicate orientation and direction of transcription. The promoter of the *IS10* element may serve as promoter for adjacent outside genes (pOUT).

Insertion of *Tn10* within a gene, operon or upstream regulatory element may abolish the activity of the gene(s) or may modify their transcription. In the so-called polar insertions transcription is initiated within the *Tn* element but it may be terminated when rho signals are encountered. In the nonpolar insertions there are no rho sequences downstream to halt transcription. This type of *read-through* transcription may only take place in some *Tn10* derivatives but not in the wild type element. The rate of transposition for *IS10* is 10^{-4} and for *Tn10*, 10^{-7} per cell cycle.

Both the *IS10* and the *Tn10* elements can cause chromosomal rearrangements (see Fig. T65). Insertion and transposon sequence may show the portable region of homology and can undergo homologous recombination (see Fig. T66). These recombinations may generate deletions between, or inversions in, the regions in-between them at rates two orders of magnitude less frequent than transposition or lead to the formation of cointegrates.

All DNA segments flanked by *IS10* can become transposable and thus may represent new composite

transposons. *IS10* and *Tn10* may assist the fusion of different replicons and transfer information between bacterial chromosomes, plasmids, and phages. The transpositions may also generate new units of regulated gene clusters by the movement of structural genes under the control of other regulatory sequences.

The excision of the transposon may be “precise” if the nucleotide sequence is restored to its pre-insertion condition. Precise excision (average frequency 10^{-9}) may remove one copy of the 9-bp target site inverted duplications.

The “near-precise excision” events involving removal of most of the internal sequences of *Tn10* occur at a frequency of about 10^{-6} and may later be followed by precise excision of the remaining sequences. These non-transposase mediated events are also independent from the host RecA recombination functions. Precise excision is mediated by RecBC and RecF pathways. *Tn10* and *IS10* may transpose either by a non-replicative or a replicative mechanism. In the former case, the whole double-stranded element is lifted from its original position and transferred to another site. In the second case, only one of the old strands of the transposon is integrated into the new position and the other strand represents the newly replicated one.

At the target site apparently two staggered cuts are made, 9 bases apart. This causes then the 9 bp target duplications when the gap is filled and the protruding ends are used as templates Figure T67.

The transposon (ca. 46 kDa) is coded within the *IS10* right terminus by about 1,313 nucleotides. The frequency of transposition may increase up to five orders of magnitude by increasing the expression of the transposase. The transposase action prefers being

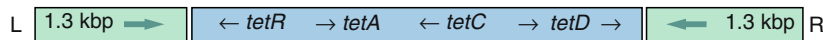


Figure T64. Structure of *Tn10*

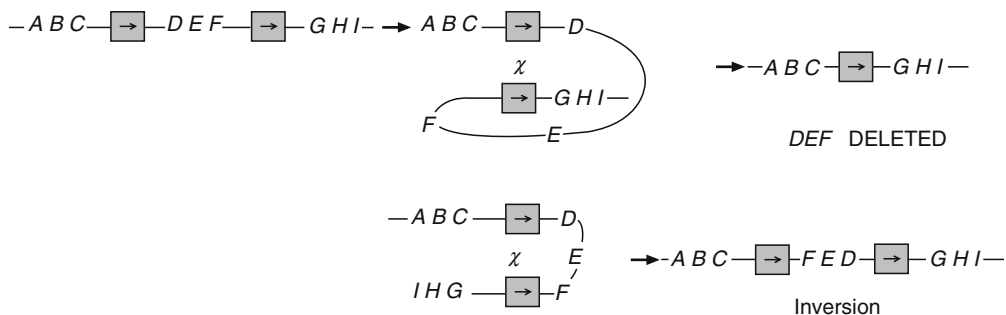


Figure T65. Generation of deletions and inversions by a portable region of homology represented by transposon *Tn10* (\rightarrow OR \leftarrow). Genes or sites are shown by capital letters in italic; χ indicates recombination

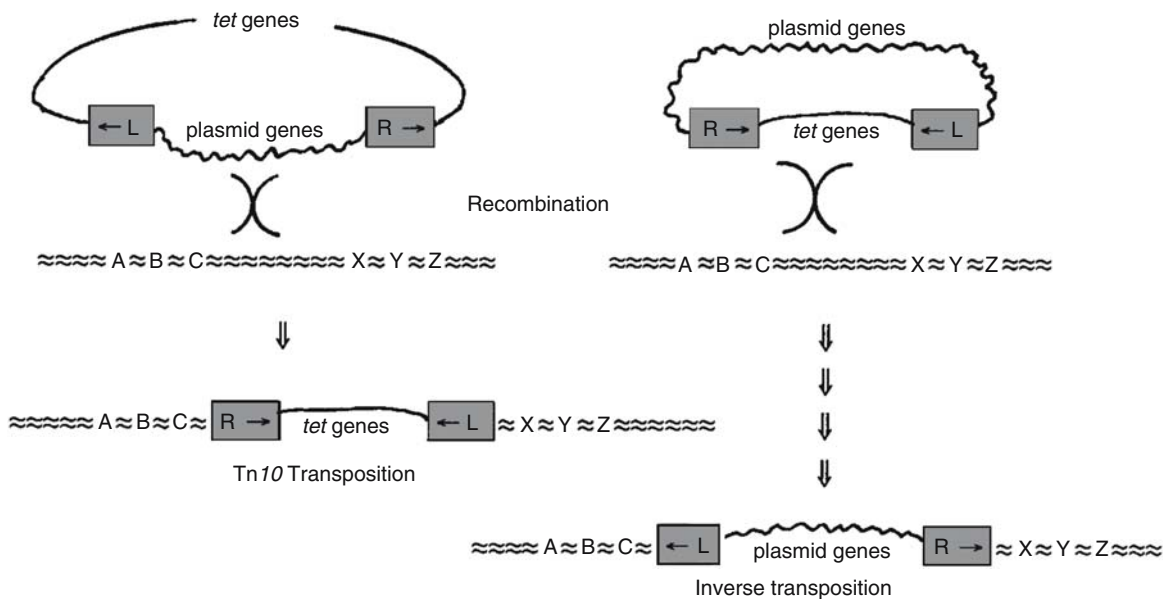


Figure T66. Tn10 transpositions. Left: the normal event, at right: the inverse transposition (or inside-out) transposition. Some other events may also lead to deletions or deletions and inversions. The L and R boxes represent Tn10 termini. The thin line stands for the transposon sequences whereas the single jagged line indicates the sequences flanking the transposon in the original location of the plasmid. The ≈≈≈ symbolizes the DNA sequences of the target

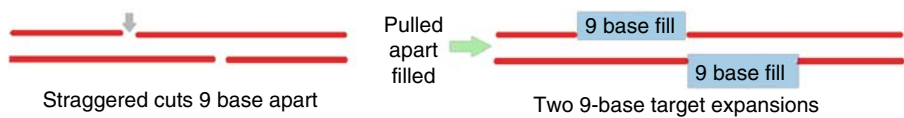


Figure T67. Target expansion

in the vicinity of the transposed sequences and its action is reduced by distance. Also, longer transposons are moved less efficiently than shorter ones. Each kb increase in length involves about 40% reduction in movement within transposon sizes 3 kb to 9.5 kb. Proteins IHF, HU and DNA gyrase also regulate transposition. The transposition frequency may also be modified (within three orders of magnitude) by the chromosomal context, i.e., cis-acting sequences. The integration hot spots appears to have some consensus sequences within the 9 bp target site in three bases (see Table T1).

Transposition seems to avoid being actively transcribed and thus the most essential genes of the

Table T1. Sites of integration hot spots

| 1 st | 2nd | 3rd position | | | |
|-----------------|-----|--------------|-----|-----|------------------|
| G | C | | | | |
| A | T | T | C | A | G |
| 90% | 98% | 63% | 23% | 12% | 2%, respectively |

recipient. The transposase gene is transcribed from a very low efficiency pIN promoter origin-ating near the *O* end of the right *IS* element. The divergent pOUT promoter opposes its transcription also. Apparently, on average, each cell generation may not produce one molecule of transposase. Two *dam* (adenine) methylation sites (GATC) are located within pIN and the activity of this promoter is facilitated in the absence of methylation by the host *dam* methylase (located in *E. coli* at 74 min). Actually, the transposase promoter is usually hemi-methylated. An increase in the number of Tn10 copies per cell reduces transposase activity because the pOUT promoter generates an antisense RNA transcript that may pair to a 35-base complementary region of the pIN promoter region. The transposase activity is also regulated by fold-back inhibition (FBI), hindering the attachment of the Shine-Dalgarno sequence of the transcript to the ribosome. The Tn10 system is protected from transposase activation by inhibition of read-through.

Transposons inserted into a particular gene cause mutations because of the disruption in the continuity

of the coding sequences. Transposon mutagenesis has considerable advantage over chemical or radiation mutagenesis because it induces mutation only at the site of insertion while chemicals may affect several genes simultaneously. In addition, mutagenesis with *Tn10* labels the gene by tetracycline resistance, an easily selectable marker. Transposons may also label foreign genes cloned in *E. coli* or *Salmonella*. The tetracycline-resistance gene has been extensively used for monitoring insertions that result in the loss of tetracycline resistance but retain other (selectable) markers in the cloning vector. ▶IHF, ▶HU, ▶gyrase, ▶antisense RNA, ▶FBI site, ▶readthrough, ▶transposable elements bacteria; Craig N 1989 Mobile DNA. In: Berg DE, Howe MM (Eds.) Amer Soc Microbiol, Washington, DC, pp 227.

Tn Syndrome: A rare autoimmune disease involving exposure on the surface of erythrocytes, platelets, granulocytes, and lymphocytes of the normally hidden Tn antigen. In patients, both Tn+ and Tn- hematopoietic cells show up and leukemia, thrombocytopenia and nephropathy appear. The Tn membrane glycoprotein is incompletely glycosylated. The altered Tn loses a terminal galactose due to a defect in the T-synthase enzyme, encoded at 7p14-p13. A somatic mutation in the Xq23 gene, COSMC, alters a molecular chaperone required for the proper folding of the enzyme. (See Vainchenker W et al 1985 J Clin Invest 75:541; Ju T, Cummings RD 2005 Nature [Lond] 437:1252).

TNA: (L)- α -Threo-furanosyl-(‘-2’)-oligonucleotides. These molecules contain 4-carbon (tetrose) sugars rather than pentose and are capable of pairing with RNA and DNA.

TncRNA (tiny noncoding RNA): ▶RNA noncoding

TNF (tumor necrosis factor): Proteins ($M_r \approx 17$ K) that are selectively cytotoxic or cytostatic to the cancer cells of mammals. They are relatively harmless to normal cells by being lymphokines. They are defense molecules against intracellular pathogens. The TNF family includes diverse transmembrane proteins with high homology in the receptor-binding regions. TNF was originally discovered in rodent cells infected by bovine *Mycobacterium* and then with endotoxin. The serum of these animals produced hemorrhagic necrosis and occasionally complete regression of transplanted tumors. The mature human TNF α consists of 157 amino acids after trimming off 73 amino acids from the pre-TNF. It has receptor sites on the surface of tumors and its action is synergistic with γ interferon. TNF α and TNF β have similar functions and display $\approx 30\%$ homology. TNF α plays a promoting role in obesity and inflammatory metabolic diseases (diabetes, atherosclerosis, hypertension,

asthma, osteoarthritis, cancer, etc.). TNF α inhibitors are used for antiinflammation (rheumatoid arthritis) therapy. The relatively small molecule, trifluoromethylphenyl indole, causes a very high (600-fold) dissociation of the trimeric structure of TNF α . This observation may be exploited for the development of new drugs (He MM et al 2005 Science 310:1022).

The two TNF genes each have 3 introns in their 3 kb sequence. In mice, it is localized within the *H-2* (histocompatibility cluster) and in humans in the homologous *MHC* region in chromosome 6p23, either between HLA-DR and HLA-A or proximal to the centromere. The genes were cloned and sequenced in the mid-1980s. TNF α and IL-1 are the major inflammatory cytokines whereas IL-10 and TGF β , IL-R and TNF-R are anti-inflammatory. TNF is produced mainly by macrophages. A TNF β deficiency may increase chromosomal instability and may lead to cancerous transformation. The tumor necrosis family of proteins includes FASL, CD40L, LT and β , CD30L, CD27L, 4-1BBL, OX40L, TRAIL, OPGL, LIGHT, APRIL, and TALL. Estrogen deficiency and ovariectomy stimulate osteoclastogenesis (bone loss) by T cell-produced tumor necrosis factor (TNF α). This process is mediated by enhanced production of interleukin-7 (Ryan MR et al 2005 Proc Natl Acad Sci USA 102:16735). ▶lymphokines, ▶cytokines, ▶endotoxin, ▶hemorrhage, ▶necrosis, ▶interferons, ▶histocompatibility, ▶HLA, ▶TNF-R, ▶TRAF, ▶Crohn's disease, ▶arthritis, ▶macrophage, ▶TACE, ▶TACI, ▶TNFR, ▶TRAIL, ▶NGF, ▶lymphotoxin, ▶LT α , ▶HVEM, ▶transposase, ▶IL-7, ▶IL-32, ▶asbestos; Kassiotis G, Kollias G 2001 J Clin Invest 107:1507; Liu Y et al 2003 Nature [Lond] 423:49; review of inflammation and diseases: Hotamisligil GS 2006 Nature [Lond] 444:860.

TNFR (tumor necrosis factor receptor, p55, p75): Similar receptors in both animals and plants may be involved in processes of differentiation. TNFR-1 and -2 are distinguished; TNFR-1 mediates different effector functions through separate pathways. The intracellular portion of TNFR-1 contains a 70-amino acid death domain, which mediates signals for apoptosis and the activation of NF- κ B. TNF binds to the extracellular domain of TNFR-1 resulting in its trimerization. The TNF1 attracts the adaptor TRADD (tumor necrosis factor receptor associated death domain) and TRAF2 and TRAF1. Subsequently, the TNFR1 recruits FADD (Fas associated death domain). TRAF2 (tumor necrosis factor associated protein 2) is contacted by TRAF1 and RIP (receptor interacting protein). This complex then signals for apoptosis, JNK/SAPK and NF- κ B activation. Protein SODD (457-amino acid silencer of death domains)

is expressed in all human tissues and interacts with the intracellular domain of TNFR-1 but not with TNFR-2, TRADD, FADD or RIP, and interferes with all TNF signaling through TNFR-1. JNK does not participate in the apoptotic pathway and the activated NF- κ B works against apoptosis though inflammation may result. ▶TNF, ▶TRAF, ▶NF- κ B, ▶nitrogen fixation [ENOD], ▶apoptosis, ▶Jun, ▶Fas, ▶NGF, ▶Paget's disease, ▶APRIL, ▶BAFF, ▶Blys; Locksley RM et al 2001 Cell 104:487.

TNG: A panel of 90 independent radiation hybrid clones constructed at Stanford University by irradiation of 50 Krad x-rays. This panel is used for the construction of a high-resolution STS map. ▶radiation hybrid panel, ▶STS; Robic A et al 2001 Mamm Genome 12:380; Olivier M et al 2001 Science 291:1298.

Tnp: A transposase enzyme. ▶Tn5

Tnt: A nonviral, retrotransposable element. ▶transposable elements

TNT: A solution containing 10 mM Tris.HCl buffer (pH 8.0), 150 mM NaCl, 0.05% Tween 20.

Toad: *Bufo vulgaris*, 2n = 36; *Xenopus laevis*, 2n = 36 (see Fig. T68). ▶frogs



Figure T68. Toad

TOASTS: Traced orthologous amplified sequence tags.

Tobacco (*Nicotiana* spp): The smoking tobacco is an allotetraploid (*N. sylvestris* \times *N. tomentosiformis*) 2n = 48. The basic chromosome number generally is x = 12; however, diploid forms with 2n = 20 (*N. plumbaginifolia*) and 2n = 18 (*N. langsdorffii*), and in the *Suavolens* group, 2n = 36 (*N. benthamina*), 2n = 46 (*N. caviola*), 2n = 32 (*N. maritima*), 2n = 36 (*N. amplexicaulis*), 2n = 40 (*N. simulans*), 2n = 44 (*N. rotundifolia*) are also found. For genetic studies the diploid species are most useful (*N. plumbaginifolia*). For transformation, *N. tabacum* is used most commonly because of the easy regeneration of plants from single cells. Antibiotic resistant chloroplast mutations are available. The S strain is a streptomycin

resistant mutant of the variety Petite Havana. Mutation, recombination and transformation techniques are available for its plastid genome, using primarily antibiotic resistant ctDNA mutations. ▶*Nicotiana*, ▶smoking

Tobacco Mosaic Virus: ▶TMV

Tobacco Necrosis Virus (TNV): An icosahedral single-stranded RNA virus of \approx 4 kb. It is a root plant pathogen. ▶icosahedral

Tobacco Satellite Necrosis Virus (TSNV): A 17 nm diameter, single-strand RNA (\approx 1.2 kb) virus that depends on TNV for its replication. ▶tobacco necrosis virus

Tocopherol α (vitamin E): Tocopherol, α deficiency results in nutritional muscular dystrophy and sterility, although, normally, humans with regular diet do not show any need for it. Vitamin E may be beneficial as it is an antioxidant and regulates nerve functions and atherosclerosis. Vitamin E is a lipid-soluble molecule and plant oils are a major source. ▶vitamin E, ▶atherosclerosis

T-Odd Virus: Bacteriophages with odd number designations such as T3, T5, T7, etc. ▶bacteriophages

Toeprinting: A procedure for mapping the translation initiation ternary complex (EI1A•GTP•tRNA) to the ribosome. In one approach, a 32 P-labeled oligonucleotide is annealed to the mRNA, downstream (3') from the presumed site of initiation, and reverse transcriptase is used for the extension of the radioactive primer up to the position of the bound ribosome where the chain growth stops. Various types of purification may be used for the isolation and identification of the initiation complex. ▶elongation factors, ▶protein synthesis, ▶ribosomes, ▶mRNA surveillance; Ringquist S, Gold L 1998 Methods Mol Biol 77:283; Dmitriev SE et al 2003 FEBS Lett 533/C:99.

TOFMS (time-of-flight mass spectrophotometry): A powerful technique used for the analysis of the primary structure of proteins. ▶mass spectrum, ▶matrix-assisted laser desorption time of flight mass spectrometry, ▶MALDI; Verentchikov AN 1994 Anal Chem 66:126; She Y-M et al 2001 J Biol Chem 276:20039.

TOGA (total gene expression analysis): A completely automated technology for the simultaneous analysis of the expression of nearly all genes. Basically, it selects a four-base recognition endonuclease site and an adjacent four nucleotide parsing sequence (a syntactical determinant, e.g., for *MspI* CCGGN₁N₂-N₃N₄) and their distance from the 3'-end of an mRNA (from the polyA tail). These generate a specific, single identity label for each mRNA. The

parsing sequences also serve as parts of the PCR primer-binding sites in 256 PCR-based assays, which determine the presence and concentration of that mRNA in a tissue. ►microarray hybridization, ►SAGE, ►RNA fingerprinting; Sutcliffe JG et al 2000 Proc Natl Acad Sci USA 97:1976; expanded TOGA: <http://www.tigr.org/tdb/tgi/ego>.

TOGA (Tiger Orthologous Gene Alignment): A database generated by pair-wise comparison between tentative consensus sequences in different organisms: <http://www.tigr.org/tdb/tgi.shtml>.

Togavirus: RNA plus strand viruses of about 12 kb. The capsid proteins are synthesized only after completion of replication. This viral family includes rubella, yellow fever, and encephalitis viruses. ►RNA viruses, ►plus strand

Toggle Switch, Genetic: ►Gene-Switch cassette, ►synthetic biology

Toilet: The medical meaning is cleansing, clearing.

Tolerance of antibiotics: The infectious organism does not die but stops reproducing. ►antibiotic resistance

Tolerance, Immunological: Non-reactivity to an antigen that under other conditions would evoke an immune response. Antigens provided to fetuses or neonates with immature immune systems can induce tolerance. In adults, a very high or very low dose of the antigen may cause tolerance. The tolerance is the result of either clonal elimination or inactivation of lymphocytes in the thymus. Liver transplantation may induce systemic immune tolerance for certain (kidney, heart) allografts. ►lymphocytes, ►immune response, ►antigen, ►allograft, ►immunosuppressants; Gaunt G, Ramin K 2001 Am J Perinatol 18(6):299; Salih HR, Nussler V 2001 Eur J Med Res 6(8):323; Chang CC et al 2002 Nature Immunol 3:237.

Tolerization: CD4⁺ CD25⁺ T cells secure tolerance to organ-specific self-antigens. The Foxp3 transcription factor mediates the process and its defect cause immune reaction in humans and mice. Elimination of these factors is tolerization of both autoreactive and alloreactive lymphocytes. This may be a precondition to successful stem cell therapy. ►T cell, ►B cells, ►immune reaction, ►autoimmune diseases, ►FKH, ►stem cells

Toll (*Drosophila*, 3–91, human homolog TRAF6): Toll encodes a signaling protein operating through the NF-κB receptor in both the fly and humans, and the MyD88 adaptor protein mediates it. For the activation of NF-κB, IRAK (interleukin associated receptor kinase) and the TRAF6 (tumor necrosis factor associated receptor) protein, activated by IL-1, are required. This pathway is essential for the immune

system. The human Toll-like receptors (hTLR) are transmembrane glycoproteins that respond to bacterial lipoproteins (TLR2), lipopolysaccharides (TLR4), unmethylated CpG-DNAs (TLR9), etc., with activation of apoptosis, bacterial killing, tissue injuries and the induction of the innate immune response (Beutler B 2004 Nature [Lond] 430:257). The toll-like receptors TLR7 and TLR8 mediate the recognition of guanine and uridine-rich single-stranded RNA oligonucleotides, which stimulate dendritic cells and macrophages to secrete interferon-α and cytokines (Hell F et al 2004 Science 303:1526). The Toll-like receptor includes recognition sites for the innate immune system. TLRs signal through TRAF3 and TRAF6 effectors (Häcker H et al 2006 Nature [Lond] 439:204). TLR receptor signaling may not be required for adjuvant-enhanced antibody response as thought earlier (Gavin AL et al 2006 Science 314:1936). The *Toll/spaetzle/cactus* gene cassette is involved in the control of the antifungal peptide, drosomycin production. ►morphogenesis {52} in *Drosophila*, ►IRAK, ►TRAF, ►IL-1, ►IL-12, ►MyD88, ►NF-κB, ►ATF3, ►apoptosis, ►CD14, ►innate immunity, ►antimicrobial peptides, ►pattern recognition receptors, ►inflammation; Kobayashi K et al 2002 Cell 110:191; Pasare C, Medzhitov R 2003 Science 299:1033; Takeda K et al 2003 Annu Rev Immunol 21:335; crystal structure of TLR3: Choe JH et al 2005 Science 309:581; toll receptors: Gay NJ, Gangloff M 2007 Annu Rev Biochem 76:141.

Tolloid: ►bone morphogenetic protein

TOM (transfer outer membrane): A protein complex that regulates transport through the outer layer of the mitochondrial membrane. ►mitochondria, ►TIM

Tomato (*Solanum lycopersicum*, 2n = 24): The tomato has about 8–10 related species. It is one of the cytologically and genetically best-known autogamous plants and is suitable for practically all modern genetic manipulations. Its genome size is bp/n ≈ 6.6 × 10⁸. ►coffee; for gene index: <http://www.tigr.org/tdb/tgi.shtml>; <http://zamir.sgn.cornell.edu/mutants/>; expression database: <http://ted.bti.cornell.edu/>; EST database: <http://biosrv.cab.unina.it/tomatestdb>.

Tomato Bushy Stunt Virus: A single-strand RNA virus of about 4,000 bases enveloped by an icosahedral shell consisting of 180 copies of a 40-kDa polypeptide. ►icosahedral

Tomography (body section radiography): Tomography is conducted by a tomograph in which a source of X-radiation moves in the direction opposite to that of a film, recording the image clearly only in one plane and blurring the remaining images. In computerized

axial tomography (CAT scan), the scintillations produced by the radiation are recorded on a computer disk and the cross section of the body is analyzed electronically. Positron emission tomography (PET) involves the use of positron-labeled metabolites (e.g., γ -ray emitting glucose) (see Fig. T69). Along the path of the radiation, positrons and electrons collide and the local concentration of the isotopes is recorded electronically. Electron tomography permits the three-dimensional reconstruction of cells, organelles, and supramolecular assemblies (Luci  V et al 2005 *Annu Rev Biochem* 74:833). Single-photon emission computed tomography (SPECT) takes γ -ray photographs around the body and a computer reconstructs three-dimensional images resulting in great resolution even of overlapping organs. Optical coherence tomography (OCT) resolves details in tissues at 1–15 μm in situ and it is thus one to two orders of magnitude finer than the ultrasound (Fujimoto JG 2003 *Nature Biotechnol* 21:1361). Ultrasonic tomography uses ultrasound scanning. The radiation may not be without risk (L brich M et al 2005 *Proc Natl Acad Sci USA* 102:8984). Gene expression tomography uses sliced brain sections in a cryostat. It obtains three-dimensional images of the expression pattern of particular genes using axial rotation (Brown VM et al 2002 *Physiol Genomics* 8:159). The RNA transcripts may be amplified by quantitative reverse PCR. ►X-rays, ►ultrasonic, ►sonography, ►nuclear magnetic resonance spectroscopy, ►imaging, ►RT-PCR; Czernin J, Phelps ME 2002 *Annu Rev Med* 53:89; Cristofallini M et al 2002 *Nature Rev Drug Discovery* 1:415.

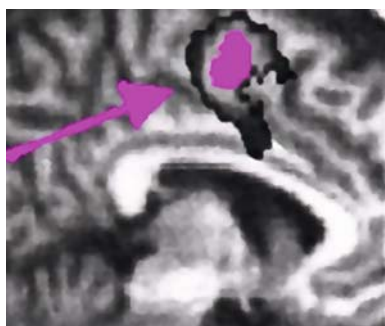


Figure T69. Pet scan of the brain; note different activity area at the arrow

Tongue Rolling: A human hereditary trait. Although it is frequently considered to be dominant, its inheritance is somewhat complex. Sturtevant AH (1940 *Proc Natl Acad Sci USA* 26:100) discovered it; he was the same person who first constructed a map of genes on a chromosome. Identical twins may be discordant for

the trait (Matlock P 1952 *J Hered* 43:24). This trait seems to also be associated with moving the ears.

Tonoplast: An elastic membrane ($\approx 8\text{ nm}$) that surrounds the vacuoles. Several proteins control the traffic through this membrane. ►vacuoles; Maeshima M 2001 *Annu Rev Plant Physiol Plant Mol Biol* 52:469.

Tooth (pl. teeth): See the Figure T70. The crown (at top) is covered by enamel and it is remodeled after eruption. The cusp pattern varies in different species and it is regulated by an ectodin protein, secreted as an inhibitor of bone morphogenetic protein (see Fig. T70) (Kassai Y et al 2005 *Science* 309:2067). Teeth and bone DNA, present in small quantities, can be amplified by PCR and used for the analysis of forensic and ancient samples (Alonso A et al 2001 *Croatian Med J* 42:260; Kemp BM, Smith DG 2005 *Forensic Sci Int* 154:53). High-resolution micro-computed tomography permits detection of small differences in adult tooth morphology that are determined easily in embryonic development. Such a technology detected that the molars of Neanderthals grew very much the same way as in modern humans (Macchiarelli R et al 2006 *Nature [Lond]* 444:748). ►bone morphogenetic protein, ►tomography; gene expression in tooth: <http://bite-it.helsinki.fi/>.

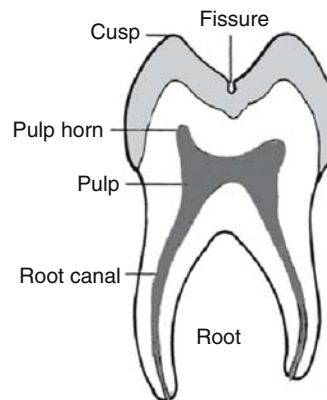


Figure T70. Posterior tooth of vertebrate

Tooth Agensis: Tooth agenesis is caused by a dominant (chromosome 4p) mutation in the homeodomain of transcription factor MSX1. It involves failure to form the second premolars and the third molars. Tooth development is under the control of many genes. Among them fibroblast growth factor (FGF) and bone morphogenetic (BMP) play pivotal and multiple roles. FGF and BMP regulate MSX1 and PAX9 transcription factors. ►homeodomain, ►Rieger syndrome, ►amelogenesis imperfecta, ►FGF, ►BMP, ►PAX, ►MSX1, ►oligodontia, ►hypodontia

Tooth Development: ▶[anodontia](#); Tucker A, Sharpe P 2004 *Nature Rev Genet* 5:499.

Tooth Malposition: Apparently, an autosomal dominant gene controls the various misplacements or underdevelopment of the incisors and the canine teeth. ▶[Hallermann-Streiff syndrome](#), ▶[Jackson-Lawler syndrome](#), ▶[amelogenesis imperfecta](#), ▶[cherubism](#)

Tooth Size: The tooth size appears to be influenced by the human Y chromosome as indicated by observations on various sex-chromosomal dosages.

Tooth-and-Nail Dysplasia (Witkop syndrome, TNS): In tooth-and-nail dysplasia, most commonly, the incisors, canine teeth and some of the molars are not or poorly developed. In some cases the condition is accompanied with abnormal toenails in children. Mutations at an MSX1 (4p161) subunit—a transcriptional repressor—seem to account for the phenotype. ▶[hypodontia](#), ▶[Hallermann-Streiff syndrome](#), ▶[dental no-eruption](#), ▶[dentin dysplasia](#), ▶[denticle](#), ▶[MSX1](#); Jumlogras D et al 2001 *Am J Hum Genet* 69:67.

5'-TOP (5'-terminal oligopyrimidine tract): mRNAs are part of the protein synthetic machinery and they are translated under the control of S6 kinases that are targets of insulin signaling in mammals. Cell growth (not cell division) is controlled by this process. ▶[S6](#), ▶[insulin-like growth factors](#); Crosio C et al 2000 *Nucleic Acids Res* 28:2927.

Top Agar: An agar solution of ~0.6% generally containing 0.5% NaCl and some organic supplements. About 2 mL of the solution, with suspended bacterial cells, is spread over the agar medium (30 mL/10 cm Petri plates) to initiate selective bacterial growth, e.g., in Ames tests. ▶[Ames test](#)

Top-Down Analysis: Starting with a mutant phenotype, the physiological or molecular mechanism responsible for the alteration is investigated. In contrast, the bottom-up analysis first studies the molecules and then the analysis is extended to their relationships to the phenotype. Currently, the major endeavor is to go beyond the role of individual molecules and major interest is being focused on the critical domains of the molecules. ▶[reversed genetics](#)

Top-Down Mapping: Top-down mapping uses either traditional genetic recombinational analysis or radiation hybrid maps. ▶[mapping genetic](#), ▶[radiation hybrids](#), ▶[bottom-up map](#)

Topical Reversion: The back mutation is the result of alterations within the gene rather than due to extragenic suppression. ▶[reversion](#), ▶[suppressor extragenic](#), ▶[suppressor intragenic](#)

Topoisomerase (TOP): Topoisomerases are enzymes which alter the tertiary structure of DNA without a

change in the secondary or primary structure. The monomeric topoisomerase I (10q12-q13.1) nicks and closes single strands of DNA and changes the linking number in one strand. The dimeric topoisomerase II can cut and reattach both strands of the DNA and affect linking number in both strands.

Topoisomerase II (17q21-q22) disentangles DNA strands and plays an important role in DNA replication, transcription and recombination, suppression of mitotic recombination, stabilization of the genome (chromosome breakage), regulation of supercoiling, eukaryotic chromosome condensation, control of segregation of the chromosomes, regulation of the cell cycle, and nuclear localization of imported molecules. The mitochondrially located Top1mt is encoded at 8q24.3. Topoisomerases are important objects in cancer therapy research. Charvin G et al 2005 (cited in the caption in Figure T71), outlines mechanisms of action of the different topoisomerases. The prokaryotic topoisomerases I—in contrast to the eukaryotic ones—require Mg^{2+} and single-stranded DNA segments and relax only the negatively supercoiled molecules. TOP I activity is required for the proper segregation of prokaryotic chromosomes (Zhu Q et al 2001 *Proc Natl Acad Sci USA* 98:9766) and has been located to human chromosome.

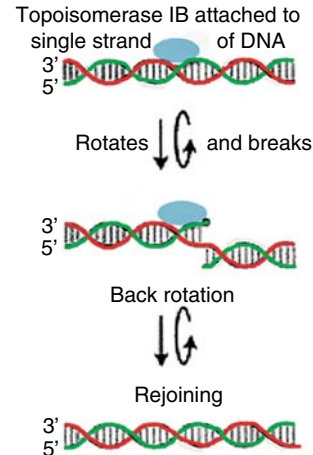


Figure T71. Redrawn after Charvin G et al 2005 *Annu. Rev. Biophys. Biomol. Struct.* 34:201

The human topoisomerase I consists of 765 amino acids. Prokaryotic DNA topoisomerase III supports the movement of the DNA replication fork and can also function as an RNA topoisomerase and can interconvert RNA circles and knots. The eukaryotic topoisomerase III (17p12-p11.2) is homologous with prokaryotic topoisomerase. Mice with knocked-out DNA topoisomerase III β are viable but senesce earlier and have about a 40% shorter life span. Chromosomal abnormalities in *top3 β ^{-/-}* mice might lead to a persistent increase in apoptotic cells, which

might in turn lead to the progression of autoimmunity (Kwan KY et al 2007 Proc Natl Acad Sci USA 104:9242). ▶DNA replication, ▶gyrase, ▶linking number, ▶linking number paradox, ▶mtDNA, ▶camptothecin, ▶p53; Wang JC 1996 Annu Rev Biochem 65:635; Changela A et al 2001 Nature [Lond] 411:1077; Champoux JJ 2001 Annu Rev Biochem 70:369; Wang JC 2002 Nature Rev Mol Cell Biol 3:430; evolution of topoisomerases: Forterre P et al 2007 Biochimie 89:427; topoisomerases as therapeutic targets of infection: Tse-Dinh YC 2007 Infect Disord Drug Targets 7:3; see Fig. T72.

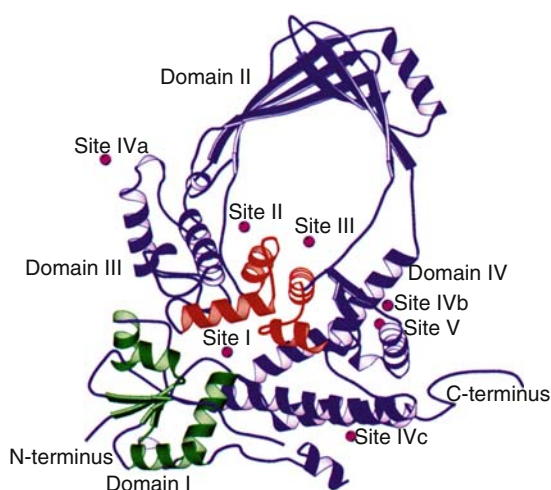


Figure T72. The 67-kDa fragment of DNA topoisomerase I of *E. coli* displaying major domains and nucleotide-binding sites. (From Feinberg H, Changela A, Modrigón A 1999 Nature Struct. Biol. 6:961)

Topological Filter: The topological filter is synonymous with two-step synopsis. The assumption is that synopsis requires an interaction between DNA *res* sites and the three subunits of a resolvase enzyme (step 1). After this initial step, the II and III subsites of the resolvase-*res* dimers pair in a parallel manner and the subunits interwrap. Then, the two I subsites of the resolvase dimer bind resulting in a productive synaptic complex (Step 2), capable of initiating DNA change. ▶synopsis, ▶res, ▶resolvase; Watson MA et al 1996 J Mol Biol 257:317.

Topological Isomers of DNA: ▶linking number

Topomap: A topomap displays genes that show correlated expression across a large set of microarray experiments.

Toponome: A single-cell-localized organization of proteins, carbohydrates, lipids, and nucleic acids. ▶MELK, ▶genetic networks

TORC (transducer of regulated CREB): A coactivator of CREB, a CRE (cyclic AMP-response element) binding protein. The glucose level is regulated in animal cells by insulin and glucagons, and TORC plays a central role in the homeostasis of glucose levels as outlined in the oversimplified chart (see Fig. T73). ▶gluconeogenesis, ▶CRE, ▶glucagons, ▶diabetes, ▶cAMP, ▶PKA, ▶CREB, ▶AMPK; Koo S-H et al Nature [Lond] 438:1109.

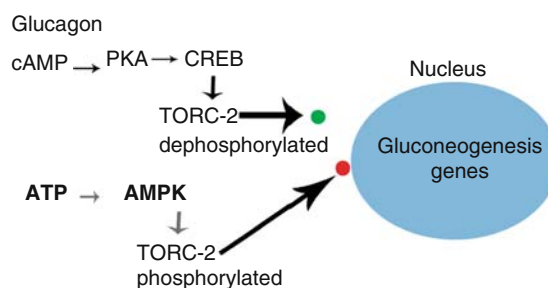


Figure T73. When TORC-2 is dephosphorylated gluconeogenesis genes are turned green in the nucleus. When TORC-2 is phosphorylated gluconeogenesis is attenuated

TORF: An open reading frame identified with the aid of a transposon. ▶ORF, ▶transposon

TORs (target of rapamycin): TORs are phosphatidylinositol kinases of yeast (TOR1, TOR2). They are also called RAFT1 and FRAP. TORs convey resistance to FKBP. The C-terminal domains of the TOR family are homologous to the catalytic domain of PI(3)K. TORs block the turnover of nutrient transporters, autophagy, and the interphase of the cell cycle but promote protein kinase C signaling, actin and cytoskeleton organization, and tRNA and ribosome formation, transcription and translation. TOR may be involved in the regulation of life span of *Drosophila* through affecting nutrition (Kapahl P et al 2004 Current Biol 14:885). The movement of TOR from the cytoplasm to the nucleus is controlled by the nutritional status in yeast (Li H et al 2006 Nature [Lond] 442:1058). The TORC1 complex is sensitive to rapamycin but the TORC2 is not. TORC1 positively regulates ribosome biogenesis, translation and nutrient import and blocks stress-responsive transcription. TORC2 mediates cell growth through actin organization (Wullschlegel S et al 2006 Cell 124:471). TORs play a central role in the regulation of several human diseases such as hamartomas and other hypertrophic diseases (Inoki K et al 2005 Nature Genet 37:19). ▶rapamycin, ▶PIK, ▶FK506, ▶PI[3]K, ▶S6K, ▶autophagy, ▶cell cycle, ▶aging, ▶cytoskeleton, ▶protein kinases, ▶cisplatin, ▶Akt, ▶leukemia; Schmelzle T, Hall MN 2000 Cell

103:253; Dennis PB et al 2001 Science 294:1102; Schalm SS, Blenis J 2002 Current Biol 12:632.

Tormogen: A component cell of the bristle that secretes the bristle socket. The other bristle cells are the trichogens that secrete the bristle shaft, also a neuron, which contacts the shaft and through its axon connects with the nervous system.

Toroid/Toroidal: A body or surface generated by the rotation of a plane curve or circle. It may assume the shape of a ring/doughnut or may resemble a barrel. ▶torus; Hud NV, Vilfan UD 2005 Annu Rev Biophys Biomol Struct 34:295.

Torpedo Model: ▶transcription termination in eukaryotes

Torsion Dystonia: ▶idiopathic torsion dystonia, ▶dystonia

Tortoiseshell Fur Color: Develops in female (cats) heterozygous for the X-chromosome-linked genes black and yellow colors because of selective, alternate inactivation of the two mammalian X-chromosomes. The tortoiseshell animals have mixed patches of black and yellow fur (Fig. T74). These fur patterns occur in the XX (female) or exceptionally in the XXY Klinefelter male cats. (See Lyon hypothesis, lyonization, calico cat).



Figure T74. Back of a tortoiseshell cat

Torus: A ring-shaped emergence, swelling, or a bordered pit. ▶toroid

Totipotency: A characteristic of zygotic cells that permits differentiation into any type of cell or structure, including the whole organism. Initially, the paternal genome of animals is highly condensed and it is bound by protamines, which are replaced by histones before the S phase. Histone H3.1 is, however, absent from the paternal genome before DNA replication. The paternal genome displays H3K4me1, H3K9me1, and H3K27me1 (single-methylated lysines) but their dimethylation is largely postponed after DNA replication. The paternal genome is demethylated globally but not the maternal genome. For totipotency, the maternal transcription factors Oct3/4, Sox2, and the Polycomb group proteins are essential. By the two-cell stage the differences diminish yet the blastomeres maintain totipotency to the eight-cell stage. Between the eight and 16-cell stages polarization is initiated and this signals a switch to transition and to pluripotency. From pluripotency, totipotency is reestablished by the differentiation of the germline from the soma. These processes require numerous genetic and epigenetic factors (Surani MA et al 2007 Cell 128:247).

In the germline of *Caenorhabditis* the expression of translational regulators is required for the maintenance of totipotency. In *mex-3* and *gld-2* double mutants, germ cells transdifferentiate into somatic cells of muscles and neurons (Ciosk R et al 2006 Science 311:851). Plant cells maintain their totipotency in diverse adult tissues and after dedifferentiation may initiate other types of differentiations and of somatic cells entire organisms may be regenerated in cell cultures. Totipotency of animal cells is much more limited although lower animals such as hydra and earthworms may regenerate from differentiated tissues. The embryonic stem cells (ES) of mouse come close to totipotency/pluripotency inasmuch as they can be transferred to mouse embryos and can contribute to the formation of various cell types, including the germline. After special treatments, differentiated animal cells may also revert to stem cell status. ▶morphogenesis, ▶somatic embryogenesis, ▶redifferentiation, ▶multipotent, ▶pluripotency, ▶ES, ▶nuclear transplantation, ▶stem cells

Touch-and-Go Pairing: The end-to-end synapsis of the sex chromosomes in the heterogametic sex of some insects (see Fig. T75).

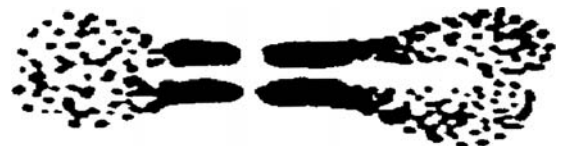


Figure T75. Touch-and-go-pairing. After Schrader F 1940 Proc Natl Acad Sci USA 26:634

Touch-Down PCR: ►hot-start PCR

Touch-Sensitivity: In mammals, the brain sodium channel BNC1 mediates touch sensitivity. ►degenerin; Welsh MJ et al 2002 J Biol Chem 277:2369.

Toulouse-Lautrec, Henri (1864–1901): One of the most remarkable painters of the end of nineteenth-century Paris life. He was a colleague of van Gogh and an influential precursor of modern art and was thought to suffer from pycnodysostosis. His parents were first cousins. This diagnosis of his genetic malady has been questioned [Nature Genetics 11:363], and it appears that deficiency of cathepsin K might have been involved. ►pycnodysostosis, ►cathepsins

Tourette's Syndrome (Gilles de la Tourette disease, GTS): A human behavioral anomaly causing motor and vocal incoordination (tic, twitching), stuttering (echolalia), the use of foul language (coprolalia), obsessions, and hoarding. The onset is between 7 to 14 years of age and three-fourths of those affected are male. The genetic determination is apparently dominant with incomplete penetrance and expressivity. Male:female ratio of 4.3:1 has been reported. Genes in several chromosomes (4q, 5q, 8p, 18q, 7q, 9, 3, 11q23, 17q) have been implicated. 238 nuclear families yielding 304 “independent” sibling pairs and 18 separate multigenerational families, for a total of 2,040 individuals using whole-genome screen for 390 microsatellite markers, indicated strong linkage for a region on chromosome 2pA (Tourette Syndrome Assoc. Internat. Consort. Genet 2007 Am J Hum Genet 80:265). A paracentric inversion involving chromosome 18q22 causes delayed replication in a sequence across at least 500 kb (State MW et al 2003 Proc Natl Acad Sci USA 100:4684). A sequence variant in Slit and Trk-like1 (SLITRK1)—encoding a single-pass transmembrane protein—has been identified at 13q31.1 (Abelson JF et al 2005 Science 310:317).

The frequency of the defective gene(s) was estimated to be 0.4 to 0.9%, and a prevalence of 1 to 0.02% has been observed in different populations. Some of the mild cases are suspected to be responsible for male alcoholism and female obesity. The expression of the condition is frequently much influenced by the environment. ►affective disorders; Zhang H et al 2002 Am J Hum Genet 70:896.

Townes-Brocks Syndrome (SALL1, 16q12.1): A highly variable dominant malformation with good penetrance. The symptoms include imperforate anus, polydactyly, syndactyly, abnormal earlobes, hearing deficit, kidney and heart anomalies, and mental retardation. The majority of the individuals display mutation in the SALL gene encoding a 1,325 amino acid protein with double Zn-finger domains. The normal protein is a transcriptional repressor and it is

associated with heterochromatin. ►penetrance, ►Zinc finger, ►heterochromatin; Netzer C et al 2001 Hum Mol Genet 10:3017.

Toxic Shock Syndrome: TSS is caused by infection of *Staphylococcus aureus*/*Streptococcus pyogenes* Gram-positive bacteria. It affects, primarily, menstruating women. It begins with sudden high fever, vomiting, diarrhea, and muscle pains (myalgia). Later, rash, hypotension, and potentially death may follow. Although septic shock has been attributed mainly to the cell wall lipopolysaccharides (present in Gram-negative bacteria) and peptidoglycan and lipoteichoic acid (present in Gram-positive bacteria), actually the unmethylated 5'-CpG-3' prokaryotic DNA may be responsible for the immune reaction. These bacterial superantigens (SAG) bind directly to the class II histocompatibility complex on the antigen-presenting cells and to specific variable regions of the β -chain of the T cell receptor and evoke very severe response. Plasmids or phages carry the bacterial enterotoxin genes. ►Gram-negative/positive, ►peptidoglycan, ►teichoic acid, ►*Streptococcus*, ►*Staphylococcus*; McCormick JK et al 2001 Annu Rev Microbiol 55:77.

Toxicogenomics: Toxicogenomics applies microarray hybridization techniques for the detection of genes that are turned on or off upon exposure of animals to toxic substances. ►microarray hybridization, ►genetox; Simmons PT, Portier CJ 2002 Carcinogenesis 23:903.

Toxin Targeting: ►toxins, ►magic bullet, ►immunotoxin; Goodsell DS 2001 Stem Cells 19:161.

Toxins: Toxins are organic poisons. A plasmid gene of *E. coli* produces colicins and *Shigella* bacteria may affect sensitive bacteria in several ways. The cholera toxin is produced by the bacterium *Vibrio cholerae* and it interferes with the active transport through membranes thus causing the loss of excessive amounts of fluids and electrolytes in the gastrointestinal system. The *Bordetella pertussis* toxin, pertussin, contributes to high levels of adenylate cyclase and thereby to the symptoms of whooping cough. Bungarotoxin (from *Bungarus multicinctus*) and cobrotoxin (from Formosan cobra) in snake venoms block the acetylcholine receptors (McCann CM et al 2006 Proc Natl Acad Sci USA 103:5149) or interfere with ion channel functions. Bungarotoxin has an LD50 value in mice of 0.15–0.21 $\mu\text{g/g}$. Other bacterial toxins include the tetanus toxin, diphtheria toxin, botulin, etc. The diphtheria toxin (of *Corynebacterium diphtheriae* if it carries a temperate phage with the *tox* gene) is one of the most dreaded human poisons (sensitivity is encoded in human chromosome 5q23) with a minimal lethal dose of 160 $\mu\text{g/kg}$

in guinea pigs. Mice and rats are, however, insensitive to this toxin. It inactivates eukaryotic initiation factor eIF-2 in translation on the ribosomes. The fungus *Amanita phalloides* toxin, amanitin (amatoxin), is a poison of RNA polymerase II. About two dozen cytochalasins are synthesized by different fungi and are composed of substituted hydrogenated isoindole rings fused with a macrocyclic ring (large organic compound). Colchicine is a plant alkaloid poison of the spindle fibers. The seed toxin of the plants *Strophantus* and *Acocanthera* is a blocking agent for membrane transport and is used as a selective agent in mammalian cell cultures. Abrin (from a legume) and ricin (from castor bean seeds) are inhibitors of the attachment of aminoacylated t-RNAs to the ribosomes. The piscine toxin, tetrodotoxin (from *Spherooides rubripes*; LD₅₀ in mice 10 µg/kg), and the dinoflagellate, *Gonyalux* species, saxitoxin (LD₅₀ in mice 3.4–10 µg/kg), locks the sodium ion channels and blocks neurotransmission. The curare toxins were obtained originally as an arrow poison from the bark of the trees *Strychnos* and *Chondodendron*. The sources of other curare toxins, bamboo curare, pot curare, gourd curare, etc., are members of the *Menispermaceae* family and are highly poisonous muscle relaxants. They block the acetylcholine receptors and some ion channels. Some of the curare toxins were used medically for treatment of tetanus shock and in surgery to alleviate muscle rigidity. ▶colicins, ▶amatoxin, ▶diphtheria toxin, ▶cytochalasins, ▶aflatoxins, ▶anthrax, ▶colchicine, ▶abrin, ▶ricin, ▶antibiotics, ▶ion channel, ▶acetylcholine receptors, ▶neurotransmitters, ▶LD₅₀, ▶laboratory safety; Schiavo G, van der Goot G 2001 Nature Rev Mol Cell Biol 2:530; Nesioy D et al 2004 Nature [Lond] 429:429; <http://www.epa.gov/iris>.

Toxmap: A geographic information system which provides facts of toxic substances released to the environment by the major manufacturing industries based on government mandated reports: <http://toxmap.nlm.nih.gov/toxmap/main/index.jsp>.

Toxoid: An inactivated bacterial toxin, which may still incite the formation of antitoxins and retain antigenicity.

Toxoplasmosis: Opportunistic infection of about 25% of the human populations by *Toxoplasma* protozoa reducing nerve connections. It is frequently lethal in AIDS and other immune-compromised people. Meiotic recombination among different strains may greatly enhance their virulence. The high virulence of the parasite *Toxoplasma gondii* is due to a secreted serine-threonine kinases (ROP) encoded in chromosome VIIa (Taylor S et al 2006 Science 314:1776; Saeij JPJ 2006 Science 314:1780).

▶AIDS, ▶apicoplast; Grigg ME et al 2001 Science 294:161; Su C et al 2003 Science 299:414.

TP53 (tumor protein): TP53 is now called p53, a tumor suppressor. ▶p53

TPA: A phorbol ester (12-o-tetradecanoyl phorbol 13-acetate) that promotes neoplastic growth after induction has taken place. ▶carcinogens, ▶cancer, ▶phorbol esters

TPA: An inducer protein; a mitogen activating protein kinase C. ▶protein kinases

TPA (Third Party Annotation Sequence Database): An annotation for a sequence that the submitter derived from GenBank primary data: <http://www.ncbi.nlm.nih.gov/Genbank/TP.html>; http://www.ebi.ac.uk/embl/Submission/align_top.html.

TPEA (3' end amplification) PCR: TPEA PCR permits the detection of mRNA at the single cell level (Dixon AK et al 1998 Nucleic Acids Res 29:4426; Subkhankulova T, Livesey FJ 2006 Genome Biol 7: R18). ▶PCR, ▶mRNA

TPK1, TPK2, TPK3: Catalytic subunits of A-kinase. ▶protein kinases

TPM: ▶two-phase mutation model

TPN: TPN is a triphosphopyridine nucleotide; TPNH is the reduced form. They are synonymous with the analogs α-NADP and α-NADPH, respectively. Many enzymatic reactions require β-NADP and β-NADPH (nicotinamide adenine dinucleotide phosphates). ▶NAD, ▶NADP⁺

TPO: TPO modulates megakaryocyte differentiation along with EPO and various cytokines. ▶EPO

TPR: ▶tetratric sequences

TPX2: A microtubule-associated protein. It is required for spindle assembly. Binding to importin α inactivates it but RAN•GTP reverses the binding. ▶microtubule, ▶importin, ▶RAN, ▶spindle; Wittmann T et al 2000 J Cell Biol 149:1405; Gruss OJ et al 2001 Cell 104:83.

T_R: A regulatory T cell. ▶T cells

TR3: ▶nur77

tra (*transformer*): A gene (chromosomal location 3–45) of *Drosophila* that controls sterile male development in XX flies; XY *tra/tra* males are, however, normal males. *tra* acts in cooperation with *tra2* (2–70). Tra and Tra2 proteins mediate sex-specific processing pre-mRNAs of *dsx* (*doublesex*, 3–48.1) and *fru* (*fruitless*, 3–62.0). The transcripts occur in both sexes but are processed differently. In the male germline, Tra2 is required for normal spermatogenesis. Tra2 also

mediates the sex-specific processing of *exu* (*exuperantia*, 2–93) and *att* (*alternative-testes-transcript*, chromosome 3 at 92E3–92E4). The prokaryotic *tra* genes in conjugative plasmids control the conjugal transfer of DNA. ▶sex determination, ▶tra genes

tra Genes: (more than 17) mediate the conjugal transfer of the F and other conjugative plasmids. ▶tra, ▶conjugation, ▶ori_T, ▶relaxosome, ▶plasmids

Trabant: A terminal chromosomal appendage (see Fig. T76). ▶satellited chromosome



Figure T76. Trabant

Trace Elements: Trace elements are only required in minute amounts.

Tracer: A (radioactively) labeled molecule that permits the identification of the fate of the molecules into which it has been incorporated. ▶isotopes

Trachea: The duct leading from the throat (larynx) to the lungs of animals or the duct system of insects through which air is distributed into the tissues. ▶FGF

Tracheid: A long, lignified xylem cell specialized for transport and support in plants.

Trachophyte: A vascular plant endowed with xylem, phloem, and (pro)cambium in-between. ▶xylem, ▶phloem, ▶cambium

Tracking: A mechanism to ensure that transposition occurs between two appropriate *res* (recombination sites). Experimental proofs for successful tracking (reporter rings) are not unequivocal. ▶reporter ring

Tracking Dyes: In electrophoresis, loading buffers permit the visualization of the front migration toward the anode. Bromophenol blue in 0.5 × TBE buffer moves at the same rate as double-stranded linear DNA of 300 bp length. Xylene cyanol FF moves along with 4 kb linear double-strand DNA. ▶electrophoresis, ▶electrophoresis buffers

Tradescantia Species: The *Tradescantia* species occur in the polyploidy range of 2x to 12x. The plants develop ca. 100 stamen hairs in their flowers (see Fig. T77). Each hair represents a single cell line (see Fig. T78). When plants heterozygous for anthocyanin markers are exposed to mutagen, somatic mutations can be assessed as differently colored cell lines in the large number of flowers that single plants may form. Some

of the species have been favorites for cytologists. ▶bioassays in genetic toxicology, ▶somatic mutation; pictures are the courtesy of A Sparrow, and GP Rédei unpublished.



Figure T77. *Tradescantia* stamens



Figure T78. *Tradescantia* stamen hairs

TRADD (tumor necrosis factor receptor associated death domain): ▶tumor necrosis factor, ▶death domain, ▶apoptosis, ▶TRAF

TRAF: A tumor necrosis factor-associated receptor and a signal transducer for some interleukins. TRAF5 is involved in CD40 and CD27-mediated signaling to lymphocytes. TRAF6 activates IκB kinase through a polyubiquitin chain. ▶TNF, ▶TNFR, ▶CRAF, ▶interleukins, ▶TRADD, ▶IRAK, ▶NF-κB, ▶IκB, ▶ASK1, ▶Toll, ▶MATH, ▶Ire, ▶CD27, ▶CD40, ▶ubiquitin; Tada K et al 2001 J Biol Chem 276:36530; Li X et al 2002 Nature [Lond] 416:345.

Tragedy of the Commons: The title of an article published in 1968 by Garrett Hardin (Science 162:1243) where he called attention to the limitations of the “common”—the earth—and the unlimited use of its resources and “freedom to breed” (overpopulation) which will inevitably lead to tragedy because there are no other solutions than the use of

temperance to avoid the consequences of the inevitable necessity. ▶human population growth, ▶cooperation, ▶prisoner's dilemma

TRAIL (Apo-2L, 3q26.1-q26.2): A tumor necrosis factor related apoptosis-inducing ligand which attaches to the death receptor DR4 and mediates apoptosis. DR4 does not respond to FADD like the Fas, TNFR-1, and DR3 system. It has five receptors. TRAIL also activates NF-κB. The nontoxic TRAIL causes preferential killing of neoplastic cells in animal models, especially in combination with radiation therapy of cancer. It appears, however, that it does not discriminate sufficiently between normal human liver cells and liver cancer cells. ▶apoptosis, ▶CD4, ▶death domain, ▶death receptor, ▶FAS, ▶FADD, ▶TNF, ▶TNFR, ▶TWEAK, ▶NF-κB, ▶imaging; Kontny HU et al 2001 Cell Death Differ 8:506; collection of papers in Vitam Horm 2004 vol 67:1–453.

Trailer Sequence: A trailer sequence follows the termination codon at the 3'-end of the mRNA. It is not translated and yet it may have a regulatory function. ▶polyA mRNA

Training Set: A set of observations used to fit the parameters of the classifier of the set. Such sets are generally used for discriminant analysis or multivariate analysis. ▶discriminant function, ▶multivariate analysis; Tsytkin Y 1971 Adaptation and learning in automatic systems, Academic Press, New York.

Trait: A distinguishable character of an organism that may or may not be inherited.

TRAM (translocating-chain associating membrane proteins): TRAMs are membrane-spanning glycoproteins associated with the nascent peptide chain while the SRP mediates its transfer to the endoplasmic reticulum. ▶SRP, ▶protein targeting, ▶translocons, ▶translocase, ▶signal hypothesis

TRAM: Transverse rectus abdominis muscle.

Tramp: An Apo-3 type TNF/NGF receptor. ▶Apo-3, ▶TNF, ▶NGF

Tramp: A polyadenylation cofactor complex of Trf4p (poly A polymerase)-Mtr4p (RNA helicase)-Air2p (zinc knuckle protein) involved with the 3'-5' exonuclease participating in RNA maturation and quality control (LaCava J et al 2005 Cell 121:713; Wyers F et al 2005 Cell 121:725).

Trance (RANK/ODF/OPGL): A tumor-necrosis factor-related activation-induced cytokine ligand (encoded at 13q14) that regulates T cell-dependent immune reactions and bone differentiation, bone mass, and Ca²⁺ metabolism. High levels of the RANK ligand (RNKL) may lead to bone breakdown (osteoporosis),

and estrogen treatment reduces bone loss. The RANKL cytokine triggers migration of human epithelial cancer cells and melanoma cells and leads to metastasis of cancer where RANK is expressed. Cancer metastasis to bones can be blocked using osteoprotegerin but not to other organs (Jones DH et al 2006 Nature [Lond] 440:692). Osteoprotegerin is a TGF-family osteoblast-secreted decoy receptor binding to osteoclasts; it inhibits their maturation. ▶TNF, ▶osteoclast, ▶osteoblast, ▶osteoporosis; Pearce RN et al 2001 Proc Natl Acad Sci USA 98:11581; Theill LE et al 2002 Annu Rev Immunol 20:795.

Trans: A trans position indicates that two genetic markers are not on the same molecule or not on syntenic parts of the chromatids. ▶cis arrangement, ▶syteny, ▶chromatid

Trans Arrangement of Alleles: The trans arrangement of alleles indicates that they are not in the same chromosome (DNA) strand (they are in repulsion). This is in contrast with the cis arrangement (coupling) where the two alleles are within the same strand. ▶coupling, ▶repulsion, ▶cis

Transacetylase: A protein which transfers an acetyl group from an acetyl coenzyme A (Acetyl-CoA) to another molecule. The third structural gene of the lactose operon (*lacA*) encodes a 275-amino acid polypeptide that forms a dimer of 60 kDa that is a transacetylase. ▶lac operon

Trans-Acting Elements: Proteins that are synthesized anywhere in the genome but which regulate transcription by attachment to specific sites of a gene. ▶cis-acting element

Transactivation Responsive Element (TAR): In the HIV transcript the Tat protein binds to the TAR sequence near the 5'-end. This binding then mediates an increased expression of the viral genes and the synthesis of more mRNA. The Rev protein binds to a specific RNA site and to the rev-responsive element (RRE), and facilitates the export of the unspliced transcript to the cytoplasm where viral structural proteins and enzymes are made. ▶acquired immunodeficiency, ▶VP16, ▶transactivator, ▶VDR

Transactivator: A protein domain attached to a specific inhibitory protein that may prevent blocking of transcription and may increase the transcription of the target gene(s) by several orders of magnitude. ▶transactivation responsive element, ▶Switch-Gene, ▶VP16, ▶p53, ▶tetracycline, ▶STAT, ▶two-hybrid method; Devaux F et al 2001 EMBO Rep 2:493; Lottmann H et al 2001 J Mol Med 79:321.

Transactive Catastrophy: The similar base sequences in different organisms or even within the same genome that may have different functional meanings.

Transaldolase Deficiency (TALDO1, 11p15.5-p15.4, a pseudogene is at 1p34.1-p33): Transaldolase deficiency causes cirrhosis of the liver and infantile hepatosplenomegaly (enlargement of the spleen and liver) and accumulation of metabolites of the pentose phosphate pathway (ribitol, D-arabitol and erythrol) in the urine and blood plasma. Male mice lacking transaldolase (TAL^{-/-}) are sterile because of defective forward motility. TAL^{-/-} spermatozoa show loss of mitochondrial transmembrane potential and mitochondrial membrane integrity because of diminished NADPH, NADH, and GSH (Perl A et al 2006 Proc Natl Acad Sci USA 103:14813). ▶[cirrhosis of the liver](#), ▶[pentose phosphate pathway](#), ▶[GSH](#); Verhoeven NM et al 2001 Am J Hum Genet 68:1086.

Transaminases: ▶[aminotransferases](#)

Transcapsidation (heteroencapsidation): The viral coat protein and the enclosed genetic material are of different origin (wolf in a sheep's skin). ▶[pseudovirus](#); Quasba PK, Aposhian HV 1971 Proc Natl Acad Sci USA 68:2345.

Transchromosomal (transchromosomal, TC): A cell which contains foreign chromosomal segments, e.g., a mouse cell with human chromosomal fragment(s). Human chromosome 21 or its fragments in mouse cells provide means of experimentation with Down's syndrome in mice (O'Doherty A et al 2005 Science 309:2033). ▶[chromosome uptake](#), ▶[somatic cell hybrid](#), ▶[alien addition](#), ▶[alien transfer](#), ▶[alien substitution](#), ▶[microcell](#), ▶[Down's syndrome](#); Tomizuka K et al 2000 Proc Natl Acad Sci USA 97:722.

trans-Cinnamic Acid: *trans*-cinnamic acid is formed from phenylalanine by phenylalanine ammonia-lyase and it is converted to a large number of compounds in plants (see Fig. T79). ▶[chalcones](#)

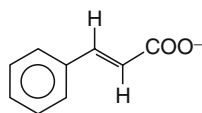


Figure T79. *trans*-Cinnamic acid

Transcobalamin (TCN1): A ligand and transporter of the B12 vitamin; it is encoded in human chromosome 11q11-q12.

Transcobalamin (TC2): A recessive condition which causes megaloblastic anemia, located at human chromosome 22q11 qter. ▶[megaloblastic anemia](#), ▶[anemia](#)

Transconjugant: The bacterial genetic material was (partly) derived by recombination during conjugation. ▶[conjugation](#)

Transcortin Deficiency (CBG): A dominant, human chromosome 14q31-q32 reduction in a corticosteroid-binding globulin. ▶[corticosteroid](#)

Transcribed spacer: A DNA element between genes that is transcribed but eliminated during the processing of the primary transcript. ▶[primary transcript](#)

Transcript: An RNA copied on DNA and complementary to the template. The average number of transcripts per genes is variable and it has been estimated to range from 0.3 to more than 9,400 copies in single human cells. The ENCODE project found 5.4 transcripts per human gene loci formed by alternative splicing. The low copy transcripts are very difficult to recognize. In the relatively small yeast genome, 606 genes showed no mRNA transcripts and 3,796 (~69%) displayed one or fewer transcripts per cell and only ~0.04% had more than 50 transcripts (Akashi H 2003 Genetics 164:1291). Highly important genes have biased usage of the synonymous codons and an abundance of isoacceptor tRNAs. Natural selection for efficient synthesis appears to favor shorter proteins in yeast but not necessarily in other eukaryotes. ▶[transcription](#), ▶[isoacceptor tRNAs](#), ▶[codon usage](#), ▶[intergenic transcript](#), ▶[transfrags](#), ▶[antisense transcript](#), ▶[ENCODE](#), ▶[alternative splicing](#); Velculescu VE et al 1999 Nature Genet 23:387; ▶[human transcript \[database\]](#)

Transcript Cleavage Factor: The transcript cleavage factor induces cleavage and then the release of the 3'-end of a 1- to 17-nucleotide RNA transcript while the 5'-end is still associated with the polymerase. The process may not terminate transcription and transcription may be reinitiated without a deletion in the transcript. In prokaryotes, *GreA* and *GreB*, in eukaryotes transcription factor TFIIIS carry out such functions. The role of the process may be to remove wrong sequences, facilitating the transition from initiation to the elongation phase and the escape of the polymerase from the promoter complex. ▶[RNA polymerases](#), ▶[promoter](#), ▶[transcription complex](#), ▶[transcription factors](#); Conaway JW et al 1998 Cold Spring Harbor Symp Quant Biol 63:357.

Transcript Elongation: Transcription has four basic phases: 1) promoter binding and activation of the RNA polymerase; 2) RNA chain initiation, followed by escape of polymerase from the TATA site; 3) transcript elongation; 4) termination of transcription and transcript release. The elongation phase in *E. coli* is marked by the release of the σ subunit of the

polymerase, the exit of the polymerase from the promoter, and the tight association between the polymerase, DNA template and the nascent transcript ternary complex. Transcript elongation in eukaryotes is quite similar. The rate of elongation varies because of sites of pause, arrest, and termination. In eukaryotes, in vivo the rate of transcription is ~1,200–2,000 nucleotides/minute but in vitro it is only 100–300/minute. Some of the DNA-binding proteins (such as repressors, CCAAT-binding proteins, etc.), gaps in the DNA, or drugs may interfere with elongation although few generalizations are possible at this time. In some instances, the RNA elongation and DNA replication may conflict. During development a variety of controls regulate transcript elongation. The rapid early embryonal development involves relatively shorter transcripts. The crystal structure and function of the RNA elongation complex of *Thermus thermophilus* bacterium has been elucidated (Vassilyev DG et al 2007 Nature [Lond] 448:157). ▶**promoter**, ▶**transcription factors**, ▶**σ**, ▶**walking**, ▶**transcription rate**, ▶**mediator complex**, ▶**elongator**, ▶**elongin**, ▶**ELL**, ▶**RNA polymerase**, ▶**error in transcription**, ▶**tryptophan operon**, ▶**transcription termination**, ▶**attenuation**, ▶**chromatin remodeling**, ▶**TRAP**, ▶**operon**, ▶**inchworm model**, ▶**DRB**, ▶**NELF**, ▶**TFIIS**, ▶**TEFb**, ▶**leukemias [MLL]**, ▶**Cockayne syndrome**, ▶**von-Hippel-Lindau syndrome**; Weliky Conaway J, Conaway RC 1999 Annu Rev Biochem 68:301; Wind M, Reines D 2000 Bioassays 22:327; Touloukhonov I et al 2001 Science 292:730; Pal M, Luse DS 2003 Proc Natl Acad Sci USA 100:5700; Shilatifard A et al 2003 Annu Rev Biochem 72:693.

Transcript Mapping: RNA transcripts are hybridized with specific DNA probes and subsequently the (not annealed) single strands are digested by S1 nuclease. Thus, the resistant (annealed) fragments represent the homologous tracts and demarcate the transcript. For the process of mapping an entire genome, sequence-tagged sites (STS) of cDNAs are used. By the PCR method, the STS sequences can be amplified and their position can be mapped either by YAC clones or by radiation hybrid panels. Using a high throughput system in yeast, 6.5 million probes of both strands of the DNA were interrogated. On rich media, 85% of the yeast genome is expressed. In addition to the expected transcripts, operon-like transcripts were also found. The intergenic regions did not separate some transcripts of adjacent genes, and different parts of the same gene expressed at different levels. Transcript mapping revealed an unexpectedly complex organization of this relatively simple eukaryotic genome (David L et al 2006 Proc Natl Acad Sci USA 103:5320). ▶**nucleic acid hybridization**, ▶**S1 nuclease**, ▶**STS**, ▶**radiation hybrid**, ▶**YAC**, ▶**PCR**, ▶**differential hybridization mapping**, ▶**transfrag**;

Barth C et al 2001 Curr Genet 39(5–6):355; Rinn JL et al 2003 Genes Dev 17:529; global transcript tiling: Bertone P et al 2004 Science 306:2242.

Transcriptase: DNA-dependent RNA polymerase or RNA-dependent DNA polymerase or RNA-dependent RNA polymerase enzyme. ▶**RNA polymerase**, ▶**reverse transcription**

Transcription: The synthesis of RNA complementary to a strand of a DNA molecule. In prokaryotes the majority of the transcriptionally active genes are located in the leading strand of replication and are transcribed in the same direction as the DNA synthesis. In the absence of a functional DNA helicase, genes involved in the replication of the lagging strand are hampered by the transcription complex fork and stalled for many minutes. If, however, the DNA helicase is present the replication fork on the lagging strand can quickly pass the RNA polymerase complex. In prokaryotes, transcription and translation are coupled unlike in eukaryotes where the mRNA must be released through the nuclear pore complex into the cytoplasm. Transcription is most commonly regulated by a variety of proteins (transcription factors). In the red clover necrotic mosaic virus (RCNMV), a subgenomic portion (sgRNA) of one of the two RNA genomes (RNA-1), a 34-base portion of the RNA-2, is required for the transactivation of transcription of sgRNA. In eukaryotes, transcription takes place in higher order transcriptional domains (16 in the mouse cell), which are usually independent from the replicational domains. In yeast, transcription and replication appear independent. Based on 678 loci, the Spearman rank correlation coefficient was found to be 0.45 (Washburn MP et al 2003 Proc Natl Acad Sci USA 100:3107). In *Drosophila*, transcriptional activity is correlated with DNA replication at the early S phase.

Transcription in eukaryotes is regulated by the intragenic pattern of the nucleosomal structure. In order to access the gene by RNA polymerase the nucleosomal arrangement must be loosened at the 5'-end of the gene but nucleosomal assembly is maintained downstream to prevent illegitimate transcription initiation. As transcription proceeds the nucleosomal structure is modified in front of the polymerase and reformed as it passes through a particular region. Histone acetylation at the promoter and other critical regions assures the beginning and continuation (elongation) of transcription. Histone deacetylation is mediated by methylation of histone H3 at lysine 36. H3 methylation at lysine 36 is brought about by protein complex Set2, which interacts with RNA polymerase 2 during elongation but not during transcription initiation. The Rpd3 smaller unit is attracted to H3Lysine36

(H3K36) and is involved in deacetylation of the 3'-coding sequences. The larger unit mainly carries out the deacetylation and suppression of the 5'-end promoter region. The Rpd3S and Set2 have functions similar to Spt in chromatin remodeling and function. The histone variant H2A.Z is localized to the nucleosome-free region ca. 200 bp upstream of the first codon of the promoter of many genes. It assists in chromatin remodeling by SWR1 (Lieb JD, Clarke ND 2005 Cell 123:1187). DNA topoisomerase II β (Topo II β), which breaks double-stranded DNA, is required in a signal-dependent manner for the initiation of transcription. Other essential factors include DNA-binding transcription factors, activating protein 1, DNA-dependent protein kinase 1, Ku86, Ku70, CBP coactivator and Pol II that were also recruited. The PARP-1 co-repressor complex (nucleolin, nucleophosmin, heat-shock protein 70) was rapidly eliminated after induction (Ju B-G et al 2006 Science 312:1798).

►pol, ►class II and class III genes of eukaryotes, ►transcription complex, ►transcription factors, ►transcription termination, ►regulation of gene activity, ►open transcription complex, ►chromatin remodeling, ►nucleosomes, ►histones, ►histone variants, ►signal transduction, ►mitochondria, ►mitochondrial genetics, ►chloroplasts, ►chloroplast genetics, ►replication fork, ►transcription complex, ►regulation of gene activity, ►Set motifs, ►Rpd3/Sin3, ►Spt, ►inchworm model, ►antitermination, ►RNA polymerase, ►transcription rate, ►pause transcriptional, ►Spearman rank-correlation test, ►antisense transcription, ►topoisomerases, ►DNA-PK, ►Ku86, ►Ku70, ►CBP, ►PARP, ►nucleolin, ►nucleophosmin, ►heat-shock proteins; Cold Spring Harbor Symp Quant Biol vol 63, 1999; Lee TI, Young RA 2000 Annu Rev Genet 34:77; Johnson KM et al 2001 Curr Biol 11:R510; Nature Rev Mol Cell Biol 2002 3:11; Kapranov P et al 2002 Science 296:916; Schübeler D et al 2002 Nature Genet 32:438; transcription/translation tool: <http://www.cbs.dtu.dk/services/VirtualRibosome/>.

Transcription Coactivator: A transcription coactivator activates RNA polymerase II but does not bind to DNA. (See Oswald F et al 2001 Mol Cell Biol 21:7761).

Transcription Cofactor: A transcription cofactor links a transcription factor to the transcription complex without binding directly to the DNA.

Transcription Complex: The TATA box-associated complex has the components TFIIA, TFIIB, TFIID, TFIIE, TFIIIF, TFIIH, TFIIJ, TFIIF, and RNA polymerase II. After the Pol II enzyme moves downstream and away from the preinitiation complex and is phosphorylated by a CTDK and TFIIH kinase

action, it can continue transcription in the absence of other regulatory factors although generally specific transcription factors (transactivators) may boost and regulate its activity (see Fig. T80).



Figure T80. Human TFIIE β c structure as determined by nuclear magnetic resonance analysis. This transcription factor binds to the DNA where the promoter opens up when RNA polymerase II initiates transcription. (From Okuda M et al 2000 EMBO J 19:1346. Courtesy Professor Y. Nishimura.)

Usually, a low level of phosphorylation of the heptapeptide repeats of the C terminus (CTD) of the largest subunit of the RNA polymerase is conducive to attraction to the promoter sequences and to the initiation of transcription. The yeast protein FCP is phosphatase, associated with the RNA polymerase II complex, and it facilitates the association of the polymerase to the preinitiation complex. Some transcription factors also play a role in translation. ►RNA polymerase, ►transcription factors, ►regulation of gene activity, ►SRB, ►TBP, ►snRNA, ►transcription factors, ►open promoter complex, ►Hogness (-Goldberg) box, ►Pribnow box, ►transcription shortening, ►CTD, ►elongation factors, ►TCF, ►nucleic acid chain growth; Wolfberger C 1999 Annu Rev Biophys Biomol Struct 28:29; transcriptional regulatory networks: Lee TI et al 2002 Science 298:799.

Transcription Corepressor: A transcription corepressor represses RNA polymerase II without binding to DNA.

Transcription, Ectopic: ►transcription, ►illegitimate

Transcription Factories: A transcription factory is formed when active genes move to shared nuclear subcompartments for transcription and move apart as

transcription ceases (Osborne CS et al 2004 Nature Genet 36:1065). Regions of different chromosomes may make contact within the nucleus and influence gene regulation (Dillon N 2006 Chromosome Res 14:117). Although the chromosomes have some special territories within the nucleus, the intermingling of territories can be visualized at finer resolution (Branco MR, Pombo A 2006 PLoS Biol 4(5):e138). Although some research has indicated that the nuclear periphery is a repressive compartment, newer work indicates that transcription of the mammalian β major-globin gene (responsible for thalassemia) begins at the periphery and that its transcription increases as it moves toward the interior. The locus control region assists in moving the β -globin gene from the nuclear periphery toward the nuclear interior during the maturation of erythroid cells (see Fig. T81). The DNA-dependent RNA polymerase II becomes hyperphosphorylated as it moves to the interior transcription factory (Ragoczy T et al 2006 Genes Dev 20:1447). In yeast, the *GAL* genes move to the nuclear periphery—near the nuclear pore complex—upon becoming transcriptionally activated by members of the SAGA histone acetyltransferase complex (Sus1, Ada2) (Cabal GG et al 2006 Nature [Lond] 441:770). Similarly, the activated subtelomeric hexokinase isoenzyme 1 (*HXK1*) gene moves to the nuclear periphery. This move, controlled by the 3'-untranslated region, is consistent with efficient processing and export of mRNA through the nuclear pore. If the gene was activated by VP16, it moves away from the periphery and induction by galactose abrogated. Accordingly, the nuclear position plays an active role in optimal gene expression (Taddei A et al 2006 Nature [Lond] 441:774). ▶chromosome territories, ▶nucleolus, ▶LCR, ▶RNA polymerase, ▶pol II, ▶SAGA, ▶VP16, ▶hexokinase; Lanctôt C et al 2007 Nature Rev Genet 8:104.

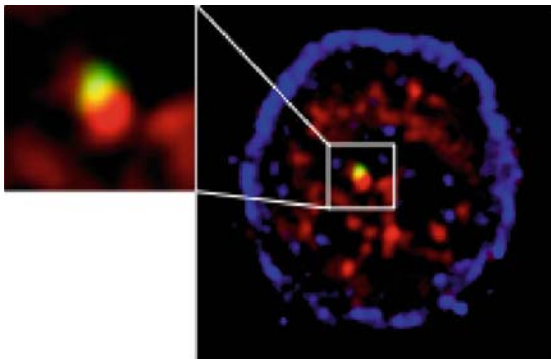


Figure T81. The β -globin locus (green) in the interior of the nucleus (blue) is associated with hyperphosphorylated Pol II (red). Courtesy of Tobias Ragoczy and Mark Groudine, Fred Hutchinson Cancer Research Center

Transcription Factors: A large number of different proteins that bind to either short upstream elements, terminator sequences of the gene, or to the RNA-polymerases and modulate transcription. These specific transcription factors occur in very large numbers and are essential for the function of genes in a particular manner. The $\sim 6,300$ genes of budding yeast are regulated by about 200 transcription factors. Zinc-finger proteins equipped with specific DNA-binding abilities are suitable for engineering functional roles and altered phenotypes such as drug resistance, temperature tolerance, and various developmental pathways (Park K-S et al 2003 Nature Biotechnol 21:1208). The general transcription factors have highly conserved sequences and are interchangeable even among such diverse organisms as mammals, *Drosophila*, yeast, and plants. The TAF proteins, by virtue of their different domains, can modulate the transcription of different genes. Also, the large TAF_{II} protein associated with the TFIID complex, by acetyl-transferase activity, can remodel the chromatin structure and using its amino-terminal kinase activity can transphosphorylate TFIIF and thus modulate transcription of protein genes in two different ways. TFIIB is also capable of self-acetylation as a means of regulating transcription (Choi CH et al 2003 Nature [Lond] 424:965). The specific transcription factors may form a large combinatorial network with various promoter elements.

The transcription factors for RNA polymerase I, transcribing ribosomal RNA genes, show a relatively simple organization (see Fig. T82).



Figure T82. Some transcription factors of RNA polymerase I

The UBF (upstream binding factor) binds upstream in the promoter and regulates transcription by acting as an assembly factor for the transcription complex. TIF-1 or its vertebrate homolog SL1 is required for the attachment of Pol I to the promoter and the accessory proteins A and B assist in the transcription.

The tRNAs, 5S rRNAs and some other small RNAs are transcribed by RNA polymerase III (Pol III). This enzyme has a requirement for protein factor TFIIB and in case of transcribing the 5S rRNA it also requires TFIIIA and TFIIC for the assembly of the transcription complex. Proteins TFIIIA and C, however, are detached after TFIIB binds and only the latter stays on the DNA when Pol III lands and the

transcription begins. TFIIB is not required for the transcription of the tRNAs. The Pol III transcription units also have internal control regions A (box 5'-TG GCNNAGTGG-3') and B (box 5'-GGTCGANN-3') or similar sequences. The U6 snRNA gene of yeast has an elaborate promoter (TATA box, downstream T₇ tract, upstream segment) in the non-transcribed strand. It provides a scaffold for the recruitment for the RNA polymerase III but it is deficient at a subsequent step of promoter opening by TFIIB. It is thus a rare type of single-strand promoter (Schröder O et al 2003 Proc Natl Acad Sci USA 100:934).

The transcription factors required for RNA polymerase II (Pol II), which transcribe protein-coding genes form the most elaborate complex.

The general transcription complex is initiated by binding the TBP (TATA-box-binding protein) subunit of general transcription factor TFIID to the TATA box of eukaryotes (Hogness box) (see Fig. T83). The TFIID complex exists in different forms (α and β) depending on its association with the TAF_{II}-30 protein (in β) or its absence (in α). The TATA box is present in upstream region genes, coding for protein and transcribed by RNA polymerase II. TFIID also attracts TFIIB. TFIID also brings the cleavage-polyadenylation specificity factor (CPSF) to the preinitiation complex and this assists in the formation of the 3'-end of the mRNA. After this, TFIIF, TFIIIE, and TFIIF proteins attach to RNA polymerase II (Pol II) to the TATA box. TFIIF expresses a DNA helicase function (encoded by xeroderma pigmentosum genes XPB and XPD) and a cyclin-dependent protein kinase activity (encoded by CDK7). TFIIF also stimulates transcript elongation by stimulating the phosphorylation of polymerase II and it plays a role in Pol I transcription. In addition, TFIIF stimulates a phosphatase, specific for the largest subunit of the RNA polymerase. The TFIIS protein factor in eukaryotes and *GreA* and *GreB* stimulates transcript cleavage and readthrough. It is a coactivator and regulator of transcription and it binds 3' to the TATA box. The Pol II is inactive at this stage until TFIIF phosphorylates the bound Pol II using ATP as a phosphate donor. The targets of phosphorylation are

several sites near the COOH-end of the largest subunit of pol II. TFIIF also has a helicase, ATPase, and nucleotide excision repair activities. It also mediates promoter melting and promoter clearance. Some genes may be transcribed without the kinase activity of TFIIF yet they need its helicase function. Eukaryotic RNA polymerase II generally contains nine or 12 subunits. The largest subunit is usually about 200 kDa. There are 26 (yeast) to 52 (mammals) repeats (Tyr-Ser-Pro-Thr-Ser-Pro-Ser) close to the carboxyl end. The phosphorylated Pol II then moves out of the complex and can now initiate transcription. The specific transcription factors are operative in special genes and at special tissues and time frames. The transcription factors may also bind a variety of other proteins before or during transcription and thus provide a great variety of fine-tuning of gene expression (Hager GL et al 1992 Curr Opin Genet Dev 12:137). The not absolutely essential TFIID TATA box-binding protein associated factors dTAF_{II} 42 and dTAF_{II} 62 form a heterotetramer resembling the heterotetrameric core of the histone octamer in the nucleosome. The TBP protein subunit of TFIID may also be dispensable in case TAF_{II}30 is present (named TFTC [TBP-free TAF_{II}-containing complex]). The general transcription factors are the basic instruments of transcription initiation but the modulation and regulation of transcription requires a large number of specific factors, activators, coactivators, suppressors and their interactions. Transcription factors with altered specificities can be generated in the laboratory using structure-based design and molecular technology. Besides the general transcription factors that are involved with almost all RNA polymerase II transcribed genes, specific and inducible transcription factors, activators and coactivators as well as chromatin reorganization factors also play an important role. Transcription factors participate in regulatory networks and display altered interactions to varying degrees. A few transcription factors serve as permanent hubs but most act transiently only during certain conditions (Luscombe NM et al 2004 Nature [Lond] 431:308). Quantifying the affinities of molecular interactions is

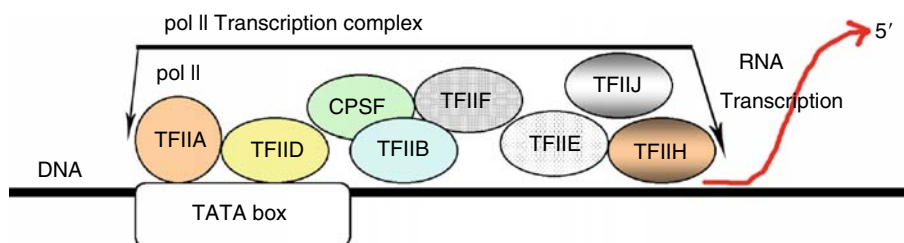


Figure T83. General transcription complex

difficult because of the large number of variables involved. Also, the interactions are transient and exhibit nanomolar to micromolar affinities, leading to rapid loss of bound material or little bound material. Protein-protein and protein-DNA binding microarrays are especially susceptible to loss because of their stringent wash requirements and may lose weakly bound material. A high-throughput microfluidic platform capable of detecting low-affinity transient binding events on the basis of the mechanically induced trapping of molecular interactions eliminates the off-rate problems facing current array platforms and allows for absolute affinity measurements. Basic helix-loop-helix (bHLH) transcription factors generally bind to a consensus sequence of 5'-CANNTG-3' (N is any nucleotide) called enhancer box or E box, which is the second most conserved motif in higher eukaryotes. Members of the bHLH family show mid- to low nanomolar DNA binding affinities and have off rates above 10^{-2} s^{-1} for their consensus sequences with orders of magnitude higher off rates for non-consensus sequences. The transcription factor binding energy topographies were measured with highly integrated microfluidic devices. The biological function of two yeast transcription factors could be successfully predicted by combining purely in vitro biophysical measurements with informatics knowledge of the genome (Maerkl SJ, Quake SR 2007 Science 315:233).

In the roots of *Arabidopsis*, 80% of the transcription factors seem to be regulated by their upstream noncoding sequences and about one-fourth of the transcription factors are regulated posttranscriptionally by microRNAs or intercellular protein movement (Le J-Y et al 2006 Proc Natl Acad Sci USA 103:6055) (see Fig. T84).

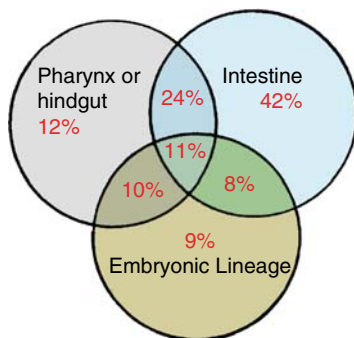


Figure T84. Transcription factor (117) interactions with 72 genes in *Caenorhabditis*. (After Deplancke B et al 2006 Cell 125:1193)

The human genome has ~1,850 transcriptional regulators; that of *Arabidopsis* has 1,533 (~5.9%) whereas *Drosophila*, *Caenorhabditis* and budding

yeast have 635 (4.3%), 669 (3.5%) and 209 (3.5%), respectively. Tissue-specific transcription factors (FOXA2, HNF1A, HNF4A and HNF6) bound to 4,000 orthologous gene pairs in hepatocytes have been purified from human and mouse livers. Despite the conserved function of these factors, 41 to 89% of their binding events seem to be species specific (Odom DT et al 2007 Nature Genet 39:730). These molecules may be further explored for basic research and gene therapy. Viral repressors may prevent the association of RNA polymerase II with the transcriptional preinitiation complex. Using multiphoton microscopy special transcription factor functions can be visualized in vivo (Yao J et al 2006 Nature [Lond] 442:1050). Procedures have been developed for probabilistic predictions for the identities of binding sites and their physical binding energies between transcription factors and DNA (Kinney JB et al 2007 Proc Natl Acad Sci USA 104:501). The nucleosomal structure in eukaryotes must accommodate transcription factors so they can reach the DNA. It seems that spontaneous unwrapping of nucleosomes rather than histone dissociation or chromatin remodeling provides the means for access to the DNA (Bucceri A et al 2006 EMBO J 25:3123).

►TF, ►TBP, ►mtTF, ►transcription complex, ►DNA binding, ►SRB, ►CTD, ►CDK, ►SWI, ►class II and class genes, ►Pol II [RNA polymerase II], ►RNA polymerase, ►regulation of gene activity, ►genetic networks, ►genome-wide location analysis, ►protein synthesis, ►gene therapy, ►ABC excinuclease, ►transcriptional activators, ►co-activators, ►nuclear receptors, ►transcriptional modulation, ►transcript elongation, ►STAGE, ►TFIIS, ►mtTFA, ►CAAT box, ►enhancer, ►regulation of gene activity, ►chromatin, ►chromatin remodeling, ►nucleosome, ►FOX, ►HNF, ►FACT, ►coactivator, ►transactivator, ►SAGA, ►HMG, ►promoter, ►open promoter complex, ►GAGA, ►gene number, ►transcription rate, ►inchworm model, ►pause transcriptional, ►NAT, ►mediator, ►elongator, ►FACT, ►PITSLRE, ►reinitiation of transcription, ►JASPAR, ►xeroderma pigmentosum, ►multiphoton microscopy, ►Hogness (-Goldberg) box, ►Pribnow box, ►transcription complex; Myer VE, Young RA 1998 J Biol Chem 273:27757; Riehmman JL et al 2000 Science 290:2105; Conaway RC, Conaway JW 1997 Progr Nucleic Acid Res Mol Biol 56:327; Hampsey M 1998 Microbiol Mol Biol Rev 62:465; Pauli MR, White RJ 2000 Nucleic Acids Res 28:1283; Lemon B, Tjian R 2000 Genes & Development 14:2551; Misteli T 2001 Science 291:843; Svejstrup JQ 2002 Current Opin Genet Dev 12:156; Burley SK, Kamada K 2002 Current Opin Struct Biol 12:225; Warren AJ 2002 Current Opin Struct Biol 12:107; Roulet E et al 2002 Nature Biotechnol 20:831; Ponting CP 2002 Nucleic

Acids Res 30:3643; Gerland U et al 2002 Proc Natl Acad Sci USA 99:12015; Cosma MP 2002 Mol Cell 10:227; Lee TI et al 2002 Science 298:799; Bushnell DA et al 2004 Science 303:983; transcriptional regulatory code: Harbison CT et al 2004 Nature [Lond] 431:99; statistical detection of cis-regulatory motifs in eukaryotes: Gupta M, Liu JS 2005 Proc Natl Acad Sci USA 102:7079; transcription factor binding site detection: Li X et al 2005 Proc Natl Acad Sci USA 102:16945; transcription factor binding site identification by immunoprecipitation: Euskirchen GM et al 2007 Genome Res 17:898; <http://www.ifti.org>; <http://compel.bionet.nsc.ru/FunSite.html>; <http://www.gene-regulation.com/pub/databases.html>; transcriptional start site database: <http://dbtss.hgc.jp>; transcription factor binding sites: <http://bio.chip.org/mapper>; binding sites: <http://genome.imim.es/datasets/abs2005/index.html>; transcription factor binding site tools in humans and mouse: http://hscl.cimr.cam.ac.uk/TFBSCluster_genome_portal.html; comparative genomics-based resource for initial characterization of gene models and the identification of putative cis-regulatory regions of RefSeq Gene Orthologs: <http://genometra-fac.cchmc.org>; mammalian binding site prediction: <http://pdw-24.ipk-gatersleben.de:8080/VOMBAT/faces/pages/choose.jsp>; transcription binding site prediction: <http://www.bioinfo.biocenter.helsinki.fi/poxo>; promoter models and binding sites: <http://www.gene-regulation.com/pub/programs/cma/CMA.html>; transcription factor binding sites in yeast: <http://cgl.iis.sinica.edu.tw/~mybs/>; over-represented binding sites: <http://www.cisreg.ca/oPOSSUM/>.

Transcription Factors, Designed: These include DNA-binding Zinc-finger domains fused to either gene activation or suppression domains. Such constructs may up- or down-regulate the expression of selected targets by affecting chromatin remodeling. ▶ [zinc finger](#), ▶ [polyamide](#), ▶ [fermentation](#); Urnov FD et al 2002 EMBO Rep 3:610; Rebar EJ et al 2002 Nature Med 8:1427; Blancafort P et al 2003 Nature Biotechnol 21:269.

Transcription Factors, Inducible: Inducible transcription factors are proteins that are synthesized within the cell in response to certain agents or metabolites. They bind to short upstream or downstream DNA sequences and affect transcription, frequently by looping the bound DNA back to the promoter area and forming an association with the other protein factors and the general transcription factors. Such transcription factors may be hormones, heat-shock proteins (DNA binding site consensus: CNGAANNTCCNNG), phorbol esters (TGACTCA), serum response elements (CCATATAGG), etc. These protein factors exert their specificity in gene regulation not only by discriminative ability for

individual genes (since their numbers must be lower than that of the genes), but by their modular assembly. ▶ [transcription factors](#), ▶ [hormone response elements](#), ▶ [heat-shock proteins](#), ▶ [HSTF](#), ▶ [regulation of gene activity](#); Mathew A et al 2001 Mol Cell Biol 21:7163; regulated combinations: Setty Y et al 2003 Proc Natl Acad Sci USA 100:7702.

Transcription Factors, Intermediary: Intermediary transcription factors do not associate directly with the promoter but either affect the conformation of the DNA or “adapt” other proteins to the transcription complex. ▶ [open promoter complex](#), ▶ [regulation of gene activity](#); Steinmetz AC et al 2001 Annu Rev Biophys Biomol Struct 30:329.

Transcription Factor Map: The transcription factor map identifies the binding sites of transcription factors in the genome. The binding sites are important in the regulation of development, differentiation, and carcinogenesis. The positions can be revealed by enhancer-binding assays (Hallikas O et al 2006 Cell 124:47) or alternatively a paired-end ditag procedure can be used. The latter procedure found 542 binding sites for p53 (Wee C-L et al 2006 Cell 124:207). ▶ [enhancer](#), ▶ [transcriptome](#), ▶ [p53](#), ▶ [DNA binding protein domains](#), ▶ [paired-end diTAG](#)

Transcription Illegitimate (ectopic transcription): Illegitimate transcription takes place when very low-level transcripts are detected in organs, tissues or developmental stages where these special transcripts are not expected to occur. Usually, nested primers are employed for the amplification. ▶ [housekeeping genes](#), ▶ [tissue-specificity](#), ▶ [nested primer](#); Salbe C et al 2000 Int J Biol Markers 15:41.

Transcription Initiation (transcription start): The DNA forms a transcription bubble when transcription begins. In about 60% of the human genes CpG sequences are located 5' in the early-replicating, highly acetylated gene-rich regions (Cross SH et al 2000 Mamm Genome 11:373). The phage T7 RNA polymerase undergoes a major conformational change at the amino-terminal 300 residues. This then entails the loss of the promoter-binding site and facilitates promoter clearance when the initiation is followed by transcript elongation. The RNA transcript peels off of a seven-base pair heteroduplex and an exit tunnel is created for the enhanced processivity of the elongation complex. ▶ [replication bubble](#), ▶ [promoter clearance](#), ▶ [processivity](#), ▶ [TSS](#); Yin YW, Steitz TA 2002 Science 298:1387; Young BA et al 2002 Cell 109:417; Pokholok DK et al 2002 Mol Cell 9:799; <http://elmo.ims.u-tokyo.ac.jp/dbtss>.

Transcription Rate: The transcription rate may vary from gene to gene and site. Based on fluorochrome

labeling of the β -actin RNA and serum induction indicated 1.1 to 1.4 kb per minute. Yeast RNA polymerase II can synthesize 1.2 kb long sequences/min. The single-subunit bacteriophage RNA polymerase can incorporate in vitro 12–24 kb nucleotides/minute. The bacterial enzyme can build in 3–6 kb/min in vivo and 0.6–2 kb/min in vitro. ▶RNA polymerase, ▶transcription factors, ▶transcript elongation, ▶error in transcription; Brem RB et al 2002 Science 296:752.

Transcription Shortening: RNA polymerase II (RNAP II) hydrolyzes the 3' end of the transcript as part of the process of reading through pause signals and also secures fidelity of the transcription. It requires a TFIIS protein.

Transcription Termination in Eukaryotes: The ribosomal gene cluster is generally terminated much beyond the 28S rRNA gene and at about 200 bp upstream from the core promoter of the following pre-rRNA cluster. In mouse, the Pol I termination signal contains a Sal I box (5'-AGGTCGACCAG [T/A][A/T]NTCCG-3') preceded by T-rich clusters. The actual termination is within the T-rich area and it is assisted by the Sal I box and the T-rich sequences around it. In humans, the conserved repeats (5'-GACTTGACCA-3') terminate pre-tRNA transcription. In *Xenopus* (5'-GACTTGC-3'), repeats and T-rich sequences in the spacer region bring about termination. Probably some proteins bind to the Sal I box. Recently, polypeptide chain release factors (RF) have also been identified in eukaryotes. In yeast, the carboxy-terminal domain (CTD) of the DNA-dependent RNA polymerase II (Pol II) contains a consensus sequence YSPTSPS in multiple copies. Different phosphorylation patterns recruit RNA processing factors after phosphorylation of CTD serine 2. These factors are required for both transcription and termination of transcription. Although Pol II proceeds with transcription beyond the polyadenylation signal, the polyadenylation system cleaves the transcript and the RNA is degraded by the Rtt103 complex and the Rat1/Rai 5'→3' exonucleases joined to the 3'-end of the protein genes, ending transcription (Kim M et al 2004 Nature [Lond] 432:517). The termination mechanism in humans is very similar to that in yeast and it occurs co-transcriptionally (CoTC) by an exonuclease called Xrn2 (West S et al 2004 Nature [Lond] 432:522). The termination in this manner is called torpedo model because the transcription is "torpedoed" at the end. The *Drosophila* N-TEF protein releases the Pol II transcript in an ATP-dependent manner. The Reb-1 yeast protein stops the polymerase and mediates the transcript release. The mouse TTF-1 protein, similarly to Reb-1, binds to the DNA and

brings about termination. Thus the termination mechanisms in different species vary substantially.

In case of DNA, template damage during transcription ubiquitylation at the carboxy-terminal repeat domain (CTD) takes place. If the serine 5 residue (involved in chain elongation) and CTD is phosphorylated, ubiquitylation is inhibited (Somesh BP et al 2005 Cell 121:913).

In the mtDNA a 34 kDa protein (mTERM) is bound to a 13-residue sequence embedded in the tRNA^{Leu(UUR)} and the complex is required for termination of transcription. The MAZ protein may regulate the transcription from different promoters in closely spaced genes. The poly(A) signal is required for the termination of transcription but before the actual termination pretermination cleavage of the RNA transcript takes place. Therefore, before Pol II is released from the DNA it must transcribe the pretermination cleavage site and also the poly(A) signal. ▶polyadenylation signal, ▶transcription termination in prokaryotes, ▶mRNA, ▶rho factor; Langst G et al 1998 EMBO J 17:3135; Dye MJ, Proudfoot NJ 2001 Cell 105:669.

Transcription Termination in Prokaryotes: Transcription termination in prokaryotes can be rho-independent (intrinsic terminators exist in the RNA polymerase) and rho-dependent, i.e., the RNA polymerase requires the cofactor rho for termination of transcription. The terminator regions in various systems have similar structures. They consist of palindromic sequences that can fold back into a hairpin. In the rho-independent terminator there are one or more G≡C rich sequences in the stem; at the base of the stem there are about six consecutive U residues. This structure mediates a pause in the movement of the RNA polymerase thus causing dissociation from the DNA template because the ribosyl-U of the transcript can make only weak hydrogen bonds with the deoxyribosyl-A in the DNA. In the rho-dependent termination, rho recognizes 50 to 90 bases before the hairpin facilitates termination. The *E. coli* protein NusA promotes folding of the hairpin and termination. The λ N protein promotes antitermination. Polypeptide release factors (RF) may also be used in both prokaryotes and eukaryotes. On lambda phage templates, the N-terminal of the 109-amino acid Nun protein of phage HK022 blocks transcription by binding to BOXB on the nascent RNA transcript of the pL and pR operons; and the C-terminal domain interacts with the RNA polymerase. If the RNA polymerase ternary complex (at 3'-OH end) cleaves the transcript, transcription may be reinitiated as long the upstream sequences remain firmly aligned with the DNA. The prokaryotic proteins *GreA* and *GreB* and the eukaryotic TFIIS may favor transcript cleavage.

(See Fig. T85, ▶antitermination, ▶lambda phage; Washio T et al 1998 Nucleic Acids Res 26:5456; Gusarov I, Nudler E 2001 Cell 107:437; Unniraman S et al 2000 Nucleic Acids Res 30:675; Kashlev M, Komissarova N 2002 J Biol Chem 277:14501).

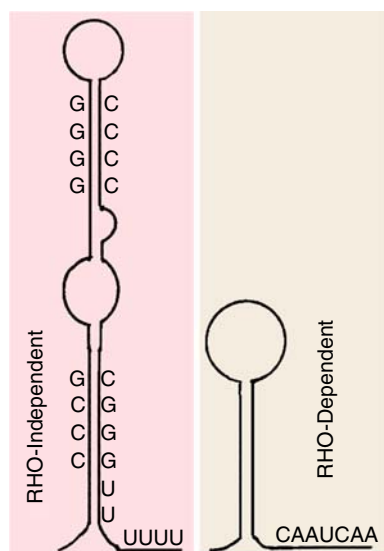


Figure T85. Transcription terminator sequences in prokaryotes

Transcription Unit: The DNA sequences between the initiation and termination of transcription of a single or multiple (co-transcribed, multi-cistronic) gene(s).

Transcriptional Activators: Transcriptional activators are proteins that facilitate the activity of DNA-dependent RNA polymerase(s) in prokaryotes and eukaryotes. Transcription activators may have two independent domains: DNA-binding domain and transcriptional activating domain.

These domains may not have to be covalently associated and dimeric association may carry out their function. In the abstract sketch (see Fig. T86), the dimeric activators stimulate transcription by recruiting the components of the transcription complex to the TATA box, even when transcription may be hindered in their absence or in the presence of the monomers. Employing several of the activators in a non-covalently bound bundle may enhance the potency of transcriptional activation. The addition of six or eight extraamino acids to the yeast Gal4 activator has generated artificial activators. The new activators may have higher or more specific activity. Many of the transcriptional activators (Myc, Jun, etc.) are unstable in the cell and are destroyed by calpains, lysosomal proteases and, most commonly, by ubiquitin-mediated proteolysis. Actually, the activation and the ubiquitination domains functionally

overlap. ▶positive control, ▶negative control, ▶transcription factors, ▶POU, ▶DNA binding proteins, ▶catabolite activator, ▶regulation of gene activity, ▶FK506, ▶FKBP12, ▶transcription complex, ▶GCN5, ▶transcription termination, ▶transcriptional modulation, ▶SW, ▶VDRI, ▶suppression, ▶degron, ▶N-degron, ▶N-end rule, ▶ubiquitin, ▶calpain, ▶destruction box, ▶lysosomes, ▶chromatin remodeling, ▶co-activators; Ptashne M, Gann A 1997 Nature (Lond) 386:569; Hermann S et al 2001 J Biol Chem 276:40127; Lu Z et al 2002 Proc Natl Acad Sci USA 99:8591.

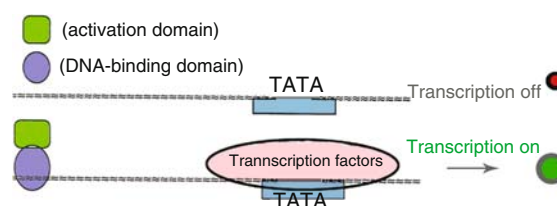


Figure T86. Transcriptional activation

Transcriptional Adaptor: A histone acetyltransferase, acylating histone in the chromatin before activation of transcription. The yeast gene *GCN5* affects, specifically, histones 3 and 4. ▶histone, ▶nucleosome, ▶transcription, ▶transcription initiation

Transcriptional Coactivator: ▶TAF_{II}, ▶co-activator, ▶GCN, ▶coactivators

Transcriptional Control: The regulation of protein synthesis at the level of transcription. ▶regulation of gene activity, ▶signal transduction, ▶transcription factors, ▶operon, ▶regulon

Transcriptional Error: When cytosine is deaminated to uracil in the template DNA strand and the error is not repaired, adenine is incorporated in the RNA transcript in place of guanine (to be inserted by the RNA polymerase). This may be translated into a defective or aberrant protein. Such a mutation may take place in nondividing cells. ▶error in translation

Transcriptional Gene Fusion Vector: The transcriptional gene fusion vectors carry transcription-termination codons (stop codons) in front of the promoterless structural gene, so when the structural gene fuses to a host promoter and is thereby expressed (transcribed with the assistance of a host promoter), it will contain only the amino acid sequences specified by the inserted DNA. ▶gene fusion, ▶read-through proteins, ▶translational gene fusion, ▶trapping promoters, see Figs. T87 and T88.

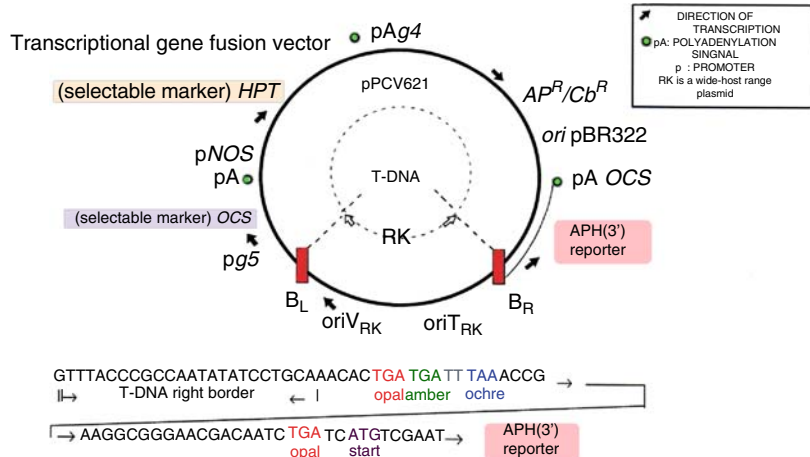


Figure T87. In the transcriptional gene fusion vector the reporter (APH[3']II, or luciferase or GUS) has no promoter and it is fused to the right border of the T-DNA. The reporter gene is expressed only if it integrates behind a plant promoter that can provide the promoter function. In front of the structural gene here, there are four nonsense codons to prevent the fusion of the protein with any plant peptides. Transcriptional fusion vectors are similar in other groups of organisms. For other symbols and abbreviation see translational gene fusion vectors. (Based on oral communications by Dr. Csaba Koncz)

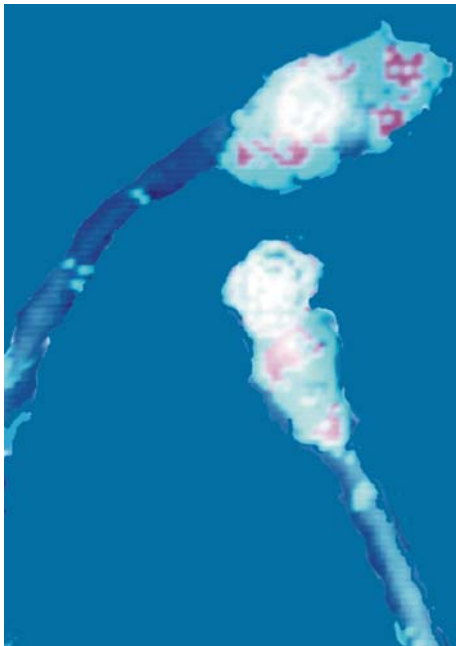


Figure T88. Transcriptional *in vivo* gene fusion of bacterial luciferase genes to a flower-bud-specific promoter of *Arabidopsis*. The highest level of expression is indicated in red (false color). The background is photographically cleared. (From Rédei GP, Koncz C, Langridge WHR, unpublished)

Transcriptional Gene Silencing (TGS): Transcriptional gene silencing is based on mechanisms of methylation of DNA and chromatin remodeling by proteins or

RNA. ►methylation of DNA, ►chromatin remodeling, ►silencer, ►dosage compensation, ►imprinting

Transcriptional Landscape: The pattern of transcriptional control signals and the transcripts generated.

Transcriptional Modulation: In many transcription factors proline- and glutamine-rich activation domains exist and modulating effects are attributed to them. ►transcriptional activators, ►transcription factor, ►transcriptional suppressor, ►WD-40; Rushlow C et al 2001 Genes Dev 15:340.

Transcriptional Noise: The variation in the rate of transcription due to the assembly of the preinitiation complex, TATA box sequence, TATA box-binding proteins, activators, coactivators, regulatory elements, reinitiation of transcription and thus translation. This noise determines the heterogeneity of gene expression in different cells of the organism and contributes to differentiation and phenotypic differences. ►noise; Blake et al 2003 Nature [Lond] 422:633.

Transcriptional Pause: Pause transcriptional.

Transcriptional Priming: Transcriptional priming occurs when multipotential progenitor cells can be induced to develop into different cell types. GATA-2 and PU.1 transcription factors may have antagonistic or cooperative effects in the determination of cell fate. GATA-2 is required for the generation of mast cells but is not required for differentiation of macrophages. The Ets family member PU.1 is necessary for myeloid and lymphoid cells but not for erythroid or

megakaryocyte lineages. In addition, PU.1 directs the differentiation of hematopoietic cells into macrophages. ►GATA, ►PU.1, ►stem cells; Walsh JC et al 2002 *Immunity* 17:665.

Transcriptional Profiling: ►microarray hybridization

Transcriptional Regulation: ►transcription factors, ►regulation of gene activity, ►quelling, ►methylation of DNA, ►co-suppression, ►posttranscriptional gene silencing, ►RNA noncoding; Carlson M 1997 *Annu Rev Cell Dev Biol* 13:1; Vaucheret H, Fagard M 2001 *Trends Genet* 17:29; Myers LC, Kornberg RD 2000 *Annu Rev Biochem* 69:729; Arnosti DN 2003 *Annu Rev Entomol* 48:579; <http://rulai.cshl.edu/TRED>.

Transcriptional Slippage: Transcriptional slippage occurs when the RNA polymerase transcribes longer or shorter RNA sequences than the actual template, either during initiation or the elongation process. Slippage generally occurs when the template has homopolymeric sequences. (See Larsen B et al 2000 *Proc Natl Acad Sci USA* 97:1683).

Transcriptional Start Site: ►TSS, ►transcription initiation

Transcriptional Suppressor: A transcriptional suppressor can tightly bind to the operator or to other upstream elements of the DNA and thus prevent the initiation of transcription by elements (activators) of the transcription complex. Mot1 is an ATP-dependent inhibitor of the TATA box-binding protein and the members of the NOT complex inhibit the transcription machinery by various ways (TBP, TAF, etc.). Heterochromatin protein (HP1) and histone methyl transferase may also repress genes. ►transcriptional activator, ►transcriptional coactivator, ►transcriptional modulation, ►nucleosome, ►mating type determination in yeast, ►silencer, ►MADS box, ►inhibition of transcription; Ma Y et al 2001 *J Biol Chem Online* Sept 27; Hwang K-K et al 2001 *Proc Natl Acad Sci USA* 98:11423.

Transcriptional Synergy: Multiple transcription factors exert greater effect together than the sum of their individual contributions to gene regulation. ►transcription factors; Green MR 2005 *Mol Cell* 28:399.

Transcriptional Targeting: Transcriptional targeting intends to limit the expression of therapeutically used transgenes to specific cells, e.g., tumor cells. This goal is achievable by the use of tissue-specific promoters, e.g., the carcinoembryonic antigen is expressed mainly in colon and liver cells. The α -fetoprotein promoter is specific for hepatocellular carcinoma. The erbB2 promoter is expressed predominantly in breast tumors and the prostate-specific

antigen is active in prostate cancer. Inducible promoters may be protected from a viral enhancer by insulator elements. ►insulator; Brand K 2004, p 531. In: *Gene and Cell Therapy*. Smyth Templeton N (Ed.) Marcel Dekker, New York.

Transcriptional-Coupled Repair: ►DNA repair, ►excision repair, ►colorectal cancer

Transcriptome: The collection of RNAs transcribed from the genome; transcriptomics is the generation and study of the mRNA profile of the cell. In a single human cell about half of all the genes may be expressed and a total of about 25,000 to 30,000 unique genes are expressed in a human body. The total number of transcripts in the different tissue cells of these unique genes was found to be 134,135. Some genes were expressed only at 0.3 copies per cell while others had up to 9,417 transcripts. About 1,000 transcripts were expressed in five copies in all cells. In some cancer cells some transcripts were present in about 10 copies but absent in normal cells. 40 genes were expressed in all types of cancer cells in about three copies, and this was twice the number for normal cells. The length of the transcripts can be determined by the use of GIS (gene identification signature). The 5' and 3' ends (18 nucleotides each) of full-length cDNAs are extracted and concatenated into paired-end ditags (PETs). These are then mapped to genome sequences to tag the ends of every gene and then these signatures indicate the complete transcription units between the end signatures (Ng P et al 2005 *Nature Methods* 2:105).

The majority of yeast genes have two or more *transcription start sites*. The analysis revealed 667 transcription units in the intergenic regions and transcripts derived from antisense strands of 367 known features. It turned out that 348 open reading frames carry start sites in their 3'-halves to generate sense transcripts starting from inside the reading frame. Thus, the budding yeast transcriptome is considerably more complex than previously thought, and it shares many recently revealed characteristics with the transcriptomes of mammals and other higher eukaryotes (Miura F et al 2006 *Proc Natl Acad Sci USA* 103:17846).

►expression profile, ►SAGE, ►MPSS, ►RIDGE, ►GIS, ►Atlas human cDNA, ►non-ribosomal peptides; Velculescu VE et al 1999 *Nature Genet* 23:387; Caron H et al 2001 *Science* 291:1289; Camargo AA et al 2001 *Proc Natl Acad Sci USA* 98:12103; Appendix II-10; Su AI et al 2002 *Proc Natl Acad Sci USA* 99:4465; Bono H, Okazaki Y 2002 *Current Opin Struct Biol* 12:355; Wu LF et al 2002 *Nature Genet* 31:255; autoannotation tool: <http://jbirc.jbic.or.jp/tact/>; plant transcriptome: <http://plantta.tigr.org>.

Transcriptome Map: 2–30 genes occupy a co-regulated domain in the genome and represent 20 to 2,000 kb. The co-regulated expression domains may control metabolic, developmental and organ-specific pathways. They also occupy nuclear sub-compartments, such as the nucleolus where ribosomal genes and proteins congregate. Neighboring genes mediate histone and nucleosome modifications involved in epigenetic changes. The nucleolus contains the ribosomal proteins and RNA. In cancer, neighboring loci can also be activated and this permits the construction of transcriptome correlation maps (Reyal F et al 2005 Cancer Res 65:1376). ▶[chromatin remodeling](#), ▶[chromosome territories](#); Kosak ST, Groudine M 2004 Science 306:644; Stolc V et al 2004 Science 306:655.

Transcripton: A unit of genetic transcription.

Transcriptosome: A complex of RNA processing proteins (capping enzymes, splicing factors, etc.) within the nucleus, associated with the COOH-terminal domain of the large subunit of RNA polymerase II. ▶[RNA polymerase](#), ▶[transcription factors](#), ▶[post-transcriptional processing](#), ▶[capping enzymes](#), ▶[splicing](#); Halle JP 7 Meisterernst M 1996 Trends Genet 12:161.

Transcytosis: Transcytosis is a process by which immunoglobulin (or other molecules) is/are transported within a vesicle from a secreting cell across the epithelial layer to another domain of the plasma membrane and also receptor-mediated processes of the capillary veins, by a type of endocytosis. ▶[endosome](#); McIntosh DP et al 2002 Proc Natl Acad Sci USA 99:1996.

Transdetermination: A particular pathway of differentiation is overruled by genetic regulation thus e.g., at the *Antp* (*Antennapedia* locus, 3–47.5) “gain of function mutants” in *Drosophila* the antenna is transformed into a mesothoracic leg or a wing in the place of an eye, etc. These changes in the developmental pattern may be associated with chromosomal rearrangements. The breakpoints may be within the promoters.

They may be altered as a cause of transcript heterogeneity and alternate splicing of the transcripts.

Transdetermination occurs in plants (snapdragon, *Arabidopsis* and others) by transforming anthers and pistil into petals and by producing sterile full flowers (see Fig. T89). In animals, transdetermination occurs by changing *Drosophila* antennae into legs, etc. Suppression of the Polycomb group of proteins by JNK signaling induces the changes in the imaginal disks of *Drosophila* (Lee N et al 2005 Nature [Lond] 438:234). ▶[morphogenesis](#), ▶[homeotic genes](#), ▶[imaginal disk](#), ▶[polycomb](#), ▶[JNK](#), ▶[stem cells](#),

▶[determination](#); Hadorn E 1978 Sci Am 219:110; Maves L, Schubiger G 1998 Development 125:115; Wei G et al 2000 Stem Cells 18:409; Glotzer M et al 2001 Annu Rev Cell Dev Biol 17:351.

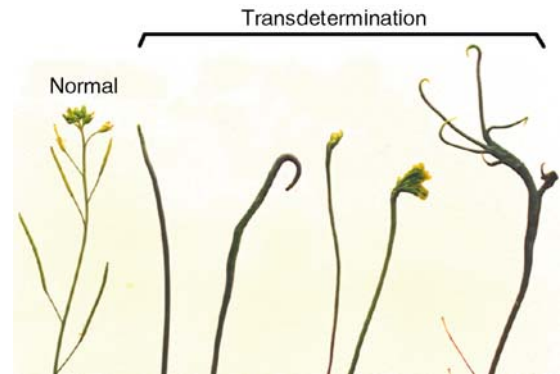


Figure T89. The apical meristem developed into horn- or antler-shape structures rather than into a normal inflorescence (at left) in *Arabidopsis* mutants (Rédei GP, unpublished)

Transdifferentiation: Transdifferentiation is a rare biological phenomenon when one type of differentiated cells is converted into another discrete type. ▶[transdetermination](#), ▶[regeneration](#)

Transdominant Molecules: Transdominant molecules are used to selectively inhibit gene expression, e.g., antisense RNA, decoy RNA, ribozymes, suppressor proteins, single-chain antibodies. ▶[antisense technologies](#), ▶[suppressor RNA](#), ▶[RNAi](#), ▶[suppressor gene](#), ▶[ribozymes](#), ▶[tumor infiltrating lymphocytes](#), ▶[tumor suppressor factors](#), ▶[TNF](#); Kamb A, Teng DH 2000 Curr Opin Mol Ther 2:662.

Transducer Proteins: Transducer proteins respond to effectors to relay information to cytoplasmic components of the excitation path to switch molecules. After the effector is diluted out, the adaptation pathway leads the restoration to the base condition. (See Wang C et al 2001 Nature [Lond] 412:285).

Transducianism: ▶[creationism](#)

Transducin: A G-protein, G_t , involved in transduction of light signals (RAS-related proteins) regulating cyclic GMP phosphodiesterase. It is activated by cholera toxin and inhibited by the pertussis toxin. ▶[G_t protein](#), ▶[cholera toxin](#), ▶[pertussis toxin](#), ▶[transduction](#), ▶[retinal dystrophy](#); Norton AW et al 2000 J Biol Chem 275:38611.

Transducing Phage: ▶[transduction](#)

Transductant: A transduced cell. ▶[transduction](#)

3' Transduction: Through retrotransposition, the 3' flanking sequences of L1 transposons may move to a position downstream to the poly(A) signal of the parental L1 sequence and it is retained there. This may occur in 10 to 20% of the new retrotranspositions. Much less frequently, 5' transduction can also occur in a similar manner. Such events may rearrange exons and regulatory sequences and may lead to the evolution of new genes. ▶LINE, ▶poly(A) signal, ▶exon shuffling; Moran JV et al 1999 Science 283:1465.

Transduction: The transfer of DNA from one cell to another. In human molecular genetics, the transduced gene, or the transgene, is expected to be expressed in the new location. ▶transformation, ▶transfection

Transduction, Abortive: Transduced DNA is not integrated into the bacterial chromosome and it therefore fails to replicate among the bacterial progenies and is diluted out during the subsequent cell divisions. The non-replicating abortively transduced genetic material is transmitted in a unilinear fashion. See Fig. T90, ▶transduction generalized, ▶transduction specialized; Stocker BAD 1956 J Gen Microbiol 15:575.

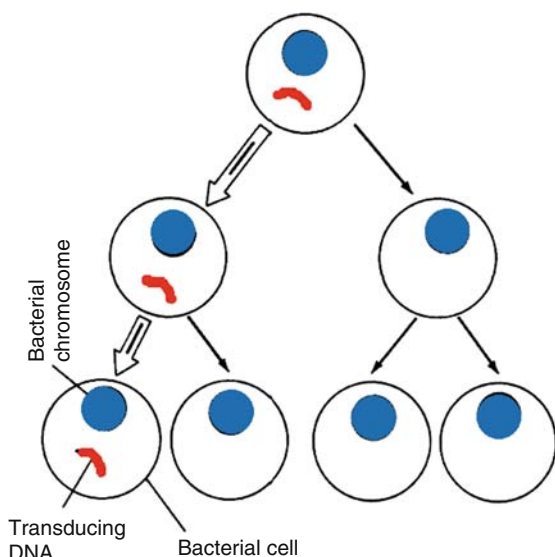


Figure T90. Abortive transduction

Transduction, Generalized: A phage-mediated transfer of *unspecified* genes among bacteria (lysogenic or non-lysogenic). The virulent phage breaks down the host cell DNA into various size fragments by the process called lysis. The transducing phage coat may then scoop up fragments of the DNA that fit into the capsule (head) that may not contain any phage genetic material. The DNA fragments enclosed in the phage head are picked up at random from the proper

size group of the bacterial DNA without regard to the genes located in the fragments. For productive transduction the transferred fragments must be stably integrated into the chromosome of the recipient bacteria. ▶specialized transduction, ▶transduction abortive, ▶transduction mapping, ▶pac site, ▶marker effect, see Fig. G23 in generalized transduction; Lederberg J et al 1952 Cold Spring Harbor Symp Quant Biol 16:413.

Transduction Mapping: Determines the map position of very closely linked bacterial genes on the basis of co-transduction frequencies; e.g., if the donor DNA is $a^+ b^+$ and the recipient bacterium is $a^- b^-$ then the recombination frequency is $[(a^+ b^-) + (a^- b^+)] / [(a^+ b^-) + (a^- b^+) + (a^+ b^+)]$. ▶transduction generalized [see Fig. G23].

Transduction, Specialized (or restricted): A temperate-phage-mediated transfer of *special* genes between bacteria. Transduction may be mediated in higher eukaryotes by horizontal transmission, transposable and retrotransposable elements. ▶specialized transduction [see Fig. G23], ▶transposable elements; Morse ML 1954 Genetics 39:984.

Transesterification: An esterase enzyme catalyzes a replacement reaction. A nucleophile displaces an alcohol during the hydrolysis of an ester. A similar reaction occurs when, in nucleic acid processing, phosphodiester exchanges take place at the splice junctions of exons and introns. ▶splicing, ▶introns

TRANSFAC: A database for transcription factors and their binding sites. ▶transcription factors; <http://www.gene-regulation.com/>; <http://www.gene-regulation.com/pub/databases.html>.

Transfection: Originally, the term was coined for introduction of viral RNA or DNA into bacterial cells and the subsequent recovery of virus particles. Today, it is used for introduction of foreign DNA into animal cells where the genes may be expressed. The delivery system may be through microinjection, bombardment (gene gun), electroporation, DEAE dextran, calcium phosphate precipitation of the target cell membranes, liposomes, and polyamidoamine dendrimers (highly branched cationic polymers). After delivery, the DNA needs protection from elimination and degradation by nucleases, opsonins, and endocytosis. Nuclear targeting may be facilitated by polyethylene glycol. Nuclear localization signals, combined with peptide nucleic acid, may facilitate homing in on the nucleus. There may be other hurdles to overcome such as cytotoxicity, condensation of the DNA, tissue targeting, etc. ▶transduction, ▶transformation genetic, ▶microinjection, ▶reverse transfection, ▶DEAE dextran, ▶biolistic transformation,

►electroporation, ►liposomes, ►receptor-mediated gene transfer, ►opsonin, ►endocytosis, ►nuclear localization sequences, ►peptide nucleic acid, ►polyethylene glycol; Földes J, Trautner TA 1964 Z Vereb-Lehre 95:57; Lug D, Saltzman WM 2000 Nature Biotechnol 18:33.

Transfectoma: A hybridoma cell producing a specific mouse/human chimeric antibody. ►hybridoma, ►antibody; Sun LK et al 1991 J Immunol 146:199.

Transfer Clockwise/Counterclockwise: The bacterial F plasmid may be integrated in different orientations and at different locations in the bacterial chromosome and thus Hfr strains may be formed that transfer the chromosome either clockwise or counterclockwise during conjugation. ►Hfr, ►conjugation, ►clockwise, ►counterclockwise

Transfer Factors: Bacterial plasmids capable of transferring information from one bacterial cell to another through conjugational mobilization. Some of the factors (e.g., ColE1) may not have genes for transfer yet they may be transferred to other cells by helper function of conjugative plasmids. These transfer factors may contain genes for resistance (transposable elements) and have great medical significance because of the transfer of antibiotic resistance and thus make the defense against pathogenic infection difficult. ►antibiotics, ►transposable elements bacterial, ►colicins, ►resistance transfer factors

Transfer Horizontal: Same as transfer lateral.

Transfer, Lateral: In lateral transfer, genetic information is transmitted by “infection” (horizontally) or by plasmids rather than by sexual means (vertical transfer). This transfer accounts for a great deal of the variation in prokaryotes. Many species of bacteria take up and maintain extracellular DNA, especially under conditions of starvation. In 22 prokaryotic genomes, the average horizontally acquired sequences constitute ~6% of the genome (Dufraigne C et al 2005 Nucleic Acids Res 33(1):e6). *Salmonella* synthesizes a histone-like nucleoid structuring protein (H-NS) that selectively silences horizontally acquired genes, which contain lower GC content than the recipient genome and thereby protects its fitness against potentially less favorable genes (Wiley Navarre W et al 2006 Science 313:236). Mitochondrial and plastid genes can also transmit horizontally during evolution of higher organisms (Rice DW, Palmer JD 2006 BMC Biol 4:31). The fraction of horizontally transferred genes is not equally frequent among and between phylogenetically distant organisms. In Archaea the Pfam family of protein domains may be laterally acquired in >50%, and in three taxonomic ranges of bacteria, the horizontal transfer

was found to be 30–50% when examined at three taxonomic ranges. In Eukarya, it was <10%. In certain gene families the horizontal transfer was more prevalent than in others (Choi IG, Kim S-H 2007 Proc Natl Acad Sci USA 104:4489). ►incongruence, ►lateral transmission; Pfam, Finkel SE, Kolter R 2001 J Bacteriol 183:6288; Koonin EV et al 2001 Annu Rev Microbiol 55:709.

Transfer Line: A polyploid species carrying a relatively short foreign chromosomal segment in its genome. The transfer is generally made either by crossing over between homoeologous chromosomes, in the absence of a gene or chromosome (chromosome 5B in wheat) that would normally prevent homoeologous pairing. It can be obtained also by (X-ray) induced translocation. Construction of such lines may have agronomic importance for introducing disease resistance or any other gene(s) that are not available in the cultivated varieties or their close relatives. ►alien addition, ►chromosome substitution, ►alien substitution, ►homoeologous chromosome; Sears ER 1972 Stadler Symp 4:23.

Transfer RNA (tRNA): Genes coding for tRNAs are clustered in both prokaryotes and eukaryotes. Some of the tRNA genes are located within the spacer regions of the ribosomal gene clusters.

The majority of tRNA genes is clustered as a group in the DNA, and frequently occurs in –two to three copies. In *Drosophila*, 284 tRNA genes have been identified. In humans there are 497 (plus 324 pseudogenes), in *Caenorhabditis* 584 tRNA genes. Some *E. coli* tRNA (86) gene clusters include genes for proteins. The tRNA genes within the cluster are separated by intergenic sequences and are transcribed as long pre-tRNA sequences. The primary transcript is processed at the 5'-end by RNase P and at the 3'-end by RNase D, BN, T, PH, RNase II, and polynucleotide phosphorylase. The pre-tRNA processing also involves joining the fragments after introns are removed by tRNA ligase multifunctional enzymes (Englert M, Beier H 2005 Nucleic Acids Res 33:388). In the *Nanoarchaeum equitans* bacterium, separate sequences code for the 5' and 3' halves of some tRNAs (Randau L et al 2005 Nature [Lond] 433:537). Before the tRNAs are released to the cytoplasm their integrity is ascertained and only the mature and structurally correct molecules are exported in a Ran-guanosine triphosphate dependent manner. Newer information indicates that in yeast tRNA can shuttle between nucleus and cytoplasm (Takano A et al 2005 Science 309:140).

Aminoacylation takes place before export from the nucleus. The tRNAs are small molecules (70–90 nucleotides). They assume a “clover leaf” secondary structure formed by single-stranded loops and

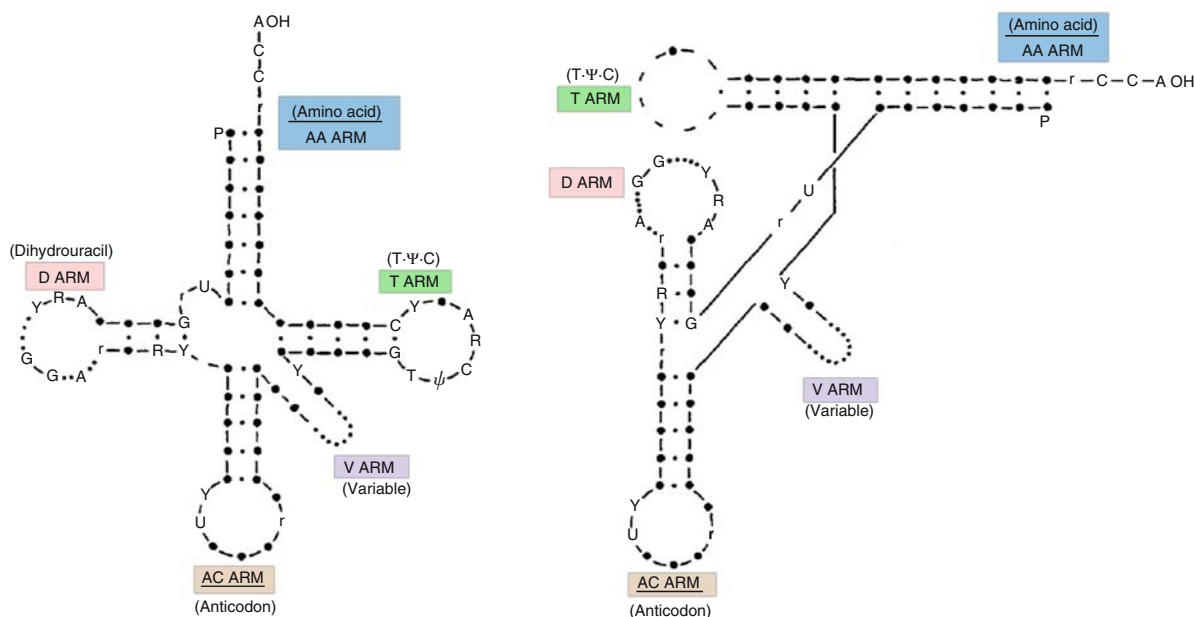


Figure T91. The general structural features of tRNAs. Left: The cloverleaf; Right: The L-shaped tertiary conformation. R stands for purine and Y for pyrimidine bases in all tRNAs; R and Y indicate the occurrence of these bases in many tRNAs; ψ is pseudouridine. (After Kim SH 1976. *Progr. Nucleic Acid Res. Mol. Biol.* 17:181.)

double-stranded sequences. *Caenorhabditis* and some other nematodes have two unusual, yet functional, types of tRNAs: one lacks the T arm and the other lacks the D arm but has a short T arm (Watanabe Y et al 1994 *J Biol Chem* 269:22902).

The functioning tRNAs assume an L-shape configuration (see Fig. T91). After being charged with amino acids (aminoacylation), they haul the amino acids to the ribosomes for translation of the genetic code (protein synthesis). The amino acids are attached to the protruding C-C-A-(OH) amino acid arm and one of the C residues interact directly at the P site with the G2252 and G2253 of the 23S ribosomal subunit of prokaryotes. The 3'-CAA is generally added enzymatically to the tRNA after transcription (Tomita K et al 2004 *Nature [Lond]* 430:700) but some bacterial tRNA genes also encode this sequence (Xiong Y, Steitz TA 2004 *Nature [Lond]* 430:640). The crystal structure and mechanism of function of the CCA-adding RNA polymerase has been elucidated (Tomita K et al 2006 *Nature [Lond]* 443:956). The anticodon loop contains a triplet complementary to the amino acid code word. This anticodon recognizes the code in the mRNA on the surface of the ribosome. The D-arm (dihydrouracil loop) is the recognition site for the aminoacyl-tRNA synthetase enzyme, whereas the T-arm (a thymine-pseudouracil [ψ]-C consensus loop) recognizes the ribosomes. There is also a small variable loop (V arm). Besides the anticodon site, the tRNAs have differences in bases at

other positions too. The tRNA^{Glu} and tRNA^{Gln} can be quite similar yet different as shown in the Figure T92 of the *Staphylococcus aureus* molecule. In eukaryotes, glutamyl-tRNA synthetase directly acylates tRNA^{Gln}. Bacteria and archaea use a tRNA-dependent transamidation process. The first step for Gln-tRNA synthesis is the formation of misacylated Glu-tRNA^{Gln} by a glutamyl-tRNA synthetase, which is used for the formation of Glu-tRNA^{Glu}. This tRNA is converted through transamidation by Glu-tRNA^{Gln}, an amidotransferase. The crystal structure of this bacterial enzyme has been determined (Oshikane H et al 2006 *Science* 312:1950; Nakamura A et al 2006 *Science* 312:1954).

The presence of modified nucleotides is characteristic for tRNAs and they modulate the anticodon domain structure for many tRNA species to accurately translate the genetic code (Yarian C et al 2002 *J Biol Chem* 277:16391). These modifications take place right after transcription or during processing. A small fraction of the base pairs in tRNA are non-conventional, i.e., G-U or A-C and these mispairings are widespread among species and have functional significance, i.e., they enhance aminoacylation and translation (McClain WH 2006 *Proc Natl Acad Sci USA* 103:4570).

The number of tRNAs in prokaryotes is higher than the number of genetic code words (64); in prokaryotes the number of different tRNA molecules may run into hundreds in the different species. In the

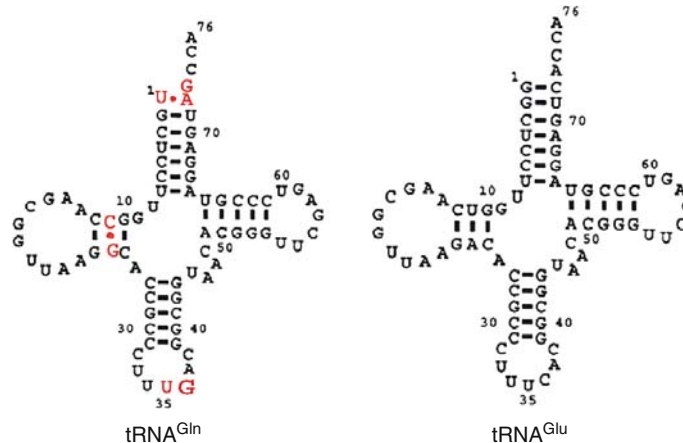


Figure T92. Differences in glutamine and glutamic acid tRNAs in *Staphylococcus*. (Modified from references cited)

nematode *Caenorhabditis elegans*, sequencing the entire genome identified 659 tRNA genes and 29 pseudogenes. Since there are only 20 amino acids, of the high number of tRNAs several deliver the same amino acid to the site of translation (isoaccepting tRNA). The amino acid accepting *identity* of transfer RNAs resides within the base sequences and structural features of the tRNAs that are then recognized by aminoacyl tRNA synthetase enzymes. The tRNAs possess dual functions: synthetase and editing, i.e., the removal of the wrong amino acid if attached. The mRNA site recognition is the property of the anticodon. The vast majority of animal and fungal mitochondria synthesize their own tRNAs (about 22). Their anticodon reads the codons by the first two bases and thus do not need isoaccepting tRNAs. Their structure usually lacks the pseudouridine loop, and there are other minor variations. The mitochondria of land plants, algae, *Paramecium*, *Tetrahymena* and *Trypanosomes* partially rely on tRNA import. Organelle tRNAs similarly to those of plants, add post-transcriptionally the 3'-CAA amino acid accepting terminus, in contrast to some cases of *E. coli*. The mitochondrial tRNAs in plants are generally quite variable and show similarities also to the chloroplast tRNAs. The chloroplast tRNAs of higher plants (about 30) may frequently be coded by more than one tract. The universal genetic code requires a minimum of 32 different tRNAs. However, in actuality 26–24 tRNAs (with special wobbles) may suffice for protein synthesis. The mammalian and some fungal mitochondria do not code for all the tRNAs required and import these nuclearly-coded molecules from the cytosol. Many fungi code for 25–27 tRNA genes, however. In *Caenorhabditis*, the tRNA gene number and the number of tRNAs are highly correlated, and the estimated number of tRNA genes is 579 plus 207 tRNA like pseudogenes. Prokaryotes and chloroplasts have a special

tRNA^{F-Met} for the initiation of translation and the same anticodon, CAU may recognize not only the Met codon (AUG) but three other initiator codons as well. Nematodes initiate translation with UUG, which is a leucine codon. tRNAs are used as primers for reverse transcription. During amino acid starvation in bacteria, the guanosine tetraphosphate (ppGpp) is manufactured on the ribosomes with the aid of cognate, uncharged tRNA. Attenuation requires the cooperation of tRNA. In eukaryotes, a unique glutamyl-tRNA reductase mediates the formation 5-amino-levulinic acid, which contributes to the porphyrin ring. ▶tRNA, ▶fMet, ▶rrn genes for tRNAs within ribosomal gene clusters, ▶aminoacyl-tRNA synthase, ▶isoaccepting tRNAs, ▶code genetic, ▶wobble, ▶isoacceptor tRNA, ▶ribosome, ▶mitochondrial genetics, ▶mtDNA, ▶chloroplasts, ▶chloroplast genetics, ▶ribonuclease P, ▶Ran, ▶stringent response, ▶attenuation, ▶porphyrin, ▶modified bases, ▶codon usage, ▶ARAGORN; Giege R et al 1993 Progr Nucleic Acid Res Mol Biol 45:129; Morl M, Marchfelder A 2001 EMBO Rep 2:17; Grosshans H et al 2000 J Struct Biol 129:288; Beuningen PJ, Musier-Forsyth K 1999 Biopolymers 52:1; Intine RV et al 2002 Mol Cell 9:113; tRNA genes: <http://www.tRNA.uni-bayreuth.de>; tRNA functional [initiator, suppressor] classification: <http://tfam.lcb.uu.se/>.

Transfer, Vertical: As per vertical transfer, genetic information is transmitted by sexual means rather than by horizontal, infection type mechanisms.

Transferase Enzymes: Transferase enzymes move a chemical group(s) or molecule(s) from a donor to an acceptor.

Transferrin (TF): A β -globulin (M_r ~75,000–76,000) that transports iron. The encoding gene is located in human chromosome 3q21; the transferrin receptor

(TfR) gene was located nearby. Adenosine ribosylation factors affect the cellular redistribution of transferrin and endocytosis. Transferrin receptor 1 facilitates the infection by New World hemorrhagic viruses (Radoshitzky SR et al 2007 Nature [Lond] 446:92). ▶endocytosis, ▶BLYM, ▶RAC, ▶receptor-mediated gene transfer, ▶hemochromatosis, ▶aceruloplasminemia, ▶atransferrinemia, ▶ferroportin, ▶blood-brain barrier; Aisen P et al 2001 Int J Biochem Cell Biol 33:940.

Transformant: A cell or organism that has been genetically transformed by the integration of exogenous DNA into its genetic material. ▶transformation

Transformation Associated Recombination (TAR): Yeast cells are transformed simultaneously by a YAC vector (TAR) with terminal human genomic repeats, such as Alu and a long piece of human genomic DNA containing interspersed repeats (Alu). Recombination between the YAC and the human genomic DNA within the homologous repeats yields large, stable circular YACs that can be used for mapping or cloning. If the TAR vector contains an *E. coli* F-factor cassette, the vector can be propagated also in bacterial cells. ▶YAC, ▶Alu, ▶F factor, ▶vector cassette; González-Barrera S et al 2002 Genetics 162:603; Kouprina N, Larionov V 2006 Nature Rev Genet 7:805.

Transformation by Protoplast Fusion: ▶protoplast fusion

Transformation, Genetic: Information transfer by naked DNA fragments or plasmid, obviating traditional sexual or asexual processes in prokaryotes and in eukaryotes. Transformation procedures may be transient when the introduced DNA is not being integrated into the genome of the cell. It may also be permanent when the exogenous DNA becomes an integral part of the recipient's genetic material.

Bacterial Transformation. Genetic transformation was discovered in bacteria in the late 1920s. It became a widely used genetic method only in the 1950. Originally, only naked bacterial DNA was used in fragments of 1/200 to 1/500 of the genome. This was provided to *competent* bacterial cells at a concentration of 5–10 µg/mL culture medium. The exogenous DNA can synapse with the bacterial genome and generally only one strand of the transforming DNA is integrated into the recipient, although some bacteria (e.g., *Haemophilus influenzae*) preferentially take up double-stranded DNA from their own species but integrate only one of the strands. Recognition of the homospecific DNA is mediated by uptake signal sequences (USS).

5'-AAGTGC GGT in the plus and 5'-AC CGCACTT in the minus strand. In the completely

sequenced genome of 1,830,137 bp, 1,465 such USS were recognized. *Neisseria gonorrhoeae* also has USS elements (5'-GCCGTCTGAA).

Bacterial transformation generally may not involve an addition, rather a replacement of a part of the DNA of the recipient cell, except when plasmids are used. The non-integrated parts of the donor DNA are degraded and the rest replicates along the genes as a permanent integral part of the bacterial chromosome. The frequency of bacterial transformation may be in the range of 1% or as low as 10^{-3} to 10^{-5} , however, using bacterial protoplasts (spheroplasts) up to 80% transformation is attainable. For bacterial transformation most commonly various genetic vectors are used. Although different empirical procedures are employed in different laboratories, some general features of the methods are obvious. For transformation, either high molecular weight (DNase-free) DNA or plasmids (phage), dissolved in $1 \times \text{SSC}$, is used. Competence in recipient bacteria is induced by CaCl_2 , MnCl_2 , reducing agents and hexamine cobalt chloride or competent cells are purchased in a frozen state from commercial sources. Highly competent cells may yield ca. 10^7 to 10^9 colonies per 1 µg plasmid DNA. The success of transformation is improved by highly nutritious culture media and good aeration. The recognition of transformant cells is greatly facilitated by selectable markers. Transformation of bacteria by electroporation may be extremely efficient (10^{10} transformants/µg DNA). Cultures in mid-log phase are chilled and washed by centrifugation in low-salt buffer. The cells (3×10^{10} /mL) are suspended then in 10% glycerol and can be stored on dry ice or -70°C for up to half year. Thawed aliquots of the cells are mixed with properly prepared donor DNA and exposed to high voltage electric field in small volumes (20–40 µL). Gram-positive bacteria such as *Bacillus subtilis*, is more difficult to transform genetically than the Gram-negative bacteria, e.g., *E. coli*. *B. subtilis* attracted interest for cloning because it is not pathogenic for humans. In the presence of the *B. subtilis* *recE* transformation is facilitated if the cell contains already a plasmid homologous to the vector. Also, spheroplasts in the presence of polyethylene glycol, take up exogenous DNA much easier. Vectors derived from *Staphylococcus aureus* containing tetracycline-(pT127) or chloramphenicol-(pC194) resistance has been successfully used for the development of vectors. *Staphylococcus aureus* is a serious pathogen. Shuttle vectors containing *E. coli* pBR322 and *S. aureus* plasmid elements were also used. Some of the antibiotic resistance genes, e.g., β -lactamase, have very different expression in different species of bacteria. *Streptomyces* were of substantial interest for transformation because of their efficient production of antibiotics. They can be transformed by a sex

plasmid, liposomes and phage vectors. ►competence, ►SSC, ►DNA extraction, ►electroporation, ►vectors, ►cloning vectors, ►liposome, ►β-lactamase, ►antibiotics, ►sex plasmid

Fungal Transformation. Is not entirely different from that in prokaryotes. Transformation of *Neurospora* started already during the early 1970 and caused genetic instabilities in the genome (see RIP). Transformation of budding yeast begun in the late 1970s and became very useful for various types of studies (cloning, YACs, gene replacement, etc.). Yeast cells are grown to about 10^7 density/mL and then suspended in a stabilizing buffer containing 1 M sorbitol. Subsequently the cell wall is removed by digestion with β-glucanase (an enzyme hydrolyzing glucan, the polysaccharide of the cell wall [yeast cellulose]). To the washed spheroplasts in sorbitol, in the presence of CaCl₂ and polyethylene glycol (PEG4000), the donor DNA is added. After about 10 min incubation of the mixture, the cells are gently embedded in 3% agar and layered over a selective medium in a Petri plate. The frequency of transformation depends a great deal on the type of vector used (between 1 to 10^6 colonies per μg DNA). Alternatively — although with lower yield — intact yeast cell have been treated with lithium salts before the DNA and polyethylene glycol is applied. This is followed by selection after spreading the cells onto the surface of selective media. This procedure does not require the production of spheroplasts and agar embedding. Both of these procedures may cause mutations. Similar methods of transformation have been used also in other fungi (*Neurospora*, *Aspergillus*, *Podospora*) and also in green algae. Shuttle vectors were advantageous for the transfer of genes between various fungi and between fungi and bacteria. ►YAC, ►gene replacement, ►episomal vector, ►integrating vector, ►replicating vector, ►centromeric vector, ►shuttle vector

Transformation of Animal Cells. The most commonly used procedures involve precipitation of the donor DNA with calcium phosphate or DEAE-dextran. The precipitated granules may enter animal cells by phagocytosis and up to about 20% of the cells may integrate the donor DNA into the chromosomes. By precipitation, physically unlinked DNA molecules can also be transformed (cotransfected) into the cultured animal cells. The polycation Polybrene (Abbott Laboratories trade name for hexadimethrine bromide) is also used to facilitate the transformation by relatively low molecular weight DNA (plasmid vectors) when some other procedures are not working. Electroporation has also been successfully applied for stable or transient introduction of DNA into the cells. Bacterial (or even plant) protoplasts can also be used to bring about fusion of cell membrane

(in the presence of polyethylene glycol) and this may be followed by transfer of plasmid DNA into animal cell nuclei. This procedure is less efficient than endocytosis mediated by calcium phosphate and the plasmids are frequently integrated in tandem into the chromosome(s) of vertebrates. The exogenous DNA may be introduced also by direct *microinjection* into (pro)nuclei or into embryonic stem cells (ES) and thus generate chimeras (see gene transfer by microinjection). In the latter case the transformed cells can be screened for insert copy number or the insert can be targeted to a specific site by homologous recombination. *Infection* of stem cells, bone marrow, zygotes, early embryos by vectors or by isolated chromosomes is also feasible (►gene transfer by microinjection). Transformation of cultured sperm cells followed by fertilization is another alternative (Kurita K et al 2004 Proc Natl Acad Sci USA 101:1263). Transformation of spermatogonial stem cells of rats with DNA containing geneticin (G418) constructs are capable of self-renewal and retain the ability to colonize recipient testes, remain euploid and thus provide a means for gene targeting and obviate the need for embryonic stem cells (Hamra FK et al 2005 Proc Natl Acad Sci USA 102:17430).

Gene replacement by homologous recombination (►targeting) is also an option. In the latter case sufficient information is required about the needs for critical cis-acting elements. The success of transformation of animal cells varies a great deal according to cell types used. Transformation of vertebrate cells became a very important tool of molecular biology and reversed genetics but unfortunately the transformed cells cannot be regenerated into complete individuals, except when germline or ES cells are transformed. In *Drosophila*, into the cloned P element an isolated gene can be inserted with the aid of genetic engineering and the element may be then microinjected into a young embryo where the DNA can integrate into the chromosome resulting in a stably transformed individual fly. The procedure is particularly effective if the P element vector is equipped also with a selectable marker. In mosquitos microinjection into the egg cells is feasible but was not very effective. A more successful approach was using viral vectors with the vesicular stomatitis virus glycoprotein envelope, which binds to the cell membrane and delivers the foreign DNA. Transgenic rhesus monkeys were produced by injecting pseudotyped replication-defective retroviral vector into the perivitelline space and later fertilized by intracytoplasmic injection of sperm (ICSI) into mature oocytes. ►hybrid dysgenesis, ►ammunition, ►smart ammunition, ►SV40 vectors, ►adenoma, ►Bovine Papilloma Virus vectors, ►retroviral vectors, ►DEAE-dextran, ►Polybrene, ►electroporation, ►polyethylene glycol,

►liposome, ►gene replacement, ►targeting genes, ►surfection, ►transgenic, ►gene therapy, ►ES, ►vesicular stomatitis virus, ►*Anopheles*, ►pseudotyping, ►ICSI, ►SMGT; Chan AW et al 2001 Science 291:309; for protocols: Ravid K, Freshney RI (Eds.) 1998 DNA Transfer to Cultured Cells. Wiley-Liss, New York.

Transformation of Plants. Can be carried out by a variety of procedures. Most extensively used were the techniques of infecting leaf or root explants or protoplasts or seeds by agrobacteria, carrying genetically engineered plasmids.

Practically all dicots can be readily transformed by agrobacteria but some monocots (*Dioscorea*, *Narcissus* and *Asparagus*) could also be transformed. The difficulty with monocot transformation by agrobacteria is apparently caused by the lack of secretion of substances needed for the activation of the virulence gene cascade or monocot cells fail to develop competence in response to infection by *Agrobacterium*. The DNA can be introduced, however by the biolistic methods.

The vector plasmids are either cointegrate or binary. Cointegrate plasmids contain in cis also the virulence genes of the Ti plasmids whereas in the binary vectors the virulence genes are carried by a separate small helper plasmid. Common features of all the vectors are that the genes to be integrated into the plant chromosome are in-between the two 25 bp inverted repeats of the T-DNA. The virulence genes and all other DNA sequences are not integrated into the host genetic material. The left and right border sequences are important for successful transformation but only a few bp of the left border and either none or 1 to 3 bp of the right border are retained in the host (►*Agrobacterium*, ►Ti plasmid). The insertional target is not strictly specified in plants yet a few base similarities are frequently found. It appears that the border repeats scout for appropriate target sites and they are appositioned there. The plasmid virulence genes direct this process also and the bacterial chromosome has also some genes that assist the transformation. The target suffers initial staggered nicks, followed by degradation, and the DNA within the 25 bp borders of the T-DNA is integrated into the chromosome (see Fig. T93). In *Arabidopsis* the histone-2A gene appears to be required for the integration of the T-DNA.

In order to be expressed, the genes within the T-DNA generally carry appropriate (plant compatible) eukaryotic promoters and polyadenylation signals to be expressed in the plant cells. Some vectors may lack promoters and can be expressed only when fused (upon integration) in vivo with plant promoters. These may be translational or transcriptional fusion vectors. The translational fusion vectors lack the

translation initiation methionine codon in order to facilitate the fusion of the structural gene in the T-DNA with some amino acid sequences of the plant host. The purpose of these types of transformation is to study the strength and tissue-specificity of different plant promoters and study the function of fusion proteins. The transcriptional fusion vectors carry one or more translational stop codons (nonsense codons) in the nucleotide tract preceding the ATG (translation initiation codon). Because of this, the structural transgene will be expressed if a genuine plant promoter will drive it and no fusion protein is obtained. These vectors are also shuttle vectors, they can be propagated in agrobacteria and *E. coli*. Being shuttle vectors greatly facilitates various manipulations. The vectors can be replicated in *E. coli* because they have the origin of replication of the pBR322 plasmid and outside the boundaries of the two T-DNA sequences carry genes *oriV* (required for replication) and *oriT* (required for transfer) in *Agrobacterium*. The latter genes were derived from the promiscuous (wide host range) RK plasmid. Aseptically (axenically) grown plant tissues may start the transformation procedure. The vector cassettes generally carry selectable markers, most commonly for resistance against hygromycin B or kanamycin. The gene fusion reporter genes may be (bacterial or firefly) luciferase or GUS (β -glucuronidase) because of the easy monitoring, and the time and space of expression of the fused reporter gene. ►transcriptional gene fusion vector, and ►translational gene fusion vector

Scalpel generally wound the plant explants as they are harvested. Then the tissues dipped into a fresh bacterial suspension (grown to a density of about 10^6 , washed and diluted to about half or less in plant nutrient solution). After the bacteria are blotted off the plant material is incubated for 2 days on the surface of an agar medium in Petri plates (see embryogenesis somatic). Following incubation the bacteria are stopped either by claforan (syn. cefotaxime) or carbenicillin and the plant cells are grown further in media containing also hygromycin or kanamycin (G418) or other selective agent depending of the vector constructs. The regenerated plants may then be grown axenically to maturity in test tubes (in case of *Arabidopsis*) or in soil (in case of larger plants). The transgenes usually segregate as dominant alleles if the plant does not have a corresponding native locus that might mask their expression.

Alternatively, the agrobacterial infection can be applied to presoaked seeds of plants and eventually a small fraction of the embryos developing after meiosis will carry the transgene. Also, seedlings or plants can be infiltrated by agrobacterial suspensions and selection carried out at large scale in soil cultures treated with an appropriate herbicide (Basta) against

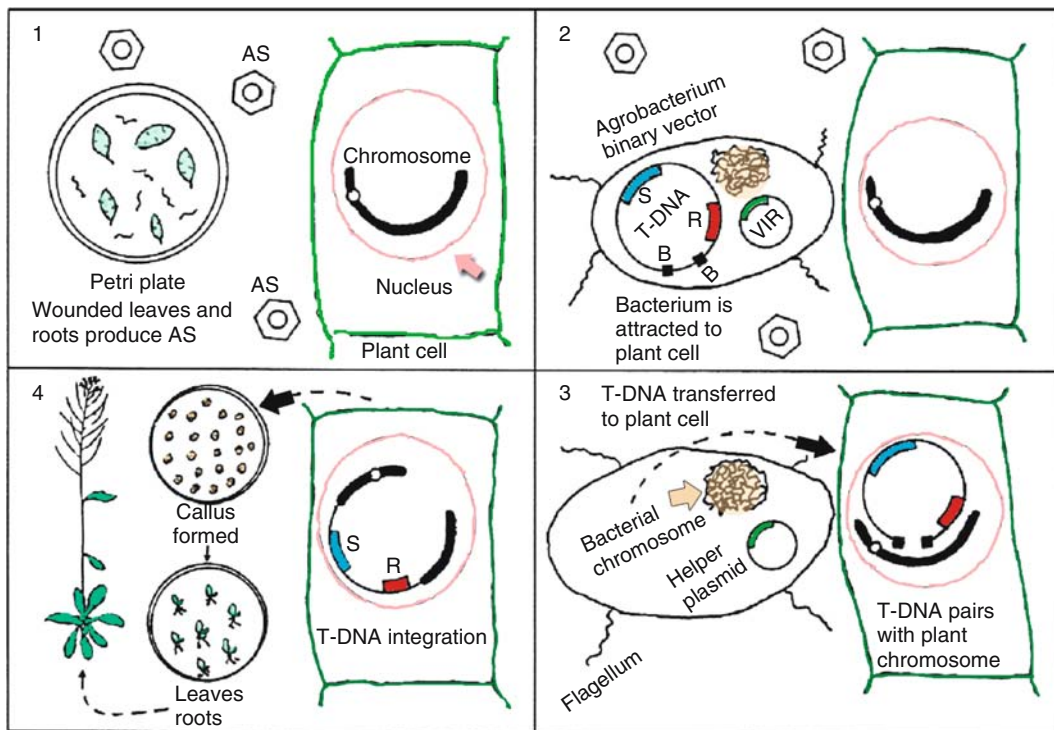


Figure T93. The major steps of transformation of plants by the use of agrobacterial binary vectors. Axenically grown leaves, roots, or stem segments are wounded. The wounding stimulates the production of phenolics such as acetosyringone (AS) and attracts the bacteria carrying the engineered plasmids with selectable markers (S) and a reporter gene (R) placed between the two border sequences (B) of the T-DNA. A small helper plasmid carries the *vir* genes required for transfer and integration of the T-DNA. Two days after infection, the bacterial growth is stopped by antibiotics. The isolated plant organs develop callus, roots, and shoots, and eventually complete plants on the selective media only if the transformation was successful. The transformation is confirmed by the expression of the reporter gene. The transformants produce seed that develops into heterozygous progeny. The antibiotic markers are dominant in the plants

what the vector carries resistance (*in planta* transformation). Plants can be transformed also by electroporation and by biolistic methods. Also cauliflower mosaic virus (CaMV) and geminivirus vectors have been developed but these are not widely used. Generally the vectors carry one desirable gene, for plant breeding purposes it may be desirable the simultaneous transfer of several genes. Assembling in a single transformation vector up to ten genes is feasible. To make such a vector construct the acceptor vector is sequentially altered by the use of two donor vectors and advantage is taken by the Cre/loxP recombination system as well by homing endonucleases (Lin L et al 2003 Proc Natl Acad Sci USA 100:5962). ▶*Agrobacterium*, ▶*floral dip*, ▶*electroporation*, ▶*biolistic transformation*, ▶*microinjection*, ▶*gene transfer by microinjection*, ▶*transformation of organelles*, ▶*genetics of chloroplasts*, ▶*genetics of mitochondria*, ▶*gene trap vectors*, ▶*Cre/loxP*, ▶*homing endonucleases*; Tzfira T et al 2004 Trends Genet 20:375.

Transformation Mapping: A procedure in prokaryotes for determining gene order within the genetic region of integration of the homologous transforming DNA. It can be used as a three-point cross but the additivity of recombination is generally imperfect in transformation. The general principle is outlined at the “bacterial recombination frequency” entry. ▶*bacterial recombination frequency*

Transformation of Organelles: Mitochondria and plastids are also amenable to transformation by exposing protoplasts to appropriate vectors in the presence of polyethylene glycol (PEG) or even more effectively by employing the biolistic procedures. The efficiency of transformation is generally somewhat low. Transformation of organelles is still struggling with methodological difficulties yet it will have great potentials upon further improvements. The number of mitochondria (and plastids) within single cells may run into around hundred or even thousands and that would make possible the amplification of

economically important proteins. Isolated mitochondria can be transformed by conjugation with bacteria. Into a DNA construct the origin of DNA transfer (oriT) is inserted and *E. coli* is transformed first and then through conjugation the construct is mobilized into mitochondria (Yoon YG, Koob MD et al 2005 Nucleic Acids Res 33:(16):2139). Transformation of organelles has the additional safety of containment of the transgenic organisms because mitochondria and plastids are usually not transmitted through the male. The rate of transfer of genes among mitochondria, plastids and nucleus is relatively rare, however it takes place. It may provide a possibility of transferring genes from, e.g., chloroplast to nucleus and the spread the gene in the population by pollination at not negligible rate (10^{-5}). ▶chloroplast genetic, ▶mitochondrial genetics, ▶metabolite engineering, ▶genetic engineering, ▶protein engineering, ▶biolistic transformation, ▶electroporation, ▶transformation, ▶human gene transfer, ▶gene therapy, ▶organelle sequence transfer, ▶Bellophage; Bogorad L 2000 Trends Biotechnol 18:257; Ruf S et al 2001 Nature Biotechnol 19:870.

Transformation, Oncogenic: change to malignant (cancerous) cell growth. Transformed animal cells are anchorage independent and typically free of contact inhibition and may initiate tumors when implanted into immune-compromised animals. Oncogenic transformation results when tumor suppressor genes are inactivated and oncogenes are activated. Spontaneous oncogenic transformation may occur on the same genetic background during repeated passage and proliferation of rodent cells. When these cells are injected into animals they become tumorigenic in the absence of any carcinogen, presumably due to large cell density and selection (Rubin H 2005 Proc Natl Acad Sci USA 102:9276). ▶cancer, ▶carcinogen, ▶gatekeeper, ▶phorbol esters, ▶tumor suppressor, ▶oncogenes; Hunter T 1997 Cell 88:333.

Transformation Rescue: introducing a viable allele or DNA sequences with the aid of transformation compensates for recessive lethal phenotype. By narrowing the transforming DNA to the minimal length that restores a viable phenotype (using restriction enzymes), the site of the damage can be estimated, cloned and sequenced. ▶transformation genetic; de Vries J, Wackernagel W 1998 Mol Gen Genet 257:606.

Transformation, Stable: produces cells which carry the transforming DNA in an integrated form and thus the acquired information is consistently transmitted to the progeny. ▶transformation transient, ▶transformation genetic

Transformation, Transient: The introduced DNA may be expressed only for a limited time (for 1 to 3 days) in the recipient cell because it is not integrated into the host genetic material. Electroporation is most commonly results in this kind of transformation. ▶transformation stable, ▶electroporation

Transformation Vectors: ▶cloning vectors, ▶vectors, ▶transformation genetic

Transformation-Competent Artificial Chromosome Vector (TAC): can carry large (40–80 kb) inserts and can be maintained in *E. coli*, *Agrobacterium tumefaciens* and expressed in plant cells. (See Liu Y-G et al 1999 Proc Natl Acad Sci USA 96:6535).

Transformed Distance (TD): is an UPGMA procedure for species i and j :

$d_{ij} = (d_{ij} - d_{ir} - d_{jr})/2 + c$ where r is a reference species within or outside the group and c is a constant to make d_{ij} positive. This TD formula is unsuitable for the estimation of branch length in evolutionary trees. ▶evolutionary tree, ▶evolutionary distance, ▶UPGMA, ▶Fitch—Margoliash method for TD

Transforming Growth Factor: ▶TGF

Transforming Growth Factor β : A superfamily of proteins that induces the change of undifferentiated tissues into specific types of tissues. TGF- β 1 peptide factor causes reversible arrest in G1 phase of the cell cycle and thus it is considered as a tumor suppressor. TGF- β 1 had been detected in cis position to several genes. These proteins are serine/threonine kinases. ▶activin, ▶bone morphogenetic protein, ▶tumor suppressor, ▶TGF

Transforming Principle: A historical term used in the early bacterial transformation reports when it was not yet proven that DNA is the agent of transformation. (See Alloway JL 1931 J Exptl Med 55:91).

Transformylase: Enzyme that adds a formic acid residue to the methionine-charged fMet tRNA ($tRNA^{fMet}$) in prokaryotes. ▶protein synthesis

TRANSFRAG: Transcribed fragment. On the average number of transfrags in ten human chromosomes were 16,864 with average length of 115 to 78 nucleotides. The average transcripts size varied substantially from 173 to 4650 nucleotides (average 680). On the average of ten chromosomes 31% of the transfrags come from intergenic regions, 26% are intronic and 5% are mRNA. 60.8% of the transcripts are from both genomic strands. Of the 178 cloned transcripts 64% are spliced of 3.2 exons and the average exon length was 238 nucleotides; 26 (14.6%) was spliced from antisense transcripts. Exclusively non-polyadenylated transcript were twice as abundant as the exclusively polyadenylated ones. Many

transcripts (36.9%) were bimorphic, i.e., they had both polyA⁺ and polyA⁻ forms. The polyA⁻ transcripts were mainly intronic. The function of many transcripts still remains unknown in 2005. ▶[transcription](#), ▶[polyadenylation signal](#), ▶[splicing](#), ▶[exon](#), ▶[intron](#), ▶[ENCODE](#); Cheng J et al 2005 Science 308:1149.

Transgene: A gene transferred to a cell or organism by isolated DNA in a vector rather than by sexual means. ▶[transformation genetic](#)

Transgene Mutation Assay: In a transgene mutation assay, a mouse transgenic for a prokaryotic reporter gene is exposed to mutagenic conditions (spontaneous or treated with an agent). The genomic DNA is isolated and rescued in phage lambda vector or used in a plasmid rescue system. The cloning bacteria are then plated and the number of mutant reporter genes compared with all the reporter genes analyzed to provide mutation frequency. Under experimental conditions, spontaneous mutation rates (*lacZ*) were observed within the range about 6 to 80×10^{-6} , depending on the tissues from where the DNA was extracted. Some transgenic lines carry p53 tumor suppressor or the RAS oncogene to test their effects on mutagenesis. Inserted genes of the P450 cytochromes may be helpful for the studies of the metabolism of promutagens and procarcinogens. ▶[host-mediated assays](#), ▶[plasmid rescue](#), ▶[lac operon](#), ▶[β galactosidase](#), ▶[vectors](#), ▶[bioassays in genetic toxicology](#), ▶[mutation detection](#), ▶[promutagen](#), ▶[procarcinogen](#), ▶[P450](#), ▶[p53](#), ▶[RAS](#); Chroust K et al 2001 Mutation Res 498:169; McDiarmid HM et al 2001 Mutation Res 497:39.

Transgenerational Effect: Epimutations transmitted to the progeny. The agouti viable yellow allele *A^{vy}* of mice may be affected in a mosaic pattern by a retrotransposon in the female germline and the alteration is not cleared during subsequent meiosis. Gestating rodent females exposed to antiandrogenic compound (vinclozolin) or an estrogen compound (methoxychlor) (see Fig. T94) reduced spermatogenic cell number and increased infertility in the male offspring and this epigenetic trait reappeared in the

four following generations studied (Anway MD et al 2005 Science 308:1466). ▶[epimutation](#), ▶[directed mutation](#), ▶[sexual selection](#)

Transgenesis: Introducing a gene by genetic transformation. *Conditional transgenesis* introduces the desired gene by *Cre*-mediated recombinase under the control of developmentally-regulated promoter. Germline stem cell transplantation may also lead to transformation. ▶[transformation genetic](#), ▶[Cre](#); Moon AM, Capecchi MR 2000 Nature Genet 26:455; Brinster RL 2002 Science 296:2174.

Transgenic: A transgenic carries gene(s) introduced into a cell or organism by transformation. Transgenic animals can potentially produce therapeutically needed proteins such as human tissue plasminogen activator (tPA) or α_1 -antitrypsin (ATT), human monoclonal antibodies, etc. Transgenic plants may have direct use in agriculture by virtue of their resistance to herbicides, pathogens or even by the production of biodegradable plastics, nutritionally safer fats and carbohydrates, various antigens that may be substituted for the standard type vaccines by eating them. The availability of transgenic crops and farm animals raised concerns by consumers and environmentalists about transfer of herbicide resistance to weeds, to introduce antibiotic resistance genes into the food chains and their potential hazards for fighting microbial infections, affecting the immune system of animals and humans, etc. Although the long-term consequences of the new technologies cannot be precisely assessed yet, there appear more advantages than risks of these new technologies. The wide-scale application of antibiotics in medicine eventually was followed by the appearance of resistance to many antibiotics. It must not be forgotten, however, that antibiotics saved and saving millions of life since the introduction of penicillin after World War II. Also, pharmaceutical research has produced and producing an ever-increasing variety of new antibiotics in order to compete with the evolutionary changes in the microbial world. While the danger of emergence of antibiotic resistant pathogens must not be ignored, the reasonable medical use of these drugs remains

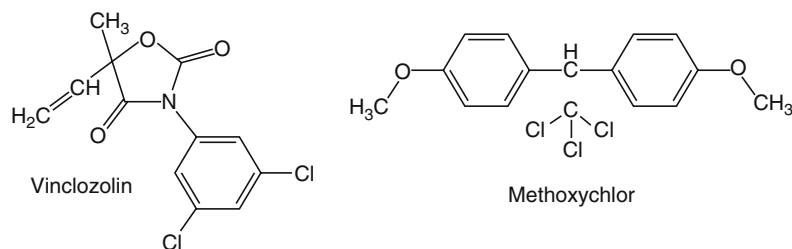


Figure T94. Left: vinclozolin; right: methoxychlor

a necessity. Viral vectors that integrate into the nucleus and can cause unavoidable deleterious modification at the site of insertion most commonly produce transgenic animals. An episomal vector (pEPI) can be delivered with high efficiency to the pig embryo by sperm-mediated gene transfer (SMGT), and the transgene is expressed in all tissues of positive fetuses that were tested, and that is retained as an episome in the course of embryogenesis and fetal development. This procedure successfully produced genetically modified animals (Manzini S et al 2006 *Proc Natl Acad Sci USA* 103:17672). ►[transformation genetic](#), ►[nuclear transplantation](#), ►[antibiotic resistance](#), ►[ANDi](#), ►[paratransgenic](#), ►[bitransgenic regulation](#), ►[genetic engineering](#), ►[gene therapy](#), ►[GMO](#); <http://www.transgenic-animals.com/>.

Transgenome: Transformed eukaryotic cells by isolated whole or parts of chromosome(s) containing transgenes in their nuclei. ►[transformation genetic \[animal cells\]](#); Porteous DJ 1994 *Methods Mol Biol* 29:353.

Transgenesis: An alternative term for (a controversial means) of transfer of genes by non-sexual means. (See Doy CH et al 1973 *Nature New Biol* 244:90).

Trans-Golgi Network (TGN): The connection of the Golgi complex exit face to transport vesicles so the molecules coming from the endoplasmic reticulum will be transported to their proper destination. ►[cis-Golgi](#), ►[Golgi](#)

Transgression: Some segregants exceed both parents and the F1 hybrids. (See Burke JM, Arnold ML 2001 *Annu Rev Genet* 35:31).

Transheterozygous Non-complementation: ►[non-allelic non-complementation](#)

Transient Amplifying Cells: In transient amplifying cells, the progeny of stem cells replicate but do not revert to stem cell status; rather they generate differentiated cells. ►[stem cells](#)

Transient Expression DNA: ►[transformation transient](#)

Transilience, Genetic: Rapid changes in fitness by a multilocus complex in response to changes in the genetic environment. (Templeton AR 1980 *Genetics* 94:1011).

Transin: Cell-secreted metalloproteinase, a homolog of stromelysin. (See Luo D et al 2002 *J Biol Chem* 277:25527).

Transinactivation: ►[co-suppression](#)

Transistor: ►[semiconductor](#)

Transit Amplifying Cell: ►[stem cells](#)

Transit Peptide: Dozen to five dozen amino acid residue leader sequences directing the import of proteins synthesized in the cytosol into mitochondria and chloroplasts. These peptides are generally rich in basic and almost free of acidic amino acids. Serine and threonine are usually very common. The transit peptide recognizes special membrane proteins, but itself is not transferred into the target organelle and it is cut off by a peptidase. The different transit-peptides do not appear to have conserved sequences. The transit peptide is targeted posttranslationally. Some mitochondrial and plastid proteins do not have these cleavable N-terminal sequences. The routing within the target seems to be influenced by the carboxy terminus or inner sequences of the proteins. Mitochondria can import several plastid proteins but the plastids do not import mitochondrial proteins. This mitochondrial import is not physiological because this organelle does not have essential specificity factors (Cleary SP et al 2002 *J Biol Chem* 277:5562). The transit peptide engages several proteins localized in the organelle membranes. Subsequently the protein inside the cell folds with the assistance of chaperonin 60. Some proteins targeted to the endoplasmic reticulum, Golgi membrane, peroxisome, etc., may carry the transit peptide at the C-end. ►[signal peptide](#), ►[chaperones](#); Jean-Benoît P et al 2000 *Plant Cell* 12:319.

Transition Matrix: The conditions of probabilities for a certain type of amino acid substitution during an evolutionary period.

Transition Mismatch: In transition mismatch, purine mispairs with a wrong pyrimidine. ►[transversion mismatch](#), ►[mismatch](#), ►[transition mutation](#)

Transition Mutation: In transition mutation, either a pyrimidine is replaced by another pyrimidine, or a purine by another purine in the genetic material leading to mutation. ►[base substitutions](#), ►[transversion](#); Freese E 1963, p 207. In: *Molecular Genetics* Taylor JH (Ed.) Acad Press, New York.

Transition Proteins: Basic proteins that replace (temporarily) histones during spermiogenesis with protamines. ►[protamine](#), ►[spermiogenesis](#); Finney LA, O'Halloran TV 2003 *Science* 300:931.

Transition State: An unstable (life time $\sim 10^{-13}$ second) intermediate between reactants and products of an enzymatic reaction: REACTANT \rightarrow TRANSITION STATE \rightarrow PRODUCT(S). Factors, which stabilize the transition state relative to the reactant are expected to lower the activation energy. ►[Φ value](#); Komatsuzaki T, Berry RS 2001 *Proc Natl Acad Sci USA* 98:7666.

Transitivity: A bioinformatics concept for sequence analysis of macromolecules. It aids in the identification of distant repeat homologues, for which no alignment has been found, provides confidence about consistently well-aligned regions, and recognizes and reduce the contribution of non-homologous repeats (Szkarczyk R, Heringa J 2004 Bioinformatics 20 (Suppl. 1):1311).

Translation: Converting the information contained in a mRNA nucleotide sequence into amino acid sequences of polypeptides on the ribosomes. mRNA is threaded through a channel wrapping around the 30S subunit of the prokaryotic ribosome and translation initiation, polypeptide chain elongation, and other functions follow (Yosupova GZ et al 2001 Cell 106:233). The translational apparatus of eukaryotes consists of more than 200 macromolecules of varying importance. Some proteins, e.g., bacterial ribosomal proteins S10 and L4, participate both in transcription and translation. ►protein synthesis, ►ribosomal proteins, ►rabbit reticulocyte in vitro translation, ►wheat germ in vitro translation, ►translation nuclear, ►decapping; Sonnenberg N et al (Eds.) 2000 Translational Control of Gene Expression, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Translation: The term “translation” is also used for the transfer of basic scientific information into clinical (bench-to-bedside) or other practical applications. ►attrition, ►roadmap

Translation Error: ►error in aminoacylation

Translation Factors: ►translation initiation

Translation Initiation: Translation initiation is usually triggered by growth factors through signaling to the RAS/RAF G proteins and MEK/MAPK proteins. Upon phosphorylation, 4E-BP1 releases the cap-binding protein eIF-4F and the mRNA cap associates with the 40S subunit of the eukaryotic ribosome. The phosphorylation of ribosomal protein S6 by protein kinase p70^{S6k} is also required. Eukaryotic initiation factor eIF-2B is active when it is bound to GTP and ensures the supply of tRNA^{Met}. Insulin and other growth factors keep eIF2B attached to GTP, whereas glycogen-synthase kinase (GSK) inactivates it because GSK inactivates insulin. In prokaryotes, the initiation begins when the ribosomal binding site of the mRNA (including the Shine-Dalgarno sequence and AUG^{fMet} codon) binds to anti-Shine-Dalgarno sequence in the 16S RNA of the 30S ribosomal subunit. The AUG codon thus is directly placed into the P pocket of the ribosome and can interact with the formyl-methionine-charged fMet-tRNA. Before the 30S subunit combines with the 50S subunit, a number

of other interactions also take place. In eukaryotes, the first step of the initiation is the (1) dissociation of the 60S + 40S ribosomal subunit mediated by eIF6 and the attachment of eIF6 to the 60S subunit. Then (2) eIF3 attaches to the 40S subunit, (3) followed by the attachment of eIF1A. Next, (4) eIF2+ GTP combines with tRNA^{Met} and the complex joins the 40S subunit with eIF1A and eIF3 already in place, forming the 43S subunit. (5) The capped mRNA plus elongation initiation factors eIF-4F, eIF-4A, eIF-4B energized by ATP→ADP mediate the attachment of the capped mRNA to the small ribosomal subunit (now 48S pre-initiation complex). (6) While eIF5 and GTPase activating protein (GAP) mediate the release of eIF2•GDP•eIF3 (7) the small subunits scans the mRNA until the AUG^{Met} is located. (8) Capturing the free 60S ribosomal subunit and restoration of the 80S ribosome and beginning of translation follows this event. ►eIF, ►protein synthesis, ►DEAD box, ►cap, ►S6 kinase, ►ribosome, ►Shine-Dalgarno sequence, ►IRES, ►initiator tRNA, ►ribosome scanning, ►PABp, ►mRNA circularization; Gingras A-C et al 1999 Annu Rev Biochem 68:913; Kimball SR 2001 Progr Mol Subcell Biol 26:155; Pestova TV et al 2001 Proc Natl Acad Sci USA 98:7029; Walker M et al 2002 Nucleic Acids Res 30:3181; prokaryotic translation initiation sites detection: <http://tico.bics.de/>.

Translation In Vitro: Translation in vitro used to be accomplished by employing isolated mRNA and other factors required for translation (see wheat germ, rabbit reticulocyte). When the isolated gene is included in an appropriate expression vector, transcription and translation may be obtained in a single step from the plasmid construct. A far more efficiently defined system of in vitro translation employs highly purified and tagged protein factors that permit an efficient purification of the products by affinity chromatography. It may yield 160 µg protein per mL/hr. It can produce modified proteins by incorporating amino acid analogs with the aid of suppressor tRNA. Radioactive tags or non-radioactive fluorescent dyes may label the translation products. ►translation, ►rabbit reticulocyte in vitro translation system, ►wheat germ in vitro translation system, ►suppressor tRNA; Shimizu Y et al 2001 Nature Biotechnol 19:751; Traverso G et al 2003 Nature Biotechnol 21:1093.

Translation, Non-contiguous: In non-contiguous translation, generally the mRNA is translated in a collinear manner into amino acid sequences without skipping any parts of the former. There are few exceptions to this continuity; 50 nucleotides in bacteriophage T4 gene 60 are skipped during translation.

Translation, Nuclear: Translation usually takes place on the ribosomes. In prokaryotes that do not have membrane-enclosed nucleus, transcription and translation are coupled. In eukaryotes intact ribosomes are limited to the cytoplasm and according to the traditional view, translation is limited to the cytoplasmic compartment. Recently, evidence has been accumulating in favor of the notion that even in mammals some translation may take place within the nucleus. The evidence for nuclear translation is based on the observation that in isolated, purified nuclei, fluorescence-labeled proteins were not present outside the nuclei. Electronmicroscopy indicated the colocalization of the nuclear translation sites with the eIF4E polypeptide elongation factor, the ribosomal subunit L7, and a β -subunit of proteasome. The presence of proteasomal activity was surprising inasmuch as that it degrades proteins. It is conceivable that most of the nuclear-translated proteins are degraded normally. Increasing the concentration of ribonucleotides lead to increased protein synthesis in the nucleus, indicating the possibility of coupled transcription and translation in the nucleus. Despite the critical evidence provided, the role and significance of nuclear translation is not entirely clear. ►protein synthesis, ►eIF4, ►proteasome; Iborra FJ et al 2001 Science 293:1139.

Translation Reinitiation: ►reinitiation

Translation Repressor Proteins: Translation repression proteins may be attached to a site near the 5' end of the mRNA and prevent the function of the peptide chain initiation factors. ►protein synthesis, ►eIF-2, ►rabbit reticulocyte, ►aconitase, ►trinucleotide repeats

Translation Termination: Translation termination takes place in the decoding A pocket of the ribosome, where the polypeptide release factors, RF1 recognizing prokaryotic stop codons UAG and UAA, and RF2 specific for UGA and UAA or RF3 without selectivity (and may cause misreading of all three stop signs) release the polypeptide chains. In eukaryotes, the eRF1 termination factor recognizes all three stop codons and eRF1 and eRF3 are interactive. Several other proteins modulate the function of the RFs. RF3 has homology to elongation factors EF-G and EF-Tu. This fact seems to indicate that termination and chain elongation processes bear similarities; in one case the stop codon is read, in the other the sense codons. The Rfs may have additional homology domains, e.g., with the acceptor stem, the anticodon helix, and T stem of tRNAs, called "tRNA mimicry". There is a conserved GGQ (Gly-Gly-Gln) group in eRF1s corresponding to the amino acyl group attached to the CCA-3' end of the tRNA. These homologies may assist their function. The yeast eRF3

is a prion-like element, ψ^+ . Interestingly, the heatshock protein 104, a molecular chaperone can cure the cell from it. After protein synthesis is terminated, the termination complex and the ribosome are recycled. In the 16S rRNA of *E. coli*, mutation at nucleotide position C1054 causes translational suppression. Similarly at the corresponding site in the 18S eukaryotic rRNA, substitutions of A or G resulted in dominant nonsense suppression while the T substitution was a recessive antisuppressor. The deletion of the site was found to have a lethal effect. Although translation termination is mediated at the ribosomes, premature termination may result not just from nonsense codons but also by decay of the mis-spliced transcripts. Bacterial mRNA truncated at the 3'-OH and without a termination codon may stall on the ribosomes. In such cases, the tRNA-like 10Sa RNA transcribed from gene *ssrA* gene of *E. coli* indirectly causes the degradation of the nascent peptide chain. The 10Sa binds to the ribosome and the ANDENYALAA amino acid sequence is added to the C-end of the peptide making it a target for carboxyl-end-specific proteases. Translation termination may regulate gene expression with the aid of some weak internal termination codons, which can be facultatively transpassed. Many human diseases are caused by improper translation termination and modulating the process may have therapeutic potentials. ►translation initiation, ►release factor, ►stop codon, ►sense codon, ►autogenous suppression, ►readthrough, ►recoding, ►EF-G, ►EF-Tu-GTP, ►chaperone, ►prion, ►protein synthesis, ►ribosome, ►phenotypic reversion, ►PABp; Song H et al 2000 Cell 100:311.

Translational Bypassing: Translational bypassing processes two separate open reading frames into one protein. Its mechanism follows. (i) The charged peptidyl-tRNA and mRNA complex arrives to the P site of the ribosome and after dissociation the mRNA slides through the ribosome (take-off). (ii) The peptidyl-tRNA searches the mRNA through the decoding center of the ribosome (scanning). (iii) The peptidyl-tRNA pairs with the appropriate codon after skipping some others (landing). (See Herr AJ et al 2000 Annu Rev Biochem 69:343; Gallant J et al 2003 Proc Natl Acad Sci USA 100:13430).

Translational Control: In translational control, protein synthesis is regulated during the process of translation on the ribosome; e.g., attenuation. The mRNA of some vitamins (B_1 , B_{12}), besides the Shine-Dalgarno sequence, is equipped with a vitamin-binding site. When the vitamin is sensed by the RNA, the Shine-Dalgarno sequence is occluded by a conformational change and thus translation of the vitamin mRNA is suspended in the final outcome reminding to

attenuation (Szostak JW 2002 Nature (Lond) 419:890). ►attenuation, ►termination factors, ►translation termination, ►terminator codons, ►regulation of protein synthesis, ►translational termination, ►suppressor RNA, ►closed-loop model of translation, ►masked RNA, ►ribosomal filter; Gale M Jr et al 2000 Microbiol Mol Biol Revs 64:1092; Johnstone O, Lasko P 2001 Annu Rev Genet 35:365; <http://utther.otago.ac.nz/Transterm.html>.

Translational Coupling: As per translational coupling, when the secondary structure of the mRNA is such that the AUG site or the Shine-Dalgarno sequence is not readily amenable for translation at the first cistron, translation started at the initiator codon of another cistron may open up for translation. Such a situation may occur in phages but rarely also in eukaryotes. (See Herr AJ et al 2000 Annu Rev Biochem 69:343).

Translational Error: ►ambiguity in translation, ►error in aminoacylation

Translational Gene Fusion Vectors: Translation gene fusion vectors carry promoterless, 5'-truncated structural Genes. When the trapped host promoter drives

these, the vectors direct the synthesis of fusion proteins containing amino acid residues coded for by both host and vector DNA sequences. See Fig. T95, ►gene fusion, ►transcriptional gene fusion, ►read-through proteins, ►trapping promoters, ►transformation genetic

Translational Hopping: Translational hopping occurs when a peptidyl-tRNA dissociates from its first codon and then reassociates with another downstream. ►aminoacyl-tRNA synthetase, ►protein synthesis, ►overlapping genes, ►translational frameshift, ►shunting, ►hopping; Herr AJ 2001 J Mol Biol 309:1029.

Translational Recoding (same as ribosomal frame shift): ►overlapping genes

Translational Research: Translational research applies basic research to a patient and determines the outcome of the treatment (Birmingham K 2002 Nature Med 8:647).

Translational Restart: ►reinitiation

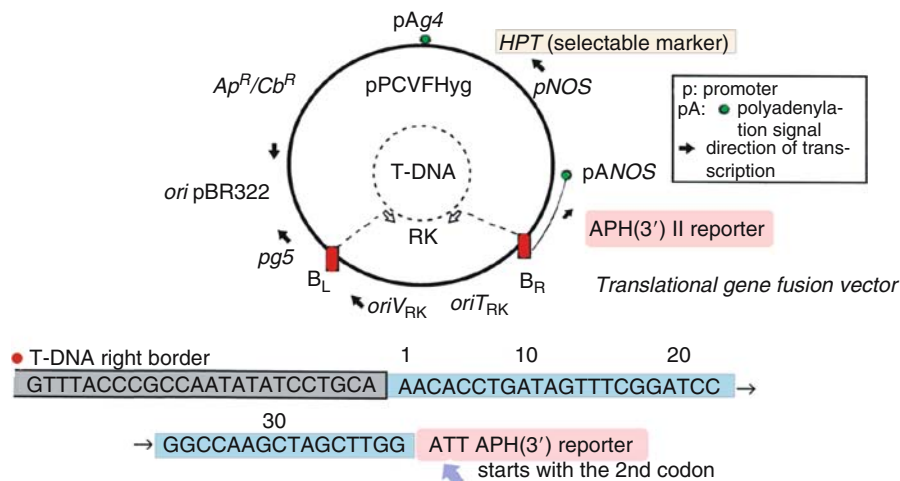


Figure T95. Agrobacterial translational in vivo gene fusion vector for plants. The critical feature is that the reporter gene is fused to the right border sequence of the T-DNA in such a manner that the translation initiator codon (AUG^{Met}) is deleted and the structural gene of the reporter begins with its second codon. It does not have a promoter either. The reporter gene can be expressed only when it is inserted and fused in the correct register into an active plant promoter. Since the AUG codon is missing, there is a good chance that the reporter protein will be fused with some plant (poly-) peptides. The use of such a vector permits an analysis of the expression of various fusion proteins on the reporter. Besides the structure, shown in detail at the lower part of the diagram, the transformation cassette contains selectable markers (e.g., HPT, permitting selective isolation of transformant on hygromycin media), ampicillin (Ap^R) and carbencillin (Cb^R) resistance for selectability in bacteria and also the replicational origin of the *E. coli* plasmid pBR322. Outside the boundaries of the T-DNA, there are genes for both vegetative (oriV) and conjugational transfer (oriT) derived from the multiple-host range RK plasmid. Only the genes between two border sequences (B_L and B_R) are inserted into the plant genome. The basic principle of this diagram has been exploited in designing vectors for other organisms. (After oral communication by Dr. Csaba Koncz.)

Translational Selection: Optimized codon usage. ▶ [codon usage](#); selection of best codons in DNA sequence: <http://genomes.urv.es/OPTIMIZER/>.

Translational Termination: Translational termination may take place by encountering stop codons, endonucleolytic cleavage, shortening the poly(A) tail, and premature decapping of the mRNA. ▶ [translational control](#)

Translesion Pathway: An SOS repair system of DNA; replication may lead to targeted mutation at the site of mismatches, such as at a thymine dimer, and at bases chemically modified or deleted by mutagens. The repair of the cis-syn cyclobutane dimers is mutational in about 6% of the cases, whereas the pyrimidine 6–4 pyrimidinone adducts are repaired in a mutagenic manner in almost 100%. The Rev proteins of yeast and the UmuC (DNA pol V) protein of *E. coli* are involved with translesion. The Rev polypeptides are subunits of DNA polymerase ζ involved in damage-induced mutagenesis. In humans, DNA polymerase η may protect cells against damage that may lead to skin cancer. In bacteria, DNA polymerases II, IV, and V are involved in translesion (Napolitano R et al 2000 EMBO J 19:6259). In bacteria, LexA represses translesion and RecA induces it. Which polymerase is selected depends on the damaging agent. The repair frequently involves mutation. In yeast, the Rad6 and Rad18 proteins are elevated upon UV irradiation and the *REV3*-encoded polymerase ζ unit and a polymerase η carry out the repair. The products of genes *REV7* and *REV1* are also required. In humans, pol ι and pol κ are additional repair polymerases. Werner syndrome protein (WRN) and the translesion polymerases, Pol μ , Pol κ , and Pol ι interact. In vitro, WRN stimulates the extension activity of these polymerases on lesion-free and lesion-containing DNA templates, and alleviates pausing at stalling lesions but increases mutation (Kamath-Loeb AS et al 2007 Proc Natl Acad Sci USA 104:10394). This replicative bypass requires multiple switching to various repair polymerases but after the bypass is completed the high-fidelity polymerases are restored to the replication primer terminus (Friedberg EC et al 2005 Mol Cell 18:499). ▶ [DNA repair](#), ▶ [DNA polymerases](#), ▶ [Y-family DNA polymerase](#), ▶ [REV](#), ▶ [ultraviolet photoproducts](#), ▶ [UMU](#), ▶ [cis-syn dimer](#), ▶ [pyrimidine-pyrimidinone photoproduct](#), ▶ [somatic hypermutation](#), ▶ [Werner syndrome](#); Livneh Z 2001 J Biol Chem 276:25639; Pham P et al 2001 Proc Natl Acad Sci USA 98:9350; Friedberg EC 2001 Cell 107:9; Rattray AJ, Strathern JN 2003 Annu Rev Genet 37:31; Prakash S et al 2005 Annu Rev Biochem 74:317.

Translin: A protein binding to GCAGA[A/T]C and CCCA[C/G]GAC sequences at the translocation

breakpoint junctions in lymphoid malignancies; it supposedly has a role in the rearrangement of immunoglobulin—T cell receptor. ▶ [immunoglobulins](#), ▶ [T cell](#), ▶ [T cell receptor](#), ▶ [TCR](#), ▶ [lymphoma](#); VanLock MS et al 2001 J Struct Biol 135:58.

Transloading: The modification of cancer vaccines by including non-self peptides so they would boost immunogenicity. ▶ [cancer gene therapy](#); Buschle M et al 1997 Proc Natl Acad Sci USA 94:3256.

Translocase: A protein complex mediating transport of proteins through cell membranes. ▶ [SecA](#), ▶ [SecB](#), ▶ [SecY/E](#), ▶ [translocon](#), ▶ [ABC transporters](#), ▶ [protein targeting](#), ▶ [signal hypothesis](#), ▶ [SRP](#), ▶ [ARF](#), ▶ [Mori](#), ▶ [DNA translocase](#); H, Ito K 2001 Trends Microbiol 9:494.

Translocation: Translocation transfers codons of the mRNA on the ribosomes as the peptide chain elongates. In general, it also refers to any type of transfer of molecules from one location to another. ▶ [protein synthesis](#)

Translocation, Chromosomal: Segment interchange between two nonhomologous chromosomes (see Fig. T96).

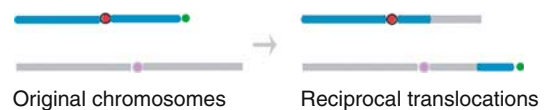


Figure T96. Chromosomal interchange

Broken chromosomes do not stick however to telomeres; the interchange must involve internal regions. Fragments may be inserted in-between two ends of an internal breakpoint, and such an aberration is called *shift*. Translocations are detectable by the light microscope, if the length of a chromosome arm is substantially altered. Translocations are usually reciprocal but during subsequent nuclear divisions one of the participant chromosomes, which carries no essential genes may be lost. Heterozygotes for reciprocal translocations display cross-shaped configuration in meiotic prophase (see Fig. T97).



Figure T97. Pairing of reciprocal translocations. Courtesy of Brinkley BR and Hittelman WN, 1975

Translocations repeatedly occur at the same locations of two non-homologous chromosomes and this may be due to the vicinity of these chromosomal sites in the nuclear architecture rather than to the special nature of the DNA sequences (Roix JJ et al 2003 *Nature Genet* 34:287). Translocation between human chromosomes 11q23 and 22q11 occurs repeatedly at frequencies in the 10^{-4} to 10^{-7} range and the breakpoints are most common within ~ 450 bp palindromic sequence of AT-rich repeats of these two regions (Kato T et al 2006 *Science* 311:971).

Translocation heterozygotes generally display 50% pollen sterility in plants because alternate and adjacent-1 distributions occur at about equal frequency in the absence of crossing over; adjacent-2 distributions, being non-disjunctional, are very rare. Note that inversion heterozygotes may also produce 50% male sterility but this occurs only if recombination within the inverted segment occurs freely (see inversion). In animals, the gametes of translocation heterozygotes may succeed in fertilization but the zygotes or early embryos resulting from such a mating are generally aborted. Translocation homozygosity may not have any phenotypic consequence; however, it has been shown that many types of cancerous growth are associated with translocation breakpoints. Apparently, the DNA rearrangements in the vicinity of the genes interfere with the normal regulation of their activity as a kind of position effect. Translocation breakpoints reduce the frequency of crossing over between the breakpoint and the centromere (*interstitial segment*). Recombination in translocation homozygotes may be normal. Because the reciprocal interchange physically alters the synteny of genes, linkage groups may be reshuffled as a consequence of the exchange. Because translocations partially join two linkage groups, they can be exploited for assigning genes to chromosomes. The number of crosses to localize a gene to a chromosome may thus require fewer crosses. Also, the reduction of recombinations around the breakpoints may call attention to linkage over a somewhat larger chromosomal tract rather than a single marker. Furthermore, the association of certain genes with sterility may also be used as a chromosomal marker for the breakpoints. The sterility marker may not always be very useful because it can be recognized only later during development (after sexual maturity). (See Tennyson RB et al 2002 *Genetics* 160:1363). Continued.

Translocation Complex: The interchanged chromosomes of eukaryotes; members of the group are inherited as a complex that alone contributes viable gametes to the progeny.

Translocation Heterozygote: At least two of the chromosomes of the genome are reciprocally

exchanged (mutually translocated) whereas the corresponding homologous chromosomes are not involved in translocation within the same cell nucleus. ▶translocation chromosomal, ▶genome, ▶homologous chromosomes, see Fig. T98.

According to some estimates, there is an about 0.004 chance that a human baby will carry a translocation. Many types of tumors carry translocations and the pattern involved is not a haphazard one. Potential oncogenes (MYC, RAS, SRC) are frequently translocated into the 14q11 region, the location of the T cell receptors (TCR) α and δ . MYC translocated to immunoglobulin genes is common in B cell neoplasia and Burkitt's lymphoma. The chain formation question is intriguing as in how these special translocations are controlled. One interpretation may be that the gene fusions involved may lead to the creation of highly selective combinations to stimulate proliferation. ▶adjacent disjunction, ▶position effect, ▶synteny, ▶multiple translocations, ▶cancer, ▶telomere, ▶B chromosomes, ▶trisomic tertiary, ▶chromosomal rearrangement, ▶oncogenes, ▶Burkitt lymphoma, ▶promoter swapping, ▶unbalanced chromosomal constitution; Generoso WM 1984, p 369. In: *Mutation, Cancer and Malformation*. Chu EHY, Generoso WM (Eds.) Plenum, New York; translocation break-point mapping by in wheat by microarrays: Bhat PR et al 2007 *Nucleic Acids Res* 35:2936.

Translocation Ring: Multiple reciprocally translocated chromosomes, after terminalization, are attached end-to-end forming a ring of several chromosomes. (See Fig. T99, ▶ring bivalent, ▶complex heterozygotes, ▶terminalization).

Translocation Test, Heritable: ▶heritable translocation tests under bioassays in genetic toxicology. In some organisms, translocation testers have been developed to expedite linkage analysis. A clear and early marker is translocated to several (tester) chromosomes. Then, the gene to be identified regarding its chromosomal position is crossed with all the translocation testers available. If according to previously obtained information from crosses involving non-translocated chromosomes, the marker in the tester showed independent segregation but was crossed with the translocation testers it is linked to a single specific chromosome, its chromosomal position is revealed. The frequency of translocation may vary a great deal according to the species. In the *Oenothera* plants translocations are widespread and in *Oenothera lamarckiana* all the chromosomes are involved in translocations.

Translocon: The multiprotein complex (SecYp, SecGp, SecE in bacteria, Sec61p, Sbh1p, Ssh1p in yeast,

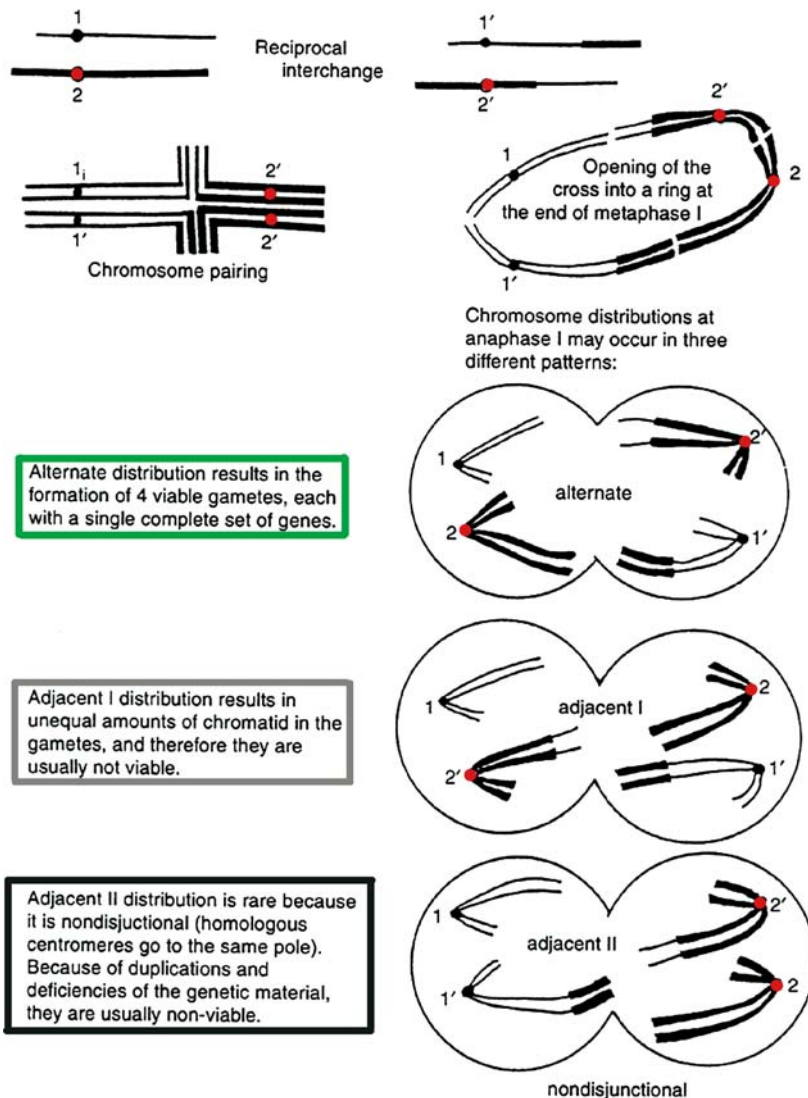


Figure T98. Consequences of recombination in translocation heterozygotes



Figure T99. Six reciprocal translocations resulting in a ring of 12 in *Rheo discolor* (Sax KJ 1935 Arnold Arboretum 16:216)

sec61 α , β , γ in mammals) involved in the transport of proteins through 40–60 Å diameter aqueous pores in membranes, the endoplasmic reticulum. In bacteria,

the DnaK chaperones keep the nascent polypeptide chains in shape until their synthesis is completed. ▶translocase, ▶protein targeting, ▶SRP, ▶TRAM, ▶ABC transporter, ▶ARF, ▶DnaK; Hamman BD et al 1997 Cell 89:535; Heritage D, Wonderlin WF 2001 J Biol Chem 276:22655; cryoelectronmicroscopic revelation of structure of *E. coli* protein-conducting channel bound to translating ribosomes: Mitra K et al 2005 Nature [Lond] 438:318.

Transmembrane Proteins: Transmembrane proteins generally have three main domains; the amino terminus reaches into the cytoplasm where it usually associates with other cytosolic proteins, the hydrophobic domain generally makes seven turns within the cell membrane and the carboxylic end serves as a receptor for extracellular signals (see Fig. T100).

►cell membrane, ►membrane proteins, ►signal transduction, ►INT3 oncogene, ►KIT oncogene, ►MAS1 oncogene, ►seven membrane proteins, ►receptors; Baldwin SA (Ed.) 2000 Membrane Transport. Oxford University Press, New York; Hessa T et al 2005 Nature [Lond] 433:377; <http://pdbtm.enzim.hu>; transmembrane helix localization: <http://localodom.kobic.re.kr/LocaloDom/index.htm>.

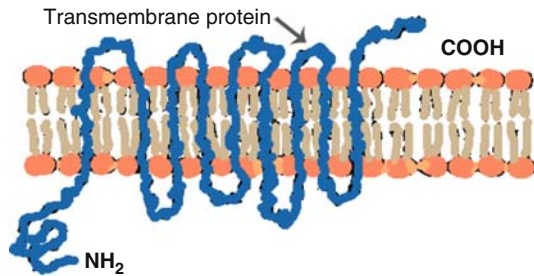


Figure T100. Transmembrane protein

Transmethylation: ►methylation of DNA

Transmission: Transmission indicates whether a particular gene or chromosome survives meiotic or post-meiotic selection and is recovered in the zygotes, embryos, or adults. Apoptotic mechanisms eliminate defective differentiating spermatogonia and elongating spermatids. During oogenesis, apoptosis is less active. This may be the cause of the long-standing knowledge that many (chromosomal) defects are preferentially or to a large extent transmitted through the egg. Transmission is generally reduced if the chromosomes have deficiencies, duplications or structural rearrangements, meiotic drive, maternal-fetal incompatibilities, etc. Monosomes and trisomes also have impaired transmission as well as defective genes. Segregation distorter genes and gametophyte factors may cause reduced transmission. Genetic factors located within the cellular organelles and infectious heredity usually display uniparental (maternal) transmission. *Vertical transmission* indicates transfer by the gametes and *horizontal transmission* means spread of a condition through infectious agents without the involvement of the host genetic system. Horizontal transmission is indicated by sequenced genomes, e.g., in the archaeobacterium *Holobacterium halobium* the dihydrolipoamide dehydrogenase gene displayed 50% homology to that of Gram-positive eubacteria but only 25% to other archaeobacteria. In the *Bacillus subtilis* genome, 10 nucleotide sequences were detected that are of infectious prophage origin.

Transformation by foreign DNA presents the best-documented case for horizontal transfer. Apparent homologies among genes carried by taxonomically

different organisms may be interpreted as convergent evolution. Although horizontal transmission of genes is a fact, during the evolution of higher organisms its role might have been only marginal compared to the Darwinian process (Kurland CG et al 2003 Proc Natl Acad Sci USA 100:9658). The findings of transposable element (SINE) homologies in organisms widely separated taxonomically may be assumed to have origin in retroviral infections. Some of the homologous retrotransposons still carry the characteristic terminal repeats in, e.g., *Vipera ammodytes* and the bovine genome. The transfers might have also been mediated by parasites, such as ticks (*Ixodes*), common to a very wide variety of vertebrates (from reptiles to humans). ►megaspore competition, ►meiotic drive, ►preferential segregation, ►gene conversion, ►certation, ►self-incompatibility, ►infectious heredity, ►transformation, ►transposable elements, ►transposon, ►retroposon, ►retrotransposon, ►intein, ►apoptosis, ►lateral transmission

Transmission Disequilibrium Test (TDT): The TDT is used to ascertain whether a tentative association between two traits is or is not transmitted from the heterozygous parents. This test is not applicable meaningfully to a population where one of the alleles has very high frequency because in such a case the association will appear high, although no causal relationship may be present. The TDT test is not a genetic linkage test. The TDT test can be used to estimate quantitatively the distribution of k offspring carriers of a mutation among r affected progeny by truncated binomials.

$$\text{if } k = r \quad t^k (1 - t^{s-r}) / \{1 - [t^s + (1 - t)^s]\}$$

$$\text{if } 0 < k < r \quad \binom{r}{k} t^k (1 - t)^{r-k} / \{1 - [t^s + (1 - t)^s]\}$$

$$\text{if } k = 0 \quad (1 - t)^r [1 - (1 - t)^{s-r}] / \{1 - [t^s + (1 - t)^s]\}$$

where t = the segregation parameter, s = the size of the sibship.

Segregation distortion can also be determined on the basis of m carriers of the mutation among s genotyped progeny:

$$\text{if parent is typed: } \binom{s}{m} t^m (1 - t)^{s-m}, \text{ if parent is inferred: } \binom{s}{m} t^m (1 - t)^{s-m} / \{1 - [t^s + (1 - t)^s]\}$$

(Formulas adopted from Hager J et al 1995 Nature Genet 9: 299) ►association test, ►association mapping, ►segregation distortion, ►binomial distribution, ►binomial probability, ►sib TDT, ►SDT, ►genomic control; McGinnis R 2000 Am J Hum Genet 67:1340.

Transmission Genetics: Transmission genetics is actually a misnomer because all genetics deals with inherited (transmitted) properties of organisms and in case there is no transmission there is no genetics. The term has been used to identify those aspects of genetics that deal only with the transmission of genes and chromosomes from parents to offspring involving also the study of segregation, recombination, mutation and other genetic phenomena without the use of biochemical and molecular analyses. It is used in the same sense as classical or Mendelian genetics. ▶ [molecular genetics](#), ▶ [reversed genetics](#)

Transmitochondrial: Cells containing mitochondrial DNA introduced exogenously. The procedure is suitable to produce animal models for human mitochondrial diseases. ▶ [mtDNA](#), ▶ [heteroplasmy](#), ▶ [mitochondrial diseases in humans](#); Hirano M 2001 Proc Natl Acad Sci USA 98:401.

Transmitter-Gated Ion Channel: The transmitter-gated ion channel converts chemical signals, received through neural synaptic gates, to electric signals. The channels in the postsynaptic cells receive the neurotransmitter. The process results in a temporary permeability change and a change in membrane potential, depending on the amount of the neurotransmitter. Subsequently, if the membrane potential is sufficient, voltage-gated cation channels may be opened. ▶ [ion channels](#)

Transmogrification: A complete metamorphosis of living creatures, such as in the case of mythological chimeras, satyrs, mermaids, etc. Genetic engineering and organ transplantation in medicine now bring into reality—in some way—the formerly imaginary beings; animals and plants expressing bacterial genes or vice versa. ▶ [chimera](#), ▶ [homeotic genes](#), ▶ [gene fusion](#), ▶ [allografts](#)

Trans-Morphism: Variations in the low-copy repeats are situated in trans position (repulsion), i.e., one variant in one, the other is in the other homologous chromosome. ▶ [cis-morphism](#)

Transmutation: Changing one species into another (an unproven idea). Also, changing one isotope into another by radioactive decay or changing the atomic number by nuclear bombardment.

Transomic: ▶ [transsomic](#)

Transorientation Hypothesis: The transorientation hypothesis suggests a fourth site (D [decoding]) on the ribosome (besides A, P, and E) and assumes that the EF-G-GTP and tRNA ternary complex rotation (transorientation) moves the tRNA from the D site to the A site during protein synthesis. ▶ [ribosomes](#); Simonson AB, Lake JA 2002 Nature [Lond] 416:281.

Transpeptidation: The transfer of an amino acid from the ribosomal A site to the P site. ▶ [protein synthesis](#), ▶ [aminoacyl-tRNA synthetase](#)

Transpiration: Releasing water by evaporation through the stoma in plants, and through exhalation, through the skin, etc., in animals. ▶ [stoma](#)

Transplacement: Gene replacement with the aid of plasmid vectors. ▶ [gene replacement vector](#), ▶ [localized mutagenesis](#), ▶ [targeting genes](#)

Transplantation: The transfer of tissues or subcellular organelles or other cellular components from one site to another within an organism or between related or unrelated organisms. Transplantation among genetically non-identical organisms may have serious immunological barriers. ▶ [grafting](#), ▶ [grafting in medicine](#), ▶ [graft rejection](#), ▶ [graft-versus-host disease](#), ▶ [stem cells](#)

Transplantation Antigens: Proteins on the cell surface, encoded by the major histocompatibility (MHC) genes; they play a major role in graft (allograft) rejection in mammals. The rejection may depend on the perception of the foreign antigens (tissues) by the lymphoid organs. Transplantation of lost or severely damaged body parts (limbs, face) is technically feasible but the reconstruction surgery—unless from the patient's own body—mandates life-long treatment with immunosuppressors. The French facial tissue transplantation also used twice hematopoietic stem cells from the facial donor tissues in the hope that immune tolerance may develop. Despite these efforts, acute rejection was experienced three weeks after the surgery. Even with the use of all immunosuppressive methods available, rejection may occur within one or two years after the transplantation. These plastic surgeries involve also psychological problems along with the medical ones (Okie S 2006 New Eng J Med 354:889). ▶ [HLA](#), ▶ [mixed lymphocyte reaction](#), ▶ [microcytotoxicity assay](#), ▶ [transplantation](#)

Transplantation In Utero: Postnatal transplantation of foreign tissue generally results in adverse immunological reaction and rejection of the engraftment. This is very serious problem in blood transfusion, grafting, and stem cell therapy. Immature fetuses do not have yet fully developed immune systems. Therefore, attempts have been made to introduce foreign tissue (human hemopoietic stem cells) into developing fetuses at about the first third or even shorter period of pregnancy in the goat (Zeng F et al 2005 DNA Cell Biol 24:403), sheep (Zanjani ED et al 1992 J Clin Invest 89:1178), monkeys (Harrison MR et al 1989 Lancet 2(8677):1425) and other animals. Such transplants were highly successful and various types

of human tissues differentiated and were identified in the animals after two years without rejection. Such a procedure obviates the use of immunosuppressive treatment. By the use of green fluorescent protein markers the right topography of the differentiated tissue could be followed (Zeng F et al 2006 Proc Natl Acad Sci USA 103:7801). ►stem cells, ►hemopoiesis, ►immunosuppression, ►immune tolerance

Transplantation of Organelles: As per transplantation of organelles, nuclei, isolated chromosomes, mitochondria, and plastids can be transferred into other cells by cellular (protoplast) fusion and by microinjection. In case of nuclear transplantation, the resident nucleus is either destroyed (by radiation) or evicted by the use of the fungal toxins, cytochalasins. The enucleated cell is called *cytoplast* and the nucleus surrounded by small amount of cytoplasm is a *karyoplast*. After introduction into the cytoplast of another nucleus by fusion, a *reconstituted cell* is obtained. The individual components are labeled either genetically or by radioactivity or by staining or even mechanically (by 0.5 µm latex beads). The transferred organelles may express their genetic information and can be isolated efficiently and identified if selectable markers (e.g., antibiotic resistance) are used. Defective livers may be repopulated with normal liver cells expressing transgenic BCL-2 because of its protection against apoptosis mediated by FAS. Without BCL-2, the transplanted liver cells do not survive. Such a procedure may eventually become an alternative to liver transplantation. ►cell fusion, ►transformation genetic, ►nuclear transplantation, ►apoptosis, ►paternal leakage, ►rejection; Kagawa Y et al 2001 Adv Drug Deliv Rev 49:107; Kuhholzer B, Prather RS 2000 Proc Soc Exp Biol Med 224:240.

Transplastome: The plastid genome, containing DNA introduced by transformation. ►plastome, ►chloroplasts, ►chloroplast genetics

Transponder (microtransponder): A few hundred micrometer wide silicon chip-based device for memory storage. When prompted by laser light it emits a radio signal that transmits its identification number. In a manner similar to DNA chips, it may assist identification of DNA sequences that are recognized by a probe. ►DNA chips, ►probe

Transport Elements, Constitutive (CTE): CTE permit the transport of spliced and non-spliced RNAs (such as viral RNAs, U snRNAs, tRNAs) although unspliced mRNAs are not exported from the nucleus. ►splicing, ►nuclear pore, ►RNA export, ►RNA transport

Transportan: ►cell-penetrating peptide

Transporters: Permease proteins that assist the transport of various molecules and ions through membranes.

►membranes, ►receptors, ►G-proteins, ►ABC transporters, ►CAT transporters, ►GLAST, ►PROT, ►GLYT, ►rbat/4F2hc, ►ASCT1, ►TAP, ►DNA transport; Sprong H et al 2001 Nature Rev Mol Cell Biol 2:504; Alper SL 2002 Annu Rev Physiol 64:899; <http://plantst.sdsc.edu>; transporter classification: <http://www.tcdb.org/>.

Transportin: A 90 kDa protein, distantly related to importin, which mediates nuclear transport with the M9, 38-amino acid, transport signal by a mechanism different from that of the importin complex. ►importin, ►karyopherin, ►nuclear localization sequences, ►nuclear pore, ►RNA export, ►export adaptor; Lai M-C et al 2001 Proc Natl Acad Sci USA 98:10154.

Transposable Elements: Transposable elements occur in the majority of organisms. Their major characteristic is that they are capable of changing their position within a genome or may move from one genome to another. Transposable elements are classified into two major groups. Class I elements transpose with an RNA intermediate. Class II elements rely on a cut-and-paste mechanism. Elements that lack terminal repeats are unable to transfer horizontally. The estimated rate of transposition is about 10^{-5} to 10^{-4} per element in *Drosophila*. The frequency of transposition may be regulated also by the host genome in lower and higher organisms as well as by methylation of the transposase. Transposable elements can remain silent in the host genomes as of cryptic elements. In such cases, epigenetic mechanisms suppress their activity (Slotkin RK, Martienssen R 2007 Nature Rev Genet 8:272). Also, the various types of elements may have intrinsic differences in mobility. The eukaryotic elements can be either retrotransposons (retrovirus-like) and have long direct terminal repeats (Class I.1) or do not have long terminal repeats (Class I.2), also called retroposons. Both types of Class I elements also possess active or inactive reverse transcriptase. The Class II elements have inverted terminal repeats that code for transposase. Transposition may take place through an RNA intermediate or directly by DNA. Transpositions may take place by homologous recombination between elements located at different map positions in the genome. Close to 50% of the human genome consists of transposons and about 70% of the maize genome is transposable. Transposable elements may have an evolutionary role in the remodeling of the genomes. Transposable elements are transmitted from generation to generation but selection may act against them because insertions may damage the genes; and an equilibrium may generally be reached. The I element of hybrid dysgenesis in *Drosophila*

carries an internal sequence that regulates copy number. After about 10 generation of the inclusion of the first I element, transposition is ‘tamed’, i.e., this internal sequence slows down the movement of the transposon. Elements with regulated transposition rate are successful in invading a population and after a burst their activity is limited and their presence is secured (Le Rouzic A, Capi P 2005 Genetics 169:1033). The strength of selection for host alleles controlling transposition may be estimated according to Charlesworth and Longley (Genetics 112:359):

$s \approx -\delta u = \left[\frac{\bar{n}(u-v)}{2H} + \frac{\bar{n}\pi}{2(1-2\pi)} \right]$ where δu = change in the rate of transposition, n = copy number, u = rate of transposition, v = rate of excision per element, H = harmonic mean of the rate of transposition, π = sterility or lethality caused by the transposition. The spliceosomes, telomerases, and the ability of immunoglobulin genes to transpose may have originated from transposons. The whole-genome sequencings revealed the existence of transposable elements that were not detectable by the methods of classical genetics. About 3% of the *Drosophila* genome is transposable. A survey of 13,799 human genes revealed that 533 (~4%) included some type of a transposable element (Nekrutenko A, Li W-H 2001 Trends Genet 17:619). A survey of 25,193 human proteins revealed that 4,653 human genes carry similarities to sequences in putative transposable elements. Since during evolution many rearrangements have taken place, the exact number of contribution of the transposable elements is not easy to ascertain (Britten R 2006 Proc Natl Acad Sci USA 103:1798). Transposable elements frequently generate chromosomal aberrations such as deletions, duplications, inversions, translocations, etc. *Doc1420* LINE element of *Drosophila* can generate an adaptive pesticide resistance through truncation of a gene (Aminetzach YT et al 2005 Science 309:764).
 ▶transposable elements bacterial, ▶retroposon, ▶transposable elements fungal, ▶transposable elements animal, ▶transposable elements plants, ▶transposable elements viral, ▶transposons, ▶transposase, ▶Polintons, ▶cut-and-paste, ▶isochores, ▶transposon footprint, ▶second cycle mutation, ▶hybrid dysgenesis, ▶transposon conjugative, ▶spliceosome, ▶telomerase, ▶immunoglobulins, ▶selfish DNA, ▶transposon — recombination, ▶genome-defence model; Helitron, Berg DE, Howe MM (Eds.) 1989 Mobile DNA. Amer Soc Microbiol Washington, DC; Kidwell MG, Lisch DR 2000 Trends Ecol Evol 15:95; Lönning W-E, Saedler H 2002 Annu Rev Genet 36:389; ecological/evolutionary significance: Brookfield JFY 2005 Nature Rev Genet 6:128, classification: Wessler SR 2006 Proc Natl Acad Sci USA 103:17600; transposon insertion site profiling chip (TIP-chip):

Whelan SJ et al 2006 Proc Natl Acad Sci USA 103:17632.

Transposable Elements Animal: ▶copia, ▶P element, ▶LINE, ▶SINE, ▶hybrid dysgenesis, ▶R2Bm, ▶immunoglobulins

Transposable Elements, Bacterial: Bacterial transposable elements may be classified according to the Gram-negative host (Tn3, Tn5, Tn7, Tn10) or gram-positive host (Tn554, Tn916, Tn1545, Tn551 and Tn917, Tn4556, Tn4001). The large transposon such as Tn916 and Tn1545 are capable of conjugative-like transfer to other cells. ▶insertion elements, ▶non-plasmid conjugation

Transposable Elements Fungal: ▶Ty, ▶transposable elements yeast

Transposable Elements, Plants: ▶Ac-Ds, ▶Spm (En), ▶Dt, ▶Mu, ▶Tam, ▶TAG, ▶controlling elements, ▶somaclonal variation, ▶retrotransposons, ▶retrotransposon, ▶transposons, ▶Helitron, ▶pack-MULEs; Wessler SR 2001 Plant Physiol 125:149; Jurka J, Kapitonov VV 2001 Proc Natl Acad Sci USA 98:12315; Feschotte C et al 2002 Nature Rev Genet 3:329.

Transposable Elements, Yeast: ▶Ty [including δ , ▶ σ , ▶ τ], ▶ Ω , ▶mating type determination, ▶*Schizosaccharomyces pombe*

Transposant: An individual/line generated with the aid of a gene trap vector. ▶gene trap vector

Transposase: An enzyme mediating the transfer of transposable genetic elements within the genome. The transposase function may be a part of the transposable element or it may be provided from trans position for elements that are defective in the enzyme. The transposase of phage MU first cuts away the transposons from the flanking DNA. Then it inserts the cleaved ends into the new DNA target site. The conserved DD35E motif is essential for both of these reactions and a single active site is responsible for the cleavage as well as for the transfer (D: aspartic acid, 35: amino acids, E: glutamic acid). Before transposition the multimeric transpososome is assembled, including the transposon ends and proteins (such as the tetrameric MuA protein of bacteriophage Mu). ▶transposon, ▶transposable element, ▶Tn10, ▶cut-and-paste; Goldhaber-Gordon I et al 2003 Proc Natl Acad Sci USA 100:7509.

Transposition: The transfer of a chromosomal segment to another position. The transposition may be *conservative* when the segment (transposon) is simply transferred to another location or it may be *replicative* when a newly synthesized copy is moved to another place while the original copy is still retained where it was (see Fig. T101).

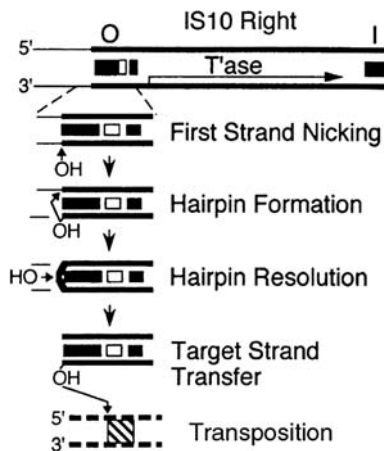


Figure T101. A model of transposition by IS10 of transposable element Tn10. (Courtesy of Mizuuchi K. From Kennedy AK et al 2000 Cell 101:295)

Transposition usually requires that both terminal repeats of the transposon would be intact. *One-sided transposition*—when one terminal repeat is lost—may still be feasible by replicative transposition. In *Drosophila*, ~80% of the mutations were attributed to transpositions. *Non-linear transposition* takes place when the transposon ends are located in different molecules. The latter type of event may generate diverse chromosomal rearrangements. ▶insertion element, ▶transposons, ▶transposable elements, ▶cut-and-paste, ▶Tn, ▶hybrid dysgenesis, ▶immunoglobulins, ▶mating type determination in yeast, ▶*Schizosaccharomyces pombe*, ▶transposon—recombination

Transposition Immunity (target immunity): In target immunity, the transposable element does not move into a replicon, which already carries another transposon or the inverted terminal repeats of a transposon. Transposition immunity is overcome by high expression of the transposase or defects in the terminal repeats of the resident transposon. Transposition of Tn7 is inhibited by the presence of Tn7 sequences within the same replicon. ▶transposition, ▶transposable elements, ▶Tn3, ▶insertional mutation; Manna D, Higgins NP 1999 Mol Microbiol 32:595.

Transposition Induction: In transposition induction, the normal rate of transposition of the Ty1 yeast retrotransposon is about 10^{-5} – 10^{-7} per element per cell division, its rate can be substantially increased if in a multicopy plasmid pGTy1. The Ty element is under the control of an inducible *GAL1* promoter. Transposition of Ty is controlled also by *RAD25* and *RAD3*. ▶Ty, ▶galactose utilization, ▶RAD3, ▶RAD25, ▶transposase; Staleva L, Venkov P 2001 Mutation

Res 474:93; Eichenbaum Z, Livneh Z 1998 Genetics 149:1173.

Transposition Site: The target of insertion is generally not random. The bacterial Tn10 prefers 5'-NGCTNAGCN-3'. The mariner transposon selects CAYA-TA-TRTG environment. Tn5 prefers a palindrome-like sequence flanked by A and T: A-GNTY-WRANC-T. The insertion element IS231A likes a site within an S-shaped DNA. Retroviral elements show predilection for DNA around nucleosomes and cruciform DNA. Bacteriophage Mu is inserted nearly at random yet some preferences for a pentamer within a 23–24-bp tract and avoidance of the *lacZ* control region has been noted. ▶transposons, ▶cruciform DNA, ▶nucleosomes, ▶Mu bacteriophage; Haapa-Paananen S et al 2002 J Biol Chem 277:2843.

Transposome: A complex of a transposase, the transposon, and other proteins mediating the insertion of the transposon into a target DNA. ▶transposon, ▶transposase; Hoffman LM et al 2000 Genetica 108:19.

Transposon: ▶Tn, ▶transposable elements, ▶retroposon, ▶retrotransposon, ▶TRIPLES

Transposon, Conjugative: A diverse group of broad host-range transposons varying in size from 18 to over 150 kb double-stranded DNA. They occur in different *Bacteroides* species. After excision they form a circular intermediate molecule that can integrate into the DNA of another cell by a conjugation-like process. When a transposon excises it carries along a 6 bp adjacent sequence of the host. The excision may be followed by restitution—without duplication—at the original host site or it may leave a footprint at the original location. Transposons may trigger the movement of other transposable elements. ▶transposable elements, ▶plasmid, ▶conjugation; Hinerfeld D, Churchward G 2001 Mol Microbiol 41:1459.

Transposon Footprint: Short insertions left behind in the original target after the transposon exited from the sequences. These nucleotides may be the consequence of the genetic repair after excision, e.g., the sequence before the insertion CTGGTGGC after excision may become: CTGGTGGC-TGGTGGGC or CTGGTGGGcTGGTGGC. ▶transposable elements, ▶second cycle mutation; Plasterk RH 1991 EMBO J 10:1919; Hare RS et al 2001 J Bacteriol 183:1694.

Transposon Mutagenesis: As per transposon mutagenesis, transposable and insertion elements can move in the genome (mobile genetic elements) and may insert within the boundary of genes. Such an insertion, by virtue of interrupting the normal reading frame, may

eliminate, reduce, or alter the expression of the gene and the event is recognized as a mutation. Recently, it has been shown that many of the insertions do not lead to observable changes in the expression of the genes, or their effect is minimal and only sequencing of the target loci reveals their presence. Mutations so generated have great advantage for genetic analysis because the insertion serves as a tag on the gene permitting its isolation and molecular study. Many of the insertions are retrotransposons and in plants commonly located within introns. In animals the comparable elements are frequently within intergenic regions. In *Caenorhabditis*, transposons—but not retrotransposons—tend to be located within sequences of high recombination. In *Drosophila*, such differences were not confirmed. Coupling a site-specific DNA-binding domain (DBD) of a polydactyl zinc-finger protein E2C to the *Sleeping Beauty* transposase produced a transposable element specific to human chromosome 17 (Yant SR et al 2007 Nucleic Acids Res 35(7):e50). ▶[gene tagging](#), ▶[insertional mutation](#), ▶[scanning transposon mutagenesis](#), ▶[transformation](#), ▶[TraSH](#), ▶[labeling](#), ▶[gene isolation](#), ▶[plasmid rescue](#), ▶[suicide vector](#), ▶[retrotransposon](#), ▶[retroposon](#), ▶[sleeping beauty](#); Mills DA 2001 Curr Opin Biotechnol 12:503; Dupuy AJ et al 2001 Genesis 30:82.

Transposon—Recombination: In transposon recombination, transposons may induce various types of chromosomal rearrangements and deletions in both prokaryotes and eukaryotes. The bacterial transposons (Tn), the *Drosophila* P elements, the budding yeast Ty elements, and under some conditions (but not under others) the plant transposons too may enhance a somewhat or even dramatically homologous recombination at the sites of their insertion. The recombination in plants may precede meiosis. ▶[transposon](#), ▶[Tn](#), ▶[hybrid dysgenesis](#), ▶[Ty](#); Xiao Y-L et al 2000 Genetics 156:2007.

Transposon Tagging: Tagging a gene by the insertion of a transposon. The insertion disrupts the continuity of the gene, causing a mutation and thereby the success of the tagging is identified by the phenotype. Subsequently, using the labeled transposon as a probe can aid the isolation of the gene. ▶[transposon mutagenesis](#), ▶[probe](#), ▶[gene isolation](#); Long D, Coupland G 1998 Methods Mol Biol 82:325; Pereira A, Aarts MG 1998 Methods Mol Biol 82:329; Kumar A et al 2000 Methods Enzymol 328:550.

Transposon Vector: A transposon vector can be used for introducing genes into the somatic cells of animals by microinjection into embryos of vertebrates or into invertebrates. These vectors must include transposase function, selectable marker(s) and a chosen gene.

The *Drosophila* Mariner-like, Tc1-like or Sleeping Beauty vectors appeared more successful and safer than viral vectors. ▶[vectors](#), ▶[mariner](#), ▶[hybrid dysgenesis](#), ▶[piggyBAC](#), ▶[Sleeping Beauty](#), ▶[P-element vector](#); Izsvak Z et al 2000 J Mol Biol 302:93; Grossman GL et al 2000 Insect Biochem Mol Biol 30:909.

Transposon-based Sequencing: The transposon-based sequencing is used primarily for sequencing cDNA. Various transposons (Mu, Tn5) or repetitive DNAs are introduced at random into the cells and isolated on the basis of the selective markers (antibiotic resistance) within the transposon. Sequencing employs primers, which are specific for the ends of the transposon. ▶[EST](#), ▶[DNA sequencing](#); Yaron SN et al 2002 Nucleic Acids Res 30:2460; Shevchenko Y et al 2002 Nucleic Acids Res 30:2469.

Transposons, Animal: ▶[transposable elements animal](#)

Transposons, Bacterial: DNA segments which can insert into several sites of the genome and contain gene(s) besides those required for insertion; they are generally longer than 2 kilobases. It has been suggested that the introns of eukaryotic cells might have been introduced into the genes by broad host-range phages or transposons. ▶[Tn](#), ▶[insertion elements](#), ▶[accessory proteins](#)

Transposons, Fungal: ▶[Ty](#)

Transposons-Controlling Elements, Plant: The major transposable elements in maize are *Ac-Ds*, *Spm*, *Dt*, and *Mu*. Besides these, there are much less well defined controlling elements: *Bg* (*Bergamo*), *Fcu* (*Factor Cuna*), *Mr* (*Mutator of R*), *Mrh* (*Mutator of a1-m-rh*), *Mst* (*Modifier of allele R-st*), *Mut* (controlling element of *bz1-m-rh*), *Cy* (regulatory element of *bz1-rcy*). ▶[controlling elements](#), ▶[Ac-Ds](#), ▶[Spm](#), ▶[Dt](#), ▶[Mu](#), ▶[Tam](#), ▶[Ta](#)

Transresponder: The ABL oncogene is activated (transresponds) by translocation to BCR in the Philadelphia chromosome and causes chronic myelogenous leukemia in more than 90% of the cases. ▶[BCR](#), ▶[ABL](#), ▶[Philadelphia chromosome](#), ▶[leukemia](#); Gardner DP et al 1996 Transgenic Res 5:37.

Trans-Sensing: Trans-sensing is an interaction between somatically “paired” homologous chromosomes affecting gene expression in diploids. ▶[transvection](#); Tartof KD, Henikoff S 1991 Cell 65:201.

Transsexual: A transsexual has an innate desire to change her/his anatomical sex to the other form. The volume of the central subdivision of the bed nucleus of the strial terminals of the brain is larger in males than in females. In male-to-female transsexuals, this particular area of the brain is female sized. Thus this

anatomical condition may be a determining factor for transsexualism and sex hormone production. Estrogen family drug treatment may cosmetically help to improve the size of the breast. ►[sex determination](#)

Transsomic Line: The transsomic line carries micro-injected chromosomal fragments in the cell nucleus.

Trans-Splicing: Trans-splicing is the splicing together of exons that are not adjacent within the boundary of the gene but are remotely positioned and may be even in different chromosomes. ►[introns](#), ►[regulation of gene activity](#), ►[tau](#), ►[SL1](#), ►[SL2](#); Vandenberghe AE et al 2001 *Genes Dev* 15:294; Denker JA et al 2002 *Nature [Lond]* 417:667.

Transthyretin: A homotetrameric 55 kDa protein in the brain facilitating thyroxine transport and mediating association of retinol to retinol-binding protein. It also binds the β fragment of amyloid proteins and is instrumental in Alzheimer disease and other amyloid diseases. Genistein is an inhibitor of the dissociation of the transthyretin tetramers and also inhibits amyloidogenesis (Green NS et al 2005 *Proc Natl Acad Sci USA* 102:14545). Thus consumption of soybean products may be preventive or therapeutic. ►[goiter](#), ►[retinol](#), ►[Alzheimer disease](#), ►[prion](#), ►[amyloidosis](#); Li MD et al 2000 *J Neurosci* 20:1318.

Trans-Translation: Trans-translation may occur if the stop codon and the preceding end of the mRNA are lost and using another template RNA completes the translation. ►[recoding](#), ►[tmRNA](#); Lee S et al 2001 *RNA* 7:999; Bessho Y et al 2007 *Proc Natl Acad Sci USA* 104:8293.

Trans-Vection: ►[cis-vection](#), ►[transacting element](#), ►[cis-trans effect](#)

Transvection: A synopsis-dependent modification of activity in “pseudoalleles.” In paired chromosomes genes in trans position may affect the expression of an allele. It has also been called trans-sensing. It has been interpreted as the result of interaction between DNA binding proteins attached to the two synapsed promoters. ►[co-suppression](#), ►[RIP](#), ►[trans-sensing](#), ►[pseudoalleles](#); Lewis EB 1951 *Cold Spring Harbor Symp Quant Biol* 16:159; Matzke M et al 2001 *Genetics* 158:451; Duncan IW 2002 *Annu Rev Genet* 36:521.

Transversion Mismatch: A mispairing involving either two purines or two pyrimidines. ►[mismatch](#), ►[transition mismatch](#)

Transversion Mutation: The substitution of a purine for a pyrimidine, or a pyrimidine for a purine in the genetic material. ►[base substitutions](#), ►[base substitution mutations](#); Freese E 1959 *Brookhaven Symp Biol* 12:63.

Trap: The same as CD40 ligand.

TRAP (testis-specific cytoplasmic poly[A] polymerase): TRAP controls germ cell morphogenesis. ►[poly-adenylation signal](#); Kashiwabara S-I et al 2002 *Science* 298:1999.

TRAP (tryptophan RNA-binding attenuation protein): In *Bacillus subtilis* when activated by L-tryptophan, this protein binds to the mRNA leader causing a termination of transcription. This is in contrast to the situation in *E. coli* where the attenuation is brought about by an altered secondary structure of the nascent RNA transcript. Some sort of attenuation takes place also in eukaryotes but the mechanism of that is not entirely clear yet.

The *mtrB* gene in *B. subtilis* encodes the TRAP protein containing 11 identical subunits and it binds single-stranded RNA. The β -sheet subunits form a wheel-like structure with a hole in the center and tryptophan is attached to the clefts between the β -sheets resulting in circularization of the RNA target in which eleven U/GAG repeats are bound to the surface of this ondecamer (11 subunit) protein modified by tryptophan. TRAP may regulate both transcription and translation. Similar mechanisms occur also in some other bacterial species. ►[tryptophan operon](#), ►[attenuator region](#); structure in: Antson AA et al 1999 *Nature (Lond)* 401:235; Yakhnin AV, Babinzke P 2002 *Proc Nat Acad Sci USA* 99:11067; Chen G, Yanofsky C 2003 *Science* 301:211; Gollnick P et al 2005 *Annu Rev Genet* 39:47.

TRAP/DRIP/ARC: A part of a multiprotein complex of transcriptional regulators. (See Crawford SE et al 2002 *J Biol Chem* 277:3585).

Trapoxin: An inhibitor of histone deacetylase. ►[histone deacetylase](#)

TRAPP: A Golgi-associated protein for docking vesicles. ►[Golgi](#), ►[vesicles](#)

Trapping Poly-A Tails: In the process of trapping poly-A tails, the UPAS Trap suppresses nonsense-mediated RNA surveillance and permits targeting transcriptionally silent genes in embryonic stem cells. ►[nonsense-mediated RNA surveillance](#), ►[stem cells](#); Shigeoka T et al 2005 *Nucleic Acids Res* 33(2):e20.

Trapping Promoters: When a promoterless structural gene is inserted into a host genome with the assistance of a transformation vector, the inserted sequences may become “in-frame” located within the host chromosome and a host promoter may drive the transcription of the foreign gene that in the vector had no promoter. Since the promoter and upstream regulatory elements control the transcription, directly

or in association with transcription factors, the expression pattern (timing, tissue site) may be altered and the intensity of expression may be increased or decreased according to the nature of the promoter (see Fig. T102). ▶gene fusion, ▶transcriptional gene fusion vectors, ▶translational gene fusion vectors, ▶read-through proteins, ▶gene trapping, ▶expression trapping, ▶targeted trapping, see photo; Medico E et al 2001 *Nature Biotechnol* 19:579; mouse gene trap consortium (IGTC): www.genetrap.org; splinkerette; mouse embryonic stem cell trap library: <http://baygenomics.ucsf.edu>.

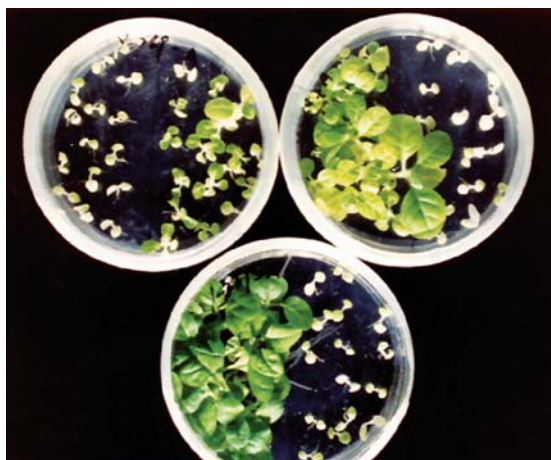


Figure T102. Transgenic tobacco seedlings segregate for kanamycin-sensitivity and resistance. A promoterless vector introduced the aminoglycoside gene into the cells. The structural gene was expressed only when it trapped a tobacco promoter. The strength of the promoters varied and consequently the degree of resistance too. Each Petri plate was divided into two sections and in one section all the small, bleached, sensitive seedlings died. (From Yao Y, Rédei GP, unpublished)

TraSH (transposons site hybridization): Genes are disrupted by transposons and changes in functions are compared—by microarray hybridization—to that in the wild type genome. ▶transposons mutagenesis, ▶microarray hybridization

Trastuzumab/Herceptin: is a monoclonal antibody used for specific cancer therapy. A new generation of HER2 breast cancer drug is Lapatinib. ▶biomarker, ▶Herceptin

Traveler's Diarrhea: is caused generally by bacterial (*E. coli*, *Salmonella*) infection.

TRCF (transcription repair coupling factor): A eukaryotic repair helicase corresponding to *UvrA* in *E. coli*;

it is encoded by yeast gene *MFD* (mutation frequency decline, Li BH et al 1999 *J Mol Biol* 294:35).

TRD (transmission ratio distortion): ▶meiotic drive, ▶segregation distorter

TRE: Thyroid hormone responsive element in the rat growth hormone gene with a consensus of AGGTCA...TGACCT. ▶ERBA, ▶hormone response elements, ▶regulation of gene activity; Oofusa K et al 2001 *Mol Cell Endocrinol* 181:97.

Treacher Collins Syndrome (TCOF1): A dominant (human chromosome 5q32-q33) complex defect of the face with an incidence of $\sim 2 \times 10^{-5}$. Mutation in the treacle, a 26-exon phosphoprotein is involved in neural crest cell formation. Treacle affects mammalian ribosomal DNA transcription by interaction with an upstream binding factor, which controls RNA polymerase I (Valdez BC et al 2004 *Proc Natl Acad Sci USA* 101:10709; Dixon J et al 2006 *Proc Natl Acad Sci USA* 103:13403).

Treadmill Evolution: ▶Red Queen hypothesis

Treadmilling: Is the addition of microtubule subunits to the growing plus end and loss of subunits at the minus end. ▶microtubules, ▶dynamic instability; Shaw SL et al 2003 *Science* 300:1715.

TREC (TCR excision unit including the recombination signals): ▶TCR genes

Tree of Life: ▶evolutionary tree

Trees: ▶forest trees

Tree Edit Distance: The minimal weighted number of changes required to change one tree of descent into another. ▶string edit distance, ▶evolutionary tree

Trehalose (α -D-glucopyranosyl- α -D-glucopyranoside): A non-reducing disaccharide, which accumulates in the yeast cell wall under conditions of stress. The use of trehalose for platelet and other cell preservation by freeze-drying has applied significance. Trehalose 6-phosphate regulates starch synthesis in plants by post-translationally activating ADP-glucose phosphorylase (see Fig. T103) (Kolbe A et al 2005 *Proc Natl Acad Sci USA* 102:11118). ▶inflorescence; Darg AK et al 2002 *Proc Natl Acad Sci USA* 99:15898.

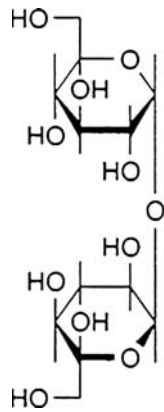


Figure T103. Trehalose

TREMBL: A computer annotated protein sequence extension of the SWISS-PROT. ▶[SWISS-PROT in databases](#)

***Treponema pallidum*:** Spirochete bacterium with completely sequenced (1998) genome of 1,138,006 bp including 1041 open reading frames. It is responsible for the potentially deadly disease of syphilis. Due to protective immunity, waves of infections occur with 8–11 year periods in the populations (see Fig. [T104](#)) (Grassly NC et al 2005 Nature [Lond] 43 3:417).

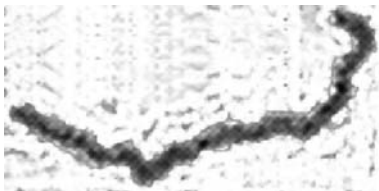


Figure T104. *Treponema*

Many of the nineteenth to twentieth century artists (Maupassant, Daudet), the famous philosopher Friedrich Nietzsche suffered from mental illness caused by the infection. *Treponema denticola* causes periodontal (bleeding gum) disease. ▶[leptospirosis](#), ▶[spirochetes](#); Fraser CM et al 1998 Science 281:375.

Trexon (transposed exon): Short duplicated modular units in the DNA with inverted terminal repeats. ▶[transposon](#), ▶[exon](#)

TRF: ▶[T cell replacing factor](#), ▶[a lymphokine](#)

TRF (thyrotropic release factor): ▶[corticotropin](#)

TRF1 (TATA-box-binding protein related factor): is a tissue- and gene-specific binding protein with preference for one of the two *Tudor* locus (2-[97]) promoters of *Drosophila*. The protein product of *tud*

has maternal effect and it is expressed mainly in the embryos and pupae. (See Takada S et al 2000 Cell 101:459; ▶[histones](#)).

TRF1: 60 kDa telomeric TTAGGG repeat binding protein negatively regulates telomere extension and facilitates its interaction with the telomerase enzyme. ▶[telomeres](#), ▶[telomerase](#), ▶[RAP](#), ▶[tankyrase](#); Nakamura M et al 2001 Curr Biol 11:1512.

TRF2: (telomeric repeat-binding factor-2): One of the proteins, which protect telomeric ends of the chromosomes. TRF2 inhibition may lead to apoptosis, mediated by p53 and mutated ataxia telangiectasia genes. TRF2 is associated with RAD50, MRE11 and BS1 proteins. Oxidative damage (e.g., 8-oxoguanamine lesion) greatly reduces the affinity of both TRF1 and TRF2 (Opresko PL et al 2005 Nucleic Acids Res 33:1230). TRF2 mutations predispose to premature aging, cancer and ultraviolet sensitivity (Muñoz P et al 2005 Nature Genet 37:1063). ▶[TRF1](#), ▶[telomeres](#), ▶[apoptosis](#), ▶[ataxia telangiectasia](#), ▶[p53](#), ▶[RAD50](#), ▶[Mre](#), ▶[oxidative DNA damages](#), ▶[Nijmegen breakage syndrome](#); Fairall L et al 2001 Mol Cell 8:351.

T-RFLP: The procedure has been successfully exploited for the estimation of genetic diversity within bacterial populations. It involves PCR amplification of a gene of interest (often 16S rRNA genes) with fluorescent dye-labeled primers, followed by multiple single restriction digests done in parallel. The resulting fragments are then separated by capillary electrophoresis with an internal size standard to determine the lengths of the terminal (fluorescently labeled) fragments. Each distinct terminal restriction fragment is considered an operational taxonomic unit (OTU), thus the choice of restriction enzymes can impact the number of OTUs observed in each sample and the calculation of diversity statistics (Collins RE, Rocap G 2007 Nucleic Acids Res 35:W58). ▶[RFLP](#); restriction enzyme choice: <http://rocaplab.ocean.washington.edu/tools/repk>.

Trg: Bacterial transducer protein with attraction to ribose and galactose. (See Beel BD, Hazelbauer GL 2001 Mol Microbiol 40:824).

Triabody: Trimeric antibody built of three single chain pairs of the variable heavy and light chain regions of antibody. ▶[antibody chimeric](#), ▶[diabody](#), ▶[recombinant antibody](#); Le Gall F et al 1999 FEBS Lett 453 (1–2):164.

Triacylglycerols (synonym triglycerides): are uncharged esters of glycerol and thus called also neutral fats. Triglycerides are energy storage compounds and contain four times as much energy in the human body than all the proteins combined. By lipase, they are

hydrolyzed into glycerol and fatty acids. Lipolysis is controlled by cAMP in the adipose (fat) cells. Insulin inhibits lipolysis. Impaired long-chain fatty acid oxidation, triglyceride breakdown defects, triglyceride transfer (MTP, 4q22-q24) in abetalipoproteinemia, hypertriglyceridemia (15q11.2-q13.1) a dominant hyperlipidemia and it is a risk for heart disease, etc. are diseases involved in triglyceride metabolism. ►epinephrine, ►norepinephrine, ►glucagon, ►adrenocorticotrophic hormone, ►fatty acids, ►triglycerol; Zimmermann R et al 2004 Science 306:1383.

Triad Test: is an association mapping procedure where the two parents and the proband are tested, and it may involve unrelated control(s). ►association mapping; Epstein MP et al 2005 Am J Hum Genet 76:592.

Triage: Assignment of priorities in medicine or in the regulation of cellular metabolism.

Triallelic Inheritance: The manifestation of the recessive disease e.g., the Bardet-Biedl syndrome may require the expression of three mutant alleles. ►digenic disease, ►Bardet-Biedl syndrome, ►epistasis; Katsanis N et al 2001 Science 293:2256.

Triangulation Number: Represents the number of protein subunits (facets) in an icosahedral viral capsid. ►icosahedral, ►capsid; Paredes AM et al 1993 Proc Natl Acad Sci USA 90:9095.

Tribe: Descendants of a female progenitor or a taxonomic group below a suborder or a group of primitive people with a common origin, culture and social system.

Tribolium castaneum (n = 10, 200 Mb): red flour beetle, object of cytological and population genetics studies. The body segmentation gene (*mlpt*) produces polycistronic mRNA (Savard J et al 2006 Cell 126:559). For a genetic map see Beeman RW, Brown SJ 1999 Genetics 153:333; Klingler M 2004 Current Biol 14:R639; <http://www.ksu.edu/tribolium/>; <ftp://ftp.ncbi.nlm.nih.gov/genomes/>; <http://www.bioinformatics.ksu.edu/BeetleBase/>; <http://www.intlgenome.org/viewOrganisms.cfm?organismID=1000185>.

TriC: is a ring complex of eukaryotic chaperonin. TriC-P5 is synonymous with CCT γ , Bin2p, Cct3p. ►chaperonins; Dunn AY et al 2001 J Struct Biol 135:176.

Tricarboxylic Acid Cycle: ►Krebs-Szentgyörgyi cycle

Trichocyst: An organ of protozoa that may extrude fibrous shafts and may serve as an anchor or defensive or offensive tool.

Trichogen Cell: ►tormogen

Trichogyne: Hypha emanating from the protoperithecium, to what the conidia are attached prior to fertilization in some ascomycetes. ►hypha, ►conidia

Trichome: Hair or filament in plants, algae and animals; some plant hairs may be single filaments or they may have tripartite termini (see Fig. T105). (See Szymanski DB et al 2000 Trends Plant Sci 5:214, photo above).



Figure T105. Trichome

***Trichomonas vaginalis*:** Is an infectious, non-mitochondrial protozoan parasite of the human female and male sexual organs and urinary tract and it is transmitted by sexual intercourse (see Fig. T106). It may cause severe discomfort. Other species may infect domestic animals and also birds and invertebrates. *Trichomonas* and other protists do not have the regular type mitochondria but only mitosomes. The sequenced genome of *T. vaginalis* is about 176 megabase with a predicted protein-coding gene number of 59,681, 479 tRNA and about 250 rRNA genes (Carlton JM et al 2007 Science 315:207). ►mitosome, ►Entamoeba, ►Giardia, ►Protozoa



Figure T106. Trichomonas

Trichorhinophalangeal Syndrome (TRPS1): Dominant or recessive human chromosome 8q24 defect involving multiple exostoses (bone projections), mental retardation, protruding ears, sparse hair on the scalp, bulbous nose and short stature. Mutation in a zinc-finger protein gene is responsible for TRPS1. TRPSIII is most severe ►Langer-Giedion syndrome

Trichostatin A: An antifungal antibiotic, an inhibitor of histone deacetylase of yeast. Trichostatin may reverse the effect of methylation and activate methylated genes. In some instances low doses of

5-aza-2'-deoxycytidine along with trichostatin are required for substantial expression of originally methylated and silent cancer genes. Trichostatin increases the number of root hairs and their pattern of *Arabidopsis* (Xu C-R et al 2005 Proc Natl Acad Sci USA 102:14469). ▶[histone deacetylase](#), ▶[fragile X](#), ▶[root](#); Marks PA et al 2001 Curr Opin Oncol 13:477.

Trichothiodystrophy (TTD, 19q13.2-q13.3): is a collective name for autosomal recessive human diseases involving low-sulfur abnormalities of the hair. The *Tay syndrome* involves also ichthyosiform erythroderma (scaly red skin), mental and growth retardation, etc. The *Pollitt syndrome* (trichorrhhexis nodosa or trichothiodystrophy neurocutaneus) displays low cystin content of the hair, and the nails, and the head and the nervous system are also defective. Xeroderma pigmentosum IV includes trichothiodystrophy and sun- and UV-sensitivity. Also called PIBIDS. This type of mutation lacks helicase and excision repair activity because of the defect in the interaction between one of the xeroderma pigmentosum and the p44 protein subunit of the transcription factor TFIIH. Some TDD mutations are temperature-sensitive. ▶[hair-brain syndrome](#), ▶[xeroderma pigmentosum](#), ▶[Cockayne syndrome](#), ▶[excision repair](#), ▶[transcription factors](#), ▶[temperature-sensitive mutation](#), ▶[ichthyosis](#); Vermeulen W et al 2001 Nature Genet 27:299; de Boer J et al 2002 Science 296:1276.

Triclosan (trichlorinated diphenyl ether): Antibacterial and antifungal agent (blocking lipid biosynthesis) used in antiseptics, soaps, and other cosmetics.

Tricotyledony: is a relatively rare and generally not inherited developmental anomaly in plants (see Fig. T107). In some families of plants there is a higher than average tendency for the condition.



Figure T107. Tricotyledonous *Arabidopsis* seedling

Tricyclo-DNA: Tricyclo-DNA and -RNA can be used in antisense technologies to block selectively the expression of genes (see Fig. T108). ▶[antisense technologies](#); Renneberg D et al 2002 Nucleic Acids Res 30:2751.

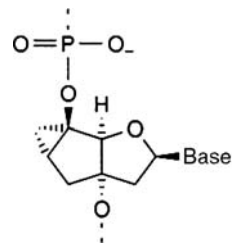


Figure T108. Tricyclo-DNA

TRID: is a TRAIL decoy receptor. ▶[TRAIL](#)

Tricuspid Atresia: is an agenesis of the tricuspid valve, which connects the right atrium to the right ventricle of the heart. Some other heart defects may be associated with it. The condition is generally sporadic but some cases are familial and involve defects of the Zfp2/Fog2 Zinc-finger protein.

Triethylene Melamine (TEM): Alkylating agent (see Fig. T109). ▶[TEM](#)

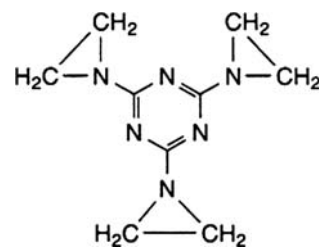


Figure T109. Triethylene melamine

Trigger Factor (TF, ~48 kDa): is a prolyl isomerase enzyme (PPI) associated with the 50S ribosome unit of bacteria or with the GroL chaperone. It may aid translocation of molecules through the cytoplasmic outer membrane. In bacteria TF and DnaK may cooperate in protein folding but they are not indispensable at intermediate temperatures. Cyclosporin or FK506 does not inhibit TF and it is only moderately related to cyclophilins of FKBP. ▶[PPI](#), ▶[GroL](#), ▶[cyclosporin](#), ▶[FK506](#), ▶[cyclophilins](#), ▶[chaperone](#), ▶[GroEL](#), ▶[DnaK](#), ▶[Clp](#), ▶[protein sorting](#); Liu Z et al 2001 FEBS Lett 506:108; Patzelt H et al 2001 Proc Natl Acad Sci USA 98:14244; Ferbitz L et al 2004 Nature [Lond] 431:590.

Trigger Loop: is a part of RNA polymerase II complex just beneath the A site of ribosome; it triggers the formation of a phosphodiester bond during transcription of RNA and assures fidelity (Wang D et al 2006 Cell 127:941).

Triglyceride: Same as triacylglycerol.

Triglyceridemia: ►familial hypertriglyceridemia

Trihybrid Cross: The parental forms are homozygous altogether for 3 allelic pairs at (unlinked) loci, e.g., AABbDd × aabbDD and therefore in the F₂ 8 phenotypic classes may be distinguished. ►gametic array, ►Mendelian segregation

Tri-isosomic: in wheat, 20''+ i'', 2n = 43, ['' = disomic, '' = trisomic, i = isosomic]

Trillium: Species have one of the largest normal chromosomes (2n = 10) in plants, about 50 times larger than *Arabidopsis*, a plant with one of the smallest chromosomes (2n = 10) (see Fig. T110).



Figure T110. *Trillium* is from Sparrow AH, Evans HJ 1961 Brookhaven Symp Biol 14:76; *Arabidopsis* karyotype is the courtesy of Lotti Sears

TRIM (tripartite interaction motif): Retrovirus/lentivirus can be restricted after entry into the cells by the TRIM5α protein variants (Sayah DM et al 2004 Nature [Lond] 430:569). The TRIM proteins form a family and different members may occur in different mammals. ►retrovirus restriction factors; Song B et al 2005 J Virol 79:6111.

Trimester: Period of three months; the human pregnancy of 9 months includes 3 trimesters.

Trimethoprim (3,4-diamino-5-[3,4,5-trimethoxybenzyl]pyrimidine): An antibiotic.

Trimethylaminuria (1q23-q25): Defect in flavin monooxygenase and failure of detoxification of drugs and endogenous amines. Afflicted persons exhale fish odors.

Trimming: The processing of the primary RNA transcripts to functional mRNA or ribosomal and tRNA. The cleavage of pre-rRNA transcripts by RNase III into 16S, 23S and 5S rRNA as well as into the tRNAs contained within the spacer sequences of

the co-transcripts. The cleavage takes place at the duplex sequences forming the stem of the rRNA loops. ►post-transcriptional processing, *rrn* genes for diagram, ►introns

Trinomial Distribution: $(1 + 2 + 1)^n$ can be expanded to predict the segregation of the genotypic classes (note that the quotients within parentheses must not be added!)

$$1(1 + 2)^n + \frac{n!}{1(n-1)!}(1 + 2)^{n-1} + \dots + \frac{n!}{(n-1)!1}(1 + 2)^{n-(n-1)} + 1(1 + 2)^{n-n}$$

An example for three pairs of alleles:

$$1(1 + 2)^3 + \dots + \frac{3!}{1(2)!}(1 + 2)^2 + 1$$

$$1 + (3 \times 2) + (3 \times 4) + 8 + 3 \times (1 + 2 + 2 + 4) + 3 \times (1 + 2) + 1$$

When rewritten in a symmetrical distribution: 1:2:1:2:4:2:1:2:1:2:4:2:4:8:4:2:4:2:1:2:1:2:4:2:1:2:1 the 27 terms indicate that triple heterozygotes are 8, double heterozygotes 4, and single heterozygotes are 2 in a distribution in compliance with Mendel's law.

►binomial, ►multinomials

Trinucleotide Repeats: are microsatellite sequences displaying some clustering in yeast and other genes. In more than ten human neurodegenerative diseases CAG (glutamine codons) are repeated many times. The resulting polyglutamine (polyQ) oligomers seem to be the cause of the diseases or the disease accumulates the polyglutamine tracts. Diminished folding capacity of proteins seems to be involved in the trinucleotide repeat diseases (Gidalevitz T et al 2006 Science 311:1471). Autophagy more readily eliminates the polyglutamine tracts from the cytoplasm than from the nucleus (Iwata A et al 2005 Proc Natl Acad Sci USA 102:13135). The long polyglutamine sequences (most frequently beyond 35–40) interfere with CREB-dependent transcription by interacting with transcription factor TAF_{II}130. The polyglutamine proteins are more resistant to decay. Transglutaminase inhibitors (cystamine [←decarboxylated cysteine], monodansyl cadaverin [←decarboxylated lysine]) may alleviate apoptosis of the cells. RNAi may alleviate the problems normally associated with polyglutamine tracts (Caplen NJ et al 2002 Hum Mol Genet 11:175). Several small molecules are potent inhibitors of polyglutamine aggregation and suppress neurodegeneration in vivo (Zhang X et al 2005 Proc Natl Acad Sci USA 102:892). Unusual, common feature of these diseases that in successive generations the symptoms

appear earlier and with greater severity (anticipation) as gain-of-function mutations. The repeats form a hairpin structure and interfere with DNA replication. Also, the CpG sequences are likely to be methylated. Cis elements may contribute to instability (Cleary JD, Pearson CE 2003 Cytogenet Genome Res 100:25). The nature of the repeats may vary and may involve CGG, GCC, CAG, CTG sequences in different autosomes and the X chromosome, respectively. These repeats may expand (from a few [5–50] in the normal to hundreds of copies) in an unstable manner in the 5'-untranslated region of the FMR1 gene and cause translational suppression by stalling on the 40S ribosomal RNA. Defects in DNA repair may contribute to instability. Flanking sequences of the polyglutamine tracts affect the degree of misfolding and toxicity (Duennwald ML et al 2006 Proc Natl Acad Sci USA 103:11045). More than 40 human anomalies are attributed to changes in the repeats.

In *E. coli*, the larger expansions occur predominantly when the CTG trinucleotides are in the leading strands and deletions are mainly on the opposite lagging strands. The toxic effect of polyglutamine tracts can be genetically suppressed in *Drosophila* by proteins homologous to heat shock protein 40 and a tetratricopeptide, both containing chaperone-like a domain. The instability caused by the repeats is more common in meiosis than in mitosis. In yeast the CAG/CTG repeat meiotic instability is based on double-strand DNA break repair (see Fig. T111).

It has been suggested that the DNA polymerase stalls within the CTG-CAG repeat sequences and cause nicks and double-strand breaks that promote homologous recombination in lower and higher eukaryotes at 10% or higher frequency. Polyglutamine expansions can affect transcription and can be one of the causes of the disease (Helmlinger D et al 2006

Trends Genet 22:562). ▶anticipation, ▶resveratrol, ▶Huntington's chorea, ▶Machado-Joseph disease, ▶ataxia, ▶Kennedy disease, ▶polysyndactyly, ▶spinocerebellar ataxias, ▶dentatorubral-pallidoluysian atrophy, ▶Jacobsen syndrome, ▶fragile sites, ▶fragile X, ▶FRAXA, ▶FRAXE, ▶Friedreich's ataxia, ▶myotonic dystrophy, ▶epilepsy, ▶myoclonic epilepsy, ▶muscular dystrophy, ▶methylation of DNA, ▶translation repressor proteins, ▶SRY, ▶human intelligence, ▶FMR1 mutation, ▶schizophrenia, ▶neurodegenerative diseases, ▶pre-mutation, ▶ERDA1, ▶dinucleotide repeats, ▶microsatellites, ▶tetratricopeptide sequences, ▶chaperone, ▶heat-shock proteins, ▶TAF_{II}, ▶CREB, ▶slipped-structure DNA, ▶RNAi, ▶homopolymeric amino acids, ▶autophagy, ▶oxoguanine; Claude T et al 1995 Annu Rev Genet 29:703; Orr HT, Zoghbi HY 2000 Cell 101:1; Cummings CJ, Zoghbi HY 2000 Annu Rev Genomics Hum Genet 1:281; Cleary JD et al 2002 Nature Genet 31:37; Hum Mol Genet 2002 11:1909–1985; Pluciennik A et al 2002 J Biol Chem 277:34074; Napierala M et al 2002 J Biol Chem 277:34087; Pearson CE et al 2005 Nature Rev Genet 6:729; Gatchel JR, Zoghbi HY 2005 Nature Rev Genet 6:743; therapeutic approaches: Di Prospero NA, Fischbeck KH 2005 Nature Rev Genet 6:756; Orr HT, Zoghbi HY 2007 Annu Rev Neurosci 30:575; repeats and human disease review: Mirkin SM 2007 Nature [Lond] 447:932.

Trinucleotide-Directed Mutagenesis (TRIM): Introduction into the coding sequences of a gene(s) trinucleotide analogs such as 9-fluorenylmethoxycarbonyl (Fmoc) trinucleotide phosphoramidites. The synthetic analogs convey resistance to nucleases and are effective in induction of specific mutations. ▶trinucleotide repeats, ▶phosphoramidates; Sondek J, Shortle D 1992 Proc Natl Acad Sci USA 89:3581.

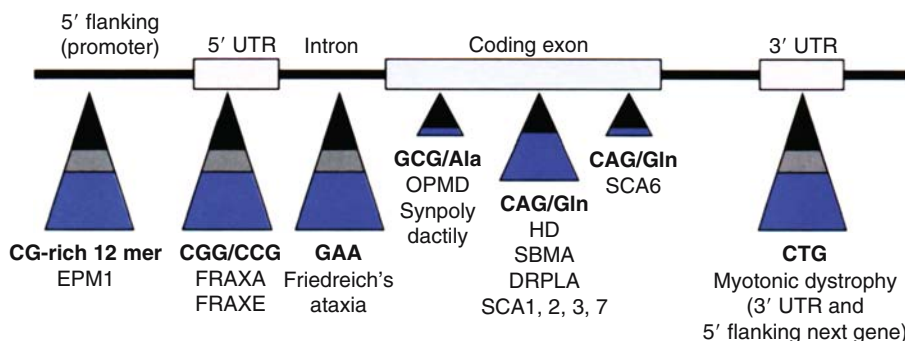


Figure T111. Location of expanded trinucleotide repeats in diseases. EPM: myoclonous epilepsy; FRAXA: fragile X syndrome; OPMD: Muscular atrophy; HD: Huntington chorea; SBMA: Kennedy disease; DRPLA: dentatorubralpallidoluysian atrophy; SCA: spinocerebellar ataxia. The size of the triangles indicates the size of the repeat expansions. Top triangle: normal, gray in the middle: unstable premutational, bottom of the triangle: pathological condition. (Courtesy of Lunkes A et al 1998, p 149. In: Molecular Biology of the Brain. Higgins SJ (Ed.) Biochemical Society, London, UK)

TRIO (in human genetics): mother + father + child are available for study.

Trioma: ▶heterohybridoma

Triose: is a sugar with 3 carbon backbone.

Triosephosphate Isomerase Deficiency (TPI1): is encoded in human chromosome 12p13 but pseudogenes seem to be present at other locations. The level of activity of the enzyme varies. Null mutations are not expected to be viable since this is a key enzyme in the glycolytic pathway. The symptoms may be quite general weakness, neurological impairment, anemia, recurrent infections, etc. ▶glycolysis

Trip1 (thyroid hormone receptor): ▶Sug1

Triparental Human Embryo: Can be produced if a fertilized human egg nucleus is transferred into the egg of another female and implanted into a foster mother. The purpose of such an experiment would be to get rid of defective mitochondria of the first female and secure a healthy offspring. Such a procedure is not allowed in the USA but it has been approved in the United Kingdom in 2005. ▶multiparental offspring, ▶ART, ▶mitochondrial diseases in humans; Check E 2005 Nature [Lond] 437:305.

Tripeptide Discriminator (tripeptide anticodon): is part of the prokaryotic and eukaryotic translational release factors that recognize nonsense codons in mRNA and terminate protein synthesis. ▶release factor; Nakajamura Y, Ito K 2002 FEBS Lett 514:30.

Tripeptidyl Peptidase (TPPII): is a large protein complex outside the lysosomes with activity resembling the proteasome. ▶proteasomes

Triplasmy: is heteroplasmy for three different types of mtDNA. ▶heteroplasmy, ▶mtDNA

Triple A Syndrome: ▶achalasia-addisonianism-alacrima

Triple Helix Forming Oligonucleotides (TFO): May bind to polypurine-polypyrimidine tracts in the major groove of the DNA helix by Hoogsteen or reverse Hoogsteen bonding and prevent the access of transcription factors. This may block transcription and cleave the DNA but may enhance repair DNA synthesis. In the triplex sequences, mutation rate in SV40 increased more than an order of magnitude in the suppressor gene, supFG1, employed as reporter, with 30 nucleotide long AG sequences (AG30). Shorter sequences or oligonucleotides of all four bases were either not or were much less effective. The triplex structure in xeroderma pigmentosum or in the Cockayne syndrome cells was not effective for mutation enhancement, indicating the requirement of excision repair for the events. TFOs may be used for targeting specific genes and prevent their

transcription or to induce mutation. ▶TPO, ▶LNO, ▶DNA kinking, ▶triplex, ▶DNA repair, ▶SV40, ▶supF, ▶xeroderma pigmentosum, ▶Cockayne syndrome, ▶Hoogsteen pairing, ▶antisense technologies, ▶psoralen dyes, ▶locked nucleic acids, ▶pseudoknot, ▶targeting genes, ▶inhibition of transcription, ▶helix; Grimm GN et al 2001 Nucleosides Nucleotides Nucleic Acids 20:909.

Triple Test: used for the identification of Down syndrome by assaying chorionic gonadotropin, unconjugated estriol and α -fetoprotein levels. ▶Down's syndrome, ▶gonadotropin, ▶estriol, ▶fetoprotein

Triple-A Syndrome: ▶ALADIN

Triple-Stage Quadrupole/Ion-Trap Mass Spectrometry: is proteome analytical procedure. ▶mass spectrometer, ▶electrospray, ▶ESI, ▶CID

TRIPLES (transposon-insertion phenotypes): is a database with information on phenotype, protein localization and expression on the results of transposon mutagenesis in yeast. ▶insertional mutation, ▶transposon; <http://ygac.med.yale.edu>.

Triplet Binding Assay: A historically important method to determine the meaning of genetic triplet codons. A single type of radioactively labeled amino acid, charged to the cognate tRNA was allowed to recognize and bind to ribosomes with mRNA attached. Each type of charged tRNA then recognized only the corresponding code and the ribosomes were then trapped on the surface of a filter. Synthetic polynucleotides (mRNA) of known base composition retained only the cognate aminoacylated tRNA and thus provided the base composition and sequence of the true coding triplets. (See Fig. T112, ▶genetic code; Nirenberg MW, Leder P 1964 Science 145:1399).

Triplet Code: ▶genetic code

Triplet Expansion: ▶trinucleotide repeats

Triplex: Three-stranded nucleic acid structure, e.g., an RNA oligo-nucleotide may bind within the strand or to double-stranded DNA and result in antisense effects. Triplex strands occur transiently in genetic recombination. Triplex forming oligonucleotides may increase somatic mutation and recombination by the mechanism of nucleotide exchange repair (see Fig. T113). Some DNA polymerases (T7, Klenow fragment) can elongate a DNA strand from primers forming triple helices of 9–14 deoxyguanosine-rich residues. Triplex-forming oligonucleotides (TFO) may be used for sequence-specific control of gene expression. ▶antisense RNA, ▶Hoogsteen pairing, ▶helix, ▶peptide nucleic acid, ▶TFO, ▶H-DNA,

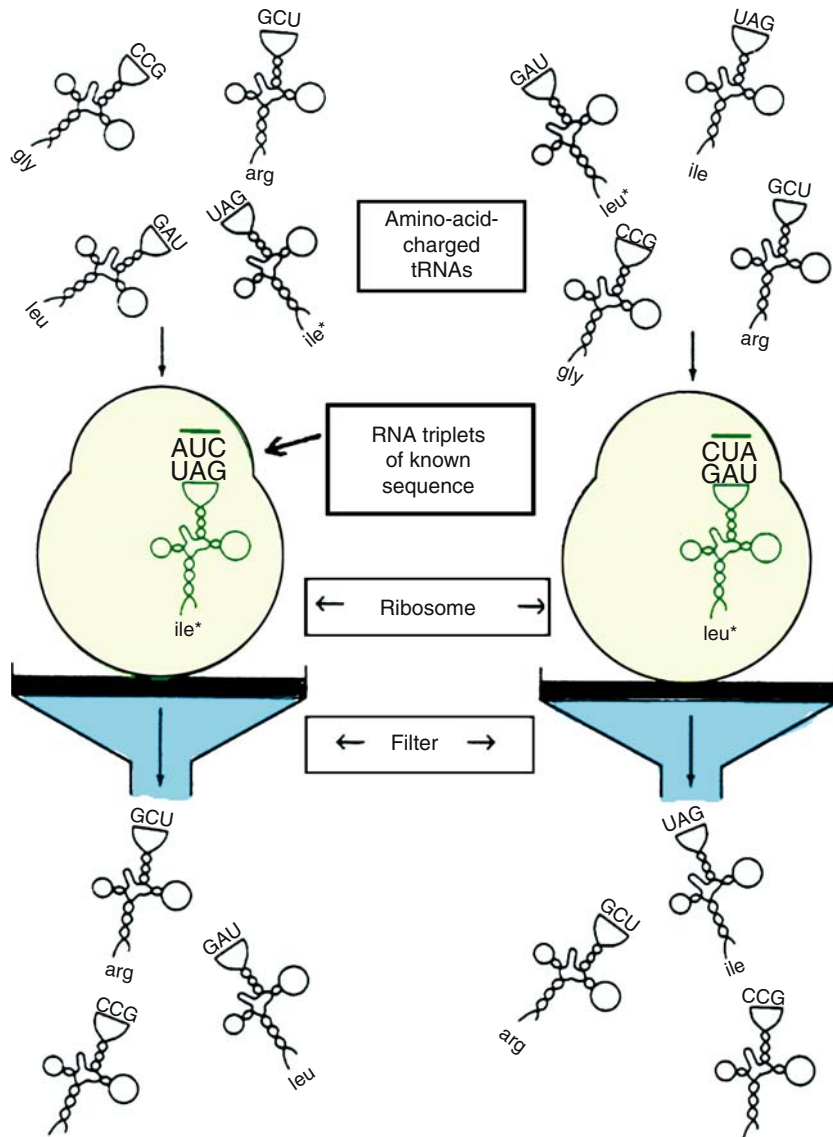


Figure T112. Triplet binding assay



Figure T113. Triplex. H: Hoogsteen pairing, RH: reverse Hoogsteen R: purine, Y: pyrimidine. Other configurations are also possible. (Hoyne PR et al 2000 Nucleic Acids Res 28:770)

►nodule-DNA, ►excision repair, ►Klenow fragment, ►isomerization of strands; Vasquez KM, Wilson JH 1998 Trends Biochem Sci 23:4; Luo Z et al 2000 Proc Natl Acad Sci USA 97:9003; Datta HJ

et al 2001 J Biol Chem 276:18018; Rocher C et al 2001 Nucleic Acids Res 29:3320; Knauert MP, Glazer PM 2001 Hum Mol Genet 10:2243; Coman D, Russu IM 2004 Nucleic Acids Res 32:878.

Triplex: A polyploid with three dominant alleles at a gene locus. ►autopolyploid, ►trisomy

Triplicate Genes: Triplicate genes convey identical or very similar phenotype and in a diploid, when segregate independently, display an F₂ phenotypic ratio of 63 dominant and 1 recessive.

Triploblasts: Animals with ecto-, meso- and endodermal germ layers. ►diploblasts

Triploid: A cell or organism with three identical genomes. Triploids ($3x$) are obtained when a ($4x$) is crossed with a diploid ($2x$). The majority of edible bananas, several cherry and apple varieties, and many sterile ornamentals (chrysanthemums, hyacinths) are triploid. The seedless watermelons, produced by crossing tetraploids with diploids are triploids and have commercial value. Triploid sugar beets are produced in a large-scale agriculturally because they offer of $\approx 10\%$ or higher sugar yield per acre than the parental diploid varieties. Triploidy in humans may occur by fertilizing a diploid egg (digyny) by a monosomic (normal) sperm or by the union of a normal haploid egg and two spermatozoa (diandry). The green toad (*Bufo viridis*) is triploid but surprisingly reproduces bisexually. ▶ [trisomic](#); Zaragoza MV et al 2000 Am J Hum Genet 66:1807; Stöck M et al 2002 Nature Genet 30:325.

Triplo-X: Triplo-X females (XXX) occur in about 0.0008 of human births. Their phenotype is close to normal and they can conceive. Yet they are somewhat below average in physical and mental abilities although they tend to be somewhat tall. With an increasing number of X-chromosomes beyond 3, the adverse effects are further aggravated. ▶ [sex determination](#), ▶ [sex chromosomal anomalies in humans](#), ▶ [trisomy](#), ▶ [Turner syndrome](#); Barr ML et al 1969 Can Med Assoc J 101:247.

Tripsacum: ▶ [maize](#)

Triradial Chromosome: A triradial chromosome may be formed by fusion of broken translocated chromatids in a three-armed way (see Fig. T114). (See Jenkins EC et al 1986 Am J Med Genet 23:531).



Figure T114. Triradial

Tris-HCl Buffer: The tris-HCl buffer contains tris-[hydroxymethyl]aminomethane and hydrochloric acid; it is used in various dilutions within the pH range 7.2–9.1.

Triskelion: Three-legged proteins on the surface of vesicles built of three clathrin and three smaller proteins (see Fig. T115). ▶ [clathrin](#), ▶ [endocytosis](#);

Umgewickell E 1983 EMBO J 2:1401; Fotin A et al 2004 Nature [Lond] 432:573.

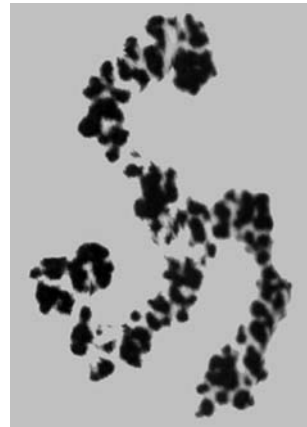


Figure T115. Triskelion (Redrawn after Ungewickell E, Branton D 1981 Nature [Lond] 289:420)

Trismus-Pseudocamptodactyly Syndrome (17p13.1): Camptodactyly, arthrogryposis, foot deformity, and failure to open the mouse completely due to defect in the myosin heavy chain gene (MYH8). ▶ [camptodactyly](#), ▶ [arthrogryposis](#), ▶ [myosin](#); Veugelers M et al 2004 New England J Med 351:460.

Trisomic: A cell or organism with one or more chromosomes (but not all) represented three times. ▶ [trisomy](#), ▶ [trisomic analysis](#), ▶ [triploid](#)

Trisomic Analysis: Trisomics have one or more chromosomes in triplicate (AAA) and thus produce both disomic (AA) and monosomic (A) gametes for gene loci in those chromosomes (see Table T2).

Male transmission of the disomic gametes is usually poor, it rarely exceeds 1%.

The transmission of disomic gametes through females varies according to the chromosome (genes) involved and depends also upon environmental conditions; most commonly this transmission is $1/4$ or $1/3$ of the normal (monosomic) gametes. The few viable human sex-chromosome trisomics (XXX, XXY, XYY) are either sterile or have very poor fertility because of the failure of normal development of the ovaries and testes (gonadal dysgenesis). From a single alternative allelic pair (A/a), disomics produce either A or a gametes. In contrast, trisomics potentially produce a maximum of five kinds of gametes, three disomic and two monosomic. The frequency of these five types of gametes depends also on the distance of the gene from the centromere, i.e., whether *chromosome segregation* (no crossing over between gene and centromere) or *maximal* (see Table T3).

Table T2. Gametic output of trisomics

| Genotype ↓ | Chromosome segregation | | | | | Maximal equational segregation | | | | |
|---------------|------------------------|----|----|---|---|--------------------------------|----|----|---|---|
| | AA | Aa | aa | A | a | AA | Aa | aa | A | a |
| AAa (duplex) | 1 | 2 | 0 | 2 | 1 | 5 | 6 | 1 | 8 | 4 |
| Aaa (simplex) | 0 | 2 | 1 | 1 | 2 | 1 | 6 | 5 | 4 | 8 |

Table T3. Phenotypic proportions in the F₂ of trisomics (disomic and trisomic pooled)

| Transmission [‡] & genotype ↓ | Chromosome segregation | | | Maximal equational segregation | | |
|---|------------------------|------|-----------------|--------------------------------|------|---------|
| | Dom. | Rec. | aaa (%) | Dom. | Rec. | aaa (%) |
| DUPLEX (AAa) | | | | | | |
| Male and female | 35 | 1 | 0 | 22.04 | 1 | 1.39* |
| Female only | 17 | 1 | 0 | 13.40 | 1 | 1.39 |
| None | 8 | 1 | 0 | 8 | 1 | 0.00 |
| Simplex (Aaa) | | | | | | |
| Male and female | 3 | 1 | 11 [§] | 2.41 | 1 | 13.9* |
| Female only | 2 | 1 | 11 | 1.77 | 1 | 13.9 |
| None | 5 | 4 | 0 | 1.25 | 1 | 0. |

[‡]refers to transmission of the disomic gametes
^{*}1/576 tetrasomics (aaaa) are not included
[§]1/36 tetrasomic (aaaa) is not included
^{*}25/576 tetrasomics (aaaa) are not included

In order to obtain two identical recessive alleles from a duplex, the chromosomes must form trivalents and recombination must take place between the gene and the centromere, following which the anaphase I distribution must move the two exchanged chromosomes toward the functional megaspore (equivalent to secondary oocyte in animals). At the most favorable coincidence of these events, in only half of the cases can we expect the two identical alleles to move into the same megaspore (equivalent to egg in animals).

Thus, the maximal chance of having a tetrad with a double recessive gamete (*aa*) will be $1/3 \times 1/2 = 1/6$. These fractions are based on one reductional and two equational disjunctions at meiosis I ($1/3$), while two alternative disjunctions at anaphase II ($1/2$) are the determining factors of the outcome.

The phenotypic segregation can be derived from the gametic output by random combinations. One factor, the transmission difference between the female and male gametes, seriously alters the theoretically expected proportions (see Table. T4).

Table T4. Phenotypic ratios in test-cross progenies (trisomics + disomics)

| Genotypes of cross ↓ | Only female transmission of disomic gametes | No transmission of disomic gametes |
|-------------------------|---|------------------------------------|
| | Dom.: Rec. | Dom.: Rec. |
| AAa x aa | 5:1 | 2:1 |
| Aaa x aa | 1:1 | 1:2 |

The genetic behavior of all chromosomes not present in triplicate in the trisomics is consistent with disomy. When the trisomic individuals are phenotypically distinguishable per se (do not require cytological identification of the chromosomal constitution), trisomy may be used very effectively to assign genes to chromosomes, irrespective of their linkage relationship. The segregation in a duplex will

not be 3:1 but it will vary (most commonly) between 17:1 to 8:1, as predicted by the table. In this case, the gene *a* is located in the chromosome that is triplicated. Genes in the disomic set of chromosomes are expected to display 3:1 segregation. In case telotrisomics are crossed with disomics ($\text{---} \text{---} \text{---} a \text{---}$, $\text{---} \text{---} a \text{---}$, $\text{---} \text{---} A \text{---}$ x normal disomic *a/a*), the dominant allele will be very rare among the diploid offspring but may be expressed in every individual of $2n + \text{telochromosome}$. Mapping can be done also by properly constructed isotrisomics, tertiary trisomics, and compensating trisomics. Genetic mapping with the aid of multipoint trisomic data is feasible also in humans (see Fig. T116). ▶disomic, ▶monosomic, ▶gonadal dysgenesis, ▶chromosome segregation, ▶maximal equational segregation, ▶mapping by dosage effect, ▶trisomy, ▶Down's syndrome, ▶Patau syndrome, ▶Edwards syndrome; Rédei GP 1982 Genetics. Macmillan, New York; Li J et al 2001 Am J Hum Genet 69:1255.

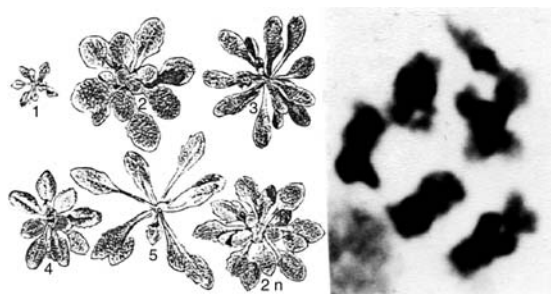


Figure T116. Left: The four primary trisomics (1–4) and a telotrisomic (5) of *Arabidopsis*. At the lower right corner is a normal disomic individual ($2n$). All are in columbia wild type background, grown under short daily light periods. At right: The chromosome complement of a primary trisomic. Note the trivalent association at the upper right area. (The photomicrograph is the courtesy of Dr. Lotti Steinitz-Sears)

Trisomic, Complementing: Trisomic complementing can be of three types; one is an apparent trisomic only because it involves a normal biarmed chromosome, while the two other chromosomes are actually telosomes, representing the left and right arms of the intact, normal chromosome. The second complementing type also involves one biarmed normal chromosome, but the two telosomes represent a pair of identical arms; thus, in essence this case is very similar to that of a secondary trisomic, having three identical arms and one single different arm. In the third type, in a normal biarmed chromosome, the second chromosome has an arm identical to the first but its second arm is a translocated segment from a non-homologous chromosome, and the third chromosome has a different translocated arm linked

to the centromere and to an arm of a normal chromosome. ▶trisomic analysis; scheme from GP Rédei's Lecture Notes 1980.

Trisomic, Primary: In a primary trisomic, the chromosome number is $2n + 1$, and the triplicate homologous chromosomes are structurally normal. ▶trisomic analysis

Trisomic, Secondary: In a secondary trisomic, the extra chromosome is an isochromosome, i.e., its two arms are identical; such a chromosome is an isochromosome. ▶trisomic analysis, ▶isochromosome

Trisomic, Tertiary: In a tertiary trisomic, the extra chromosome is involved in a reciprocal translocation and is partly homologous with two standard chromosomes. ▶trisomic analysis

Trisomy: Trisomy involves one or more but not all chromosomes of a genome in triplicate; trisomics are aneuploids. They may arise by selfing triploids when some of the extra chromosomes are lost. Nondisjunction during meiosis may also lead to trisomic progeny. Trisomy may exist in various forms. The phenotype of the trisomics varies, depending upon what genes are in the trisome. The phenotype may be very close, almost indistinguishable from that of normal disomics, and in other cases it may be lethal. Only a few of the autosomal human trisomies permit growth and development beyond infancy. Trisomy 9 allows near normal life expectancy although it also involves developmental and mental retardation. Individuals with trisomy 21 (Down's syndrome) also reach adulthood but remain mentally subnormal. Trisomy 22 may exist in mosaic form and the afflicted individuals are retarded in growth and mental abilities. About 3/4 of the trisomy 8 cases are mosaics, mentally retarded, and affected by head abnormalities to a variable degree, according to the extent of mosaicism. Trisomics for chromosome 11 have a variable extra long arm in chromosome 11 and accordingly exhibit brain and other internal organ damage of variable extent. Trisomics for the long arm of chromosome 3 have a very short life and variable abnormalities in internal organs and body development and severe mental retardation. Trisomy for the short arm of chromosome 4 is characterized by serious malformations of the brain, head, extremities, genitalia, and such individuals usually die early. About 1/3 of the abortuses, due to autosomal trisomy, involve chromosome 16; these are never carried to term. Trisomy 13 (Patau's syndrome) and trisomy 18 (Edwards syndrome) are live-born but die very early. Trisomy 16 is responsible for about 7.5% of all spontaneous abortions. XYY trisomies are apparently never found in spontaneously aborted or stillborn fetuses. All other autosomal human trisomies lead to

abortion at various stages after conception. Sex-chromosomal trisomy generally does not compromise viability of humans yet such individuals are usually sterile and display gonadal dysgenesis and a variety of physical and most commonly mental retardation as well. The vast majority of trisomics are the result of disomic female gametes. Paternal nondisjunction accounts for only a very small frequency of autosomal trisomy. However, 80% of 45 + X monosomies involve the loss of a paternal sex chromosome. Analytical procedures of about 65% efficiency exist for the detection of trisomy during the first trimester (Wapner R et al 2003 *New England J Med* 349:1405).

Trisomy is useful in plants for assigning genes to chromosomes. Microcell-mediated chromosome transfer permits the inclusion into mouse cell of only fragments of the third chromosome. The fragments are produced by chromosome breakage with the aid of ionizing radiation. The size and content of the fragments so generated is beyond precise experimental control; nevertheless, information can be obtained about the effects of segments smaller than an entire extra chromosome. Homologous recombination by gene targeting would appear to be a more desirable tool for generating segments of designed contents. Unfortunately, the frequency of this type of recombination is low. A chicken pre-B cell line (DT40) is known, however with 3–4 orders of magnitude higher homologous recombination. Technology is available for the transfer of human chromosomes to these chicken cell lines. The truncated human chromosomes from the chicken cell lines can then be reintroduced into human cells in culture. Another approach is the construction of human artificial chromosomes and minichromosomes (see Fig. T117).

The presence of an extra chromosome in yeast involves a number of phenotypes that are independent of the identity of the individual extra chromosome; all of these include defects in cell cycle progression, increased glucose uptake, and increased sensitivity to conditions interfering with protein synthesis and protein folding. These phenotypes reflect the consequences of additional protein production, imbalances in cellular protein composition and proliferative disadvantage (Chan LY et al 2007 *Science* 317:916). ▶trisomics, ▶trisomic analysis, ▶Down syndrome, ▶Edwards, ▶Patau's, ▶Klinefelter syndromes, ▶sex determination, ▶sex-chromosomal anomalies in humans, ▶cat-eye syndrome, ▶aneuploidy, ▶targeting genes, ▶chromosome uptake, ▶human artificial chromosome, ▶minichromosome, ▶microcell; Hassold TJ, Jacobs PA 1984 *Ann Rev Genet* 18:69; Robinson WP et al 2001 *Am J Hum. Genet* 69:1245.

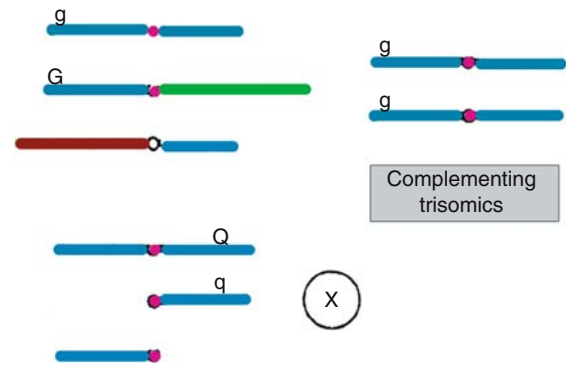


Figure T117. In the complementing trisomics there is only one normal representative of a particular chromosome. For the homologous arms it may be compensated by translocations containing jointly the entire chromosome (1) or by two complementary isochromosomes (2). The complementing trisomics (2). The complementing trisomics can also be used to assign genes to chromosome arms. In case (1) the predominant fraction in the $2n$ progeny is expected to be recessive because only the non-translocation strand is transmitted by the monosomic gamete. The wild-type allele (G) can be transmitted only after recombination. In contrast, the $2n+1$ progeny should be almost all wild type (except when recombination occurs between gene and centromere). In selfing of genotype (2) the $2n$ and most of the $2n+1$ progeny are expected to be of dominant phenotype; however, when recombination occurs between (q) and centromere, the recessive allele is included in the normal chromosome. Such a setup as (2) can be exploited only if the two telochromosomes are not distributed together in the majority of anaphases I's of meiosis

Trisomy, Segmental: ▶segmental aneuploidy

Tristetraprolin (TTP): A zinc-finger protein, inhibitory to TNF- α by destabilizing its mRNA, although TNF and agents that stimulate TNF stimulate its production too. TTP binds to A-U-rich (AUR) 3' untranslated sequences and responds to cytokines and other regulatory molecules. The Dicer and Argonaute proteins of the RNAi and microRNA pathways are also required for the AUR decay (Jing Q et al 2005 *Cell* 120:623). TTP and several homologous proteins control also apoptosis. ▶TNF, ▶zinc fingers, ▶DNA-binding protein domain, ▶RNAi, ▶antiviral protein; Johnson BA, Blackwell TK2002 *Oncogene* 21:4237.

Tritanopia: ▶color blindness

Tritelosomic: Tritelosomic occurs in wheat, $20'' + t'''$, $2n = 43$, [$''$ = disomic, $'''$ = trisomic, t = telosomic].

Table T5. The major species of *Triticum*

| Diploids (2n = 14) genomic formula former designation* and species, respectively | | |
|--|----------------|--|
| <i>T. monococcum</i> | A | <i>T. boeoticum</i> *, <i>T. aegilopoides</i> , <i>T. thoudar</i> , <i>T. urartu</i> |
| <i>T. speltoides</i> | S (= G?) | <i>Aegilops speltoides</i> *, <i>Aegilops ligustica</i> * |
| <i>T. bicornis</i> | S ^b | <i>Aegilops bicornis</i> * |
| <i>T. searsii</i> | S ^s | <i>Aegilops searsii</i> * |
| <i>T. longissimum</i> | S ^l | <i>Aegilops longissima</i> * (<i>Aegilops sharonensis</i> ?) |
| <i>T. tauschii</i> | D | <i>Aegilops squarrosa</i> *, <i>T. aegilops</i> |
| Tetraploids (2n = 28) | | |
| <i>T. turgidum</i> | AB | <i>T. dicoccoides</i> *, <i>T. dicoccon</i> , <i>T. durum</i> *, <i>T. polonicum</i> *, <i>T. carthlicum</i> *, <i>T. persicum</i> * |
| <i>T. timopheevi</i> | AG | <i>T. araraticum</i> , <i>T. dicoccoides</i> var. <i>nudiglumis</i> , <i>T. armeniacum</i> |
| Hexaploids | | |
| <i>T. aestivum</i> | ABD | <i>T. vulgare</i> *, <i>T. spelta</i> *, <i>T. macha</i> *, <i>T. sphaerococcum</i> *, <i>T. vavilovii</i> * |

Trithorax: *Drosophila* gene (3–54.2) regulating embryonic development (head, thorax, abdomen). Some of the alleles cause homeotic developments. The heterozygotes for the *trx^D* mutation display patchy variegation. ▶developmental-regulator effect variegation, ▶homeotic genes, ▶mll, ▶bithorax, ▶polycomb, ▶SET motif, ▶epigenesis, Petruk S et al 2001 Science 294:1331.

Triticale: A synthetic species produced by crossing wheat (*Triticum*) and rye (*Secale*) and doubling the chromosome number. The wheat parent may be tetraploid (2n = 28) or hexaploid (2n = 42) and the rye is generally diploid (2n = 14). Therefore, the amphidiploids may have the chromosome number of either 2n = 42 (hexaploid) or 2n = 56 (octaploid). As a crop variety, the former is used. On some soils suitable primarily for rye, the *Triticale* may provide grains with a milling quality approaching that of wheat. The new hybrids generally have shrunken kernels because some rye genes cause poor development of the endosperm. Breeding efforts have largely solved these problems and the commercial varieties have rather plump grains. ▶*Triticum*, ▶*Secale*, ▶amphidiploid, ▶chromosome doubling, ▶species synthetic; Gustafson JP 1987 Plant Breed Rev 5:41.

Triticalsecale: ▶*Triticale*

Triticum (common wheat and relatives): *Triticum* form a series of allopolyploids (see Table T5) (Huang S et al 2002 Proc Natl Acad Sci USA 99:8133). The common bread wheat, *T. aestivum* (both winter and spring forms), and the *T. durum* (*T. turgidum*) are used mainly for various pastas (macaroni, spaghetti, etc). The wheat kernel contains ca. 60–80% carbohydrates

(starch), 8–15% protein that is usually low in lysine, tryptophan, and methionine (see Fig. T118). Some wild relatives of the cultivated wheats produce kernels with higher amounts of protein than the commercial varieties, and chromosomal engineering can transfer these favorable traits. Wheats are the staple food for about 1/3 of the human population. ▶allopolyploids, ▶polyploidy, ▶monosomic analysis, ▶nullisomic, ▶glutenin, ▶celiac disease; Sears ER 1974 Handbook of Genetics. In: King RC (Ed.) Vol 2. pp 59–91, Plenum; Peng J et al 2003 Proc Nat Acad Sci USA 100:2489; extensive genomic information: Genetics 168 (2) 2004; <http://compbio.dfci.harvard.edu/tgi/>; <http://www.ksu.edu/wgrc/>; hexaploid heat transcript estimation: <http://www4.rothamsted.bbsrc.ac.uk/whets>.



Figure T118. Wheat species: From right to left: *Triticum monococcum*, *T. turgidum* (*durum*), *T. timopheevi*, *T. aestivum* (Chinese Spring [most widely used for cytogenetic studies]), *T. compactum*, *T. spelta*. (Courtesy of Dr. Carlos Alonso-Arnedo)

Tritium (H^3): ► **isotopes**

Triton X-100: A non-ionic detergent (MW 537). It used for the extraction of proteins and the solubilization of biological materials. The reduced form is preferred when spectrophotometric measurement is required. Molar absorption is 1.46×10^3 at pH 8, 20°C in 1% sodium dodecylsulfate (SDS) at 275 nm. Ammonium cobalthiocyanate reacts with it as a blue precipitate.

Tritordeum: An allohexaploid hybrid of tetraploid wheat (A, B genomes) and barley (H) of allooctaploid (ABDH) constitution. ► *Triticum*, ► *Hordeum*, ► **allopolyloid**; Hernandez P et al 2002 Genome 45:198.

Tritryp: ► **trypanosomatids**

Trituration: The disintegration into cells or homogenization of tissues or mixing different components of various materials.

Trivalent: In a trisomic or polyploid individual, three chromosomes may associate during meiotic prophase (see Fig. T119). In the trivalent association at any particular place, only two homologous chromosomes can pair, however, at a specific time and site.



Figure T119. Trivalent

trk (TRK) Oncogene: The product of the TRK gene is a receptor in membranes (tyrosine kinase activity) for NGF (nerve growth factor). It is localized to human chromosome 1q23-q24. TRK affects axonal and dendritic growth, synapsis, cytoskeleton assembly, membrane traffic, signal transduction, etc. ► **nerve growth factor**, ► **ovary**; Nakagawara A 2001 Cancer Lett 169:107; Huang EJ, Reichardt LF 2003 Annu Rev Biochem 72:609.

T

tRNA (transfer RNA): The shortest RNA molecule in the cell (ca. 3.8S), consisting of about 76 to 86 nucleotides. tRNAs carry amino acids to the ribosomes during protein synthesis. The majority of cells have 40 to 60 types of tRNAs because most of the 61 sense codons have their own tRNA in the eukaryotic cytosol. The tRNAs, which accept the same amino acid are known as *isoaccepting tRNAs*. In the human mitochondria, there are only 22 different tRNAs and in plant chloroplasts, about 30. tRNA is frequently called an adaptor molecule because it adapts the genetic code for the formation of the primary structure of protein. Rarely (ca. 1/3000), a tRNA is charged with the wrong amino acid, and in

these cases the complex is usually disrupted and the tRNA, recycled. The tRNA genes may occur in between ribosomal RNA genes (promoter - 16S - - tRNA - 23S - 5S - tRNA - tRNA...) or they frequently form independent clusters of different tRNA genes (promoter - tRNA¹ - tRNA² - tRNA³ - •). The different cognate tRNA groups are generally identified by a superscript of the appropriate amino acid, e.g., tRNA_{Met}. Sometimes, individual tRNA genes may be present in multiple copies. The tRNA gene clusters are transcribed into large primary molecules that require successive cleavage and trimming to form the mature tRNA. The endonuclease, RNase P (a ribozyme) recognizes the primary transcript, whether it is a single tRNA sequence or a cluster of rRNA or tRNA genes, and cleaves at the 5' terminus where the tRNA begins. For the tRNA to become functional, RNase D cuts at the 3'-end, and stops at a CCA sequence if any, or the 3'-end receives through post-transcriptional synthesis (by tRNA nucleotidyl synthetase) one, two, or three bases; thus, tRNA always ends with a 3'-CCA_{OH} sequence. This 3'-OH end becomes the amino acid attachment site of the tRNA (► **transfer RNA**). During the process of maturation, through modification of the original bases, thiouridine (S4U), pseudouridine (ψ), ribothymidine, dihydrouridine (DHU), inosine (I), 1-methyl-guanine (m¹G), 1-dimethyl-guanine (m¹dG), and N⁶-isopentenyl adenosine (i⁶A) may be formed within the tRNA sequence. ► **transfer RNA**, ► **amino acylation**, ► **aminoacyl-tRNA synthetase**, ► **protein synthesis**, ► **trimming**, ► **ribozyme**, ► **intron**, ► **pseudouridine**, ► **ribothymidine**, ► **dihydrouridine**, ► **isopentenyladenosine**, ► **hypoxanthine [for inosine]**, ► **mitochondrial diseases in humans**, ► **tRNA nucleotidyl transferase**; Söll D, Rajbahandary UL (Eds.) 1994 tRNA, Structure, Biosynthesis and Function. AMS Press, Washington, DC; <http://medlib.med.utah.edu/RNAmods/>.

tRNA Cleavage: In tRNA cleavage, T even phages may cripple a bacterial host tRNA and the viral-coded isoaccepting tRNA is then substituted for that of the host. (See Amitur M et al 1987 EMBO J 6:2499; Kaufmann G 2000 Trends Biochem Sci 25(2):70; Meidler R et al 1999 J Mol Biol 287:499).

tRNA Deacylase: tRNA deacylase cuts off the tRNA D-amino acids from the polypeptide chain after the complex reaches the P site on the ribosome. ► **protein synthesis**, ► **aminoacyl-tRNA synthetase**; Ferri-Fioni ML et al 2001 J Biol Chem 276:47285.

tRNA Mimicry: In tRNA mimicry, certain set of translation factor proteins resemble tRNA in shape and may even mimic tRNA in deciphering

the genetic code. (See Nakamura Y 2001 J Mol Evol 53(4–5):282).

tRNA Nucleotidyl Transferase: Attaches after transcription CCA-3'-OH to the 3'-end of the amino acid accepting arm of tRNA without relying on a template. Before building this 3'-end of the tRNAs a nuclease must remove the tail of the primary transcript at a 'discriminator' position, which may be the 73th base. Some prokaryotic tRNA transcripts already contain CCA ends and thus the tRNA nucleotidyl transferase is not indispensable yet advantageous because it may repair the amino acid acceptor. The CCA transfer enzyme is not choosy; it recognizes all tRNAs irrespective their amino acid specificity. Most of the U2 snRNAs in humans also carries CCA ends. ▶tRNA, ▶transfer RNA; Vasil'eva IA et al 2000 Biochemistry [Moscow] 65:1157; Cho HD et al 2002 J Biol Chem 277:3447.

tRNA-SE: is a fast computer program capable of identifying 99–100% of tRNA genes in DNA sequences with extremely low false positives. It may be applied also to the detection of unusual tRNA homologs such as selenocysteine tRNA, tRNA pseudogenes, etc.

Trophectoderm: An extra-embryonic tissue at the blastocyst stage of mammalian development. It is also the founder cell population of the chorionic cells of the placenta. Its function is nutrient exchange and protection of the embryo against the maternal immune system. It also signals to gastrulation. ▶blastocyst, ▶chorion, ▶gastrula

Trophoblast: The surface cell layers of the blastocyst embryo connecting to the uterus.

Trophozoite: Growing and actively metabolizing cells of unicellular organisms vs. the cysts.

Trophophoresy: Propagating of species and disseminating them into new habitats by transferring them as food. ▶co-evolution

Tropic: Indicates after a word that something is aimed at it. e.g., T-tropic means that a virus targets T cells or directed at a site in some way.

Tropic Hormone: Stimulates the secretion of another hormone at another location.

Tropism: Growth of plants in the direction of some external factors.

Tropomodulin: Maintains actin filament growth by capping the pointed ends of the actin filaments. (See Littlefield R et al 2001 Nature Cell Biology 3:544).

Tropomyosin (TPM): is a skeletal muscle fiber protein with two chain α -helical coiled coil is essential for muscle filament stabilization and regulation of contraction. It bonds to actin. TPM3 is encoded at 1q22-q23. Endostatin binds tropomyosin. ▶troponin, ▶endostatin, ▶actin; MacDonald NJ et al 2001 J Biol Chem 276:25190; Brow JH et al 2005 Proc Natl Acad Sci USA 102:18878.

Troponin: Ca^{2+} -binding, regulatory polypeptides in the muscle tissue. Troponin C binds four molecules of calcium. Troponin I has an inhibitory effect on myosin and actin, and troponin I binds tropomyosin, an accessory protein. In the relaxed muscles, troponin I binds to actin and moves tropomyosin to the position where actin and myosin would interact at muscle contraction. When the level of Ca^{2+} is high enough troponin I action is blocked so myosin can bind actin again allowing the muscle to contract. Troponin C is related in function to calmodulin. In the *nemaline* (thread-like) *myopathy* at 19q13.4 the sarcomeric thin-filament protein (TNNT1) is truncated. This recessive/dominant, infant-lethal disease has an incidence of ~ 0.002 in the Amish populations. ▶calmodulin, ▶signal transduction, ▶myotonic dystrophy, ▶receptor tyrosine kinase, ▶myopathy, ▶arthrogryposis; Johnston JJ et al 2000 Am J Hum Genet 67:814; Hinkle A, Tobacman LS 2003 J Biol Chem 278:506, structure: Takeda S et al 2003 Nature [Lond] 424:35.

Trospa: ▶Lyme disease

TRP (transient receptor potential): plasma membrane ion channel components in control of active and passive Ca^{2+} stores and are activated by 1,4,5-trisphosphate receptors. ▶phosphoinositides, ▶SOC, ▶ion channels; Montell C et al 2002 Cell 108:595; Clapham DE 2003 Nature [Lond] 426:517; Vanketechalam K, Montell C 2007 Annu Rev Biochem 76:387.

Trp: ▶tryptophan operon, ▶tryptophan

TRPC (transient receptor potential channel): Protein sensors for temperature, osmolarity, mechanical stress, taste and axon guidance (Wang GX, Poo M-m 2005 Nature [Lond] 434:898).

TRRP (transactivation/transformation-domain associated protein): is a member of the ATM protein superfamily and it is a co-factor of cMYC-mediated transformation. The yeast homolog (Tra1) is a component of the histone acetyltransferase (HAT), SAGA, PCAF and NuA4. Trap is essential for normal development. (See terms mentioned; Herceg Z et al 2001 Nature Genet 29:206).

True Breeding: absence of segregation among the offspring.

Truncation: is a cut-off point; e.g., in artificial selection individuals before or beyond an arbitrarily determined point are discarded or maintained, respectively. Also a cloned eukaryotic-gene without a polyadenylation signal or an incomplete upstream control element may be called truncated. ▶selection; Crow JF, Kimura M 1979 Proc Natl Acad Sci USA 76:306.

Truncation Selection: Individuals with more mutations are more likely to be removed from the population and individuals with fewer mutations may survive and maintained.

Trypanosomatids: are three major species of protozoa, *Trypanosoma brucei* (~genes 9,068), *T. cruzi* (~12,000) and *Leishmania major* (8,311) protozoa spread by the tse-tse fly (*Glossina*) and other bug bites and cause sleeping sickness, Chagas disease and other serious diseases of animals and humans. As the Venn diagram below shows that about two third of their genes are very closely related (see Fig. T120) (El-Sayed NM et al 2005 Science 309:404). The three species (Trityp) have variable numbers of transposons; most of them are not intact, however. Various developmental stages are distinguished on the basis of the relative position of the flagella (basal flagella: trypomastigote, median: epimastigote, apical: promastigote, no flagella: amastigote). Flagellar motility of *Trypanosomes* in the blood stream is essential for survival and flagellar proteins may be targeted as a control measure of the parasites (see Fig. T121) (Broadhaed R et al 2006 Nature [Lond] 440:224). The *Trypanosomas* may reach a level of 10^9 – 10^{10} individuals per mL blood of mammals. The chromosomes are small and variable in number because in addition to the stable chromosomes mini-chromosomes are also found. *T. brucei* has only 11 pair larger chromosomes whereas *T. cruzi* and *L. major* have ~28 and 36 pairs, respectively. In addition they have various, undetermined numbers of minichromosomes. The ca. 100 minichromosomes (50 to 150 kb) contain open reading frames for the variable surface glycoproteins (VSG). These sequences are transcribed only when transposed to expression sites in the 0.2 to 6 megabase long 20 maxichromosomes. Since some of the genes may be present in more than single copy in different chromosomes, these organisms may resemble allodiploids. The VSG genes are pseudo-genes, which generate mosaics by ectopic recombination. The genes do not have introns and some of the tandem arrays of genes are transcribed as long polycistronic pre-mRNA. At the 5'-end each primary transcript is capped by a 39-nucleotide, spliced leader

RNA (SLRNA). This cap itself is transcribed as a 139 base sequence but the 100 base sequence is not used in this trans-splicing reaction. The *Trypanosomas* have homologs of the mammalian U2, U4 and U5 small nuclear RNAs in the form of ribonucleoprotein particles (RNP). The mRNAs are polyadenylated. In *T. brucei* there is a family of about 1,000 genes involved in the recurring production of a great repertory of *variant antigen type* (VAT). At each flare-up of division of the parasite, it switches on the production of a different type of antigen (serodeme). The more than million molecules of antigens on the surface of its cells are the phosphatidylinositol-anchored (about 60 kDa) *variable surface glycoproteins* (VSG). These proteins are linked to the membrane by glycosylphosphatidyl inositol (GPI) anchors. Analogs of these proteins may be used for therapeutic purposes (Smith TK et al 2004 EMBO J 23:4701). All the different VSGs have at least one N-linked oligosaccharide and several cysteine residues near the N-end, and some similarities within the 50–100 amino acids at the C-terminus. Because of the rapid switches in production to new antigens, the vertebrate cell's immunological surveillance system cannot adapt rapidly enough to contain the infection. In chronic infections 50–100 different antigens may be produced. Although a particular *Trypanosoma* has only 1/million or less chance per cell division to switch to the production of a different antigen yet because of their immense number, the parasite has a good chance to escape the immune system of the mammalian host. At any one time only one of the VSG genes is expressed in the protozoan. The switching is not a direct response to the host antibody rather that acts

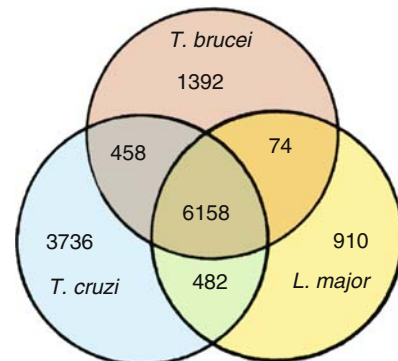


Figure T120. Clusters of orthologous genes



Figure T121. Trypanosoma

only as a selecting mechanism. The switching of transcription may require a shut-off of a gene or a gene conversion type process takes place. The expressed surface antigen gene, the so-called *expression-linked copy* (ELC), is always located in the telomeric regions of the chromosomes. Its promoter is located, however, 50 kbp upstream. In addition, non-VSG genes are also located in the expression region; these are called *expression site associated genes* (ESAG). The expression of these basic, silent genes requires a transposition into the activation region, in a manner similar to the mating type switching in yeast. The switching apparently depends on expression-linked copies (ELC) of the mini exon dependent transcription into 140-base long eukaryotic type mRNA (called also medRNA). Because of this effective switching, there are serious problems in developing vaccines against the *Trypanosomas*. *Trypanosomas* may also display genetic recombination, duplications, deletions and uniparental inheritance mediated by the kinetoplast (Gaunt MW et al 2003 Nature [Lond] 421:936). *Trypanosomas* practice RNA editing by a high molecular mass RNP complex, which contains a 42 kDa protein that recognizes both dsDNA, dsRNA but not the DNA/RNA hybrid molecules. This protein is an endo- and exoribonuclease and functions in also in the mitochondria (Brecht M et al 2005 Mol Cell 17:621). Mutants can be produced that turn on simultaneously more than one type surface glycoproteins. *Trypanosomas* take up transferrin (a β -globulin) from the host cells through about 20 homo- or heterodimeric transferrin receptors, which are activated alternatively just as the VSG genes. The different transferrin receptors make possible for the parasite to adapt to different hosts. The TbAT1 nucleoside transporter confers melaminophenyl arsenical susceptibility whereas defects in TbAT1 render the cells resistant to the trypanocide. ▶kinetosome, ▶*Leishmania*, ▶mating type determination in yeast, ▶flagellar antigen, ▶intron, ▶transporters, ▶RNA editing, ▶Chagas disease, ▶Apolipoproteins; Coppens I, Courtoy PJ 2000 Annu Rev Microbiol 54:129; Navarro M, Gull K 2001 Nature [Lond] 414:759; Spadilero B et al 2002 J Cellular Biochem 85:798; Beverly SM 2003 Nature Rev Genet 4:11; *T. cruzi* sequenced genome: El-Sayed NM et al 2005 Science 309:409; *T. brucei* genome sequence: Berriman M et al 2005 Science 309:416, *T. cruzi* proteome: Atwood JA III et al 2005 Science 309:473; <http://www.tigr.org/tdb/tgi.shtml>; *T. cruzi* database: <http://tcruzidb.org/>.

Tryphine (pollenkitt): Lipids and proteins filling the depressions of the pollen surface.

Trypomastigote: ▶*Trypanosoma*

Trypsin: A proteolytic enzyme synthesized as an enzymatically inactive zymogen, trypsinogen that is activated by proteolytic cleavage. The 6,000 Mr pancreatic trypsin inhibitor inactivates it. Trypsin specifically cleaves polypeptides at the carbonyl sides of Lys and Arg. Ser 195 and His 57 are at its active site.

Trypsinogen Deficiency (TRY1): is a 7q22-ter recessive hypoproteinemia and insufficient amino acid level. It is very similar to enterokinase deficiency. ▶enterokinase deficiency

Tryptases: in the form of heparin-stabilized tetramers function similarly to trypsin-like serine proteases mainly in the mast cells. ▶mast cell, ▶trypsin, ▶heparin

Tryptic Peptides: The products of digestion of a protein by trypsin. ▶trypsin

Tryptophan: Is an essential aromatic amino acid (MW 204.22) (see Fig. T122), soluble in dilute alkali, insoluble in acids and it is degraded when heated in acids. Its biosynthetic pathway (*with enzymes involved in parenthesis*): Chorismate- > (anthranilate synthase) - > Anthranilate - > (anthranilate-phosphoribosyltransferase) - > N-(5'-Phosphoribosyl)-anthranilate - > (N-(5'-phosphoribosyl)-anthranilate isomerase) - > Enol-1-o-carboxyphenylamino-1-deoxyribose phosphate - > (indole-3-glycerol phosphate synthase) - > Indole-3-glycerol phosphate - > Indole - > (tryptophan synthase) - > Tryptophan. In *E. coli* the first two enzymes shown constitute a single anthranilate synthase complex. Tryptophan is converted to formylkynurenine by *tryptophan dioxygenase* (tryptophan pyrrolase). Through the action of an *aminotransferase* tryptophan gives rise to indole-3-pyruvate which after *decarboxylation* forms indole-3-acetic acid, one of the most important plant hormone (auxin). Tryptophan and phenylalanine contribute to the formation of lignins, tannins, alkaloids (morphine), cinnamon oil, cloves, vanilla, nutmeg, etc., flavors. ▶chorismate, ▶tyrosine, ▶phenylalanine, ▶melanin, ▶plant hormones, ▶pigments in animals, ▶Hartnup disease, ▶attenuator, ▶tryptophan operon, ▶fragrances

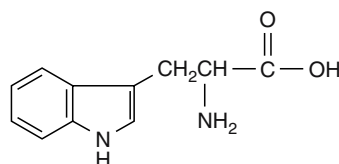


Figure T122. Tryptophan

Tryptophan Operon: Contains five structural genes, in *E. coli* they have been mapped (at 27 min) in exactly

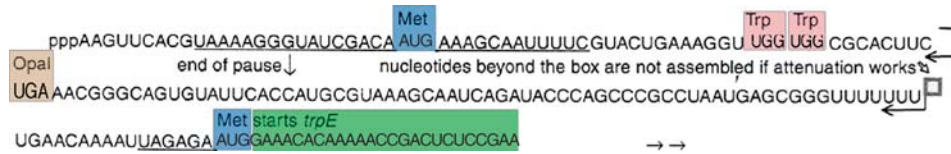


Figure T123. Part of the bacterial trp operon

the same order as their sequence of action in the biosynthetic path (► [tryptophan](#)). This operon has a principal promoter and a secondary low-efficiency one. Between the operator and the proximal gene there is a 162 bp leader sequence (*trpL*) including an attenuator site *a*. (► [temperature sensitive controlling sequences of transcription](#)). When there is sufficient amount of tryptophan in the cell and all the tRNA^{Trp} are charged with the amino acids, transcription of the leader sequence stops at base 140. Thus, synthesis of the specific mRNA temporarily ceases when there is no immediate need for tryptophan (see Fig. [T123](#)).

The site of attenuation (*a*) is within the *trpL* (tryptophan leader) sequences. Before attenuation becomes effective, the RNA polymerase pauses at the *tp* site in the *trpL* (►attenuation). Two main mechanisms, repression and attenuation regulate expression of this operon. Repression prevents the initiation of transcription. The repressor is transcribed from the *trpR* gene (located at 100 min) and the tRNA^{Trp} is coded by gene *trpT* (84 min) whereas the aminoacylation of this tRNA is determined by gene *trpS* (74 min). The product of *trpR* is an aporepressor, i.e., it becomes active only when combined with tryptophan its corepressor (see tryptophan repressor).

The primary sequence of the leader sequence is as shown below (the underlined sequences indicate ribosome binding, tryptophan codons and critical codons in outline); see above. The tryptophan repressor alone may reduce transcription by a factor of 70 and attenuation may decrease it 8 to 10 fold but by the combination of these two controls transcription may be reduced by 8×70 (=560) or 10×70 (=700) fold. In *Rhodobacterium sphaeroides* the tryptophan operon is shared between the two chromosomes of this bacterium.

Bacillus subtilis regulates seven genes of tryptophan biosynthesis; six of them (*TrpEDCFBA*) are clustered within a 12-gene aromatic supraoperon. The seventh gene (*TrpG*) is unlinked and it is in the folate operon. TRAP regulates by attenuation as it binds to a specific site in leader sequence of the *trp* operon and facilitates a terminator formation of the RNA transcript. In addition, TRAP binds to the ribosome-binding sequence in the *trpG* mRNA and thus inhibits translation. An anti-TRAP (AT) protein signals to the tRNA^{Trp} and then it is not charged with tryptophan.

The uncharged tRNA induces the synthesis of AT. Linking AT to TRAP prevents TRAP binding to the RNA. As a consequence tryptophan biosynthesis is promoted (Valbuzzi A, Yanofsky C 2001 Science 293:2057; Gutierrez-Preciado A et al 2005 Trends Genet 21:432).

In *Neurospora* there are also 5 distinct genetic loci controlling tryptophan biosynthesis. These genes are derepressed coordinately with histidine, arginine and lysine loci and this phenomenon is called *cross-pathway regulation*. Humans do not have tryptophan synthetic genes and depend on it (essential amino acid) in the food. ▶tryptophan, ▶helix-turn-helix, ▶lac operon, ▶repressor, ▶tryptophan repressor, ▶essential amino acids, ▶TRAP, ▶antitermination, ▶attenuation; Yanofsky C 1981 Nature [Lond] 289:271; *Bacillus subtilis*: Gollnick P et al 2005 Annu Rev Genet 39:47.

Tryptophan Repressor: Consists of a repressor protein (using a helix-turn-helix motif) for binding to the operator site of the tryptophan operon and becomes active only when it is associated also with tryptophan. Actually the binding of tryptophan to the repressor protein facilitates the more intense binding of the complex due to a conformational change of the repressor protein. In prokaryotes besides the repressor attenuation is another regulatory mechanism. *E. coli* and *Bacillus subtilis* use somewhat different mechanisms of control. In *E. coli* tryptophan activates a repressor, which binds to the promoter-operator region and inhibits the initiation of transcription. In *B. subtilis* tryptophan activates the RNA-binding protein TRAP. TRA bound to the leader sequences terminates transcription. In *E. coli* uncharged tRNA^{Trp} accumulation stalls when tries to translate the two Trp codons in the leader-peptide coding region. This causes transcription termination. In contrast in *B. subtilis* uncharged tRNA^{Trp} actually activates transcription and translation of this operon. The antitermination protein AT then inhibits TRAP, activated by tryptophan. ▶negative control, ▶tryptophan operon, ▶attenuator region, ▶Lac operon, ▶positive control, ▶arabinose operon, ▶helix-turn-helix motif, ▶conformation; Khodursky AB et al 2000 Proc Natl Acad Sci USA 97:12170; Yanofsky C 2004 Trends Genet 20:367.

Tryptophan Zipper: is a structural motif that can stabilize the hairpin structure of short peptide chains of 12 to 16 amino acids with the aid of cross-strand pairs of indole rings. It does not require metal or disulphide links.

Tryptophanase (*tna*): is a bacterial operon including major genes A, B and a permease with a 319 bp leader encoded (by *tnaC*) preceding gene *tnaA*. It degrades L-tryptophan to indole, pyruvate and ammonia. Tryptophan regulates it by induction and antitermination. ▶ [induction](#), ▶ [antitermination](#); Gong F et al 2001 Proc Natl Acad Sci USA 98:8997.

Tryptophanyl tRNA Synthase (WARS): charges tRNA^{Trp} by the amino acid tryptophan. The gene WARS is in human chromosome 14. ▶ [aminoacyl-tRNA synthetase](#)

ts: indicates temperature-sensitivity of an allele. ▶ [temperature-sensitive mutation](#)

T_S: ▶ [T cell](#)

Tsarevitch Alexis: great-grandson of Queen Victoria who inherited her new mutation causing classic hemophilia. ▶ [hemophilias](#), ▶ [Queen Victoria](#)

tsBN2: is a temperature-sensitive baby hamster kidney (BHK) cell line. ▶ [hamster](#)

TSC: is a reduced representation shotgun sequencing data set. ▶ [shotgun sequencing](#)

TSE (transmissible spongiform encephalopathy): ▶ [encephalopathy](#), ▶ [prion](#)

Tse-Tse Fly: African fly of the genus *Glossina*, host of the parasitic *Trypanosomas*, causing sleeping sickness, a disease characterized by relapsing fever, enlargement of the lymph glands, anemia, severe emaciation and eventually death in humans and domestic animals. ▶ [Trypanosomas](#); Akman L et al 2002 Nature Genet 32:402.

TSG (tumor susceptibility gene): Acts as transcriptional cofactor and also as a nuclear hormone receptor-mediated transactivation. TSG101 protein regulates cell growth and division, MDM2 protein and affects ubiquitination. It controls also epidermal growth factor receptor trafficking by interacting with the endosomal transport. There is ~94% homology between the mouse and the human proteins. ▶ [MDM2](#), ▶ [ubiquitin](#), ▶ [EGFR](#), ▶ [endocytosis](#); Teh BT et al 1999 Anticancer Res 19(6A):4715; Lu Q et al 2003 Proc Natl Acad Sci USA 100:7626.

TSHB: thyroid-stimulating hormone, thyrotropin. ▶ [animal hormones](#)

Tsix: ▶ [Xist](#)

Tsr: Bacterial transducer protein recognizing serine as an attractant and leucine as a repellent. ▶ [transducer proteins](#)

TSS: Transcription start site. (See <http://dbtss.hgc.jp/>).

T-Strand: A single-stranded intermediate of the T-DNA that is transferred from the Ti plasmid of *Agrobacterium* to the plant nucleus through the nuclear pores under the guidance of a virulence gene-encoded protein which is covalently attached to its 5'-end. ▶ [transformation](#), ▶ [T-DNA](#), ▶ [Ti plasmid](#)

tTA (tetracycline transactivator protein): is a fusion protein of the *tet* (tetracycline) repressor of *E. coli* and the transcriptional activation domain VP16 of herpes simplex virus. This system is generally driven by the *tetP* promoter which is actually a minimal immediate early cytomegalovirus (CMVIE) promoter, preceded by 7 copies of *tetO*, the tetracycline resistance operator of transposon 10 (*Tn10*). In the presence of tetracycline, this system is expressed at very low level and by removal of tetracycline the gene(s) under its control (e.g., luciferase, β -galactosidase) may be expressed at three orders of magnitude higher level. The system can be used also under the control of other promoters that suit best for regulating the expression pattern of the gene of interest. ▶ [rtTA](#), ▶ [tetracycline](#), ▶ [split-hybrid system](#); Gossen M, Bujard H 1995 Science 268:1766.

t-Test: is used for the estimation of the statistical significance of the difference(s) between means. The *t* value is the ratio of the observed difference to the corresponding standard error: $t = (\bar{x} - m) / (s / \sqrt{n})$ where \bar{x} and *m* are the two means, *n* = population size, *s* = standard deviation. More commonly the significance of the difference between two means is calculated as $t = \frac{m_1 - m_2}{\sqrt{[e_1]^2 - [e_2]^2}}$ where *m*₁ and *m*₂ are the two means (\bar{x}) and *e*₁ *e*₂ are the standard errors of the two means determined as $e = \frac{s}{\sqrt{n}}$ and $s = \sqrt{V}$ where $V = \text{variance} = \frac{\sum[(x - \bar{x})^2]}{n-1}$. When the *t* value is available the probability of the difference is determined with the aid of a “t table”. ▶ [Student's t distribution](#)

TTKs: are tubulin-associated kinases. ▶ [tubulin](#)

TTP (tris-tetrapolin): cDNA shares 102 amino acid sequences in its product with TIS11 (insulin and serum-responsive transcription factor). ▶ [TIS11](#), ▶ [insulin](#), ▶ [serum response element](#), ▶ [transcription factors](#)

T-Tropic: The T lymphocyte is targeted (e.g., by a virus).

TU: Protein elongation factor (EF-TU) in prokaryotes binds aminoacyl-tRNA to the ribosomal A (acceptor) site. It is a guanine nucleotide-binding RAS-like protein. EF-TU.GTP, ►aminoacyl-tRNA, ►ribosome, ►protein synthesis, ►RAS; Zvereva MI et al 2001 J Biol Chem 276:47702.

Tubal Ligation: Surgical fertility control by constricting of the Fallopian tube, usually by placing a plastic ring on it. ►sterilization humans, ►salpingectomy

Tube Nucleus: It is in the vegetative cell at the tip of the growing pollen tube. It has only physiological and no genetic role because it does not enter the embryosac. ►gametophyte

Tuber: An underground enlarged stem, specialized for food storage, e.g., in potato.

Tubercidine (7-deazadenosine): ►deazanucleotides

Tuberculosis: ►mycobacteria

Tuberous Sclerosis: ►epiloia

Tuboplasty: Surgical repair of a defect on an internal tube such as the Fallopian tube.

Tubulins: Globular polypeptides of α and β subunits (50 kDa, each with about 40% homology and very similar in structure [β sheets surrounded by α helices]) are G-proteins concerned with signal transduction of nerve cells and are components of microtubules such as the spindle fibers and the cytoskeleton. Mutations in α -tubulin cause abnormal migration of neurons in mice and lissencephaly in humans (Keays DA et al 2007 Cell 128:45). Both subunits can bind one guanine nucleotide, which is an exchange cable on the β but not on the α binding site. The folding of the tubulins requires cytosolic chaperonins, cofactors A, C, D and E, ATP and GTP. The bacterial plastid septation protein FtsZ filamenting temperature-sensitive septal peptidoglycan (Z ring) displays structures similar to tubulins and participates in the septation of the cell (see Fig. T124). FtsZ may have a GGGTGTG motif and has GTPase activity. FtsZ3 with the GGGAGTG motif has no and FtsZ84 with the AGGTGTG sequence have reduced GTPase activity. FtsZ recruits then addition cell division proteins. In the spore-forming bacteria (*B. subtilis*) initially two Z rings are formed, one at both poles but only one is activated as the genetic material passes to the spore. In the chloroplasts a nuclear encoded ftsZ protein and

dynamain function in fission (Yoshida Y et al 2006 Science 313:1435). The mitochondria apparently do not need ftsZ. ►spindle, ►cytoskeleton, ►chaperonins, ►peptidoglycan, ►septum, ►GTPase, ►chloroplasts, ►mitochondria, ►FtsZ, ►lissencephaly; Oakley BR 2000 Trends Cell Biol 10:537; Thanbichler M, Shapiro L 2006 Cell 126:147; Z ring regulation: Lutkenhaus J 2007 Annu Rev Biochem 76:539.

Tudor (*tud*, 2–97): *Drosophila* gene locus involved in embryonic development. ►TRF1

Tudor-SN: Protein containing the Tudor protein of *Drosophila* and five staphylococcal nuclease domains. It is a component of the RISC silencer complex. ►RISC; Maurer-Stroh S et al 2003 Trends Biochem Sci 28:69.

TUF (transcripts of unknown function): The number of RNA transcripts (from intergenic regions, introns and antisense DNA strands) far exceeds the number of protein-coding mRNAs (Johnson JM et al 2005 Trends Genet 21:903; Willingham AT, Gingeras TR 2006 Cell 125:1215). They are parts of the operational system of the genome. ►non-coding RNA, ►antisense RNA, ►RNAi, ►microRNA

Tukey's Test: is an analysis of variance test for determining whether there is a significant difference between three or more group means, two comparisons made at a time. This is a non-additivity test.

$$S_{AB} = \frac{[\sum_{i=1}^r \sum_{j=1}^c \{y_{ij}(\bar{y}_i - \bar{y}_{..})(\bar{y}_j - \bar{y}_{..})\}]^2}{S_A S_B}$$

Where the sum of squares is S_{AB} , r is the number of rows, c = number of columns, y_{ij} = observations in the i^{th} cell, \bar{y}_i = mean of the i th row, $\bar{y}_{..j}$ = mean of the j th column and $\bar{y}_{..}$ = mean of all observations. (See Tukey JW 1949 Biometrics 5:232; ►analysis of variance).

Tularemia: is an extremely dangerous infection causing sudden fever, weakness, bodyache in humans and animals. It is caused by as few as 10 cells of the bacterium *Francisella tularensis* transmitted by arthropod vectors. It may also spread by airborne dust. Without antibiotic treatment the mortality is 5–30%. Currently no vaccine is available. The sequenced genome of the bacterium is 1,892,819 bp. ►biological warfare, ►inflammasome; Larsson P et al 2005 Nature Genet 37:153.

Tulip Mania: ►symbionts hereditary, ►tulips broken

Tulips, Broken: Variegation caused by infection with the tulip-breaking virus. Floriculturists value the plants displaying this sectoring. ►tulip mania, ►broken tulips



Figure T124. Septation by bacterial Z ring

Tulips-PCR (touch up and loop incorporated primers PCR): See Ailenberg M, Silverman M 1999 *Bio-techniques* 29:1018.

Tumbling: results when the bacterial flagella (singular: flagellum) rotate clockwise.

TU/ml: Transforming unit per mL, i.e., the number of cells expressing a transgene. ▶[transgene](#), ▶[transformation genetic](#)

Tumor: An abnormal clump of cells originated by benign or malignant growth. Malignant tumors may be invasive and show metastasis, common in many types of cancer. Mutant genes, chromosome breakage and viral infections altering the normal regulation of cell proliferation may cause it (see Fig. T125). Tumorigenesis is generally a multi-phase process involving activation of cell cycle promoting genes and inactivation of tumor suppressors. Active MAPKK may stimulate tumorigenesis if transfected into mouse cells. The type of the tumor is different in different cancers and even within a single cancer may vary a great deal because of the frequent chromosomal breakage and other mutations as a consequence of cancerous growth. The origin and maintenance of the tumorous condition requires the emergence of special tumor stem cells brought about by asymmetric division of normal somatic cells (Gonzalez C 2007 *Nature Rev Genet* 8:462). Their characterization, using molecular markers may be facilitated by microarray analysis of the biopsies. Plant tumorous growth is often called callus that is never metastatic although the crown gall tumors of plants may be spread by new foci of infection of the inciting bacterium, *Agrobacterium tumefaciens*. Plant viruses and higher concentrations of phytohormones may also cause tumors. ▶[oncogenes](#), ▶[cancer](#), ▶[SV40](#), ▶[adenoviruses](#), ▶[Agrobacterium](#), ▶[genetic tumors](#), ▶[tumor in situ](#), ▶[cancer](#), ▶[MAPKK](#), ▶[habituation](#), ▶[CATRI](#), ▶[microarray hybridization](#), ▶[cancer gene therapy](#), ▶[RAS](#), ▶[PIK](#), ▶[TOR](#); Shaw RJ, Cantley LC 2006 *Nature [Lond]* 441:425.

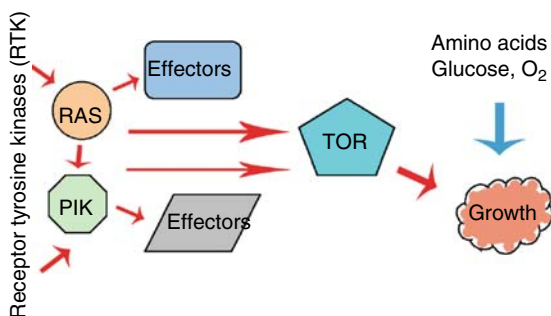


Figure T125. General growth regulatory pathways

Tumor Antigens: are MHC-associated peptides recognized by CTLs as tumor antigens. The MHC class I tumor peptides are also called CTL epitopes. Mutant chaperone can convert a glycosyltransferase into a tumor-specific glycopeptidic neo-epitope (Schietinger A et al 2006 *Science* 314:304). ▶[MHC](#), ▶[CTL](#), ▶[epitope](#), ▶[glycosyltransferases](#), ▶[dendritic cell vaccine](#), ▶[tumor vaccination](#), ▶[cancer](#)

Tumor, In Situ: Dormant, tiny clumps of tumor cells, usually revealed by autopsies of breast, prostate and thyroid glands. The microscopic cells may never develop into cancer because the lack of appropriate blood supply (angiogenesis). The in situ tumors may originate by genetic instability but unless they succeed in recruiting new blood vessels, they are unable to proliferate into neoplasias. There is a balance between the angiogenic growth factors such as FGF, VEGF, IL-8, and PDGF and the angiogenic inhibitors of the body (thrombospondin, canstatin [24 kDa human basement membrane-derived antiangiogenesis protein], tumstatin [cleavage fragment of the α -3-chain of collagen type IV that prevents blood circulation], endostatin, angiostatin, interferon α/β . Genetical and environmental factors control the balance among the pro- and anti-angiogenic factors. (See terms at corresponding entries, ▶[tumor](#)).

Tumor Infiltrating Lymphocytes (TIL): seek up tumors. TIL are isolated from solid tumors and cultured in single-cell suspension in a medium containing interleukin 2 (IL-2). Through genetic engineering they may be equipped with the gene of tumor necrosis factor through transformation by retroviral or other vectors. The transformed cells may selectively kill then cancerous tumor cells. ▶[cancer gene therapy](#), ▶[tumor necrosis factor](#), ▶[retroviral vectors](#), ▶[lymphocytes](#); Smyrk TC et al 2001 *Cancer* 91:2417.

Tumor Necrosis Factor: ▶[TNF](#)

Tumor Necrosis Factor Receptor: ▶[TNFR](#)

Tumor Progression: ▶[evolutionary clock](#)

Tumor Promoter: ▶[phorbol ester](#)

Tumor Suppressor Gene: Its loss, inactivation or mutation (even haploinsufficiency) permits neoplastic growth by deregulation. They most commonly have a role in the cell cycle or in the regulation of RNA polymerase II or III. Also, inhibition of peptide chain elongation may be a mechanism of tumor suppression. (Genes with cytostatic or cytotoxic effects are excluded from this category of tumor suppressors). Actually, the majority of cancer cells display deletions that may indicate the loss of a tumor suppressor gene; for the direct proof further evidence

is required for the loss of a tumor suppressor (see Fig. T126). Animal models are available for many human tumor suppressors (Hakem R, Mak TW 2001 Annu Rev Genet 35:149). Tumor suppressor genes

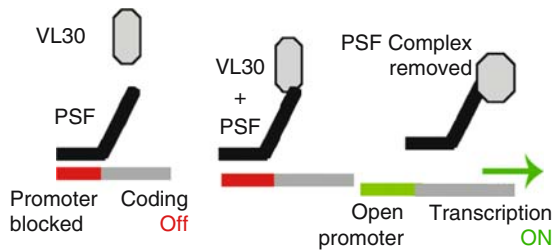


Figure T126. A tumor suppressor path

are widely scattered in the human genome: p53/TP53 (17p13.1), retinoblastoma (RB1, 13q14.1-q14.2), adenomatous polyposis of colon (APC, 5q21-q22), deleted in colorectal cancer (DCC, 18q21.3), neurofibromatosis (NF1, 17q11.2), von Hippel-Lindau syndrome (VHL, 3p26-p25), Wilms tumor (WT1, 11p13), breast cancer (BRCA1, 17q21), Cyclin-dependent kinase inhibitor CDKN2A, (9p21), patched homolog PTCH (9q22.3), tuberous sclerosis (TSC2, 16p13.3; TSC1, 9q34), etc. Mutation in the polycomb group protein enhancer of zeste homolog (EZH2) may increase its expression and represses the function of many genes that are apparent suppressors of tumorigenesis and thus promotes lethal metastasis of prostate cancer (Varambally S et al 2002 Nature [Lond] 419:624). The methyltransferase Suv39h1 normally methylates histone H3 lysine 9 and may silence growth-promoting genes. By the use of RNAi, tumor suppressor genes can be inactivated and the procedure permits their identification (Westbook TF et al 2005 Cell 121:837; Kolfshoten IG et al 2005 Cell 121:849). Ras transgenic mice carrying intact, X-linked, functional Suv39h1 developed lymphomas only at a median of 305 days. Suv39h1 deficient homozygotes (female) or hemizygotes (male) succumbed to death at a median time of 66 days. The methyltransferase acted as a tumor suppressor by promoting senescence (Braig M et al 2005 Nature [Lond] 436:660). The protein spliceosome factor (PSF) has an RNA and DNA binding domain and can bind to the P450ssc gene, which initiates also the steroidogenic pathway. The retrotransposon VL30 – a multiple element in the mouse genome and also in the human genome – regulates the function of PSF (Song X, Garen A 2005 Proc Natl Acad Sci USA 102:12189) by binding its RNA transcripts to the RNA binding domain (RBD) of PSF. Subsequently PSF is removed from the promoter and the oncogene is transcribed (See diagram redrawn and modified after Desisseroth A 2005 Proc Natl Acad Sci USA

102:12292). ▶cancer, ▶malignant growth, ▶transformation oncogenic, ▶p53, ▶p73, ▶p16, ▶p16^{INK4} p21, ▶retinoblastoma [Rb], ▶ELL, ▶elongin, ▶DPC4, ▶PTEN, ▶PPP2R1B, ▶pol III, ▶tumor suppressor factors, ▶RNAi, ▶polycystic kidney disease, ▶breast cancer, ▶prostate cancer, ▶oncogenes, ▶cell cycle, ▶apoptosis, ▶colorectal cancer, ▶tumor suppressor factors, ▶LOH, ▶oncogenes, ▶immunosuppression, ▶histone deacetylase, ▶gate-keeper genes, ▶caretaker genes, ▶hypermethylation; Robertson GP et al 1999 Mol Cell Biol Res Comm 2:1.

Tumor Suppressor Factors: The development of tumors follows multiple routes yet genes involved in the general control of differentiation, as revealed by studies of *Drosophila* morphogenesis, seem to be involved. Mammalian homologs of *Drosophila hedgehog* (*hh*), sonic hedgehog (SHH), Indian hedgehog (IHH) and desert hedgehog (DHH) seem to be entailed in holoprosencephaly, a developmental anomaly connected to cancer. The receptor of *hedgehog* of *Drosophila* is *smoothed*, and its suppressor is *patched* which may be concerned with the development of basal cell carcinoma and defects in the central nervous and skeletal systems. The *cubitus interruptus* (*ci*) *Drosophila* gene appears to function as an effector of *hh* and similarly to the GLI genes of humans are responsible for a type of brain tumor and for the cephalopolysyndactyly syndrome. The decapentaplegic (*dpp*) *Drosophila* protein bears similarity to the mammalian tumor growth factor (TGF) and to the bone morphogenetic protein 4 (BMP4), causing defects in limb and gut formation. The effector of the mammalian TGF- β receptor (DPC4) involved in pancreatic tumors has its homolog in the *Drosophila mad* gene. The *Drosophila wingless* locus corresponds to the mammalian WNT loci controlling mammary tumors. The *Drosophila zeste-white-3* gene codes for a signal molecule similar to a mammalian glycogen synthase kinase, and the *Drosophila armadillo* gene, encoding β -catenin, is also an oncoprotein, controlling intestinal tumors. Naïve CD4⁺ T cells respond to MHC-II tumor antigenic signal carried by macrophages and along with interferon- γ inhibit tumor cell growth (Corthay A et al 2005 Immunity 22:371). Fe chelators have potent and broad antitumor activity and can overcome resistance to established chemotherapeutics because of their unique mechanism of action (Whitnall M et al 2006 Proc Natl Acad Sci USA 103:14901). (Based to some extent on Dean M 1996 Nature Genetics 14:245, ▶immunological surveillance, ▶Tid50, see terms mentioned in the alphabetical list).

Tumor Susceptibility: May be determined by mutation of some major tumor suppressor (RAS, CyclinD1,

RB, p16, etc.) genes, favorable combination(s) of minor genes may be responsible for the “sporadic” cases of cancer. ▶tumor suppressor gene, ▶onco-genes; for a list of mouse susceptibility loci see Balmain A, Nagase H 1998 Trends Genet 14:139.

Tumor Vaccination: Immunization by increasing the efficiency of tumor-specific antigen presentation or enhancing the activity of tumor-infiltrating T cells. The purpose is to generate antitumor immune reaction. Cancer cells may be ex vivo genetically modified and reintroduced into the body. Introducing into the cancer cells a range of cytokines e.g., IL-12 may enhance T cell response. The T cells of the tumor can be genetically modified to secrete effector molecules to enhance the immune response against the tumor or increase their potentials for binding of tumor antigens. Introduction of the wild type tumor-suppressor genes may also be an option. Transformation by GM-CSF may recruit monocytes/macrophages and APCs by a process called *cross priming*. Some tumors may mask the immunogenic potentials within the cells. In such cases, antisense technologies (against IGF or TGF or IL-10), intrabodies, triple helix formation, and inactivation by the use of ribozymes may help in silencing the endogenous inhibitors. It is also possible to introduce into the tumor activation enzymes that can convert pro-drugs into highly cytotoxic anticancer compounds or transfect the cells with toxin genes.

Because of pleiotropy and protein interactions, the genetic modifications may not always be favorable for goals. Within the same individual, molecular heterogeneity may exist among the cancer cells. Therefore, only multivalent cancer vaccines may achieve relevant goals. Favorable results were obtained in animal models with the combinations of IL-4 + IL-12, co-stimulatory molecules + IL-12, interferon- γ + IL-2, etc. Often, tumor cells have no or very weak antigen-presenting mechanism(s), and do not express the co-stimulatory proteins. Melanoma cells over-produce IL-10, a cytokine that down-regulates the path of CTL formation. The Fas-ligand expressing lymphocytes may be the targets of the up-regulated Fas, produced by tumor cells, especially when exposed to certain types of chemotherapy. As a consequence, the apoptotic process may weaken immunotherapy against cancer. Cancer may involve tumor-specific immunodeficiency but low doses of IL-2, administered over long periods may strengthen the immune system. It is essential that in therapy against cancer the various treatments be effective against cancer cells without attacking the normal cells and balance the antitumor and autoimmune responses. ▶cancer gene therapy, ▶tumor infiltrating lymphocytes, ▶CTL, ▶antigen presentation,

▶immune system, ▶interferon, ▶vaccines, ▶dendritic cell vaccine, ▶cross-priming, ▶GM-CSF, ▶co-stimulator, ▶antisense RNA, ▶intrabody, ▶triple helix formation, ▶ribozyme, ▶IGF, ▶TGF, ▶IL-10, ▶lipids cationic, ▶co-stimulator, ▶LAK, ▶Fas, ▶apoptosis, ▶autoimmune disease, ▶effector cell; Gunzer M, Grabbe S 2001 Crit Rev Immunol 21 (1–3):133; Tada Y et al 2003 Cancer Gene Ther 10:134.

Tumor Viruses: Tumor viruses induce or participate in the formation of tumors (cancer). Their genetic material can be DNA (such as, SV40, adenoviruses, papilloma virus, hepatitis-B virus, Epstein-Barr virus, adenoma virus, herpes virus, pox virus) or RNA (such as the retroviruses causing leukemia, lymphoma, AIDS, Kaposi’s sarcoma, avian leukosis virus, mammary tumor viruses, etc). The DNA viruses can integrate into the mammalian genetic material and activate cell replication by overwhelming the function of the tumor suppressor genes. The genetic material of the DNA tumor virus has no counterpart in the host genetic material. The genetic material of the RNA tumor virus is replicated by reverse transcription and produces a double-stranded DNA counterpart of the genome. The viral RNA is then transcribed from the cellular DNA template. Most of the oncogenes in the cells (c-oncogenes) correspond to the v-oncogenes in the virus. The class I RNA tumor viruses themselves do not induce tumors unless they pick up growth-regulating genes from cell. The class II type RNA viruses do not contain oncogenes and induce cancer only when the proviral DNA integrates in the vicinity of cellular oncogenes (c-oncogenes). ▶SV40, ▶adenovirus, ▶Epstein-Barr virus, ▶papilloma virus, ▶polyoma, ▶Rous sarcoma, ▶retroviruses, ▶oncogenes; Barbanti-Brodano G et al (Eds.) 1995 DNA Tumor Viruses, Plenum, New York; McCance DJ (Ed.) 1998 Human Tumor Viruses. AMS Press, Washington, DC.

Tumor-Associated Antigen: Over-expressed normal self-proteins of cancer cells. They may incite immune reaction by breaking the self-tolerance limit. Examples: oncofetal differentiation, nuclear proteins, such as carcinoembryonic, melanoma-associated proteins, etc. ▶MAGE, ▶HER2

Tumorigenesis: The formation of tumors. It is usually based either on the activation of proto-oncogenes or the inactivation of tumor suppressor genes. The former mechanism generally involves dominant-acting genes, the latter is usually based on recessive loss of function. Before genetic instability, characteristic for cancer or cancer-prone cells appears, an ATR/ATM-regulated DNA damage control system may be activated. Mutations in ATM-Chk2, p53

pathway might allow, however cell proliferation, cell survival, increased chromosomal instability, and eventually progression to cancer (Bartkova J et al 2005 Nature [Lond] 434:864). Fourier-transform infrared spectra (FT-IR) reveal structural modifications at many points in the DNA and marked differences between the primary and metastatic states. ▶cancer, ▶neoplasia, ▶FT-IR, ▶telomerase, ▶tumor suppressor, ▶proto-oncogenes, ▶chromosome breakage, ▶apoptosis, ▶DNA repair, ▶radiation effects, ▶environmental mutagens, ▶carcinogenesis, ▶ATM, ▶ATR, ▶CHK2, ▶p53

Tumorous Hybrids: ▶genetic tumors

Tumor-Specific Antigen: Endogenous tumor cell-surface antigens that can be presented by major histocompatibility molecules to T cells. These antigens are absent from normal cells and are modified in response of viral transformation or genetic or somatic mutations in oncogenes. ▶MHC, ▶T cell, ▶antigen presenting cell

TUNEL ASSAY (terminal deoxytransferase-mediated deoxyuridine nick end-labeling): Tunnel assay uses usually biotin-labeled uridine and a streptavidin or avidin-labeled enzyme, and at the reaction site color develops. ▶biotinylation, ▶terminal nucleotidyl transferase; Maciorowski Z et al 2001 Cytometry 46(3):159; Yamamoto-Fukud T et al 2000 Histochemistry J 32(11):697.

Tunica: The cell layer in the plant apical meristem wrapping the inner corpus. (See Fig. T127).

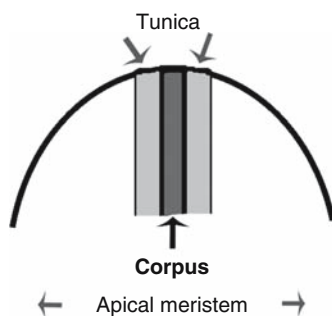


Figure T127. Tunica

Tunneling: connecting through a structured path. ▶channeling

TUP1: A general suppressor of sugar (and other) metabolism of yeast; its product is a trimeric G-protein. It is similar to AAR1 and AAR2. TUP forms a repressor complex with yeast protein Cyc8, RNA polymerase II, and Srb10. ▶proteins, ▶glucose

effect; Groucho, Tel, SRB, Wu J et al 2001 Mol Cell 7:117.

Tupaia: A family of prosimii. *Tupaia*, 2n = 62; *Tupaia glis*, 2n = 60; *Tupaia montan*, 2n = 68. ▶prosimii

Turbid Plaque: ▶plaque

Turbidity: Turbidity is commonly used for measuring total cell numbers in liquid cultures as long as the cell density is not excessive. It is measured as optical density (OD) = x/l , where x = cell density and l = the light path in the cuvette of the spectrophotometer. Turbidity is expressed also as $\log(I_0/I)$ where I_0 = incident light, I = transmitted light (at e.g., 550 nm wavelength). The number of viable cells is determined by plating. ▶plating efficiency, ▶cell growth

Turcot Syndrome (9p22, 54q21-q22, 3p21.3): An autosomal recessive malignant tumor of the central nervous system (glioma), associated with polyposis. Defects in the mismatch repair system predispose for this tumor. ▶polyposis adenomatous, ▶Gardner syndrome, ▶PMS1, ▶mismatch repair

Turgid: Expanded because of water uptake.

Turgor: Intracellular pressure caused by water absorption.

Turing, Alan (1912–1954): A mathematician, philosopher, and pioneer in computing and bioinformatics who intended to develop machines and software that work like the human brain.

Turkey: *Meleagris gallopavo*, 2n ≈ 80.

Turner's Rule: Turner's rule deals with the thermodynamics of helix formation of ribonucleotides, which also involves mismatches (Freier SM et al 1986 Biochemistry 25:3209).

Turner Syndrome: Based on an X0 chromosomal constitution in some female mammals. Its incidence in humans is ≈ 0.0003 but the frequency in abortuses may be 0.01 to 0.02. The missing short arm is critical for the Turner symptoms. Turner females usually have short stature, webbed skin on a broad neck, under-developed genitalia and sterility, heart problems, proclivity to kidney disease, diabetes, and hypertension but are generally of normal or near normal intelligence (see Fig. T128). Mathematical abilities are generally reduced (dyscalculia). The retention of the paternal X usually results in better cognitive abilities (imprinting).

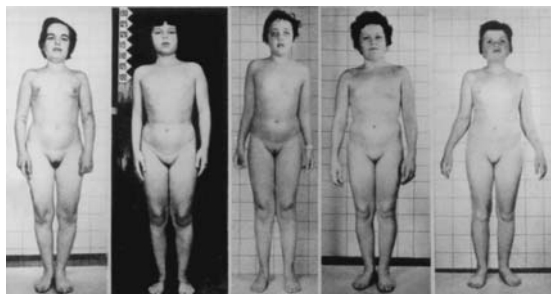


Figure T128. Turner syndrome females of different ages. With three doses of the long arm but only one short arm of the X chromosome. Despite the variations in appearance the similarities of the unrelated individuals is obvious. (Courtesy of Lindsten J et al 1963 *Ann Hum Genet* 26:383)

In some instances they are also fertile; most of these cases are probably XO/XX mosaics. In a study among 410 Danish women with Turner syndrome, only the 45, X/46,XX or 46,XX with structural abnormality of one of the X-chromosomes were found to give birth after spontaneous pregnancy. After egg donation, some Turner patients can deliver children although there may be a higher chance for chromosomal anomalies among the offspring (Birkabaek N et al 2002 *Clinical Genet* 61:35). The symptoms are similar even when only the one of the short arms of one of the X-chromosomes is missing. The single X chromosome is maternal in 75% of the cases. The underlying mechanism is puzzling because males normally have a single X, while even in females one of the X-chromosomes is inactive, except during oogenesis and the first few weeks of embryogenesis. The majority of studied female animals with single X (pigs, cattle, horse) are abnormal but the XO female mice appears rather normal and fertile. In *Drosophila*, the XO individuals are sterile males. In Turner syndrome, the most critical is the loss of the distal (pseudoautosomal) part of the short arm of the X chromosome (see Fig. T129). Some of the human developmental difficulties may be normalized by estrogen treatment. Artificial insemination or intra-uterine implantation may permit reproduction. About 15% of the X chromosomes in Turner patients are dicentric. ▶[trisomy](#), ▶[sex determination](#), ▶[sex chromosomal anomalies in humans](#), ▶[human chromosome map](#), ▶[prenatal diagnosis](#), ▶[MSAFP](#),



Figure T129. Normal human X-chromosome

▶[Noonan syndrome](#), ▶[imprinting](#), ▶[pseudoautosomal](#), ▶[ART](#), ▶[dicentric chromosome](#); Zinn AR et al 1993 *Trends Genet* 9:90; Sybert VP, McCauley E 2004 *New England J Med* 351:1227.

Turnip (*Brassica campestris*): A polymorphic species with chromosome number $2n = 2x = 20$, *Brassica napus* is $2n = 4x = 38$, AACC genomes. ▶[Brassica oleracea](#)

Turnip Crinkle Virus (TCV): A plant RNA virus related to the Tomato Bushy Stunt Virus.

Turnover: The depletion-repletion cycle of molecules or cells. The age of cells in the human body is not easy to determine. Nuclear weapon testing after World War II increased the ^{14}C level in the atmosphere but after 1963 an exponential decrease followed international agreements of testing. The level of ^{14}C in the DNA paralleled this trend and thus it became possible to infer the age of cells, i.e., the time when the DNA and the cell replicated. Occipital neurons in the adult human brain were as old as the individual, indicating that postnatal neurogenesis did not take place in this region. In contrast, non-neural cells were replaced by cell division. This type of procedure makes possible the study of cell turnover that may be important for normal physiology and pathology (Spalding KL et al 2005 *Cell* 122:133).

Turnover Number: The number of times an enzyme acts on a molecule in a unit of time at saturation.

Turnover Rate: The pace of decay and replacement of a molecule.

Tus Gene Products: Proteins that sense the *Ter* (transcription termination) sequence signals in DNA replication in *E. coli*. ▶[DNA replication](#), ▶[replication bidirectional](#), ▶[prokaryotes](#), ▶[RTP](#); Henderson TA et al 2001 *Mol Genet Genomics* 265:941.

TUSC (Trait Utility System for Corn): TUSC generates insertional mutations in maize with the aid of transposable elements like *Mutator*. ▶[insertional mutation](#), ▶[Mu](#)

Tv/Rcas Vector: The Rous sarcoma avian virus proviral vector (maximum carrying capacity 2.5 kb) first mediates in vitro the production the avian leukosis virus (AVL) coat protein. The protein is required for the recognition of the avian retroviral receptor (tv-a), transfected into mouse cells. The replication competent virus thus can produce high titer in the mouse cells infected and can be injected into mice. ▶[Rous sarcoma](#), ▶[retroviruses](#); Fisher G et al 1999 *Oncogene* 18:5253.

Tweak (Apo3-L, 17p13.3, TNF-related weak inducer of apoptosis): A TNF ligand with similarity to CD120

and CD95. The related motif of its mouse homolog displays greater similarity. It is a factor in the Klippel-Trenauney syndrome. ▶TNF, ▶CD95, ▶CD120, ▶Klippel-Trenauney syndrome; Kaplan MJ et al 2000 J Immunol 164:2997; Schneider P et al 1999 Eur J Immunol 29:1785.

Tween 20 (polyoxyethylene sorbitan, monolaurate): An anionic biological detergent with about 50% lauric acid; the rest comprises of myristic, palmitic, and stearic acids.

Twigdam: Technical Working Group on DNA Analysis Methods. It is concerned with forensic application of DNA analytical and statistical techniques ▶DNA fingerprinting

Twin Hybrids: ▶complex heterozygotes

Twin Meiosis: Twin meiosis may occur in diploid *Schizosaccharomyces* when after copulation the two nuclei undergo separate meioses.

Twin Spots: Twin spots are visible if (mitotic) somatic crossing over takes place between appropriately marked chromosomes, or may be caused by nondisjunction (see Fig. T130). ▶mitotic crossing over; Rédei GP, Sandhu SS 1988 Mutation Res 201:337.

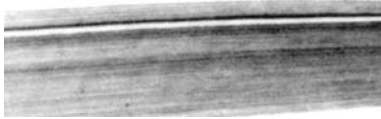


Figure T130. Wheat leaf displaying white and dark green twin sectors on pale green background in a heterozygote for the hemizygous ineffective *Neatby's Virescent* gene. (See ▶hemizygous ineffective)

twine: *Drosophila* homolog of *Cdc25* meiosis-specific gene. ▶cdc25, ▶azoospermia

T

Twinning: The phenomenon of developing two (or multiple) zygotes from a single impregnation in usually uniparous mammals. The frequency of twins is different in various ethnic groups. Among Nigerians it may be as high as 4.5% and in some South American and Far-East populations it may be as low as 0.8%. In the USA, its frequency among whites was found to be about 0.89 to 0.94% and among blacks, 1.37%, before the widespread use of fertility promoting drugs.

Following in vitro fertilization about half of the births are multiple. Between 1980 and 1997, twinning increased by 52% and the frequency of triplets and higher order gestations has quadrupled in the USA. Multiple births involve considerable medical risk to the babies and mother. The gestation time is

frequently reduced by four weeks for twins, by six weeks for triplets and by 10 weeks for quadruplets. The mortality rate (~16%) and developmental anomalies are higher. The lower birth weight involves the risk for physical and mental handicaps. "Multi-fetal reduction" during the first 9–12 weeks of gestation by injecting potassium chloride into one or more of the fetuses may alleviate medical problems but may cause the loss of the pregnancy entirely. The procedure also involves serious ethical dilemmas, religious conflicts, psychological and other trauma (Elster NJD 2000 FertilSteril 74:617.) Twins are either *monozygotic* (identical) or *dizygotic* (fraternal). The former are derived from a single fertilized egg and the latter develop from two separate eggs fertilized by different sperms. In the overwhelming majority of cases, monozygotic twins are genetically identical whereas the dizygotic twins are comparable to any other siblings. It is possible that some dizygotic twins display higher similarity if one unfertilized egg gave rise to two blastomeres and two separate sperms fertilized each. Another possibility is if one of the polar bodies (identical to the egg) becomes an egg due to a developmental mishap. The identity of monozygotic twins may be somewhat reduced due to epigenetic changes (epigenetic shift).

In an unusual case of twins (Souter VL et al 2007 Human Genet 121:179), both had a 46, XX/46,XY chromosome complement in peripheral lymphocytes, skin fibroblasts, and gonadal biopsies. The proportion of XX to XY cells varied between the twins and their tissues. The cells were chimeric, and shared 100% of maternal alleles and approximately 50% of paternal alleles in the DNA analysis of skin fibroblasts. Possibly, earlier the egg divided and each was fertilized by a different sperm or a single egg was fertilized by two spermatozoa resulting in a triploid zygote, which later split and lost one or another set of chromosomes and became cytologically euploid (see Fig. T131).

Although after birth monozygotic twins appear entirely identical, during development, due to differences of methylation and histone acetylation, phenotypic differences may arise (see Fig. T132) (Fraga MF et al 2005 Proc Natl Acad Sci USA 102:10604). In a unique incident, a monozygotic twin suffering from ovarian failure was able to conceive and deliver apparently healthy offspring, after transfer of ovarian cortical tissue from her healthy sister. (Sherman J et al 2005 New England J Med 353:58).

The frequency of twinning has a genetically determined component as the studies of various ethnic groups indicate. There are indications that the genetic component plays a greater role in dizygotic twin birth than in monozygotic births.

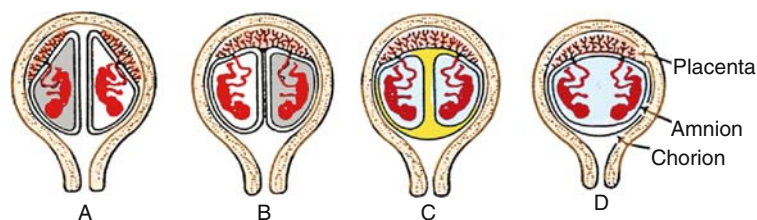


Figure T131. Human twins can be either mono- or dizygotic and the two conditions can be distinguished also on anatomical basis of the developing fetus. Monozygotic twins are surrounded by a common chorion (c and d) or even by a single amnion (D). (A) and (B) are most likely dizygotic. (Modified after Stern, C. Principles of Human Genetics, Freeman, San Francisco)



Figure T132. Monozygotic (1st and 3rd) and dizygotic twins (2nd and 4th)

Monozygotic twins are expected to be of the same sex. Exceptionally, one of the XY male twin embryos may lose the Y chromosome and develop into an XO (possibly mosaic) female. The XO human cells develop into Turner syndrome females, unlike in *Drosophila* where XO individuals are sterile males. Non-concordance for sex in identical twins may be the result of mutation in autosomal or X-chromosomal sex-reversal genes. Sometimes it is difficult to distinguish between identical and non-identical twins on the basis of phenotypic similarities. DNA fingerprinting may resolve the problem. Dermato-glyphics may not always be conclusive due to developmental differences in digital, palmar, or plantar (sole) ridge counts in monozygotic twins. Mono- and dizygotic twins provide useful tools for the study of inheritance of polygenically determined human traits. Among women of families with dizygotic twins, the rate of twinning is about double that of the general population and may be attributed to hereditary hormone levels. The inheritance of twinning through the male parent is lower than through the female. Monozygotic twinning may not or may have very low genetic component. There are statistical methods for the discrimination between identical (MZ) and non-identical (DZ) twins based on concordance of alleles (DNA or any other type).

Maynard Smith and Penrose (Ann. Human Genet. 19:273) worked out the following formula for the probability of concordance for DZ

$$\text{twins: } P = \left(1 + 2 \sum_{i=1}^n p_i^2 + 2 \left[\sum_{i=1}^n p_i^2 \right]^2 - \sum_{i=1}^n p_i^4 \right) / 4 ,$$

where i stands for the phenotype of the markers, n = number of alleles, p_i = allelic frequencies calculated on the basis of the binomial distribution for the various types of matings. ▶DNA fingerprinting, ▶fingerprints, ▶forensic genetics, ▶heritability estimation in humans, ▶freemartin, ▶superfetation, ▶multipaternal litter, ▶multiparous, ▶zygosis, ▶concordance, ▶discordance, ▶co-twin, ▶quadruplex, ▶ovulation ovary, ▶SRY, ▶sex reversal; Jones H, Schnorr JA 2001 Fertil Steril 75:11; Boomsma D et al 2002 Nature Rev Genet 3:972; epigenetics of twins: Petronis A 2006 Trends Genet 22:347.

Twins: ▶twinning

Twinscan: A gene-finder program (similar to GENSCAN) suitable to analyze homologous sequences and genes of two related genomes. ▶GENSCAN, ▶SGP-1; Korf I et al 2001 Bioinformatics 17, Suppl. 1:S40; Wei C et al 2005 Genome Res 15:577.

Twintron: ▶intron group III

Twist (*Drosophila* gene *twi*, 2–100): The lethal embryo is twisted in the egg case as the germ cell layers are defective. Mutation in the human homolog is responsible for the Saethre-Chotzen syndrome. Twist mediates also metastasis by reducing e-cadherin-controlled cell adhesion (Yang J et al 2004 Cell 117:927). ▶cadherins, ▶metastasis, ▶Chotzen syndrome

Twisting Number: The twisting number characterizes DNA supercoiling by indicating the number of contortions (writhing) and the number of twists, i.e., the number of nucleotides divided by the number of nucleotides per pitch. ▶supercoiling, ▶DNA

Twitchin: A myosin-activated protein kinase.

Two-Component Regulatory Systems: In bacteria, pairs of proteins transduce environmental signals. In one of the proteins, ca. 250 amino acids at the C-terminus and ca. 120 amino acids at the N-terminus are conserved. They control chemotaxis, virulence, nitrogen assimilation, dicarboxylic acid transport, sporulation, etc. They function by autophosphorylation of a histidine residue by the γ phosphate of ATP (see Fig. T133). The phosphate is then transferred to an aspartate, in the *response regulator*, that modifies regulatory activity of the C-terminal output domain. The system is also called a phosphorelay. A specific phosphatase may reset the system. Frequently, more than two components are involved. ▶[signal transduction](#); Itou H, Tanaka I 2001 J Biochem 129:343.



Figure T133. Two-component regulatory system

Two-Dimensional Gel Electrophoresis: In two-dimensional gel electrophoresis, the (protein) mixture is first separated by isoelectric focusing, and then separated by size using a slab of SDS polyacrylamide gel. Thus all proteins, except those rare molecules that have identical charge and molecular size, are distinguished. For the detection of small quantities of the molecules, they are either labeled radioactively or by non-radioactive means. A single two-dimensional gel slab permits the separation of hundreds or thousands of proteins at a time (see Fig. T134).

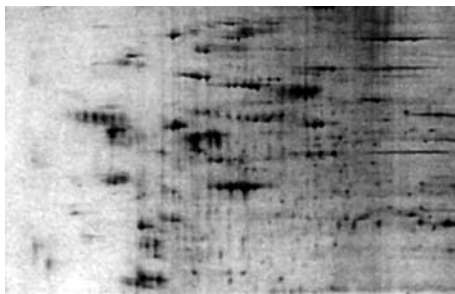


Figure T134. Two-dimensional gel electrophoresis of proteins. (Courtesy of ESA Inc. Chelmsford MA 01824-4771)

For the identification of proteins of very low abundance affinity purification may be required. The technique is used extensively in proteomic analyses. The definitive identification of proteins is hindered often by the fact that the concentration of individual

proteins may vary 5–7 orders of magnitude. The two-dimensional electrophoretic analyses of the proteome may have important potential for the understanding of disease development (Hanash S 2003 Nature [Lond] 422:226). In the immobilized pH gradient gel electrophoresis (IPG) the pH gradient is fixed in the acrylamide gel. In the differential in-gel electrophoresis (DIGE) uses two pools of proteins labeled with different fluorescent dyes and then separated in two dimensions. ▶[electrophoresis](#), ▶[isoelectric focusing](#), ▶[microchannel plate](#), ▶[FTICR](#), ▶[proteome](#), ▶[normalome](#); Hoving S et al 2002 Proteomics 2:127; Ros A et al 2002 Proteomics 2:151; Gromov PS et al 2002 Progr Biophys Mol Biol 80:3; <http://www.expasy.ch/ch2d/>; <http://proteomics.cancer.dk/>; <http://us.expasy.org/>; <http://www.wzw.tum.de/proteomik/lactis>.

Two-Hit Hypothesis: The two-hit hypothesis assumed that in order to develop cancer, two genetic alterations must take place in succession. Some chromosomal aberrations are also known as two-hit causes because two breaks are necessary to bring about an inversion or translocation. ▶[kinetics](#), ▶[Knudson two-mutation theory](#)

Two-Hybrid Method: Genetic constructs of yeast facilitate the study of protein-protein interactions. The GAL4 protein is both an enzyme and an inducer (see Fig. T135). The native GAL4 protein contains an N-terminal UAS (upstream activator sequence) DNA-binding region and a carboxyl-terminal transcription-activating region. These regions—in close vicinity—are required for the activation. Thus fusing the N-terminal of a protein (bait) and the C terminal of another protein (prey) can help study interaction between two proteins. If the two proteins interact, they reconstitute the link between the binding, and the activating domains and transcription (expression) of the reporter gene (represented by the turned on light bulb) may proceed. Thus to see expression, the DNA binding domain (DBD) must bind to the UAS element and contact established with the other protein element, which is often called *prey* and is attached to a transcriptional activator. The DBD + bait (hybrid I) and the prey + activator (hybrid II) are separately inactive. The expression of the downstream reporter gene requires interaction between the *two-hybrid* proteins. The most commonly used binding component is derived from the Gal4 or LexA proteins and the bacterial LacZ or luciferase is employed as a reporter. The receptor domain, usually called bait, may occur on a plasmid, which may also carry sequences to promote dimerization and thus the required protein interaction. The Gal bait (in contrast to the majority of LexAs) usually also contains nuclear localization sequences.

Efficient prey vectors may contain the VP16 activation domain or the Gal4 region II. The B42 bacterial activator is weaker than the other two but has affinity for a wider range of proteins and suppresses (squashes) the toxic effects that Gal4 and strong transcriptional activators may have on yeast. The two-hybrid method in yeast is very simple to use. Strains with the bait can be mixed and mated with strains with the prey and then plated on selective media where the interactions are readily detectable. The advantage of the two-hybrid method is that it can be used to test protein interactions, determine the amino acid sequences critical for interactions, and screen gene libraries for binding proteins or activators.

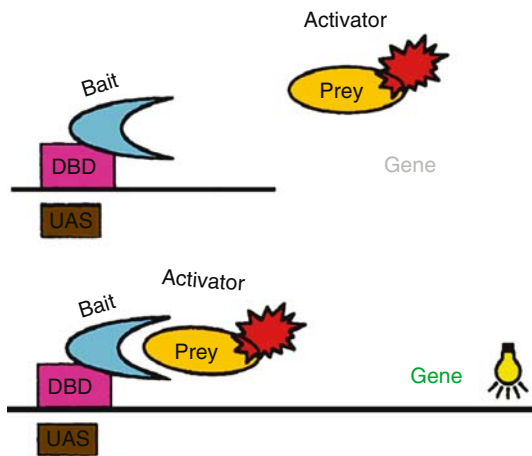


Figure T135. Two-hybrid method

The system is also suitable for testing any molecule (including aptamers) that may affect interactions, e.g., in the development of specific drugs. The system can be used in studies of the cell cycle and transcription factors, tumorigenesis, tumor suppression, etc. In some instances, positive (i.e., non-relevant for the purpose of the study) activation of the reporter gene may also occur. This interference can be reduced or eliminated by selective systems. False negative interactions are observed when the protein-protein interactions are low, there are problems with the intracellular folding of the proteins, or when other domains of larger proteins hinder proper interactions. The cases of false negatives may be low, yet may be very important in pharmacological studies. Some proteins may require a third (protein or non-protein) element for stabilization, bridging, or modification and then only a ternary complex is active. Systems have been constructed that prevent interactions between proteins. The URA3 reporter gene product converts fluoroorotic acid—with assistance of other genes—into fluorodeoxyuridine monophosphate, an analog of thymidylate synthase, which inhibits DNA

synthesis and can be used for contraselection. The two-hybrid method applied sequentially or simultaneously to large gene pools may detect interacting systems of genes. It may also place functionally unknown open reading frames into a biological context of a metabolic role. *Two-bait* systems have been developed for the possible detection of (allelic) variants of the same protein. Mammalian two hybrid procedures may facilitate the detection of interacting proteins in mammalian systems that depend on post-translational modifications not available in yeast cells. Protein-RNA interactions are studied by the *three-hybrid* systems. The *reverse two-hybrid* system detects mutations that are unable to bring the activation element to the DNA binding domain and thus cannot convert a potentially toxic compound to a toxic compound or into a suicide inhibitor. ▶galactose utilization, ▶split-hybrid system, ▶three-hybrid system, ▶reverse two-hybrid system, ▶four-hybrid system, ▶suicide inhibitor, ▶recruitment, ▶epistasis, ▶pleiotropy, ▶suppressor second site, ▶VP16, ▶one-hybrid binding assay, ▶aptamer, ▶microarray hybridization, ▶interaction trap, ▶genetic networks, ▶networks, ▶proteomics; Brent R et al 1997 Annu Rev Genet 31:663; Fields S, Song O 1989 Nature [Lond] 340:245; Shioda T et al 2000 Proc Natl Acad Sci USA 97:5220; Hirst M et al 2001 Proc Natl Acad Sci USA 98:8726; Fang Y et al 2002 Mol Genet Genomics 267:142; Uetz P 2002 Current Opin Chem Biol 6:57; Stelzl U et al 2005 Cell 122:957; <http://dip.doe-mbi.ucla.edu/>.

Two-Phase Mutation Model (TPM): In the TPM, microsatellite instability may be due to the gain or loss of a number of repeats. ▶IAM, ▶SMM, ▶microsatellite

Two-Photon Microscopy: In two-photon microscopy, a fluorochrome is excited almost simultaneously by two photons of lower energy. This allows reduced light scattering and less photo damage of the sample.

Two-Point Cross: The two-point cross involves differences at two gene loci, e.g., $AB \times ab$ or $Ab \times aB$.

Two-Step Synapsis: ▶topological filter

Two-Tailed Test: The two-tailed test estimates deviations in both directions from the mean.

Ty: Non-viral retroelements (retrotransposons) in the nucleus of budding yeast (*Saccharomyces cerevisiae*). Ty elements occur in several related forms and are designated Ty1 (25–30 copies), Ty2 (10 copies), Ty3 (2–4 copies), etc. The elements are flanked by long terminal direct repeats (251 – 371-bp) that are designated as δ for Ty1 and Ty2, and σ for Ty3. The open reading frame between the repeats (LTR) in Ty1 and Ty2 is identified as ϵ . Elements resembling these

terminal repeats, δ (ca. 100 copies), σ (20–30 copies), and τ (15–25 copies) are also found. The terminal repeats contain sequences identified as U3 (unique for 3'), R (repeated), and U5 (unique for 5' end) similarly to the designations in retroviruses. These LTRs contain the upstream gene activation sequence, TATA box, and polyadenylation, transcription, and termination signals. They also include the TG...CA bases involved in the integration of the reverse transcripts into the chromosomes. All the retroelements are generally flanked in the host by 5-bp target duplications. The open reading-frames, distinguished as TYA and TYB between the ends, are also similar and resemble retroposons of other organisms. The TYA protein may be processed through proteolysis into several smaller proteins involved in the formation of the shell of the VLP (virus-like particle). TYB contains genes for protease (*pro*), integrase (*int*), reverse transcriptase (*rt*) and RNase H (*rnH*) but no *env* gene is present as would be expected for retroviruses. Although most of the Ty elements and the independently standing termini are intact, some contain deletions up to a few kb, and the LTR sequences may be truncated. There may be apparent insertions and duplications within the Ty elements or inversion(s) involving parts of a LTR. The heterogeneity of the coding regions is due to base substitutions.

Ty retrotransposons transpose by synthesizing an RNA that is reverse-transcribed into DNA for integration. The Ty1 transcripts represent about 0.8% of the total RNA in the cell but the Ty cDNA is present in less than one copy per haploid cell before integration because of the inefficient processing of the transcript. The rate of Ty1 transposition is about 10^{-5} to 10^{-7} per element per cell division. The Fus3 protein kinase, the transcription factor TFIIB and nucleotide exchange repair modulate the transposition of Ty. The reverse-transcribed DNAs can integrate into Ty elements with the aid of recombination factors of the host and form tandem elements. RNA polymerase II transcribes them and the transcripts are polyadenylated. Transcription may be prevented by mutations symbolized as *spt* (suppressor of Ty). The transcription of Ty elements may be induced by sex pheromones synthesized by the *MATa* or *MATa* genes but not in the *MATa/Mat a* diploids. *MAT* homozygotes do not affect the transcription of Ty RNA. The Ty RNA can be packaged into virus-like particles (VLP). Proteolysis is involved in the processing of the TYA and TYB products, required for the completion of VLPs. The reverse transcription appears to be primed by tRNA^{Met}. Degradation of the template RNA is due to RNase H. During reverse transcription, recombination, sequence modifications, and deletions may occur at high frequency. Transcription of Ty is regulated by several *PST*

(suppressor of transposition), *ROC* (reducer of overproduction of transcripts), and *TYE* (Ty enhancer) genes. Presumably, about 100 host genes affect the Ty1 retrotransposition cycle. About half of them are involved in the production of the cDNA and the rest affect steps following Ty replication (Griffith JL 2003 et al 2003 Genetics 164:867). Transcription may be increased by exposure to UV light, ionizing radiation, chemical mutagens, and the culture media and it is elevated 20 fold at low temperature. The RAD52 group of recombinational repair genes inhibits the transposition of Ty. Insertion into and activation of these particular genes measure the frequency of transposition by genetically tagged Ty elements.

The VLP is made in the cytosol but must enter the nucleus for transposition to take place. Insertion of Ty into structural genes eliminates their function and reversion by excision is very rare because the target site is modified by the event. Insertion within non-coding sequences may activate or silence previously inserted elements. Ty1 and Ty2 elements appear to be distributed at random throughout the genome but the family of Ty3 elements is far more restricted. The Ty3 element inserts at the transcription initiation sites of tRNA genes by pol III. The transcription factors TFIIB and TFIIC are required for this type of insertions. The Ty1 element has preference for integration into the 5'-sequences of pol II-transcribed genes. Ty5 integrates preferentially into heterochromatin. Ty, δ , σ , and τ are commonly targeted to the vicinity of tRNA genes (hot spots). The insertions are usually directed into the leader sequences (promoter sites) or near the 5'-end of the coding region. Among the abundant Ty elements, recombination may occur and cause chromosomal rearrangements and deletions. Recombination is most common between LTR (δ) repeats. Gene conversion may also occur between these elements. Ty elements may incite deletions, inversions, and translocations with all the phenotypic consequences. The mutation rate within Ty elements was estimated to be 0.15 per Ty per replication cycle, i.e., about 1/15 of the retrotranspositions result in some types of mutation. Multiple copies of Ty1 may involve co-suppression, i.e., silencing of the elements (Garfinkel DJ et al 2003 Genetics 165:83). This rate of mutation is approximately 4 to 6 orders of magnitude higher than that in the rest of the nuclear genome but is comparable to that in RNA viruses. The high mutation rate is attributable to the lack of proofreading ability of the reverse transcriptase. The mutations in Ty (about 30% of all) occur within the seven bases of the primer-binding site (PBS) where minus strand replication is primed by a tRNA. Imprecise cutting by RNase H causes some mutations. Another error-prone event is the addition

of nucleotides immediately adjacent to the tRNA primer-binding site. After the replication system reaches the 5'-end, nucleotide additions take place at the 3'-end. After the second-strand transfer, partial DNA•DNA duplexes are formed and the recessed 3'-ends prime the completion of the double strand synthesis. As a consequence of the addition of nucleotides, the 3'-end of the minus strand cannot anneal precisely with the plus-strand DNA template. In order to reconstitute the 5'-LTR of the Ty, the mispaired 3'-primer ends are extended by reverse transcription. This process incorporates then the mispairs into the Ty element that will integrate into the yeast chromosome. The mismatches must then be fixed by DNA repair. Additional mutational mechanisms may also occur. These mutational processes are not unique features of the Ty elements but are also used by other retroelements. Retroviruses are somewhat different, however, because they show frameshift mutations and complex rearrangements. The Ty elements have been utilized as vectors (pGTy), as insertional mutagenic agents (transposon tagging), and for fusion of TyA proteins with certain proteins of interest, to facilitate the purification of epitopes. Similar transposable elements occur also in other fungi (*Candida*, *Pichia*, *Hansenula*). ▶retroposon, ▶retrotransposon, ▶transposition induction, ▶reverse transcription, ▶strong-stop DNA, ▶mating type determination in yeast, ▶protease, ▶integrase, ▶epitope, ▶*Saccharomyces cerevisiae*, ▶pol II, ▶pol I, ▶DNA repair, ▶fus3, ▶TFIIH, ▶VLP; Boeke JD et al 1988 Mol Cell Biol 8:1432; Jordan IK, McDonald JF 1999 Genetics 151:1341; Wickner RB 2001, p 473. In: Fundamental Virology. Knipe DM, Howley PM (Eds.) Lippincott Williams & Wilkins, Philadelphia, PA, USA; Umezū K et al 2002 Genetics 160:97; Zhu Y et al 2003 Proc Natl Acad Sci USA 100:5891.

Ty δ: A terminal repeat of the Ty insertion element. ▶Ty

Tyk2: A non-receptor tyrosine kinase. ▶Janus kinases

Tylosis: The formation of animal callus. ▶keratosis

Type III Secretion System: ▶secretion systems

Typing: The determination of the blood group antigens and HLA. It is a general classification by type. Also, DNA typing by fingerprinting using restriction enzyme-generated fragment pattern. ▶blood groups, ▶HLA, ▶DNA fingerprinting

Tyrosinase: ▶albinism

Tyrosine: A non-essential aromatic amino acid (MW 181.19), soluble in dilute alkali (see Fig. T136). Its biosynthetic pathway is with enzymes involved in parenthesis: Chorismate -> (chorismate mutase) -> Prephenate -> (prephenate dehydrogenase) -> 4-Hydroxyphenyl pyruvate -> (amino trans-ferase

with glutamate NH₃ donor) -> Tyrosine. Tyrosine can be derived also from phenylalanine by dehydroxylation. Tyrosine is a precursor for norepinephrine, epinephrine, 3,4-dihydroxy-phenylalanine (dopa), dopamine, and catechol that form the catecholamine family of animal hormones. ▶phenylalanine, ▶chorismate, ▶pigmentation of animals, ▶alkaptonuria, ▶tyrosinemia, ▶tyrosine aminotransferase, ▶tyrosine kinase, ▶animal hormones, ▶goiter, formula above.

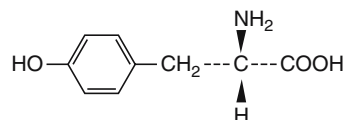


Figure T136. Tyrosine

Tyrosine Aminotransferase (TAT, Richner-Hanhart syndrome): TAT converts tyrosine into p-hydroxyphenylpyruvate. Glucocorticoid hormones induce it. TAT deficiency occurs rarely in humans and is controlled by a recessive gene (ca. 11 kb, 12 exons) in human chromosome 16q22.1-q22.3 (and mouse in chromosome 8). The condition involves elevated level of tyrosine and in some cases an increased urinary excretion of p-hydroxyphenylpyruvate and hydroxyphenylacetate. The disease generally involves corneal ulcer, palm keratosis (callous skin), and mental and physical retardation. The mitochondrial enzyme is under the control of another gene. A TAT regulator gene may be located in the human X-chromosome and glutamic oxaloacetic transaminase (16q21) also regulates its activity. ▶tyrosine, ▶tyrosinemia

Tyrosine Hydroxylase (TYH): TYH is encoded in human chromosome 11p15 (mouse chromosome 7), which controls the synthesis of dopamine from phenylalanine. Dopamine is a hormone involved with adrenergic neurons, the sympathetic nerve fibers that liberate norepinephrine when an impulse passes the nerve synapse. This enzyme may play a key role in fetal development and in manic depression. The microsatellite sequence in the first intron serves normally as a transcriptional enhancer of the gene. ▶tyrosine, ▶manic depression, ▶DOPA; Albanèse V et al 2001 Hum Mol Genet 10:1785.

Tyrosine Kinases (protein tyrosine kinase): Tyrosine kinase activity is essential for many processes of the signal transduction, tissue differentiation involving oncogenesis, and signaling to immunoreceptors. The most frequently activated proteins are phospholipase C-γ, phosphatidylinositol 3-kinase, and GTPase activating kinase. ▶oncogenes ABL, ▶ARG, ▶Btk, ▶Btk, ▶FES, ▶FGR, ▶FLT, ▶FHS, ▶ERBB1, ▶Fyn, ▶RAF, ▶SRC, ▶KIT, ▶LCA, ▶Lyn,

►MET, ►RET, ►Syk, ►YES, ►ZAP-70, ►morphogenesis in *Drosophila* [*tor*], ►sevenless, ►SOS, ►insulin [receptor β -chain], ►TCR [T cell receptor], ►EGFR, ►PDGF, ►MCSF, ►VEGF, ►Steel factor, ►hepatocyte growth factor, ►trk, ►neurotrophin, ►FGF, ►receptor tyrosine kinase, ►signal transduction, ►protein kinases, ►kinome; Latour S, Veillette A 2001 Curr Opin Immunol 13:299; Wang Z et al 2004 Science 304:1164; tyrosine kinase inhibitors: Levitzki A, Mishani E 2006 Annu Rev Biochem 75:93.

Tyrosine Phosphatases (protein tyrosine phosphatase, PTP): The PTP family of enzymes has at least 40 known members. Some have properties of transmembrane receptor proteins (RPTP) and the cytosolic forms have a characteristic ca. 240-amino acid catalytic domain. Each PTP has also a phosphate-binding, 11-residue motif containing catalytically active Cys and Arg. The proteins have critical roles in signal transduction relevant to growth, immune response, proliferation, and differentiation. Dimerization negatively regulates the activity of receptor tyrosine phosphatase- α . ►signal transduction, ►PTK, ►synaps; Stetak A et al 2001 Biochem Biophys Res Commun 288:564; substrates: Tiganis T, Bennett AM 2007 Biochem J 402:1; Liu Y et al 2007 Nature Rev Immunol 7:202.

Tyrosine Protein Kinase: ►tyrosine kinase, ►phosphorylase

Tyrosine Transaminase: ►tyrosine aminotransferase

Tyrosinemia (FAH): The recessive gene responsible for the anomaly is in human chromosome 15q23-q25. Its prevalence is about 1/2,000 live births. FAH involves increased levels of tyrosine in the blood and a lack of

p-hydroxyphenylpyruvate oxidase, but the primary enzyme defect appears to be fumarylacetoacetase deficiency leading to accumulation of succinylacetone and succinylacetoacetate. Defects in porphyrinogenesis appear secondary. Because of the deterioration of the liver, as secondary symptoms, accumulation of methionine and other amino acids in the blood and urine is frequent. The particular odor of the body fluids may be due to α -keto- γ -methiolbutyric acid. Prenatal diagnosis of FAH relies on amniotic fluid analysis for succinylacetolactone or measurement of fumarylacetoacetase in cultured amniotic cells. Low tyrosine diet alleviates the symptoms but to avoid liver cancer, liver replacement before age two is advisable. This type of tyrosinemia involves various kinds of chromosomal anomalies. Tyrosinemia II (16q22.1-q22.3) is a deficiency of tyrosine aminotransferase. Tyrosinemia Type III (12q24-qter) is due to a deficiency of 4-hydroxyphenyl-pyruvate dioxygenase. This disease does not usually involve dysfunction of the liver. The condition can be detected prenatally but carriers cannot be identified. Mice mutants homozygous for FAH but heterozygous for alkaptonuria were partially normalized in their hepatocytes. The tyrosine degradation pathway: tyrosine \rightarrow (tyrosinemia type II) \rightarrow 4-OH-phenylpyruvate \rightarrow (tyrosinemia type III) \rightarrow homogentisic acid \rightarrow (alkaptonuria) \rightarrow maleylacetoacetate \rightarrow fumarylacetoacetate \rightarrow (tyrosinemia type I) \Rightarrow fumarate and acetoacetate. ►tyrosine aminotransferase, ►genetic screening, ►methionine adenosyltransferase deficiency, ►methionine biosynthesis, ►amino acid metabolism, ►liver cancer, ►mosaic, ►gene therapy, ►alkaptonuria; Jorquera R, Tanguay RM 2001 Hum Mol Genet 10:1741.

Tyrosinosis: ►tyrosine aminotransferase

Historical vignettes

Aristotle reviews the ancient theories of sex determination, but finds them unsatisfactory:

“Some suppose that the difference [between sexes] exists in the germs from the beginning; for example, Anaxagoras and other naturalists say that the sperm comes from the male and that the female provides the place [for the embryo], and that the male comes from the right, the female from the left, since in the uterus the males are at the right and the females at the left. According to others, like Empedocles, the differentiation takes place in the mother, because, according to them, the germs penetrating a warm uterus become male, and a cold uterus female...” (Generation of Animals, Book IV, Part I, Para. 2).

Peter Starlinger (discoverer of insertion mutations in bacteria with Heinz Saedler in 1972 [Biochimie 54:177]) noted in 2005 in Annu Rev Plant Biol 56:1

“It was only then that we realized the relation of these element to McClintock's transposable elements, in spite of the fact that I had known McClintock's work since my student days, and in spite of a series of seminars that we had held on this topic in the institute in Cologne. Sometimes we are blind!”

U

U: Denotes uracil. ►pyrimidines

U: Symbol for uranium.

U-937: Refers to human monocyte line. ►monocytes

U Protein (unwinding protein): Unwinds the DNA strands at a distance from a ►nick. (See Basak S, Nagaraja V 2001 J Biol Chem 276:46941).

U RNA (ubiquitous RNA): Denotes a snRNA. Its transcript has a 2,2,7-trimethyl guanosine cap and may have modified U residues; it does not have a poly-A tail. ►snRNA, ►snurposome, ►cap, ►poly-A tail

U1 RNA: This has complementary sequences to the 5' consensus sequences of the splice sites and probably plays a role in mRNA processing from the primary transcript. Mutated U1 snRNA may be a strong inhibitor of gene expression (Fortes P et al 2003 Proc Natl Acad Sci USA 100:8264). ►hnRNA, ►RNA; McNamara-Schroeder KJ et al 2001 J Biol Chem 276:31786.

U2 RNA (snRNA): Apparently, this recognizes the 3' end of introns at the lariat and is involved in splicing. ►lariat, ►splicing, ►introns

U3 snRNP: Most abundant of the U RNA ($\approx 10^6$ molecules/cell) processes near the 5' end of the ribosomal RNA transcripts. It stays on and generates a 5' knob characteristic of rRNA only. Binding U3 of the snRNP initiates processing, especially the transcripts of 18S rRNA. ►rRNA, ►snRNP, ►ribosome; Venema J et al 2000 RNA 6:1660.

U7 snRNA: Involved in the processing of the 3' end of the histone pre-mRNAs. In *Drosophila*, it contains 71 nucleotides. In vertebrates it is located in the Cajal bodies. ►Cajal body; Dominski Z et al 2003 Proc Natl Acad Sci USA 100:9422.

U8 snRNP: Required for the upstream cleavage of 5.8S and for cutting off 28S RNA ca. 500 nucleotides at the 3' end. ►rRNA, ►snRNP, ►ribosome; Peculis BA, Steitz JA 1994 Genes Dev 8:2241.

U12 snRNP: A spliceosomal component along with other U snRNAs. ►spliceosome; Otake LR et al 2002 Mol Cell 9:439.

U14 snRNP: A maturase for 18S rRNA. ►ribosome; Newman DR et al 2000 RNA 6:861.

U22 snRNP: Essential for processing both ends of 18S rRNA, separated by about 2,000 nucleotides.

UAA: Refers to the ochre codon of translation termination. ►code genetic, ►translation termination

U2AF: A protein assisting U2 snRNA recognition. U2AF family proteins regulate both steroid hormone receptor-mediated transcription and alternative splicing (Dowhan DH et al 2005 Mol Cell 17:429). Phosphorylated DEK protein assists U2AF in intron removal (Mendel Soares LM et al 2006 Science 312:1961). ►U2 RNA, ►alternative splicing; Guth S et al 2001 Mol Cell Biol 21:7673.

UAG: Refers to the amber codon of translation termination. ►code genetic, ►amber suppressor

UAS: Denotes upstream activating sequences (which regulate gene transcription). They behave in the same manner as enhancers. UAS encode DNA-binding proteins, e.g., the GAL4 UAS codes for a 100 kDa protein and protects its 17 bp palindromic sequence against DNase I digestion or methylation. These proteins bind to special DNA sequences and to other proteins in the transcriptional complex. Transcriptional activation and binding may rely on more than one tract of amino acids. ►promoter, ►galactose utilization, ►two-hybrid method; Blackwood EM, Kadanaga JT 1998 Science 281:61.

uAUG: In 3 to 10% of the RNA transcripts translation initiation codons occur in the 5'-untranslated sequences (5'-UTR) of viruses, fungi, plants and mammals. The open reading frame due to uAUG may have an untranslated intercistronic region relative to the downstream ORF or they may overlap or it may be in-frame. uAUGs may have regulatory functions. (See Rose JK, Iverson L 1979 J Virol 32:404).

UBC2 (E2): Refers to ubiquitin-conjugating enzymes. From UBC ubiquitin is transferred to a lysine residue of the target protein. Ubc2/Rad6 - Rad18 proteins have functions in both proteolysis and DNA repair. Ubc2 proteins occur in many isoforms within the same organism. ►ubiquitin, ►E2, ►Rad 18, ►isoform; Ptak C et al 2001 Mol Cell Biol 21:6537.

UBC3/Cdc34: A ubiquitination enzyme required for G1→S phase transition in the cell cycle. ►ubiquitin, ►Cdc34

Ubc9: A ubiquitin interacting protein. It is involved in the control of the cell cycle from G2→M, and in the degradation of diverse proteins in a variety of organisms. ►ubiquitin, ►UBL; Kaul S et al 2002 J Biol Chem 277:12541.

UbcD1: This ubiquitin protein of *Drosophila* degrades some telomere associated proteins and thus controls the proper detachment and attachment of the telomeres during mitosis and meiosis. ►telomere,

►ubiquitin; Bocca SN et al 2001 *Biochem Biophys Res Commun* 286:357.

UBE3A: A ubiquitin ligase gene plays a role in Angelman syndrome. ►ubiquitin, ►Angelman syndrome; Kishino T et al 1997 *Nature Genet* 15:70.

Überoperon: Includes gene neighborhoods where individual operons may show rearrangement in different species, yet remain in the functional and regulatory context (Lathe WC III et al 2000 *Trends Biochem Sci* 25:474). Rogozin and associates (Rogozin IB et al 2002 *Nucleic Acids Res* 30:2212) named this phenomenon genome hitchhiking. The largest such neighborhood in prokaryotes includes 79 genes. Most, albeit not all these genes, share a known functional role. ►operon, ►supraoperon

UBF (upstream binding factor): In association with protein SL-1 UBF, controls the transcription of rRNA genes by RNA polymerase I. These protein factors differ even among closely related species; they are members of the high mobility group proteins. ►high mobility group proteins, ►transcription factors, ►SL1; Santoro R, Grummt I 2001 *Mol Cell* 8:719; Chen D, Huang S 2001 *J Cell Biol* 153:169; Stefanovsky VY et al 2001 *Mol Cell* 8:1063.

Ubiquilin: A protein that stimulates the biosynthesis of neurofibrillary tangles in Alzheimer's disease and Lewy bodies in Parkinson's disease. ►Alzheimer's disease, ►Parkinson's disease, ►Lewy body, ►tau; Mah AL et al 2000 *J Cell Biol* 151:847.

Ubiquinones (coenzyme Q): Lipid-soluble benzoquinones mediate electron transport. The reduced form is a potent lipid-soluble antioxidant capable of inhibiting lipid peroxidation. ►cytochromes, ►lipids, ►peroxides; Elias M et al 2001 *J Biol Chem* 276:48356.

Ubiquitin: This acidic polypeptide (~76 amino acids) is ubiquitously present in prokaryotic and eukaryotic cells. It may be associated with H2A histone and the conjugate is called UH2A. It binds to other proteins and proteolytic enzymes and then degrades the ubiquitinated proteins. In the majority of cases the degradation takes place in the cavity of the (20S–26S) proteasomes, cylindrical complexes of proteases, or the ligand-bound molecule can be internalized into vacuoles and degraded by lysosomal enzymes. Ubiquitination is involved in many aspects of cellular regulation, DNA repair, stress response, cell cycle progression, formation of the synaptonemal complex, signal transduction and apoptosis. Ubiquitin stress alters proteasome composition by enhanced loading of deubiquitinating Ubp6 to the proteasome (Hanna J et al 2007 *Cell* 129:747). A cascade of conjugating, activating and carrier enzymes recognizes ubiquitin. The E1 enzyme forms a thiol ester with ubiquitin using ATP energy.

The E1-ubiquitin complex then transfers UB to the carrier E2 which with the aid of E3 ligases mediates the association of E2 with the target proteins. For catalysis, the E3 ligases use either a HECT or a RING finger domain. The ubiquitin E3 ligase complexes may be SCF (Skp1-Cdc53/CUL1-F-box proteins), APC (anaphase promoting complex) and the VCB-like family (VHL-ElonginC/ElonginB) proteins. SCF-βTrCP is also a ubiquitin ligase. Several other molecules are also involved. The ubiquitin complex is degraded by deubiquitinating cysteine protease enzymes (DUBP). The signals for degradation are PEST sequence at the C-ends, N-end rule domains and phosphorylation. The human ubiquitin genes are encoded at chromosome 17p11.1-p12 and polyubiquitin at 12q24.3. Polyubiquitin is a chain of several ubiquitin molecules linked by lysine (K-48 or K-63). Some protein molecules may be degraded co-translationally in case they are defective or if their folding is slow. Ubiquitin may have non-destructive functions as well such as processing signaling molecules in the cell and facilitating the expression of genes (Finley D 2001 *Nature [Lond]* 412:283; Mukhopadhyay D, Riezman H 2007 *Science* 315:201). ►monoubiquitin, ►histones, ►proteolytic, ►lactacystin, ►lysosomes, ►proteasomes, ►PEST, ►Ubc, ►UBP, ►CDC34, ►Ubl, ►PIC, ►sentrin, other entries listed separately, ►SCF, ►Skp1, ►Cul-lins, ►D box, ►K-box, ►F-box, ►APC, ►VHL, ►E1, ►E2, ►E3, ►Socs-box, ►Rbx1, ►PEST, ►N-end rule, ►destruction box, ►multivesicular body, ►IκB, ►antigen processing and presentation, ►lid, ►SUMO, ►Huntington's chorea; Hershko A, Ciechanover A 1998 *Annu Rev Biochem* 67:425; Pickart CM 2001 *Annu Rev Biochem* 70:503; Weismann AM 2001 *Nature Rev Mol Cell Biol* 2:169; Conaway RC et al 2002 *Science* 296:1254; Walden H et al 2003 *Nature [Lond]* 422:330; Liu YC 2004 *Annu Rev Immunol* 22:81; regulation: Gao M, Karin M 2005 *Mol Cell* 19:581; unfolding: Irbäck A et al 2005 *Proc Natl Acad Sci USA* 102:13427; ubiquitin chain assembly: Hochstrasser M 2006 *Cell* 124:27; ubiquitin binding domains: Harper JW, Schulman BA 2006 *Cell* 124:1133.

Ubiquitous RNA: ►URNA

Ubistatins: These are block binding ubiquitinated substrates to the proteasome. ►ubiquitin; Verma R et al 2004 *Science* 306:117.

UBL: Refers to ubiquitin (Ubc9) interacting protein operating on many different proteins under various names such as sentrin and SUMO-1. ►ubiquitin, ►Ubc, ►E2, ►SUMO

UBP: A group of (16 in budding yeast) ubiquitin degrading enzymes or de-ubiquitinating enzymes or isopeptidases. UBPs may regulate gene silencing,

differentiation and cell division (cyclins, Cdks, MPF, etc.). ▶ubiquitin, ▶cell cycle, ▶cyclins, ▶CDK, ▶silencer, ▶MPF, ▶morphogenesis; Lin H et al 2000 Mol Cell Biol 20:6568.

UBR: An enzyme that mediates the formation of thioester with ubiquitin and UBC. ▶UBC; Kwon YT et al 1998 Proc Natl Acad Sci USA 95:7898.

UCE (upstream control elements): These regulate transcription. ▶regulation of gene activity

UDG (uracil-DNA-glycosylase): This repair enzyme is capable of removing accidentally incorporated U or deaminated C, which is followed by the removal of the apyrimidinic site with the aid of AP endonuclease. There are two nuclear-coded UDG enzymes in the mammalian cells; one of them is in the mitochondria. ▶DNA repair, ▶excision repair, ▶AP endonuclease; Dinner AR et al 2001 Nature [Lond] 413:752.

UDP: Uridine diphosphate is formed from uridine monophosphate and gives rise to uridine triphosphate by using ATP as the phosphate donor (see Fig. U1).

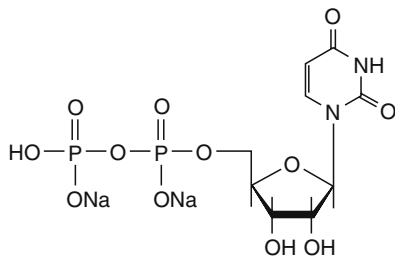


Figure U1. UDP-5'diphosphate Na

UEP: ▶unit evolutionary period

UEP (unique event polymorphism): Includes SNIPS, INDELs and microsatellite sites that facilitate characterization of haplotypes.

UGA: Refers to opal stop codon. ▶code genetic

UGT/UGPGT (uridinediphosphate-glucuronosyltransferase): Detoxifies various lipid-soluble toxins by conjugation with glucuronic acid, makes them water-soluble, excretable and may prevent mutation and cancer. Its phosphorylation controls substrate-specificity (Basu NK et al 2005 Proc Natl Acad Sci USA 102:6285). ▶Crigler-Najjar syndrome

UH2A: ▶ubiquitin

UhpB: *E. coli* kinase involved in the regulation of sugar phosphate transport.

uidA: The gene for β-glucuronidase. ▶β-glucuronidase

Ulcer: A condition characterized by corruption of the surface or deeper cell layers of the body, e.g., gastric ulcer, an ulceration inside the stomach or diabetic ulcers of the legs, or genital ulcers in the case of sexually transmitted disease. ▶Crohn's disease

Ulcerative Colitis: This is an inflammatory bowel disease (IBD) like Crohn's disease. It is apparently under the control of several chromosomes and genes. ▶inflammatory bowel disease

Ullrich Congenital Muscular Dystrophy (Ullrich disease): ▶muscular dystrophy

Ullrich-Turner Syndrome: This is the the same as Turner's syndrome.

Ulna: The larger bone of the forearm opposite the thumb.

Ulnar-Mammary Syndrome: ▶Schinzel syndrome

Ultimate Mutagen: Some chemical substances (promutagens) become mutagenic only after activation. In this process, first proximal mutagens are formed that may be subsequently converted to a form (ultimate mutagen) that is genetically most reactive with the DNA. ▶activation of mutagens

Ultrabar: ▶Bar mutation

Ultracentrifuge: Laboratory equipment suitable for the separation of cellular organelles and macromolecules by high (over 20,000 revolution/minute) centrifugal force in an evacuated and refrigerated chamber. At maximal speed it may exceed the gravitational force several hundred thousand times. The *analytical ultracentrifuge* monitors continuously or intermittently the boundary of movement of macromolecules in a solute (e.g., Cs₂SO₄). The more commonly used *preparative ultracentrifuge* fractionates organelles or macromolecules in sucrose or CsCl. The suspended material forms a band corresponding to its density and the density of the solute. Chloroplasts in sucrose gradients can be identified by color; DNA bands in CsCl can be identified by staining with the dye ethidium bromide. The bands, containing homogeneous material, can be removed by careful suction from the centrifuge tubes or by drop-wise collection through a hole punctured at the bottom with a syringe needle. (See Laue TM, Stafford WF III 1999 Annu Rev Biophys Biomol Struct 28:75; ▶Lamm equation).

Ultraconserved DNA Elements (UCE): 200-base pair or shorter or longer and entirely or almost entirely identical sequences in the human, rat and mouse genomes and are well conserved in chicken, dog and fish as well. They occur frequently in overlapping exons in genes involved in RNA processing or in introns or nearby genes regulating transcription and

development. Sequences longer than 100 nucleotide are common in both RNA and DNA binding and in transcriptional regulation. Less than 50 nucleotide ultraconserved elements are common in microRNA, other non-coding RNA and transcription factor binding sites. The ultraconserved sequence elements in whole human and mouse genomes follow the power law distribution and apparently have evolutionary significance (Salerno W et al 2006 Proc Natl Acad Sci USA 103:13121). Their distribution along the chromosomes is not random but they are absent in human chromosome 21 and their numbers are significantly depleted in the case of segmental duplications and copy number variants. Their conservation across phylogenetic entities indicates positive selection rather than neutrality in evolution. UCEs indicate enhancer-like activity of these elements (Derti A et al 2006 Nature Genet 38:1216). ▶[mutation neutral](#), ▶[networks](#); Bejarano G et al 2004 Science 304:1321.

Ultradian: Occurring periodically but less frequently than once a day. ▶[circadian](#)

Ultrasonic (ultrasound): Refers to radiation in excess of 2×10^4 hertz/second, generally 5×10^5 hertz/sec. It is used for breaking down cells, treatment of arthritis and for tomographic examination or sonography, etc. Prenatal ultrasonic scanning of fetuses is widespread in the developed world and there is no convincing evidence of adverse effects. There has been much speculation about increase of left-handedness, lower cognitive development and cancer but experimental data have not confirmed these conjectures in large human populations. Ultrasound increases the delivery efficiency of exogenous nucleic acid to the intended target. The ideal system enhances gene expression in the target without having any effect on non-target tissues. Ultrasound may be able to provide this localization in somatic gene therapy as well. Low doses of about 100 mW cm^{-2} do not appear to have lasting and harmful effects. ▶[arthritis](#), ▶[tomography](#), ▶[sonography](#); see reviews in Prog Biophys Mol Biol 93:2007.

Ultrastructure: A fine structure beyond the resolution of the light microscope.

U

Ultrathin-Layer Gel Electrophoresis: Along with capillary microelectrophoresis it is well suited for rapid automated separation of biopolymers, e.g., nucleic acids as needed for the genome sequencing projects. (See Guttman A, Ronai Z 2000 Electrophoresis 18:3952).

Ultraviolet Light (UV): Refers to emission below the wavelength of violet (400–424 nm). UV-A has the most effective emission between 315 and 400 nm, UV-B between 280 and 315 nm and UV-C between 200 and 290 nm wavelengths. Nucleic acids have maximal absorption at about 260 nm. The absorption

maximum may depend on base composition and pH. The maximal genetic effects of UV light coincide with the absorption maximum of nucleic acids. The major genetic effect of UV-B light is the generation of pyrimidine dimers and pyrimidinones. UV-A causes the production mainly of oxoguanine and reactive peroxides (Besaratina A et al 2005 Proc Natl Acad Sci USA 102:10058) and this part of the UV spectrum is particularly carcinogenic if the DNA repair system is inefficient (Kozmin S et al 2005 Proc Natl Acad Sci USA 102:13538). Another study has indicated that UV-A-induced cyclobutane pyrimidine dimers are the major cause of DNA lesions in the human skin (Mouret S et al 2006 Proc Natl Acad Sci USA 103:13765). These compounds may damage the DNA and interfere with replication and transcription and can cause mutation and induce cancer. UV-B has immunosuppressive potential whereas UV-A is inert in this respect but it may suppress the UV-B effects. This protective effect is due to the induction of skin heme oxygenase. Oxidation of the membrane proteins may affect the signal transduction pathways and activate genes of the cellular defense systems. In prokaryotes, the LexA repressor is inactivated leading to the upregulation of genes mediating mutation, recombination and DNA repair. In yeast, cell cycle genes and various kinases are activated. In animal cells, AP and NF- κ B transcription factors may be activated through the RAS signal transduction pathways. In plant cells, UV exposure may increase the synthesis of UV-absorbing flavonoids and phenylpropanoids and activates the octadecanoid defense pathway of fatty acids and generates less than 0.2 cyclobutane dimers per gene. In plants, transposons like *Mu* may enhance the mutagenic effects of UV-B radiation. Ultraviolet light in general has low penetration into biological material and a few cell layers may completely trap it. Nearly 100 genes of *Arabidopsis* are activated by UV-B and 7 are repressed (Ulm R et al 2004 Proc Natl Acad Sci USA 101:1397). The DNA must have a protection mechanism to convert dangerous electronic excitations by UV into less harmful vibrational energy and assure photostability (Satzger H et al 2006 Proc Natl Acad Sci USA 103:10196). ▶[DNA repair](#), ▶[genetic repair](#), ▶[physical mutagens](#), ▶[light response elements](#), ▶[light-sensitivity diseases](#), ▶[signal transduction](#), ▶[RAS](#), ▶[cyclobutane](#), ▶[pyrimidine dimer](#), ▶[8-oxodeoxyguanine](#), ▶[flavonoids](#), ▶[phenylpropanoids](#), ▶[fatty acids](#), ▶[electromagnetic radiation](#), ▶[Mu](#), ▶[JUN](#), ▶[excimer](#), ▶[melanocortin](#)

Ultraviolet Photoproducts: ▶[cyclobutane ring](#), ▶[pyrimidine-pyrimidinone](#), ▶[Dewar product](#), ▶[cis-syn photoproduct](#), ▶[translesion pathway](#), ▶[DNA repair](#)

Ultraviolet-Sensitivity Syndrome (UV^S S): RNA synthesis is inhibited in the cells by ultraviolet light. It appears to be different from xeroderma pigmentosum but is similar to the Cockayne syndrome. Ultraviolet-sensitivity is caused by a defect in the RAD genes required for genetic repair. ▶[xeroderma pigmentosum](#), ▶[Cockayne syndrome](#)

Ultraviolet Spectroscopy: Used to measure the absorption of (\approx monochromatic) UV light and thus qualitatively or quantitatively identifies molecules such as DNA and RNA.

Umbilical Cord: Cord, which attaches the fetus to the mother during pregnancy. The placental blood in the umbilical cord contains stem cells suitable for repopulating the bone marrow. ▶[stem cells](#)

UME: Denotes a unique mutational event which is a marker of evolutionary significance.

UML: Provides guidelines for data macromolecular structure and function presentation (Booch G et al 1997 The Unified Modelling Language User Guide, Addison-Wesley, Boston, Massachusetts).

UMP: This denotes uridine monophosphate. ▶[UDP](#)

UMU (UV mutagenesis): Genes *UmuC* and *UmuD* are involved in repairing the DNA damaged by ultraviolet light. UmuD' is a post-translationally processed active form of the UmuD protein. ▶[DNA repair \[SOS repair\]](#), ▶[translesion pathway](#)

Unami: Describes the taste of monosodium glutamate, a flavor enhancer in some oriental foods. ▶[taste](#)

Unbalanced Chromosomal Constitution: Parents heterozygous for inversions or translocations are functionally normal but may transmit to their offspring (unbalanced) duplication-deficiency gametes resulting in various physical and mental disabilities depending on the chromosomal region(s) involved (see Fig. U2). The frequency of unbalanced gametes (duplication/deficiency and duplication and deficiency) is more than 2% in the conceptuses.

This is, however, the lowest estimate because very frequently pregnancy is terminated before the current methods of analysis can detect fertilization. Even greater is the uncertainty about the frequency of chromosomal anomalies in the human sperm and egg that are extremely difficult to analyze cytologically. An unbalanced karyotype may be due to trisomy (in ~ 20 –30% of spontaneous abortions). Monosomy has been observed in about 5 to 10%, triploidy in 6 to 7%, and tetraploidy in 2 to 4% of the spontaneously aborted fetuses. Although spontaneous abortion is extremely undesirable, suffering due to chromosomal anomalies experienced by live offspring is far more. There is no effective cure for unbalanced chromosomes. ▶[translocation](#), ▶[inversion](#); Levy B et al 1998 Genet Med 1:4.

UNC-6: A protein of the netrin family in *Caenorhabditis elegans* which guides ventral migration of the axon growth cone. The 407-amino acid TGF- β -like protein

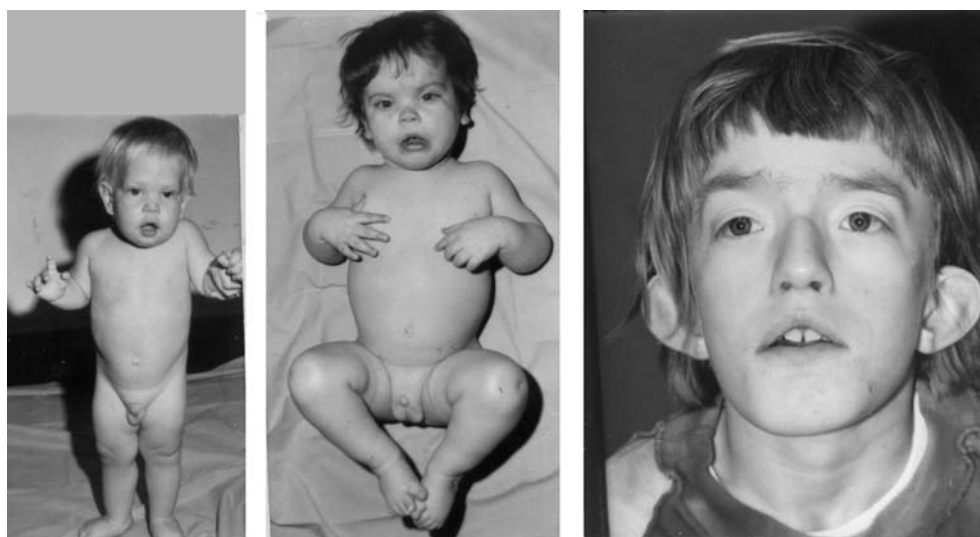


Figure U2. Unbalanced Chromosomal constitution inherited from phenotypically normal carrier parents. Left: Deficiency for the short arm of Chromosome 18. Middle: Duplication of the tip of the short arm of Chromosome 3. (Courtesy of Dr. Judith Miles). Right: Duplication of part of the long arm of Chromosome 4, resulting from a translocation heterozygosity involving Chromosomes 20 and 4. (Courtesy of Dr. D.L. Rimoin)

encoded by the UNC-129 gene has a similar function. ▶[netrins](#), ▶[semaphorins](#), ▶[TGF](#); Merz DC et al 2001 Genetics 158:1071.

UNC-33: A *Caenorhabditis* protein regulating axon extension. ▶[CRMP](#), ▶[axon](#); Ricard D et al 2001 J Neurosci 21:7203.

UNC-43: Encodes a calcium/calmodulin-dependent serine/threonine kinase type II and its mutation is responsible for multiple behavioral defects in *Caenorhabditis*. (See Sagasti A et al 2001 Cell 105:221).

unc-86 (uncoordinated): The *Caenorhabditis* gene has a pivotal role in determining neural identities. (See Burglin TR, Ruvkun G 2001 Development 128:779).

Uncertainty: ▶[Heisenberg's uncertainty](#)

Uncharged tRNA: This has no amino acid attached to it. ▶[tRNA](#)

Uncoating: During the initiation of infection the viral genome dissociates from the other constituents of the virus particle and is injected into the bacterium (see Fig. U3).

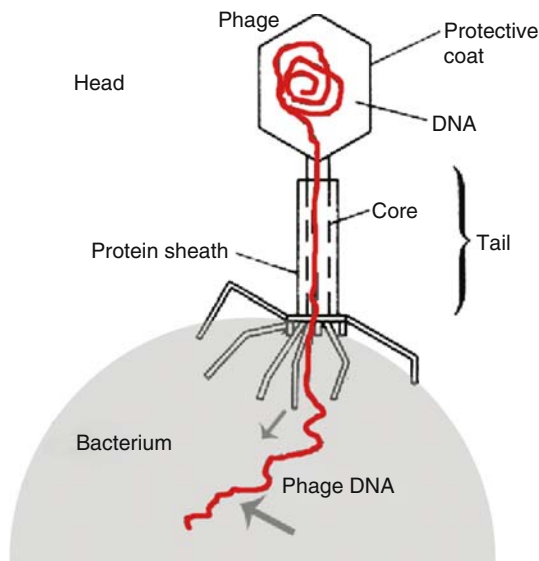


Figure U3. Uncoating of phage DNA

U

Uncompetitive Inhibitor: ▶[regulation of enzyme activity](#)

Uncoupling Agent: This uncouples electron transfer from phosphorylation of ADP, e.g., dinitrophenol. ▶[cold-shock proteins](#)

Uncoupling Protein (mitochondrial UCP): Uncouples oxidative phosphorylation from ATP synthesis and generates heat to safeguard against cold. Noradrenaline and adrenalin regulate it. UCP-3 is a member of

the mitochondrial transporter family in the skeletal muscles and controls metabolic rate and glucose homeostasis. UCP-1 is present in the brown adipose tissue and is involved in fat combustion and heat generation. UCPs play an apparent role in obesity, macrophage-mediated immunity and in the control of ROS. ▶[ROS](#); Jarmuszkiewicz W 2001 Acta Biochim Pol 48:145.

Underdominance: Refers to inferiority in performance or fertility or proportion of hybrids in feral populations. It may be caused by Robertsonian fusion, transposable element, meiotic drive, post-implantation selection, etc. ▶[overdominance](#), ▶[Robertsonian translocation](#), ▶[meiotic drive](#); Davis S et al 2001 J Theor Biol 212:83.

Underwinding: Characterizes negative supercoiling. ▶[supercoiling](#)

Unequal Crossing Over: Occurs between repeated sequences in the gene that may pair obliquely and therefore in the recombinant strands may have either more or less copies of the sequences than in the parental ones (see Fig. U4).



Figure U4. Unequal crossing over

The extra DNA material may not be needed for the species and thus can be used for evolutionary experimentation and may contribute to the evolution of new function(s). The frequency of such events may vary, e.g., in *Arabidopsis* $\sim 3 \times 10^{-6}$ has been observed. This estimate is within the range of mutation frequency and lower than that found at the *Bar* locus of *Drosophila* where unequal crossing over was first identified at a variable rate of 0.03 to 0.11. ▶[duplication](#), ▶[Bar locus](#), ▶[intragenic recombination](#); Bridges CB 1936 Science 83:210.

UniBLAST: Provides information on UniGene clusters, which are similar to the one interested in. ▶[UniGene](#), ▶[BLAST](#)

Unidentified Reading Frame: ▶[URF](#)

Unidirectional Replication: The replication fork moves only in one direction, left or right from the origin. ▶[replication fork](#), ▶[bidirectional replication](#); Maisnier-Patin S et al 2001 J Bacteriol 183:6065.

Unified Genetic Map: Such a map represents similarities in the distribution of nucleotide sequences across phylogenetic groups and is expected to not only

provide tools for evolutionary studies, but also assist in transferring economically advantageous genes to crops. The ancestral chromosomal pattern is shared between many species. Unique sequences characterize species that are more closely related. ►SCEUS, ►evolution, ►comparative maps, ►CATS, ►mapping genetic, ►physical map, ►integrated map; O'Brien SJ et al 1993 *Nature Genet* 3:103.

Unfolded Protein Response (UPR): The accumulation of unfolded proteins in the endoplasmic reticulum (ER) activates the transcription of molecular chaperones such as BiP, GRP, calreticulin and protein disulfide isomerase in the nucleus so that protein folding can proceed as needed. Misfolded proteins may, however, lead to cell death if UPR cannot alleviate the problems and reactive oxygen species accumulate (Haynes CM et al 2004 *Mol Cell* 15:767). UPR signaling is mediated by endoplasmic reticulum transmembrane protein, Ire1 (inositol-requiring kinase 1), which has both kinase and nuclease domains, and by PERK (protein kinase-like endoplasmic reticulum kinase). Protein P58^{IPK} is a cytoplasmic co-chaperone and is associated with the endoplasmic reticulum protein translocation channel Sec61 complex. P58^{IPK} recruits heatshock protein 70 (HSP70) chaperone to the cytosolic face of Sec61. Proteins that enter slow ER can be exposed to proteasome in a co-chaperone dependent manner and thus the unfolded protein overload is reduced (Oyadomari S et al 2006 *Cell* 126:727). BAX and Bak proapoptotic proteins activate IRE1 α signaling and provide a physical link between the core apoptotic pathway and UPR (Hetz C et al 2006 *Science* 312:572). Various adverse physiological conditions, toxins, inhibitors of the calcium pump, genetic defects altering protein structure, etc. evoke UPR. Proteasome inhibitors disrupt UPR in myeloma cells (Lee A-H et al 2003 *Proc Natl Acad Sci USA* 100:9946). Sialoglycolipid ganglioside can induce UPR and neuronal apoptosis (Tessitore A et al 2004 *Mol Cell* 15:753). Mutations in the editing domain of alanyl-tRNA synthetase disrupt fidelity of translation leading to misfolded proteins, cell death and neurodegeneration (Lee JW et al 2006 *Nature [Lond]* 443:50). ►endoplasmic reticulum, ►BiP, ►GRP, ►calreticulin, ►PDI, ►UPR, ►proteasome, ►gangliosides, ►apoptosis, ►BAK, ►BAX, ►endoplasmic reticulum-associated degradation, ►Sec61, ►heat-shock proteins; Rügsegger U et al 2001 *Cell* 107:103; Ma Y, Hendershot LM 2001 *Cell* 7:827; Calfon M et al 2002 *Nature [Lond]* 415:92; Kaufman RJ et al 2002 *Nature Rev Mol Cell Biol* 3:401; Harding HP et al 2002 *Annu Rev Cell Dev Biol* 18:575; Ma Y, Hendershot LM 2004 *Nature Rev Cancer* 4:966; Schröder M, Kaufman RJ 2005 *Annu Rev Biochem* 74:739; protein quality control: Bakau B et al 2006 *Cell* 125:443.

UNG (uracil nucleotide DNA glycosylase): This DNA repair enzyme removes mis-incorporated uracil from the DNA. Deaminase may convert cytosine to uracil and then UG mismatch is formed that is either repaired by UND or the DNA strand is broken but either way it can result in mutagenic alteration. The removal of uracil from viral RNA by host UNG is detrimental to the pathogen. ►DNA repair, ►glycosylases, ►immunoglobulins; Krokan HE et al 2001 *Progr Nucleic Acid Res Mol Biol* 68:365.

Uniformity Principle: ►Mendelian laws

UniGene: A database of human and other organisms' ESTs and sequences of known genes to assist in identifying those which belong to the same cluster and have similar functions. This collection is suitable for microarrays and large-scale study of gene expression. ►EST, ►locuslink/ENTREZ GENE; Schuler GD et al 1997 *J Mol Med* 75:694; Zhuo D et al 2001 *Genome Res* 11:904; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unigene>; sets of transcript sequences: <http://www.ncbi.nlm.nih.gov/UniGene/build2.html>; transcriptome of various eukaryotic species: <http://www.ncbi.nlm.nih.gov/UniGene/>.

Unikont: ►bikont

Unilateral Incongruity: A special type of incompatibility when only the females of one of the related species are compatible with the males of the other species. In other words, it is a unidirectional compatibility. ►self-incompatibility; Bernacchi D, Tanksley SD 1997 *Genetics* 147:861.

Unimodal Distribution: Has only one major peak (see Fig. U5).



Figure U5. Unimodal distribution

Unineme: Refers to a single strand (e.g., of DNA or post-mitotic chromosome before the S phase).

Uninformative Mating: Does not shed light on the genetic constitution of the parents because it lacks clarity regarding linkage of the markers that may have poor penetrance or expressivity or both or the traits concerned are under polygenic control.

Uniparental Disomy (UPD): Both homologous chromosomes are inherited from only one of the parents in a diploid. UPD involves an epigenetic change like

imprinting. When the two chromosomes are identical the case is called *isodisomy*, if they are different it is known as *heterodisomy*. For e.g., in 10% of the Russel-Silver syndrome cases a 35 Mb segment at 7q31-ter is maternally inherited as an isodisome. Uniparental disomy may be caused by the loss of one chromosome in a trisomics or duplication of a monosome. In a female cystic fibrosis patient markers on chromosome 7 indicate non-paternal disomy (Spence JE et al 1988 *Amer J Hum Genet* 42:217). In human UPD acrocentric isochromosomes and Robertsonian translocations between non-homologous chromosomes predominate. ▶ [imprinting](#), ▶ [epigenesis](#), ▶ [nondisjunction](#), ▶ [trisomy](#), ▶ [monosomic](#), ▶ [isochromosome](#), ▶ [Robertsonian translocation](#), ▶ [hydantidiform mole](#); Kotzot D 2001 *J Med Genet* 38:497.

Uniparental Inheritance: In the absence of male transmission of plastids and mitochondria, the genetic material of these organelles is transmitted to the progeny only through the egg. Also, telochromosomes and large deletions can generally be transmitted only through the female, if transmitted at all. In some species of *Mytilus* (mussel) one set of mtDNA is preferentially transmitted through the female whereas the other set is inherited paternally (Kenchington E et al 2002 *Genetics* 161:1579). The latter phenomenon is *doubly uniparental inheritance*. ▶ [mtDNA](#), ▶ [ctDNA](#), ▶ [doubly uniparental inheritance](#), ▶ [paternal leakage](#), ▶ [mitochondrial genetics](#), ▶ [chloroplast genetics](#), ▶ [imprinting](#)

Unipolar Depression: Refers to periods of depression with generally debilitating consequences but usually last for a shorter duration. A single nucleotide replacement (Arg441→His) in the tryptophan hydroxylase-2, a rate-limiting step in serotonin biosynthesis, causes 80% loss in serotonin production and it may be one of the causes of unipolar depression (Zhang X et al 2005 *Neuron* 45:11). ▶ [bipolar mood changes](#), ▶ [affective disorders](#)

Uniporter: A transporter, which transports a type of molecule without coupling it to any other.

UniProt (universal protein resource): The most comprehensive information source on proteins from several resources. (See <http://www.uniprot.org>).

Unique DNA: DNA present in a single copy per genome. ▶ [singlet](#)

UniSTS: A marker information database, which is a unified non-redundant view of sequence-tagged sites (STS); it can be used for e-PCR. ▶ [STS](#), ▶ [e-PCR](#); <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unists>.

Unit Evolutionary Period (UEP): Refers to time in million years (MY) required for the fixation of 1% divergence in two initially identical nucleotide sequences.

Unitig: ▶ [scaffolds in genome sequencing](#), ▶ [U-unitig](#)

Univalent: Denotes an eukaryotic chromosome without a pair. In case the chromosomes in a hybrid are not sufficiently homologous, they may form univalents and their distribution to the poles in meiosis may be disorderly. The frequency of univalents may permit conclusions regarding the lack of relatedness of the parental forms (see Fig. U6). ▶ [triticale](#)

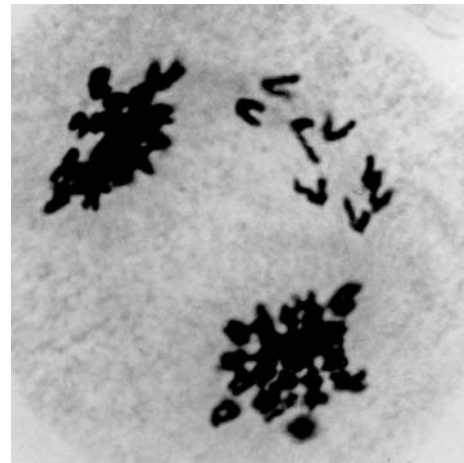


Figure U6. Hybrid of an octaploid ($2n = 56$) and hypoploid ($2n = 41$) hexaploid triticale. The female gamete contributed 28 and the male only 20 chromosomes. Therefore, there are 20 bivalents and 8 univalents in meiosis. Seven out of 8 univalents represent the *D* genome of wheat. Generally, the lagging univalents are not incorporated into the functional gametes because they fail to reach the poles. Usually, they divide belatedly. (Courtesy of Kiss Á 1966 *Z Pflanzenzücht* 55:309).

Universal Bases: The natural nucleoside of hypoxanthine or the synthetic 6-hydroxy- and 6-amino-5-azacytosine nucleosides or 1-(2'-deoxy- β -D-ribofuranosyl)-3-nitropyrrole may serve for modified nucleotides in recognition of G, T and U with equal efficiency for Watson-Crick pairing (see Fig. U7).

The latter maximizes stacking while minimizing hydrogen pairing without sterically disrupting the double helix. Some of the analogs lower, whereas others increase the melting temperature of the polynucleotides that contain them. These may be used to synthesize oligonucleotide probes and primers when the exact sequence needed cannot be inferred because of the redundancy of the genetic code. Oligonucleotides containing the 5-nitroindole base may be easily detected by an antibody. In SNIPs the mismatched base

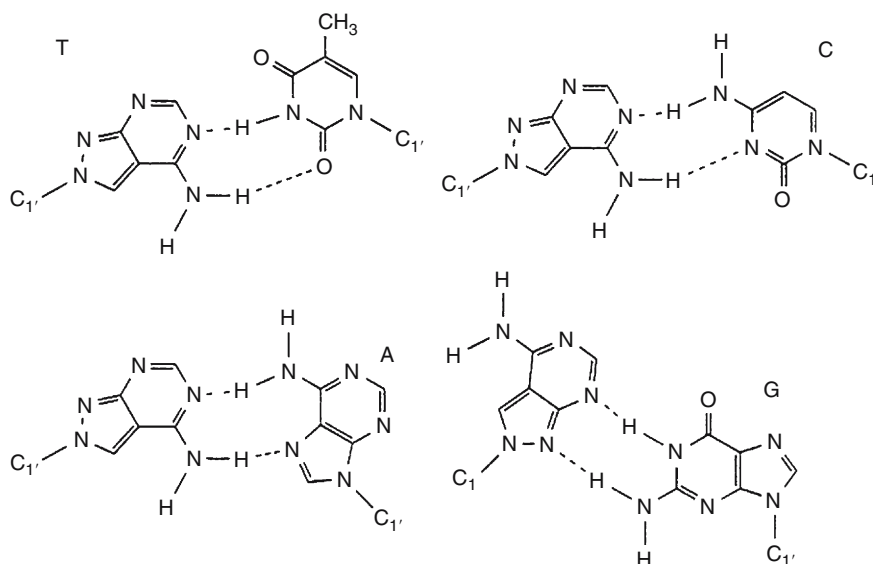


Figure U7. Pairing of the bases T (thymine), C (cytosine), A (adenine) and G (guanine) with N^8 -(2'-deoxyribofuranoside) of 8-AZA-7-deazaadenine, a universal base.

can be identified easily. The addition of analogs to the 5' end may enhance the stability of the analog oligonucleotide on the chips. The presence of these universal bases may alter nucleic acid-protein interactions. When in an A:C mismatch 3-nitro-pyrrole replaced C the fidelity of ligation increased substantially. The incorporation of nitroazole analogs may increase the stability of triplex sequences. Klenow fragment polymerase inefficiently incorporated nitro-pyrrole derivatives and the analog generally terminated further chain extension. ►hydrogen pairing, ►probe, ►primer, ►DNA chips, ►azacytidine, ►PCR, ►SNIPs, ►sequence saturation mutagenesis; Loakes D 2001 Nucleic Acids Res 29:2437; Seela P, Debelak H 2000 Nucleic Acids Res 28:3224.

Universal Code: The majority of DNAs across the entire phylogenetic range use DNA codons in the same sense. Notable exceptions exist in the mitochondria and in a few species. ►genetic code; O'Sullivan JM et al 2001 Trends Genet 17:20.

Universal Donor: ►ABO blood group

Universal Recipient: ►ABO blood group

Universal Trees: Display the evolution of orthologous proteins across taxonomic boundaries. (See Brown JR et al 2001 Nature Genet 28:281).

Univoltine: Having one generation annually.

Unix: A multi-user, multi-tasking computer system for servers, desktops and laptops. (See <http://www.ee.surrey.ac.uk/Teaching/Unix/>).

Unnatural Amino Acids: These are not coded for by the natural genetic system. The amber suppressor tyrosyl-tRNA synthetase of *E. coli* can translate the suppressor codon as tyrosine in the bacterium. When the enzyme is expressed in *Saccharomyces cerevisiae* it can aminoacylate the tRNA_{CUA} but it does not aminoacylate any of the regular cytoplasmic tRNAs. The bacterial tRNA_{CUA} is transported into the yeast cytoplasm and participates efficiently in translation. Mutations can be selected, which under specific conditions can translate certain unnatural phenylalanine and tyrosine amino acid derivatives in prokaryotic and eukaryotic systems. Thus, by such a technology the classic 20-amino acid code can be expanded and the consequences of these unnatural amino acids on the proteins can be determined. The incorporation of unnatural amino acids into proteins requires a unique codon suppressor tRNA and the corresponding aminoacyl-tRNA synthetase. The specificity of the aminoacyl tRNA can be modified by mutations at the active site and selection of the enzyme, which can specifically acylate the tRNA with the unnatural amino acid but not the conventional amino acid. At present more than 30 unnatural amino acids can be added to proteins using the procedure (Turner JM et al 2006 Proc Natl Acad Sci USA 103:6483). Actually, >190 unnatural amino acids are available commercially and >90 unnatural backbone and side-chain analogs can be enzymatically charged to tRNA (Hartman MCT et al 2006 Proc Natl Acad Sci USA 103:4356). Using an appropriately designed frameshift suppressor, tRNAs with four-base anticodons can deliver simultaneously two or three unnatural amino acids in response to the

quadruplet codons CGGG and GGGU into a neuroreceptor of *Xenopus* oocytes. The frameshift suppressor effectively competes with an amber suppressor if delivered in excess (Rodriguez EA et al 2006 Proc Natl Acad Sci USA 103:8650). A genetically engineered ribosome, ribo-X, is more efficient at readthrough of amber codons with an attached unnatural amino acid, because of reduced affinity of the 30S ribosome for release factor RF-1 that is normally supposed to terminate the translation (Wang K et al 2007 Nature Biotechnol 25:770). ▶amino acids, ▶aminoacylation, ▶genetic code, ▶suppressor tRNA, ▶aminoacyl-tRNA synthetase, ▶selenocystein, ▶pyrrolysine, ▶orthogonal mRNAs; Chin JW et al 2003 Science 301:964; structural requirement in tRNA synthetase: Kobayashi T et al 2005 Proc Natl Acad Sci USA 102:1366; expanded genetic code: Wang W et al 2006 Annu Rev Biophys Biomol Struct 35:225; Liao J 2007 Biotechnol Progr 23:28.

Unnatural Bases: ▶modified bases, ▶base analogs

Unordered Tetrads: These tetrads do not contain the spores in a linear order as generated in the first and second meiotic divisions (see Fig. U8). In contrast to ordered tetrads, unordered tetrads require the presence of three genetic markers and two of them must be in

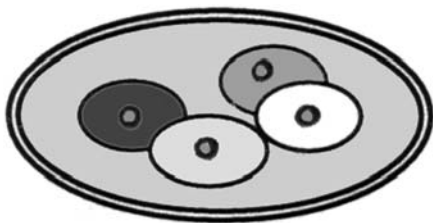


Figure U8. Unordered tetrad

different chromosomes to be able to calculate gene—centromere distances. Again—as in ordered tetrads—it is important to determine the frequencies of tetatype tetrads for at least three markers considered and for this p is designated as the tetatype frequency of say a and b , and q is the tetatype frequency of b and c , and similarly r is the tetatype frequency for a and c . The exchange frequency between a and its centromere = x , between b and its centromere = y , and between c and its centromere = z . Furthermore, the following three equations are needed:

$$\begin{aligned} p &= x + y - 3/2xy & q &= y + z - 3/2yz \\ r &= x + z - 3/xz \end{aligned}$$

The values, p , q and r being known, the unknown quantities, the recombination frequencies (x , y and z)

between the three genes and their centromeres can be determined by solving the three equations:

$$\begin{aligned} x &= 2/3 \left(1 \pm \sqrt{\frac{4 - 6p - 6r + 9pr}{4 - 6q}} \right), \\ y &= 2/3 \left(1 \pm \sqrt{\frac{4 - 6p - 6q + 9pq}{4 - 6r}} \right) \text{ and} \\ z &= 2/3 \left(1 \pm \sqrt{\frac{4 - 6q - 6r + 9qr}{4 - 6p}} \right). \end{aligned}$$

Once the recombination frequency between a gene and its centromere becomes available, the exchange frequencies between additional genes and their centromeres can also be calculated by the formula: $s = \frac{2(v-t)}{2-3t}$ where s = the unknown recombination frequency between marker d and its centromere, t = the known recombination frequency between gene e and its centromere, and v = the tetatype frequency for the unmapped gene d and the mapped gene e . ▶tetrad analysis; Emerson S 1963, p. 167 Methodology in Basic Genetics, Burdette, WJ, [Ed.] Holden-Day, San Francisco.

Unphased Diploid Population: The linkage phase of the heterozygotes is unknown.

Unrooted Evolutionary Trees: These do not indicate the initial split of the branching. ▶evolutionary tree; Steel M, McKenzie A 2001 Math Biosci 170:91.

Unsaturated Fatty Acid: This contains one or more double bonds. ▶Omega-3-fatty acids

UNSCARE: United Nations Committee on Effects of Atomic Radiation.

Unscheduled DNA Synthesis: The replication of the DNA is outside the normal S phase and this indicates a repair replication. The tests are generally carried out on cultured hepatocytes or fibroblasts exposed to certain treatment(s) and the incorporation of radioactive thymidine is monitored by either autoradiography or scintillation counting. The data are compared with concurrent controls that have not been exposed to any mutagen. Although the procedure appears attractive it is not very effective and practical for the identification of mutagens or carcinogens. ▶bioassay in genetic toxicology, ▶DNA polymerases; Zbinden G 1980 Arch Toxicol 46:139; Hoege C et al 2002 Nature [Lond] 419:135.

Unstable Genes: These have higher than average mutation rate. Usually instability is caused by the movement of insertion or transposable elements (see Fig. U9). Higher mutation rate may also be due to deficiency of genetic repair or defects in DNA

replication. ▶DNA repair, ▶insertional mutation, ▶transposable elements, ▶error in replication, ▶fractional mutation, ▶variegation, ▶genomere

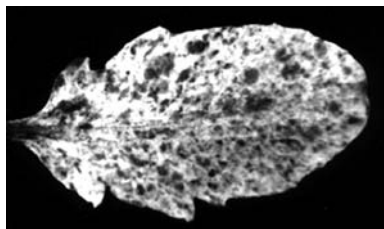


Figure U9. Unstable genes

Unstructured Proteins: These lack three-dimensional (globular) structure in free state but may become structures upon binding to other macromolecules. The adaptability of their structure is an advantage in regulatory functions. ▶phosphorylation; Wright PE, Dyson HJ 1999 *J Mol Biol* 293:321; Iakoucheva LM et al 2004 *Nucleic Acids Res* 32:1037.

Unsupervised Learning: Identifies new, so far undetected, shared pattern(s) of sequences in macromolecules and determines the positive and negative representatives of the pattern(s). The information permits correlations between structure and function in languages as well as in proteins without direct human intervention in the details. ▶supervised learning, ▶support vector machine; Wallis G, Baddeley R 1997 *Neural Comput* 9:883; Hatzivassiloglou V et al 2001 *Bioinformatics* 17 Suppl 1:S97; Solan Z et al 2005 *Proc Natl Acad Sci USA* 102:11629.

Untoward Pregnancy: Pregnancy that terminates with congenital malformation or stillbirth or infant death within 14 days after delivery. ▶congenital

Untranslated Regions (UTR): These are the leader sequences upstream from the first methionine codon and the downstream sequences beyond the stop codon of the mRNA. The upstream and downstream regions include various control elements and at the 3' end in eukaryotes the polyadenylation signal is situated. The untranslated regions of the mRNA do not code for any amino acid sequence. The 3'-UTRs in RNAs control translation, the fate of germ line cells, life cycle, anterior-posterior axis of development, meiotic cycles by binding proteins similarly to the DNA binding proteins. The ENCODE project observed that most of the longer protein-coding transcripts differ only in their UTRs but the coding regions are shared. ▶upstream, ▶downstream, ▶stop codon, ▶polyadenylation, ▶ENCODE; Kuersten S, Goodwin EB 2003 *Nature Rev Genet* 4:626; eukaryotic regions: <http://www.ba.itb.cnr.it/UTR/>.

Unusual Bases: Refer to modified forms of the normal DNA or RNA bases; they may be common in tRNA. Their incorporation into the DNA may lead to base substitution mutations. Methylation of C and A nucleotides may lead to imprinting, transient genetic variations in expression and alteration of RFLP. DNA containing an unnatural base pair can be amplified and function as a template for the site-specific incorporation of base analog substrates into RNA via transcription. Base-pairing in such a case takes place by specific hydrophobic shape complementation between the bases, but lacks hydrogen-bonding interactions. In replication, this unnatural base pair exhibits high selectivity in combination with the usual triphosphates and modified triphosphates, gamma-amidotriphosphates, as substrates of 3' to 5' exonuclease-proficient DNA polymerases, allowing PCR amplification. In transcription, the unnatural base pair complementarity mediates the incorporation of these base substrates and their analogs, such as a biotinylated substrate, into RNA by T7 RNA polymerase (Hirao I et al 2006 *Nature Methods* 3:729). With this system, functional components can be site-specifically incorporated into a large RNA molecule. ▶tRNA, ▶RFLP, ▶imprinting, ▶methylation of DNA, ▶Bar, ▶modified bases; Barciszewski J et al 1999 *Mol Biol Rep* 26:231.

Unverricht-Lundborg Disease (EPM1): ▶myoclonic epilepsy

Unwindase: Refers to double-stranded RNA helicases that unwind in a single step the entire length of a molecule in an ATP-dependent process. ▶DexH, ▶NPH; Nishikura K 1992 *Ann NY Acad Sci* 660:240.

Unwinding Protein: Facilitates unwinding of a DNA double helix and stabilizing single strands. The nucleotide triphosphate (NTP)-dependent RNA helicases are required for unwinding of double-stranded RNA and replication of many pathogenic viruses. ▶DNA replication, ▶helicase; Dillingham MS et al 2001 *Proc Natl Acad Sci USA* 98:8381.

Unzipping of DNA: Refers to the separation of the double-stranded structure. Depending on the base composition, the threshold force required is about 12 pN (piconewton). One joule is the work done when a force of 1 N acts through a distance of 1 meter. ▶joule; Cocco S et al 2001 *Proc Natl Acad Sci USA* 98:8608.

uORF: Denotes upstream open reading frame which may play a regulatory role in protein synthesis.

UP Elements (upstream elements): In the DNA, (−40 to −150 sites from the initiation of transcription) are recognition sites for the α subunit of the prokaryotic RNA polymerase which boost (30 to 300-fold) the frequency of transcription initiation. The −46 to −38 element, 5'-AAAAAARNR-3'

stimulates transcription up to 170-fold, the -57 to -47 element, 5'-AWWWWT TTTT-3' stimulates transcription up to 16-fold (Estrem ST et al 1999 Genes & Develop 13:2134). [W = A or T, R = A or G, N = no single base pair is present in 70% of the population and no 2 bp make up 95% of the population]. The α subunit C-terminal domain and the σ subunit bind initially to the -35 sequence and in the final isomerization the downstream double helix is embedded in the β/β' jaws leading to the transcriptionally active complex (Sclavi B et al 2005 Proc Natl Acad Sci USA 102:4706). ►transcription factors, ►promoter, ► σ , ►FIS, ►CRP, ►RNA polymerase, ►isomerization of strands, ►gyrase, ►topoisomerase, ►triplex

Up-and-Down: The structural arrangement of helical protein bundles comparable to the meander of β -sheets. ►meander, ►protein structure

UPE: Refers to the upstream promoter element. ►promoter

UPGMA (unweighted pair group method with arithmetic means): These are formulas for determining evolutionary distances. ►transformed distance, ►evolutionary distance; Kim KI et al 2002 Animal Genet 33:19.

UPR (unfolded protein response): Regulates gene expression when the endoplasmic reticulum does not function properly. It may control chaperones, phospholipid biosynthesis, secretory pathways and degradation of proteins associated with the endoplasmic reticulum under stress or even without stress. ►endoplasmic reticulum, ►chaperones, ►unfolded protein response; Bertolotti A, Ron D 2001 J cell Sci 114:3207.

Upregulation: Refers to increasing activity by regulation. ►downregulation, ►regulation of gene activity

Upstream: This is in the direction of the 5' end of polynucleotides (DNA). ►downstream

Upstream Activation Sequence: ►UAS

Upstream Regulatory Sequence (USR): This is the regulatory element in the promoter region.

U

Uptag: ►bar code genetic

Uptake: Eukaryotic cells may incorporate nuclei, plastids and mitochondria, pseudovirions, plasmids, liposomes and various other macromolecules besides smaller organic and inorganic molecules. Viruses move from cell to cell through the plasmodesmata and through the vascular system of plants. Plant viruses generally encode a movement protein that modifies the plasmodesmata, binds to single-stranded nucleic acids and associates with the cytoskeleton and the endoplasmic reticulum. (See Tzfira T et al 2000 Annu Rev Microbiol 54:187).

Uptake, Selective: Inorganic or organic molecules are not taken up by a stochastic process but the uptake is regulated by special mechanisms. ►ion pumps, ►transformation, ►conjugation

Uracil: A pyrimidine base in RNA; 2,4-dioxypyrimidine, MW 112.09, soluble in warm water but insoluble in ethanol. ►pyrimidines

URE (ureidosuccinate utilization): Cytoplasmic proteins involved in nitrogen metabolism in yeast are responsible for the production of a protein analogous to prion. ►prion; Baxa U et al 2002 Proc Natl Acad Sci USA 99:5253.

Urea Cycle: Describes the formation of urea ($[\text{NH}_2]_2\text{CO}$) from amino acids and CO_2 ; ornithine is converted to citrulline which in turn is converted to arginine. The hydrolytic cleavage of arginine produces urea and regenerates ornithine and thus the cycle is complete. The urea cycle in the mitochondria secures homeostasis for ammonium with some independence of the nitrogen intake. The mutation in the ornithine transporter (encoded at 13q14) involves the symptoms of hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. ►arginine, ►ornithine, ►citrulline carbamoylphosphate synthetase deficiency, ►amino transferase

Uredium: A uredospore producing sorus, a type of sporangium of fungi and protozoa (see Fig. U10). ►stem rust, ►sorus

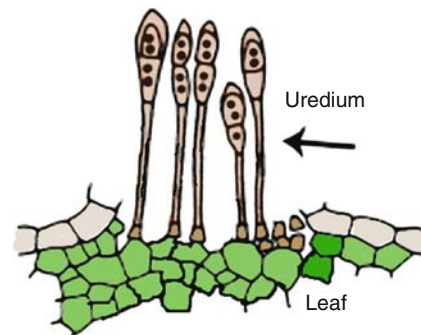


Figure U10. Uredium

Uremia: Refers to urine in the blood caused by a variety of factors.

Ureotelic: Excreting urea. ►Urea (NH_2CONH_2), ►Urea cycle

Urethan ($\text{CH}_3\text{H}_7\text{NO}_2$): This is a toxic (lethal dose 2g/kg in rabbits) liquid (at 48–50 °C). It causes chromosomal breakage and mutation; it is also antineoplastic.

URF (unidentified reading frame): Capable of transcription (open) but the gene product has not been identified. ►[reading frame](#)

Uric Acid: A degradation product of xanthine and it is excreted in the urine (see Fig. [U11](#)). It is secreted in particularly high amounts in hyperuricemic individuals under dominant and polygenic control, as well as in glycogen storage diseases, HPRT deficiency and gout. Birds and reptiles normally excrete high amounts. ►[glycogen storage diseases](#), ►[gout](#), ►[HPRT](#), ►[Lesch-Nyhan syndrome](#), ►[xanthinuria](#)

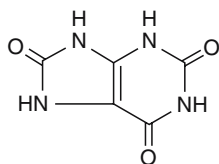


Figure U11. Uric acid

Uricotelic: Excretes uric acid. ►[uric acid](#)

Uridine: Uracil + ribose, an RNA nucleoside. ►[pyrimidines](#)

Uridine Diphosphate Glucuronosyl Transferase: Encoded in human chromosome 2; this group of enzymes is glucuronate steroid hormones. ►[Crigler-Najjar syndrome](#)

Uridine Monophosphate Synthetase Deficiency (UMPS): ►[oroticaciduria](#)

Uridylate: Refers to the nucleotide of uracil. It contains uracil + ribose + phosphate.

URL (uniform resource locator): The generic name for an Internet resource, such as WWW page; Gopher menu (<http://www.sc.edu/bck2skol/fall/lesson12.html>), a file transfer protocol server, etc. ►[bookmarks](#)

URNA: This is a uridine-rich nuclear, non-coding RNA involved in transcript processing within the cell nucleus. (See Dye MJ et al 2007 Cold Spring Harbor Symp Quant Biol 71:275; Matera AG et al 2007 Nature Rev Mol Cell Biol 8:209).

21U-RNA: 21U-RNAs are precisely 21 nucleotides long, begin with a uridine 5'-monophosphate but are diverse in their remaining 20 nucleotides, and appear modified at their 3' terminal ribose. 21U-RNAs originate from more than 5,700 genomic loci dispersed in two broad regions of chromosome IV of *Caenorhabditis*—primarily between protein-coding genes or within their introns. These loci share a large upstream motif that enables accurate prediction of additional 21U-RNAs. The motif is conserved in other nematodes, presumably because of its importance for producing these diverse,

autonomously expressed, small RNAs (Ruby JG et al 2006 Cell 127:1193). ►[small RNA](#)

U-RNP: U-RNA associated with proteins involved in processing the primary transcripts of genes within the nucleus.

Urocortin: A neuropeptide similar to urotensin and corticotropin releasing factor. It elicits the synthesis adrenocorticotrophic hormone and is therefore involved in stress-related endocrine, autonomic and behavioral responses. ►[adrenocorticotropin](#), ►[urotensin](#), ►[corticotropin releasing factor](#); Parkes DG, May CN 2000 News Physiol Sci 15:264.

Urogenital: Denotes both the system of urine secretion and the reproductive organs.

Urogenital Adysplasia: Autosomal dominant failure to develop one or both kidneys, frequently coupled with wide set eyes, low set ears and other anomalies. The incidence among newborns may be as high as 4.5% and among adults 0.3%. ►[kidney disease](#)

Urokinase (uPA): A plasminogen activator. The urokinase receptor is a glycosyl-phosphatidyl-inositol-linked cell surface protein that regulates cell adhesion. It has been suggested that urokinase is a requirement for some cancerous growths. Some catechins (present in green teas) appear inhibitory to uPA. ►[plasminogen](#), ►[CAM](#), ►[intravasation](#), ►[anthrax](#); Andreassen PA et al 1997 Int J Cancer 72:1; Plesner T et al 1997 Stem Cells 15:398; crystal structure: Huai Q et al 2006 Science 311:656.

Uropathy: Refers to diseases of the urogenital system.

Urotensins: These are short bioreactive peptides of 41 (urotensin I) and 12 (urotensin II) amino acids, respectively. ►[urocortin](#); Lewis K et al 2001 Proc Natl Acad Sci USA 98:7570.

URS: These are upstream regulatory/repressing sequences which are the binding sites for various transcription factors. ►[promoter](#), ►[transcription factors](#), ►[regulation of gene activity](#), ►[UAS](#); Hanna-Rose W, Hansen U 1996 Trends Genet 12:229.

Urticaria, Familial Cold (Muckle-Wells syndrome, 1q44): Autosomal dominant disease is characterized by reoccurring, transient burning papules and macules on the skin, cold-sensitivity, and is frequently associated with progressive deafness and renal amyloidosis (fibrillary protein deposits in the kidneys). ►[cold hypersensitivity](#)

Use and Disuse: ►[Lamarckism](#)

Usher Syndrome (USH): The condition is hereditary yet the pattern of inheritance is quite variable although in most cases it is probably autosomal recessive. It is characterized by deafmutism, retinitis pigmentosa,

mental disabilities and ataxia. Three types of the syndrome are usually distinguished on the basis of the severity and onset of the disease. The prevalence is around $4 - 5 \times 10^{-5}$. USH1 has a pre-pubertal onset; seven loci are associated with it. About 75% of the afflicted individuals have a severe defect in the USH1B gene in human chromosome 11q13.5, encoding myosin VIIA. USH1A is in chromosome 14q32 (Heilig R et al 2003 Nature [Lond] 421:601). Other types of the disease all involving hearing deficit and some other anomalies have been reported: USH1D and DFNB12 (10q21-q22), USH1F (chr. 10q21-q22, protocadherin), USH1E (21q21) USH2A (1q41). USH1G encodes a scaffolding protein. USH1D encodes a type of cadherin (CDH23) that causes stereocilia disorganization in waltzing mouse with hearing deficit (Bolz H et al 2001 Nature Genet 27:108). A milder form has been assigned to 1q32. Myosin VIIA may be involved in the transport between the outer and inner layers of the photoreceptors of the eye. In type IIa form a 171.5 kDa protein is involved that has a laminin epidermal growth factor and fibronectin type III motifs pointing to the involvement of defects in cell adhesion. USH1C involves a defect in the PDZ domain (involving PSD-95, DLG and ZO-1 proteins) of harmonin. The PDZ modules interact with all other proteins concerned with signaling and the cytoskeleton. Deletions of the USH1C gene may lead to infantile hyperinsulinism, enteropathy (intestinal disease) and deafness. USH3 (3q21-q25) encodes a 120-amino acid protein concerned with recessive, progressive hearing loss and severe retinal degeneration. ▶retinitis pigmentosa, ▶ataxia, ▶deafmutism, ▶deafness, ▶waltzing mouse, ▶myosin, ▶cadherin, ▶hypoglycemia, ▶EGF, ▶laminin, ▶fibronectin, ▶CAM; Verpy E et al 2000 Nature Genet 26:51; Bolz H et al 2001 Nature Genetics 27:108; Bork JM et al 2001 Am J Hum Genet 68:26; Ahmed ZM et al 2001 Am J Hum Genet 69:25; Joensuu T et al 2001 Am J Hum Genet 69:673; Adato A et al 2005 Hum Mol Genet 14:347.

USM (ubiquitous somatic mutations): These are attributed to defects in DNA repair (mismatch repair) and in DNA replication. ▶DNA repair, ▶unstable genes

U-snRNP: A splicing factor of RNA transcript. ▶splicing, ▶spliceosome; Xue D et al 2000 EMBO J 19:1650.

USP (chromosome-specific unique sequence probes): Employ locus-specific fluorescent DNA sequences which are suitable for the identification of small deletions and duplications. ▶FISH, ▶chromosome painting, ▶WCPP, ▶telomeric probes

Ustilago maydis (n = 2): Basidiomycete that has been extensively used for meiotic and mitotic analysis of

recombination and for the isolation of biochemical mutations, etc. The 20.5-million base genome contains 6,902 protein-coding genes (see Fig. U12). Its pathogenicity is controlled by 12 clusters of genes encoding secreted proteins (Kämper J et al 2006 Nature [Lond] 444:97). This fungus causes the ear smut of maize. The haploid forms are non-pathogenic. Several other *Ustilago* species are pathogenic to other Gramineae. ▶fungal life cycles; Banuett F 1995 Annu Rev Genet 29:179.



Figure U12. *Ustilago* on maize ear

UTase (uridylyl transferase): Catalyzes the transfer of uridylyl group to the P_{II} regulatory subunit of adenylyl transferase (ATase), an enzyme which transfers an adenylyl group from ATP to a tyrosine-hydroxyl in glutamine synthetase. The complex ATase • P_{II}-uridylyl catalyzes phosphorolytic deadenylylation of glutamine synthetase. Glutamine synthetase is an enzyme involved in many functions. ▶glutamine synthetase, ▶glutamate dehydrogenase

UTE (untranslated exon): May play a role in alternative splicing of transcripts. ▶alternative splicing; Chen C et al 2002 Proc Natl Acad Sci USA 99:2930.

Uterine Cancer: Cancer of the uterus may be treated by anti-estrogens similarly to breast cancer. The response to tamoxifen is very limited, however. Cervical cancer usually does not respond to such treatment and surgery and radiation are used. ▶breast cancer

Uterus: The hollow female abdominal organ where the fertilized egg is embedded for the development of the embryo. The pear-shaped uterus (~5 × 7.5 cm in humans) is connected to the vagina through the narrow neck-like passage, the cervix, permitting the entry of the spermatozoa, to retain the conceptus and open to release the embryo at birth. The ovaries are connected to the uterus by the oviducts (see Fig. U13). The uterus is lined by endometrium that feeds the early embryo. Its outer layer is shed during menstruation and regenerated thereafter. When the blastocysts reach a state ready for implantation, the uterus becomes receptive under the influence of the ovarian steroid hormones—progesterone and oestrogen. Luteinizing hormone, secreted by the ovaries, is essential for ovulation and for the programming of progesterone and oestrogen. The duration of this oestrus cycle is about 4 days in mice and almost

a week in humans. ►gonads, ►ovary, ►blastocyst, ►oestrus, ►luteinizing hormone, ►fallopian tube, ►morsus diaboli, ►fertilization, ►embryogenesis in animals, ►menstruation, ►vagina, ►endometrium, ►tamoxifen, ►cervical cancer; Wang H, Dey SK 2006 Nature Rev Genet 7:185.

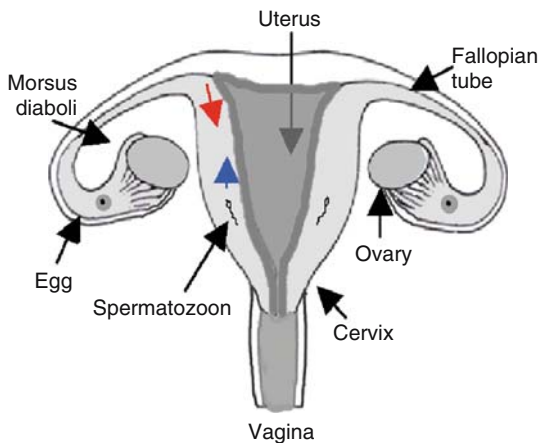


Figure U13. The abstract outline of the female reproductive tract; the red arrow indicates the path of the egg and the blue arrow indicates the direction of movement of the spermatozoa

Utility Index for Genetic Counseling: If the mother is heterozygous for a recessive disease allele d/D and other linked alleles (M_1/M_2), i.e., she is DM_1/dM_2 and the frequency of recombination between the two loci is r , half of her sons will be afflicted by the disease and $1-r$ frequency of M_2 sons is expected to express the disease (as long as penetrance and expressivity are high). A small r helps predictability. If her husband's genotype is DM_1 , among her M_1M_2 daughters $1-r$ will be a carrier of the recessive disease allele d but one must know for sure which of the codominant M alleles is syntenic with d . In the case of X linkage, for prediction on the basis of the M markers, the genetics counselor should know the genotype of the affected grandfather (dM_1 or dM_2). If the frequencies of the M_1 and M_2 markers is x_1 and x_2 , respectively and the grandfather is dM_2 , then the probability that the mother being informative for genetic counseling is $= 2x_1x_2$. Roychoudhury and Nei have described this as the *utility index of a polymorphic locus* for genetic counseling. If the grandfather has the recessive allele m and the grandmother is either MM or Mm , their heterozygous (Mm) daughter must have inherited the M allele maternally and the expected frequency of informative mothers is $(1-x)x$. In case both M and m grandfathers are considered, the utility index of the mother becomes: $(1-x^2)x$.

Genetic information about the mother can also be obtained from her children. In case the X-linked

disease gene deemed to be in coupling with another marker, the Bayesian probability for coupling is $(1-r)^2/[(1-r)^2 + r^2]$ and the probability for repulsion is $r^2/[(1-r)^2 + r^2]$ if the mother has already two afflicted sons. If the mother has both normal and afflicted sons: n_1 (DM_1), n_2 (DM_2), n_3 (dM_1) and n_4 (dM_2), the probability for coupling that she has 4 ($=n$) sons with the genotypes above is: $r^{n_2+n_3}(1-r)^{n_1+n_4}/2^n$; in case of repulsion the probability is: $r^{n_1+n_4}(1-r)^{n_2+n_3}/2^n$. The posterior probability that she is in coupling is $1/(1+\rho^\alpha)$ where $\rho = r/(1-r)$ and $\alpha = n_1 + n_4 - (n_2 + n_3)$, and in case $\alpha = 0$, the linked markers will not help in the prognosis. For repulsion, the probability is $1/(1+\rho^{-\alpha})$. The probability of the genotype of the next offspring depends on the tightness of linkage.

In the case of *autosomal dominant* disease in the presence of D , the disease is expected and both parents are informative. If the mother is M_1M_2 and the father is M_1M_1 and the recombination frequency between the M and the D loci is r , the probability that the offspring of M_1M_1 genotype will have D is $1-r$. DD homozygotes are very rare because their occurrence depends on the product of the frequency of the D gene, which is usually in the 10^{-5} range. In case there are multiple alleles at a locus, the total frequency of informative parents is

$$1 - \sum X_i^2 - (\sum X_i^2)^2 + \sum X_i^4.$$

In a mating of $(Dm/dM) \times (dM/dm)$, the offspring homozygous for m has a probability of $1-r$ to carry the dominant disease gene, D $1-r$ but the one with the dominant M phenotype is expected to be D at a frequency of $(1+r)/3$. If the affected parent D is heterozygous and the other parent is dd , the frequency of informative families is $2(1-x)x^4$. In case the mating is $(DdM_1M_2) \times (ddM_1M_2)$, the children are $n_1(DdM_1M_1)$, $n_2(DdM_1M_2)$, $n_3(ddM_1M_1)$ and $n_4(ddM_1M_2)$, respectively. The linkage phase can be estimated as discussed earlier for X linkage [coupling: $1/(1+\rho^\alpha)$, repulsion $1/(1+\rho^{-\alpha})$]. All children of parent DdM_1M_2 will be informative, except when the spouse is ddM_1M_2 and all the progeny will be heterozygous for the M locus but the probability that all children would be of such genetic constitution is $(0.5)^n$. The proportion of informative families when $n > 1$ is: $2x_1x_2(1 - 0.5^{n-1}x_1x_2)$. If there are multiple markers, the proportion of informative families (with x_i frequency of the i th allele) is:

$$2 \sum_{i < j} X_i X_j (1 - 0.5^{n-1} X_i X_j).$$

In the case of *autosomal recessive* diseases the calculation of the mathematical probabilities of informative families is more complex and biochemical or molecular (DNA) analyses are preferred.

►DNA fingerprinting, ►genetic counseling, ►counseling genetic, ►risk, ►paternity testing; Roychoudhury AK, Nei M 1988 Human Polymorphic Genes, Oxford University Press, New York.

UTP: Denotes uridine triphosphate (see Fig. U14).
►UDP

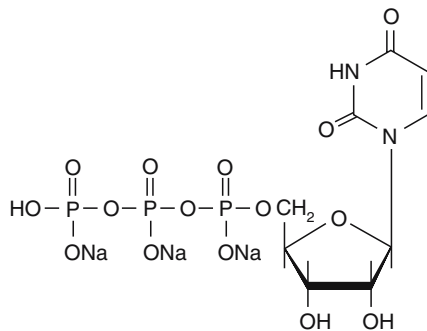


Figure U14. Uridine triphosphate

UTR: ►untranslated region

Utrophin: ►dystrophin (DRP2)

U-Unitig: ►scaffolds in genome sequencing, ►unitig

UV: ►ultraviolet light, ►cyclobutane dimers

Uvomorulin (UM): A transmembrane glycoprotein, also known as E-cadherin. ►cadherins

UvrABC: An endonuclease complex of uvrA, uvrB and uvrC and these enzymes are involved in the excision of ultraviolet light-induced pyrimidine dimers. After the dimer is recognized, cuts are made on both sides of the dimer and thus the damaged area of about 12 nucleotides is excised. ►DNA repair, ►ABC excinucleases, ►excision repair

UV Spectrophotometry of Proteins: Prepare a series of dilutions (20 to 3,000 µg/mL) from a pure 3 mg/mL standard bovine serum albumin (BSA). Make a blank and a series of dilutions of the sample to be tested. Determine UV absorption at 280 nm. BSA, 3 mg/mL is expected to have an absorption of 1.98. Calibrate the sample relative to the standard. In case the absorptivity of the protein to be tested is known use the formula for the calculations (a_{280} = the absorption in the units of mg/mL per centimeter path b).

$$\frac{O.D_{280}}{a_{280} \times b}$$

Historical vignettes

“The attainment...of fundamental knowledge is usually of the utmost immeasurable practical importance in the end”.

HJ Muller 1916, quoted by Elof Carlson
(30 years later [in 1946] Muller received the Nobel Prize)

Priority has been of important concern to authors from the early days of genetics. In his book “A History of Genetics” (Harper & Row, New York, 1965) AH Sturtevant writes on p. 27:

In a letter received and published by Roberts, de Vries later stated that he had worked out the Mendelian scheme for himself, and was then led to Mendel’s paper by reading Bailey’s copy of Focke’s reference. In 1954, nineteen years after the death of de Vries, his student and successor Stomps reported the de Vries had told him that he learned of Mendel’s work through receiving a reprint of the 1866 paper from Beijerinck, with a letter saying that he might be interested in it. This reprint is still in the Amsterdam laboratory, as has been stated.

V

V Gene: Codes for the variable region of the antibody molecule.

V or V_{\max} : The maximal velocity of the reaction when the enzyme is saturated with substrate.

v-mos: ► [Moloney mouse sarcoma](#)

v-Oncogene: ► [oncogenes](#)

V-point: The progression of the cell cycle beyond this point (≈ 6 h before the S phase) requires no insulin but only IGF-1. ► [cell cycle](#), ► [insulin](#), ► [insulin-like growth factor](#)

Vaccines: A suspension of killed or attenuated pathogens or recombinant protein or DNA or capsular polysaccharides conjugated to a carrier protein for generating an immune defense system. The most successful vaccines (measles, mumps, rubella) are composed of antigens generated against disease-causing microorganisms and injected into the blood-stream to stimulate the development of circulating or serum antibodies (immunoglobulin G). More recently efforts have been made to develop vaccines that activate mucosal immunity. Membranes of the body, covering the gastrointestinal tract, the air-intake organs and the reproductive system are covered with mucosa. The aim of this procedure is to trap infectious agents at the port of entry. The mucosa can develop sufficient quantities of immunoglobulin A. These new vaccines may be orally delivered and do not have to be injected. Dendritic cells, which are most active in antigen presentation, can be targeted by microparticles conjugated with monoclonal antibodies. These can then reach the lymph nodes and stimulate both cytotoxic T cells as well naïve T cells and the enhanced immune response is proven by increased interferon- γ secretion (Kwon YJ et al 2005 Proc Natl Acad Sci USA 102:18264).

Some vaccines use live microorganisms that have been genetically engineered by removal of part of their genome so that they do not cause the disease yet promote the production of IgA and some also IgG (see Fig. [V1](#)). Other approaches include the introduction of the genes of cytotoxic lymphocyte epitopes into the cells. The presence of CpG oligonucleotide motifs in the vector plasmid appears to enhance the immunogenicity of DNA vaccination in humans. Genetically engineered vaccines may be produced in transgenic plants as well and they may eventually be edible. After infection by the lymphocytic choriomeningitis virus, mice may clear the LCMV and gain

lifelong immunity to reinfection because the DNA containing LCMV sequences is transcribed in the animals represents a new type of DNA vaccination. Prophylactic vaccination against retroviral diseases is hampered by the apparent poor immune reaction against these agents. Bovine leukemia virus (BLV), which produces a relative paucity of variants that confound the cytotoxic T cells (CTL) can, however, be vaccinated successfully by using a viral glycoprotein, gp51 epitope. Several poxviruses, modified vaccinia virus, replication-defective adenovirus, etc., appear to boost the DNA vaccines' effectiveness for primed CD $^{+}$ T cells. Some adjuvants (alum, monophosphoryl lipidA, oil/water emulsion, etc.) have also revealed beneficial effects in some cases. A new approach to vaccination is the use of antibodies against cytokines that accumulate in inflamed or tumor tissues (Zagury D et al 2001 Proc Natl Acad Sci USA 98:8024). Synthetic polysaccharide antigen conjugated with protein (tetanus toxoid) yields an effective vaccine at an economically low cost (Verez-Bencomo V et al 2004 Science 305:522). The availability of completely sequenced genomes of viral and bacterial pathogens permits vaccine design by bioinformatics seeking out unique, potentially antigenic sequences without growing the target organisms. This approach is known as *reverse vaccinology* (Mora M et al 2003 Drug Discovery Today 10:459). The post-exposure prophylactic vaccines are administered after acute infections by tetanus, diphtheria and rabies. The latter type of vaccination follows a somewhat different logic than the prophylactic type (and it is somewhat controversial) yet its efficacy is corroborated by medical practice. The effectiveness of the vaccines may be boosted by the increase in CD4 and CD8 T lymphocyte activity and helps to reduce the proliferation of the pathogen (Autran B et al 2004 Science 305:205). When administered with various interleukins and other chemokines, their effectiveness may be enhanced. After successful vaccination, the T cell may clonally expand in 7–10 days and antigen-specific CD8 $^{+}$ T cells may increase 100,000-fold and differentiate into effector helper T (TH) cells and cytotoxic killer cells (NK). After the removal of the antigen the number of the antigen-specific cells contract (in 2–4 weeks) and a fraction of the T cells differentiate into memory cells for long-term protection. In germinal centers and plasma foci short-lived antibody cells and longer lasting memory B cells are formed. Once an antigen presenting dendritic cell locates an antigen-specific T cell by immunological synapse, various proteins (TCR-MHC, CD2, CD8 LFA-1, PKC, Lck, Fyn, CD4, CD45) are recruited within the central SMAC region and this further strengthens the immunological response. The number of T cells may be stimulated to increase 100 to

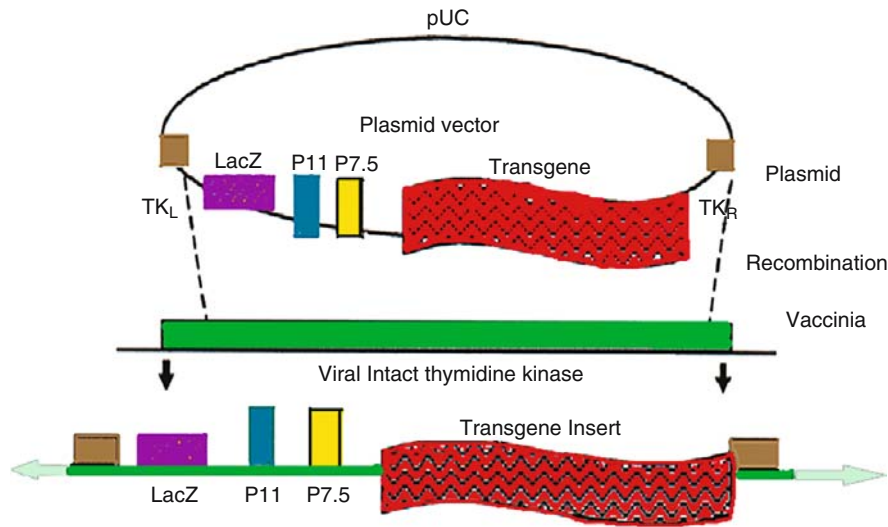


Figure V1. Construction of a recombinant vaccinia genome (LacZ bacterial reporter, P11 and P7.5 are promoters, TK: thymidine kinase fragments, pUC plasmid provides origin of replication and ampicillin resistance [β -lactamase])

1,000-fold within a few days. The innate immune system helps to direct the activated T cells to the sites of pathogen invasion. B1 B cells produce small amounts of immunoglobulin M (IgM) and immunoglobulin A (IgA) even in the absence of a specific antigen. High affinity B cells are produced by affinity maturation. These B cells may migrate to the plasma foci, induce strong germinal center responses and affinity maturation and probably generate long-life memory B cells. Antigen presenting cells may take up attenuated bacterial pathogens (*Listeria monocytogenes*), which do not replicate and are rapidly destroyed. After destroying them, the phagolysosomes release the antigens for endogenous processing and presentation and stimulate CD8⁺ effector T cells. The intracellular replication deficient vaccine strain is rapidly cleared from normal and immunocompromised animals but antigen-specific T cells are stimulated and the animals acquire resistance to the wild type bacteria in a directed manner (Bouwer HGA et al 2006 Proc Natl Acad Sci USA 103:5102).

Some vaccines are highly effective and long-lasting, but vaccination against many other infections demands substantial improvements (Pulendran B, Ahmed R 2006 Cell 124:849). [▶immune system](#), [▶immunization](#), [▶lymphocytes](#), [▶mucosal immunity](#), [▶CTL](#), [▶epitope](#), [▶immunization genetic](#), [▶peptide vaccine](#), [▶cancer prevention](#), [▶therapeutic vaccine](#), [▶plant vaccines](#), [▶subunit vaccine](#), [▶memory immunological](#), [▶TCR](#), [▶TLR](#), [▶PAMP](#), [▶PRR](#), [▶CD2](#), [▶CD4](#), [▶CD8](#), [▶CD45](#), [▶LFA](#), [▶PKC](#), [▶Lck](#), [▶Fyn](#), [▶immunoglobulins](#), [▶adjuvant immunological](#), [▶acquired immunity](#), [▶innate immunity](#), [▶tumor vaccination](#), [▶cytokines](#), [▶variola](#), [▶germinal](#)

[center](#), [▶SMAC](#), [▶immunological synapse](#), [▶Listeria](#); Nature Medicine 4(5), 1998 May supplement; Burton DR 2002 Nature Rev Immunol 2:706.

Vaccinia Virus: Closely related to small pox (variola) and cowpox viruses. It does not occur in nature and is found in the laboratory only where these two viruses are handled. Thus, it appears to have been somehow derived from variola and cowpox. Vaccinia vectors have been used to express antigens of unrelated pathogens (AIDS virus, hepatitis B) and employ them for immunization. The virus contains a DNA genome of about 190 kbp with nearly 260 potential open reading frames and around 200 bp telomeric sequences (see Fig. V2). These viruses direct replication and transcription in the cell cytoplasm by viral-encoded enzymes. Therefore, insertion of the viral genome by recombination is not a major threat. Vaccinia virus appears to be relatively safe yet periodically (every 10 years) laboratory workers should be vaccinated against it and the handling should be under containment level 2. Vaccinia virus with a deletion in the serpin gene and expressing IFN- γ replicated to high titer in vivo were avirulent in both immunocompetent and immunocompromised



Figure V2. Vaccinia virus of $\sim 360 \times 270 \times 250$ nm (Redrawn after Cyrklaff, M. et al. 2005 Proc. Natl. Acad. Sci. USA 102:2772)

animals, indicating its potential for the production of efficacious and safe vectors against smallpox and other diseases (Legrand FA et al 2005 Proc Natl Acad Sci USA 102:2940). Vaccinia vectors appear to be effective against some tumors and metastasis when injected directly into the neoplasia. Vaccinia virus infects productively the majority of mammalian and avian cells but the Chinese hamster ovary cells are not infected and the replication of the virus may not be completed in primary lymphocytes or macrophages. For infection, the virus requires the presence of the E3L vaccinia protein or a homolog of it. These proteins facilitate viral binding to Z-DNA. Vaccinia protein F11L interacts with RhoA and blocks downstream effectors and RhoA signaling is required for both vaccinia morphogenesis and virus-induced cell motility (Valderrama F et al 2006 Science 311:377).

Mouse antibody constructed from the Chimpanzee Fab domain completed with the human $\gamma 1$ heavy chain constant region provided an effective response to vaccinia virus B5 envelope protein. It protected mice from intranasal challenge against the virus even 2 days after exposure. The chimpanzee/human mAb provides effective prophylaxis and immunotherapy of smallpox (Chen Z et al 2006 Proc Natl Acad Sci USA 103:1882). ▶immunization, ▶immunotherapy, ▶Fab, ▶antibody, ▶Xgal, ▶ β -galactosidase, ▶bio-hazards, ▶serpins, ▶interferon, ▶Rho; Kim Y-G et al 2003 Proc Natl Acad Sci USA 100:6974, diagram of the genome redrawn after Chakrabarti S et al 1985 Mol Cell Biol 5:3403.

Vacuoles: These vesicles within plant and fungal cells are filled with various substances (nutrients, products of secondary metabolism, enzymes, crystals, solutes). Vacuoles may occupy minimal space in meristematic cells of plants whereas in older cells they occupy up to 90% of the cell inner volume. The elastic tonoplast membrane surrounds the vacuoles and permits a change in their size. They may regulate the osmotic pressure of the cytosol by releasing smaller molecules or polymerizing them as needed to maintain a constant value in the cytoplasm. Vacuoles also

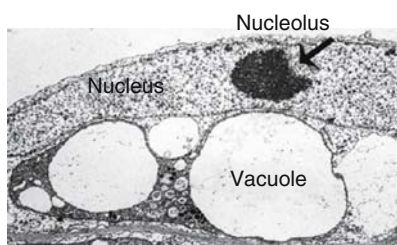


Figure V3. Large vacuoles in a plant cell (bottom) and an oblong nucleus with nucleolus (top)

regulate pH by a similar balancing action. They supply the cells with storage nutrients, hydrolytic enzymes, anthocyanin pigments, and in some cases various toxic substances such as tannins, phenolics and alkaloids. Vacuoles are inherited by the partition of the cytoplasm but if a particular cell becomes vacuole free its progeny may generate them de novo. ▶lysosomes, ▶cells, ▶membrane fusion; Klionsky DJ, Ohsumi Y 1999 Annu Rev Cell Dev Biol 15:1; Rojo E et al 2001 Developmental Cell 1:303; Weisman LS 2003 Annu Rev Genet 37:435.

Vagility: Refers to the ability of organisms to disperse in a natural habitat, it is thus a factor of speciation and survival.

Vagina: The female organ of copulation beginning at the vulva and extending to the cervix of the uterus. *Vaginismus* is an involuntary painful contraction of the vaginal muscles and may cause severe pain especially in intercourse. An autosomal recessive condition of vaginal atresia (absence of vagina) is known. In general, the term denotes an anatomical sheath. The vaginal epithelium may harbor several species of bacteria even under completely healthy conditions and without any symptoms; the most common of such bacteria are various lactobacilli (Hyman RW et al 2005 Proc Natl Acad Sci USA 102:7952). ▶clitoris, ▶fallopian tube, ▶ovary, ▶egg, ▶migraine, ▶uterus, ▶vulvovaginitis, ▶microbiome

Vaginal Plug: After successful copulation in mice, part of the male ejaculate forms a vaginal plug that closes the vagina for 16–24 hours and in some strains even for a few days. The presence of the plug reveals to the breeder the success of the mating. ▶mating plug

Valence (valency): The valence of an antibody indicates the number of antigen-binding sites. In chemistry, it indicates the number of covalent bonds an atom can form and it is also called oxidation number, e.g., O^{2-} or Na^{+} or Ca^{2+} .

Validation: Refers to the confirmation of experimental results or working hypotheses by repeated tests (proof of principle). It is the process of determining the degree to which a model is an accurate representation of real life facts. Validation is important as one depends increasingly on predictions by computer models. Validation of a target may be based on the expression of genes in the pathway, the use of microRNA or RNAi blocks or mutation or knockout in the system. ▶proof-of-concept; Benson JD et al 2006 Nature [Lond] 441:451.

Valine Biosynthesis: ▶isoleucine-valine biosynthetic pathway

Valinemia: ▶hypervalinemia

Valyl tRNA Synthetase (VARS): This is encoded in human chromosome 9. VARS charge tRNA^{Val} by the amino acid valine. ▶aminoacyl-tRNA synthetase

VAMOS (variability modulation system): Denotes the expression of *reactivity* of females, measured on the basis of the percentage of sterility in daughters in hybrid dysgenesis. Reactivity is modulated by various factors such as temperature, age of the females over generations and inhibitors of DNA synthesis and ionizing radiation. ▶hybrid dysgenesis

VAMP (vesicle associated membrane protein, synaptobrevin): This is a synaptic protein. ▶syntaxin, ▶synaptobrevin, ▶SNARE

Van Buchem Disease (17q11.2): A form of osteosclerosis. ▶sclerosteosis; Loots GG et al 2005 Genome Res 15:928.

Van der Waals Force: Refers to weak, short-range attraction between non-polar (hydrophobic) molecules.

Van der Woude Syndrome: A dominant, human chromosome 1q32-q41-located cleft lip and palate syndrome. ▶cleft palate, ▶harelip, ▶epithelial cell, ▶popliteal pterygium; Schutte BC et al 2000 Genome Res 10:81.

Van Gogh, Vincent (1853–1890): The famous Dutch painter may have suffered from intermittent porphyria and periods of deep depression (see Fig. V4). The beautiful *Starry Night* painting was attributed to a hallucinatory spell experienced during a bout of bipolar disorder and heavy drinking of absinth. The *Drosophila* gene named *vangogh* modulates the expression of *wingless*. The mammalian homolog

(*Vangl2*) of this *Drosophila* gene encodes a four-transmembrane PDZ protein, which along with *Scrb1* (scribble) regulates a signaling pathway involved in planar orientation of the epithelium and the stereocilia. ▶depression, ▶bipolar mood disorder, ▶PDZ, ▶stereocilia, ▶porphyria, ▶wingless; Montcouquiol M et al 2003 Nature [Lond] 423:173; <http://www.med.wayne.edu/elab/vangogh/MainIndex.htm>.

Vancomycin (C₆₆H₇₅Cl₂N₉O₂₄): An extremely potent glycopeptide antibiotic effective against gram-positive bacteria by blocking the cross-linking of adjacent peptidoglycan strands by peptide bonds in bacterial cell wall synthesis (see Fig. V5). It also inhibits transglycosylation, which connects the existing glycan strands. In recent years *Streptococcus pneumoniae*, responsible for pneumonia, bacterial meningitis and ear infection, as well as several *Enterococcus* species have acquired tolerance or resistance to this antibiotic. Vancomycin tolerance is due to mutation in the Vancomycin signal transduction sensor kinase (VncS). Upon autophosphorylation in the presence of ATP, VncS-P is generated. As a consequence the Vancomycin sensor regulator (VncR) is phosphorylated to VncR-P and the defense genes (resistance to the infection) of the cells are turned off. In Vancomycin (and some other antibiotic) sensitive strains VncS dephosphorylates VncR. The efficacy of Vancomycin as an antibiotic is due to its binding to the D-Ala—D-Ala moiety of the bacterial peptidoglycan precursors and thereby hindering growth of the cell wall. In the resistant strains, the dipeptide is replaced by the depsipeptide D-Ala—D-Lac reducing sensitivity to the antibiotic by three orders of magnitude. (Depsipeptide is a member of the bicyclic peptide class of histone deacetylase [HDAC] inhibitors that was first isolated as a fermentation product from *Chromobacterium violaceum*). The level of resistance depends on the number of peptidoglycan precursor molecules that carry this replacement. Vancomycin resistance may be overcome by chlorobiphenyl vancomycin derivatives, which interact with penicillin-binding protein-1 (PBP1b) although they do not bind the enzyme (Chen L et al 2003 Proc Natl Acad Sci USA 100:5658). IfD-Ala—D-Lac is selectively disrupted by small molecules (prolinol derivatives) (see Fig. V6) sensitivity to Vancomycin is restored. Reengineering Vancomycin for dual D-Ala-D-Ala and D-Ala-D-Lac binding can effectively counter resistance of the bacteria (Crowley BM, Boger DL 2006 J Am Chem Soc 128:2885). A neoglycosylation procedure increases efficacy 40-fold (Griffith BR et al 2007 J Am Chem Soc 129:150). ▶antibiotics, ▶tolerance of antibiotics, ▶antibiotic resistance, ▶non-ribosomal peptide; Chiosis G, Boneca IG 2001 Science 293:1484; Eggert US et al 2001 Science 294:361; Reynolds AM et al 1996 J Infect 32:11.



Figure V4. Sorrowful Old Man (Van Gogh, 1890). Reproduced with permission of the Kröller-Müller Museum, Otterlo, The Netherlands

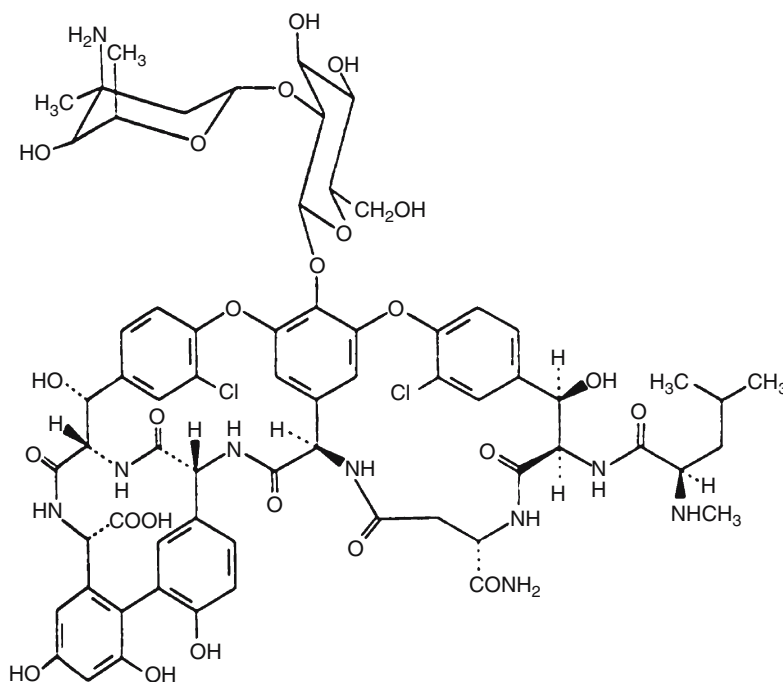


Figure V5. Vancomycin

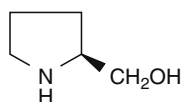


Figure V6. L-Prolinol [(S)-(+)-2-pyrrolidinemethanol]

Vanilla (*Vanilla planifolia*): This is a tropical spice tree;
 $2n = 2x = 32$.

Vanillin ($C_8H_8O_3$): A flavoring agent and an analytical reagent. It is an antimutagen, anticlastogen, anticarcinogen and an inhibitor of non-homologous end-joining and DNA-PK. ▶clastogen, ▶NHEJ, ▶DNA-PK; Durant S, Karran P 2003 Nucleic Acids Res 31:5501.

Váradi-Papp Syndrome: ▶orofacial-digital syndrome V

Variability: Denotes the condition of being able or apt to vary.

Variable: A condition or treatment that may be replaced by the experimenter or that may change during the study. The pre-analytical variables are known or unknown factors that may be present before or arise during the analysis. In clinical studies the pre-analytical variables may contribute to serious errors in the evaluation. In experimental research the variables may be under more stringent control than in observational studies.

Variable Number Tandem Repeats: ▶VNTR

Variable Regions: These regions of the antibody are situated at the amino end of both light and heavy chains, and this region determines antibody specificity and antigen binding. ▶immunoglobulins, ▶antibody

Variable Surface Glycoprotein: ▶Trypanosoma

Variance: The mean of the squared deviations of the variates from the mean of the variates:

$$V = \sum [(x - \bar{x})^2] / n - 1 \quad \text{where } x \text{ are the variates and } \bar{x} \text{ is the mean of the variates and } n \text{ is the number of variates (individuals).}$$

▶variate, ▶invariance, ▶standard deviation, ▶standard error, ▶analysis of variance, ▶intraclass correlation, ▶genetic variance

Variance Analysis: ▶analysis of variance

Variant: Refers to a cell or individual different from the standard type.

Variant Detector Array (VDA): Uses oligonucleotide labeled probes to locate/identify particular genes in microarrays. ▶microarray hybridization, ▶oligo-labeling probes

Variate: A variable quantity measured in a sample of a population.

Variation: Can be *continuous* and individual measurements do not fall into discrete classes, e.g., traits determined by polygenic systems. In the case of *discontinuous* variation the measurements can be classified into distinct classes such as the qualitative traits (black and white [no gray]) in a segregating population (see Fig. V7). ▶variance, ▶genetic variance, ▶continuous variation, ▶discontinuous variation, ▶SNIP; Crawford DC et al 2005 Annu Rev Genomics Hum Genet 6:287.

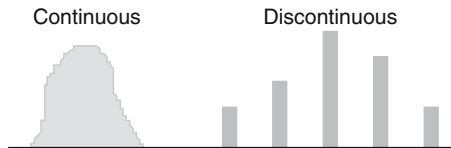


Figure V7. Variation

Variation, Mathematical: This is illustrated by an example. How can a cell express 3 different receptors of a pool of 10 receptors? The solution is $\frac{10 \times 9 \times 8}{1 \times 2 \times 3} = 120$. ▶combination

Varicella-Zoster Virus: This member of the Herpes virus family causes chickenpox and shingles. Vaccination effectively reduces mortality due to chickenpox but its effect on shingles is still unknown. The Oka vaccine strain is a live attenuated virus that is routinely administered to about 40 million children in the United States and Europe to prevent chickenpox. It is effective and safe but occasionally produces a rash. The vaccine virus has accumulated mutations at more than 30 loci during its attenuation and after administration, but the rashes are not explained by their reversion, unlike complications reported in the case of other viral vaccines. The host genotype and immune status also affect the extent of response to the vaccine (Quinlivan ML et al 2007 Proc Natl Acad Sci USA 104:208). Insulin degrading enzyme (IDE) is a cellular receptor of the virus and mediates cell-to-cell spread (Li Q et al 2006 Cell 127:305). ▶herpes, ▶shingles, ▶chickenpox

Variegation: Refers to sector formation or mosaicism of the somatic cells due a number of different mechanisms such as nondisjunction, somatic mutation, segregation of organelles (chloroplasts) deletion and disease (see Figs. V8 and V9). Heterochromatin may cause variegation of genes in its close vicinity by transient modulation of the exposure of the DNA to transcription factors. In *Drosophila* more than 15 genes act as suppressors of variegation (*Su[va]*). ▶uniparental inheritance, ▶lyonization, ▶broken tulip, ▶transposable elements, ▶position effect, ▶piebaldism, ▶spotting, ▶mitotic recombination,

▶nondisjunction, ▶developmental-regulator effect variegation, ▶heterochromatin; Ahmad K, Henikoff S 2001 Cell 104:839; Sjiv IS et al 2007 Nature [Lond] 447:399.

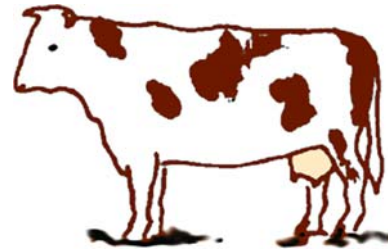


Figure V8. Mosaicism in cattle

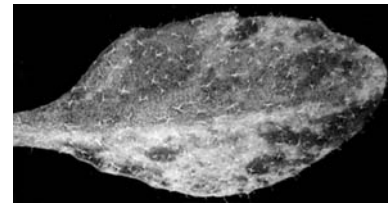


Figure V9. Variegation in a plant leaf

Variety: Refers to an organism of a distinct form or function. ▶cultivar, ▶cultigen

Variogram: A plot of genetic distance relative to geographic distance. ▶genetic distance

Variola: This is the technical term for smallpox virus, pox virus, vaccinia and biological weapons.

Variolation: The earliest form of vaccination known at least by the sixth century. Infective material from the smallpox lesions was transferred to healthy individuals to provide resistance against the disease with an expectation of not more than ~4% fatality versus 20–30% from natural infection. ▶vaccine, ▶pox virus

Varkud Plasmid: ▶*Neurospora* mitochondrial plasmids

Vas Deferens: An excretory channel of the testis connected to the ejaculatory duct of the sperm. ▶CBAVD, ▶P2X

Vascular Cell Adhesion Molecule (VCAM): ▶metastasis

Vascular Diseases: ▶cardiovascular diseases

Vascular Endothelial Growth Factors (VEGF): These are required for vasculogenesis and are particularly active in some tumor tissues to provide the necessary blood supply for proliferation. VEGFs depend on their appropriate (VEGFRs) integrin cell adhesion receptors (De S 2005 Proc Natl Acad Sci USA 102:7589). The receptor (VEGFR2) is a tyrosine kinase. In human

primary lymphedema (Milroy disease) VEGFR-3 tyrosine kinase activity is deficient. Mouse mutants with a defect in receptor-3 of VEGF die of cardiovascular failure (9.5 d) before birth. VEGF has been considered as a potential benefit in case heart disease damages the blood vessels. The peptide QK binding to the interface of VEGF receptor can induce endothelial cell proliferation and blood capillary formation. Therefore, QK has biomedical (therapeutic and diagnostic) potential (D'Andrea LD et al 2005 Proc Natl Acad Sci USA 102:14215). VEGF can also cause vascular permeability and the accumulation of fibrin barrier around tumors and wounds. The leakage can reduce metastasis of tumors and can induce obstruction and necrosis of blood vessels (infarction). VEGF not only promotes tumor growth and reduces metastasis, but it may also facilitate atherosclerosis (Weis SM & Cheresh DA 2005 Nature [Lond] 437:497). The endocrine-gland-derived endothelial growth factor (EG-VEGF) is selectively expressed only in the ovary and other steroid-producing tissues (testis, adrenal and placental tissues). ▶angiogenesis, ▶Flk-1, ▶Flt-1, ▶neuropilin, ▶tyrosine kinase, ▶VEGF, ▶polyposis hamartomatous, ▶KDR, ▶Peg-3, ▶angiopoietin, ▶atherosclerosis, ▶hypoxia, ▶wound healing, ▶lymphedema, ▶phospholipase, ▶macular degeneration; Ferrara N 1999 J Mol Med 77:527; Bellamy WT et al 1999 Cancer Res 59:728; LeCouter J et al 2001 Nature [Lond] 412:877; Niethammer AG et al 2002 Nature Med 8:1369; <http://www.researchvgef.com>.

Vascular Targeting: For the development and maintenance of tumors, an ample supply of blood is a requisite. The monoclonal antibody to bFGF and VEGF may block the required angiogenesis factors. Similarly, integrins (CD51/CD61) are also required for angiogenesis and they can be interfered with by their cognate monoclonal antibodies. Anti-endoglin antibody, especially with conjugated ricin, may lead to anti-tumor effects. ▶angiogenesis, ▶angiostatin, ▶endostatin, ▶ADEPT, ▶VEGF, ▶FGF, ▶integrin, ▶endoglin

Vascular Tissue: In plants, this includes the xylem, the phloem, the (pro)cambium and the surrounding fibrous parenchyma. In animals the blood vessels are the primary vascular tissue. ▶phloem, ▶xylem, ▶cambium, ▶parenchyma, ▶proteoglycan

Vascularization: Refers to the development of veins and other vessels. ▶vasculogenesis

Vasculogenesis: Refers to the differentiation of mesodermal cells into hemangioblasts. ▶hemangioblast, ▶blood formation, ▶angiogenesis, ▶CXCR

Vasculopathy: Vascular retinopathy, cerebretinal vasculopathy, endotheliopathy with retinopathy, nephropathy and stroke all map to 3p21.1-p21.3.

The abnormalities of the vascular system cause Raynaud's disease, migraine, retinal vein impairment, visual disease, renal disease, neurological problems and possibly premature death. ▶Raynaud's disease; Ophoff RA et al 2001 Am J Hum Genet 69:447.

Vasectomy: The surgical removal of the vas deferens (ductus deferens), the excretory channel of the semen. It is a method of fertility control for males. ▶birth control drugs; Sandlow J et al 2001 Fertil Steril 75:544; Weiske WH 2001 Andrologia 33:125.

Vasodilator: Causes expansion of (blood) vessels.

Vasopressin: ▶antidiuretic hormone, ▶oxytocin (see Fig. V10)

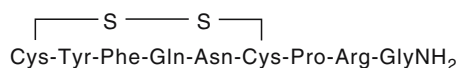


Figure V10. Human vasopressin

VASP: A profilin-binding protein. ▶profilin

VAT: Denotes variant antigen type. ▶Trypanosoma

V-ATPases: These are vascular ATPases in control of ionic homeostasis. ▶APPase, ▶homeostasis

Vaults: These are large (42 × 75 nm, 12.9 MDa) predominantly cytoplasmic ribonuclein particles present across phylogenetic ranges. The mammalian vaults include the vault poly(A)DP-ribose polymerase, telomerase associated protein 1 and one or more non-translated RNAs (Poderycki MJ et al 2005 Nucleic Acids Res 33:893). Vaults are involved in detoxification and many cellular and developmental processes (Gopinath SCB et al 2005 Nucleic Acids Res 33:4874). (See Stephen AG et al 2001 J Biol Chem 276:23217).

Vav Oncogene: Found in human chromosome 19p13.2-p12, and appears to be GDP→GTP exchange factor requiring tyrosine phosphorylation. It regulates lymphocyte development and activation. ▶oncogenes, ▶B lymphocytes, ▶T cell receptor

vBNS (very high-speed Backbone Network Service): This is a computer network linking five supercomputer centers to facilitate fast scientific communication and remote control by the use of special equipment.

vCJD: A variant of the Creutzfeldt-Jakob disease, a possible contagious form of the mad cow disease; it infects humans as well, especially those homozygous for codon 129 methionine of the prion. ▶Creutzfeldt-Jakob disease, ▶encephalopathies, ▶prion

VCP (vasoline containing protein): Involved in lipid metabolism. ▶T cell receptor

V(D)J (variable[diversity]junction): Sequences in immunoglobulins where antibody diversity is generated by recombination at the RSS (recombinational signal sequence) sites. Several factors are important for V(D)J recombination: DNA-dependent protein kinase, Artemis, CRCC4 and ligase IV. The recombination may show tissue/organ specificity. ►immunoglobulins, ►T cell receptor, ►RSS, ►RAG, ►Artemis, ►DNA-PK, ►CRCC, ►ligase DNA, ►non-homologous end-joining; Gellert M 1992 Annu Rev Genet 26:425; Gellert M 1997 Adv Immunol 64:39; Bassing CH et al 2002 Cell 109:S45; Dai Y et al 2003 Proc Natl Acad Sci USA 100:2462; Xiong N et al 2004 Proc Natl Acad Sci USA 101:260.

VDR (vitamin D3 receptors): Receptors that control homeostasis, growth and differentiation. They preferentially bind to response elements of direct repeats, palindromes and inverted palindromes of hexameric core-binding domains, particularly well when they are spaced by three nucleotides. They can dimerize with 3,5,3'-triiodothyronine, a thyroid hormone receptor that can direct sensitivity of ligands for transactivation. ►vitamin D, ►transactivator, ►hormone response elements

Vector: Generally an insect or other organism transmitting parasites and/or pathogens. It also refers to any gene carrier derived from plasmids, viruses or produced synthetically such as liposomes or polyethylene particle driven by motor proteins along the microtubules. ►vectors, ►vectorette, ►vector cassette, ►liposome; Suh J et al 2003 Proc Natl Acad Sci USA 100:3878.

Vector, Algebraic: ►matrix algebra

Vector Cassette: A transformation construct carrying all essential elements (including reporter genes, selectable marker, replicator, etc.), and it can be used for the insertion of different DNA sequences. ►vectors, ►reporter gene, ►transformation, ►knockout, ►targeting genes

Vectorette: A short DNA sequence serving as a specific linker-primer for PCR amplification. It generally contains an inner, non-complementary sequence (bubble), flanked by two short pieces of duplex DNA (see Fig. V11). The 5' end may be either blunt or complementary to a restriction site, depending on the restriction enzyme used to digest the DNA. An overhang may prevent ligation of the 3' end. ►polymerase chain reaction, ►amplification, ►linker, ►primer, ►ligase, ►blunt end, ►overhang, ►restriction enzyme, ►splinkerette; Eggert H et al 1998 Genetics 149:1427; Devon RS et al 1995 Nucleic Acids Res 23:1644.

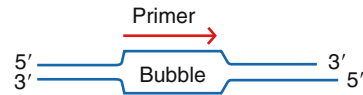


Figure V11. Vectorette

Vectors: These molecular genetic constructs are generally circular plasmids that can introduce exogenous genetic material into prokaryotic and eukaryotic cells. They may be *cloning vectors* that only replicate the DNA according to the plasmid replicon. The *expression vectors* carry genes complete with all the elements required for expression (promoter, structural gene, termination signals, etc.). *Gene fusion vectors* do not have promoters and the expression of the transferred gene is contingent on fusion with a host cell promoter. *Shuttle vectors* can carry the DNA among different hosts (such as *E. coli* and COS cells, *Agrobacterium* and plants). All vectors must have at least a replicator site, selectable marker(s) and mechanisms for the introduction of parts of their sequences into the host genetic material. ►cloning vectors, ►cosmids, ►phagemids, ►fosmids, ►ColE1, ►plasmovirus, ►yeast vectors, ►viral vectors, ►excision vectors, ►plasmids, ►transposable elements, ►NOMAD, ►BAC, ►BIBAC, ►YAC, ►HAC, ►PAC, ►transcriptional gene fusion vector, ►translational gene fusion vector, ►targeting vector, ►polyethyleneimine, ►pBR322, ►pUC vectors, ►transposon vector, ►liposomes, ►nanoparticles, ►cancer gene therapy, ►RetroTet-Art vector, ►polyplexes; vector database: <http://seq.yeastgenome.org/vectordb/>.

Vectors for Pathogens: See human pathogen vectors: <http://www.vectorbase.org/>.

VEGA (vertebrate genome annotation): A central depository for manual annotation of different vertebrate (human, mouse zebrafish) finished genome sequences. ►annotation of the genome; <http://vega.sanger.ac.uk/index.html>.

Vegetal Pole: Refers to the lower end of the animal egg where the yolk is concentrated. The opposite end of the egg is known as the animal pole. After fertilization the yolk moves to the central position and becomes the starting site of the differentiation of axes (anterior-posterior, dorsal-ventral, median-lateral) of the embryo. ►morphogenesis *Drosophila*, ►pole cell

Vegetative Cell: Involved in metabolism but not in sexual reproduction. ►gametogenesis in plants

Vegetative Hybrids: ►graft hybrids

Vegetative Incompatibility: ►fungal incompatibility

Vegetative Nucleus (macronucleus): ▶*Paramecium*,
▶tube nucleus

Vegetative Petite: ▶petite colony mutants

Vegetative Reproduction: Commonly observed in many species of plants (grafting, rooting) and lower organisms that use fission for propagation. The advantage of this type of reproduction is that the progeny forms a genetically homogeneous clone unless or until mutation takes place. ▶somatic embryogenesis, ▶grafting, ▶regeneration, ▶clone, ▶tissue culture

Vegetative State: Denotes asexual, unconscious, non-replicating, non-infectious, etc., depending on the context.

VEGF: Smooth muscle cells synthesize vascular endothelial growth factor, which is somewhat related to PDGF. The VEGF genes are divided among eight exons and by alternative splicing three different proteins are produced. It may enhance the growth of new blood vessels. FLT-1 is one of the VEGF receptors. ▶signal transduction, ▶PDGF, ▶vascular endothelial growth factor, ▶neuropilin, ▶angiopoietin, ▶vascular targeting

Vehicle: ▶vectors

Velans: ▶*gaudens*

Velocardiofacial Syndrome (VCFS): A heart and face, kidney, parathyroid and thymus defect caused by deletion in human chromosome 22q11. The gene most commonly affected is UFD1-l (ubiquitin fusion degradation; 22q11.2). ▶DiGeorge syndrome, ▶face/heart defects, ▶claudin, ▶tight junction, ▶schizophrenia, ▶deletion 22q11.2

VENA (plural venae, adj. venous): A vein that carries blood towards the heart.

Veneering of Antibody: Refers to the generation of a humanized antibody where some of the surface regions of the mouse antibody framework are replaced by human sequences in order to reduce immunogenicity. ▶antibody, ▶humanized antibody

Venn Diagrams: Data are represented by circles or ovals according to their common features, overlapping functions or exclusion (see Fig. V12). The three circles generate seven ($2^3 - 1$) areas that may be shaded or otherwise marked. Such diagrams may represent interactions of proteins or interactions among environmental effects.

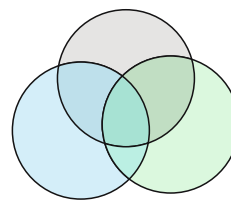


Figure V12. Venn diagram

Venom: A (highly) toxic secretion of some serpents and insects. Some types of venoms have medical applications, e.g., for hemostasis. ▶hemostasis, ▶mast cells; toxin database: <http://ntrc.tamuk.edu/cgi-bin/serpentarium/snake.query>.

Venous Malformation (VM): This is caused by mutation at loci 1p21-p22 and 9p21. VM can occur in any tissue but is most common in the skin and muscle; it causes pain and bleeding, and even death at times.

Vent: A DNA polymerase extracted from *Thermococcus litoralis*. ▶recursive PCR

Ventral (from the Latin venter meaning abdomen): This is related to the position on the side opposite to the back.

Ventricular: An adjective that means belonging to a ventriculus (a cavity such as in the heart).

Venture: Variable number repeating elements (40 to >150) of 14–15 nucleotides, rich in guanine. The shorter VENTR alleles are associated with susceptibility to insulin-dependent diabetes mellitus (IDDM) but one of the long repeats ($14 \times 50 = 700$ nucleotides) appears to be protective against IDDM. ▶diabetes mellitus, ▶imprinting, ▶VNTR

Venules: These are small vessels that collect blood from the capillary veins.

Venus: A yellow derivative (YFP) of the green fluorescent protein (GFP). ▶aequorin

Venus Mirror: ▶pedigree, ▶female (see Fig. V13)



Figure V13. Venus mirror

Vermiculite: A commercial silicate medium to grow plants under greenhouse conditions.

Vermilion Eye Color of Insects: This is controlled by the *v* locus of *Drosophila* encoding tryptophan pyrrolase, an enzyme that converts tryptophan to formylkynurenin. The recessive vermilion eye color is actually bright scarlet because the brown ommochrome is not formed. The *v* eye discs when transplanted into normal tissues develop wild-type eye color. ►animal pigments, ►ommochromes, ►tryptophan

Vernalization: Some biannual or winter annual species of plants have a low temperature requirement for the induction and completion of the bolting and flowering stage of development. This need can be satisfied in spring planting by exposing the germinating seeds to near freezing temperatures for a genetically determined and variable period. It is also known as yarowization (in Russian yarowie kchleba means spring cereal). In *Arabidopsis*, the *FLC* is one of the loci to repress vernalization response. The other vernalization gene *FRIGIDA* (*FRI*) has been cloned. *VRN2* is a nuclear zinc finger protein that mediates the level of *FLC*. The *VRN/VIN* proteins deacetylate methylated histones H3K27me and H3K9me during vernalization-induced epigenetic silencing of the *FLC* (Mylne JS et al 2006 Proc Natl Acad Sci USA 103:5012). The *LHP1* (like heterochromatin protein) also assists in the maintenance of epigenetic silencing of the *FLC*. The *VRN1* gene of the A genome of wheat has also been cloned (Yan L et al 2003 Proc Natl Acad Sci USA 100:6263). Vernalization in cereals is controlled by MADS box transcription factors (Trevaskis B et al 2003 Proc Natl Acad Sci USA 100:13099). Apparently, low temperature and other gene products modulate the level of its transcript supposedly by demethylation of specific DNA sites. ►photoperiodism, ►photomorphogenesis, ►floral induction, ►histones; Reeves PH, Coupland G 2001 Plant Physiol 126:1085; Gendall AR et al 2001 Cell 107:525; Macknight R et al 2002 Plant Cell 14:877; Sung S, Amasino RM 2004 Nature [Lond] 426:159; Bastow R et al 2004 Nature [Lond] 426:164; Henderson IR et al 2003 Annu Rev Genet 37:371; molecular mechanisms: Sung S, Amasino RM 2005 Annu Rev Plant Biol 56:491.

Versenes (EDTA): These widely used laboratory chelating agents may cause chromosome breakage at higher concentrations (see Fig. V14). ►EDTA

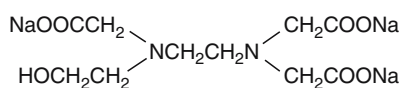


Figure V14. EDTA

Vertebrates: These are animals with a spinal column (chordates) such as fishes, amphibians, reptiles, birds and mammals. (See VEGA for genomes vertebrate browser: <http://genome.ucsc.edu/>; <http://vega.sanger.ac.uk/index.html>).

Vertex (plural: vertices; node): ►networks

Vertical Resistance: The host plant is resistant to a specific race of the pathogenic microorganism.

Vertical Transmission: ►transmission

Very Low Density Lipoprotein: ►VLDL

Vesicles: These are membrane-surrounded sacs in the cell, generally performing storage and transport functions.

Vesicular Stomatitis Virus (VSV): A negative-strand RNA virus of 11,161 nucleotides, enclosed by a nucleocapsid (N). N is a 35-turn helix within the membrane-surrounded oval particles. There is a transmembrane G protein on the surface of the virion for binding cell surface receptors, required for infection. VSV viruses can be engineered into useful genetic vectors. An oncolytic variant is involved in antitumor activity and at the same time establishes an antiviral state that protects against toxicity in healthy cells (Bell JC et al 2002 Curr Gene Ther 2:243). ►CO₂ sensitivity, ►viral vectors, ►lentiviruses

Veterinary Medicine: ►databases; <http://netvet.wustl.edu/vetmed/health.htm>.

Veto Cell: This recognizes T cells and inactivates them. ►immune suppression; Reich-Zeliger S et al 2000 Immunity 13:507.

Vg-1: A protein that sends signals in animals to develop head and other nearby organs.

VG5Q: 4,049 bp DNA tract (chromosome 5) with a 2,145 ORF encoding 714 amino acids responsible for susceptibility to the Kippel-Trenauney syndrome. ►ORF, ►Kippel-Trenauney syndrome

VHL: ►von Hippel-Lindau syndrome

Viability: Refers to the ability to survive; this is a property of organisms depending on genetic, developmental and environmental factors. A normal human fetus may become viable outside the womb after its weight reaches about 500 g and around 20 weeks after gestation. The viability of a mutant is often expressed as the survival rate relative to the wild type.

Vibrio cholerae: Cause of cholera (see Fig. V15). The toxin is encoded in a filamentous phage (CTX φ) and the same extracellular protein secretion pathway that facilitates the horizontal spread of the phage, releases it. The integration of this virus requires host recombinase XerC and XerD. It takes place at a 28 bp



Figure V15. Diagram of *Vibrio cholerae*

site (*difI*) in bacterium chromosome 1. The single-stranded phage genome forms a hairpin structure and thus creates a recombination site for XerCD. XerC mediates a single pair of strand exchanges and integration at *difI* (Val M-E et al 2005 Mol Cell 19:559). *Vibrio* contains two chromosomes ($\sim 2.9 \times 10^6$ and $\sim 1.1 \times 10^6$ bp) encoding 2770 and 1115 ORF, respectively (see Fig. V16). The major virulence factor, CT and the toxin-coregulated, TCP are in the longer chromosome. The bacterium also contains a pathogenicity island (VPI) which apparently does not have a viral origin. The integron island involved in gene integration and dissemination is in the smaller chromosome. Chitin, present in the natural aquatic environment of the pathogen due to the shedding of crustacean exoskeleton, induces natural competence for transformation (Meibom KL et al 2005 Science 310:1824). Virstatin inhibits the expression of cholera toxin and the toxin coregulated pilus of the bacterium and protects mice from intestinal colonization (see Fig. V17) (Hung DT et al 2005 Science 310:670). Several members of the *Vibrios* are pathogenic and their genomes have been sequenced (Ruby EB et al 2005 Proc Natl Acad Sci USA 102:3004). ▶[cholera toxin](#); Heidelberg J et al 2000 Nature [Lond] 406:477; transcriptome: Xu Q et al 2003 Proc Natl Acad Sci USA 100:1286.

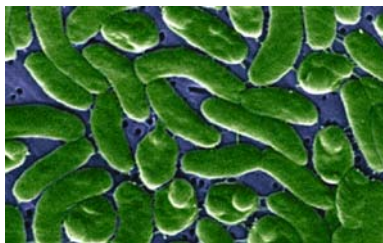


Figure V16. *Vibrio vulnificus*, saltwater parasite (Courtesy of CDC Public Health Image Library)

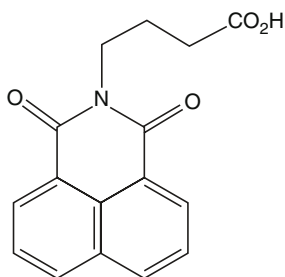


Figure V17. Virstatin

Vicariance: The occurrence of a species in a habitat other than expected or a function not expected by an organ.

Vicia faba: ▶[broad bean](#), $2x = 2n = 12$; its large chromosomes are well suited for cytological study. With the exception of the two largest chromosomes, the rest are acrocentric (see Fig. V18) (Courtesy of Dr. A. Sparrow). ▶[favism](#), ▶[vicin](#)



Figure V18. *Vicia faba*

Vicine: An alkaloid produced by *Vicia sativa* (vetch) may be the source of this cyanoalanine toxin which is especially hazardous for people and animals on a low sulphur diet. ▶[favism](#)

VIGS (virus induced gene silencing): Infecting viruses may silence the host plant genes as well as transgenes in plants may silence viral genes by the mechanism of RNAi. ▶[RNAi](#); Fagard M, Vaucheret H 2000 Plant Mol Biol 43:285; Voinnet O 2005 Nature Rev Genet 6:206.

Villus: Refers to vesicular projections on a membrane (see Fig. V19). The amniotic villi, near the end of the umbilical cord, are sampled for genetic examination during prenatal amniocentesis. The intestinal villi facilitate food absorption and their structure may be affected by intestinal cancer. ▶[amniocentesis](#)



Figure V19. Intestinal villi with blood vessels inside

Vimentin: A constituent of the filament network extending through the cytoplasm of eukaryotic cells. ▶[intermediate filaments](#), ▶[aggresome](#); Perez-Martinez C et al 2001 J Comp Pathol 124:70; Mor-Vaknin N et al 2003 Nature Cell Biol 5:59.

Vinblastine and Vincristine: These are antineoplastic alkaloids (interfere with microtubules and the cytoskeleton) from the shrub *Vinca rosea*. (See Fig. V20, ►microtubule, ►cytoskeleton; Gigant B et al 2005 Nature [Lond] 435:519).



Figure V20. *Vinca rosea*

Vinculin: A protein binding α -actinin, talin, paxillin, tensin, actin filaments and phospholipids; it also mediates the assembly of the cytoskeleton. (See mentioned items under separate entries, ►adhesion; Kálmán M, Szabó A 2001 Exp Brain Res 139:426; crystal structure of human vinculin: Borgon RA et al 2004 Structure 12:1189).

Violent Behavior: In humans, impulsive aggression has been attributed to reduced levels of 5-hydroxyindole-3-acetic acid in the cerebrospinal fluid and a nonsense mutation in MAOA enzyme results in aggressive behavior in a kindred. ►MAOA, ►behavior in humans

VIP16: A herpes simplex virus-encoded protein; it is a potent activator that controls the transcription of immediate early viral genes through interaction with the host cell factors. It is used for studies of molecular interaction with promoters and transcription factors.

VIR Genes: ►virulence genes *Agrobacterium*

VirA: Denotes agrobacterial kinase phosphorylating the product of virulence gene *VirG*.

Viral Budding: ►budding

Viral Cancer: ►cancer, ►oncogene

Viral Capsid: ►capsid; <http://viperd.b.scripps.edu/>.

Viral Encephalitis: Caused by neurotropic flaviviruses such as the Japanese encephalitis virus and the West Nile virus. Targeting a common domain of the envelope protein by short hairpin or RNAi delivered to the brain of mice by lentiviral vector secured complete protection against the disease (Kumar P et al

2006 PLoS Med 3(4):e96). ►RNAi, ►West Nile virus, ►lentiviruses

Viral Envelope: A protein-lipid coat of viruses. ►virus

Viral Ghost: Refers to empty viral capsids, without their own genetic material but they can be filled with DNA and become a genetic vector. ►transformation genetic, ►generalized transduction

Viral Oncogene: ►v-oncogene

Viral Vectors: These are *in vitro* genetically modified viral DNA (e.g., adenovirus, SV40, bovine papilloma, Epstein-Barr, BK viruses and Baculovirus [Polyhedrosis] virus), containing non-viral genes to be introduced into eukaryotic cells. A minimal viral vector contains only the replicational origin of the virus and the packaging signals but the other viral genes involving replication, virion structure and pathogenicity sites are removed. The removed viral DNA or RNA is replaced by a cassette of transgenes required for experimental purposes. *Autonomous stable viral vectors* have also been constructed that replicate in the cytoplasm. In order to prevent destruction of the cells, their copy number is limited by introducing copy number regulators. From the *bovine papilloma virus* (BPV) autonomous (episomal) and shuttle vectors have been constructed that maintain low (10–30) copies in the cytoplasm. The *shuttle vectors* can be rescued from the mammalian cells and can propagate various protein genes in another cell depending on a number of intrinsic and extrinsic factors. The *Epstein—Barr virus* (EBV) vector can be propagated in the cytoplasm of various types of mammalian cells at low copy number (2–4) and is suitable for the study of gene expression, regulatory proteins, etc. It can also be maintained in the nucleus of, e.g., B lymphocytes. The vector has up to 35 kb carrying capacity and can be rescued. The *BK* (baby kidney) *virus* has been advantageously used for human cells. Truncated retroviral HIV vectors (may not be able to recombine and reconstitute pathogenic forms) may be useful because they can be introduced into non-dividing cells. Lentivirus vectors can also pass into non-dividing cells such as hepatocytes, hematopoietic stem cells and neurons, in contrast to the most widely used mouse leukemia retrovirus (MuLV) vectors, which require DNA replication for integration. For human applications, *replication-deficient retroviral* vectors can accommodate 9 kb exogenous DNA and they are generally used in *ex vivo* studies. *Adenovirus vector* can carry 7.5 kb DNA and can be taken up by the cell, by a specific virus receptor and the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ surface integrins. The adenoviral, herpes simplex, vaccinia and the autonomous parvovirus vectors are not integrated into the human genome and therefore do not lead to permanent genetic change

and the treatment has to be reapplied periodically (in weeks or months). The *adeno-associated virus* can integrate into the chromosomes in dividing cells but it is episomal in stationary stage cells. Most of the current vectors may cause inflammation because of antivector cellular immunity. The *Baculovirus (Polyhedrosis) virus* is used as a vector for insect cells. The targeting of viral vectors to specific tissues can be increased by genetically engineering into the envelope protein a special receptor for a target ligand, e.g., inserting erythropoietin into the Moloney murine leukemia retrovirus or adding an integrin sequence to the avian retrovirus envelope. The vesicular stomatitis virus (VSV) and the gibbon ape leukemia retrovirus (GALV) offer some target specificity but they form only 10^7 to 10^9 cell forming units (CFU)/mL and therefore all the target cells of the body cannot be reached. In order to target the vector to particular cell type the envelope protein of the virus must be so modified that it would recognize the target cell membrane receptor. In order to pass the membrane and move into the cell, the envelope protein—receptor complex must undergo a conformational change. The modified envelope protein, however, may not form an effective complex resulting in very low level of passing of the vector into the target cell. New technology (ligands specific for fibronectin and collagen of the cell matrix) may facilitate the enrichment of the vector in the extracellular matrix of the host cell facilitating a more effective uptake. *Non-viral vector*, organically modified silica (ORMOSIL) after appropriate treatment can bind the DNA and effectively deliver it to neural stem cells of the brain (Bharali DJ et al 2005 Proc Natl Acad Sci USA 102:11539). ▶virus, ▶vectors genetic, ▶parvoviruses, ▶vaccinia virus, ▶retroviral vectors, ▶Bellophage, ▶shuttle vector, ▶HIV, ▶lenti-viruses, ▶episomal vector, ▶adenovirus, ▶adeno-associated virus, ▶herpes, ▶plasmid rescue, ▶gene therapy, ▶erythropoietin, ▶ex vivo, ▶microinjection, ▶biolistic transformation, ▶liposomes, ▶transfection, ▶transformation genetic, ▶packaging cell line, ▶bio-hazards, ▶laboratory safety, ▶self-deleting vector, ▶packaging cell lines; Pfeifer A, Verma IM 2001, pp 353. In: Knipe DM, Howley PM (Eds.) *Fundamental Virology*. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania; Porcellini A Blasi AD 2004 *Methods Mol Biol* 259:155; <http://www.brc.riken.jp/lab/dna/rvd/>.

Viremia: Refers to viruses in the blood.

Virgin: Refers to an individual who has not been mated or has not had prior sexual intercourse. In *Drosophila* the females can store the sperm received during prior mating and, therefore, the paternal identity can be determined only if virgin females are used.

Virgin T Cell: ▶immune response

Virile: An adjective for having the characteristics of an (adult) male, masculine.

Virino Hypothesis: This suggests that prions are caused by small nucleic acid-containing agents. ▶prion; Dickinson AG, Outram GW 1988 Ciba Found Symp, London 135:63.

Virion: A complete virus particle (coat and genetic material).

Virion RNA: Refers to cytomegalovirus/herpes virus encoded transcripts which are packaged within the virion and delivered to the host cell to assure their immediate expression after infection.

Virioplasm (virus factory): An intercellular compartment associated with the replication of some viruses.

Viroceptors: These are parts of the viral attack mechanisms directed against the host immune system. They mimic the cell receptors and tie up cytokines and chemokines that are destined to stimulate the immune defense and weaken the antibody production. ▶anti-body, ▶immune system, ▶interferons; Upton C et al 1991 *Virology* 184:370.

Viroid: A non-encapsidated RNA (ca. 1.2×10^5 daltons) which is capable of autonomous replication and (plant) pathogenesis, such as the potato spindle tuber viroid. Viroids are single-stranded, circular or linear RNA molecules with extensive intramolecular complementarity. These agents are localized in the nuclei of plants and do not seem to occur in animals although it was earlier assumed that prions were viroids. They are probably the smallest nucleic acid agents causing infectious diseases. (See Elena SF et al 2001 *J Mol Evol* 53(2):155; Rezaian MA 1999 *Curr Issues Mol Biol* 1:13; viruses and virions: <http://www.ncbi.nlm.nih.gov/genomes/VIRUSES/viruses.html>; <http://www.dpvweb.net/>).

Virosomes: These are liposomes with associated viral proteins and are expected to be used as vehicles for gene therapy. ▶liposome; Yomemitsu Y et al 1997 *Gene Ther* 4:631.

Virtual: This has the same properties as the real but it is not real; it is an imaginary concept. ▶digital gene, ▶genetics digital

Virtual Reality Training: Medical students learn surgery on three-dimensional models rather than on patients.

Virulence: Determines or indicates the infectivity or pathogenicity of an organism. It has recently been discovered that several bacterial species of different structure and functions acquired a shared

mechanism for virulence. About 15–20 protein genes with relatively low G-C contents (below 40%) are assembled in a “pathogenicity island” of either the bacterial chromosome or in a plasmid. These genes encode the molecular machinery (Type III virulence) to produce and transmit the bacterial toxins to their target. Inflammatory responses of the host fight *Shigella* bacteria. The O antigen on the surface of the lipopolysaccharide coat protects the bacteria. Glycosylation of this antigen enhances type III secretion, aids the injection of the toxin and contributes to serotype divergence (West NP et al 2005 Science 307:1313). In *Salmonella* species a 65–100 kb plasmid carries the genes required for systemic infection. A *Yersinia* effector protein (Yopj), a cysteine protease, specifically blocks the host signal transduction system at MAPKK. Yopj-related proteins occur in other bacterial pathogens of animals and plants. ►neurovirulence, ►signal transduction, ►avirulence, ►SAR, ►host-pathogen relations, ►pathogenicity island, ►secretion systems, ►*Shigella*, ►*Yersinia*; Mahan MJ et al 2000 Annu Rev Genet 34:139; Cotter PA, DiRita VJ 2000 Annu Rev Microbiol 54:519; bacterial virulence factor database: <http://www.mgc.ac.cn/VFs/>.

Virulence Genes of *Agrobacterium*: The Ti plasmid carries—in an about 35 kb DNA—major (*A*, *B*, *C*, *D*, *E*) and minor (*F*, *H*) virulence genes that mediate the process of infection and T-DNA transfer. The *VirA* gene codes for a single protein that is a transmembrane receptor. Its N-terminal periplasmic region responds to sugars and pH whereas the periplasmic loop between the two membrane layers responds to phenolic compounds (e.g., acetosyringone, secreted by the wounded plant tissues). This substance plays an important role in the induction of the cascade of all *Vir* genes although *VirA* itself is constitutive yet it is modulated by several factors. The C-terminus of *VirA* protein is autophosphorylated. *VirG* also codes for a single protein, a transcriptional regulator. For expression, it requires phosphorylation by *VirA*. *VirG* regulates by feedback the phosphate metabolism, mediated by *VirA*, and these two genes together are involved in conjugational transfer. The *VirB* operon encoding 11 proteins is also a conjugational mediator. The *VirB* complex is assembled at the cell pole and has an essential role in targeting the plant cell. *VirB7* to *VirB10* are minimally required for the formation of the pole *VirB* complex (Judd PK et al 2005 Proc Natl Acad Sci USA 102:11498). *VirB1* is a lysozyme-like protein. *VirB4* serves as a docking protein, along with other proteins, for strand transfer during infection (Middleton R et al 2005 Proc Natl Acad Sci USA 102:1685). *VirC* determines the host range and the C1 protein binds to the *overdrive* repeats near the right border of some octopine plasmids. The *VirD*

genes are responsible for four polypeptides. *VirD1* is a topoisomerase, *VirD2* is an endonuclease; in addition, this locus codes for a binding protein and a pilot protein guiding the T-DNA to the plant chromosome. *VirD2* interacts with the TATA box-binding protein and a nuclear protein kinase of plants (Bakó L et al 2003 Proc Natl Acad Sci USA 100:10108). *VirD4*, *VirB4* and *VirB11* also perform an ATPase function. *VirE2* codes for a binding protein, which coats the T-strand, mediates the transfer of single strand DNA into the plant nucleus (Zupan JR et al 1996 Proc Natl Acad Sci USA 93:2392). For stable transformation, viral protein 1 (VIP1) interacts with host cell H2A histone (Li J et al 2005 Proc Natl Acad Sci USA 102:57330). *VirF* probably encodes an extracellular protein that regulates *Vir* functions. *VirH* product may metabolize plant phenolics. Nopaline plasmids contain the gene *tzs* (trans-zeatin secretion) and *pin* (plant inducible) *F* loci. The chromosomal virulence loci (*ChvA*, *ChvB*, *Chv*, *pse*) are involved in the production of bacterial surface polysaccharides. Chromosomal genes *cbg*, *pgl*, when present, may enhance virulence. A single-stranded T-DNA complexed with proteins is transferred to the plant cells. Plant proteins are also involved in the transformation process (Tzfira T, Citovsky V 2002 Trends Cell Biol 12:121). ►*Agrobacterium*, ►Ti plasmid, ►T-DNA, ►overdrive, ►transformation genetic, ►crown gall, ►CRAFT, ►MPF; Winans SC et al 1999, p. 289. In: Kaper JB, Hacker J (Eds.) Pathogenicity Islands and Other Mobile Virulence Elements. Amer Soc Microbiol Washington, DC; Dumas F et al 2001 Proc Natl Acad Sci USA 98:485; Christie PJ et al 2005 Annu Rev Microbiol 59:451.

Virulent: In general, this is the poisonous form of prokaryotes. The virulent bacteriophages do not have the prophage life style and after reproduction they destroy the host bacteria by lysis. ►prophage, ►lysis

Virus: This is a small particle containing either double- or single-stranded DNA or RNA as genetic material. A generalized structure is diagrammed here; the architecture of viruses shows great variations from icosahedral to filamentous forms (see Fig. V21).

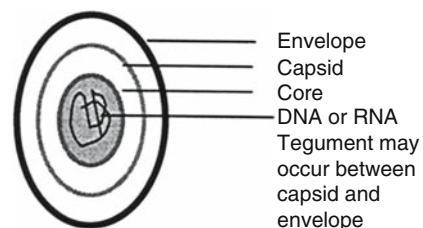


Figure V21. Generalized diagram of a viral structure

Viruses are the ultimate parasites because they lack any element of the metabolic machinery and are totally dependent on the host for assistance to express their genes. They are generally so small in size (15–200 nm) that light microscopy cannot reveal them, except the pox viruses which may be up to 450 nm in length. There are about 1,500 virus species. Bacterial, animal and plant viruses exist. The majority of plant viruses have single-stranded RNA genetic material but a few have double-stranded DNA, e.g., CaMO. Viruses have attracted new interest in nanotechnology as biological platforms, as vehicles for delivery into cells, for encapsulation of organic and inorganic molecules, etc. (Douglas T, Young M 2006 *Science* 312:873). ► **animal viruses**, ► **herpes**, ► **acquired immunodeficiency**, ► **plant viruses**, ► **bacteriophages**, ► **oncogenic viruses**, ► **retroviruses**, ► **cauliflower mosaic virus**, ► **mimivirus**, ► **TMV**, ► **nanotechnology**; Whittaker GR et al 2000 *Annu Rev Cell Dev Biol* 16: 627; for a chronology of virology: see Oldstone MBA, Levine AJ 2000 *Cell* 100:139; Sharp PM 2002 *Cell* 108:305; Virus Particle Explorer: <http://viperdb.scripps.edu/>; virus genome and protein sequence bioinformatics: <http://athena.bioc.uvic.ca/>; viral genomes: <http://gibv.genes.nig.ac.jp/>; <http://www.ncbi.nlm.nih.gov/genomes/VIRUSES/viruses.html>; http://www.biochem.ucl.ac.uk/bsm/virus_database/VIDA.html; plant viruses and viroids: <http://www.dpvweb.net/>.

Virus, Computer: A deliberately generated destructive program that can be spread through borrowed computer disks as well as network services. The damage to the files can be usually prevented by the use of continuously updated virus monitoring and eliminating programs.

Virus Hybrid: When the 2b gene of cucumber mosaic RNA virus is replaced by its homolog of tomato, virulence of the interspecific hybrid virus increases. ► **vaccinia virus**

Virus Morphology: ► **development**, ► **T4**, ► **lambda phage**, ► **retroviruses**

Virus Receptors: These are cell surface proteins that mediate viral entry into the host cell. The proteins can be cell adhesion molecules (CXCR4, CD4, dystroglycan, integrins, ICAM, major histocompatibility antigens, etc.), extracellular matrix proteins (heparan sulfate glycoaminoglycan, sialic acid derivatives) and complement control proteins (CD46, CD55), aminopeptidase-N, lipoprotein receptors, coxsackie virus and adenoviral receptors (CAR1), etc. Some receptors may serve several different viruses and some viruses can take advantage of more than one type of receptor. Single amino acid replacements in

the receptor either abolish or facilitate the uptake of the virus. (See Baranowski E et al 2001 *Science* 292:1102; Bomsel M, Alfsen A 2003 *Nature Rev Mol Cell Biol* 4:57).

Virus Reconstitution: ► **reconstituted virus**

Virus Resistance: The Fv and Rfv genes of mouse provide resistance against mouse leukemia (Friend virus) by encoding a retroviral envelope protein or the viral gag (group specific antigen). In the latter case the Fv gene product blocks the entry of the virus into the nucleus or these proteins may exercise a dominant negative effect on the virus that happens to be there. Introducing into the plant genome tobacco mosaic virus coat protein genes restricts the virulence of the virus in normally susceptible plants. ► **CRISPR**

Virus Transport to the Cell Nucleus: This is mediated by GAG matrix associated protein (MA) and the VPR gene product in the case of HIV. MA includes a nuclear localization sequence (NSL) and a signal targeting the cell membrane. When the NLS is phosphorylated, the MA becomes part of the pre-integration complex. Further phosphorylation detaches the MA from the membrane. ► **acquired immunodeficiency**, ► **nuclear localization sequence**; Bell P et al 2001 *J Virol* 75:7683.

Virus-Free Plants: Plants regenerated under axenic conditions from apical meristems are generally free of virus disease until they are reinfected. Plants so obtained are commercially useful for the production of virus-free seed stocks. Antisense RNA constructs may render plants virus resistant. (See Hammond J, Kamo KK 1995 *Mol Plant Microbe Interact* 8:674).

Virus-like Particles (VLP): These are artificial constructs of a viral protein capsid enclosing a core particle passenger. Such protein cage structures have shown increasing promise as therapeutic and diagnostic vectors, imaging agents, and as templates and microreactors for advanced nanomaterials synthesis. This type of biomimetic self-organization can combine the natural characteristics of virus capsids with the exquisite physical properties of nanoparticles. The principle challenges for nanoparticle delivery include limited lifetime in body fluids, nanoparticle transduction across the cellular membrane, avoidance of the exocytotic pathways and target specificity. A gold core functionalized with a coating of carboxylated polyethylene glycol (PEG) can allow efficient assembly of VLPs (Sun J et al 2007 *Proc Natl Acad Sci USA* 104:1354).

Virusoid: 300–400 nucleotide long RNAs, pathogenic to plants and accompany other plant viruses. ► **viroid**

Viscosity: The internal friction of fluids expressed as dyne-seconds/cm² called poise unit. ▶stoke, ▶dyne

Visfatin: A cytokine secreted by adipocytes that mimics the effects of insulin. ▶adipocyte, ▶insulin; Fukuhara A et al 2005 Science 307:426; this paper has been retracted. (Science 318: 565 [2007]).

Visible Mutation: Can be identified by the phenotype seen.

Vision: ▶rhodopsin

Vista: A visualization tool for alignment; also a computer program.

Vital Genes: ▶lethal mutation

Vital Stain: Colors living cells without serious damage to viability.

Vital Statistics: Pertains to birth, marriage and death registrations. Such information may assist in constructing human pedigrees and provide important facts about family histories, congenital and hereditary disease, longevity, etc.

Vitalism: A theory of the nineteenth century and earlier, which postulates that living beings are controlled not only by physical and chemical mechanisms, but life is also associated with a transcendental vital force. However, there still remain phenomena like the development of an embryo or regeneration from single cells that cannot be fully explained in physico-chemical terms although vitalism is no longer a viable idea since Friedrich Wöhler synthesized urea in 1828 from inorganic ingredients. (See Hein H 1972 J Hist Biol 5:159).

Vitamin A: Also known as retinol, it is synthesized from carotenoids. Its deficiency results in visual and skin anomalies (see Fig. V22). However, excessive amounts may be harmful. With the aid of three transformation vectors the β -carotene pathway has been introduced into the carotenoid-free rice endosperm enabling the production of provitamin A and correcting the deficiency in the diet. ▶retinol, ▶retinal

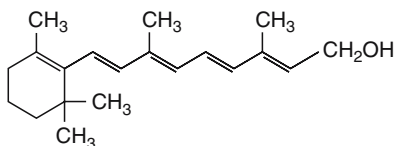


Figure V22. Vitamin A (all trans retinol)

Vitamin B₁: ▶thiamin (see Fig. V23)

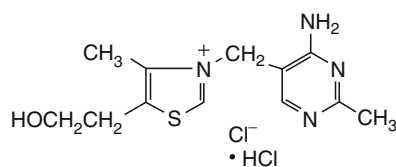


Figure V23. Vitamin B₁

Vitamin B₂: ▶riboflavin, ▶riboflavin retention deficiency

Vitamin B₆: ▶pyridoxine

Vitamin B Complex: Includes thiamin, riboflavin, nicotinic acid (amide), pantothenic acid, pyridoxin and vitamin B₁₂.

Vitamin B₁₂ Defects: Vitamin B₁₂ or its coenzyme form has a MW of about 1,355. It is composed of a core ring with Cobalt (Co³⁺) at its center and to it, through isopropanol, a dimethyl benzimidazole ribonucleotide is joined; it also contains a 5'-deoxyadenosine. It is usually isolated as a cyanocobalamin because during the process of purification a cyano group may be attached to the cobalt at the place where the 5'-deoxyadenosyl group is positioned in the coenzyme. B₁₂ is not synthesized in plants and animals

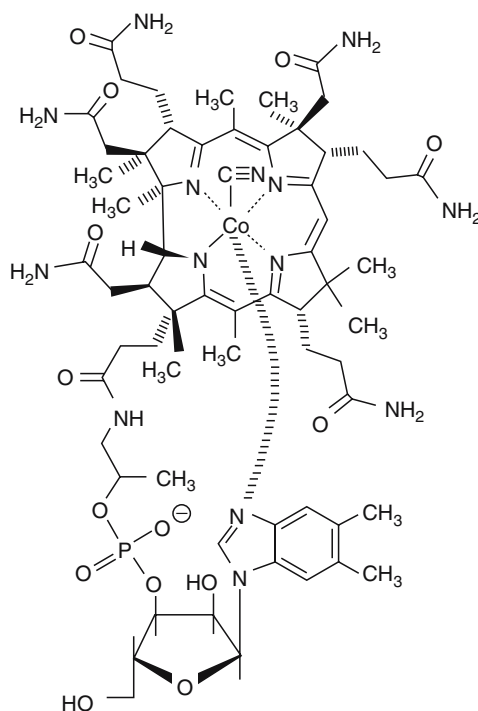


Figure V24. Vitamin B₁₂

and is not usually present in the diet. Intestinal microorganisms produce it from the meat consumed and it is absorbed when the so-called “intrinsic factor,” a glycoprotein, is available in satisfactory amounts. If the intake is less than 3 µg/day, pernicious anemia develops in humans (see Fig. V24). Autosomal recessive mutation may prevent the release of the lysosomally stored vitamin and B₁₂ deficiency may result. Cysteinurias is often called cobalamin F (cbl F) disease. In methylmalonicacidemia combined with homocystinuria, methylmalonyl-CoA mutase and homocysteine methyl-tetrahydrofolate methyltransferase (cbl C) deficiencies are involved. ►methylmalonicaciduria, ►cysteinuria, ►amino acid metabolism, ►cobalamin; Banerjee R, Ragsdale SW 2003 *Annu Rev Biochem* 72:209.

Vitamin C: ►ascorbic acid, formula given here (see Fig. V25)

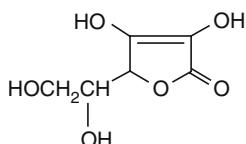


Figure V25. Vitamin C

Vitamin D: An antirachitic, fat soluble vitamin, whose deficiency leads to rickets and defects in bone development and maintenance. Vitamin D² (ergocalciferol) (see Fig. V26) is formed upon irradiation of ergosterol and vitamin D³ (cholecalciferol) from 7-dehydro-cholesterol. Children need about 20 µg/day in their diet. Autosomal recessive human defects in vitamin D receptors (12q12-q14) do not respond favorably to vitamin D fortified diet. Several cancer cells are inhibited by vitamin D³ and it may induce apoptosis. The use of a sunscreen may reduce the amount of vitamin D below a desirable level. ►Williams syndrome, ►VDR, ►hormone-response

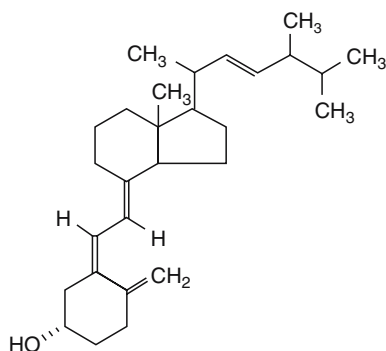


Figure V26. Ergocalciferol

elements; McGuire TF et al 2001 *J Biol Chem* 276:26365; formula.

Vitamin E (tocopherols): Vitamin E is an antioxidant (in several different forms) normally present in satisfactory amounts in a balanced diet (see Fig. V27). Transgenic plants expressing homogentisic acid geranylgeranyl transferase display increased amounts of vitamin E and antioxidant ability (Cahoon EB et al 2003 *Nature Biotechnol* 21:1082). In an autosomal recessive condition vitamin E malabsorption has been observed, causing intestinal and nervous anomalies and accumulation of cholesterol. The severe symptoms could be alleviated by 400–1,200 international units (IU) of vitamin E. It appears that the affected individuals lack an α-tocopherol binding protein, required to build it into very low-density lipoproteins. In a transgenic mouse model vitamin E reduced chromosomal damage and hepatic tumors. The familial vitamin E deficiency is under autosomal recessive control in humans. Doses of 400 IU may be very harmful. ►tocopherols, ►VLDL, ►atherosclerosis; Azzi A et al 2002 *FEBS Lett* 519:8.

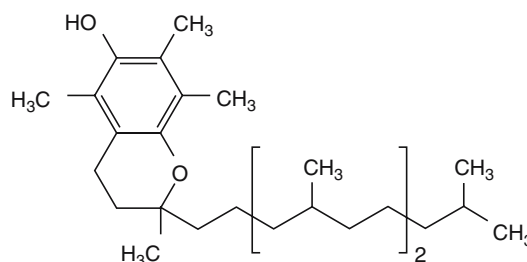


Figure V27. Tocopherol

Vitamin K (phylloquinone): A plant lipid cofactor of blood coagulation (vitamin K₁) and a related substance, menaquinone (vitamin K₂) is synthesized by intestinal bacteria of animals; the synthetic menadione (vitamin K₃) also has some vitamin K activity. The name K was derived from the Danish word koagulation. ►vitamin K-dependent blood clotting factors

Vitamin K-Dependent Blood Clotting Factors: Some autosomal recessive bleeding diseases respond favorably to the administration of vitamin K (see Fig. V28). It is required for post-translational modification of at least six proteins involving the conversion of the NH₂-end of glutamic acid into γ-carboxyglutamic acid. Deficiency of this process may occur as a consequence of treatment by coumarin drugs—such as warfarin—used as anticoagulants. A vitamin K-dependent blood coagulation factor is encoded at 2p12 and its mutation is caused by vitamin K-dependent carboxylase (GGCX) in the microsomes

of the liver and includes bleeding disease. Similarly, vitamin K 2,3-epoxide reductase (VKOR) mutations (16p12-q21) in a transmembrane protein of the endoplasmic reticulum lead to familial bleeding. ►prothrombin deficiency, ►resistance to coumarin-like drugs, ►antihemophilic factors, ►warfarin, ►γ-glutamyl carboxylase, vitamin K-dependent blood clotting factors; Li T et al 2004 Nature [Lond] 427:541.

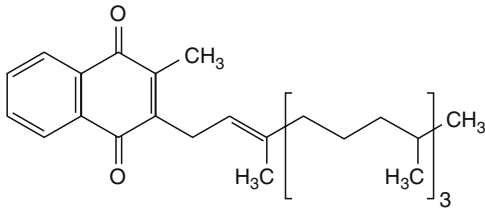


Figure V28. Vitamin K

Vitamins: These are dietary supplements, without measurable caloric value. They serve the role of coenzymes. Widespread dietary supplements can cause selective accumulation of vitamin deficient genotypes in human populations (Lucock M, Yates Z 2005 Nature Rev Genet 6:235).

Vitelline Layer: A yolk (heavier) layer around the eggs.
In mammals it is (a thinner) zona pellucida. ►egg

Vitellogenin: Refers to yolk protein. In honeybees the amount of yolk protein is proportional to longevity because it protects from oxidative stress. ► **longevity**, ► **oxidative stress**; Seehuus A-C et al 2006 Proc Natl Acad Sci USA 103:962.

Vitiligo: Dominant (1p31.3-p32.2) halo skin spots (may be identical on opposite sides of the body) present after birth that may spread or regress. Apparently, loci in several autosomes are also involved in susceptibility. It is an autoimmune disease with an incidence of ~1%. ▶[piebaldism](#), ▶[nevus](#), ▶[skin diseases](#); Alkhatteeb A et al 2002 Hum Mol Genet 11:661; Fain PR et al 2003 Am J Hum Genet 72:1560.

Vitrification: A procedure of protecting sensitive biological material (enzymes, seeds) from deterioration by coating with sugar mixtures (e.g., sucrose and raffinose) which, however, readily dissolve when needed. Vitrification literally means the formation of a glass-like structure. Human oocytes can be preserved in an appropriate vitrification medium and frozen in liquid nitrogen. ►[cryopreservation](#); Yokota Y et al 2001 Steril Fertil 75:1027.

Vitronectin (S protein): A fluid phase protein in the cell binding the C5b-9 complement component which

prevents its attachment to the membrane and thus interferes with lytic activity. ► [complement](#); Tomasini BR, Mosher DF 1991 *Progr Hemost Thromb* 10:269; Seger D et al 2001 *J Biol Chem* 276:16998.

Vivipary: Refers to giving birth to live offspring. In plants the seed germinates before shedding from the fruits. This phenomenon is genetically controlled through abscisic acid metabolism. ► [ABA](#); Paek NC et al 1998 Mol Cell 8(3):336; Jones HD et al 2000 Plant J 21:133.

V(J)D Recombinase: Assembles immunoglobulins and T cell receptors. The activity of this enzyme is facilitated by histone acetylation. ▶immunoglobulins, ▶T cell receptors, ▶antibody gene switching, ▶RSS, ▶accessibility, ▶SCID, ▶ligase, ▶RAG, ▶histone acetyltransferase; Fugmann SD et al 2000 Annu Rev Immunol 18:945; Gellert M 2002 Annu Rev Biochem 71:101; Jung D, Alt FW 2004 Cell 116:299.

VLDL (very low density lipoprotein): This is the 55 nm precursor of LDL and triglycerides. Its core contains cholesteryl ester. In muscle capillaries and adipose tissues the VLDL-triglycerides are removed and exchanges take place with other lipoproteins resulting in the loss of proteins except apolipoprotein B-100 and a smaller (22 nm) particle size. It is now called LDL (low-density lipoprotein). The VLDLR receptor gene (9p24) is very similar to the LDLR but it contains an additional exon. ►low-density lipoproteins, ►familial hypercholesterolemia, ►sitosterolemia, ►sterol, ►Alzheimer's disease, ►hypertension, ►apolipoproteins; Merkel M et al 2001 Proc Natl Acad Sci USA 98:13294.

VLP: A virus-like particle, such as some transposable elements (retroposons). ▶Ty, ▶retroposons

V_{\max} : The maximal level of enzyme activity (maximal velocity reaction).

v-mil: ►MIL, ►MYC

vMIP: ►herpes virus, ►chemokines

VNC: Refers to viable but non-cultivable microbial cells. They may be transgenic (genetically modified) and they may be protected by nucleic acids.

VNO: ► vomeronasal organ, ► olfactogenetics

VNTR (variable number tandem repeats): Loci are used in forensic DNA fingerprinting. These repeats may display hundreds of alleles per single locus and are extremely polymorphic in restriction fragments. They are useful as physical markers for mapping. Also, because matching patterns occur by a chance of 10^{-7} to 10^{-8} only, they are well suited for criminal, personal

and legal identification on the basis of minute amounts of DNA extracted from drops of body fluids, blood or semen. VNTR can also be used for taxonomic and evolutionary studies of animals and plants. ▶DNA fingerprinting, ▶diabetes mellitus, ▶MVR, ▶MLVA, ▶trinucleotide repeats, ▶SSM; Le Stunff C et al 2001 Nature Genet 29:96.

Vogt-Spielmeyer Disease: This is also known as Batten disease. ▶ceroid lipofuscinosis

Volatility: Refers to the proportion of point mutations that encodes a different amino acid. The arginine codon CGA has eight potential ancestor codons, i.e., non-stop codons that differ from CGA by one point mutation. Four of the potential ancestor codons of CGA encode another amino acid. Thus, the volatility is 4/8. If the selection pressure for a particular protein is high, the demand for amino acid replacement increases. ▶selection pressure; Plotkin JB et al 2004 Nature [Lond] 428:942.

Vole: *Microtus agrestis*, 2n = 50; *Microtus arvalis*, 2n = 46; *Microtus montanus*, 2n = 24.

Volicitin: ▶biological control

Volt (V): The unit of electric potential. In case the resistance is 1 Ω (Ohm = 1 V/A = 1 m² kg sec⁻³ A⁻²) and the electric current is 1 ampere, the voltage is 1. ▶ampere, ▶watt

Voltage-Gated Ion Channels: These channels are opened/closed for the transport of ions in response to a change in voltage across cell membranes. ▶ion channels, ▶signal transduction

Volunteer: This plant sprouts from the seed shed on the field and appears after the regular harvest season. The farmer does not plant it.

Vomer nasal Organ (VNO): This is a pair of chemosensory organs at the base of the nasal cavity in the majority of higher animals, except birds and some monkeys and apes (humans). VNO is stimulated by pheromones. MHC class I peptides act as chemosensory signals to the sensory neurons (Leinders-Zufall T et al 2004 Science 306:1033). The signaling through GTP-binding proteins requires 1,4,5-trisphosphate rather than cAMP. In humans, pheromones play either no role or only a subordinate role and the VNOs are apparently non-functional. Apparently, the vision-based signaling-sensory mechanism has replaced the chemical-based system in the social/reproductive activities of hominoids and Old World monkeys (Zhang J, Webb DM 2003 Proc Natl Acad Sci USA 100:8337). In mouse 187 and in rat 102 V1R genes have been identified but in dogs only 8, cows 32 genes and in the marsupial opossum 49 function (Grus WE

et al 2005 Proc Natl Acad Sci USA 102:5767). ▶olfactogenetics, ▶phosphoinositides, ▶cAMP, ▶pheromones, ▶major histocompatibility complex, ▶marsupial; Lane RP et al 2002 Proc Natl Acad Sci USA 99:291.

v-Oncogene: Viral oncogene, homologous to a c-oncogene, but carried by oncogenic viruses, capable of causing cancerous growth. ▶oncogenes, ▶cancer, ▶c-oncogene, ▶retrovirus

Von Gierke Disease: ▶glycogen storage disease

Von Hippel-Lindau Syndrome (VHL): A dominant phenotype (human chromosome 3p26-p25) involving tumorous growth primarily of the blood vessels of the eye (hemangioma) and the brain (hemangioblastoma). The central nervous system, kidneys (phaeochromocytoma) and the pancreas may also become tumorous. The incidence estimates vary between 0.00002 and 0.00003, and the mutation rate appears to be about $2-4 \times 10^{-6}$. The primary cause of the tumor is the inactivation of the VHL tumor suppressor gene. The VHL protein forms ternary complexes with Elongin C and Elongin B and CUL2 (see Fig. V29). This complex marks HIF (hypoxia-inducible factor) for degradation by the proteasome. RBX1 helps to recruit the ubiquitinating proteins. With the assistance of the normal pVHL, the α subunit of HIF is degraded and the level of oxygen increases. This process results in the activation of the CXCR4 chemokine receptor. HIF, with the cooperation of other proteins, e.g., VEGF, promotes the formation of blood vessels that are required for cancerous growth. When pVHL protein formation is reduced or prevented, HIF remains active and creates conditions for angiogenesis and cancerous growth. It is believed that VHL is a negative regulator of VEGF by association with complexes (SCF) which target proteins for degradation. The VHL gene falls in the same area as the RCC gene. The VHL inactivation seems to affect TGF-α and that may stimulate the renal carcinogenic path. ▶ELONGIN, ▶VEGF, ▶CXCR,

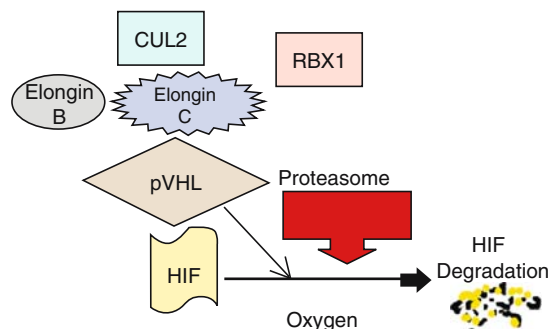


Figure V29. HIF pathway in VHL

►eye diseases, ►kidney diseases, ►phaeochromocytoma, ►polycythemia, ►mutation rate, ►renal cell carcinoma, ►hypernephroma, ►RCC, ►SCF, ►SKP, ►cullin, ►angiogenesis, ►wound healing, ►proteasome, ►elongin, ►Rbx1, ►ubiquitin, ►HIF, ►hypoxia; Iwai K et al 1999 Proc Natl Acad Sci USA 96:12436; de Paulsen N et al 2001 Proc Natl Acad Sci USA 98:1387; Ivan M et al 2001 Science 292:464; Friedrich CA 2001 Hum Mol Genet 10:763.

Von Neumann–Morgenstern Gamble: Seriously or terminally ill patients may chose an experimental drug or treatment that may improve the quality of life but may further aggravate the illness and even shorten life.

Von Recklinghausen Disease (NF1): A dominant, human chromosome 17q11.2 neurofibromatosis, a skin tumor with characteristic café-au-lait spots. Some other features include are pseudoarthritis, glioma, mental retardation, hypertension, hypoglycemia, etc. The mutation rate is $\sim 10^{-4}$. The basic defect appears to be in a cytoplasmic GAP protein. ►neurofibromatosis, ►GAP, ►elephant man, ►café-au-lait spot

Von Willebrand's Disease (VWD): A complex, hereditary bleeding condition due to a deficiency of a large antihemophilic cysteine-rich glycoprotein (2813-amino acids) in the blood plasma, platelets and subendothelial connective tissue. It is different from hemophilias inasmuch as the bleeding from the gastrointestinal, urinary system and the uterus is prolonged. Several forms of this disease have been identified on the basis of which component of the large gene is affected. The type III form is characterized by very severe symptoms and is the least common type of VWD. The most common type VWD protein has a binding domain to antihemophilia factor VIII and its defect appears as a relatively rare recessive. There is also an X-linked form. The bleeding can be readily stopped upon supplying normal blood to the patients. The most common dominant gene which leads to a reduction of this glycoprotein has been assigned to human chromosome 12pter-p12.3. In its ~ 180 kb it contains 52 exons. Exon 28 is the largest encoding domains A1 and A2. Domains D1-D2-D'-D3-A1-A2-A3-D4-B1-B2-B3-C-1-C2-CK are distinguished. Its highly homologous pseudogene is located in 22q11.2. At least 22 human genes carry homologies to the A domain of chromosome-12 gene. The frequency of heterozygotes has been estimated to vary from 1.4 to 5%, and thus VWD appears quite frequent although some other estimates are much lower. Recurrence risk for the dominant form, if one of the parents is affected, is about 50%. Both heterozygotes and homozygotes may express VWD. Percutaneous

umbilical blood sampling (PUBS) may permit prenatal diagnosis. ►hemophilias, ►antihemophilic factors, ►Glanzmann's disease, ►hemostasis, ►prenatal diagnosis, ►epiphyseal dysplasia; Sadler JE 2002 Science 297:1128; Manucci PM 2004 New England J Med 351:683.

Von Willebrand–Jürgen's Syndrome: ►thrombopathic purpura

VP: Refers to viral proteins such as the VP1, VP2 and VP3 of Simian virus 40. ►SV40

VP16 (α -transinducing factor, α -TIF): Refers to a herpes simplex virus transcription activation domain that can boost the expression of other genes by a factor of 10^5 . The normally minimal activation is due a peptide module of VP16 called ATF14. A small synthetic molecule, less than 1/5 of ATF14, is almost as efficient and more resistant to proteolytic degradation (Minter RA et al 2004 J Am Chem Soc 126:10504). ►transactivator; Hirst M et al 2001 Proc Natl Acad Sci USA 98:8726.

Vpg: A genome-linked (polio) viral protein (22 amino acids) attaches to the 5' end of RNA viruses and acts as a primer in the replication of the nucleic acid. ►primer

VRE (ventral response element): This is involved in the regulation of ventral development by preventing switching on an activator that operates dorsal development.

vRNA: ►vault

Vrolik Disease: ►osteogenesis imperfecta Type II

VSG: Refers to variable surface glycoprotein. ►Trypanosoma, ►Borrelia, ►telomere switching

VSP (very short patch repair): A prokaryotic repair involving T-G mismatches by restoring the original base pairs. (See Lieb M et al 2001 J Bacteriol 183:6487).

VSV: ►CO₂ sensitivity

V-type ATPases: These are responsible for the acidification of cellular organelles (vacuoles, lysosomes, Golgi complex) by the maintenance of the vacuolar-type ATPase—proton pump in plant and animal cells. ►Golgi complex, ►lysosomes, ►ATPase; Gruber G et al 2001 J Exp Biol 204:2597.

V-type Position Effect: A variegated expression of genes transposed into the vicinity of heterochromatin. This phenomenon is common in *Drosophila* but only a few cases have been observed in plants. One of the most common causes of variegation is the movement of insertion or transposable elements or sorting out of plastid-DNA encoded mutations. ►position effect,

►heterochromatin, ►variegation, ►chloroplast genetics, ►transposable elements

Vulva: This is the outer region of the external female genital organ, the vaginal orifice and organs associated with it.

Vulvovaginitis: An autosomal dominant allergy to semen resulting in vaginal inflammation lasting from a couple to several hours after coitus. The most common cause is, however, infection or candidiasis. ►candidiasis; Eschenbach DA 2004 New England J Med 351:851.

Historical vignettes

RC Punnett (Heredity 4:9) gives the following account: “I was asked why it was that, if brown eye were dominant to blue, the population was not becoming increasingly brown eyed: yet there was no reason for supposing such to be the case. I could only answer that the heterozygous browns also contributed their quota of blues and that somehow this led to equilibrium. On my return to Cambridge I at once sought out GH Hardy with whom I was then very friendly. For we had acted as joint secretaries to the Committee for the retention of Greek in the Previous Examination and we used to play cricket together. Knowing that Hardy had not the slightest interest in genetics, I put my problem to him as a mathematical one. He replied that it was quite simple and soon handed to me the now well-known formula $p^2 + 2pq + q^2$ (where p , $2q$ and r the proportions of AA, Aa, and aa individuals in the population varying for the A-a difference). Naturally pleased at getting so neat and prompt an answer I promised him that it should be known as ‘Hardy’s Law’— a promise fulfilled in the next edition of my Mendelism. Certain it is...that ‘Hardy’s Law’ owed its genesis to a mutual interest in cricket.”

Vannevar Bush, Director of the US Office of Scientific Research and Development, 1938 on science policy: “Scientific progress on a broad front results from the free play of free intellects, working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown.”

W

w: A symbol of map distance. ▶ θ , ▶map distance, ▶cM, ▶recombination, ▶mapping function

W Chromosome: This corresponds to the Y chromosome in heterogametic females, WZ in birds and butterflies. ▶chromosomal sex determination

w Locus: The first mutation discovered in *Drosophila* by Morgan is involved in the control, production and distribution of brown (ommochrome) and red (pteridine) pigments of the eyes and ocelli and some other anatomical structures. The gene (at 1–1.5) apparently encodes an ATP-binding membrane transport protein for the precursors of the pigments. More than 200 alleles have been identified within a 0.03 centimorgan region, which has been mapped by intragenic recombination into 7 domains. The wild type allele is incompletely dominant over many mutant alleles. The alleles do not show partial complementation with the exception of the w^{sp} (white spotted) allele that displays allelic complementation with the majority of other alleles in the presence of the z^a (*zeste*). The latter is a regulatory gene at 1–1.0 location and *zeste* encodes a specific protein binding to the promoters of *w*, *Ultrabithorax* (*Ubx*) and *decapentaplegic* (*dpp*). ▶map unit, ▶recombination, ▶morphogenesis in *Drosophila*, ▶eye color, ▶Tangier disease

W Mutagenesis: A tendency of increased mutation after Weigle reactivation. ▶Weigle; Yatagai F et al 1983 Adv Space Res 3(8):65.

W Point: A stage just before the S phase when animal cells still have serum growth factor requirement to enter the S phase. ▶cell cycle

W Reactivation: This is the same as Weigle reactivation.

Waardenburg Syndrome: Autosomal dominant forms may be distinguished on the basis of displacement (type I) and without displacement (type II) of the eyelids. Variegation in the color of the iris, white forelock, eyebrows and eyelashes, syndactyly, heart problems, hearing defects may occur as autosomal recessive anomaly. Dominant mutations in the SOX10 gene may affect the neural crest-derived cell lineages. The Waardenburg syndrome type 2 gene (MITF [microphthalmia-associated transcription factor]) converts fibroblasts into melanocyte-like cells by transactivation of a tyrosinase gene. If MITF is inactive hypopigmentation occurs. Mutation in the PAX3 transcription factor is responsible for hearing and pigmentation defects of type 1 form caused by failure of

transactivation of MITF. Human chromosomal locations are type I 2q35, type IIA 3p14.1-p12.3 and type IIB 1p21-p13.3. The type III form also called Klein-Waardenburg syndrome is at 2q35 location. The syndrome may be haplo-insufficient. The merle phenotypes observed in several breeds of dogs are characterized by hypopigmentation and by hearing and eye defects is caused by insertion of SINE elements into the *SILV* (silver) gene, responsible for pigmentation. The merle phenotype is similar to the Waardenburg type II anomaly (Clark LA et al 2006 Proc Natl Acad Sci USA 103:1376). ▶PAX, ▶DiGeorge syndrome, ▶eye defects, ▶eye color, ▶polydactyly, ▶microphthalmos, ▶haplo-insufficient, ▶Shah-Waardenburg syndrome, ▶dog; Sánchez-Martín M et al 2002 Hum Mol Genet 11:3231.

Waardenburg-Shah Syndrome: ▶Shah-Waardenburg syndrome

WAF: ▶p21

WAGR: ▶Wilms tumor

Wahlund's Principle: When two populations, each with different allelic frequencies and both in Hardy-Weinberg equilibrium, are mixed by migration, there is an overall decrease in heterozygotes: $\bar{H} = 2\bar{p}\bar{q}[1 - (\sigma^2/\bar{p}\bar{q})]$. The decrease in overall heterozygosity indicates the degree of heterogeneity between the two populations and $(\sigma^2/\bar{p}\bar{q})$ is the Wahlund's variance of gene frequencies. ▶allelic frequencies, ▶migration; Yasuda N 1968 Am J Hum Genet 20:1.

Wald-Wolfowitz Test: Used for comparison of two unmatched, supposedly continuous distributions and the null hypothesis is that the two samples are distributed identically. ▶null hypothesis, ▶logistic regression; Hays WL, Winkler RL 1970 Statistics: Probability, Inference, and Decision. Holt, Reinhart and Winston, New York.

Waldemar of Prussia: A hemophiliac great-grandson of Queen Victoria. ▶hemophilia A, ▶Queen Victoria

Waldenström Syndrome: ▶macroglobulinemia

Walker Boxes (P-loops): These are nucleotide triphosphate-binding amino acid sequences in several proteins. Box A promotes branch migration in Holliday junctions during recombination mediated by the Ruv B protein. Walker A: GlyXXGlyXGlyLysThr, Walker B: AspGluXAsp. The Lys residue binds the γ -phosphate of nucleotides directly. ▶branch migration, ▶Holliday junction, ▶RuvABC; Walker JE et al 1982 EMBO J 1:945; Hishida T et al 2001 J Biol Chem 274:25335.

Walker-Wagner Syndrome: An autosomal recessive hydrocephalus (accumulation of fluid in the enlarged

head) generally associated with retinal detachment, congenital muscular dystrophy and lissencephaly. ▶[Miller-Dieker syndrome](#), ▶[hydrocephalus](#), ▶[prenatal diagnosis](#), ▶[head/face/brain defects](#), ▶[lissencephaly](#)

Walker-Warburg Syndrome (HARD, 9q31): Refers to autosomal recessive hydrocephalus agyria and retinal dysplasia that was originally described as lissencephaly. ▶[Miller-Dieker syndrome](#); Beltrán-Valero de Barnabé D et al 2002 Am J Hum Genet 71:1033.

Walking: ▶[chromosome walking](#)

Walking of Transcriptase: Describes transient halting of the movement of the RNA polymerase ternary complex (polymerase, DNA, transcript) by sequentially providing subsets of the four ribonucleotides. ▶[transcript elongation](#)

Wallaby: *Wallabia bicolor*, 2n = 11 in males and 10 in females; *Wallabia eugenii* 2n = 16.

Wallaby: A non-viral retrotransposable element named after the jumping small Australian kangaroo. ▶[retroposon](#)

Walnut (*Juglans* spp): Occurs in both wild and cultivated forms; 2n = 2x = 32.

Walnut Comb: In poultry, it is determined by the genetic constitution *RrPp*, and as a result of epistasis, occurs in 9/16 frequencies in F₂ after brother-sister mating of the same double heterozygotes (see Fig. W1). The other phenotypes in the segregating F₂ are rose *Rr/RR, pp* (3), pea *rr, PP/Pp* (3), and single *pp, rr* (1).

Walrus: *Odobenus rosmarus*, 2n = 32.

Waltzing Mouse: A chromosomal deletion causing involuntary movements.

Wanda: ▶[fish orthologous genes](#)

Wandering Spots: An older method of sequencing short oligonucleotides. (Le Gall O et al 1988 J Gen Virol 69:423).

Warburg Effect: ▶[glycolysis](#)

Warburg Micro Syndrome (2q21.3): A condition characterized by autosomal recessive microcephaly, micropupil, congenital cataract, mental and physical retardation, underdeveloped genitalia, facial

hairiness, hypoplasia of the corpus callosum and other anomalies. The molecular defect appears to be in the RAB3 GTPase activating protein. ▶[corpus callosum](#), ▶[RAB](#), ▶[Griscelli syndrome](#); Aligianis IA et al 20005 Nature Genet 37:221.

Ward-Romano Syndrome (WRS, 11p15.5): An autosomal dominant or recessive LQT disease involving anomalous heart muscle fibrillations, fainting (syncope) and possibly sudden death. It is the same as long QT syndromes. ▶[LQT](#), ▶[electrocardiography](#), ▶[ion channels](#), ▶[HERG](#), ▶[Jarvell and Lange-Nielson syndrome](#), ▶[long QT syndrome](#), ▶[Andersen syndrome](#)

Warfarin (C₁₉H₁₆O₄, named after Wisconsin Alumni Research Foundation): This is a slightly bitter, water and alcohol soluble compound. It depresses the formation of prothrombin, necessary for blood clotting, and may cause fragility of the capillary veins leading to hemorrhages. It is used in certain surgeries and treatment of diseases that block arteries by blood clots. It is also a rodent poison. A single ingestion may not necessarily be very hazardous to humans but rats or mice consuming it repeatedly in baits suffer internal bleeding and die. The antidote of warfarin is vitamin K. Warfarin inhibits vitamin K epoxide reductase. Mutations in rodents may make them resistant to warfarin. ▶[anticoagulation factors](#), ▶[prothrombin deficiency](#), ▶[coumarin-like drug resistance](#), ▶[vitamin K-dependent clotting factors](#), ▶[chondrodysplasia](#); Van Aken H et al 2001 Clin Appl Thromb Hemost 7:195; Loebstein R et al 2001 Clin Pharmacol Ther 70(2):159.

Wasp: Wiskott-Aldrich syndrome proteins that regulate the assembly of actin monomers into filaments and regulate the cytoskeletal organization and motility of cells. WASF1 encoded at 6q21-q22 and WASF3 at 13q13 are effectors for the signal transmission from tyrosine kinase receptors to the cytoskeleton. The function of WASF2 (1p36.11-p34.3) is also similar. The latter has a pseudogene at Xp11.22. ▶[Wiskott-Aldrich syndrome](#), ▶[actin](#), ▶[cytoskeleton](#); Ward ME et al 2004 Proc Natl Acad Sci USA 101:970.

Wasp: *Habrobracon* spp. 2n = 20 for female, 2n = 10 for male. The males hatch from unfertilized eggs and are haploid. The females come from fertilized eggs and are diploid. They are heterozygous for any of the

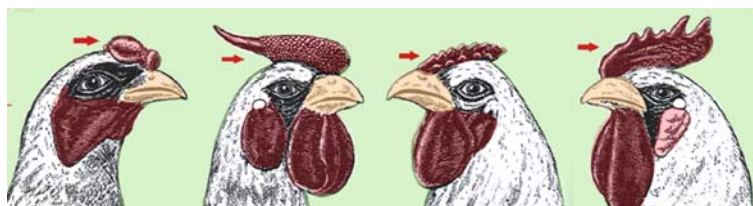


Figure W1. From left to right: Walnut, Rose, Pea, Single comb

nine sex factors. As a result of inbreeding, sex factor homozygotes occasionally arise that are sterile “biparental males” (see Fig. W2). Gynandromorphs occur in wasps but these are different from those in *Drosophila* because the haploid sectors are not necessarily male sectors as expected from the loss of one set of chromosomes. Although in insects circulating sex hormones do not seem to exist, some type of diffusible substance affects the chromosomally male sectors. Exceptional gynandromorphs may arise by fertilization of binucleate eggs. Gynandromorphic tendency is genetically determined. ►social insects, ►honey bee; Page RE et al 2002 Genetics 160:375; Cowan DP, Stahlhut JK 2004 Proc Natl Acad Sci USA 101:10374.

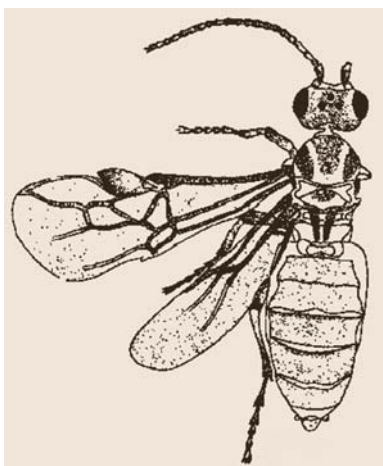


Figure W2. Wasp (Right-side wings and legs removed)

Watercress (*Rorippa nasturtium-aquaticum*): This is a northern European vegetable with $x = 16$ but the species may be diploid, sterile triploid or tetraploid.

Watermelon (*Citrullus vulgaris*): An annual fruit, $2n = 22$. Triploids are grown commercially and crossing tetraploid plants with diploids produces the seeds. The fruits of the triploid plants are practically seedless and are therefore easier to eat (see Fig. W3). According to some reports, triploids have a higher sugar content than either of the parental forms.

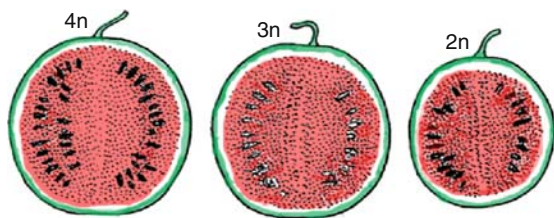


Figure W3. Watermelon. (Diagram of watermelons modified after Eigsti OJ, Dustin P Jr 1955 Colchicine, Iowa State College Press, Ames, Iowa)

Watson and Crick Model: This has been described by Watson JD, Crick FHC in 1953 (Nature [Lond] 171:964) and it became the world’s most famous biological model ever conceived. (See Fig. W4 of the model, and Fig. W6 for historical documents: <http://osulibrary.orst.edu/specialcollections/coll/pauling/dna/>).

It is interesting to note in the first DNA models of Watson and Crick (1953) only two hydrogen bonds have been shown between G and C. The third hydrogen bond between G and C was first mentioned in a paper by Pauling and Corey in 1956 (Waine-Hobson S 2006 Nature [Lond] 439:539). The genome of the first human being that was entirely sequenced in 2007 belongs to James Watson (Project Jim). He agreed that his DNA sequence should be added to public databases but requested that his *ApoE* gene status – which is indicative of a risk for Alzheimer’s disease – be blanked out. It is likely that other disease susceptibility gene sequences will not be made public either (Marshall E 2007 Science 315:1780).

Watt (W): The product of volts and amperes in the case of direct current. $1\text{ W} = 1\text{ joule/sec} = 0.293\text{ calories/sec} = 1/735\text{ HP (horse power)}$. In other words, 1 W power is generated by the electric potential between two points of 1 volt and 1 ampere current. ►volt, ►ampere

Wax Coat: ►eceriferum

WCPP (whole chromosome painting probe): Contains a combination of many probes, specific for a single chromosome and thus may label with color its entire length. The multicolor labeling probes may permit the differentiation of all chromosomes in a single karyotype. ►chromosome painting, ►USP, ►FISH, ►GISH

WD-40: Refers to a repeat (N) motif of tryptophan (W) - aspartic acid (D) in several eukaryotic regulatory proteins (absent in prokaryotes) (see Figs. W5); WD repeats are involved in signal transduction, RNA processing, developmental regulation, cell cycle, vesicular traffic, etc. ►signal transduction; Neer EJ et al 1994 Nature [Lond] 371:2987; Smith TF et al 1999 Trends Biochem Sci 24:181.

W-DNA: Refers to a left-handed zig-zag duplex with the same directions as B-DNA but other characteristics match those of the Z-DNA. ►DNA types

Weasel: *Mustela erminea*, $2n = 44$; *Mustela frenata*, $2n = 44$.

WEB Service: This is a standard system of communication of machines in a network.

WEBB (WB): A very rare blood group involving an altered glycosylation of glycophorin. ►glycophorin,

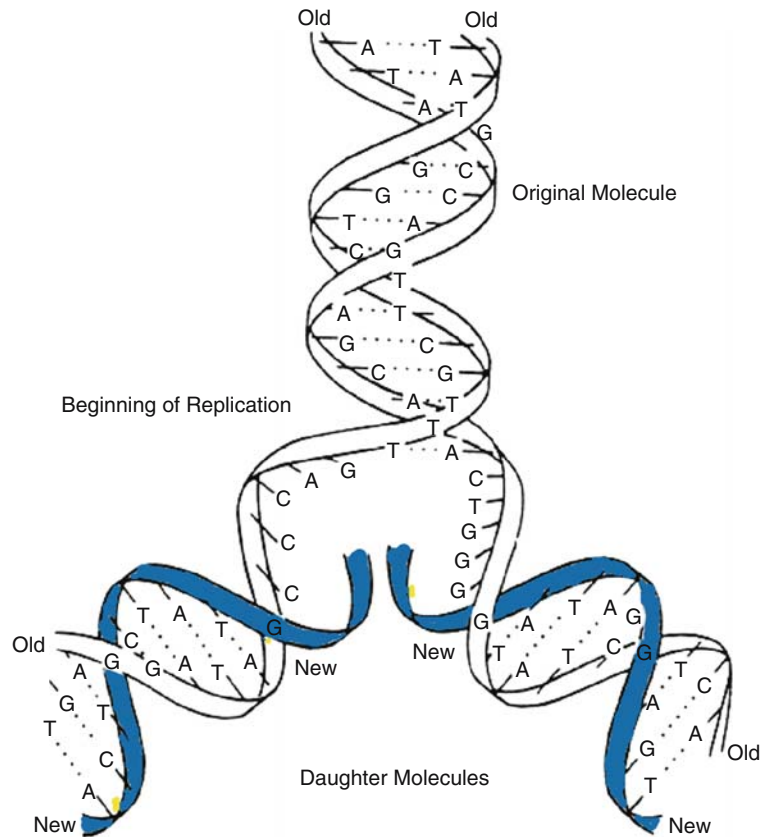


Figure W4. The double-stranded DNA molecule is joined through 2 and 3 hydrogen bonds between the A = T and G = C nucleotides, respectively. The staircase-like ribbons represent the sugar-phosphate backbone of the double helix. During replication the old plectonemic strands unwind and each old separated strand serves as a template for the formation of the new molecules that are composed from one old and one new single strand (►DNA replication, ►replication fork). This is, therefore, known as the semi-conservative mode of replication. The model is consistent with most genetic phenomena (mutation, recombination, gene expression, etc.). Since the model was originally proposed, the details of the mechanisms of the DNA transactions have been worked out in greater detail but basically none of the essential features had to be revised. This model served as a basis for the *central dogma of genetics* indicating that the flow of information is from the DNA to the RNA and to protein. During the 1960s it was discovered that through reverse transcriptase information can be directed by reverse transcription from the RNA to the DNA but not from protein to the RNA and the DNA. The discovery of prions makes the role of proteins in heredity somewhat ambiguous. All other proposals concerning hereditary molecules (besides the DNA and the RNA) have now faded into oblivion

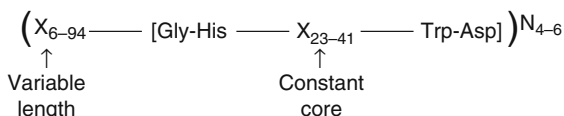


Figure W5. WD-40

►Gerbich, ►En, ►MN, ►blood groups; Reid ME et al 1985 Biochem J 232:289.

WEBIN: A nucleotide sequence information form to the EMBL database. It is offered by the European

Bioinformatics Institute: <http://www.ebi.ac.uk/embl/Submission/webin.html>; Webin qualifiers: <http://www.ebi.ac.uk/embl/WebFeat/index.html>.

WEE1: A protein kinase which inactivates the *CDK1/cdc2* gene product through phosphorylation of the tyrosine-15 residue. Wee1 is subject to proteolysis in a Cdc34-dependent way before the S phase can be completed. ►kinase, ►Mik1, ►cell cycle, ►cdc, ►checkpoint; Tzivion G et al 2001 Oncogene 20:6331; Bartholomew CR et al 2001 Mol Cell Biol 21:4949; crystal structure: Squire CJ et al 2005 Structure 13:541.

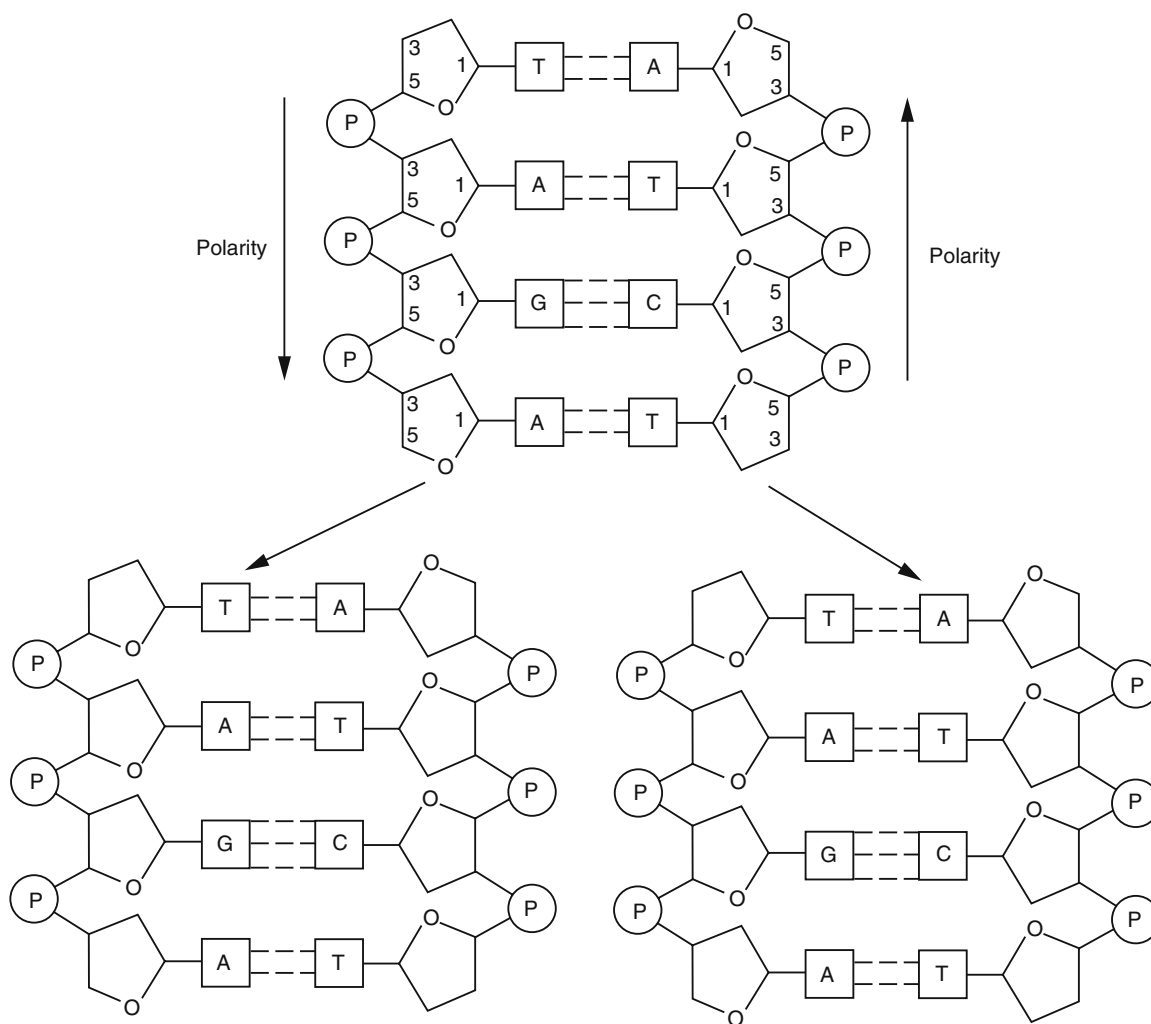


Figure W6. The Watson & Crick model as represented by Josse JJ, Kaiser AD, and Kornberg A, 1961 J Biol Chem 236:864

Wegener Granulomatosis: An autosomal dominant condition characterized by the presence of a ~29 kDa serine protease antigen, identical to myeloblastin. It is a very serious ailment primarily affecting the upper and lower airways and kidneys. ▶myeloblast, ▶Goodpasture syndrome

Weibel-Palade Bodies: These are $0.1\text{--}0.2\text{ }\mu\text{m} \times 4\text{ }\mu\text{m}$ membrane-enclosed bodies found around the platelets or in the endothelium of all animals. They store in their $150\text{--}200\text{ }\text{\AA}$ tubules the von Willebrand glycoprotein. ▶von Willebrand disease; Denis CV et al 2002 Proc Natl Acad Sci USA 98:4072.

Weighted Mean: Refers to the calculated mean multiplied by the pertinent frequency, e.g., in a population the mean value of the homo- and heterozygous dominants (*AA* and *Aa*) is 250 and that of the

homozygous recessives (*aa*) is 200, and the respective frequencies are 0.8 and 0.2, then the weighted mean of the population is $(250 \times 0.8) + (200 \times 0.2) = 240$.

▶mean

Weigle Mutagenesis: Denotes an increase in mutation of phage by mutagenic treatment of the host. (See Weigle JJ 1953 Proc Natl Acad Sci USA 39:628; Bhattacharyya SC et al 1991 Can J Microbiol 37:265).

Weigle Reactivation: An increase in phage survival when mixed with host cells exposed to low doses of UV light. ▶DNA repair, ▶marker rescue, ▶multiplicity reactivation; Calsou P, Salles B 1991 Mol Gen Genet 226:113.

Weismannism: Inheritance takes place by the transmission of the genetic determinants through the germ line (Keimbahn) and environmentally-induced phenotypic

variations are not inherited. ► [germ line](#); Weismann A 1985 Die Continuität des Keimplasmas als Grundlage einer Theorie der Vererbung. Fischer, Jena, Germany.

Weissenbacher-Zweymuller Syndrome (WZS, 6p21.3): A condition characterized by neonatal small jaws (micrognathia), hip and/or shoulder bone defects (rhizomelic chondrodysplasia), general underdevelopment of bones that may improve in later years optic nerve defects, myopia and deafness. Some of the symptoms resemble those of the Stickler syndrome. The basic defect is in the collagen gene COL11A2. ► [collagen](#), ► [Stickler syndrome](#)

Welander Distal Myopathy (WDM, 2p13): A dominant late-onset muscular dystrophy. ► [muscular dystrophy](#), ► [Miyoshi myopathy](#)

Werdnig-Hoffmann Disease: A recessive (5q12.2-q13) infantile muscular dystrophy primarily affecting the spinal cord muscles. The prevalence is approximately 1×10^{-4} . The gene frequency has been estimated to be around 0.014 and the frequency of heterozygotes about 0.02. It encodes a protein that shows homology to dystrophin. The survival rate varies according to the severity of symptoms. A subunit of transcription factor TFIIF usually suffers deletions. ► [dystrophin](#), ► [muscular dystrophy](#), ► [neuromuscular diseases](#), ► [spinal muscular atrophy](#), ► [transcription factors](#)

Werner Syndrome (WRN): Involves premature aging, hardening of the skin, cataracts, atherosclerosis, diabetes mellitus, etc. The gene expression profile is similar to that seen in normal aging (Kyng KJ et al 2003 Proc Natl Acad Sci USA 100:12259). Cultured cells have higher chromosome breakage and mutability. Neoplasias develop frequently. Ulceration around the ankles and soft tissue calcification are symptoms of this condition, unrelated to aging. It was earlier held that the recessive defect was controlled by human chromosome Xp12-p11.2 but recent linkage information, including complete sequencing on the basis of positional cloning, confirms its location at 8p12. WRN contains four structurally folded domains comprising an exonuclease, a helicase, a winged-helix and a helicase-and-ribonuclease D/C-terminal domain. The protein is required for focus forming activity in DNA replication (FFA). It contains 1,432 amino acids and resembles RecQ type ATP-dependent helicases (homologous to budding yeast *SGS1* and *SRS2* genes). Defects in the helicase (frameshift, nonsense mutation) explain most of the symptoms in terms of a flaw in DNA metabolism. WRN also interacts with DNA polymerase δ . However, the amino end domain of WRN shows 3'→5' exonuclease activity and it may be involved in genetic recombination and/or repair. Forced telomerase activity substantially extends the life span of cultured WRN

cells. The WRN gene may be inactivated by CPG island hypermethylation at its promoter. Since WRN involves DNA repair, inactivation may lead to loss of exonuclease-mediated DNA repair and increased chromosomal instability as well as to apoptosis, induced by a camptothecin analog (irinotecan), a topoisomerase inhibitor. Thus, cancer cells may become more amenable to chemotherapy (Agrelo R et al 2006 Proc Natl Acad Sci USA 103:8822). Normal fibroblasts and U2OS osteosarcoma cells rendered deficient in WRN exhibit reduced phosphorylation of p53 and histone H2AX in response to T-oligo (telomere single-strand overhang) treatment indicating its role in the processing of telomeric DNA and subsequent activation of DNA damage responses (Eller MS et al 2006 Proc Natl Acad Sci USA 103:15073). There is evidence that the genome instability in WS cells depends directly on telomere dysfunction, linking chromosome end maintenance to chromosomal aberrations in this disease (Crabbe L et al 2007 Proc Natl Acad Sci USA 104:2205). ► [aging](#), ► [progeria](#), ► [helicase](#), ► [exonuclease](#), ► [FFA](#), ► [Bloom syndrome](#), ► [co-suppression](#), ► [RNAi](#), ► [atherosclerosis](#), ► [telomeres](#), ► [translesion](#); Kamath-Loeb AS et al 2000 Proc Natl Acad Sci USA 97:4603; Shen J-C, Loeb LA 2000 Trends Genet 16:213; Kawabe Y et al 2001 J Biol Chem 276:20364; Kipling D et al 2004 Science 305:1426.

Wernicke-Korsakoff Syndrome: A chromosome 3p14.3 recessive disorder involving transketolase deficiency caused by the lowered ability of the enzyme to bind thiamin pyrophosphate. Another transketolase deficiency has been traced to Xq28. This dysfunction of energy metabolism leads to neuropsychiatric anomalies, especially in alcoholics and when the level of thiamin is low in the diet. ► [thiamine pyrophosphate](#)

West Nile Virus (WNV, Flaviviridae): A single-stranded RNA virus. E-glycoprotein is its most important protein, both structurally and for infection (see Fig. W7). Of the two strains, lineage 1 has caused most of the health problems in the US. Outbreaks of the epidemic have been described in Africa, the Mid East and southern Europe. About 29 species of mosquitos transmit the virus to birds and from birds to humans. In North America the human- and bird-biter forms of the *Culex* mosquitos form hybrids and may facilitate the severity of transfer between these species (Fonseca DM et al 2004 Science 303:1535). If infected mosquitos feed in close vicinity of non-infected individuals, the secreted saliva is sufficient for transmission of the virus in an appreciable frequency (5.8%) even when the blood of vertebrates does not contain the virus (non-viremic). This contributes to the rapid spread of the disease (Higgs S et al 2005 Proc Natl Acad Sci USA 102:8871). The symptoms include

fever, headache, gastrointestinal and mental changes (memory loss, depression); rash, cough and other symptoms may also be manifested. The virus appears genetically quite stable. The fatality ranges from 4 to 14% but in older or immune-compromised persons the risks may be more than double. The most effective diagnosis reveals immunoglobulin M (IgM) in the cerebrospinal fluids. RNAi holds promise for effective medication against viral encephalitis at least in mice. However, mosquito control is the key to prevention.

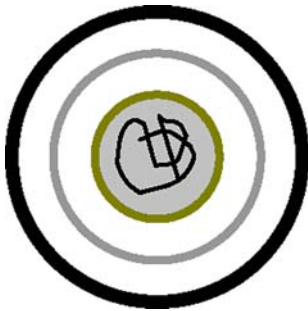


Figure W7. West Nile virus with heavy capsule and two concentric lipid layers surrounding the core with RNA

DNA vaccine coding for the RNA transcript of the related Kunjin flavivirus has protective effects against the West Nile Virus (Hall RA 2003 Proc Natl Acad Sci USA 100:10460). ▶[immunization genetic](#), ▶[viral encephalitis](#); Petersen LR, Marfin AA 2002 Annals Int Med 137:E173; Brinton MA 2002 Annu Rev Microbiol 56:371; <http://westnilemaps.usgs.gov>; <http://www.cdc.gov/ncidod/dvbid/westnile/>.

West Syndrome (ARX, Xp22.13; ISSX, Xp21.3-p22.1): This involves an X-linked central nervous defect, hypsarrhythmia (electroencephalographic anomaly) resulting in infantile spasms and mental retardation. Its incidence is $2-5 \times 10^{-4}$ at birth. The basic defect may be in the serine-threonine kinase 9 region. ▶[epilepsy](#), ▶[mental retardation X-linked](#); Kalscheuer VM et al 2003 Am J Hum Genet 72:1401.

Western Blot (Western hybridization): Refers to the identification of polypeptides separated electrophoretically on SDS polyacrylamide gels, then transferred to nitrocellulose filter and labeled by immunoprobes such as radioactive or biotinylated antibodies. ▶[immunoblotting](#), ▶[gel electrophoresis](#), ▶[far-western hybridization](#); Towbin H et al 1979 Proc Natl Acad Sci USA 76:4350; Burnette WN 1981 Anal Biochem 112:95.

Weyers Acrofacial/Acroental Dysostosis: An allelic variation in the gene locus at 4p16 encoding the Ellis-van Creveld syndrome. ▶[Ellis-van Creveld syndrome](#)

WGRH (whole genome radiation hybrid): Formed when the donor is a diploid cell line for the generation of radiation hybrids. ▶[radiation hybrid](#); Vignaux F et al 1999 Mamm Genome 10:888.

WGA (whole genome association, whole genome assembly, whole genome array). Whole genome association study attempts to identify all the genetic factors involved in the development of a particular disease. The PLINK software tool can handle a very large set of data involving five main domains of function: data management, summary statistics, population stratification, association analysis, and identity-by-descent estimation (Purcell S et al 2007 Am J Hum Genet 81:559). ▶[microarray hybridization](#), ▶[genome annotation](#)

WGS (whole-genome shotgun sequencing): Developed by Craig Venter and associates at Celera Genomics, Rockville, MD, USA. The genome is sheared into a few thousand base pair long pieces and cloned into sequencing vectors. Each fragment end (~500 bp) is covered by the sequencing several times and then assembled into overlapping segments by end-sequences. In this way oriented, contiguous sequences (contigs or scaffolds) are generated. Between the scaffolds a physical gap may remain until the physical map is “finished” and the complete genome is reconstructed with the aid of high-power computers. The scaffolds are also mapped to eukaryotic chromosomes and chromosome arms with the aid of sequence-tagged sites. The heterochromatic regions (mainly around the centromeres and near the telomeres) are unstable when cloned and thus resist sequencing. These regions contain transposons and redundant ribosomal RNA genes with a few interspersed ORFs. For the repeated sequences the WGS method provides less resolution (She X et al 2004 Nature [Lond] 431:927). The function of the sequences is indicated by annotation using Genscan or Genie computer software. ▶[shotgun sequencing](#), ▶[mate pair](#), ▶[sequence-tagged sites](#), ▶[transposon](#), ▶[ribosomal RNA](#), ▶[ORF](#), ▶[annotation](#), ▶[gene ontology](#), ▶[scaffolds in genome sequencing](#), ▶[genome projects](#); Adams MD et al 2000 Science 287:2185; <http://www.ncbi.nlm.nih.gov/projects/WGS/WGSprojectlist.cgi>.

Whale: *Baleonoptera* species are $2n = 44$; *Kogia breviceps*, $2n = 42$.

Wheat: ▶[Triticum](#)

Wheat Germ In Vitro Translation: Cell-free wheat germ extracts can be used for the translation of viral, prokaryotic and eukaryotic mRNAs into protein. The supernatant of the extract must be chromatographically purified from inhibitory endogenous amino

acids and pigments before translation. Tritin, one of the endosperm proteins, inactivates the ribosomes and thus reduces the efficiency of the system unless carefully removed. The extract contains tRNA, rRNA and other factors required for protein synthesis. Phosphocreatin and phosphocreatine kinase additions are needed for supplying energy. Spermidine is added to stimulate the translation efficiency and prevent premature termination of the polypeptide chain. Magnesium acetate and potassium acetate, mRNA (to be translated) and amino acids (including one in a radioactively labeled form) are also necessary. Incubation is at 25°C for 1 to 2 hours. In general, the procedure is very similar to the rabbit reticulocyte system. ► [rabbit reticulocyte in vitro translation system](#); Erickson AH, Blobel G 1983 *Methods Enzymol* 96:38.

Whim Syndrome (2q21): Refers to hypogammaglobulinemia, neutropenia, myelokathexis (retention of bone marrow neutrophils) and papilloma virus susceptibility due to mutations in the chemokine receptor CXCR4. ► [gammaglobulin](#), ► [neutropenia](#), ► [neutrophil](#), ► [CXCR](#), ► [papilloma virus](#); Hernandez PA et al 2003 *Nature Genet* 34:70.

Whipple's Disease: An infectious disease caused by *Tropheryma whipplei* bacteria.

White Blood Cell: ► [leukocyte](#)

White Forelock: ► [forelock](#), ► [white](#)

White Leghorn (chicken): Has genes controlling the color of the plumage *CC*, *OO*, *II*; the color is white (see Fig. W8). *C* and *O* both are needed for pigmentation but *I* is an inhibitor of color. ► [White Silkie](#), ► [White Wyandotte](#)



Figure W8. White leghorn rooster

White Matter: ► [gray matter](#)

White Silkie (chickens): They are of the constitution *cc*, *OO*, *ii* and have white feathers because only one of the two dominant genes, *O*, required for pigmentation is present. ► [White Leghorn](#), ► [White Wyandotte](#)

White Wyandotte (chickens): They have the genes *CC*, *oo*, *ii* and are white because only one, *C*, of the two dominant genes is present but not the other, *O*. ► [White Leghorn](#), ► [White Silkie](#)

Whooping Cough: A respiratory disease in humans caused by the pertussis toxin of the bacterium *Bordatella pertussis* (3,816 genes). Species such as *B. paraptus* (4,404 genes) and *B. bronchiseptica* (~5,007 genes) are related pathogenic species for various mammals (Parkhill J et al 2003 *Nature Genet* 35:32). ► [pertussis toxin](#), ► [microfluidics](#)

Whorl: Refers to a circular or spiral arrangement of structures, such as various parts of flowers or the dermal ridges in a human fingerprint. ► [fingerprinting](#), ► [flower differentiation](#)

Wide Cross: Refers to hybridization between plants of different species or genera.

Widow's Peak: An autosomal dominant pointed hairline in humans (see Fig. W9).



Figure W9. Widow's peak

Wilcoxon's Signed-Rank Test: A non-parametric substitute for the t-test for paired samples (see Table W1). The desirable minimal number of paired samples is 10 and it is expected that the population would have a median, be continuous and symmetrical. The differences between the variates are tabulated and ranked; the largest receives the highest rank. In the case of ties, each should be assigned to a shared rank. The smaller group of signed-rank values is then summed as the T value. This T value is compared with figures in a statistical table. If the value obtained is smaller than that in the body of the table under probability and on the line corresponding to the number of pairs tested, then the null hypothesis is rejected and the conclusion is justified that the two samples are different.

Example: Since T being 8.0 according to the first line of Table T1, the difference between the two sets of data is significant at the level of 0.05 probability but not at the 0.01 level.

Table W1. Wilcoxon's Signed-Rank Test

| Pairs | Difference | Signed | Ranks | Probability | | |
|----------------|------------|--------|-------|-------------|------|------|
| | | + | – | <i>n</i> | 0.05 | 0.01 |
| 1 | +6 | 7 | | 10 | 10 | 5 |
| 2 | +5 | 6 | | 11 | 13 | 7 |
| 3 | +10 | 10 | | 12 | 17 | 10 |
| 4 | –3 | | 4 | 14 | 25 | 16 |
| 5 | +4 | 5 | | 16 | 35 | 23 |
| 6 | +7 | 8 | | 18 | 47 | 33 |
| 7 | –2 | | 3 | 20 | 60 | 43 |
| 8 | –1 | | 0.5 | 22 | 75 | 55 |
| 9 | +9 | 9 | | 24 | 91 | 69 |
| 10 | –1 | | 0.5 | 26 | 110 | 84 |
| <i>T</i> = 8.0 | | | | | | |

A more general procedure for determining the probabilities depends on determining the *Z* value either for threshold probabilities or more precisely by using a table of the cumulative normal variates (such as the *Biometrika Tables for Statisticians*, Vol. 1, Pearson ES, Hartley HO, (Eds.), Cambridge University Press, Cambridge). *Z* values larger than 1.960, 2.326 and 3.291 correspond to *P* 0.05, 0.01 and 0.001, respectively. These probabilities rule out the null hypothesis.

$$Z = \frac{\mu - T - 0.5}{\sigma} \text{ and } \mu = \frac{n(n+1)}{4} \text{ and } \sigma = \sqrt{\frac{[2n+1]\mu}{6}}$$

where *n* = the number of paired data. ►non-parametric statistics, ►Mann-Whitney test, ►Student's *t* distribution, ►QTL

Wild Type: The standard genotype (that is most common in wild [feral] populations). ►isoalleles

Wildervanck Syndrome: This appears to be a X-linked dominant deafness, frequently associated with other disorders. Approximately 1% of deaf females is affected by it. It does not occur in males, presumably because it is lethal when homo- or hemizygous. It has been suggested that it is polygenically determined but the mechanism of male exclusion is as yet unknown. ►deafness, ►sex-limited, ►imprinting

Wildfire Disease of Plants: Caused by the toxin (methionine analog) of the bacterium *Pseudomonas tabaci*, and it leads to necrotic spots on the leaves. ►*Pseudomonas*

Williams Factor (Flaujeac factor deficiency): An autosomal recessive mutation in human chromosome

3q26-qter causing deficiency of a high molecular weight kininogen, a precursor of a blood clotting factor. ►kininogen, ►blood clotting pathways, ►antihemophilic factors

Williams Syndrome (Williams-Beuren syndrome, WMS): This autosomal dominant condition involves stenosis (narrowing) of the aorta, arteries and lungs, elfin face (elfins are diminutive mythological creatures), malformation of teeth and stature, mental deficiency and excessive amounts of calcium in the blood (hypercalcemia) and in some tissues. Cognitive abilities are impaired in an unusual fashion. During infancy patients are poor in language skills but their performance is relatively better in numerical intelligence tests. By adulthood the trend is reversed indicating that these abilities are under the control of two different developmental modules. Various types of deletions in different chromosomes (15, 4, 6) have been suspected. Chromosome-specific probes have revealed a ~1.5 Mb deletion of 7q11.23. This region harbors several genes including the GTF21RD1 basic transcription factor and the Williams syndrome transcription factor (WSTF/WCRF/ACF), which bears structural similarity to a 180 kDa chromatin-remodeling factor. The differences in the phenotypes of affected individuals may be due to the dosage effect of the chromosomal segments of this tract. Lower calcium in the diet may alleviate some of the symptoms. Vitamin D2 anomaly is suspected. The function of the Williams factor is unrelated. Recent findings have indicated the involvement of LIMK protein kinases (carrying two LIM domains) that are serine/threonine/tyrosine kinases and regulate

actin in the cytoskeleton. Under normal conditions RAC-GTP activates the LIM kinases that in turn phosphorylate cofilin and inactivate it. Dephosphorylation permits the formation of active cofilin that is associated with actin. The actin—cofilin association is apparently mediated by phosphoinositides (PtdInsP₂). Defects (heterozygosity for a mutation) in LIMK lead to abnormal neuronal connections. Elastin defects characterize the symptoms of the Williams syndrome. ▶supravalvular aortic stenosis, ▶cutis laxa, ▶cardiovascular diseases, ▶dwarfism, ▶vitamin D, ▶Williams factor, ▶LIM domain, ▶face/heart defects, ▶cofilin, ▶actin, ▶phosphoinositides, ▶human intelligence, ▶module, ▶Marfan syndrome, ▶BTK; Peoples R et al 2000 Am J Hum Genet 66:47; MorrisCA, Mervis CB 2000 Annu Rev Genomics Hum Genet 1:461; Sumi T et al 2001 J Biol Chem 276:23092; Urbán Zs et al 2002 Am J Hum Genet 71:30; Bayés M et al 2003 Am J Hum Genet 73:131; Tassabehji M et al 2005 Science 310:1184.

Wilms Tumor (WT): This is usually associated with a deletion in the short arm of human chromosome 11 extending from 11p13 to 11p15.5 (WT1) spanning several genes and is frequently referred to as the WAGR syndrome (Wilms tumor-aniridia-genitourinary anomalies and RAS oncogene-like function). The condition is characterized by symptoms of all or parts of the functions implied by WAGR. Wilms tumor is caused by a mutation in a cancer-suppressor transcription factor and splicing factor with 4 Zn finger domains. Wilms tumor is extremely complex and additional WT genes in chromosomes 16q, and 1p, 4p, 8p, 14p, 17p and q, 18q have also been implicated. The transcript displays alternative splicing. Wilms tumor suppressor gene is expressed only in the maternally transmitted allele. Prevalence is about 10^{-4} during the first five years of age. Recent evidence has revealed a WT gene in the 17q12-q21 region. The WT1 gene also regulates muscle differentiation. The WT1 gene affects the SRY locus in the Y chromosome and that explains the symptoms associated with genitourinary development when it is altered. The different functions are based on isoforms of the protein. ▶aniridia, ▶RAS, ▶deletion, ▶hypertension, ▶kidney diseases, ▶Zinc finger, ▶breast cancer, ▶imprinting, ▶isoform, ▶Rhabdomyosarcoma, ▶Denys-Drash syndrome, ▶Frasier syndrome, ▶acatalasemia; Hossain A, Saunders GF 2001 J Biol Chem 276:16817; Hammes A et al 2001 Cell 106:319.

Wilson Disease (WD): Recessive disease encoded in human chromosome 13q14.2-q14.3. It affects primarily persons of age 30 and above although juvenile forms have also been described. The major symptoms are cirrhosis of the liver and psychological ailments caused by a deficiency of ceruloplasmin resulting in copper accumulation. In this as well as other diseases

involving cirrhosis of the liver, at the upper and lower margin of the cornea (see Fig. W10) a greenish narrow ring (↑) occurs. The basic defect is in a copper transporting ATPase of the mitochondria. Inactivation of the enzyme (ATP7B or ATP7A) causes neurodegeneration and overexpression can lead to resistance to therapeutic drugs. Mutations in the N domain of the enzyme prevent tight ATP binding and can lead to >30 forms of Wilson disease (Dmitriev O et al 2006 Proc Natl Acad Sci USA 103:5302).

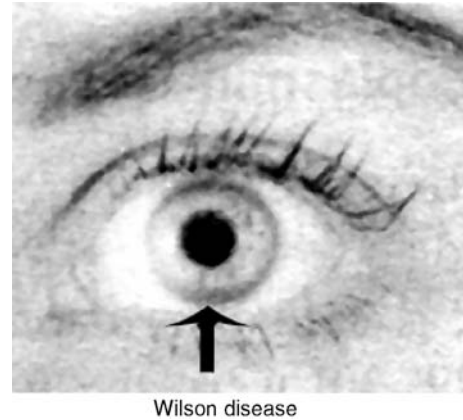


Figure W10. Wilson disease

XIAP (X-linked inhibitor of apoptosis) inhibits caspases and copper metabolism in WD and other copper toxicosis diseases. Intracellular copper alters the conformation of XIAP and lowers its ability to inhibit caspase. This results in sensitivity to apoptosis (Mufti AR et al 2006 Mol Cell 21:775). The prevalence of WD in the USA is about 3×10^{-5} . A similar anomaly has been observed in Long-Evans Cinnamon (LEC) rats that may serve as an animal model for the study of the disease. Prenatal diagnosis of offspring of carrier parents may be possible by using linkage with DNA markers. ▶Menkes disease, ▶acrodermatitis, ▶hemochromatosis, ▶mitochondrial disease in humans, ▶neurodegenerative diseases

Winged Helix Protein: This class of the helix-turn-helix proteins uses a β -hairpin (a wing) to bind the DNA. ▶DNA-binding protein domains; Gajiwala KS, Burley SK 2000 Curr Opin Struct Biol 10:110.

Wingless (wg/Dint-1; 2–30): *Drosophila* gene is involved in morphogenetic signaling and its homologs are found in all vertebrates and invertebrates. The mouse homolog is *Wnt*. Components of the *Wnt* cascade are altered in breast and colon cancers in mice and in human melanomas. The path of *Wg* function is depicted (see Fig. W11).

Fz (*fizzled trichomes*) and Dally (*division abnormally delayed*, controls heparan sulfate) are

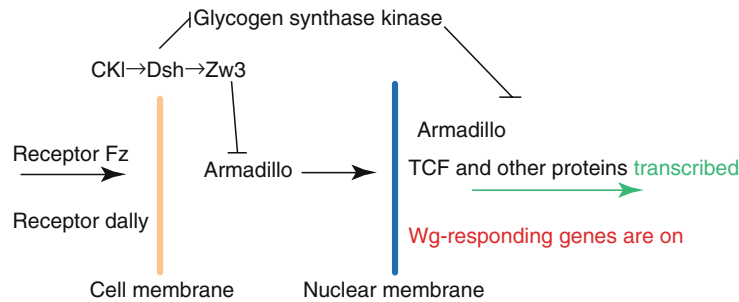


Figure W11. Path of Wg function

G protein-like receptors. *Dsh* (*dishevelled*) mitigates the block by *Zw3* (*zeste white*), Armadillo is a β -catenin-like protein. *TCF* (*ternary complex factors*) co-activate transcription. Dsh protein blocks glycogen synthase kinase (GSK3) that would be a negative regulator of Armadillo. CK1 (a serine kinase, called casein kinase) phosphorylates Dsh~Zw. Actually, Wg is involved in more complex functions. Wg also signals to the epidermal growth factor (EGF) receptor. WNT-4 duplication in humans and mice masculinizes XX individuals. In the Sertoli and Leydig cells DAX1, an antagonist of SRY, is upregulated. The *Wnt* pathway is involved in signaling to somatic stem cells and the maintenance of cancer (Reya T, Clevers H 2005 Nature [Lond] 434:843). One study has revealed 238 potential regulators of the Wnt pathway and half of them have human orthologs and several of them are involved in human disease (DasGupta R et al 2005 Science 308:826). The secretion of Wnt ligand requires a transmembrane protein (Wentless [Wls]/Eveness interrupted [Evi]). *Wls* is in chromosome 3 of *Drosophila* within 68A/B band; homologs are present in the *Caenorhabditis* and human genomes (Bänziger C et al 2006 Cell 125:509; Bartscherer K et al 2006 Cell 125:523). ▶organizer, ▶EGF, ▶Armadillo, ▶adrenal hypoplasia congenital, ▶sex reversal, ▶catenins, ▶GSK, ▶TCF, ▶heparin sulfate, ▶morphogenesis in *Drosophila*, ▶zeste, ▶SRY, ▶Wolffian duct, ▶Gardner syndrome; Kühl M et al 2000 Trends Genet 16:279; Peifer M, Polakis P 2000 Science 287:1606; Wilkie GS, Davis I 2001 Cell 105:209; van de Wetering M et al 2002 Cell 109:S13; Peifer M, McEwen DG 2002 Cell 109:271; Mosimann C et al 2006 Cell 125:327; review: Clevers H 2006 Cell 127:469; <http://www.stanford.edu/~rnusse/wntwindow.html>.

Winner's Curse: A finance/business concept. In competitive bidding, the winner may be the loser. This may be the case when the highest bidder overestimates the value of an item/stock or any other object in a bidding competition (e.g., at an auction) and it turns out that, even if some preferential values are added, the value of the purchase is lower than estimated/expected.

A similar situation may be observed in population genetics when screening is conducted for a low expression, rare allele. Before the tests are carried out the frequency of carriers or homozygotes for the disease can be only guessed. If the size of the population studied is too small, the information gathered may not be reliable and useful. If a very large population is tested—at great expense—and the results are still ambiguous, the investment in labor and other means is not worthwhile. Thus, the winner (the thorough investigator) suffers the curse of being a loser. ▶game theory, ▶critical population size, ▶mutation rate; examples for winner's curse: <http://www.techcentralstation.com>.

Wiskott-Aldrich Syndrome (WAS, Xp11.23-p11.22): This X chromosomal immunodeficiency disease causes eczema, reduced platelet size, bloody diarrhea, greater susceptibility to infections, lymphocyte malignancies and usually death before the age of 10. The prevalence is about 4×10^{-6} . The affected individuals are deficient in a 115 kDa lymphocyte membrane protein and the platelets are abnormally low in a glycoprotein (sialophorin). Carriers may be identified by linkage, lymphocyte analysis and nonrandom inactivation of the X chromosomes. WAS is allelic to the human Xp11.23 thrombocytopenia gene. This gene includes 12 exons in 9 kb genomic DNA and encodes 502 amino acids. The involvement of CDC42 signaling defect is likely. Cdc42-GTP is a far better agonist for the protein WASP than Cdc4 2-GDP (Leung DW, Rosen MK 2005 Proc Natl Acad Sci USA 102:5685). The WAS protein (WASP) mediates cytoskeletal rearrangement and transcriptional activation of T cells. ▶immunodeficiency, ▶T cell, ▶cytoskeleton, ▶thrombocytopenia, ▶thrombopathic purpura, ▶cancer, ▶CDC42, ▶agonist, ▶podosome, ▶WASP, ▶platelet; Silvin C et al 2001 J Biol Chem 276:21450; Devriendt K et al 2001 Nature Genet 27:313; Caron E 2002 Current Opin Cell Biol 14:82.

Witkop Syndrome: ▶tooth-and-nail dysplasia

WL (working level): Used for the characterization of short-lived radon decay products in 1 liter of

air resulting in the ultimate emission of 1.3×10^{-5} MeV of alpha radiation energy. WL is also defined as 2.08×10^{-5} joule h m⁻³. WLM (working level/month) = exposure of 170 h at 1 WL. ►radon

WNT1 (cysteine-rich glucoprotein ligand): The ~18 vertebrate genes have numerous and diverse roles in signaling to development, particularly along the anterior-posterior body axis. ►INT1 oncogene in mouse, ►wingless gene product in *Drosophila*, ►morphogenesis in *Drosophila* {63}, ►pattern formation, ►organizer, ►Gardner syndrome, ►gonads; Skromme E, Stern CD 2001 Development 128:2915.

Wobble: The 5'-base of the anticodon can recognize more than one kind of base at the 3' position of the codon, e.g., both U or C in the mRNA may pair with G, and both G and A may pair with U, or A or U, or C may recognize I (inosinic acid at the 5'-position in the anticodon). There is no AAA anticodon for Phe but the GAA anticodon recognizes both UUU and UUC codons in the mRNA. The GUU and GUC codons of Val are decoded by an anticodon AAC. Inosinic acid occurs in the anticodon of 8 tRNAs of higher eukaryotes, in 7 of yeast and in the tRNA^{Arg}₂ of prokaryotes and plant chloroplasts. Inosine may be formed from adenosine by adenosine deaminases. In tRNAs, however, a different dimeric deaminase, encoded in yeast by *Tad2* and *Tad3* genes, is active. This deaminase is related to the cytidine deaminase (CDA). According to the classical or universal genetic code of 61 sense and 3 missense codons, a minimum of 32 tRNAs would be required to recognize all the amino acids. Further simplifications permit protein synthesis, however, by 22–24 tRNAs. In the human genome tRNA genes have been found all over the genome yet 140 tRNA genes are crowded in a 4 Mb region of chromosome 6. The altered mitochondrial code requires modifications in the anticodon wobble. ►genetic code, ►tRNA, ►anticodon, ►isoacceptor tRNA, ►mtDNA, ►hypoxanthine, ►decoding; Crick FHC 1966 J Mol Biol 19:548; Agris PF 1991 Biochemie 73:1345; Lim VI 1994 J Mol Biol 240:8; Sibley AP et al 1986 FEBS Lett 194:131.

Wolbachia: Refers to an endocellularly infectious group of bacteria of arthropods, nematodes and crustaceans that are transmitted maternally and may cause feminization, cytoplasmic incompatibility and thelytoky. *Wolbachia* is localized to the stem cell niche of *Drosophila* germarium (Frydman HM et al 2006 Nature [Lond] 441:509). Infected males cannot produce viable offspring with uninfected females because of cytoplasmic incompatibility. They are compatible, however, with infected females and produce offspring. In some *Culex* mosquitoes variations have been found in cytoplasmic incompatibility controlled

by two prophage genes of *Wolbachia* involving ankyrin repeats (Sinkins SP et al 2005 Nature [Lond] 436:257). Antibiotics can cure incompatibility in many instances. The removal of *Wolbachia* by antibiotics from parasitic wasps stops oogenesis. *Wolbachias* as endosymbionts of filarial nematodes are responsible for the river blindness disease (filariasis). *Wolbachia* infection of flies with some oogenesis defect causing *Drosophila* *Sex-lethal* alleles surprisingly restores fertility (Starr DJ, Cline TW 2002 Nature [Lond] 418:76). *Wolbachia* may serve as an agent to block the spread of malaria by causing sterility in the insect host (Ito J et al 2002 Nature [Lond] 417:452). There are several related species. The *W. pipientis* genome of 1,267,782 bp has been sequenced and it appears to contain an unusually high number of mobile elements as well as essential difference in metabolism compared to related species e.g., *Rickettsia* (Wu M et al 2004 PLoS Biol 2:327). ►cytoplasmic incompatibility, ►thelytoky, ►symbionts hereditary, ►segregation distorter, ►pronucleus, ►Rickettsia, ►ankyrin; Stouthammer R et al 1999 Annu Rev Microbiol 53:71; Zimmer C 2001 Science 292:1093; Dedeine F et al 2001 Proc Natl Acad Sci USA 98:6247; Saint André v A et al 2002 Science 295:1892; <http://troi.cc.rochester.edu/~wolb/FIBR/database.html>.

Wolcott-Rallison Syndrome (WRS, 2p12): Involves mutation in the translation initiation factor EIF2AK3. The recessive disorder affects neonatal or infantile insulin-dependent diabetes. Later, bone defects (epiphyseal dysplasia, osteoporosis), retarded growth, liver and kidney malfunction, mental retardation and heart disease may complicate the condition. ►EIF2

Wolf: (*Canis lupus*, 2n = 78), a carnivorous mammal, which can form fertile hybrids with domesticated dogs (*Canis familiaris*, 2n = 78) as well as with the coyote (*C. latrans*, 2n = 78) but not with foxes (*Vulpes vulpes*, 2n = 36). Domesticated dogs appear to be much closer evolutionarily to wolves (on the basis of mtDNA) than to coyotes. ►fox

Wolf-Hirschhorn Syndrome: A condition, which involves deletion (unequal crossing over, insertion) in one of the short arms of human chromosome 4p16.1 (usually the paternal) resulting in severe growth, mental, face and genitalia defects, etc. The deletion generally eliminates HOX7 (homeobox 7), responsible for normal development in humans and mice. Hemizygosity for the gene is sufficient for the disease. The severity of the disease is affected by alteration at adjacent sites (Bergmann D et al 2005 Trends Genet 21:188). ►deletion, ►hemizygous, ►homeobox, ►homeotic genes, ►Huntington's chorea; Näf D et al 2001 Am J Hum Genet 10:91; Zollino M et al 2003 Am J Hum Genet 72:590.

Wolffian Ducts: Develop as a precursor of the male gonads of vertebrates. This development is enhanced under the influence of testosterone hormone. The male gonad (testes) is formed by the Sertoli cells that eventually surround the spermatogonia. The Leydig cells (Yao H-C et al 2002 *Genes Dev* 16:1433) secrete the steroid testosterone and the Sertoli cells produce the anti-Müllerian hormone (human chromosomal location 12q13), which causes regression of the uterus and the Fallopian tubes. ►gonads, ►Müllerian ducts, ►DSS

Wolf-Parkinson-White Syndrome: A heart disease with a short P and a long QRS phase of electrocardiography. It is also called preexcitation syndrome because the heart ventricles are excited prematurely. It may cause increased palpitations and sudden death. The causes are complex; dominant defects at chromosome 7q3 have been implicated and a mitochondrial component may also be involved. ►electrocardiography, ►mitochondrial diseases in humans [Leber hereditary optic dystrophy].

Wolfram Syndrome (DIDMOAD): Mutation in human chromosome 4p16.1 gene encoding a ~100 kDa transmembrane protein involves diabetes insipidus, diabetes mellitus, optic atrophy and deafness. It has been proposed that a large mitochondrial deletion extending over several coding sequences (7.6 kb) is responsible for these diseases but it has not been confirmed. ►diabetes, ►optic atrophy, ►deafness, ►mitochondrial diseases in humans; Strom TM et al 1998 *Hum Mol Genet* 7:2021.

Wolman Disease (lysosomal acid lipase deficiency): A condition due to autosomal recessive genes in the long arm of human chromosome 10q24-q25 and in mouse chromosome 19. The early onset forms are due to a deficiency of this enzyme (cholesteryl ester hydrolase) and are characterized by liver and spleen enlargement, failure to feed normally and death by the age of 2 to 4 months. The accumulation of cholesterol esters is caused by mutant alleles of the same locus. In some forms survival is till the teens. ►cholesterol, ►lysosomes, ►lipase; Du H et al 1998 *Hum. Mol. Genet* 7:1347.

Woodchuck: ►*Marmota monax*

Woodrats: There are many species mainly with $2n = 52$.

Woods' Light: Refers to an ultraviolet light source with nickel oxide filter and with a maximal transmission at about 365 nm while most other spectral regions are blocked. ►ultraviolet light

Woolly Hair: This may be black (and autosomal dominant) or blond (and autosomal recessive). In both cases, the hair is short and tightly curled.

Wordmatch: Finds exact matches of a given size between two protein sequences. (<http://ocgc.ca/programs/emboss/wordmatch.html>).

Working Hypothesis: This is an experimentally testable assumption regarding a problem.

Worm Genetics: An informal reference to *Caenorhabditis elegans*. ►*Caenorhabditis*

Woronin Bodies: These occur around fungal pores supposedly to protect against excessive leakage if the cells are damaged. (See Tenney K et al 2000 *Fungal Genet Biol* 31:205).

Wortmannin: A protein from *Penicillium fumiculosum*/*Talaromyces wortmanni* which is a stimulator of neutrophils and inhibitor of PIK, DNA-PK and thus inhibits the repair of double-breaks in the DNA (see Fig. W12). Wortmannin modulates the phosphatidylinositol metabolic pathway. ►neutrophil, ►PIK, ►DNA-PK, ►phosphatidylinositol; Wang H et al 2001 *Nucleic Acid Res* 29:1653.

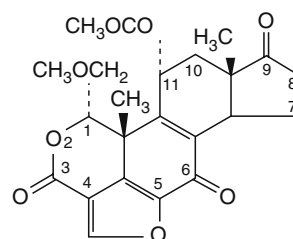


Figure W12. Wortmannin

Woude Syndrome: ►van der Woude syndrome

Wound Healing: Requires angiogenesis, which can be provided by administering angiogenic proteins such as vascular endothelial growth factor (VEGF) or placental growth factor. To ensure a stabilizing effect, the delivery of multiple growth factors may be helpful. Hypoxia-inducible factor (HIF) can stimulate angiogenesis. HIF-1 heterodimer has two subunits α and β . The former has an oxygen-sensitive degradation domain (ODD). This domain is prolyl hydroxylated in an oxygen-dependent manner and can bind the von Hippel-Lindau protein and consequently the HIF-1 α subunit is degraded by the proteasome under normal oxygen tension. Under hypoxia, HIF-1 α can heterodimerize with HIF- β and upon entering the nucleus it induces gene expression. The prevention of HIF- α degradation or its overexpression results in nuclear translocation and VEGF expression under normal oxygen level. If the ODD domain is removed, VEGF and other genes are upregulated. In a specially engineered vector complex on a fibrin surgical matrix, entrapped in a DNA nanoparticle delivered to the dermal wound of mice resulted in potent therapeutic

effects (Trentin D et al 2006 Proc Natl Acad Sci USA 103:2506). The disruption of the epithelial cell layer generates endogenous electric field and cell migration. Phosphatidylinositol-3-OH kinase- γ and PTEN genes are essential for electrical signal-induced cell migration and wound healing (Zhao M et al 2006 Nature [Lond] 442:457). ▶tissue engineering, ▶phosphoinositides, ▶PTEN, ▶von Hippel-Lindau syndrome, ▶VEGF, ▶angiogenesis

Wound-Healing Assay: Used to analyze cell migration. A confluent mammalian cell monolayer is scratched by a blunt pipette tip and the “wound” so generated heals by cell migration, which can be monitored by automatic devices (Todaro GJ et al 1965 J Cell Physiol 66:325). It also detects the metastatic ability of neoplasias (see Fig. W13). ▶metastasis, ▶neoplasia



Figure W13. Wound-healing time course

Wound Response: Upon wounding one leaf physiological changes take place in other parts of the plant body and the expression of proteinase inhibitors (Pin) is triggered by glycan, jasmonate and peptide signals. The 18-amino acid peptide signal, systemin, in tomato plants, wounded by herbivorous insects, stimulates proteinase expression. Salicylic acid may block the wound response. Wounding of plants may also induce a large number of genes of different function. The plants may produce peroxides against the microbes infecting the wounds. Phenolics may accumulate, photosynthesis may be reduced and ethylene biosynthesis may be induced. ▶glycan, ▶jasmonic acid, ▶insect resistance in plants, ▶host-pathogen relationship, ▶phenolics, ▶ethylene; Zhou L, Thornburg R 1999, p 127. In: Reynolds PHS (Ed.) Inducible Gene Expression In Plants. CAB, New York.

Wrapping Choice: A generalized transducing phage “chooses” to scoop up the host rather than the viral DNA and “wraps” it into the phage capsid. ▶transduction

Wright Blood Group: A very rare blood group; the frequency of the Wr(a) antigen is about 3×10^{-4} in Europe. ▶blood groups

Wright-Fisher Model: ▶genetic drift, ▶drift genetic

Wrinkled/Smooth: This is a gene locus of pea, immortalized by Mendel’s discovery of monogenic inheritance. The recessive “wrinkled allele” turned out to be an

insertional mutation. ▶pea for photograph of wrinkled and smooth seeds.

Writhing Number: This indicates the contortion of a DNA double helix in a supercoiled state. It measures the helix axis in space. ▶linking number; Kobayashi S et al 2001 Chem Pharm Bull Tokyo 49:1053.

Wrod Score (wrong lod score): Obtained when a linkage is estimated as lod scores on the assumption of an incorrect genetic model (ϕ). The genetic model in complex traits may easily be misspecified. ▶lod score, ▶mod score, ▶model genetic; Hodge SE, Elston RC 1994 Genet Epidemiol 11(4):329.

Wrongful Birth: Potential responsibilities of a physician or a genetic counselor for negligence in informing or prenatal care of prospective parent(s) about risks involving childbirth. (See Randall KC 1979 Hofstra Law Rev 8:257).

Wrongful Life: A potential responsibility of parents, physicians and genetic counselors for not preventing the birth of a child with a serious hereditary disease or in the case of illegitimacy, which may carry a social stigma. The affected offspring may sue. ▶counseling genetic, ▶genetic privacy, ▶confidentiality, ▶paternity test; Foutz TK 1980 Tulane Law Rev 54:480.

WW Domain: A two-tyrosine motif (38–40 amino acids) of signaling proteins and a binding site for proline-rich peptides. The binding of a WW domain by Pin1 and Nedd4 proteins apparently does not require prolines for binding, rather the WW domains are binding sites for phosphoserine and phosphothreonine. Among the many diverse proteins, their ligands include Cdc25C phosphatase, microtubule associated tau, carboxy-terminal of RNA polymerase II, etc. ▶SH2, ▶SH3, ▶pleckstrin, ▶PTB, ▶signal transduction, ▶Pin1; Nedd Sudol M, Hunter T 2000 Cell 103:1001.

www (world wide web): The system is available through the Internet with the aid of a browser program, which makes possible the search through a computer linked to the system. ▶Internet, ▶HTML

wx Gene (waxy): Occurs in various cereal plants and is used as a chromosome marker (in the short arm of chromosome 9–56 of maize). In the presence of the dominant allele starch is formed (stained blue by iodine stain). If it is replaced by recessive allele, amylopectin is formed (stained red-brown) because of a defect in NDP-starch glucosyltransferase. ▶iodine stain, ▶amylopectin, ▶TILLING

Historical vignettes

Edith Kramer 2002 American J Art Therapy 40(4):218

“How can we characterize [the opposite of kitsch] good art? Three elements seem essential; evocative power, inner consistency, and an economy of means so that the quality of the work would be diminished if anything would be added or omitted.”

Apparent mutations were recorded by the ancient literature. Aristotle says, “whoever does not resemble the parent is, in some respects, a monster, because in this case nature has deviated, to a certain degree, from the hereditary type” (*Generation of Animals*, Book IV, Part 3, Para. 1).

In 1844 WH Prescott retells the *History of the Conquest of Mexico* (Dutton, New York): “I must not omit to notice a strange collection of human monsters, dwarfs, and other unfortunate persons, in whose organization Nature had capriciously deviated from her regular laws. Such hideous anomalies were regarded by the Aztecs as a suitable appendage of state. It is even said, they were in some cases the result of artificial means, employed by unnatural parents desirous to secure a provision for their offspring by thus qualifying them for a place in the royal museum.”

Thus even induced mutation had been anticipated much before it had been experimentally demonstrated by HJ Muller and LJ Stadler in the mid 1920s.

X

x: Refers to basic chromosome number. ▶ [polyploids](#), ▶ [n](#)

\bar{x} : Denotes the arithmetic mean of the sample.

X: A symbol for crossing over or chiasma.

χ^2 : ▶ [chi square](#)

X¹⁷⁷⁶ (bicentennial): A bacterial strain with an absolute requirement for diaminopimelic acid (a lysine precursor) and needed for the growth of viable bacteria, and therefore it cannot survive outside the laboratory. It was so named in the US bicentennial year at the Asilomar Conference in 1976. ▶ [Asilomar Conference](#)

X Element: ▶ [chi elements](#)

Xa: A blood coagulation factor. It is also a plasmid factor that specifically cleaves protein after Arg of the tetrapeptide Ile-Glu-Gly-Arg that connects the 31 amino terminal of phage λ cII protein. ▶ [clotting](#), ▶ [lambda phage](#); Verner E et al 2001 J Med Chem 44:2753.

Xanthine: A purine derived from either adenine through hypoxanthine by xanthine oxidase or from guanine by deamination (see Fig. X1). By xanthine oxidase it is converted to uric acid. ▶ [uric acid](#)

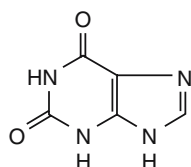


Figure X1. Xanthine

Xanthinuria (XDH, 2p23-p22): Refers to a recessive, xanthine dehydrogenase/oxidase deficiency resulting in the excretion of excessive amounts of xanthine and xanthine stones in the kidneys. The uric acid content of the urine and serum is reduced. The 36-exon gene spans ~60 kb DNA. ▶ [kidney diseases](#), ▶ [uric acid](#)

Xanthoma Cell (foam cell): Highly vacuolated because of excessive amounts of lipids.

Xanthomatosis: ▶ [cerebral cholesterinosis](#)

Xanthophyll: Refers to yellow carotenoid pigments that play an accessory role in light absorption. ▶ [photosystems](#); Ruban AV et al 2001 J Biol Chem 276:24862.

X-Box: The sequence—with some variations—of the X-boxes widely present in eukaryotes: GTTTCAT-GGAAAC. Using stringent criteria for X-boxes within 250 bp upstream of the start codon, 293 genes have been identified in *Caenorhabditis* (Chen N 2006 Genome Biol 7:R1216). X-box binding protein (XBP-1) is a transcription factor essential for hepatocyte growth, differentiation of cilia as well as for plasma cell differentiation. Overexpression of XBP-1 has been reported in breast cancer and other carcinomas (Fujimoto T et al 2007 Anticancer Res 27(1A):127). XBP1 has evolved a mechanism for “on-demand” switching of translation between two overlapping reading frames but it can provide functionality to both reading frames (Nekrutenko A, He J 2006 Trends Genet 22:645).

XBP: Encodes the 89 kDa subunit of human transcription factor TFIIF, corresponding to yeast *SSL2*, encoding a 105 kDa polypeptide. XBP-1 is required for the differentiation of plasma cells into B lymphocytes. ▶ [transcription factors](#), ▶ [B lymphocytes](#)

X2BP: MHC-II promoter binding protein, along with NF-Y and RFX. ▶ [RFX](#), ▶ [MHC](#); Reimold AM et al 2001 Nature [Lond]:412:300.

XCAP-C and XCAP-E: Proteins involved in the condensation of chromosomes. ▶ [condensin complex](#); Neuwald AF, Hirano T 2000 Genome Res 10:1445.

X Chromosomal Inactivation: ▶ [lyonization](#), ▶ [Barr body](#), ▶ [dosage compensation](#), ▶ [Xic](#)

X Chromosome: One of the sex chromosomes generally present in two doses in females and in one in males. The mammalian X chromosome developed from autosomes ~300 million years ago. In some species females are XY whereas in males either XX or XO or other chromosomal doses may be found. In species where the female is heterogametic, her sex chromosomal constitution is often designated as WZ and that of the male as ZZ. The sex chromosomes of the semi-aquatic, duck-billed platypus (*Ornitorhynchus anatinus*, 2n = 56), an egg-laying Australian mammal, share genes with the bird's Z chromosomes and the mammalian X (Grützner F et al 2004 Nature [Lond] 432:913). Sex chromosomes apparently evolved from autosomes. The PAR (pseudoautosomal) region is a relic of autosomal origin. It is assumed that the X chromosome underwent substantial evolution in humans and sequences fairly well conserved in other mammals but display only small homology with the bird's Z chromosome. Some of the genes were acquired from autosomes, other genes were retained or transposed to autosomes because even in males (with only one X) two doses were required for certain

developmental processes. Initially, in humans 1,098 genes (7.1/Mb) and 700 pseudogenes (4.6/Mb) have been revealed in the X chromosome.

More recent analysis has revealed 696 protein-coding genes and 652 X-linked and 432 X-derived pseudogenes. About 5% of the pseudogenes displayed some transcripts, indicating their role in genetic regulation. On an average, the pseudogenes differed from the parental gene by 70 changes/1,000 nucleotides. New exons were detected in 22% of the genes and 35% displayed exon skipping. Of the earlier reported 142 putative non-coding RNAs, 64 (44%) were untranslated segments of known genes (Harsha HC et al 2005 Nature Genet 37:331). Slightly different conclusions were reached by another contemporaneous publication (Ross MT et al 2005 Nature [Lond] 434:325).

The gene density and gene size is generally smaller than in the autosomes although the largest human gene, the muscular dystrophy gene is X-linked. The frequency of CpG islands is about half in the X compared to the genome average. Approximately 10% of the so-called cancer-testis antigens are in the human X chromosome. The cancer-testis antigens are specifically expressed in many different types of cancer cells (see e.g., MAGE). Apparently 153,146 single nucleotide polymorphisms occur in the X chromosome. The euchromatic part of the X chromosome contains 57% interspersed repeats versus 45% of the genome average. The L1 family constitutes 29% of the X versus only 17% of the genome average. Several human diseases are associated with deletions or inversion in X chromosomal duplications. There is a relatively longer 2.7 Mb pseudoautosomal (PAR1) and a shorter 330 kb PAR2 region shared with the Y chromosome where recombination can occur, but in some other homologous regions (XAR) there is no recombination between X and Y. The latter types can be mapped only by radiation hybrids. Only 54 of the annotated X chromosomal genes display homologies with Y. In the PAR1 region there are 24 and in PAR2 5 genes that may recombine. The latter ones are located in three groups on both sex chromosomes but they do not recombine. About 15 of the protein-coding Y chromosomal genes lack homologies in the X chromosome. The human X chromosome has lower variability (~60%) than the autosomes. Both human and mouse X chromosomes show very close synteny. One or more of the double (or multiple) X chromosome(s) of mammals are inactivated early in female development. Yet more than 15% of the genes escape inactivation (Ross MT et al 2005 Nature [Lond] 434:325). ▶Y chromosome, ▶chromosomal sex determination, ▶dosage compensation, ▶Barr body, ▶lyonization, ▶Ohno's law, ▶monotrene, ▶pseudoautosomal, ▶sex chromosome, ▶autosome,

▶Xist, ▶Tsix, ▶Xic, ▶radiation hybrid, ▶synteny, ▶L1, ▶Y chromosome, ▶heterochromatin; Vallender EJ et al 2005 Nature Genet 37:343; Chow JC et al 2005 Annu Rev Genomics Hum Genet 6:69.

X Chromosome Counting: This mechanism is used for sex determination in the case of XX versus XO. The *xol-1* gene of *Caenorhabditis* constitutes a switch mechanism that specifies male developmental course if it is inactive. In XX nematodes *xol-1* is repressed post-transcriptionally or the RNA-binding protein encoded by the *fox-1* gene reduces its level of expression. The transcription of gene *xol-1* is suppressed primarily by SEX-1 hormone receptor protein, which binds to the promoter in XX nematodes. ▶sex determination, ▶chromosomal sex determination, ▶dosage compensation; Maxfield Boumil R, Lee JT 2001 Hum Mol Genet 10:2225.

X Chromosome Inactivation: ▶lyonization, ▶Xic

XCID: X chromosome-linked severe combined immunodeficiency. ▶SCID, ▶immunodeficiency

xDNA (expanded DNA): Differs from the natural DNA double helix in that some of the natural bases are expanded by a benzene ring (B, red) and, therefore, the molecule is broader (A: adenine [purple], T: thymine [blue]) (see Fig. X2). Besides the bases shown, the others (C and G) can also be expanded; the sugar-phosphate backbone is omitted for the sake of simplicity. The designed duplex is right-handed and antiparallel, and hydrogen-bonded in a way analogous to that of Watson-Crick DNA. The sugar-phosphate backbone adopts a regular conformation similar to that of B-form DNA. The xDNA can encode more information than the natural one because it can use 8 instead of 4 nucleotides. It is more heat resistant than the natural DNA and it fluoresces. This property may make it useful for the detection of genetic defects. ▶base analogs, ▶hydrogen pairing, ▶Watson and Crick model, ▶DNA types; Kool ET 2002 Acc Chem Res 2002 35(11):936; Liu H et al 2003 Science 302:868; Lynch SR et al 2006 J Am Chem Soc

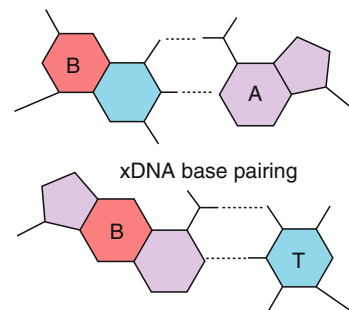


Figure X2. xDNA base pairing

128:14704; Leconte AM, Rosenberg FE 2006 Nature [Lond] 444:553.

Xenia: This is the expression of the gene(s) of the male in the endosperm (e.g., purple) following fertilization; the expression in the embryo may not yet be visible (see Fig. X3). ▶*metaxenia*



Figure X3. Xenia

Xenobiotics: Refers to compounds that do not naturally occur in living cells. They are often toxic or harmful substances.

Xenogamy: Meaning fertilized by different neighboring plants.

Xenogeneic: Refers to transplantation from another species (xenotransplantation). ▶*allogeneic*

Xenogenetics: The study of the effect of environmental factors on conditions under polygenic control. ▶*polygenic*

Xenograft: Refers to the transplantation of tissue from another species (e.g., animal→human). It poses problems of rejection and the likelihood of viral infection (e.g., porcine endogenous proviruses [PERV]) as well as the emergence of new diseases. The complement cascade of the immune system mediates the rejection. If swine, transgenic for the human complement, is used as a heart donor to baboons, the function of the heart is prolonged by several hours. The limited clinical evidence, however, does not indicate substantial risk in pig→human grafts. ▶*complement*, ▶*immune system*, ▶*transgenic*, ▶*epitope*, ▶*xenotransplantation*, ▶*gene therapy*, ▶*αGT*, ▶*PERV*; Matsunami K et al 2001 Clin Exp Immunol 126:165.

Xenology: A study of the combination of original and foreign genetic sequences within an organism or a group of organisms caused by horizontal transfer and transformation. ▶*homology*, ▶*transmission*, ▶*transformation*, ▶*infectious heredity*, ▶*orthologous loci*, ▶*paralogous loci*; Gogarten JP 1994 J Mol Evol 39:541.

Xenopus (*X. laevis*, South African clawed toad, $2n = 4x = 36$, DNA 3.1×10^9 bp): This is a species of frogs.

Being tetraploid and having a long generation time of several years does not make it a favorite object of genetic manipulations although it is an excellent object of embryological studies. The oocyte may reach 1.5 mm in size and it is thus visible by the naked eye and lends itself to various manipulations. Pioneering research was conducted with nuclear transplantation. Transformation of embryonic tissues was not as successful as expected because too few cells expressed the transgenes. Now techniques have been developed for transformation of sperms, and this will permit the study of dominant transgenes on various developmental and physiological processes. *Xenopus* (*Silurana*) *tropicalis* is the only diploid species (1.7×10^9 bp, generation time 4–6 months) but it is somewhat distantly related. *X. tropicalis* is very prolific (1,000–3,000 eggs per ovulation) and transformation is very efficient. ▶*toad*, ▶*frog*, ▶*transformation*, ▶*transgene*, ▶*Xenopus oocyte culture*; genetic regulatory networks in embryonic development: Koide T et al 2005 Proc Natl Acad Sci USA 102:4943; <http://www.dkfz-heidelberg.de/abt0135/axeldb.htm>; <http://www.nih.gov/science/models/>; <http://www.tigr.org/tdb/tgi/>.

Xenopus Oocyte Cultures: *Xenopus* frog oocytes are about 1 μ L in volume. They contain large amounts of DNA (12 pg in the nucleus, 25 pg in the nucleoli, 4 ng in the mitochondria). They can synthesize daily 20 ng of RNA and 400 ng of protein. About 10^6 to 10^7 bp DNA can be directly injected into the *germinal vesicle* (the nucleus). The injected DNA is packaged into the nucleosomal structure, and it is replicated and translated by the cellular machinery and the products are ready for analysis within a few hours. Recombinant DNA can be introduced and studied the same way. Exogenous DNA is replicated according to the cell cycle of the oocytes and no re-initiation of the foreign DNA replication occurs. All foreign DNAs are replicated according to the oocyte cell cycles and all the foreign replicational signals are overridden. Replication in the oocytes also is extremely rapid because transcription is halted during replication. *Xenopus* oocytes have been very successfully used for the structural, morphological analysis of vertebrate embryogenesis. They have proved to be extremely useful for the molecular analysis of transcription, regulation, cell-to-cell communication and early morphogenesis. ▶*oocyte*, ▶*protein synthesis*, ▶*morphogenesis*; Romero MF et al 1998 Methods Enzymol 296:17.

Xenorhabdus: *X. nematophila* is the best understood of the five identified species of *Xenorhabdus*. The bacterium colonizes the intestine of a non-feeding stage of *Steinernema carpocapsae* nematodes. The nematode is the vector that shelters the bacteria

from the competitive soil environment, and shuttles *X. nematophila* into insect hosts. The bacterium functions as a potent pathogen that infects and kills diverse insect species, which serve as the nutrient source for the development and reproduction of the nematode. Some *Xenorhabdus* species produce effective antibiotics against plant and animal pathogens. ► *Caenorhabditis*; Goodrich-Blair H, Clarke DJ 2007 Mol Microbiol 64:260.

Xenotransplantation: Refers to the transplantation of organs/tissues among different species and may involve the potential danger of transferring new viruses. On the other hand, xenotransplantation may have potentials in curing disease, e.g., the use of resistant baboon livers in the case of hepatitis B infections and baboon bone marrow for AIDS victims. The transplanted foreign cell or tissue may not function in the recipient or stimulate an adverse immune reaction. The transplanted tissue may incite the complement within minutes in hyperacute rejection. In some instances the reaction may be delayed for weeks but an acute vascular rejection may follow by interaction of the xenoreactive antibodies with the donor blood vessels. Galactose α -1,3-transferase knockout lines may overcome the immune reaction of the recipient against the graft but does not entirely solve the problem because the antibodies may attack other antigens. Genetically modified heme oxidase (HO-1) may provide some protection but it may generate toxic side effects (oxidant, bilirubin). The modification of the recipient antibodies against the transplant by genetic engineering may come into consideration. Also, e.g., the pig donor may be modified by human gene knock-ins. The porcine endogenous retrovirus (PERV) and some as yet unknown viruses may pose great risks not only to the recipient, but more importantly to the human populations also. Deleting the virus or inactivating them may become a means of protection. More research is required in this field. ► *xenogeneic*, ► *xenograft*, ► *immune tolerance*, ► *immunosuppression*, ► *grafting in medicine*, ► *rejection*, ► *baboon*, ► *hyperacute reaction*, ► *α GT*, ► *knock-in*, ► *PERV*, ► *OBA*, ► *microchimerism*, ► *1,3-galactosyl-transferase α* ; Sim KH et al 1999 Can J Gastroenterol 13:11; Lai L et al 2002 Science 295:1089; Cooper DKC et al 2002 Annu Rev Med 53:133; <http://www.fda.gov/cber/gdlns/clinxeno.htm>.

Xenotropic Retroviruses: These are replicated only in the cells of species other than the species from which the virus originated. ► *ecotropic* and *polytropic virus*

Xeroderma Pigmentosum (XP): The primary symptoms may develop during the first year of life as extremely pronounced freckles induced by sunshine proliferate and appear as skin cancer (see Fig. X4). In some cases

the central and peripheral nervous systems are also affected. Usually A (9q22.2-q31), B (2q21), C (3p25), D (19q13.2-q13.3), E (11p12-p11), F (16p13.2-p13.1) and G (13q32-q33) types are distinguished, the other complementation groups (H and I) are less clear. Complementation group A encodes DNA damage binding protein B, and D codes for helicases, C initiates global nucleotide excision repair and selectively repairs cyclobutane pyrimidine dimers rather than 6–4 photoproducts. The XP-D gene product is a subunit of the TFIIH transcription factor and it is regulated by vitamin D receptor-responsive genes (Drané P et al 2004 Mol Cell 16:187). XPC is homologous to yeast genes RAD23A and B and it is sometimes referred to as XPC-HR23A and B. Types F and G are defective in a DNA repair endonuclease (homologous to yeast RAD1).



Figure X4. A mild form of xeroderma pigmentosum. The initial signs are usually very heavy freckles that gradually develop into different types of skin cancer. The progress of the disease is enhanced by sunshine. A variety of ailments may accompany the main symptoms and the afflicted persons rarely reach adulthood. (Courtesy of the March of Dimes—Birth Defects Foundation)

One type of XP, XP-V patients, representing about 25% of the clinical cases of the disease, do not have a defect in nucleotide exchange repair and are not sensitive to UV radiation. In such cases the defect is caused by failure of replication of the leading strand through pyrimidine dimers. The replication (by polymerase ζ) of the lagging strand associated with the photoproduct can slowly proceed and results in an asymmetrical replication fork with an extended single strand leading strand of the parental DNA molecule. Unfortunately, pol ζ is error prone and the error-free pol η (encoded by *RAD30*) is defective in XP-V individuals. Humans have two homologs of *RAD30*.

As a consequence the patients' cells become susceptible to mutation and carcinogenesis.

Another form involving milder symptoms is also known which has an apparently dominant inheritance. In some forms the defect is not in excision repair but a post-replicative anomaly causes light sensitivity. Similar gene(s) occur(s) in mouse and five *RAD* genes of yeast also have defects in excision repair. ▶DNA repair, ▶excision repair, ▶Bloom syndrome, ▶ataxia telangiectasia, ▶Fanconi syndrome, ▶Cockayne syndrome, ▶*RAD*, ▶light-sensitivity diseases, ▶thrichothiodystrophy, ▶helicase, ▶complementation groups, ▶DDB, ▶DNA polymerases, ▶ultraviolet-sensitivity syndrome, ▶cyclobutane dimer, ▶pyrimidine-pyrimidinone photoproduct, ▶5',8-purine cyclodeoxynucleosides, ▶transcription factors, ▶vitamin D; Bootsma D et al 1998, p 245. In: Vogelstein B, Kinzler KW (Eds.) The Genetic Basis of Human Cancer. McGraw-Hill, New York.

Xerophyte: A draught-tolerant plant which thrives in low precipitation regions.

X-Family of DNA Polymerases: pol β -like nucleotidyl-transferases. Pol λ is similar to pol β . TdT is a non-templated polymerase of immature lymphocytes in the bone marrow. Pol μ is homologous to TdT. TdT promotes diversity in non-homologous end joining (HEJ). Pol μ and Pol λ are also involved in NHEJ (Nick McElhinny SA et al 2005 Mol Cell 19:157). Pol σ is a templated or non-templated enzyme establishing sister chromatid cohesion. ▶DNA polymerases, ▶nucleotidyl-transferase, ▶NHEJ; Aravind L, Koonin EV 1999 Nucleic Acids Res 27:1609; Rattray AJ, Strathern JN 2003 Annu Rev Genet 37:31.

XG (Xg[a]): A blood group antigen determining dominant factor in the short arm of the human X chromosome. It appears that this end of the X chromosome can recombine with the Y chromosome, and it does not undergo lyonization like the majority of the X chromosomal genes. ▶lyonization, ▶blood groups, ▶ichthyosis; Fouchet C et al 2000 Immunogenetics 51(8–9):688.

Xgal (5-bromo-4-chloro-3-indolyl- β -D-galactopyranoside): When β -galactosidase enzyme hydrolyzes this chromogenic substrate blue color is formed in a bacterial culture plate. ▶ β -galactosidase

XIAP: A caspase inhibitor which is a member of the human IAP family of proteins. ▶IAP, ▶caspase; Riedl SJ et al 2001 Cell 104:791.

XGLD: Denotes poly(A) polymerase. ▶symplekin

Xic (X chromosome inactivation center, Xq13.2): Its effect is somewhat similar to but unlike *Xist*, which

has a fairly localized cis effect, *Xic* extends globally on the X chromosome. *Xic* delays the replication of the X chromosome and mediates the hypoacetylation of histone 4 and contributes to heterochromatinization of that chromosome. *Xic* controls chromosome counting in dosage compensation and selects one or more of the X chromosomes for inactivation. In case there is a short transient pairing between two normal X chromosomes, which both carry the *Xic* locus, the inactivation of the X chromosomes is random. In case *Xic* and *Tsix* are deleted, X chromosome inactivation may become erratic, i.e., either it does not take place at all or both are inactivated or one is inactivated and the other is not. In case an additional copy of *Xic* is introduced by transformation and the two X chromosome cannot pair at the *Xic* site then neither of the two X chromosomes is inactivated (Carrel L 2006 Science 311:1107; Xu N et al 2006 Science 311:1149). ▶lyonization, ▶*Xist*, ▶methylation of DNA; Prissette M et al 2001 Hum Mol Genet 10:31.

XID: Refers to sex chromosome-linked immunodeficiency. ▶scid, ▶immunodeficiency

Xist (X chromosome inactive sequence transcript at Xq13.2; antisense of *XIST* is *TSIX* at Xq13.2): This gene has no protein product but its 15-kb RNA covers the genes of the inactive mammalian X chromosome beginning from the *Xic* site (Xq13.2). The *Xist* RNA gene evolved only in placental mammals by pseudogenization (functional relaxation) of a protein-coding gene (Duret L et al 2006 Science 312:1653). Deletion analysis demonstrates that the first exon of human *XIST* is sufficient for both transcript localization and the induction of silencing and that, unlike in mice, the conserved repeat region is essential for both functions. This indicates that there is a difference in inactivation between humans and mice (Chow JC et al 2007 Proc Natl Acad Sci USA 104:100104).

Underacetylated histones, methylated CpG islands and late replication of the DNA cause inactivation of the X chromosome. *Xist*-triggered inactivation is preceded by methylation of histone-3 at lysine 9. *Xist* acts in cis and may also be expressed in autosomes or in transgenes inserted in the autosomes and affect the neighboring genes. Since the X chromosomal inactivation is restricted to the copies of the X chromosome present more than once, it has been suggested that *Xist* counts (senses) X chromosomal dosage. Deletions downstream of *Xist* make it constitutive, i.e., it is expressed and causes inactivation of the X chromosome concerned. From 15 kb downstream location a 40 kb apparently antisense RNA *Tsix* is transcribed across the *Xist* locus in both X chromosomes of diploids until the determination of inactivation. Prior to the onset of the inactivation *Tsix* is transcribed in an antisense orientation only on the

X chromosome destined for inactivation and it is shut down again after the inactivation begins. Apparently, *Tsix* determines the selection of the X chromosome for inactivation by the *Xce* controlling element without affecting the silencing itself. Knockout of the paternal *Tsix* does not affect embryonal development. If the *Tsix* knockout is transmitted through the female, embryos of both sexes die because both X chromosomes are silenced in the female offspring and the single X in males. The role of *Tsix* in humans and mice is debated. The site *Xite* promotes *Tsix* persistence on the active X chromosome (Ogawa Y, Lee JT 2003 Mol Cell 11:731). In X chromosome: autosome translocations the inactivation is inefficient because the spreading of the inactivating signal is not favored by the chromatin structure (Popova BC et al 2006 Proc Natl Acad Sci USA 103:7706). It has been reported that the breast cancer gene BRCA1 alters the Xist function but this finding has not been confirmed (Xiao C et al 2007 Cell 128:977), it was, however, substantiated later (Silver DP et al 2007 Cell 128:991). ▶[lyonization](#), ▶[Xic](#), ▶[dosage compensation](#), ▶[histones](#), ▶[imprinting](#); Lee JT 2000 Cell 103:17; Matsui J et al 2001 Hum Mol Genet 10:1393; Migeon BR et al 2001 Am J Hum Genet 69:951;

Heard E et al 2001 Cell 107:727; Wutz A et al 2002 Nature Genet 30:167; Plath K et al 2002 Annu Rev Genet 36:233; Sibata S, Lee JT 2003 Hum Mol Genet 12:125; Migeon BR 2003 Nature Genet 33:337; Lee JT 2003 Nature Genet 33:337; mechanism of *Xist* effect on its partner: Carrel L 2006 Science 311:1107.

Xklp1: ▶[NOD](#)

xl: The prefix for *Xenopus laevis* toad protein or DNA or RNA, e.g., xIRNA.

XLA: X-linked agammaglobulinemia. ▶[agammaglobulinemia](#)

XLFCernunnos: A protein similar to XRCC4 with a role in NHEJ. ▶[NHEJ](#), ▶[XRCC4](#), ▶[X-ray repair](#); Ahnesorg P et al 2006 Cell 124:301.

X-Linked: The gene is within the X chromosome (see Fig. X5). ▶[Z linkage](#)

XLNO 38: A protein with homologies to nucleoplasmin. Although it is not part of the mature ribosomes, it is associated with both small and large subunits of ribosomes. Seemingly its role is chaperoning the assembly of basic proteins on ribosomal RNA precursors. ▶[chaperone](#)

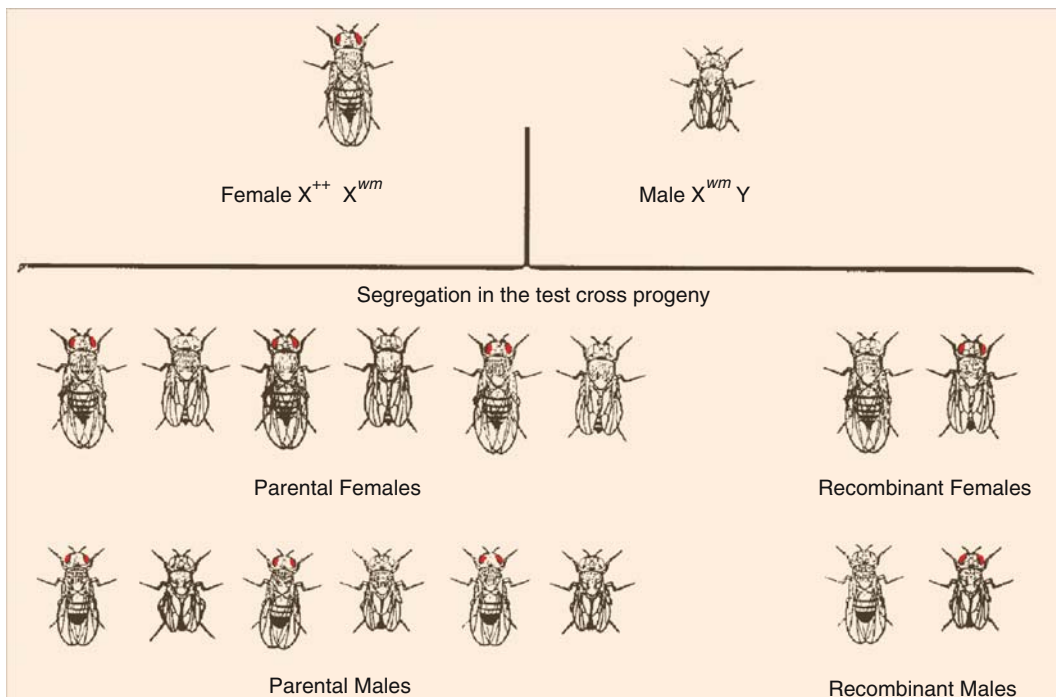


Figure X5. The female fly is heterozygous for the recessive white eye and the miniature body-size genes, the male X chromosome carries the two recessive alleles. Since in the female fly recombination is normal (unlike in the *Drosophila* male), free recombination yields $16/64 = 0.25$ recombinants in both sexes

XLP: The lymphoproliferative syndrome encoded at Xq25 causes extreme sensitivity to infectious mononucleosis and Epstein-Barr virus infection. ► [Epstein-Barr virus](#), ► [mononucleosis](#)

XML (extensible markup language): A flexible communication system that is capable of sharing format and data through the World Wide Web. ► [www](#), ► [XSL](#); <http://www.w3.org/XML/>.

XML for INSD sequence submission: <http://www.insdc.org/documents.html>; ► [INSD](#)

X-Numerator: The number of X chromosomes relative to autosomes (X:A) in the determination of sex. ► [chromosomal sex determination](#)

XO: Having a single X chromosome in a diploid cell. ► [sex determination](#), ► [Turner syndrome](#)

Xolloid: ► [bone morphogenetic protein](#)

XPA, XPD, XPF: ► [ABC excinucleases](#)

XPB: Denotes the DNA helicase. It is the equivalent of Ss12. ► [DNA repair](#), ► [excision repair](#)

XPC-HR23A or B: ► [Xeroderma pigmentosum](#)

XPG: Refers to xeroderma pigmentosum endonuclease. ► [xeroderma pigmentosum](#), ► [endonuclease](#), ► [DNA repair](#)

X-Ray Caused Chromosome Breakage: The major effects of ionizing radiations on living cells are chromosome breakage (see Fig. X6). Chromosome breakage has been extensively utilized for the genetical analyses of knocking out genes, the production of radiation hybrids, deletion mapping, genomic subtraction, etc. The destructive effects of the radiation depend on the nature of radiation. Soft X-rays having higher density of linear energy transfer, break the chromosome more effectively than the shorter wavelength and high-energy hard X-rays. The destructive effect also depends on the species exposed, the type of tissues irradiated, the physiological conditions during the delivery of the radiation, the repair system, etc. In *Drosophila* and locusts usually 1000 – 5000 R doses are employed for chromosome breakage in adults and embryos. In the case of gonadal radiation, 100 to 500 R may be effective. In the testis cells of *Macaca mulatta* monkey an increase of radiation dose from 25 R to 400 R resulted in close to exponential increase of chromosome breakage reaching about 1.5% of the chromosomes at the highest dose. In the large nuclei and chromosomes of *Trillium* and *Vicia faba* generally 100 to 500 R break the root tip chromosomes and lower doses may be sufficient if applied to pollen mother cells. For the smaller nuclei of maize 800 to 1500 R

may be chosen. The very small somatic nuclei of *Arabidopsis* may tolerate 5–10 fold higher doses of irradiation than maize. ► [radiation sensitivity](#), ► [radiation hazard assessment](#), ► [radiation effects](#), ► [LET](#), ► [radiation hybrid](#), ► [cathode rays](#); Brinkley BR, Hittelman WN 1975 Int Rev Cytol 42:49.

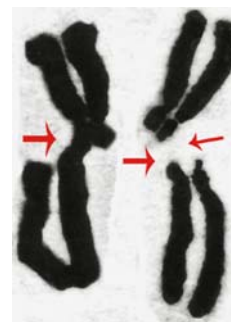


Figure X6. Single- and double-strand breaks. Courtesy of Brinkley BR, and Hittelman WN

X-Ray Crystallography: ► [X-ray diffraction analysis](#)

X-Ray Diffraction Analysis: Used for the analysis of the structure of molecules by determining the angles of electron scattering upon exposure to X-rays. When a large number of a particular type of molecules in an array is irradiated they scatter the incident electrons. Where the scattered beams cancel each other, no bright image is formed. Where however the scattered electrons reinforce each other because they diffracted by a certain common arrangement of crystals or molecules, a bright image is formed on the screen. Thus, the intensity of the spots on the screen provides a basis for calculating and determining the internal, three-dimensional structure of the object. ► [nuclear magnetic resonance spectrography](#), ► [X-rays](#); <http://www.rcsb.org/pdb/>.

X-Ray Hazard: ► [X-ray](#), ► [radiation hazard assessment](#), ► [radiation protection](#), ► [radiation effects](#), ► [X-ray caused chromosome breakage](#)

X-Ray Repair: Involves excision repair mechanisms. A human X-ray repair gene locus has been isolated through complementation of excision repair-deficient Chinese hamster ovary cells by human DNA. XRCC2 repairs DNA double-strand breaks by homologous recombination. The locus XRCC1, encoding a ligase III polypeptide, has been assigned to human chromosome 19q13.2-q13.3. XRCC4 locus (human chromosome 5) is involved in the determination of X-ray sensitivity in the G1 phase of the cell cycle but its response in the S phase appears normal, indicating that the defective mutants (in Chinese hamster ovary cells)

are deficient in the repair of DNA double strands. The XRCC9 allele is in the FANC-G complementation group of Fanconi anemia. ▶radiation sensitivity, ▶excision repair, ▶DNA repair, ▶physical mutagens, ▶X-rays, ▶Fanconi anemia, ▶X-ray caused chromosome breakage, ▶XRCC, ▶NHEJ, ▶XLF; Tebbs RS et al 1999 Dev Biol 208:513.

X-Ray Sensitivity: ▶X-ray repair, ▶X-ray caused chromosome breakage, ▶nuclear size

X-Ray Therapy: ▶radiation therapy

X-Rays: Ionizing electromagnetic radiation emitted by the cathode tubes of Röntgen machines within the range of 10^{-11} and 10^{-8} m wavelength (see Table X1). The shorter ones (hard rays) have greater penetration and lower ionization density while the longer wavelengths (soft rays) have reduced penetration and denser dissipation of the energy. Hard rays cause more discrete lesions to the genetic material, soft rays are expected to produce greater chromosomal breakage. The spectrum of the radiation may be controlled by filters. The effectiveness of the filters depends on the attenuation of the radiation by the nature of the filter. The fluence of the radiation can be defined as $I = (I_0)e^{-\mu x}$ where I = fluence at a certain depth x ; I_0 = the fluence rate at the surface and μ = the specific attenuation coefficient and μ/ρ is mass attenuation coefficient (ρ = density of the absorbing material). At photon energy MeV = 0.1, the mass attenuation coefficients (cm^2/g) are for aluminum (0.171), iron (0.370), lead (5.400), water (0.171) and concrete (0.179). ▶cathode rays, ▶ionizing radiation, ▶X-ray repair, ▶Compton effect, ▶radiation hazard assessment, ▶radiation protection, ▶radiation effects, ▶Ku

XRCC: The genes XRCC2 (7q36.1), XRCC3 (14q32.3), XRCC4 (5q13-q14) and XRCC5 (Ku70, 2q35) in humans along with RAD51 (15q15.1, 17q11-q12) and DMC control recombination and repair. XRCC1 stimulates human polynucleotide kinase and promotes the repair of single-strand DNA breaks. XRCC3 protein, in concert with RAD51C, facilitates

homologous pairing and recombinational repair. ▶X-ray repair, ▶RAG, ▶RAD, ▶Ku, ▶DNA repair, ▶DMC, ▶XLF; Whitehouse CJ et al 2001 Cell 104:107; Masson J-Y et al 2001 Proc Natl Acad Sci USA 98:8440; Brenneman MA et al 2002 Mol Cell 10:387.

Xrn1p: An exonuclease degrading RNA beginning at the 5' end.

XREF: Cross-referencing model organism genes with human disease and other mammalian phenotypes. ▶databases

XRS: Mutation conveys radiation sensitivity, DNA double-strand break repair and V(D)J recombination. ▶DNA repair, ▶V(DJ); Matheos D et al 2003 J Cell Sci 116:111.

X-SCID (X-linked severe combined immunodeficiency): ▶SCID

XSL (XSLT): A software for transforming XML documents. ▶XML; <http://www.org/TR/xslt>.

X-Stain: A fluorochrome which stains the X chromosome differently from other chromosomes. ▶chromosome painting, ▶FISH

XX Males: A normal condition in birds and some other species, but rare 5×10^{-5} condition of it is a male mammalian (human) births. The recurrence risk is, however, about 25%. Most of them (90%) have a X chromosome—Y chromosome short arm translocation. Their phenotype and infertility resemble those of Klinefelter syndrome cases although the afflicted persons tend to be shorter in stature. Their distinction from hermaphrodites requires the use of an appropriate, fluorochrome-labeled cytogenetic probe for the critical Y chromosomal segment. ▶sex determination, ▶sex chromosomal anomalies in humans, ▶Klinefelter syndrome, ▶hermaphrodite; Vidal VP et al 2001 Nature Genet 28:216.

XXX: ▶triplo-X, ▶metafemale, ▶sex chromosomal anomalies in humans

XXY: ▶Klinefelter syndrome, ▶sex chromosomal anomalies in humans

Xylan: This is poly(β -D-xylopyranose[1→4]) polysaccharide of plant cell walls. The enzyme xylanase facilitates maize pollen tube penetration into silk by xylan hydrolysis (Suen DF, Huang HC 2007 J Biol Chem 282:625). ▶silk

Xylella fastidiosa: A bacterium that causes citrus variegated chlorosis which affects a broad spectrum of crop species. It has a 2,679,305 bp sequenced genome and two plasmids (51158 bp and 1285 bp). (See Nature 406:151).

Table X1. Thickness of the protective shield needed in mm using lead, depending on voltage and amperage of the X-radiation

| Kilo Volt | milliAmpere | | |
|-----------|-------------|------|------|
| | <5 | 5–10 | 30 |
| 50 | 0.5 | 0.6 | 0.7 |
| 125 | 1.5 | 3.0 | 3.5 |
| 250 | 6.0 | 7.0 | 8.0 |
| 400 | 16.0 | 18.0 | 21.0 |

Xylem: The transporting tracheid vessels of plants carrying nutrients and water from the roots toward the leaves. ►vascular tissue, ►phloem, ►proteoglycan

Xylene ($C_6H_4[CH_3]_2$): Synonymous with xylol, this highly flammable and irritant, narcotic liquid is used as a solvent in microtechnique. The permissible threshold of vapors in the air is 100 ppm.

Xylene Cyanole FF: ►tracking dyes

Xylose (wood sugar, $C_5H_{10}O_5$): An epimer of aldopentoses. It is used in the tanning industry, as a diabetic carbohydrate food, and in clinical tests of intestinal absorption. ►epimer

Xylulose ($C_5H_{10}O_5$): An intermediate in the pentose phosphate pathway which accumulates in the urine of pentosuric patients (see Fig. X7). ►pentose phosphate pathway, ►pentosuria

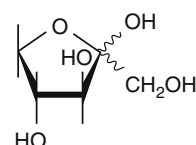


Figure X7. D-Xylulose

XY Body: ►sex vesicle

XYY: ►sex chromosomal anomalies in humans

Historical vignettes

AH Sturtevant commented on human genetics in 1954 (Science 120:405)

“Man is one of the most unsatisfactory of all organisms for genetic study. The time interval between successive generations is long, at best individual families are too small to establish ratios within them, and the test-matings that a geneticist might want cannot be made. Obviously no geneticist would study such a refractory object, were it is not for the importance that a knowledge of the subject has in other fields.”

Holger Breithaupt remarked in 2002 (EMBO Reports 3:391)

“Now imagine if Bush, Watson, Venter or Steffánsson had had to have their proposals passed by a democratically elected committee. Most likely, their obviously great ideas would have died an early and lonely death.”

Calvin B Bridges (1889–1938) was one of the most talented geneticists of all time. Most everybody can identify him as the founder of cytogenetics through his studies on nondisjunction, or with his work on salivary maps. Fewer people remember that he initiated the currently used gene symbols in *Drosophila*. Bridges also discovered the basic types of chromosomal aberrations:

“The general term ‘deficiency’ is used to designate the loss or inactivation of an entire, definite, and measurable section of genes and framework of a chromosome. A case of deficiency in the X chromosome of *Drosophila ampelophila* [currently *melanogaster*] occurred in September 1914, and has given rise to a whole series of

correlated phenomena. The first indication of this deficiency was the occurrence of a female which had failed to inherit from her father his sex-linked dominant mutant ‘bar,’ though she inherited in a normal manner his sex-linked recessive mutant ‘white.’ This female, when bred, gave only about half as many sons as daughters, the missing sons, as shown by the linkage relations, being those which had received that X which was deficient for bar” (*Genetics* 2:445, 1917).

Two years later Bridges reported duplications and translocations in the Abstracts of the Zoological Society (published in *Anatomical Record*):

“... a section of the X-chromosome, including the loci for vermilion and sable, became detached from its normal location in the middle of the X-chromosome and became joined on to the ‘zero’ end (spindle fiber) of its mate. For certain loci this latter chromosome carries two sets of genes—those present in the normal location and also the duplicating set. If a male carries the recessive genes for vermilion and for sable in the normal loci and the wild-type allelomorphs in the duplicating loci, he is wild-type in appearance precisely as though he were an XX female heterozygous for vermilion and sable. ...

“A third case is the transposition of a piece of the second chromosome to the middle (spindle fiber) of the third chromosome. The genes of this duplication piece show linkage to both the second and the third chromosome at the same time” (*Anat. Record* 15:357–358, 1919).

The basis of a crossover reducer as an inversion of the third chromosome of *Drosophila* was identified by Alfred H. Sturtevant (1891–1970) in 1926 (*Biol. Zbl.* 46:697).

Y

Y: The symbol of pyrimidines in nucleic acid sequences.

Y Box Proteins: Members of a family of transcription factors that bind to an inverted CCAAT box (Y box) that activates genes involved in cell proliferation and growth. Y box proteins interact with other proteins and modulate transcription. The absence of mouse MSY2 protein causes infertility due to developmental defects in gametogenesis in otherwise healthy-appearing male and female animals (Yang J et al 2005 Proc Natl Acad Sci USA 102:5755). (See Ladomery M, Somerville J 1995 Bioessays 17:9).

Y Chromosome: One of the sex chromosomes present in males (XY) generally. However, in some species (birds, insects, fishes) females are XY and males may be XX or XO. In organisms with homogametic males their chromosomal constitution is commonly identified as WW. In the majority of the species the Y chromosome has only genes for sex differentiation or sex determination. These genes in the non-recombinant (NRY, ~35 Mb) part are involved in sex and fertility determination whereas the other Y chromosomal genes have homologies with a common segment of the X chromosome (Xq21, 3.4 Mb with two genes) as well as sequences scattered in autosomes. Some X-transposed sequences are degenerate and contain 27 pseudogenic homologs of the X chromosomal genes. It was earlier held that the major part (~95%) of the Y chromosome lacked homology to the X chromosome and was thus unable to recombine with the X chromosome. Recent research, however, has revealed that this male-specific region (MSY, 8 Mb in the short and 14.5 Mb in the long arm) is flanked on both sides by pseudoautosomal sequences where recombination is actually a normal and frequent occurrence (Skaletsky H et al 2003 Nature [Lond] 423:825). The MSY also includes the so-called ampliconic sequences (high density of genes and repeats) with highly conserved tracts maintained by gene conversion. Of the eight large palindromes at least six contain testes determining genes. The MSY includes 156 transcription units in its euchromatic sequences. Further, 78 of the protein-coding units correspond to nine different MSY-specific gene families, encoding at least 27 distinct proteins or protein families. The TTY2 gene family includes at least 26 members arranged in tandem repeats. They are transcribed in the testis and in the adult kidney but some of them are not translated. Evolutionists have suggested that the general low gene number is a consequence of the absence of recombination. R.A. Fisher assumed that

the absence of recombination and genes is due to the fact that recombination would mess up the system of sex determination and would lead to intersexes. The diminution of the gene content of the Y chromosome has been attributed to Muller's ratchet. Molecular markers for the Y chromosome (>250) are increasing and it is now possible to trace paternal lines of evolutionary descent on the basis of variations in these chromosomes. This analysis is analogous to the use of mtDNA for the development of evidence for (mitochondrial) Eve's origin (Su B et al 1999 Am J Hum Genet 65:1718). Data on the Y chromosome should be carefully evaluated in pedigree analysis because the paternity may be equally likely for grandfather, brothers, cousins, etc., in the same family or even illegitimate male relatives. On the bases of the Y chromosomal constitution, 10 lineages appear to account for more than 95% of the current European human populations. The distribution of the Y haplotype shows more geographic than linguistic diversity because language influences were acquired more frequently than genes. The diversity of the human Y chromosome is lower than that of any other chromosome. The diversity between the human Y chromosome and that of the chimpanzee is larger (1.78%) than between the whole genomes where the difference is 1.23% (Kuroki Y et al 2006 Nature Genet 38:158). The Y chromosome of *Drosophila pseudoobscura* has no homology to that of *D. melanogaster* (Carvalho AB, Clark AG 2005 Science 307:108). ►sex determination, ►SRY, ►recombination variations of, ►Muller's ratchet, ►Eve foremother of molecular mtDNA, ►human evolution, ►F_{ST}, ►mutation rate, ►holandric genes, ►UEP, ►azoospermia, ►chimpanzee; for Thomas Jefferson's paternity analysis see Nature [Lond] 396:27; Nature [Lond] 397:32 and the rare K2 type Y chromosome (King TA et al 2007 Amer J Phys Anthropol 132:584; Owens K, King M-C 1999 Science 286:451; Kayser M et al 2001 Am J Hum Genet 68:173; Stumpf MPH, Goldstein DB 2001 Science 291:1738; Underhill PA et al 2001 Ann Hum Genet 65:43; Tilford CA et al 2001 Nature [Lond] 409:943; Hurles ME et al 2002 Genetics 160:289; Bachtrog D, Charlesworth B 2002 Nature [Lond] 416:323; Jobling MA, Tyler-Smith C 2003 Nature Rev Genet 4:598.

YAC: Refers to yeast artificial chromosome vectors equipped with a yeast centromere and some (*Tetrahymena*) telomeres in a linear plasmid containing selectable markers, ARS (autonomously replicating sequence) for the maintenance and propagation of eukaryotic DNA inserts in cloning of larger than 200 kb size sequences. YACs play an important role in identifying contigs in physical mapping of larger genomes, as well as in situ hybridization, map based gene isolation, etc. The rate of instability of YAC has been estimated to be about 2%. In mitotic yeast cells

YACs behave like other chromosomes. Meiosis can be analyzed by tetrads although recombination appears to be reduced. YACs may be maintained through some cell divisions in the mouse cytoplasm and behave like *double minute* chromosomes or they may be integrated into the mouse chromosomes. ▶anchoring, ▶contigs, ▶YAC library, ▶in situ hybridization, ▶chromosome walking, ▶pulsed field gel electrophoresis, ▶DM; Peterson KR 1999 Methods Enzymol 306:186; Brown WR et al 2000 Trends Biotechnol 18:218; Adam G et al 1997 Plant J 11:1349; Ragoussiz J, Monaco AP 1996 Methods Mol Biol 54:157, see Fig. Y1.

YAC Library: Contains large restriction fragments of genomic DNA cloned in YAC vectors and separated by pulsed field gel electrophoresis. A YAC library generally comprises 100 to 250 kb (or larger) size DNA fragments in multiple (at least five) copies if possible, covering the entire genome of an organism. Selecting the appropriate YAC clone for the purpose of finding the region of interest, the YAC library in yeast colony filter hybridization experiments is probed by RFLPs, PCR, inverse polymerase chain reaction probes,

plasmid rescue or by other means. ▶YAC, ▶contigs, ▶pulsed field gel electrophoresis, ▶colony hybridization, ▶RFLP, ▶PCR, ▶inverse polymerase chain reaction, ▶plasmid rescue, ▶probe, ▶genome project; Larin Z et al 1997 Mol Biotechnol 8:147.

YAK (*Bos grunniens*): This is a “wild ox” and also an Asian draft animal, $2n = 60$.

YAM (*Dioscorea* spp): A tropical food crop. The Asian and African species are $x = 10$ but the American are $x = 9$. The actual chromosome numbers vary from diploid to decaploid.

Yama: A Ced-3-like protease, also known as CPP32β. ▶apoptosis

Yang Cycle: The pathway of biosynthesis of ethylene from 2-keto-4-methylthiobutyrate (KMB)→ S-adenosyl-L-methionine (AdoMet)→5'-methylthioadenosine (MTA)→5'-methylthioribose (MTR)→5'-methylthioribose-1-phosphate (MTR-1-P)→KMB. AdoMet is then converted to 1-amino-cyclopropane-1-carboxylic acid (ACC) by ACC synthase and ACC oxidase generates ethylene. ▶ethylene,

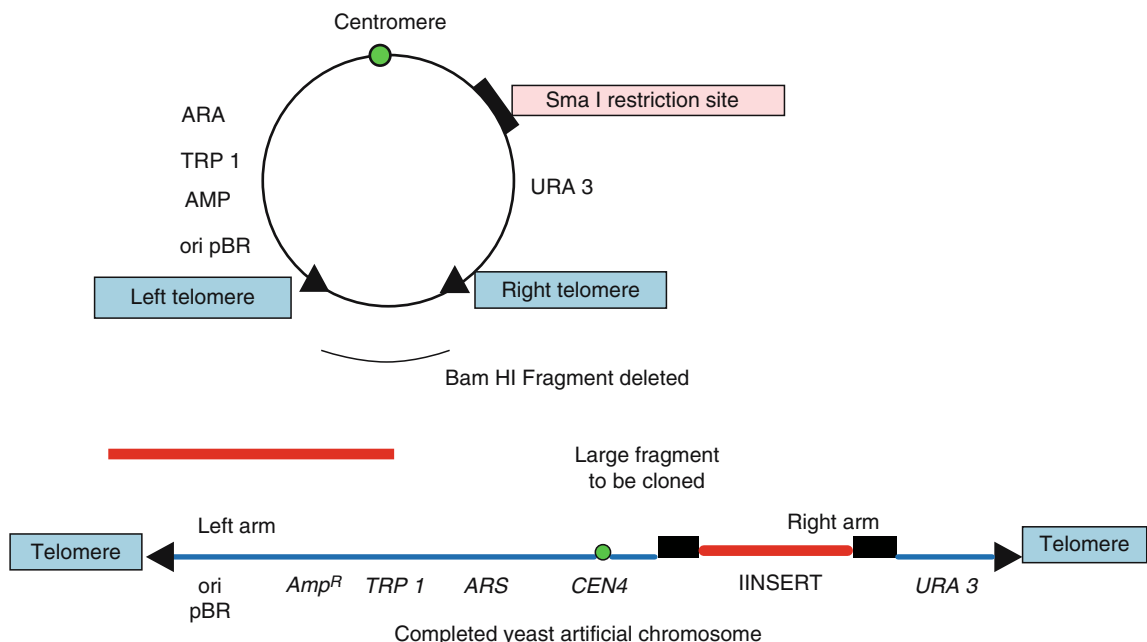


Figure Y1. Top: A circular yeast plasmid with *Tetrahymena* telomeres. A segment of the pBR322 prokaryotic plasmid contains the replicational origin and the *Amp^R* gene (selectable in *E. coli* for ampicillin resistance). The *ARS* (autonomous replication sequence), cloned centromere of yeast chromosome 4 (*CEN 4*), restriction enzyme recognition sites where the plasmid can be opened for insertion and later ligation are shown. The *TRP1* (tryptophan) AND *URA 3* (uracil) genes of yeast serve to ascertain that both arms are present and the transformant can synthesize tryptophan and uracil. A piece of the plasmid between the two Bam sites and also the yeast *HIS* (histidine) gene are deleted. Because of the pBR322 sequences, this vector replicates in *E. coli* as well as in eukaryotic cells. All details are not shown and the diagram is not to scale. Other YAC vectors are similar but not identical with this model. Bottom: Completed linear YAC. (Modified after Burke DT et al 1987 Science 236:806)

► **plant hormones**; AdoMet, Pardee AB 1987 J Cell Physiol Suppl 5:107.

YAP1: Refers to yeast transcription factor which regulates oxidative stress. ► **oxidative stress**; Wood MJ et al 2004 Nature [Lond] 430:917.

Yarrowization: ► **vernalization**

YBP: Years before present.

Y Chromosomal Linkage: ► **holandric genes**

Ycp: ► **yeast centromeric vectors**

Ydj1: Refers to the yeast homolog of DnaJ. ► **DnaJ**, ► **chaperones**

Yeast (budding yeast): ► *Saccharomyces cerevisiae*

Yeast (fission yeast): ► *Schizosaccharomyces pombe*

Yeast Artificial Chromosomes: ► **YAC**

Yeast Centromeric Vectors (Ycp): These carry centromeres, telomeres and ARS, and they can be linear or circular. Their stability improves with increasing length (see Fig. Y2). ► **YAC**, ► **vectors**

Yeast Cell Density Test: Cell suspension at 0.1 O.D. (optical density) at 600 nm corresponds to $\sim 3 \times 10^6$ cells per mL.

Yeast Episomal Vector: Carries the origin of replication of the 2 μ m yeast plasmid and can be propagated independently in the cytoplasm or integrated into a chromosome. ► *Saccharomyces cerevisiae*, ► **yeast plasmid 2 μ m**, ► **vectors**

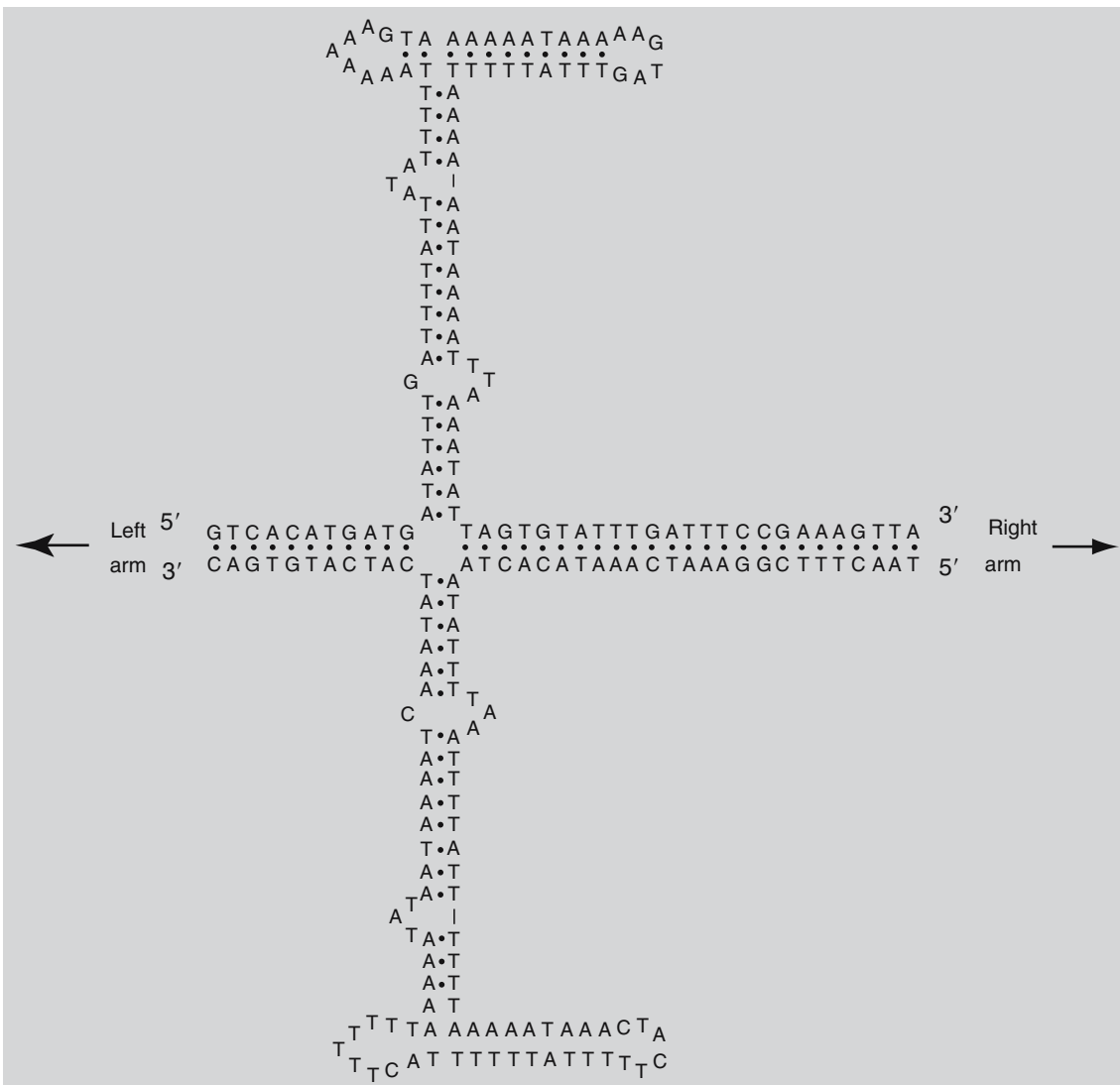


Figure Y2. Yeast centromeric region 3. From Clark L et al Stadler Symp 13:9

Yeast Hybrids: ▶two-hybrid method, ▶split-hybrid system, ▶three-hybrid system, ▶reverse two-hybrid system, ▶four-hybrid system, ▶one-hybrid binding assay

Yeast Integrating Vector (YI): Replicated only by the host, it behaves like a gene in the chromosome, can show homologous recombination, duplications and substitutions like bacterial episomes. Although it can generate chromosomal rearrangements its stability is extremely high but its ability to transform is extremely low. ▶vectors

Yeast Plasmid 2 μm: This circular duplex DNA plasmid of 6,318 bp contains genes for replication and can thus maintain a copy number of about 50/cell but it lacks any selectable marker in native form. By attaching it to the pBR322 *E. coli* plasmid shuttle vectors (ca. 8.5 kbp) have been generated that carry the bacterial histidine operon (as selectable marker), and it is also expressed in bacteria as well as in budding yeast because a segment of this plasmid can serve as a promoter for the operon. ▶yeast vectors, ▶*Saccharomyces cerevisiae*, ▶histidine operon, ▶selectable marker; Velmurugan S et al 1998 Mol Cell Biol 18:7466.

Yeast Proteome: YPD has been analyzed as multi-protein complexes beyond binary interactions. The proteome represents the arrangement of the interacting networks within the cell and include the mitochondria. ▶genetic networks, ▶proteome; Wuchty S, Alamaas E 2005 Proteomics 5:444; Wiwatwattana N, Kumar A

2005 Nucleic Acids Res 33:D598; <http://www.proteome.com/>.

Yeast Replicating Vectors (Yrp): These carry autonomously replicating sequences (ARS), have moderate stability and relatively low copy number, and they may be integrated into chromosomes. ▶vectors

Yeast Transformation: Can involve a number of different changes in the yeast chromosome at the site of transformation. (See Fig. Y3, ▶transformation genetic fungal transformation).

Yeast Transposable Elements: ▶Ty, ▶Ω

Yellow Crescent: Cytoplasmic motions in the fertilized ascidian embryo may generate a yellowish area that is broken up and shared by the cleavage cells thus revealing the origin of the differentiating cell lineage.

Yellow Fever: A viral (*Flaviviridae*) tropical disease primarily caused by the *Aedes aegypti* mosquito. Symptoms include high fever, headache, aching muscles, vomiting and backache and may be followed by shock, bleeding, kidney and liver failure. Liver failure causes jaundice (giving yellow fever its name). The fatality rate is ~50%. Preventive measures are avoiding exposure to mosquito bite and vaccination. Infants under the age of 6 months, pregnant women, immunocompromised persons and people allergic to egg should not be vaccinated. The spherical virions (40–50 nm) covered by a polyhedral capsid are decorated by small spikes. The RNA genetic material of the

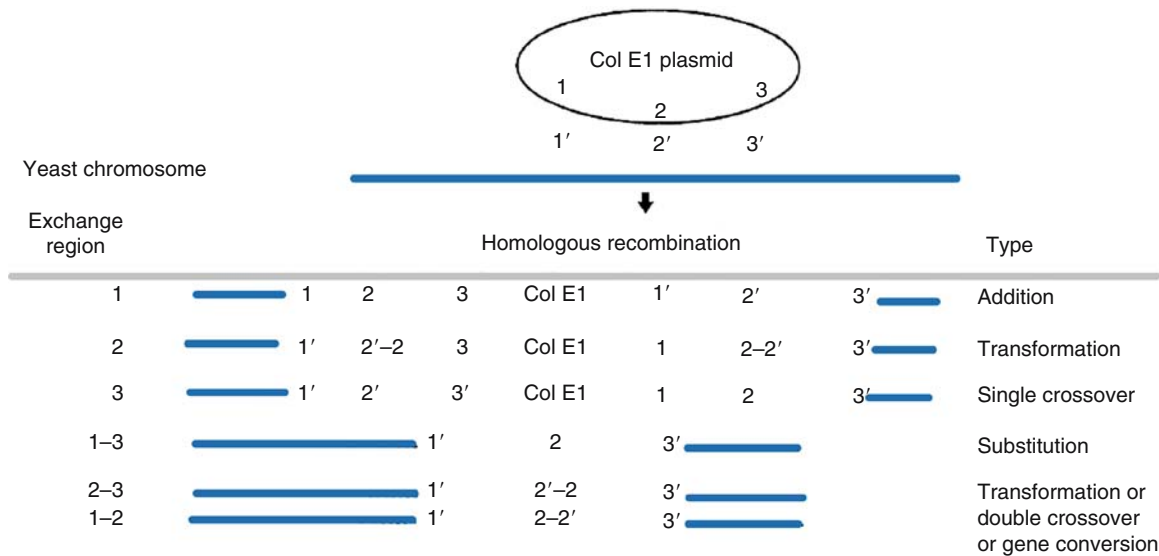


Figure Y3. The various mechanisms of transformation and recombination between plasmid and chrosomal DNA in yeast. Gene 2' is an auxotrophic marker; gene 2 is a prototrophic homologue; 1' and 3' are flanking chromosomal sequences homologous to 1 and 2 in the plasmid with a Col E1 or other replicator. (Modified after Hinnen, Botstein & Davis in *Molecular Biology of the Yeast Saccharomyces*, Strathern, et al., eds. 1981 Cold Spring Harbor Lab. Press, Cold Spring Harbor, NY.)

virus consists of a single long open reading frame of 10,233 nucleotides, which can encode a polypeptide of 3,411 amino acids. The structural proteins are located within the amino-terminal 780 residues of this polyprotein; the remainder of the open reading frame consists of non-structural viral polypeptides. This genome organization implies that mature viral proteins are produced by post-translational cleavage of a polyprotein precursor (Rice CM et al 1985 Science 229:726).

Yep: ►yeast episomal vector

YEPD: Refers to yeast-peptone-dextrose culture medium.

Yersinia: A group of gram-negative bacteria responsible for bubonic plague (characterized by enlarged lymph nodes [bubo]), gastroenteritis, etc. in rodents and humans acquired through fleabites. Generally, but not always, infectiveness of the flea carriers may be blocked during the early stages of the incubation period (Eisen RJ et al 2006 Proc Natl Acad Sci USA 103:15380). The sequenced genome of *Y. pestis* includes a 4.65 Mb chromosome and three plasmids of 96.2, 70.3 and 9.6 kb. It contains 150 pseudogenes. The genome shows frequent insertion sequences and intragenic recombinations. The bacteria secrete the Yop protein that targets primarily dendritic cells, macrophages and neutrophils of the immune system but rarely the B and T lymphocytes (Marketon MM et al 2005 Science 309:1739). YopJ acetylates and inhibits MAPK kinase activation and inhibits NF- κ B signaling, thus disarming the innate immune system. YopJ acts as an acetyltransferase, using acetyl-CoA, and modifies critical serine and threonine residues in the activation loop of MAPKK6 and prevents phosphorylation (Mukherjee S et al 2006 Science 312:1211). Yersinia protein kinase A (YpkA) disrupts the eukaryotic actin cytoskeleton. Its Rac1 binding domain mimics the host guanine nucleotide dissociation inhibitors of Rho GTPases (Prehna G et al 2006 Cell 126:869). Pneumonic plague development requires the presence of plasminogen-activating protease (Lathem WW et al 2007 Science 315:509). ►virulence, ►biological weapons, ►plague, ►plant vaccines, ►herpes, ►cytoskeleton, ►Rac, ►RHO; Parkhill J et al 2001 Nature [Lond] 413:323; Hinnebusch BJ et al 2002 Science 296:733; Cornelis GR 2002 Nature Rev Mol Cell Biol 3:742; genome: <http://bbrp.lnl.gov/bbrp/html/microbe.html>.

YES: Refers to the yeast – *E. coli* shuttle vector. ►shuttle vector; Elledge SJ et al 1991 Proc Natl Acad Sci USA 88:1731.

YES1 Oncogene: This is in human chromosome 18q21. Its protein product is homologous to that of Roux'

sarcoma virus (SRC) and it is also a protein tyrosine kinase. In association with other proteins (YAP), it acts as a transcriptional co-activator. ►tyrosine kinases, ►oncogenes, ►palmitoylation

Y-Family DNA Polymerases: These are error-prone enzymes such as the prokaryotic UmuD'₂C (pol v), Din B (pol IV) and the yeast proteins Rev1 (cooperating with pol ζ) and Rad30. They copy damaged DNA efficiently, make frequent incorporation error ($\sim 10^{-1}$ to 10^{-3}), rely on mispairing, use mismatches, misaligned templates, etc. Pol η is defective in xeroderma pigmentosum-V. Pol θ incorporates nucleotides opposite purines much more efficiently and faithfully than against pyrimidines. Human Pol θ incorporates dCTP opposite template G through the G.C + Hoogsteen base pair (Nair DT et al 2005 Structure 13:1569). It has the ability to bypass deaminated cytosine but it is error prone when the DNA is undamaged and it inserts G opposite to T or U templates; it appears to be responsible for somatic hypermutation. Human Pol θ replicates the DNA by Hoogsteen base pairing (Nair DT et al 2004 Nature [Lond] 430:377). Pol κ is activated by an arylhydrocarbon receptor (benzo[a]pyrene) and may be a repair enzyme by bypassing DNA lesions but it may insert A across abasic sites. The Rev1 polymerase uses a protein template. ►DNA repair, ►error-prone repair, ►DNA polymerases, ►error in replication, ►X family of DNA polymerases, ►Rev1, ►Hoogsteen pairing; Goodman MF 2002 Annu Rev Biochem 71:17; Rattray AJ, Strathern JN 2003 Annu Rev Genet 37:31.

YFP (yellow fluorescent protein): Used as a vital stain and is studied by FRET. ►FRET; Galperin E, Sorkin A 2003 J Cell Sci 116:4799.

YI: ►yeast integrating vector

yIF-2: Refers to the yeast eIF-5B; it is homologous to the prokaryotic IF2. ►eIF-5B

Yin Yang (YY1, NF-E1): A multifunctional zinc finger transcription factor of growth factors, hormones and cytokines. YY1 is also a potential negative regulator of the tumor suppressor p53 (Sui G et al 2004 Cell 117:859). ►DNA-binding protein domains, ►animal hormones, ►cytokines; Santiago FS et al 2001 J Biol Chem 276:41143.

Yin Yang Haplotypes: These two haplotypes display differences in each SNIPs. ►haplotype, ►SNIPs; Zhang J et al 2003 Am J Hum Genet 73:1073.

Yin-Yang Crosses: A QTL is mapped by crossing to strains A and B. New strains are expected to segregate in crosses with one (A) or the other (B) and thus QTL

fine mapping becomes feasible. ►QTL; Shifman S, Darvasi A 2005 Genetics 169:849.

Y-Linked: ►holandric gene

Yohimbine: An alkaloid produced by African plants of the *Rubiaceae* and *Apocynaceae* families; their extracts have been used as an adrenergic blocking medicine for arteriosclerosis and hypertension. It is supposedly an aphrodisiac (see Fig. Y4). ►ferritin, ►aphrodisiac; Morales A 2001 World J Urol 19(4):251.

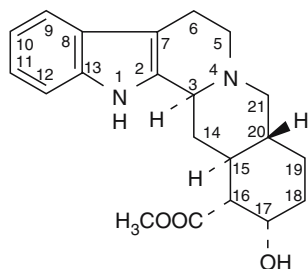


Figure Y4. Yohimbine

Yolk: The complex nutrients embedding the animal egg. ►egg, ►vitellogenin

YPD: ►yeast proteome

YPD: A yeast nutrient medium containing g/L yeast extract 10, glucose 20, Bacto-Peptone 10 or 20.

YPGE: A nutrient medium containing yeast extract (10 g), Bacto-Peptone (10 g), glycerol (20 g) and ethanol (10 g) per liter of H₂O.

YPL.db (Yeast Protein Localization database): <http://ypl.tugraz.at>.

YPT: A homolog of Sec and RAB. ►Sec, ►RAB

Y RNAs: These have a phylogenetically conserved secondary structure consisting of at least three stems and small internal loops. In humans, Y1, Y3, Y4 and Y5 have been identified but their function is unclear. It is suspected that they regulate ribosomal protein synthesis.

Yrp: ►yeast replicating vectors

YT Blood Group: Coded in human chromosome 7q.

YT Bacterial Medium: H₂O 900 mL, bacto-tryptone 16 g, bacto-yeast extract 10 g, NaCl 5 g, pH 7.0 (adjusted by 5N NaOH), filled up to 1 L and diluted to half before use.

Yttrium (Y): An extremely rare metal; the ⁹⁰Y has a half-life of 64 hours and has been used for internally exposing cancerous tissues to β-radiation. ►ionizing radiation, ►isotopes, ►magic bullet

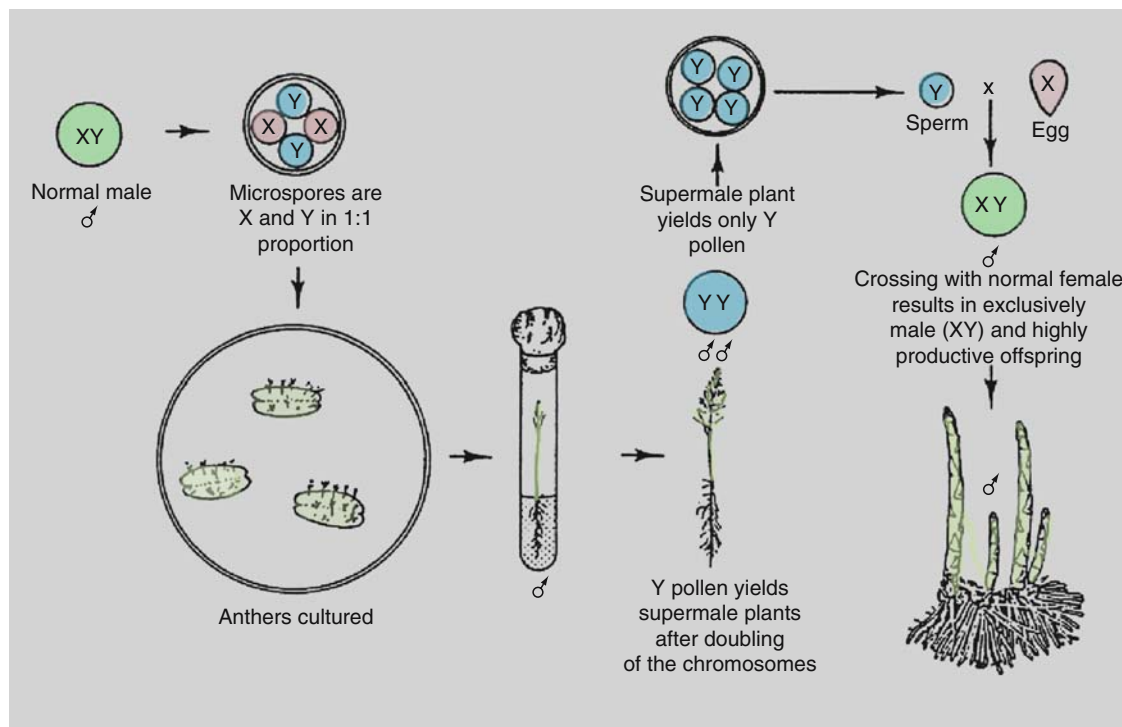


Figure Y5. Production of (YY) all-male asparagus

Yuasa Oncogene: Its human homolog is in chromosome 7.

YY Asparagus: By regeneration of plants from microspores and chromosome doubling, plants can be

obtained with this chromosomal constitution. The practical advantage of this vegetatively reproducible plant is the approximately 30% higher yield of edible spears. (See Fig. Y5, for embryogenesis, somatic).

Historical vignettes

Oscar Hertwig on genetics: “The hypothetical idioblasts... are according to their different composition, the bearers of different properties, and produce by direct action, or by various methods of cooperation, the countless morphological and physiological phenomena, which we perceive in the organic world. Metaphorically they can be compared to the letters of the alphabet, which, though small in number, when combined form words, which in their turn, combine to form sentences or to sounds, which produce endless harmonies by their periodic sequence and simultaneous combination.” (*The Cell*, Macmillan, New York, 1895, page 340)

Although Friedrich Miescher a contemporary of Mendel described nucleic acids in 1871, there remained an almost century-long disconnect between his findings and Mendel's. It is interesting to note that the nature of the mechanisms of fertilization remained an enigma even to Miescher. “So werden wir von allen seiten genöthigt, es mit Bestimmtheit auszusprechen: *Es giebt keine spezifischen Befruchtungsstoffe*. Die chemischen Thatsachen haben secundäre Bedeutung; sie sind einem höheren Gesichtspunkt untergeordnet.” (Miescher. 1874). [There is no specific fertilization-substance. The chemical realities have secondary meaning; they are subject to a higher order of strategy.] (Miescher F 1874 Die Spermatozoen einiger Wirbelthiere. Ein Beitrag zur Histochemie. Verhandl Naturforsch Ges Basel 6, (issue I):138–208.)

Z

Z (or *z* or *Z* score): The standard normal probability density function calculated by the formula:

$$Z = \frac{1}{\sigma\sqrt{2\pi}} e^{-(Y-\mu)^2/2\sigma^2}$$

where *Y* is the normal variate, $\pi \cong 3.14159$ and $e \cong 2.71828$, μ is the mean and σ is the standard deviation. The *z* values are generally read from statistical tables. *Z* indicates the height of the ordinate of the curve and thereby the density of the items. ► [standard deviation](#), ► [normal distribution](#), ► [confidence intervals](#), ► [F distribution](#)

Z Buffer: Na₂HPO₄·7H₂O 0.06 M, NaH₂PO₄ 0.04 M, KCl 0.01 M, MgSO₄·7H₂O 0.001 M, β-mercaptoethanol 0.05 M, pH 7. Do not autoclave it.

Z Chromosome: Refers to the sex chromosome present in both sexes of a species with heterogametic females (thus comparable to the X chromosome). Males are ZZ and females are WZ. ► [W chromosome](#), ► [sex determination](#)

Z Disc (Z-disk): ► [sarcomere](#)

Z Distribution: A statistical device for testing the significance of the differences between correlation coefficients in case the null hypothesis is not $r = 0$. The relation of *z* to *r* has been elaborated by R.A. Fisher as $z = (1/2)[\ln(1 + r) - \ln(1 - r)]$ and its standard error as $\sigma_z = \frac{1}{\sqrt{(n-3)}}$. For routine calculations, tables are available in statistical textbooks. ► [covariance for correlation coefficient](#)

Z DNA (zig-zag DNA): A relatively rare left-handed double helix that may be formed in the short (8–62 bp) regions of alternating purines and pyrimidines (ATGTGTGT, GCATGCAT). The polyGC.polyGC sequences are most favorable for B→Z transition. In some species CA/TG repeats are most conducive for Z DNA formation. Alternating purine-pyrimidine tracts may also modulate the transcription in a plus or minus direction. Base sequences near the transcription starting point favor the formation of Z DNA and it may stimulate transcription. Nucleosomes are not formed in the Z DNA tract, thus facilitating the access of transcription factors. In some genes, however, such as in the constitutive nucleolin gene, Z DNA in the promoter downregulates transcription. Vaccinia virus is no longer lethal in mice if the Z DNA binding site is lost. Four families of proteins bind to the crystal structure of Z DNA: ADAR1, an editing enzyme, LM1, an interferon inducible

protein, E3L, a pox virus virulence factor and an orthologue of PKR, interferon-induced protein kinase. Z DNA occurs in a dynamic state; it is formed and then it can revert to the B form of the DNA. There is a transition point between the common B and Z DNA forms (see Fig. Z1). The handedness changes abruptly from left to right by a sharp turn of the phosphate backbone. At the transition point an adenine (A0) and thymine (T0), respectively, are extruded as shown by the crystal structure (Ha SC et al 2005 Nature [Lond] 437:1183). B-Z DNA conformational polymorphism is optically detectable on single-walled carbon nanotubes in whole blood, tissue and within living mammalian cells (Heller DA et al 2006 Science 311:508). The figure shows space-filling models (modified after Dickerson RE et al 1982 Science 216:475). In mammals, Z DNA forming sequences induce a high level of chromosomal instability by generating double-strand breaks and large deletions. These deletions at the Z DNA may raise the incidence of certain cancers by increased transcription (Wang G et al 2006 Proc Natl Acad Sci USA 103:2677). In bacteria, the Z DNA related deletions are short.

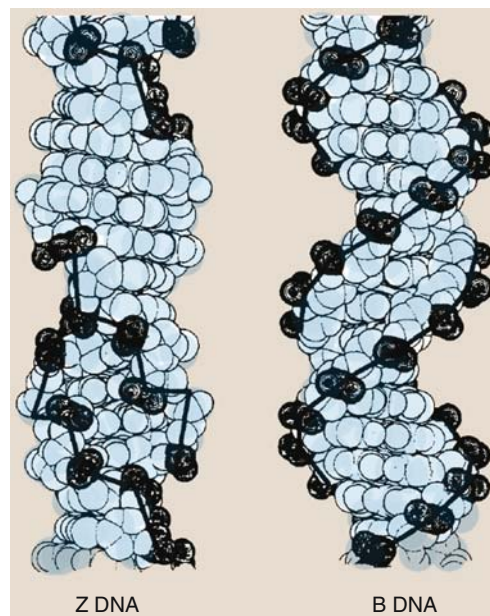


Figure Z1. The heavy black line represents the sugar-phosphate backbone

An alternating deoxycytidine-deoxyguanosine dinucleotide repetitive sequence [d(CG)*n*] can potentiate transcription in yeast when placed approximately three helical turns (28 bp) upstream of the cytochrome *c* 1 (CYC1) TATA box. Transcriptional activation by the d(CG)₉ repeat sequence depends on

the Z conformation. The activation is core promoter-specific and most effective when situated 28 bp or below upstream of the TATA box. Changing the distance between the d(CG)₉ repeat sequence and the TATA box modulates the extent of activation. Linker-DNA region is formed at the Z DNA structure with two flanking nucleosomes. Z DNA creates an open chromatin state at the promoter by displacing nucleosomes from its environs and establishing the boundaries of its neighboring nucleosomes (Wong B et al 2007 Proc Natl Acad Sci USA 104:2229). ▶DNA types, ▶ADAR, ▶RNA editing, ▶nanotechnology; Liu R et al 2001 Cell 106:309; Rothenburg S et al 2001 Proc Natl Acad Sci USA 98:8985; Rich A, Zhang S 2003 Nature Rev Genet 4:566.

Z Inactivation: The Z chromosome of birds has the same role in sex determination as the X chromosome in mammals yet its genes are not inactivated in homogametic individuals. ▶dosage compensation; Kuroda Y et al 2001 Chromosome Res 9:457.

Z Linkage: Refers to genes syntenic in the Z chromosome. ▶X-linked

Z Ring: Same as Fts Z ring. ▶tubulin

Z RNA: This left-handed molecule may occur in double-stranded RNA and is similar to Z DNA. ▶Z DNA, ▶ADAR; structure and origin: Placido D et al 2007 Structure 15:395.

Z Scheme: An additional (zig-zag) scheme to generate enough ATP by photosynthesis. Through a two-step process (photosystem I and II) an electron passes from water but there is not enough energy in a single quantum of light to energize the electron directly and

efficiently all the way from PS II to the top of PS I and make NADP⁺. The leftover energy makes pumping H⁺ possible across the membranes to capture some light energy for synthesizing ATP. The redox state of plastoquinone regulates the transcription of genes encoding the reaction center proteins of both photosystem I and II. ▶photosystems; Prince RC 1996 Trends Biochem Sci 21:121; Allen JF 2003 Science 299:1530; Allen JF, Martin W 2007 Nature [Lond] 445:610, see Fig. Z2.

Z Score: ▶Z

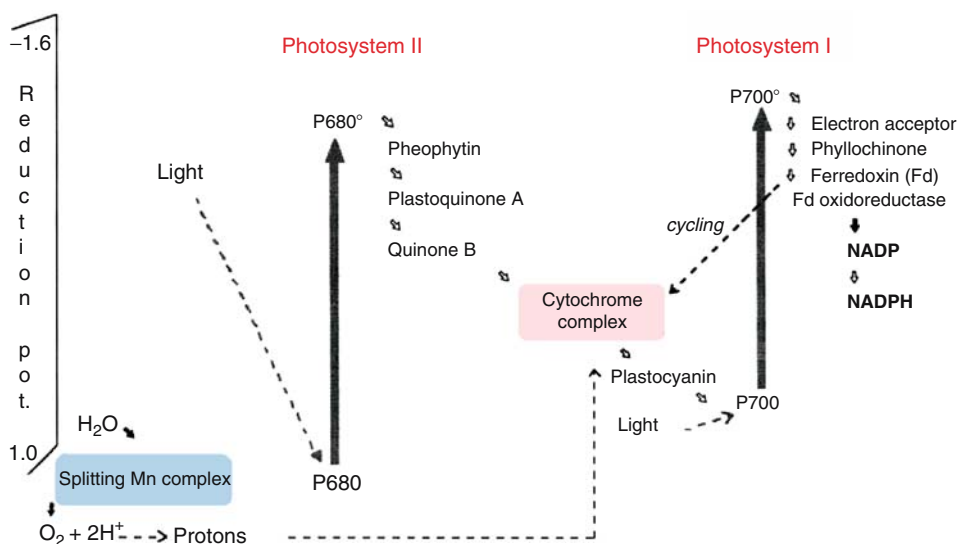
z Value: The natural logarithm of the ratio of two estimated standard deviations. ▶variance

ZAG (Zn-α₂-glycoprotein): Though this resembles MHC class I heavy chain molecules, it is different because it cannot bind β₂-microglobulin. It occurs in the majority of body fluids and is apparently involved in inducing fat loss in adipocytes. It accumulates in breast cancer cells and other cells in serious distress (cachexia). ▶MHC, ▶HLA, ▶obesity; Kennedy MW et al 2001 J Biol Chem 276:35008.

Zanier-Roubicek Syndrome: ▶ectodermal dysplasia, ▶hypohidrotic

ZAK (zipper sterile-α motif kinase): A mixed lineage kinase (MLK) in signal transduction.

ZAP-70 (zeta-associated protein 70): A cytosolic protein tyrosine kinase expressed only in T cells and natural killer cells. By binding to phosphorylated ζ-chains of the CD3 T cell antigen-receptor complex, it assists in the activation of T cells. Its defect may lead to severe combined immunodeficiency. ZAP-70 tyrosine kinase signals to the CXCR4 chemokine receptor



and thus regulates the migration of T lymphocytes. It seems to be involved in arthritis in mice. ►SHP-1, ►CD3 T cell, ►CXCR, ►killer cell, ►immunodeficiency, ►tyrosine kinases, ►retroviral restriction factors; Ottoson NC et al 2001 J Immunol 167:1857; Sakaguchi N et al 2003 Nature [Lond] 426:454, crystal structure: Deindl S et al 2007 Cell 129:735.

ZBP1 (Zipcode binding protein): ►mRNA migration

Zea mays (L.): ►maize

Zeatin (6[4-hydroxy-3-methyl-cis-2-butenylamino]purine): Refers to a cytokinin plant hormone. In *Agrobacterium* T-DNA-located *ipt* gene encodes an isopentenyl transferase that mediates the synthesis of transzeatin and isopentenyl adenosine. In plant tissue culture media it is a commonly used alternative to kinetin, benzylamino purine or isopentenyl adenosine. ►plant hormones

Zebra: *Equus quagga* $2n = 44$; it can form hybrids with both horses (*Equus caballus*, $2n = 64$) and donkeys ($2n = 62$). *Equus grevyi*, $2n = 46$ (see Fig. Z3); *Equus zebra hartmanniae*, $2n = 32$. The Zebra duiker (*Cephalophus zebra*, $2n = 58$) is not a member of the Equidae family but is the male member of a bovine species.

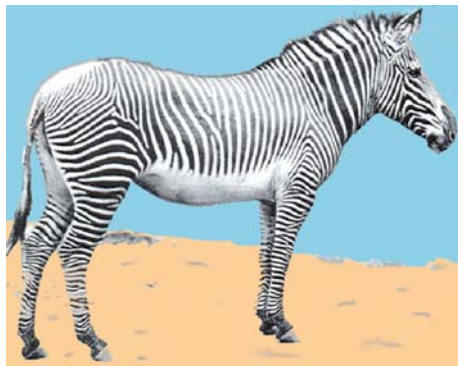


Figure Z3. *Equus grevyi*

ZEBRA (Zta): A non-acidic activator protein of the lytic cycle of the Epstein-Barr virus; it promotes the assembly of the DA complex (TFIID-TFIIA) of transcription factors. ►transcription factors, ►open transcription complex, ►DA

Zebrafish (*Brachydanio rerio*, $2n = 50$): A 3–4 cm tropical freshwater fish; the genome size is about 2×10^9 bp (see Fig. Z4). It is easy to breed and becomes sexually mature in 2–3 months (4 generations/year).

The embryogenetic pattern is laid down in 12 hours, and it is well suited for the analysis of developmental pathways and cell lineages in this small vertebrate. Hundreds of eggs are laid externally. The embryos are transparent and permit observation of gastrulation, development of the brain and heart, etc. Haploids survive for several hours and mutants are available. About 600 genes involved in its development have been identified, and in 1998 a 3350 cM map of 3.3 cM resolution became available. The zebrafish genome has extensive homology to that of humans. ►EP, ►medaka, ►GloFish; Fishman MC 1997 Methods Cell Biol 52:67; Detrich HW III et al 1999 (Eds.) The zebrafish: Biology. Academic Press; radiation hybrid map: Geisler R et al 1999 Nature Genet 23: 86; Hukriede NA et al 1999 Proc Natl Acad Sci USA 96:9745; Woods IG et al 2000 Genome Res 10:1903; Shin JT, Fishman MC 2002 Annu Rev Genomics Hum Genet 3:311; hematopoiesis: de Jong JLO, Zon LI 2005 Annu Rev Genet 39:481; human disease model: Lieschke GJ, Currie PD 2007 Nature Rev Genet 8:353; <http://zebra.sc.edu>; <http://zfish.uoregon.edu/ZFIN/>; <http://zfin.org>; <http://depts.washington.edu/fishscop/>; <http://www.tigr.org/tdb/tgi.shtml>; <http://zfin.org>; <http://zf-espresso.tuebingen.mpg.de>.



Figure Z4. Zebrafish

Zebu (*Bos indicus*): $2n = 60$. ►Santa Gertrudis cattle

Zein: A prolamine protein in maize (homologous to gliadin in wheat) that may account for up to 50% of the grain proteins. It does not have high nutritional value (and is therefore undesirable) because of the low lysine and tryptophan content. It is deposited in zein bodies at the place of synthesis. In the high-lysine maize varieties (*opaque*, *floury*) prolamines are very low and non-prolamine proteins increase. ►high-lysine corn, ►glutenin

Zeitgeber: A rhythmic external signal for the circadian change. ►circadian rhythm

Zeitnehmer: An internal signal for rhythmicity in response to the zeitgeber or even in its absence. ►circadian rhythm, ►zeitgeber

Zellweger Syndrome (ZS): A brain-liver-kidney (cerebrohepatorenal) recessive disease involving human chromosome 7q11.12-q11.13; but over a dozen other loci may have similar effects. The basic defect is due to peroxisome anomalies. ►microbodies, ►neuro-muscular diseases, ►chondrodysplasia punctata, ►cataract, ►pseudo-Zellweger syndrome

Zero, Absolute: The minimum lowest temperature; Kelvin 0° = Celsius $- 273.15^{\circ}$.

Zero Time Binding: Refers to the status of reassociation of two single-strand palindromic DNAs at the beginning of an annealing kinetics experiment. These are the fastest reassociating fractions because they are repeats and are close to each other. ►c₀t curve

zeste (z, chromosome 1.10 of *Drosophila*): The protein kinase product apparently alters the chromatin structure and affects the expression of *w*, *Ubx*, *dpp* by attaching to their promoters. Its action bears similarity to *Polycomb*. The zeste-white3 complex regulates the spindle attachment to the cortical actin. ►w locus, ►Polycomb; McCartney BM et al 2001 Nature Cell Biol 3:933.

Zeugopodium: Corresponds to the radius, the ulna, the tibia and the fibula.

ZFX (human chromosome Xp22.3-p21.2): This Zinc finger protein similar to Zfy was believed to be responsible for feminization of some XY individuals and gonadal dysgenesis. It is not a primary sex determining protein. ZFX escapes inactivation in humans but not in mice. It controls pluripotency of stem cells. ►pluripotency; Palmer MS et al 1990 Proc Natl Acad Sci USA 87:1681.

ZFY (zinc finger Y, Yp11.3): A sequence in the Y chromosome assumed to be involved in the maturation of testes or sperm. A 729 bp intron located immediately upstream of the Zinc finger exon shows no or very little sequence variation in worldwide human samples. ►Zinc finger, ►ZFX

Zidovudin: ►AZT

zif: ►NGFI-A

Zig-Zag Inheritance: ►criss-cross inheritance

Zig-Zag Model of Chromosome Fiber: Radiation-induced DNA breaks revealed fragment sizes of 78 bases, which corresponds to one turn of the DNA around the nucleosome. Additional peaks between 175 and 450 bases reflect the relative position of the nearest neighbor nucleosomes. Calculations and other considerations seem to support a zig-zag model of the chromatin fiber rather than a simple helical

model (Rydberg B et al 1998 J Mol Biol 284:71). ►solenoid

Zinc Finger Nucleases: These are limited-specificity nucleases that can recognize certain DNA sequences and cause small deletions at selected targets. The Zn fingers prefer guanine-rich tracts, particularly 5'-GNN-3' triplets. Each nuclease unit may have three fingers and each grabs one triplet, i.e., a total of nine bases. The dimeric structure of the nuclease cleaves both strands in a tract lying between the G-rich sequences (see Fig. Z5). Non-homologous end-joining may follow the double-strand breaks and thus somatic and germ line mutations may occur. Zinc finger nucleases are associations of the Zinc finger with, e.g., a FokI restriction endonuclease (target GGATG(N)_{9/13}) and can thus be targeted to specific mammalian genes (Porteus MH 2006 Mol Ther 13:438) or can be used to repair specific defective genes in plants by targeted homologous recombination (Wright DA 2005 Plant J 44:693). ►non-homologous end-joining, ►gene therapy; Bibikova M et al 2002 Genetics 161:1169; Miller JC et al 2007 Nature Biotechnol 25:778.

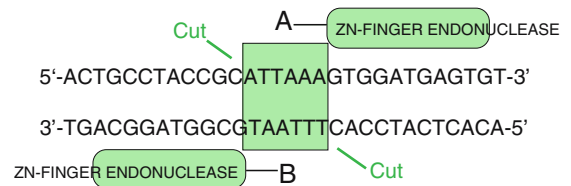


Figure Z5. Diagram of a dimeric (A and B) zinc-finger endonuclease and its mode of cleavage (at the green lines) of DNA. The subunits recognize the DNA sequence by the green shaded square domain. The zinc-fingers bind to the G-rich repeats. (Modified after Bibikova M et al 2002 Genetics 161:1169)

Zinc Fingers: These are binding mechanisms of transcription factors and other regulatory proteins containing tandemly repeated cysteine and histidine molecules and they fold in a “finger-like” fashion cross-linked to Zn. They contain other highly conserved amino acids—phenylalanine (F), leucine (L) and tyrosine (Y). Some Zinc finger proteins bind the RNA to the DNA. About 0.7% of the proteins in budding yeast and the nematode *Caenorhabditis elegans* contain Zn finger motifs; in yeast most commonly 2/molecule and in *Caenorhabditis* up to 14/molecule. Using DNA microarray designs, putative Zn finger transcription factor binding sites can be identified. By designing new Zinc finger motifs, specific regulation of gene expression is possible (Reynolds L et al 2002 Proc Natl Acad Sci USA 100:1615). Zinc is an essential

element for life and it is a cofactor for several enzymes. ▶hormone receptor, ▶DNA-binding protein domains, ▶microarray hybridization, ▶acrodermatitis enteropathica, ▶ZFY, ▶RING finger, ▶binuclear Zinc cluster, ▶Cys₄ receptor, ▶GATA, ▶LIM; Rubin GM et al 2000 Science 287:2204; Bulyk ML et al 2001 Proc Natl Acad Sci USA 98:7158; Pabo CO et al 2001 Annu Rev Biochem 70:313; binding tools: <http://www.scripps.edu/mb/barbas/zfdesign/zfdesignhome.php>; Zn finger protein design: <http://bindr.gdcb.iastate.edu/ZiFiT/>.

Zinc Knuckle (Zf-CCHC): A Zn-binding motif commonly found in the nucleocapsids of retroviruses (e.g., HIV) and in regulatory proteins of diverse eukaryotes. Its sequence is CX₂CX₄HX₄C where X can be different amino acids. These protein motifs are involved in binding RNA or single-strand DNA. (See Le Thuy et al 2001 Mol Cell Biol 21:8346).

Zinc Ribbon Fold (CXXC(H)-15/17-CXXC): This is present in diverse binding proteins. ▶binding proteins, ▶transcription factors

Zinc Ring Finger: ▶RING finger

ZIP1, ZIP2: Protein factors that mediate phosphorylation of potassium ion channels by protein kinase C. ▶protein kinase, ▶ion channel

Zipcode: ▶mRNA migration

Zipper Domain: Refers to part of dimeric DNA-binding proteins where the two subunits are held together by repeating amino acid residues; in the other parts the subunits are separated from each other. ▶leucine zipper

Zoidogamy: In this fertilization takes place by motile antherozoids. ▶siphonogamy

Zollinger-Ellison Syndrome (Wermer syndrome MEN 1): A multiple endocrine adenomatosis (neoplasia) encoded in human chromosome 11q13. ▶adenomatosis multiple endocrine

Zona Pellucida: A yolky layer around the mammalian egg. Zona pellucida domains are present in dauer larvae of nematodes and mechanotransducers in *Drosophila* and are involved in other functions. The domain ~260 amino acids have eight conserved cysteines near the carboxyl end and are often glycosylated. ▶fertilization [animals], ▶vitelline layer, ▶egg, ▶dauer larva, ▶mechanosensory genes; Jovine L et al 2002 Nature Cell Biol 4:457; Jovine L et al 2005 Annu Rev Biochem 74:83.

Zonoskeleton: This includes the scapula, the clavicle and the hip bones.

Zonula Occludens: A tight cell junction mediated by ZO proteins associated with a 210–255 kDa membrane-tied guanylate kinase. ▶MAGUK, ▶ELL; Meyer TN et al 2002 J Biol Chem 277:24855.

Zoo Blot: Southern hybridization experiments with probes derived from a variety of different species to test potential homologies. (See Rijkers T, Ruther U 1996 Biochim Biophys Acta 1307:294).

Zoo FISH: Fluorescent in situ hybridization maps for several species to study the evolutionary relations of their chromosomes. ▶FISH

Zoonosis (zoonotic infection): Animal pathogens transferred to humans (by e.g., grafts, food) may lead to the development of new human diseases under natural conditions. ▶grafting in medicine, ▶acquired immunodeficiency, ▶xenotransplantation, ▶Dengue fever, ▶Ebola virus, ▶Pox Virus, ▶West Nile Virus, ▶sleeping sickness, ▶influenza, ▶SARS, ▶encephalopathies, ▶mycobacteria, ▶plague, ▶laboratory safety; Weiss RA 1998 Nature Med 4:391.

Zoospore: This is a motile (swimming) spore.

Zootype Hypothesis: According to this, HOX-type homeobox genes are present in all metazoa. ▶homeotic genes

ZP1, ZP2, ZP3: Refer to zona pellucida glycoproteins. ▶fertilization, ▶zona pellucida

ZPA (zone of polarizing activity): Determines the anterior/posterior differentiation of the limbs and is located behind AER in the limb bud. ▶AER, ▶limb bud

ZPK: Denotes a leucine zipper protein kinase. ▶DNA-binding protein domains

ZPR: Refers to zinc finger protein binding to the epidermal growth factor receptor. ▶zinc fingers, ▶EGFR

Zta: ▶ZEBRA

Zuotin: Z DNA and tRNA binding protein of yeast. It has structural homology with DnaJ and is functionally related to the mammalian chaperone MIDA1, required for cellular growth. ▶chaperones, ▶DnaK, ▶MIDA1; Braun EL, Grotewold E 2001 Mol Biol Evol 18:1401.

Zwischenferment: ▶G6PD

Zwitterion: A dipolar ion with separated positive and negative poles.

ZygDNA: It has been reported that 0.1 to 0.2% of the eukaryotic DNA may not be replicated until

late leptotene–zygotene. This delayed replication involves dispersed 4–10 kb stretches and it has been assumed that these segments (ZygDNA) code for genes with products aiding chromosome pairing. It is assumed that a leptotene (L) lipoprotein is involved in the delayed replication. (L) ▶ [meiosis](#); Hotta Y et al 1985 Cell 40:785.

Zygomeres: Refer to hypothetical initiators of chromosome pairing in the DNA.

Zygomorphic: A structure of bilateral symmetry, like a snapdragon flower (see Fig. Z6).



Figure Z6. Zygomorphic. Courtesy of Dr. Z. Schwarz-Sommer

Zygonema: Denotes the chromosome at the zygotene stage. ▶ [meiosis](#), ▶ [zygotene stage](#)

Zygosis: Twins can be identical (monozygotic, MZ) or non-identical (dizygotic, DZ). The distinction is not always simple because dizygotic twins (like any siblings) may show several identical features, depending on the genetic constitution (consanguinity) of the parents. If the probability of monozygosis between twins with identity in a genetic marker is designated as $P(A_1/B)$ where A_1 and B are different markers and the probability of the twins being either dizygotic or erroneously assumed to be monozygotic is: $1 - P(A_1/B)$. The calculation may be based on the formula:

$$P(A_1/B) = \frac{1}{1 + [Q \times L]}$$

where Q is the dizygotic:monozygotic proportion in the population (DZ/MZ), and L = likelihood ratio of the conditional probabilities for DZ and MZ twins would be identical for a particular genetic condition. The conditional probabilities that if one of the twins is of a particular dominant type, the second would also be of the same type at dizygosis is $0.5 - 1.0$, and at monozygosis 1.0. In the case of recessive markers, these probabilities are 0.25 and 1.0, respectively. The probabilities also depend on the genetic constitution of the parents. Recessive markers may be expressed only if both parents carry that particular allele. If either of the parents is homozygous for a dominant marker, then both twins must carry that marker, irrespective of zygosity. L can be computed as $L = \frac{P[DZ]}{P[MZ]} L_1 \times L_2 \dots L_n$ where $\frac{P[DZ]}{P[MZ]}$ is the empirical probability of the DZ:MZ proportions in the general population, and $L_1 \times L_2 \dots L_n$ are the conditional probabilities for the genetic markers 1 to n used, either 0.25 or 1.0. Further complications may arise if either the penetrance or expressivity of the markers varies. The DZ:MZ proportions may vary generally from 0.65:0.35 to 0.70:0.30 but are somewhat different in various ethnic groups, depending on the age of the mother, the use of fertility drugs and artificial insemination, etc. DNA markers, either by RFLP or the PCR method of typing, can better resolve the problem than using blood types or other genetic analyses. ▶ [conditional probability](#), ▶ [likelihood](#), ▶ [RFLP](#), ▶ [PCR](#), ▶ [DNA fingerprinting](#), ▶ [twinning](#), ▶ [monozygotic](#), ▶ [dizygotic](#), ▶ [concordance](#), ▶ [discordance](#)

Zygosity: ▶ [zygosis](#)

Zygospore: This is formed by the fusion of two spores or two multinucleate gametangia. ▶ [heterothallism](#), ▶ [homothallism](#), ▶ [gametangia](#)

Zygote: A cell resulting from the union of two gametes of opposite sexes. ▶ [gamete](#)

Zygotene Stage: This stage of meiosis occurs when the homologous chromosomes (supposedly) begin to synapse. The pairing usually begins at the termini and proceeds toward the centromeric region. At this stage the synaptonemal complex is detectable by electron microscopy. The intimate bivalent pairing appears to be a requisite for chiasma formation as well as for genetic recombination (see Fig. Z7). ▶ [meiosis](#), ▶ [chiasma](#), ▶ [synaptonemal complex](#), ▶ [association point](#), illustration after K. Bela \hat{r} .



Figure Z7. Zygotene

Zygotic Combinations: ►Punnett square, ►allelic combinations

Zygotic Gene: During embryo development this gene is involved in the early control of differentiation in contrast to the maternal effect genes, which are transcribed from the maternal genome and their product is transused to the embryo. ►maternal effect genes, ►morphogenesis

Zygotic Gene Activation: After fertilization there is a transition from maternal to zygotic control of development. This process in mouse begins after G₂ of the one cell embryo (Schultz RM 1993 Bioessays 15:531). In humans it seems to be somewhat delayed.

Zygotic Induction: Usually the integrated λ prophage is inherited as an integral gene of the bacterial chromosome. However, when a lysogenic Hfr cell carrying λ is crossed to a *non-lysogenic* F⁻ recipient, the prophage leaves the chromosomal position (induction) and becomes an infectious vegetative phage after replicating to about 100–200 particles. After zygotic induction, only the markers transmitted before the position of the prophage has changed are recovered in the recombinants. Zygotic induction does not occur if the F⁻ cells are *lysogenic*, irrespective of whether or not the Hfr is lysogenic. The F⁻ recipient is immune to superinfection by free λ phage and it cannot support the vegetative development of the chromosomal λ phage transmitted by the Hfr donor. This indicates that the F⁻ cytoplasm carries an immunity substance or a repressor. ►lysogeny, ►Hfr, ►F⁻, ►lysogenic repressor, ►lambda phage; Hayes W 1965 The genetics of bacteria and their viruses. Wiley, New York.

Zygotic Lethal: A genetic factor that permits the function of the gametes but kills the zygote. The two systems presented here occur in the plant *Oenothera*, which carry translocation complexes. Letters printed in gray indicate lack of zygote

| | | Male gametes | |
|----------------|---|--------------|----|
| | | A | B |
| Female gametes | A | AA | AB |
| | B | AB | BB |

Figure Z8. In zygotic lethality only the heterozygotes are viable and both types of homozygotes are lethal

| | | Male gametes | |
|----------------|---|--------------|----|
| | | A | B |
| Female gametes | A | AA | AB |
| | B | AB | BB |

Figure Z9. Gametic lethal factors A and B are unable to form selfed zygotes and only the heterozygous embryos are viable. Only the female can contribute viable B gamete and the male produces viable A gametes

formation (see Figures Z8 and Z9) ►translocation, ►complex heterozygote, ►translocation [in animals], ►*Oenothera*

Zymogen: An inactive enzyme precursor. ►regulation of enzyme activity

Zymogram: Electrophoretically separated isozymes are identified in the electrophoretic medium (starch, agarose) by supplying a chromogenic substrate in situ and this reveals the position of the functionally active enzyme bands. ►electrophoresis, ►isozyme

Zymolase: This hydrolyzes 1→3 glucose linkages such as those existing in yeast cell walls; it is not an exactly defined mixture of proteins extracted from *Athrobacter luteus*.

Zymosan: A cell wall extract with a variety of components interfering with the C3 complement. ►complement; Ohki K et al 2001 Immunol Cell Biol 79:462.

Zymotype: This is an electrophoretically determined pattern of enzymes (proteins) which is characteristic of individuals or group of individuals. ►isozymes, ►electrophoresis, ►zymogram

Historical vignettes

“I have a rather strange feeling about our DNA structure. If it is correct, we should obviously follow it up at a rapid rate. On the other hand it will at the same time be difficult to avoid the desire to forget completely about nucleic acid and to concentrate on other aspects of life.” (*JD Watson's letter to Max Delbrück on March 22, 1953. Quoted after HF Judson 1979 The Eighth Day of Creation. Simon and Schuster, New York, p. 229*)

Evelyn Witkin (2002) in reminiscing about the pre-Watson and Crick and Hershey and Chase era at the Cold Spring Harbor Laboratory writes (*Annu. Rev. Microbiol.* 56:1):

“Although Avery et al (1) had demonstrated in 1944 that the genetic material is DNA, the prevailing attitude at Cold Spring Harbor had been respectful skepticism. Some suggested that the transforming DNA in their experiments had activated genetic information already present or somehow caused a directed mutation. Others believed that the minuscule trace of protein still contaminating the DNA was the active agent. Delbrück declared DNA to be a “stupid” molecule, incapable of carrying genetic information.”

In 1962 Francis Harry Compton Crick, James Dewey Watson and Maurice Hugh Frederick Wilkins were jointly awarded the Nobel Prize in Physiology or Medicine “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material”.

In 1969 the Nobel Prize in Physiology or Medicine was shared by Max Delbrück, Alfred D Hershey and Salvador Luria.

Appendix



Gregor Mendel among fellow monks in Alt Brunn *circa* 1862. In front of him sits Abbot FC Napp who accepted him to the Augustinian Order in 1843. In 1868, Mendel became Abbot and Anselm Rambousek (standing second from left) followed him in that position in 1884 after his death. This photograph sheds some light on the characters of his fellows. While some look bored or argumentative, Mendel studies a fuchsia plant. Fortunately, he did not continue with this ornamental plant with chromosome numbers $2n = 22, 55, 66$ and 77 , that frustrated others before and after his time. He had perhaps good luck but his genius was needed for recognizing his luck. (The photograph is the courtesy of Dr. V Orel.)

Reviews of Author's Books

NATURE (Lond) 302:169 "...sections dealing with molecular genetics ... are remarkably clear and up to date." "...this one is one of the best textbooks of general genetics". "The book is extremely well illustrated..."

THEORETICAL AND APPLIED GENETICS 66:38 "...a balanced treatment of almost all genetics disciplines"

HEREDITY 33:123 "...unusually good value."

QUARTERLY REVIEW OF BIOLOGY 74:74 "The author clearly met his goal: to facilitate communication and understanding across all biological sciences". "...this book should prove very useful as a quick desk reference for students, professionals and non-professionals."

AMERICAN JOURNAL OF MEDICAL GENETICS 83:145 "He undauntedly covers the entire field of contemporary genetics including not only the classical areas of formal genetics and cytogenetics but also the latest global molecular advances and their applications". "I found the contents very useful..."

ACTA PÆDIATRICA 87:1211 "The strength of the book lies in its brief explanations ... it is invaluable for anyone interested in this rapidly evolving area, including scientists, teachers, students, and laymen."

ANNALS OF INTERNAL MEDICINE 130:168 "This book is a valuable reference tool and will be of interest to a wide audience. Other books, including glossaries and dictionaries of genetics are available but are more limited in coverage".

ANNALS OF THE ENTOMOLOGICAL SOCIETY OF AMERICA 91:894 "The preparation of a book like this is a massive task. If it is done well, it can provide a valuable central resource to information that might otherwise take a lengthy search to uncover". "In this case ... the overall effort has been very successful."

HortScience 33:1274 "The book is attractive and user-friendly." "This manual is by far the best I have used".

MUTATION RESEARCH FORUM 1999 May "... this book is a true information warehouse". "The words in this book came through as if someone were talking directly to me." "The investment ... is worth it."

JOURNAL OF PHYTOPATHOLOGY 147:623 "This giant volume is recommended to those who are in contact with the genetic aspects of questions in their

field of research or practice." "The most important feature of this book is that all concepts are explained not just defined." "The style is clear even for the beginner".

ACTA AGRONOMICA HUNGARICA 47(2):237 "...although a number of dictionaries or glossaries of genetics already exist, this ... is quite different from the others in-as-much as it is much more comprehensive, and not only defines the concepts but explains them in concise plain language"... "fills a void".

CHOICE 1998, 36-1563 "...outstanding compendium of genetics"... "Highly recommended for biologists".

GENOMICS & PROTEOMICS 2003 (Nov./Dec):56. "useful resource...50% more information than in the first edition".

GENOMICS REVIEWS (2004, Internet). "Excellent resource."

Book News (2004, Internet). "By authoring the work single-handedly (clearly a labor of love) Redei (emeritus, U. of Missouri) could maintain a consistency of approach and avoid redundancy and yet still attain impressive breadth and depth in a compact reference."

GENOMICS & PROTEOMICS (2003, Nov/Dec):56. "...useful resource... 50% more information than in the first edition".

NÖVÉNYTERMELÉS (2003, 52:724). "...excellent tool...I recommend it to the attention of everybody". (translated from Hungarian)

CHOICE (2004, 882:41-2549). "...an expanded version of the highly acclaimed Genetics Manual... reflects recent developments in genetics, molecular and cell biology, genomics and proteomics." ... "valuable... Recommended".

BOOKWORKZ (2004, Internet). "...incomparable reference...thorough coverage of modern genetics, genomics, and proteomics".

E-STREAMS (2004, 7[1]:2969). "This is a highly usable item and provides effective and efficient access to relevant topics."

THE SCIENCE ADVISORY BOARD (2004, Internet). "... the best got even better." "This book is indispensable, as a reference for research universities, for high schools, for public libraries, and because of the relatively modest price ...it is affordable for individuals too."

BIOspectrum (2004, 10:653). "it is truly wonderful". "Most students, scientists, all geneticists, including human geneticists, the general public interested in natural sciences, teachers and journalists can benefit from it to a great degree. It is a must for larger biological libraries!" (translated from German).

CLINICAL CHEMISTRY (2004, 50:1719–1720). "... the book has an encyclopedic quality, far surpassing a dictionary." "...many readers will find themselves engrossed in this fascinating book." ... "This is a wonderful book..."

PROTEOMICS (2004, 4:544–545). "Once you start reading this book it is difficult to put down. It is a valuable source of such a breadth of information that would surely be difficult to find elsewhere." "...a highly recommended one-stop resource for medics, grad students and researchers."

GENETIC ENGINEERING NEWS (2004, 24(6), March 15): "...genomics and post-genomics terms, including concepts, theories, and applications, explained

concisely for novices and comprehensive enough for those with expertise."

REFERENCE REVIEWS (2004, 18(62004):43–44): "excellent volume"... "is a readable, accessible, well thought out and extremely useful reference book."

MICROBE (Amer. Soc. Microbiol.) (2004, May): "It is impressive that a single author can put together a dictionary of this size and make it useful to the general scientific reader."... "Rédei's definitions are accurate"... "[he] is a clear winner."

THE CHEMICAL EDUCATOR (2005, 10(6):56–57) "Rédei has eminently succeeded in attaining his goal." "Numerous cross-references link the short entries into a most encyclopedic, up-to-date text."... "gold mine of valuable...information."

MEDICAL REFERENCE SERVICES QUARTERLY (2006, 2[(1):104) "...high quality reference book" "this is the most comprehensive..."

About the Author

George P. Rédei is Professor Emeritus at the University of Missouri, Columbia. Born in Vienna, Austria he completed his formal education in Hungary. Rédei is affiliated with the University of Missouri since 1957 where he has taught formal courses in basic genetics, analytical genetics, history of genetics and genetic engineering. He has been visiting professor at several leading institutions in Germany, Hungary and China.

Rédei has introduced *Arabidopsis* to genetic research in the USA and published seminal research papers on classical, molecular, population genetics and history of genetics in *Science*, *Nature*, *Cell*, *Genetics*, *Canadian Journal of Genetics and Cytology*, *Journal of Heredity*, *Genome*, *Experientia*, *EMBO Journal*, *Proceedings of the National Academy of Sciences USA*, *Genes &*

Development, *Molecular and General Genetics*, *Development*, *Mutation Research*, *Annual Review of Genetics*, *Advances in Genetics*, *Bibliographia Genetica*, *Biochemical Genetics*, *Theoretical and Applied Genetics*, *Biologisches Zentralblatt*, *Protoplasma*, *Plant Physiology* and other international journals. More than 50,000 students have used his textbook, *Genetics* (translated also into many foreign languages). Preceding editions and translation of the present volume have been bestsellers.

Rédei is a foreign member of the Hungarian National Academy of Sciences since 1990 and in 2004 the University of Missouri named a section of the new Life Sciences Building in his honor.